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Executive summary
INTRODUCTION

Department of Reproductive Health and Research

The WHO Department of Reproductive Health and Research (RHR) was created in November 1998 by joining the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP) and the former WHO Division of Reproductive Health (Technical Support) (RHT). The WHO Administration brought these two entities together with the aim of integrating research and action in reproductive health into one Department. Within WHO, the Department is located in a cluster called Family and Community Health (renamed in 1999 from Health Systems and Community Health).

The Department has set itself the mission of "helping people to lead healthy sexual and reproductive lives". The overall aim in this regard is to strengthen the capacity of countries to enable people to promote and protect their own health and that of their partners as it relates to sexuality and reproduction and to have access to and receive quality reproductive health services when needed.

In 1999, the Department decided that it would conduct its work within a matrix structure, in which staff work in task-oriented teams. This led to the establishment of four Teams within the Department:

—Research and Evidence
—Development of Norms and Tools
—Technical Support to Countries
—Advocacy and Human Rights.

These Teams reflect the Department’s strategic operational division of work.

The specific areas of work of the Department, selected on the basis of the comparative advantage of the Department, and to which each of the four Teams contributes, are as follows:

—Planning and Programming for Reproductive Health
—Sexual Development, Maturation and Health
—Fertility Regulation
—Maternal and Perinatal Health
—Unsafe Abortion
—Reproductive Tract Infections (including cervical cancer/infertility)
—Female Genital Mutilation and Other Harmful Practices.

UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction

The UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), which was established in 1972 by WHO, continues to exist as an entity within RHR. The cosponsors of HRP—the United Nations Development Programme (UNDP), the United Nations Population Fund (UNFPA), WHO, and the World Bank—together with major financial contributors and other interested parties, make up HRP’s governing body, the Policy and Coordination Committee (PCC), which sets policy, assesses progress, and reviews and approves HRP’s budget. Broad strategic advice on HRP’s work is provided by the Scientific and Technical Advisory Group (STAG) (Annex 1). (In 1999, STAG assumed the responsibility for reviewing, and advising on, the work of the whole Department.) The Scientific and Ethical Review Group Panel (Annex 2) reviews all projects involving human subjects and research in animals and contributes to ethical debate on matters relating to reproductive health. The Toxicology Panel (Annex 3) is a complementary review body to the Scientific and Ethical Review Group Panel which provides expertise in the evaluation of pharmacokinetic, metabolic, endocrinological, toxicological, teratogenicity, carcinogenicity and mutagenicity studies of drugs, procedures or devices developed or studied by HRP or referred to it for advice. In addition, HRP has several scientific committees that advise on detailed research strategies.

WOMEN’S PERSPECTIVES AND GENDER ISSUES

Within RHR, this activity falls under the team for Advocacy and Human Rights. Th component seeks to:

—ensure that a gender analysis be brought to bear across the Department;
—ensure that women and women’s perspectives are brought into the Department’s overall structure and decision-
Countries need sound information from good quality research as the basis for policy-setting and implementation of programmes aimed at improving reproductive health of their people. The Department is committed to generating, synthesising, disseminating and implementing forms of care based on evidence that is reliable, up-to-date and relevant to the needs of the countries. The objective of the Planning and Programming group is to assist countries in the development of reproductive health programmes relevant to their needs.

The Planning and Programming group also acts as a data clearing house through its evidence activities, conducts research relevant to implementation of reproductive health programmes, works with the Team on Development of Norms and Tools on reproductive health indicators and the development of essential care practice guides and, finally, through technical support to countries assist countries in the implementation of evidence-based practices and programmes.

**Research and evidence**

The main objective of the Planning and Programming group related to this area is to generate and synthesize evidence for clinical and programmatic actions for improving reproductive health in under-resourced settings. In this context, an initiative entitled *Mapping best reproductive health practices* was launched in 1997. This activity has produced a substantial body of evidence on high-priority reproductive health problems. New systematic reviews of interventions for emergency contraception, antibiotic prophylaxis for incomplete abortion, misoprostol for labour induction have been published and a considerable number of previous reviews have been updated. A systematic review on “integration in the health sector” has also been initiated. In 1999, the second issue of *The WHO reproductive health library* was published in English and Spanish. Both versions were well-received by health workers around the world. A randomized controlled trial to evaluate a programme of active dissemination using *The WHO reproductive health library* in district hospitals in three countries was approved and initiated. This trial will evaluate a strategy to implement evidence-based reproductive health practices in 40 hospitals in Mexico, South Africa and Thailand. The Department continues to maintain key reproductive health databases. These are used to produce estimates of the magnitude of important reproductive health indicators. In 1999, work on new estimates of maternal mortality and perinatal mortality was initiated.

**Development of norms and tools**

In 1999, a manual entitled *Reproductive health in conflict and displacement* was published. Also, a strategy for dissemination, adaptation and use of the Department’s technical documents was in preparation in collaboration with other agencies (including NGOs and bilateral arrangements). Further work on the development of a set of internationally agreed reproductive health indicators is planned for 2000.

**Technical support to countries**

The strategic approach to the introduction of contraceptive technologies, developed by HRP, has been adapted to address other reproductive health issues. The approach consists of three stages to introduce new or underutilized technologies and to improve the quality of care in reproductive health programmes.
Stage I assessments examine users’ needs and perspectives, available technologies and the capabilities of the service delivery system with the aim of determining the need for introducing new or underutilized technologies. A draft field guide for conducting Stage I assessments was prepared for field-testing in 1999 and a Stage I assessment of reproductive health needs was completed in the Lao People’s Democratic Republic. Initial planning began for an assessment in China concerning IUD introduction.

Stage II involves action research to design and test optimal models for introducing technologies or services, while improving the overall quality of care. Stage II projects continued in 1999 in Bolivia, Myanmar and Zambia, and were completed in South Africa.

Stage III uses research results and lessons learned in Stage II for policy and programme development in replication or “scaling-up” of activities. In Brazil, an evaluation of activities replicating a new model for reproductive health services developed in one municipality was begun. In Vietnam, a strategy, developed in Stage II, for introducing depot medroxyprogesterone acetate (DMPA), while simultaneously improving the quality of care in provision of all contraceptive methods is now being utilized for an expansion to 34 provinces.

Support to countries in their efforts to introduce the female condom has continued through the development of a guide for national planning and programming (in collaboration with UNAIDS and the Female Health Company), research on the feasibility and safety of re-use, and support for the development of a national introduction strategy in South Africa.

Support to the introduction of emergency contraception has continued in Indonesia, South Africa and Zambia. Service delivery research was conducted in Romania concerning the acceptability to clients and the service delivery adaptations necessary to add non-surgical abortion to existing abortion services.

SEXUAL AND REPRODUCTIVE HEALTH OF ADOLESCENTS

Under the theme of sexual development, maturation and health, activities continued to focus on adolescent sexual and reproductive health. The Department has two research objectives implemented by HRP: documentation of the context of adolescent reproductive and sexual health, including the magnitude, determinants and consequences for adolescents’ lives; and identification, through intervention research and evaluation of ongoing interventions and programmes, of optimal provision of health and information services, and best practices, that respond effectively to the needs of adolescents. During 1999, three main activities were pursued. First, a synthesis was completed of ongoing or recently completed social science research focusing on youth, that was supported by HRP within the context of previous social science research initiatives on abortion, sexual behaviour and men’s roles. The review is scheduled for publication in the Occasional Paper Series started in 1999 by the Department.

Second, support was provided for formative and intervention research studies under the social science research initiative launched in 1998 on adolescent sexual and reproductive health. In response to a call for proposals and concept papers, over 250 submissions were received from investigators in some 50 developing countries. Three regional workshops [Nairobi (Kenya), Bangkok (Thailand), and Gramado (Brazil)] were conducted in late 1998 to early 1999 in an effort to build research capacity, assist in proposal development, improve the overall quality of the most promising research proposals, and further strengthen the initiative. A total of 56 researchers from Africa, Asia and Latin America attended these three workshops. Proposals have undergone rigorous peer review and, as of January 2000, this initiative supports some 29 research projects addressing topics ranging from risk behaviours and dual protection to sexual coercion and providers’ perspectives on reproductive health services for adolescents.

And third, under an operations research project on improving reproductive health services for adolescents in French-speaking African countries, formative research was completed in one country, Côte d’Ivoire, and results are available. In addition, the Frontiers in Reproductive Health project, which is funded by the United States Agency for International Development (USAID), agreed to include Senegal in its operations research on youth in four countries. This work will be conducted in collaboration with the Department.

In 2000, HRP will continue to implement and coordinate these research initiatives in a variety of developing countries. The intention is also to develop a network of investigators participating in research supported by HRP on adolescent sexual and reproductive health. Special efforts will be made to initiate research on adolescent sexual and reproductive health in the WHO Eastern Mediterranean Region, and in Eastern Europe and its newly independent states.

Several additional research activities are envisaged, including: a regional research initiative on reproductive health needs of adolescent migrants in the countries of the Greater Mekong region (China, Lao People’s Democratic Republic, Myanmar, Thailand, Viet Nam); a facility-based study of pre-adolescent females reporting symptoms of vaginal discharge in Mongolia; and a five-year follow-up study measuring bone mineral density in young women initiating use of DMPA, norethisterone enantate (NET-EN), or combined oral contraceptives.
FERTILITY REGULATION

Development of improved and new methods of fertility regulation

Because of funding constraints, the research supported by HRP during the past year was restricted to the high-priority leads identified by the Strategic Committee on Technology Development and Assessment at its meeting in November 1997, namely emergency contraception, injectable hormonal preparations for use by women and by men, immunocontraceptives, and non-surgical methods of pregnancy termination. Progress on some of these high-priority leads has been slower than anticipated because of unexpected technical difficulties or because of delays due to prolonged discussions with potential industrial partners.

Emergency contraception

HRP has been investigating the potential of two compounds, levonorgestrel and mifepristone for emergency contraception. In August 1998, results were published from a large randomized, double-blind, multinational study of 1998 women which compared the efficacy and side-effects of levonorgestrel with the Yuzpe regimen in emergency contraception. This trial showed that the levonorgestrel regimen was better tolerated than the Yuzpe regimen and its efficacy greater. The study also found that, for both methods combined, efficacy was significantly greater the sooner treatment was started after unprotected coitus. These findings had a major impact in the communities of family planning providers, decision-makers and researchers. In 1999, further details of the study were requested from all corners of the world. The results were discussed in The Lancet and other journals and additional analyses were carried out on the effect of treatment delay on efficacy of the treatment. Drug regulatory authorities in several countries have expressed interest in registering the levonorgestrel-only method and guidelines for providers are being updated. A two-pill pack of 0.75 mg levonorgestrel has now been registered for emergency contraception in, among others, Brazil, Canada, China, France, Hungary, Jamaica, Kenya, Nigeria, Sri Lanka, the United Kingdom, the USA and Yemen. Negotiations are ongoing regarding registration of the product in several additional countries.

The potential of the antiprogestogen mifepristone for use in emergency contraception was confirmed in 1992 in two studies in which a 600 mg dose of the compound was used. HRP then compared the efficacy and side-effects of three doses (600 mg, 50 mg and 10 mg) of mifepristone when administered up to 120 hours (five days) after unprotected coitus in a randomized, multinational trial. The results of this study were published in 1999. Of the 1717 women in the study, 21 were found to be pregnant after treatment. Pregnancy risks were similar in all three treatment groups (1.1-1.3%) and the treatment appeared to prevent 85% of pregnancies. Despite the 60-fold difference between the doses used, there was no significant difference in side-effects except for the onset of next menses, which was significantly (p<0.01) related to mifepristone dose. The results of the study have several practical implications. A lower dose of mifepristone would be substantially cheaper and would make a delay in the onset of the next menses less likely.

HRP is participating, in a technical capacity, in a collaborative three-year initiative in China, which aims at developing mifepristone for indications to reduce unwanted pregnancies and recourse to abortion. Under this initiative, the clinical phase was recently completed of a randomized, double-blind trial involving 10 Chinese centres to compare the efficacy and side-effects of 10 mg and 25 mg doses mifepristone manufactured in China. The study included 3002 women and the final results are expected to be available in 2000.

An important question that remains to be answered is whether mifepristone is a better choice than levonorgestrel for emergency contraception. The levonorgestrel regimen that has been used so far shares one of the disadvantages of the Yuzpe regimen, namely the 12-hour interval between the administration of the two doses of the drug. The method would be more practical if the two doses could be administered at the same time. To determine if this would be feasible, HRP is currently carrying out a large multinational randomized double-blind study comparing the efficacy and side-effects of 10 mg of mifepristone and two treatments of levonorgestrel, i.e. two doses of 0.75 mg of levonorgestrel administered at 12-hour interval, and a single dose of 1.5 mg, when used for emergency contraception up to 120 hours after unprotected intercourse.

The copper IUD, in certain cases, can be a very good alternative to hormonal methods of emergency contraception. A meta-analysis of 19 studies of postcoital insertion of an IUD revealed an efficacy of some 15 times higher than that of the Yuzpe regimen. No prospective studies have yet reported side-effects or morbidity after insertion of the IUD for emergency contraception. In order to confirm the efficacy, acceptability, side-effects and possible complications of this method in a prospective study, HRP launched in 16 centres in China a study of the use of the TCu380A IUD in emergency contraception. The interim results of the study look very promising. Until now, no woman has become pregnant in the treatment cycle and no serious adverse events
or complications have been reported.

Some women may not use a method of emergency contraception because of religious or other reasons as they may think that the mode of action of the regimen is abortifacient or that the method acts by preventing implantation of a fertilized egg. It has been shown that the Yuzpe regimen does not interrupt an established implantation in the human. As no information exist on the mode of action of the levonorgestrel regimen of two tablets of 0.75 mg given at 12-hour interval, research is being carried out to investigate the effects of this regimen on various events leading to fertilization and the establishment of pregnancy.

**Non-surgical abortion**

The regimen of mifepristone and a prostaglandin analogue for the termination of an early pregnancy is currently registered in 13 countries, of which only one is a developing country. Several improvements are regarded as being necessary in order for the method to be of practical use in a greater number of developing countries. These include lowering of drug dose in order to lower the costs of the treatment, reduction of the duration and amount of bleeding, and increase in the usability of the methods from up to seven weeks of amenorrhoea to nine weeks.

Research conducted by HRP has already shown that in the regimen of mifepristone followed by a prostaglandin analogue (gemeprost or misoprostol) the 200 mg dose is as effective as the 600 mg dose. A recent HRP study clearly showed that, with advancing gestation, the role of the prostaglandin becomes more important. This study also found that orally administered misoprostol is less effective in pregnancies beyond seven weeks’ amenorrhoea. A worrying finding was that the rate of continuing pregnancies increased from 1.4% and 1.2% in the two earliest gestational age groups to 9.0% in the women with 4–5 weeks’ delay in menstruation (8–9 weeks’ amenorrhoea). These findings stress the importance of accurate estimation of the length of gestation before treatment, especially if oral misoprostol is used, and the importance of the follow-up of the women after treatment.

In 1999, HRP published results from a study, that was designed together with investigators in Stockholm, which compared uterine contractility after oral and vaginal administration of misoprostol. The oral administration of misoprostol did not induce regular contractility in most of the women studied. In contrast, when misoprostol was given vaginally, it resulted in slowly rising uterine tonus and regular contractility which continued beyond the four-hour observation period of the study. These findings explain why, as shown recently by other investigators, the clinical efficacy of misoprostol is relatively low after oral administration in more advanced pregnancies and why the use of vaginal administration produces better results.

A randomized, double-blind study was launched in late 1998 in 15 centres to compare efficacy of three misoprostol regimens administered two days after the administration of 200 mg of mifepristone: (i) initial oral dose of 0.8 mg continued with oral dose of 0.4 mg twice daily for 7 days; (ii) initial vaginal dose of 0.8 mg continued with oral dose of 0.4 mg twice daily for 7 days; and (iii) a vaginal dose of 0.8 mg. The recruitment target is 2250 women, 750 women for each of the three amenorrhoea categories of: (i) up to 49 days; (ii) 50–56 days; and (iii) 57–63 days. By the end of 1999, a total of 1896 women had been enrolled for this trial, which is likely to be completed during the first few months of 2000.

In 1999, results were published from an HRP-supported randomized double-blind placebo-controlled study which evaluated the effects of oral contraceptive (OC) pills on the outcome of medical abortion and the duration of post-abortion bleeding. In this study, 200 women (100 each in Hong Kong and Shanghai) in the first 49 days of pregnancy were treated with 200 mg mifepristone followed two days later by 0.4 mg misoprostol vaginally. One day later they were randomized to receive either OCs (30 μg of ethinylestradiol and 0.15 mg levonorgestrel per tablet) or placebo for 21 days. The complete abortion rates were 98% in the OC group and 99% in the placebo group. The median duration of bleeding was similar, but there was a significant fall in haemoglobin concentration by two weeks (5.3 g/dl) in the OC group. The presumptive conclusion from the study that OC pills might, in fact, increase the amount of bleeding after medical abortion was unexpected, and requires further investigation.

Previous studies suggested that misoprostol was effective for cervical priming, but the optimal dose and route of administration needed to be defined. A double-blind, placebo-controlled study was designed together with the investigators in Hong Kong to compare oral and vaginal doses of 0.2 mg and 0.4 mg of misoprostol administered three hours prior to suction evacuation in pregnancies of 8–12 weeks duration. The results of this study were published during the past year. The cumulative force required to dilate the cervix and blood loss during evacuation were significantly decreased in misoprostol-treated groups. The incidence of side-effects in the misoprostol groups was not related to the route or dose of medication. As women preferred oral administration of the drug, the investigators recommended that the oral dose of 0.4 mg, given three hours prior to vacuum aspiration, be used for cervical dilatation.

The wide availability and reasonably low price of misoprostol, compared to other prostaglandin analogues, have contributed to its use and to a renaissance of research on a misoprostol-only method of pregnancy termination in countries where mifepristone has not been available. Some providers of the method have suggested that WHO should carry out studies on the efficacy and safety of the use of misoprostol alone for early pregnancy termination in order to provide information and establish guidelines for its use.
At its December 1999 meeting, HRP’s Strategic Committee for Technology Development and Assessment felt that a comparative study could be carried out in countries and centres where abortion is legal but mifepristone is not available for political and/or economic reasons. This would enable the safety, effectiveness and acceptability of the misoprostol-alone regimen to be compared with the routine first-trimester termination method of vacuum aspiration.

A three-monthly injectable (levonorgestrel butanoate)

The most widely used injectable contraceptive is the three-monthly preparation DMPA. The high contraceptive efficacy of DMPA is offset by the high prevalence of amenorrhea associated with its use, and the slow return of fertility following its discontinuation. HRP has been investigating alternative injectable preparations which might offer significant clinical improvements over DMPA.

In collaboration with the Contraceptive Development Branch of the National Institute of Child Health and Human Development (NICHD, Bethesda, MD, USA), HRP supported the synthesis of derivatives of known progestogens as potential injectable contraceptives. More than 230 esters, ester oximes and ethers of norethisterone and levonorgestrel were prepared. After screening, toxicological and clinical testing, one compound, levonorgestrel butanoate (LNg-B), was selected for further development.

During 1999, studies were carried out to define the conditions required for the preparation of particles of LNg-B of a size range shown previously to generate the required pharmacokinetic profile. Studies were also carried out to evaluate the efficiency of different solvents in solubilizing LNg-B, to determine the percentage recovery of the solubilized material in crystalline form, and to estimate the susceptibility of the crystalline material to chemical breakdown during exposure to varying sterilizing doses of irradiation. These studies were undertaken to identify the most efficient, clinically-acceptable LNg-B synthesis procedure and to determine if irradiation can be used as a terminal sterilization procedure, thus obviating the need for the use of a more costly and logistically more difficult aseptic preparation and formulation process.

A preliminary study was carried out with seven different solvents. In this study, the volume of each solvent required to fully dissolve 10 mg of LNg-B at 60°C was found to range between 160 µL for tetrahydrofuran to 2200 µL for methanol; LNg-B proved to be insoluble in hexane. A subsequent study was then carried out to determine the solubility and recovery rates using the five solvents that were found to be most efficient in the preliminary study and which are considered to be clinically acceptable in terms of residual solvent contained in the crystalline LNg-B. This study showed recovery rates for the solubilized LNg-B that ranged between 51% with ethyl acetate and 95% with methanol. With the exclusion of ethyl acetate, the remaining four solvents yielded recovery rates ranging between 89% and 95%. Studies were also carried out to determine if autoclaving could be used as an alternative to irradiation as a sterilizing procedure.

A number of companies with experience in the synthesis of steroids and/or the formulation of steroid-containing preparations, and which have expressed an interest in synthesising and/or formulating LNg-B, have been contacted during the latter part of the past year. Subject to confirmation by these companies of their willingness to prepare this material and to reaching agreement on the time and cost estimates for this work, a company will be selected. It is estimated that a total of 1 kg will be needed to carry out confirmatory pharmacokinetics and local tolerance studies in appropriate animal models, and to initiate Phase I and Phase II clinical trials in women and men volunteers. Consultations will be initiated during the early part of the coming year, with all interested and involved parties, to finalize the synthesis and manufacturing specifications for the required dosage form of LNg-B. Subject to a successful outcome to the animal pharmacokinetics and local tolerance studies, approval to restart clinical testing will be sought from the regulatory authorities.

The current recommendation for the use of Cyclofem— the once-a-month injectable contraceptive—is to administer the first injection during the first five days of a menstrual cycle and give subsequent injections every 30 ± 3 days. However, in the case of injectable contraceptives such as DMPA, the first injection is given during the first seven days of the cycle. It would be of benefit to programmes to harmonize the administration schedule of all injectable methods.

To address this issue, a multicentre study was initiated by Family Health International in Brazil, Chile and Mexico, to describe the ovarian activity and the cervical mucus changes in women having a first injection of Cyclofem administered on day seven of their menstrual cycle and to compare these changes with a control group of women having the first injection of Cyclofem on day five of their menstrual cycle. To address possible ethnic differences, HRP supported a centre in China to take part in this study. Data collection was completed in all centres in December 1999 and data analysis is in progress.

A six/twelve monthly injectable (hCG immunoc contraceptives)

The hCG immunocontraceptive being developed by HRP is designed to provide protection against pregnancy for a period of at least six months, and perhaps as long as 12 months, depending on its composition and formulation. It is estimated that a further 5–7 years of clinical testing and product improvement will be required before a first-genera-
tion product will be available. A second-generation, totally-synthetic, bioengineered product is also under development, in collaboration with industry, and could become available within a similar, or slightly more-extended, time-frame.

Following successful completion of a Phase I clinical trial with a prototype hCG immunocontraceptive in 1986, a Phase II trial with an improved version of this preparation was initiated in early 1994 but was interrupted when unexpectedly high levels of injection-site pain and tissue reactions were encountered in the first few volunteers to receive the preparation. The research carried out since then has involved a systematic evaluation of each of the components of the preparation used in the interrupted Phase II trial in order to determine the cause of the unexpected side-effects. The source of the problem encountered in the Phase II clinical trial has been identified and a new formulation, the advanced prototype hCG immunocontraceptive, has been prepared.

The first lot of the standard preparation, produced using Good Manufacturing Practices, was available in October 1998 and was used in local tolerance and subacute toxicity studies in rabbits. Visual observation of this material at intervals of up to 12 months post-manufacture has revealed no evidence of breakdown of the emulsion. The potency of this batch of material was determined in rabbits using samples stored for eight, 20 and 30 weeks. Although some variation was seen in the antibody levels of individual rabbits, mean levels at all times after four weeks post-injection were nearly identical. These data indicate that the potency of the standard preparation is not diminished after storage for at least eight months at 4°C. The evaluation of the potency of this batch after storage for one year post-manufacture is currently under way. Preclinical animal studies with this preparation started in 1998 and are projected to continue through the first half of 2001.

Studies were carried out to evaluate the number and timing of the injections that were needed to ensure an adequate level and duration of immunity to hCG. One study in rabbits indicated that a minimum of three injections is needed to elicit a protective level of immunity of more than 12 weeks duration. An additional study was carried out to determine if reducing the overall time-frame for the three injections needed for the primary immunization would markedly affect the magnitude or duration of the elicited antibody levels. Preliminary data from these studies suggest that: (i) repeated immunizations with the hCG peptide:DT (diphtheria toxoid) conjugates does not lead to DT carrier-induced suppression of the desired immune response to the peptides; and (ii) putatively protective levels of immunity can be maintained with booster injections given at intervals of six months, or maybe longer. However, clinical studies are needed to determine if the standard preparation represents a viable six-monthly, non-hormonal, injectable contraceptive suitable for human use.

The advanced prototype hCG immunocontraceptive is considered less than optimal. Studies have continued during the past year to develop an optimized hCG immunocontraceptive containing totally synthetic immunogens that do not need a diphtheria toxoid carrier, and improved delivery systems that will permit the desired duration of protection to be achieved following a single injection. The objective of these studies is to identify B-cell stimulating and T-cell stimulating peptide sequences and constructs which are promiscuous—in the sense that they are able to elicit a safe and effective immune response irrespective of the genetic background of the immunocontraceptive recipient. Work in this area has focused on the carboxyterminal peptide (CTP) of hCG and loop B-cell peptides and T-cell peptides representing known sequences in tetanus toxoid, measles virus protein F, and malaria proteins.

Two approaches to the production of these novel immunogens are being followed: the total chemical synthesis of the constructs using classical solid-phase peptide synthesis procedures, and the use of bioengineering techniques. The relative advantages and disadvantages of these two approaches, in terms of ease and cost of production, and quality and yield of product, will be assessed in parallel.

During the past year, three additional 38–57 loop:T-cell epitope peptide constructs were prepared through chemical synthesis and one of these was tested for immunogenicity. Preliminary data obtained in rabbit studies suggest that this totally synthetic peptide construct is as immunogenic as a conjugate of the loop peptide with DT.

Collaboration between HRP and the industrial licensee of the new bioengineering technology continued during 1999. The focus of this collaboration is to develop and optimize expression systems using both prokaryotic (E. coli) and eukaryotic (Baculovirus) vectors, the objective being to develop a high-yield and low-cost biotechnological method for production of the desired immunogen constructs.

Part of the ongoing development work includes comparing immunostimulant compounds and delivery systems that have been described by other investigators with a view to determining if they might constitute improved alternatives to nor-muramyl dipeptide (nor-MDP) and water-in-oil emulsion vehicles which are currently being used in the HRP standard preparation.

Studies, reported in the Annual technical report 1998, indicated that a non-ionic block polymer was a strong adjuvant when added to the aqueous phase of the standard emulsion. Further studies carried out during 1999 suggest that inclusion of the non-ionic block polymer in the standard emulsion elicits a putatively effective level of immunity that is sustained for at least four months without inducing an unacceptable level of local reactivity at the injection site.
These responses can be obtained using much lower doses of immunogen than the standard nor-MDP-containing emulsion and this formulation represents a slight improvement over the standard delivery system for the advanced prototype immunocontraceptive.

During 1999, studies were also carried out with a proprietary new technology in which immunogens are incorporated into an inorganic/biopolymer composite, resulting in particulate material with slow-release characteristics. The results indicated that a protracted immune response can be achieved with a single injection.

In preparation for evaluation of the immune response elicited in clinical trials, further studies continue to be carried out to develop a rapid in vitro bioassay to measure the bioneutralization capacity of antibodies raised to the hCG immunocontraceptive.

**Hormonal contraceptives for men**

A number of studies in animals and men have shown that the administration of androgens alone, combinations of gonadotrophin-releasing hormone and androgens, and progestogen and androgen combinations, can suppress gonadotrophin secretion and spermatogenesis either completely to azoospermia or to a sufficiently low level of oligozoospermia to render the treated individuals infertile. The advent of a safe, effective and reversible systemic method of contraception for men is expected to provide a valuable addition to the range of methods to be offered to users of family planning and an attractive alternative to the limited options of the condom, vasectomy and withdrawal that are the only methods currently available to men. HRP is investigating, or planning to investigate, a variety of oral and injectable, androgen-alone and androgen-progestogen combinations, that can be taken at intervals of six weeks, two months or three months, to suppress sperm production.

A study cofunded by HRP in China in 1997 had indicated that there was no significant difference between 500 mg and 1000 mg of testosterone undecanoate (TU) given at six-week intervals, in terms of the number of men achieving azoospermia and the time taken to achieve it. No adverse side-effects were reported by the trial participants.

In 1999, a multicentre contraceptive efficacy study was carried out in six centres in China in which TU was given in a dose of 1000 mg during the suppression phase and in a dose of 500 mg during the efficacy phase of the trial. Although sperm reappeared in the ejaculates of some men during the efficacy phase, necessitating the reduction of the injection interval from six weeks to four weeks in one centre, the sperm concentrations did not exceed 1 million/ml and no pregnancies were reported during the six-month exposure phase of the trial. Currently, various hormonal and blood chemistry measurements are being performed and data entry and analysis are continuing. Acceptability studies, involving both the trial participants and their partners, are being done concurrently with the contraceptive efficacy study and the data obtained in these studies are also being analysed.

Pharmacokinetic studies with testosterone buciclate (TB), a long-acting ester resulting from the joint WHO/US National Institute of Child Health and Human Development (NICHD) Chemical Synthesis Programme of the early 1980s, have shown that this compound is capable of maintaining serum testosterone levels within the normal range for a period of approximately 100 days in hypogonadal men. Furthermore, in contrast to short-acting testosterone esters, such as TE, TB is not associated with a peak of testosterone release soon after injection and its release rate more closely approximates zero-order kinetics. These attributes make it an attractive option for development as a three-monthly androgen-alone injectable for men or as the androgen component of a three-monthly combined injectable contraceptive for men.

Preliminary data obtained in an earlier clinical trial involving a small number of normal men demonstrated the ability of TB to suppress gonadotrophin levels and reduce spermatogenesis. Further clinical studies of this type had to be postponed because of the need to resolve formulation problems that had become apparent with the most recent batch of material prepared for clinical testing. During the past year, HRP has been involved, with NICHD, in protracted discussions with a potential industrial partner concerning the licensing of TB and its subsequent development as a product for male contraception (either alone or in combination with a progestogen), and for androgen replacement therapy in hypogonadal men.

It is thought that the low level of spermatogenesis that persists in some men taking part in clinical trials of androgen-alone and progestogen-androgen combinations as male contraceptives, may be due to a persisting, low level of production of dihydrotestosterone (DHT). A study was carried out in Australia to see if the administration of finasteride, which prevents the conversion of testosterone to DHT, would completely suppress the severe oligozoospernia induced by exogenous testosterone to azoospermia. No evidence of improved efficacy of the treatment was found in the men receiving finasteride.

An acceptability and behavioural study was conducted part of the six-centre TU contraceptive efficacy study undertaken in China (see above). Both qualitative and quantitative approaches were used to collect information on the acceptability of male contraceptive use, family size preferences, contraceptive decision-making and perceptions on access and mode of contraceptive delivery. In another study, which is being supported in the United Kingdom, a range of psychometric tools are being developed for adaptation and
validation for the assessment of sexual and behavioural changes associated with male hormonal contraceptive use. Data should inform the approaches, and user perspectives and needs, in the development of male fertility regulation.

Cypionate acetate (CPA) given orally, daily, in combination with a TE given by weekly injections, has an antispermatogenic effect in normal men. HRP was planning to carry out a multicentre study, in six centres in both developing and developed countries, to evaluate the effects on spermatogenesis of a treatment regimen consisting of a daily oral dose of 20 mg CPA in combination with injections of 1000 mg of TU given every eight weeks. The study was to test the advantages of the combined preparation in terms of degree of sperm suppression, rapidity of suppression, and consistency of suppression. However, because of the unavailability of CPA for this study, it will now be done using NET-EN and TU.

A Phase II study to assess the contraceptive efficacy of a six-weekly DMPA and TU injectable combination regimen to be carried out in Indonesia has been planned for some time but has been held up pending the supply of TU. This study may be started during the coming biennium.

Levonorgestrel-releasing vaginal ring

In 1990, a licence agreement was concluded with a company in the United Kingdom for the manufacture and distribution of a vaginal ring developed by HRP that released levonorgestrel at the rate of 20 µg/24 hours. In a subsequent Phase III clinical trial of the ring, vaginal lesions were reported in a proportion of the users. To overcome this problem the ring was redesigned into a thinner, more flexible device. Further studies suggested that the new ring design did not induce lesions on the cervix or the vaginal wall and that the new ring geometry could be considered suitable for future development of the device. In 1997, the company decided to withdraw from the project, returning the licence to WHO. Subsequently, the Contraceptive Research and Development Program (CONRAD), Arlington, VA, USA, indicated their interest in collaborating with HRP on this project. It was planned that a higher-dose version of the redesigned vaginal ring (releasing 35 µg/24 hours of levonorgestrel) would be developed as a final product. In 1998–1999, negotiations were initiated with potential industrial partners for the production of a batch of rings suitable for clinical testing. Several options were compared, based on different manufacturing techniques. However, difficulties have been encountered in obtaining a ring at a reasonable cost.

At its December 1999 meeting, the Strategic Committee for Technology Development and Assessment recommended that no further work be carried out on this product. The Committee re-emphasised the unique potential of the vaginal ring as a long-acting method of fertility regulation under the user’s control and recommended that HRP investigate possible collaboration with other groups with promising leads in this area.

Natural family planning

The “rhythm” or “calendar” method for determining the fertile period is the method of natural family planning most commonly used worldwide. However, there has been little or no scientific evaluation of any of the suggested calendar-based rules for determining the period of abstinence.

HRP and the Institute for Reproductive Health (IRH) of Georgetown University, Washington, DC, (USA) have agreed on a common research strategy in this area. Together with IRH, HRP supported focus group discussions with users of the calendar method in four countries to investigate how couples actually identify the fertile period. Results showed a high demand in certain populations for a simplified calendar method. To meet this need, IRH conducted studies on the optimization of calendar rules, based on a re-analysis of the large data set of women’s menstrual cycles obtained from HRP’s study of the Ovulation Method. This analysis showed that a “standard rule” method, based on a fixed period of abstinence from day eight to day 19 of a cycle, would result in a very high theoretical reduction in the probability of pregnancy and would have the advantage of simplicity over the traditional “calendar rule” method.

Subsequently, IRH, with some input from HRP, planned a prospective multicentre study of the effectiveness and acceptability of a standard rule method. IRH conducted a pilot study in Bolivia and in the Philippines to test the study instruments. IRH is now initiating the main study in the same two countries among women whose cycles are 26–32 days long, with each woman being followed over 13 cycles. Additional sites are being considered in El Salvador, Kenya and Peru. HRP is exploring the possibility of supporting two sub-Saharan African centres to contribute to the above-mentioned multicentre study.

Research on lactational infertility

The aim of research on lactation and its role in the natural suppression of fertility has been to identify: (i) the determinants of the duration of lactational infertility; and (ii) ways for optimal linkage of the contraceptive effect of lactational amenorrhoea and the introduction of other methods of family planning. HRP’s main undertaking in this area was a large, prospective, multinational study on the duration of lactational amenorrhoea in relation to breastfeeding practices. Two papers (Papers I and II) from this study were published in 1998 in *Fertility and Sterility* and two additional papers (Papers III and IV) in 1999.

The objective of the analysis reported in Paper III (*Fertility and Sterility, 1999, 72:431–440*) was to determine
the risk of pregnancy during lactational amenorrhoea, relative to infant feeding status. The conclusion of the analysis was that the results support the Bellagio Consensus on the use of lactational amenorrhoea for family planning and confirm that the Lactational Amenorrhoea Method (LAM) is a viable approach to postpartum contraception.

Detailed information was collected on vaginal bleeding during the large multicentre study, which allowed analyses of patterns of menstrual return during breastfeeding, including characteristics of bleeding episodes that occurred during the first few weeks after delivery. These results were published in Paper IV (Fertility and Sterility, 1999, 72: 441–447.) The objectives were: (i) to describe and compare the duration of lochia in the women participating in the study from seven countries; (ii) to investigate the occurrence of a possible “end-of-puerperium” bleeding episode; and (iii) to determine the frequency of bleeding episodes before postpartum day 56, which applies to the practice of the LAM for contraception. The main conclusion was that the duration of lochia varied significantly among the study populations and that instances of long duration of lochia were not unusual. The significance of end-of-puerperium bleeding is unknown. Most users of LAM will not experience a postlochial bleeding episode before postpartum day 56.

Owing to the lack of funds, no new initiatives were started in this area during the last five years and, therefore, no projects were ongoing in 1999. The study investigating the relationship between physical activity and lactational amenorrhoea was completed in 1998 and its results, which were analysed in 1999, will be available in 2000.

The Scientific Review Committee for Technology Development and Assessment suggested, at its meeting in December 1999, that WHO should make efforts to improve knowledge about LAM in order to increase its use, especially in countries where the choice of contraceptive methods is limited. The Committee also recommended, subject to the availability of funds, that the planned study of the use of LAM over the extended period of 6–12 months should be carried out.

Basic research

Exploratory, goal-oriented research is being carried out by HRP to identify new leads: (i) for the development of methods that could be used to regulate male fertility; (ii) for the development of methods that could be used by women as once-a-month methods or menses inducers; and (iii) to further investigate the mechanism of progestogen-induced endometrial bleeding with a view to improving the performance and acceptability of such methods.

Male methods

The research being promoted in this area of male meth-
in their mode of administration and their mechanism of action. Three broad areas have been identified as being particularly important in this context and form the primary foci of the research being carried out under the Initiative: (i) the implantation window in the primate, at the endometrial level; (ii) the development and demise of the primate corpus luteum; and (iii) pre-implantation embryo-uterus-corpus luteum interactions.

Proposals were solicited from more than 30 investigators known to be active in the field and, from the 29 proposals received and reviewed, six were selected for support. The six proposals currently being supported cover the three broad areas of: (i) in vitro and in vivo basic research, mainly at the molecular level; (ii) research in appropriate animal models; and (iii) clinical research on mechanisms of action of alleged anti-implantation agents and menses inducers and on infertility seemingly due to endometrial or ovarian factors.

An important part of this Initiative is the exchange of research materials, information, experience and expertise, and the inter-institutional training of researchers, especially those from developing country institutions, in specialized techniques needed for this work. In this context, supplementary funding has been provided by the Rockefeller Foundation during the past year to enable a clinical research fellow from one of the centres to set up required techniques in another of the centres.

A meeting of the six principal investigators and the project review committee was held in May 1999 in Geneva. The primary objective of this first meeting was to discuss the individual projects and the overall objectives of the Initiative in order to determine if there is any overlap in the proposed work or any gaps that need to be covered.

**Endometrial bleeding**

A large proportion of the more than 15 million women using progestogen-only methods of contraception endures the irregularities in vaginal bleeding these methods induce. This has significant implications for their sexual life as well as impact on the sociocultural, economic and, for some, religious dimensions of their lives. The options offered to them to alleviate this problem are few.

Through research supported by HRP and other institutions, the mechanisms of normal menstruation are beginning to be defined under a new concept. Classically, menstrual bleeding was seen as resulting from ischemic necrosis of the endometrium, following arteriolar spasm and thrombosis mediated by prostaglandins and involving autolysis by lysozymes. Currently, the triggering mechanism of menstruation is seen as an inflammatory response to the withdrawal of progesterone, in which cells of the immune system invade the endometrium and/or are activated and release regulatory molecules which increase the production and activation of matrix metalloproteinases (MMPs) but not of their inhibitors (tissue inhibitors of metalloproteinases, TIMPs). This imbalance leads to destruction of the endometrial connective tissue and degeneration of the functionalis layer with exposure of open blood vessels and endometrial glands. In this new scheme, active tissue destruction becomes the primary event initiating menstruation.

**Mechanism of progestogen-induced endometrial bleeding**

Progestogen-induced endometrial bleeding differs from menstruation in that bleeding is intermittent, unpredictable and occurs from small superficial veins and capillaries. Previous studies provided evidence of vascular fragility, abnormal angiogenesis and disturbed mechanisms of menstruation associated with progestogen treatment.

A study was completed in Brussels (Belgium) in 23 Norplant implant users, comparing their endometrium at the onset of a vaginal bleeding episode and during non-bleeding times. The analysis of biopsies showed that abnormal endometrial bleeding is associated with focal stromal breakdown and collagen-fibre lysis. This was found to be related to the local expression and activation of MMP-1, activation of MMP-9, increased expression of MMP-2 and decreased production of TIMP-1. Further observations suggested that these events were initiated by the local expression and activation of MMP-3 in stromal cells. These are some of the strongest data establishing links between specific mechanisms and breakthrough bleeding, although direct causality remains to be proven.

In 1997, a study was launched to compare the endometrium of Norplant users and non-contracepting women in terms of vascular fragility, steroid receptors, MMP regulation, epithelial integrity, apoptosis and endometrial leukocytes. This study is based on a twinning arrangement between the University of Indonesia in Jakarta, Indonesia, and Monash University and the Prince Henry's Institute of Medical Research, both in Clayton, Australia.

Analyses of the biopsies obtained so far have provided the following preliminary findings:

(i) Reduced $\alpha$-actin in smooth muscle cells was found to be reduced around the blood vessels in the endometrium of Norplant users who experienced breakthrough bleeding, compared to those who did not have this side-effect. This is the first time that a structural vascular feature that contributes to vascular fragility is found to correlate with breakthrough bleeding.

(ii) No evidence was found for a role for altered apoptosis in either the endometrium or the blood vessels of Norplant users with or without breakthrough bleeding.
(iii) Mast cell activation was observed in the endometrium of Norplant and DMPA users, similar to pre-menstrual and menstrual controls but not at other times of the normal cycle. These mast cells produce a myriad of mediators which can trigger endometrial breakdown, for example by activating latent MMPs.

Two double-blind, randomized, placebo-controlled clinical trials were launched to assess the effects of different treatments on progestogen-induced prolonged bleeding. One, being conducted in Santiago, Chile, is testing the efficacy of monthly-administered mifepristone in improving the vaginal bleeding pattern of Norplant users.

The other is testing the effect of vitamin E as an antioxidant, and of low-dose aspirin as an anti-inflammatory agent, alone and in combination, on Norplant-induced prolonged bleeding. This study is being conducted in Beijing (China), Jakarta (Indonesia), Santiago (Chile), Santo Domingo (Dominican Republic) and Tunis (Tunisia).

A meeting co-sponsored by HRP and NICHD on "Steroids and endometrial breakthrough bleeding" was held at Monash University, Clayton, Australia, on 4–5 May 1999. Three broad areas of research were considered important for future studies. First, there is a need for a better understanding of the attitudes of women towards vaginal bleeding in diverse cultural situations. Second, studies are needed to explore the interplay between the endometrial vasculature and its environment. Third, clinical studies are needed: to investigate the effect of MMP inhibitors and oral TIMPs on vaginal bleeding in progestogen users and in women using hormonal replacement therapy; to determine the effect of selective estrogen receptor modulators on endometrial bleeding; and to evaluate further the potential role of low-dose antiprogestogen treatment in progestogen users.

**Dual-protection methods**

Until now, HRP had intended to maintain a watching brief only in this area because of the substantial investments being made by other public sector agencies and by the private sector. However, with the withdrawal of UNAIDS from this area of research and the expectation that WHO would take on this responsibility, HRP included the assessment of the effectiveness of a dual-protection preparation, with microbicidal and spermicidal properties, in the proposal it prepared and submitted to UNAIDS. The approved unified work plan and budget of UNAIDS for the 2000–2001 biennium includes the provision to HRP of US$ 400 000 for this purpose, on the understanding that HRP will contribute a similar amount to this activity. The first priority of this new research line will be collaboration in the Phase II clinical evaluation of preparations and formulations which have shown microbicidal activity in vitro, and which appear to be safe for use in vivo, as evidenced by data obtained in Phase I clinical trials.

**Users’ perspectives in the context of reproductive health**

In spite of advances in the provision of family planning services globally, the fertility regulation needs of more than 400 million individuals remain under-served. Furthermore, over 40% of those using contraceptive spacing methods discontinue the use either because of side-effects or method failure within 12 months since adoption. The strong association between these unmet needs and the dual risks of sexually transmitted infections (STIs) including HIV and unwanted pregnancy make even more salient the call to re-orient existing services to meet the demands for dual protection. A re-orientation that incorporates the perspectives of women and men and that enables couples to attain safely their sexual and reproductive goals is a central strategy of the work supported by HRP.

To advance knowledge in this field, HRP has supported focused research initiatives in three areas. The three areas are: women’s and men’s perceptions and behaviours regarding the dual risks of unplanned pregnancy and STIs; the role of men in reproductive health; and the acceptability of different fertility regulation methods. This research is generating the evidence necessary for national authorities to make informed decisions concerning the provision of services and methods of fertility regulation that are acceptable to users and meet their needs.

In 1999, findings from the qualitative research on “Family planning and sexual behaviour in the era of HIV/STI” became available from Zimbabwe. These were broadly consistent with those from the other five countries in the study—Kenya, South Africa, Tanzania, Uganda and Zambia. The study participants exhibited considerable knowledge and awareness of STIs/HIV and their modes of transmission. However, various misconceptions persist. For example, nearly all male and female groups perceived menstruation as a cleansing process which reduced the risk of women becoming infected with STIs/HIV. Men were perceived to be at a greater risk of HIV infection than were menstruating women. Such perceptions were linked to individuals not always practising safe sex. Men in the study reported that condoms were well known and easily available, and male and female participants viewed condoms as an appropriate method to prevent infection in casual relationships. Participants, however, considered the condom to be an unacceptable method within marriage and generally believed it to be ineffective in preventing pregnancy.

Several studies on the “Role of men in reproductive health” were also completed. One study conducted in Jamaica and another conducted in Turkey suggest that men from vastly different cultural settings favourably view certain male methods of contraception and are willing to
assume responsibility for the prevention of pregnancy and disease transmission. At the same time, men in these studies expressed attitudes and concerns that may constrain their full, positive participation in reproductive health matters.

The survey conducted in Jamaica gathered information on the knowledge and attitudes about contraception, contraceptive practices, reactions to pregnancy, and union formation among 714 men aged 15 to 40 who resided in Kingston, rural St. Andrew, and Hanover. A sub-sample of these men participated in focus group discussions on related topics. Findings suggest high overall levels of awareness, approval, and use of contraception. Although method-specific awareness ranged from 36% for tubal ligation to 96% for condoms, 99% of men in the sample knew of at least one method of contraception. Some 94% of men in the sample approved of family planning, and 55% practised contraception to prevent unwanted pregnancy. Despite high approval of contraception generally, men expressed concerns about the side-effects and low effectiveness of certain female methods, such as the oral contraceptive pill.

The methods accepted by men and those causing ambivalence are somewhat different in Turkey than in Jamaica. Investigators in Turkey conducted an exploratory study of the perceptions of men and women toward various contraceptive methods, including withdrawal and condoms. Nine in-depth interviews with selected key informants and ten focus group discussions with married women and men, respectively, were conducted in neighbourhoods in Umraniye, which is one of the most densely populated districts in Istanbul. There has been a sustained willingness among men in Turkey to use certain types of male methods. According to a survey, almost one in four contraceptive couples in Turkey relies on withdrawal (26% in 1988 and 24% in 1998). Far fewer, however, use condoms (7% in 1988 and 8% in 1998). Otherwise, the most commonly used modern method in Turkey has been the IUD (14% in 1988 and 20% in 1998).

A study conducted at the Shanghai Centre for STI Control and Prevention explored the impact of an educational and motivational intervention (video and discussion) on men’s attitudes toward condoms and their use. Results suggest that men who saw the video and participated in the discussion of the video more frequently answered questions on knowledge correctly and more often expressed favourable attitudes toward condoms.

In a second study at the same Centre, focus group discussions were held with male and female providers to understand providers’ perspectives of clients, counselling, and condom promotion in STI clinics. In addition, 203 clinic attendees were interviewed in-depth, an intervention to improve counselling skills was implemented, and follow-up interviews were conducted with clients using a structured questionnaire. Most notably, results highlighted the extent to which men’s risky sexual behaviours place their wives or regular partners at risk of infection. Up to 59% reported having had at least one casual partner in the month before interview. Some 14% claimed that their infections had come from a spouse or stable partner. However, of the 70% of clients who reported having sex at least once between first and second interview, 80% used a condom consistently. Embarrassment to tell one’s spouse about the infection was one reason for not using a condom.

HRP supported two studies in China that explored the acceptability of emergency contraception among women seeking abortion. One study of the knowledge, attitudes, needs, and availability of emergency contraception among women aged 18–50 years who sought to terminate a pregnancy was conducted in three maternal and child health centres in Shanghai. After women were informed about the usage and possible side-effects of the emergency contraceptive pill and IUD, they were asked about their willingness to use either method. As many as 86% of all women interviewed said that they would be willing to use either method in the future, if necessary. Young, well-educated and professional women were more often willing to use emergency contraception than were other women. Among those who were willing to use emergency contraception, the overwhelming majority (83%) preferred the hormonal pill, 8% preferred the IUD, and 9% had no preference. Emergency contraception was also found to be acceptable in Brazil, Chile, and Mexico, including for adolescents who are sexually active.

Ascertaining, from participants in a clinical trial, the acceptability of medical abortion, its administration in the home rather than at the clinic, and its provision without medical supervision is under way in 15 centres and 12 countries.

Research on users’ perspectives and the acceptability of fertility regulation methods will continue in several countries (numbers in parentheses indicate the number of studies), including Brazil (2), China (3), Iran (1), Kenya (2), South Africa (2), Tanzania (1), Thailand (1), Uganda (1), Zambia (1), and Zimbabwe (1). At its June 1999 meeting, the Scientific Review Committee approved a new study in this area, which will focus on the perceptions of couples toward contraceptive use in Pakistan.

A new series of briefs highlighting policy and programmatic implications of social science research was launched. The Social Science Research Policy Briefs have three aims: (i) to disseminate widely the findings of research; (ii) to build the analytical capacity and technical writing skills of in-country investigators through extensive collaboration during the development of these briefs; and (iii) to highlight the policy relevance and programmatic
impact of social science research. Briefs are widely disseminated to over 3000 individuals and institutions through the HRP newsletter *Progress in human reproduction research* and plans are being made to place them on the new web site.

**Safety and efficacy of existing methods of fertility regulation**

HRP’s research on safety and efficacy of existing methods of fertility regulation is concerned with adverse and non-contraceptive beneficial effects of currently available methods of fertility regulation, and the evaluation of contraceptive efficacy of these methods when this is not well known. The research methodologies employed for these evaluations include observational epidemiological research as well as randomized and non-randomized clinical trials.

In 1999, secondary analyses of data from the WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception were published on migraine and combined oral contraceptive use, the risk of stroke associated with use of different formulations of oral contraceptives (OCs), and cardiovascular risks associated with use of progestogens for therapeutic purposes. In users of low-dose OCs, there was no increase in the risk of haemorrhagic stroke whether or not women reported a history of migraine. However, the risk of ischaemic stroke was higher in women who had a history of migraine (6.6-fold) than those who did not (1.2-fold) compared with non-users. This observation underlines the conclusion from the full study data that women without cardiovascular risk factors (no history of hypertension, diabetes or hyperlipidaemia) who do not smoke and who reported that their blood pressure had been checked prior to OC use do not have an increased risk of ischaemic stroke associated with use of low estrogen dose OCs.

The secondary analyses published in 1999 also found that there was no difference in the risk of haemorrhagic stroke for users of OCs containing third generation progestogens (gestodene and desogestrel) compared with levonorgestrel-containing OCs. However, a surprising observation was that users of gestodene-containing OCs had higher risk than users of desogestrel- or levonorgestrel-containing OCs—a finding that was not replicated in an analysis commissioned by HRP from the UK General Practice Research Database (GPRD).

The second report from the WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception showed an elevated risk of venous thromboembolism (VTE), but not stroke or acute myocardial infarction, in women who had been administered progestogens for dysfunctional bleeding.

A further commissioned analysis from the GPRD revealed no cases of VTE occurring within 45 days of over 100 000 episodes of emergency contraception use (upper 95% confidence limit less than 4 per 100 000 uses).

The multicentre study of bone mass and hormonal contraceptives was published in 1999. This study sought to evaluate the effect of the use of hormonal contraceptives on bone mass in 2474 women aged 30–34 years in Bangladesh, Brazil, China, Egypt, Mexico, Thailand and Zimbabwe. Among current users of combined OCs, bone mineral density (BMD) was significantly higher for short-term users (2–3 years) compared with never-users. Among short-term users of the progestogen-only methods DMPA and Norplant, BMD was significantly lower compared with never-users. Among long-term users (four or more years) of all three hormonal methods there were no significant differences compared with never-users. Similarly, past users showed no significant differences compared with never-users. With a view to collecting further data on this topic, a five-year prospective study of bone mass in young women (age 15–19 years) and those near the menopause (age 45–49 years) has been launched in Durban, South Africa. Further research on the effect of progestogen-only contraceptives on BMD will be started in 2000.

Two papers on the main analysis of the Post-Marketing Surveillance of Norplant have been completed and will be submitted for publication in *Contraception* in early 2000, together with a short summary paper to be published around the same time in a high-impact journal. This large, long-term, controlled surveillance study of initiators of Norplant, IUD, and sterilization in developing countries, confirmed that Norplant is a safe and highly effective contraceptive.

In order to get information on the relationship between vasectomy and prostate cancer in those developing countries where vasectomy was prevalent, HRP, in collaboration with Family Health International (FHI), conducted a multicentre, hospital-based case-control study in China, Nepal and the Republic of Korea. Data collection for the study ended in 1997 and histopathological review of tissue samples was completed in 1998. The study involved 353 cases of prostate cancer and 879 controls matched to these cases. The odds ratio for the overall risk of prostate cancer was 1.21 in vasectomized compared with non-vasectomized men. Risks increased with the time since the procedure (0.75 for 10–19 years, 1.21 for 20–29 years and 1.39 for 30 or more years), though the trend was not statistically significant. The final manuscript is undergoing review prior to submission for publication. Also in collaboration with FHI, HRP is jointly funding a national multicentre case-control study of prostate cancer and vasectomy, co-ordinated by the Department of Preventive and Social Medicine, University of Otago, Dunedin, New Zealand. The main phase of this study was launched in 1997 and data collection completed by the end of 1999.

The studies of long-term safety and efficacy of the
Multiload 375 and the 20 μg levonorgestrel-releasing IUDs compared to the TCu380A device are continuing in their tenth and sixth year, respectively. Interim analysis of the nine-year data shows that the Multiload 375 has significantly higher intrauterine pregnancy and expulsion rates than the TCu380A at nine years of use. This difference in pregnancy rate is seen from the second year of use but the difference in expulsion only becomes statistically significant from the fourth year of use until the eighth. This study will continue until ten years of use have been achieved at the end of 2001, provided that adequate numbers of subjects remain in the trial.

In the ongoing study in which the initial prototype FlexiGard device is being compared to the TCu380A, 2104 women have been recruited to the FlexiGard device group and 2184 to the TCu380A group. The final data obtained after eight years show that, compared with the TCu380A, the pregnancy rate for the FlexiGard was significantly higher at one year of use but not thereafter. The cumulative expulsion rate for the FlexiGard was significantly higher at all intervals when compared to the TCu380A but the second-to-eighth-year rates calculated on an annual basis were similar. Removals for bleeding disturbances were significantly higher with the FlexiGard device from the sixth year of use.

The research instruments and logistics of the multicentre studies comparing the effects of different contraceptives used by HIV-1 seropositive women on the clinical course of HIV-1 infection and cervical/vaginal shedding of HIV-1, were revised after the pilot phase was completed in 1999. The main studies will start data collection in early 2000.

A study on the contraceptive effectiveness of the female condom will be launched in four countries in early 2000, and a consultation on the safety of female condom re-use is planned for the first half of 2000.

Development of norms and guidelines relevant to fertility regulation

The work carried out during the past year, on the development of norms and guidelines relevant to fertility regulation, has focused on: (i) increasing information about contraceptive options; (ii) the development and updating of technical and managerial guidelines and training materials on family planning methods; (iii) the development and updating of technical guidelines and training materials on family planning services; and (iv) the development of a collaborative process to support effective dissemination, adaptation and use of the documents generated by the Department.

Emergency contraception. In 1997, guidelines were prepared for service providers, policy-makers and programme managers as part of an effort to increase awareness and disseminate accurate information about the emergency use of combined oral contraceptives and copper-releasing IUDs. The English language version of the guidelines was issued in 1998. In 1999, the French translation was published and a Spanish edition was in the process of being finalized.

Information package: update on family planning methods. The Department continued to work with FHI to develop a series of fact sheets on family planning methods and their use by different groups of individuals across the life span. During 1999, draft documents were reviewed for technical content. Further review by an expert meeting was planned. The Department also collaborated with John Hopkins University in publishing the Population Report entitled Family planning methods: new guidance (Series J, Number 44, 1999).

Technical guidance on contraception and HIV. As part of the ongoing debate on whether steroid hormone contraceptives affect the risk of HIV transmission or the progression of AIDS, a review of all information and study results on HIV and contraceptive methods was prepared to assist the Department in developing technical guidelines in this area. This paper will be assessed by WHO and UNAIDS staff and will be used as background information in the planned revision of WHO’s document Improving access to quality care in family planning; medical eligibility criteria for contraceptive use.

Medical eligibility criteria for contraceptive use. In 1996, a document entitled Improving access to quality care in family planning; medical eligibility criteria for contraceptive use was distributed to policy-makers, family planning programme managers and the scientific community. It aimed to provide guidance to national family planning and reproductive health programmes in the preparation and revision of national medical and service provision guidelines based on new recommendations for initiating and continuing use of each contraceptive method. In 1999, versions of the document in Chinese, French, Indonesian, Russian, Spanish, and Vietnamese were printed. Meanwhile, discussions were held with experts to prepare for a review of the medical eligibility criteria document. In this regard an expert committee meeting is to be convened on 8–10 March 2000.

The male latex condom. In 1998, as part of the joint programme of work, UNAIDS and WHO published and disseminated a package of materials entitled The male latex condom. This package summarized the latest scientific evidence and principles of best practice in key areas of condom programming. In 1999, the Department continued work on another document provisionally entitled Specifications and guidelines for condom procurement, which focuses primarily on procurement issues related to condom quality, since these differ significantly from those used to procure other health products.
The Department collaborated with Johns Hopkins University/Center for Communication Programs on different aspects of the literature and the preparation for publication of the Popline report entitled *Closing the gap on condom use*. Information from this literature review has also been incorporated into a CD-ROM, produced by the University and UNFPA, which provides an interactive review of literature and materials that have been used around the world for condom promotion.

Collaboration also continued with the Organization of International Standardization, Technical Working Group 157 for Mechanical Contraceptives (ISO/TC/157). This Group is currently working on the revision of the *International standard for male latex condom 4074*. It is expected that the new 4074 Standard will be published by the end of 2000. WHO and UNAIDS will then undertake a scientific review of the WHO Specification to ensure consistency with the published standard.

**Social marketing of condoms.** The Department continued its collaboration with UNAIDS in the development of a comprehensive strategy to support condom programming activities for the prevention of STI/HIV/AIDS and unwanted pregnancy. Social marketing of products, services and behaviour-change communication will be part of this package of strategies designed to improve reproductive health. As part of this strategy, UNAIDS, WHO and UNFPA are planning to hold a "Social Marketing Forum". This Forum will be designed to bring together donor agencies, collaborating partners and country representatives in order to explore the comparative advantages and potential of social marketing in improving access to reproductive health services and technologies, particularly those for the prevention of STIs/HIV/AIDS and unwanted pregnancies.

**Development of technical materials for family planning service providers.** Work continued in 1999 on the preparation of sets of practical materials for clinic-based and community-based service providers. These have included counselling guides, revised screening procedures and algorithms for contraceptive method choice, and a handbook for adaptation of these materials.

A booklet entitled *WHO call to action: standardizing contraceptive eligibility criteria*, was being produced as a companion volume to *Improving access to quality care in family planning: medical eligibility criteria for contraceptive use*. This volume will advise decision-makers on how to update national family planning counselling and prescription practices. A separate document, *Improving access to quality care in family planning: a guide for providers*, was also under development and would provide method-by-method summaries of the service delivery implications of the WHO medical eligibility criteria. It is envisaged that all of these materials will be published, in English, during the course of 2000.

**WHO series of technical and managerial guidelines on contraceptive methods.** Work on the finalization of the technical and managerial guidelines on oral contraceptives was completed during 1999 and the document has been thoroughly revised according to the recommendations of the expert group meeting on medical eligibility criteria for contraceptive use. The document will be issued in 2000.

**Development of simple information/education materials on contraceptive methods.** A series of simplified companion volumes, to each of the technical and managerial guidelines, that address the needs of various levels of providers in a user-friendly format and presentation has been developed. Examples include: *Injectable contraceptives: what health workers need to know*; and *Intrauterine devices: what health workers need to know*. These documents continue to be revised to reflect the new recommendations concerning medical eligibility criteria for counselling, screening and method provision. The first two have been printed and are currently being widely distributed. A third document will be issued during the course of 2000 as will other language versions of all three brochures. Simplified guidelines for *Postpartum and post-abortion family planning: what health workers need to know* was under preparation and will be submitted for external review and publication in 2000.

French and Spanish translations of the following documents were completed in 1998-99:

--- *Health benefits of family planning*
--- *Providing an appropriate contraceptive method choice*
--- * Vasectomy: what health workers need to know*
--- *Natural family planning: what health workers need to know*
--- *Female sterilization: what health workers need to know.*

**MATERNAL AND PERINATAL HEALTH**

The main objective in this area of work is to contribute to the reduction of maternal morbidity and mortality by developing acceptable and affordable evidence-based health interventions that can be applied in developing country settings. In the research side of this work emphasis is placed on evaluation of promising interventions. This includes: preparation of systematic reviews of the literature; improvement of understanding of sociocultural factors influencing maternal health; review of methodological issues related to maternal health research; and conduct of follow-up studies of the populations included in maternal and newborn related research. The evidence generated through research is incorporated into country programmes through the development of norms and tools and of programmatic strategies with the required technical support for their implementation.
The year 1999 was a year of consolidation of this new research area. Two major randomized controlled trials were completed. The first evaluated a new model for routine antenatal care and the second the effectiveness of misoprostol for prevention of postpartum haemorrhage. The routine antenatal care trial was conducted in collaboration with four institutions in developing countries (Argentina, Cuba, Saudi Arabia and Thailand). It sought to evaluate the impact of a new antenatal care programme on the health of mothers and newborns. This new programme limits antenatal tests, clinical procedures and follow-up actions to those scientifically demonstrated to be effective in improving maternal and newborn outcomes. The selected antenatal care activities are distributed over four visits during the course of pregnancy. All data obtained during the study were analysed in Geneva during 1999. The final data analysis of the three components of the study (clinical evaluation, women/provider satisfaction, and economical evaluation) was completed by October 1999 and several papers are under preparation for publication during the year 2000. An extensive dissemination effort is being planned, including presentations at meetings and symposia, and through medical and non-medical publications.

The misoprostol trial was launched by HRP in 1997, and completed in 1999. Its objective was to evaluate the overall efficacy of oral misoprostol when used routinely for the management of the third stage of labour. The primary question was how effective is a single dose of 600 µg of misoprostol in reducing severe postpartum blood loss and the need for additional treatment in the third stage of labour when compared with an intramuscular or intravenous 10 IU dose of oxytocin. Data analysis is in progress in Geneva and it is expected that the first report will be available by April 2000.

Considerable progress was made in the implementation of other relevant trials such as the reduction of unnecessary Caesarean section and the prevention of pre-eclampsia and eclampsia. Two new activities have now been fully incorporated in the maternal health portfolio: women and providers’ perception of care, and the economic evaluation of interventions tested in randomized controlled trials. The challenge for the year 2000 is to publish the results of the completed studies, initiate the trial evaluating the effect of calcium supplementation for the prevention of pre-eclamptic and a research programme evaluating strategies for the prevention of mother-to-child transmission of HIV in developing countries. A randomized trial to evaluate an active dissemination strategy using evidence-based information included in the WHO reproductive health library to improve obstetric practices is also under way.

Activities related to implementation of evidence-based knowledge focused on the development of managerial and technical tools for strengthening programmes designed to reduce maternal and perinatal mortality and morbidity. At one level, this approach is designed to apply evidence to support technical and clinical interventions that will improve the quality of services, through the development of a strategy for the Integrated Management of Pregnancy and Childbirth (IMPAC). At another level, it aims to increase collaboration with other agencies to support the global application of all components of IMPAC. In 1999, these activities resulted in the development of several practical guides and a manual on management of complications in pregnancy and childbirth for district level health care providers, the preparation of essential care practice guides in the form of algorithmic chart booklets for pregnancy and childbirth, the drafting of an adaptation guide, and the field-testing of a planning process for district managers.

The planned work in this area covers a diverse range of issues and specific areas of collaboration within the Department. It addresses cross-cutting technical themes, such as pregnancy and childbirth, family planning, post-abortion care and the management and prevention of STIs/ HIV/AIDS in pregnancy. Cross-Cluster collaboration generally focuses on either the management of specific diseases in pregnancy such as malaria and tuberculosis or the development of generic management tools. The programmatic side of the strategy is co-ordinated with the Department’s Team for Technical Support to Countries and the Planning and Programming group, WHO Regional Offices and partner agencies. It is expected that the integration of research and programmatic efforts will have an interactive effect and will make relevant contributions towards the improvement of maternal and perinatal morbidity and mortality in developing countries.

UNSAFE ABORTION

The Department has identified unsafe abortion as a thematic area for renewed and consolidated efforts with the ultimate goal of eliminating the occurrence of unsafe abortions. This goal is to be achieved by undertaking activities, in a systematic manner, that involve all the Department’s Teams.

The Department’s global and regional estimates for the incidence of abortion and its associated mortality suggest that an estimated 45 million abortions occur each year, over 40% of which are unsafe. These estimates have been incorporated in a book entitled Sharing responsibility: women, society and abortion world-wide, published in 1999 by the Alan Guttmacher Institute. The book Abortion in the developing world was also published in 1999. This book presents results of 23 HRP-supported studies that sought to document the determinants of induced abortion in 15 developing countries of Africa, Asia, and Latin America. The key findings in this book were highlighted in a press release issued by WHO on the opening day of the 1999
for more feasible integrated approaches; and direct assist-
management into other reproductive services; advocacy
integration of RTI/sexually transmitted infection (STI)
in different country settings; reviews of previous attempts
demography of RTIs, and hence the need for this integration,
accomplish this through: a better understanding of the epi-
cerns into other reproductive health services. It attempts to
(tion of RTIs) focuses on the integration of RTI issues and con-
ition services.
reducing unsafe abortion and improving access to safe abor-
of providing abortion services by non-physicians, and on
ternal mortality. Consultations are planned to identify gaps
wifery modules. One of these modules relates to post-abor-
and midwives, the Department has developed a set of mid-
thus of unsafe abortions.

A paper was prepared to document the morbidity and
mortality caused by unsafe abortion and the cost of unsafe
abortion to health care services in Benin, Cameroon, and
Senegal. HRP is also conducting a large multinational study
on non-surgical abortion, which is near completion; results
of this study are expected by mid 2000.

In 1999, HRP examined the current provision of surgical
abortion and documented the managerial changes, resource
allocations and adaptations required to introduce medical
abortion into existing surgical abortion services in Roma-
nia. Work has also continued on the development of im-
proved methods of emergency contraception which have a
crucial role in the prevention of unwanted pregnancies, and
thus of unsafe abortions.

To support the upgrading of midwifery skills for nurses
and midwives, the Department has developed a set of mid-
wifery modules. One of these modules relates to post-abor-
tion care.

The database on abortion and abortion-related mortality
will be updated to contribute towards new estimates of ma-
ternal mortality. Consultations are planned to identify gaps
and priorities for work on unsafe abortion, on the feasibility
of providing abortion services by non-physicians, and on
reducing unsafe abortion and improving access to safe abortion
services.

REPRODUCTIVE TRACT INFECTIONS, CERVICAL CANCER AND INFERTILITY

The thematic group on Reproductive Tract Infections
(RTIs) focuses on the integration of RTI issues and con-
cerns into other reproductive health services. It attempts to
accomplish this through: a better understanding of the epide-
miology of RTIs, and hence the need for this integration,
in different country settings; reviews of previous attempts
at integration of RTI/sexually transmitted infection (STI)
management into other reproductive services; advocacy
for more feasible integrated approaches; and direct assist-
ance to countries.

Research and evidence

Prevalence rates of STIs are thought to be rapidly in-
creasing in several developing countries in the Asia-Pacific
region. In Myanmar, three studies are planned: a cross-
sectional prevalence study of lower genital tract infections;
a study of women with ectopic pregnancy involving test-
ing of tubal tissue for chlamydial antigen; and a study of
cases of ectopic pregnancy and women undergoing tubal
ligation for chlamydial antigen in the excised tubal tissue.
In Mongolia, a study will investigate attitudes and percep-
tions, concerning vaginal discharge and STIs, of mothers
and their prepubertal daughters who come for treatment at
reproductive health clinics. A sample of 500 antenatal pa-
tients attending maternity hospitals in Vientiane, Lao Peo-
ple’s Democratic Republic, will be screened for syphilis,
gonorrhoea, chlamydial infection and bacterial vaginosis.
Studies of prevalence of RTIs are also planned in Indone-
sia, Thailand, and Viet Nam.

The Department plans to be active in the area of RTI/STI
testing in the coming year. Rapid diagnostic tests for STIs
already exist and are in use in developed countries. These
tests are, however, too expensive for consideration in de-
veloping countries. A comparison of all costs incurred in
the use of rapid tests, the use of standard tests currently
used in reference laboratories in developing countries, and
the use of WHO’s Syndromic management for sexually transm
itted diseases is required. The Department plans to
conduct such a costing study to determine if advances in
rapid diagnostic techniques for STI already available have
any application in the developing world.

HRP, along with the Ford Foundation and the Rockefeller
Foundation, is conducting a project that draws upon the
existing experience in the area of social and biomedical
research on RTIs and other gynaecological morbidity. The
intention is to develop a set of guidelines on how to plan
and implement rigorous studies on the prevalence of RTIs,
and such gynaecological morbidity as prolapse, vesico-
vaginal fistulae and menstrual disorders, as well as on their
behavioural determinants and consequences for women’s
lives. When completed, the guidelines will address both
biomedical and women’s perspectives. To prepare these
research approaches, a multidisciplinary, international
consultative group has been formed, with representation
from the social, biomedical and biostatistical spheres. The
Group met in mid-1999 and presented work-in-progress on
their individual contributions. Finalization of chapters is
under way and will be completed in 2000.

In 1998, WHO had commissioned a review of the topic of
integrating STI management into family planning services.
This review was issued as a document in the Occasional
Paper Series by the Department in 1999. It concluded that
relatively little information exists on this topic and more must be known and understood about it, especially the costs and benefits in general as well as the different operational models in use, before guidance can be developed.

In 1999, the Department formed a partnership with the Frontiers project (led by the Population Council) which aims to conduct operational research in family planning. The purpose of this partnership is to develop additional case studies on integration in order to broaden the available information base about the topic.

Development of norms and tools

In an attempt to assess whether it was possible to improve the sensitivity and specificity of the vaginal discharge flow chart contained in WHO's *Syndromic management for sexually transmitted diseases*, a variety of additional tests or alternative logic was evaluated. However, none of the methods or alterations investigated represented an improvement over what was already recommended.

A process to prioritize the development of locally relevant interventions for addressing established RTIs is urgently needed. The appropriate mix of interventions for each local and/or national programme is determined by a number of interrelated factors such as prevalence and incidence of RTIs, sexual and health behaviours, local perceptions and beliefs concerning reproductive morbidity, health care seeking behaviour, availability of resources, and antimicrobial use and resistance. Typically, programme managers have imperfect data on such factors. And when data do exist, programme managers rarely have a clear process for deciding what actions might be indicated. To address this problem, the Department and the Population Council’s Horizons project are evaluating a process for making decisions about programme goals and directions and the key steps in implementing those decisions to address the problem of established RTIs. The final step is the evaluation process which will examine if the improved direction and re-prioritized interventions have been implemented and are indeed more effective.

In 1999, the Department and the Horizons project continued the development of the key components of the *Programme guidance tool for management of established reproductive tract infections* and reviewed these with outside experts in a meeting in Geneva in March. At that time, the consensus was that no further development should take place until after the approach was field-tested. Following that meeting, four sites were identified for field tests, proposals were developed and funded in three. In the coming biennium, the above activities with the Horizons project will continue.

WHO plays a key role in the development and distribution of guidelines for the management of STIs. Updated every four years or as needed, these guidelines are important in forming the basis for national guidelines for treatment of STIs and in influencing essential drug policies in countries. In 1999, the Department, in collaboration with WHO’s HIV/AIDS/STIs Initiative (HSI) and UNAIDS, organized a consultation to review the existing guidelines, assess their adequacy in light of changing patterns of epidemiology, patterns of antimicrobial resistance and the development of new antibiotics. In 2000, the Department, in collaboration with HSI and UNAIDS, will finalize and distribute the revised guidelines.

During 1999, the Department also worked with UNAIDS and the Female Health Company to develop a planning and programming guide on the female condom. Input into these materials has also been provided by many programme managers who have been working with the female condom in the field. It is expected that the document will be printed in mid-2000 for wide distribution.

Technical support to countries

HRP has continued to provide active support to countries wishing to conduct research in this area. As a component of HRP’s Long-term Institutional Development (LID) Grant, prevalence studies on ectopic pregnancy, pelvic inflammatory disease (PID) and STIs will be started in Ulaanbaatar, Mongolia and Yangon, Myanmar in 2000. The LID Grant for 1999 and 2000 for the Maternal and Child Health Institute, Vientiane, Lao People’s Democratic Republic includes studies on septic abortion and on women with symptoms of lower genital tract infection. A workshop was held in 1999 to finalise the research proposals.

Advocacy

In 1999, the Department hosted a consultation on the topic of dual protection—i.e. simultaneous protection against pregnancy and STIs. This consultation was co-funded and co-organized by WHO, UNFPA and UNAIDS. The consultation strongly endorsed the single method (condom) approach to dual protection and called for guidance and assistance from international agencies in helping countries adopt this approach. In 2000, additional co-sponsored, co-funded region-specific consultations are planned.

TECHNICAL SUPPORT TO COUNTRIES

The planning of essential activities for responding to country needs was taken into account in the process of reorganization that has taken place within HRP and in the creation of the Department of Reproductive Health and Research. The Team for Technical Support to Countries (TSC) is organized to facilitate the support required, in countries, to improve reproductive health. Such support is aimed...
at strengthening the capacity of countries and their communities to address their reproductive health needs. This includes assisting countries in building their programmatic and research capacities. It entails, at country level, identifying specific needs and ensuring appropriate actions. This is accomplished by employing diverse strategies, which include ensuring that the necessary research is conducted and that the research findings inform the development of appropriate tools and practice guidelines. This assists in determining policy and necessary resource allocation for the implementation of appropriate programmes. It is expected that the linking of research, at national and regional levels, with technical support, will facilitate a more effective response to country needs in reproductive health.

The operations of the Team cover WHO’s Africa and Eastern Mediterranean regions, the Americas regions, the Asia and the Pacific regions and, to a limited extent, Eastern Europe. For each region, there is a formally constituted Regional Advisory Panel (RAP), which assesses issues in the countries of the region and makes recommendations. These Panels are convened by the Secretariat and meet annually. Their terms of reference which guide direction and membership have been revised in order to reflect the expanded mandate of the Department. Thus, given the array of needs and diversity of issues, RAP membership, albeit small, ensures participation of national institutional heads, reproductive health programme managers, research specialists, scientific area experts, collaborating agencies, and the WHO Regional Reproductive Health Advisors.

**Africa and Eastern Mediterranean region**

The strategy for strengthening research capacity in reproductive health in the WHO African and Eastern Mediterranean Regions, which was revised in the previous biennium, continues to focus on the strengthening of selected institutions and the stimulation of interest in reproductive health in various countries. For French-speaking Africa, additional strategies for increasing research capacity include, for example, stimulating interest in research on reproductive health at country level, creating or reinforcing research networks among French-speaking African scientists and institutions, and improving the infrastructure for research by developing the human resources, strengthening libraries and promoting good management practices.

HRP collaborated with institutes in 24 countries of the African and Eastern Mediterranean Regions during 1999. Seven institutions in these countries received Long-term Institutional Development (LID) Grants, and three received a Resource Maintenance Grant (RMG), while 16 were awarded grants for library support and the purchase of consumable laboratory supplies.

During the year, regional research initiatives on two of the three priority research areas identified in the previous year continued to be developed. These were those on Female Genital Mutilation (FGM) and reproductive health services for adolescents in French-speaking Africa. The main goal of the project “Promoting Best Practice for FGM Prevention in Six sub-Saharan African Countries” is to derive and disseminate best practice for the prevention and elimination of FGM, drawing on the results of evaluation and research on FGM and of programmes to combat it in six sub-Saharan countries (Burkina Faso, Cameroon, Gambia, Ghana, Kenya and Nigeria).

An operations research project on improving reproductive health services for adolescents was continued in six French-speaking sub-Saharan countries. Other intercountry activities included research methodology training courses in Cameroon and Tunisia. In addition, a multicountry study on Family Planning and Sexual Behaviour in the Era of HIV/STDs was continued in Kenya, South Africa, Uganda, United Republic of Tanzania, Zambia, and Zimbabwe.

At the country level, research was supported under the respective LID Grants and by several of the thematic groups. Efforts continue to be made to increase the research activities of all thematic groups in Africa as well as HRP’s collaboration in the Eastern Mediterranean Region and in French-speaking Africa.

**Uganda**

Since 1998, the Department has been involved in a major technical assistance project in Uganda. Other stakeholders in this project include the Ministry of Health, various United Nations organizations, The World Bank, and several non-governmental organizations. In 1998, a consensus was reached between the various partners to develop an essential care package for reproductive health for the country. The Department has contributed by training nurses and midwives from district teams in life-saving midwifery skills and by carrying out community mobilization activities in order to develop a community response to the challenges posed by safe motherhood. In association with WHO’s Department of Child and Adolescent Health, a strategy and plan have been developed for adolescent reproductive health activities in Uganda. Also, 15 district medical officers have been trained in the Safe Motherhood District Planning process. The Mother-baby package costing spreadsheet, developed by the Department, has been applied in two districts, which provided valuable information on the cost of strengthening maternal health. The activities undertaken in this project will be reviewed in 2000.

**The Americas region**

HRP-supported collaborating institutions from the Region of the Americas are implementing a large number of research projects in topics relevant to regional and national reproductive health problems. These include studies being...
carried out by the three regional research networks for clinical and epidemiological research, social science research, and basic science research, as well as by institutions at the national level.

During 1999, centres were involved in five regional research initiatives. Three centres from Brazil, Chile and Mexico completed the multicentre research project “Acceptability of emergency contraception in Latin America”, funded by the Mellon Foundation. Institutions in Argentina, Bolivia, Cuba and Peru are implementing the multicentre social science research study on “Reality and beliefs in the sexual and reproductive decision-making process: men’s perceptions and behaviour”. Centres in Argentina, Brazil, Cuba, Guatemala and Mexico began the implementation of a multicentre study that addresses the problem of the increasing rate of Caesarean sections in Latin America. Four centres in Argentina, Colombia, Cuba and Venezuela are taking part in a multicentre trial coordinated by Oxford University, United Kingdom, that evaluates the use of magnesium sulphate for the treatment of pre-eclampsia (Magpie Trial). Lastly, four centres in Argentina, Chile and Mexico involved in basic reproductive biology research are grouped in a regional network that will study the mechanisms of action of hormonal methods used for emergency contraception.

In addition to these regional research initiatives, the centres are involved in projects which address national priorities. During 1998, from the overall number of 163 studies, 15 projects (9%) were implemented with support from HRP’s capacity building grants (LID grants, RMGs, and Re-entry Grants) and 68 projects were carried out with support from national sources (42%). The participation of the regional centres in the global research effort is exemplified by the 17 projects (10%) supported by thematic groups and the 63 studies (39%) being funded by international agencies other than WHO.

During 1998–1999, intraregional research training continued to be an important component of institutional strengthening activities. Eight research training grants were awarded in the areas of reproductive epidemiology, reproductive medicine, biostatistics, public health, and molecular biology.

The holistic coverage of reproductive health issues relevant to regional and national needs by means of scientifically—and ethically—sound research projects is increasingly the primary objective of centres and of the institutional strengthening activities deployed to assist them in this effort.

The challenge for the Regional Advisory Panel, for the centres, and for the Department is to broaden the scope of the present work, centred on research, to include technical support activities. As a first step, six topics have been identified, in coordination with the WHO’s Regional Office for the Americas, on which both research and technical support activities will be focused during the 2000–2001 biennium. These are: maternal mortality, adolescent reproductive health, perinatal health, men’s roles in reproductive health, emergency contraception, and reproductive health services. It is expected that this integration of research and technical support will facilitate a more effective response to country and regional needs in reproductive health.

Asia and the Western Pacific region

In 1998, STAG had commended and endorsed the regional strategic framework for research capacity strengthening in Asia and the Pacific, especially the efforts made to promote intraregional cooperation in reproductive health research and research capacity strengthening, including regional self-reliance in research training, regional joint research programmes and networking mechanisms at regional and national levels. The WHO Collaborating Centres and the institutes from developed countries in the region could also be included in these networks. It was important for HRP to devise mechanisms to harness and exploit the respective strengths of mature institutes and involve them in more creative ways to assist in strengthening reproductive health programmes in the neighbouring developing countries that share similar demographic and cultural identities.

In line with the recommendation made by the Regional Advisory Panel (RAP) for Asia and the Pacific, as well as by the Asia and the Pacific Symposium on “Intra-regional Cooperation in Reproductive Health Research” (Shanghai, China, 12–13 October 1998), a document entitled Sexual and reproductive health research needs and research agenda: the Asian and Pacific perspective was prepared and endorsed by the RAP at its 1999 meeting.

During 1999, work continued on the development of the following two regional research initiatives: (i) “Collaborative Reproductive Epidemiology Research: Patterns and Predictors of Caesarean Section in Asia”, an 11-country joint research programme (Bangladesh, China, Indonesia, Korea, Mongolia, Myanmar, Nepal, Philippines, Sri Lanka, Thailand and Viet Nam) coordinated by the Epidemiology Unit, Faculty of Medicine, Prince of Songkla University, Hat Yai, Thailand; and (ii) “Regional Research Initiative on Adolescent Migrants and Reproductive Health in the Greater Mekong Region”, a five-country joint research programme (China, Lao People’s Democratic Republic, Myanmar, Thailand and Viet Nam) coordinated by the Institute for Population and Social Research, Mahidol University, Nakhon Pathom, Thailand.

As a follow up to RAP’s recommendation that more training facilities should be provided within the region and within the South-to-South cooperation effort, centres in Malaysia, Singapore and Thailand hosted an increasing
number of trainees in a variety of research disciplines. In 1999, 17 Research Training Grants were provided, among which 16 were for training within the region.

Three national research institutions for training networks have been established in the region, in China, Sri Lanka and Thailand. In 1999, 9 LID Grants, and 11 RMGs were given to 20 institutions in 10 countries.

**Lao People’s Democratic Republic**

In 1998, a team from WHO headquarters visited the Lao People’s Democratic Republic to carry out an initial situation analysis. In 1999, an in-depth analysis of reproductive health services was carried out in that country and recommendations were made for improving the national reproductive health programme.

**Eastern European region**

The main objective of the Department in this region is to strengthen national capacity in reproductive health research in selected countries and to assist the WHO Regional Office for Europe in providing technical support to countries in implementing programmes in reproductive health. In January 1994, a Scientific Working Group (SWG) on reproductive health research in Eastern Europe was established to promote and coordinate research and research training in the region. The group prepared six research proposals in the areas of family planning, abortion and perinatal care.

The Centre of Public Health in Romania, with four participating centres in Armenia, Georgia, Lithuania and Russia, is managing a study on the determinants of contraceptive choice and use of fertility regulating methods in Eastern European countries. The study aims to assess the characteristics of women who do not use modern contraception (abortion clients), versus users of modern contraceptive methods, to determine specific reasons for not using a modern contraceptive method. Centres in Georgia, Hungary, Roumania and Slovenia, are participating in two multicentre randomized studies being conducted by HRP's Research Group on Post-ovulatory Methods for Fertility Regulation. One is a multicentre randomized double-blind comparison of mifepristone and two regimens of levonorgestrel (see page 9). The second is a randomized, double-blind comparison of three regimens of misoprostol after pretreatment with mifepristone for early termination of pregnancy (also described on page 10).

The Department is providing support for testing a model for perinatal death classification in four countries: Armenia, Kazakhstan, Kyrgyzstan and Russia. The study is based on the Nordic perinatal audit. A computerized version of Vitting Andersen’s dichotomising scheme defining a single or principal cause will be used.

The ninth Postgraduate Course for Training in Reproductive Medicine and Reproductive Biology was held at the University of Geneva, Geneva, Switzerland. It was partially supported by HRP. Of the 30 participants, 11 were from Eastern Europe.

**CLINICAL TRIALS AND INFORMATICS SUPPORT**

The clinical trials and informatics support group, which functions administratively within the Director's office, provides statistical and data processing support for all multicentre and some single-centre research projects undertaken by HRP, as well as technical advice on the design, management, analysis and interpretation of research projects. The group also provides support to research capability strengthening in the formulation, execution and review of institution strengthening policies in the areas of biostatistics and data processing. In addition, the group provides informatics support to the administration and management area of the Department.

During 1999, 65 single- and multicentre projects were supported, of which 20 were in the planning stage, nine were in the data collection phase, 22 were in the final analysis stage, and 14 were completed. A total of 65 000 data forms were processed and entered into computer. The group continued the review of HRP’s existing Standard Operating Procedures for research and the development of new ones in order to start a formal implementation of WHO Good Clinical Practice (GCP) guidelines in all of HRP’s research activities.

Strengthening of biostatistical and data processing capabilities of collaborating institutions continued. Staff supervised on-site centres performing data management of their own studies, and gave lectures at the Postgraduate Course for Training in Reproductive Medicine and Reproductive Biology at the Collaborating Centre in Geneva, Switzerland. Staff also presented in Geneva a seminar on GCP requirements to a meeting of principal investigators of a new HRP-supported study.

In 2000, support to the 51 current studies and any new studies will continue. Implementation of WHO Good Clinical Practice guidelines throughout HRP’s research activities will also continue. The final phase of the development of the new computing environment for statistics and data processing will be completed.

**STANDARDIZATION AND QUALITY CONTROL OF LABORATORY PROCEDURES**

Owing to the steadily decreasing need for hormonal measurements and severe financial constraints, HRP proposed in early 1999 to phase out the Matched Reagent Programme
which had been running successfully for many years in collaboration with the WHO Collaborating Centre for Research and Reference Services in the Immunoassay of Hormones in Human Reproduction, London, United Kingdom (the London Centre). This proposal was endorsed by STAG at its February 1999 meeting.

Limited supplies of well-characterized reagents for the immunoassay of reproductive hormones to laboratories collaborating with HRP continued during 1999. The standardized assay systems were well validated and used for the analysis of samples collected in the course of multicentre research projects and other HRP-supported studies, including research conducted in the context of institution strengthening activities. In addition to providing reagents, the London Centre monitored the performance of laboratories using WHO matched reagents by means of an external quality assessment (EQA) scheme.

In 1999, a total of 30 laboratories in 19 countries (17 of them developing, one developed and one country in transition) received matched radioimmunoassay (RIA) and enzyme immunoassays (EIA) reagents sufficient for 321,200 assay tubes, and 27 laboratories participated in the EQA scheme. In future, only commercially reagents will be provided and the EQA scheme will be project-oriented and provided on an ad-hoc basis.

COMMUNICATION AND DISSEMINATION OF INFORMATION

Within the new structure of the Department, work in the area of information dissemination and communication has been placed under the Team for Advocacy and Human Rights. During 1999, with a view to increasing efficiency through better utilization of available resources, steps were taken to redistribute the work among the various staff responsible for information dissemination in the new Team. The Team also started to formulate a new set of common objectives and strategies for the Department’s information dissemination and communication work.

The Department continued to produce its usual serial publications. These included two newsletters—the quarterly *Progress in human reproduction research* and the twice-yearly *Safe motherhood* newsletter. HRP issued its *Annual technical report 1998*, and RHT its *Interim progress report 1998–1999*. A new serial publication entitled *Social science research policy briefs* was started in 1999. The aim of this single-sheet flyer is to report to policy-makers summaries of research findings with policy implications from HRP’s social science research. HRP produced a total of five new non-serial publications/documents while RHT issued 23; these included other language versions of documents previously issued in English.

A particularly important publication of the Department in 1999, as in 1998, was *The WHO reproductive health library* (RHL). RHL No. 2 was published in English and Spanish during the year. The list of subscribers for this unique electronic journal continued to grow during 1999, reaching about 4500 in November for the English version and 850 for the Spanish version.

Scientific writing workshops and communication workshops for researchers and policy-makers were also conducted. These workshops aim to help centres collaborating with HRP in the strengthening of their capacity to disseminate research findings to scientists, policy-makers and the general public. During 1999, two scientific writing workshop were held. The first—a training workshop for trainers—was held in Thailand, and the second was held in Bangladesh. A communication workshop for reproductive health programme managers and policy-makers was held in Shanghai, China.

Four press releases were issued in 1999, three of which in particular generated considerable media interest. The two Internet web sites of the Department were maintained and updated regularly.

In 2000, the Department will continue to produce and disseminate relevant documents and other information materials and undertake a major overhaul of its web sites. Workshops and other assistance to strengthen the communication capacity of the collaborating centres are also planned.
Annex 1

SCIENTIFIC AND TECHNICAL ADVISORY GROUP IN 1999

Members

I. Adeokun, Association for Reproductive and Family Health, Ibadan, Nigeria
Y. Al-Mazrou, Assistant Deputy Minister, Ministry of Health, Riyadh, Saudi Arabia
J. Findlay, Prince Henry’s Institute of Medical Research, Clayton, Australia (Chairman)
B. Garcia-Guzman, Centre for Demographic and Urban Studies, Mexico City, Mexico
B. Hulka, University of North Carolina, Chapel Hill, NC, USA (Vice-chairwoman)
B.-I. Nesheim, Ulleval University Hospital, Oslo, Norway
M. Rajalakshmi, All India Institute of Medical Sciences, New Delhi, India
H. Rashad, The American University in Cairo, Cairo, Egypt
R. Vihko, The Academy of Finland, Helsinki, Finland
Xiao Shaobo, The State Family Planning Commission of China, Beijing, China

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Annex 2

SCIENTIFIC AND ETHICAL REVIEW GROUP PANEL IN 1999

G. Ada, John Curtin School of Medical Research, Canberra, Australia
A.-A. Al Meshari, King Saud University, Riyadh, Saudi Arabia
Chai Podhisita, Institute for Population and Social Research, Nakhon Pathom, Thailand
J. Cohen, Paris, France
R. Cook, University of Toronto, Toronto, Canada
I. Diamond, University of Southampton, Southampton, United Kingdom
Dwip Kitayaporn, Mahidol University, Bangkok, Thailand
M. Elder, Biggar, Lanarkshire, United Kingdom
A. Genazzani, Institute of Obstetrics and Gynaecology, Modena, Italy
A. Glasier, Family Planning and Well Woman Services, Edinburgh, United Kingdom
R. Gray, Johns Hopkins University, Baltimore, MD, USA
K. Hagenfeldt, Karolinska Hospital, Stockholm, Sweden (Chairwoman)
T. Hargreave, Western General Hospital, Edinburgh, United Kingdom
R. King, Esher, Surrey, United Kingdom
K. de Koning, Royal Tropical Institute, Amsterdam, The Netherlands
F. Larrea, National Institute of Nutrition, Mexico City, Mexico
R. Macklin, Albert Einstein College of Medicine, Bronx, NY, USA
O. Mateo de Acosta, National Institute of Endocrinology, Havana, Cuba
M. Mhloyi, Population Studies Center, Harare, Zimbabwe
Y. Murata, Osaka University Medical School, Osaka, Japan
Ngeow Yun Fong, University of Malaya, Kuala Lumpur, Malaysia
E. Pantelides, Population Studies Centre, Buenos Aires, Argentina
M. Piya-Anant, Siriraj Hospital, Bangkok, Thailand
K. Satoh, Nihon University School of Medicine, Tokyo, Japan
J. Sciarra, Northwestern University Medical School, Chicago, IL, USA
C. Shalev, The Gertner Institute for Health Policy, Tel Hashomer, Israel
S. Tabacova, National Centre of Hygiene, Ecology and Nutrition, Sofia, Bulgaria
Zhao Baige, State Family Planning Commission, Beijing, China

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Annex 3

TOXICOLOGY PANEL IN 1999

C. L. Berry, The London Hospital Medical College, London, United Kingdom
R. R. Chaudhury, National Institute of Immunology, New Delhi, India
R. Heywood, The Larches, The Lanes, Huntingdon, United Kingdom
A. Jordan, Division of Reproductive and Urologic Drug Products, Food and Drug Administration, Rockville, MD, USA
S. Price, University of Surrey, Guilford, United Kingdom
S. Tabacova, National Centre of Hygiene, Ecology and Nutrition, Sofia, Bulgaria

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Part 1. The Department's work and policies
The objectives, structure and work of the Department

J. Khanna and P.F.A. Van Look
The WHO Department of Reproductive Health and Research (RHR) was created in November 1998 by joining the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP) and the former WHO Division of Reproductive Health (Technical Support) (RHT). The WHO Administration, under the leadership of the Organization’s new Director-General, Dr Gro Harlem Brundtland, brought these two former Divisions together with the aim of integrating research and action in reproductive health into one programme. Within WHO, the Department is located in a cluster called Family and Community Health (renamed in 1999 from Health Systems and Community Health). This Cluster includes, along with RHR, the Department of Child and Adolescent Health and Development, and the Department of Women’s Health. It also includes a special cross-Cluster Initiative on HIV/AIDS/Sexually Transmitted Infections.

The Department aims to improve reproductive health throughout the world. Its work is founded on the recognition that sexual and reproductive health is influenced by poverty and growing inequity between peoples’ living standards, often within the same country. From the Department’s research and evidence-gathering come evidence-based solutions to reproductive health problems and guidance on best clinical and managerial practice to assist resource-poor countries.

GOALS AND OBJECTIVES

The Cluster goals

The Department has set itself the mission of "helping people to lead healthy sexual and reproductive lives". The overall aim of the Department in this regard is to strengthen the capacity of countries to enable people to promote and protect their own health and that of their partners as it relates to sexuality and reproduction and to have access to and receive quality reproductive health services when needed. Four programme goals guide the Department’s work. These goals seek to ensure that people can exercise their sexual and reproductive rights in order to:

1. experience healthy sexual development and maturation and have the capacity for equitable and responsible relationships and sexual fulfilment;
2. achieve their desired number of children safely and healthily, when and if they decide to have them;
3. avoid illness, disease and disability related to sexuality and reproduction and receive appropriate care when needed;
4. be free from violence and other harmful practices related to sexuality and reproduction.

The Department recognizes that it alone cannot achieve these goals. It believes that these goals will be reached only through working closely with its many partners at local, national and international levels.

Objectives

To achieve its overall aim and goals, the Department has formulated three strategic operational objectives, working closely with the other partners in the Family and Community Health Cluster:

- to promote, facilitate and conduct research to improve reproductive health;
- to support countries with knowledge and tools to formulate policies and strategies to implement appropriate interventions to improve reproductive health;
- to support countries to strengthen the capacity of communities to make informed reproductive health choices and participate in improvements in reproductive health.

STRUCTURE AND WORK

In May 1999, the professional staff of the Department got together at a retreat to decide how best to organize the wide-ranging work of the Department. A matrix structure, in which staff work in task-oriented teams (see Fig. 1), was developed by the staff. The basic structure formulated at the retreat was refined further in accordance with the guidance of the WHO Administration and this led to the establishment of four Teams within the Department:

- Research and Evidence
- Development of Norms and Tools
- Technical Support to Countries
- Advocacy and Human Rights.

These Teams reflect the Department’s strategic operational division of work. Each of these areas is headed by a Team-Coordinator.

In creating the above four Teams, emphasis was placed on how the work of the Department would best serve the needs of developing countries. For instance, the first need is to identify and evaluate reproductive health problems and to find appropriate evidence-based solutions to them. This is done through research and generation of evidence. Hence the Team for Research and Evidence. Before research solutions can be transferred to countries they need to be turned into practical norms, guidelines, tools and interventions, which is the function of the Team for Development of Norms and Tools. Next, there needs to be a mechanism for the delivery and implementation of the norms, tools and interventions that have been developed. This mechanism
is provided by the Team for Technical Support to Countries. Finally, all this work in an area as sensitive as reproductive health needs to be anchored in sound ethical values and regard for human rights. Moreover, there is a compelling need for continued advocacy for the concept of reproductive health and for the social and other changes that are needed for the achievement of overall goals in reproductive health. The Team for Advocacy and Human Rights provides this support.

The specific thematic areas of work of the Department, selected on the basis of the comparative advantage of the Department, and to which each of the four Teams contributes, are as follows:

—Planning and Programming for Reproductive Health
—Sexual Development, Maturation and Health
—Fertility Regulation
—Maternal and Perinatal Health
—Unsafe Abortion
—Reproductive Tract Infections (including cervical cancer/infertility)
—Female Genital Mutilation and Other Harmful Practices.

A Group Leader guides the implementation of activities in each of these seven areas.

For administrative purposes all staff of the Department are assigned to one of the four Teams. Functionally, however, the staff often contribute to several thematic areas of work depending on their expertise and need for their contribution. This arrangement allows the Department to approach its work in a multidisciplinary way. Moreover, it avoids the fragmentation that often arises when the structure is along the lines of strict hierarchy.

Planning and Programming for Reproductive Health

The Planning and Programming (P&P) Group acts as a data clearinghouse through its evidence activities, conducts research relevant to implementation of reproductive health programmes, works with the Team for Development of Norms and Tools on reproductive health indicators, and assists countries in the implementation of evidence-based practices and programmes. How the four Teams contribute to the work of this Group is described as follows:

The Research and Evidence Team generates and synthesizes evidence for measures needed to improve reproductive health in under-resourced settings. A specific activity of the P&P Group to which the Research and Evidence Team contributes in this regard is the initiative called Mapping Best Reproductive Health Practices. Since its launch in 1997, this initiative has produced a substantial body of reliable evidence on high-priority reproductive health problems. This has been done, among others,
through the publication of new systematic reviews of available evidence (from randomized controlled trials) on interventions for emergency contraception, antibiotic prophylaxis for incomplete abortion, and misoprostol for labour induction. Moreover, within this activity many other existing systematic reviews have been updated.

In 1999 the Team on Development of Norms and Tools supported the work of the P&P Group by publishing a manual entitled *Reproductive health in conflict and displacement*. This manual is a good example of the cross-cutting nature of the reproductive health support work undertaken in the P&P Group, which would not fit into any of the other Groups.

The Team on Technical Support to Countries contributes to the objectives of the P&P Group through the work it has undertaken in developing a Strategic Approach to Technology Introduction and Transfer. This approach uses a three-stage strategy which includes needs assessment, operations research and implementation activities—yet another example of a cross-cutting activity essential to improving reproductive health choices and services in developing countries.

The Advocacy and Human Rights Team includes staff specializing in communication and information dissemination. This Team contributes to the P&P Group’s work by facilitating the publication and dissemination of *The WHO Reproductive Health Library*. In 1999, issue No. 2 of RHL was published in both English and Spanish.

**Sexual Development, Maturation and Health**

The first of the Department’s four goals seeks to enable people to experience healthy sexual development and maturation and enhance the capacity for equitable and responsible relationships and sexual fulfilment. In this regard the Group on Sexual Development, Maturation and Health pursues two research priorities: documentation of the context of adolescent reproductive and sexual health, including the magnitude, determinants and consequences for adolescents’ lives; and identification, through intervention research and evaluation of ongoing interventions and programmes, of optimal provision of health and information services, and best practices, that respond effectively to the needs of adolescents. Social scientists within the Research and Evidence Team contribute most significantly to this work area. The knowledge generated through research within this Group is intended for use directly by countries as well as for use in the development of norms and tools related to adolescent reproductive health.

**Fertility Regulation**

All four of the Teams of the Department are involved in studies that relate to fertility regulation, in one form or another, although two Teams, Research and Evidence and the Development of Norms and Tools, make a significantly greater contribution to this work. In the area of Research and Evidence, activities relate to the three broad disciplines, namely social science research, epidemiological research (in the context of surveillance and evaluation of the safety and efficacy of existing fertility regulating methods), and biomedical research (in the context of the development and evaluation of improved and new methods of fertility regulation). The work undertaken in the Team for Development of Norms and Tools focuses on: increasing information about contraceptive options; the development and updating of technical guidelines and training materials on family planning methods; the development and updating of technical guidelines and training materials on family planning services; and developing a collaborative process to support effective dissemination, adaptation and utilization of the documents generated by the Department.

**Maternal and Perinatal Health**

The main goal in this thematic area is to reduce maternal morbidity and mortality through development of acceptable, affordable and sustainable evidence-based health programmes and evaluation of new interventions. The Research and Evidence Team contributes to this goal by conducting systematic reviews of the literature, improving understanding of sociocultural factors influencing maternal health, reviewing methodological issues related to maternal health research as well as through the conduct of large-scale intervention trials. The evidence generated is incorporated into country programmes (by the Team for Technical Support to Countries) via the standards and tools developed through the contribution of the Team for Development of Norms and Tools. The latter Team also contributes by developing programmatic strategies with the required technical support for their implementation.

**Unsafe Abortion**

The focus on unsafe abortion as a work area has as its ultimate goal the elimination of all unsafe abortions. All the four Teams contribute to the achievement of this goal. The Research and Evidence Team contributes by documenting the global dimensions of unsafe abortion through gathering, analysing and dissemination of information on the magnitude of the problem, its determinants and the groups of women most affected. The Team also develops improved methods of non-surgical abortion and investigates ways to improve services that address women’s needs for abortion-related care. Finally, it implements, monitors, and evaluates a range of programmatic activities related to unsafe abortion. The Development of Norms and Tools Team develops guidelines for the safe use of non-surgical methods of pregnancy termination with mifepristone and misoprostol. The Technical Support to Countries Team builds capacity for
participation in WHO-supported multicountry studies and for local research for solutions to local problems. The Team for Advocacy and Human Rights advocates for respect of women’s human rights and helps with dissemination of research findings and advocacy material.

**Reproductive Tract Infections (including cervical cancer/Infertility)**

The main goal of the thematic work Group on Reproductive Tract Infections (RTI) is to integrate RTI issues and concerns into other reproductive health services. Through the contribution of the Research and Evidence Team, the Group seeks to develop a better understanding of the epidemiology of RTIs in different country settings. It reviews previous attempts at programmatic integration of RTI/STI management into other reproductive services and assesses new approaches. The Group relies on the Team for Development of Norms and Tools to develop norms and standards for services, and on the Advocacy and Human Rights Team for advocating for more feasible integrated approaches.

**Female Genital Mutilation and Other Harmful Practices**

The work on Female Genital Mutilation (FGM) focuses on the obstetric sequelae as well as the sociocultural, gender and economic contexts of the practice. The objective of this work is to increase knowledge, particularly on the frequency of reproductive health consequences of FGM, in order to improve advocacy and programming as well as to develop, test and disseminate tools for research into various aspects of FGM. The Teams that are especially relevant to this work are Research and Evidence, Technical Support to Countries, and Advocacy and Human Rights.

**OTHER STRUCTURAL CHANGES**

The creation of the Department of Reproductive Health and Research necessitated reorganization of the work of the two components—HRP and the former Division of Reproductive Health (Technical Support) (RHT)—related to information dissemination and communication in order to give it a common focus and purpose. In the new structure of RHR, this work has been placed under the Team for Advocacy and Human Rights.

During 1999, with a view to increasing efficiency through better utilization of available resources, steps were taken to redistribute the work among the various staff responsible for information dissemination in the new Team. One concrete functional step was the creation of a single documents centre for the distribution of all RHR information materials. Previously, HRP and RHT distributed their documents independently. The well-developed capacity for production of documents within RHT, especially for the design and layout of documents, has now become available to the whole Department.
Women’s perspectives and gender issues

J. Cottingham, F.C.C. Bergin, A. Martin Hilber
OBJECTIVES

As endorsed by HRP’s Policy and Coordination Committee (PCC), and the Gender Advisory Panel (GAP) in January 1997, the objectives of this component are:

— to ensure that a gender analysis be brought to bear across the Department;
— to ensure that women and women’s perspectives are brought into the Department’s overall structure and decision-making processes including the establishment of national and international research priorities in reproductive health;
— to encourage a broader understanding of the Department’s work among women’s groups, and an exchange of information between those groups and the Department; and
— to integrate women’s perspectives and gender issues into the research and institution strengthening activities.

INTRODUCTION

With the restructuring involved in the establishment of the Department of Reproductive Health and Research (RHR), the work on women’s perspectives and gender issues has necessarily had to take on a broader scope. The introduction of the matrix structure in the middle of the year has implied that gender issues, as well as reproductive rights, advocacy and information, now cut across all of the Department’s work areas. This requires ongoing adaptation and assessment of the best way to work. It also means that the nature of work of the Women’s Desk is changing, with the Technical Officer currently co-ordinating the Team called Advocacy and Human Rights.

In the first half of the year, the financial situation of HRP and the Department severely restricted activities in general. For the Women’s Desk, this meant that some activities such as the dialogue meeting on reproductive rights and the expansion of the research initiative into informed consent procedures had to be postponed.

An in-depth review of the Women’s Desk and of GAP was undertaken in the second half of the year to assess achievements and to make recommendations for the future role and work of both the Desk and the Panel. This review has helped to clarify a number of issues, including future directions, which are reflected in the second part of this chapter.
WHO, the Women’s Health Project at Witwatersrand University (South Africa) and the School of Public Health, Harvard University (USA)—as well as three independent consultants (India, Kenya, USA). The Committee designed and developed a draft core curriculum for a 15-day training course for approximately 30 participants, and collectively facilitated and evaluated the pilot course in South Africa in August 1997. The Committee then solicited applications from training centres interested in adapting and offering the curriculum in their region. From more than 25 applications, four collaborating institutions were chosen: Centre for African Family Studies (CAFS), Nairobi, Kenya; Centre for the Study of State and Society (CEDES), Buenos Aires, Argentina; Key Centre for Women’s Health in Society, University of Melbourne, Melbourne, Australia; and Yunnan Reproductive Health Research Association, Kunming, China. In addition, the Social Research Center of the American University in Cairo, Egypt, joined the initiative as a partner institution for mutual exchange of curricula. A Regional Adaptation Workshop was conducted in November 1998 with representatives of the four institutions.

During 1999, each of these institutions conducted the course using their own adaptations and locally or regionally appropriate case studies and materials. The curriculum was translated into Mandarin for use in China and into Spanish for use in Argentina. Observers from the International Coordinating Committee attended each of the courses. A partial evaluation from these observations was made in November, but a full Regional Evaluation Workshop will be conducted in March 2000 involving trainers from each of the sites and the International Coordinating Committee (see section on “Planned activities for 2000–2001”). The Department provided seed money to each of the regional sites and encouraged other donors to support these courses. This approach was particularly successful in China where the Ford Foundation gave substantial support for the course, and in Kenya where the Rockefeller Foundation and USAID provided support. Both PAHO and UNFPA supported a number of participants to the course in Argentina, and WHO country offices supported several participants to attend the courses in South Africa and Kenya. To encourage participation, information about the four courses was sent to the respective Regional Offices and to RHR Collaborating Centres.

The curriculum leads participants through six modules: gender, determinants of health, reproductive rights, evidence, policy, and health systems. The first three modules provide the conceptual foundations for the course, the analytic “lenses” through which reproductive health programmes are examined. These are followed by the three application modules (evidence, policy, health systems) which provide skills for building and reshaping reproductive health systems to promote gender equality and reproductive rights. Reproductive health is the substantive focus of the course, forming the basis of all materials, examples, and exercises. Each module includes a range of optional sessions that can be used to meet the different learning objectives, allowing facilitators to choose sessions that are best suited to a given audience, or which address local concerns.

By the close of the course, participants should have acquired the skills to conduct a gender analysis of health data, health policy and services; become familiar with recent technical developments in reproductive health; developed an understanding of the links between reproductive rights and health; acquired new research, planning, advocacy and leadership skills; and incorporated a new perspective on how to improve reproductive health services in their community or country.

The final curriculum, reflecting regional adaptation and diversity, will be published in July 2001, after a further round of field testing during 2000. The course is a major contribution to making the concepts and practice of gender equality and reproductive rights accessible to health programme managers, and it is hoped that, over time, more and more RHR collaborators along with others will benefit from one or other of the regional courses.

Reproductive rights

Within the Department, the development of work in reproductive rights has been influenced by activities related to health and human rights in the Organization as a whole. A new position of Human Rights has been created to coordinate all human rights work within the Organization, including overall strategy development. This post will be housed in the Cluster on Sustainable Development and Healthy Environments. A draft position paper on health and human rights for WHO has been prepared, and an initial consultation focusing on the conflicts and interface of human rights and public health was held in December 1999 in which RHR staff participated. The evolving work within the Department will be developed in harmony with the broader Organizational approach.

Over the past year, the Department has been working closely with other departments in the Family and Community Health Cluster, particularly the Department of Child and Adolescent Health, and it played a major role in preparing an Organization-wide proposal for work on health and human rights submitted to the Government of Norway in September 1999.

Inventory of discriminatory laws and policies affecting reproductive health

In the last “dialogue” meeting organized by HRP in Casablanca, Morocco, in 1997, a recommendation was made
to review existing laws and regulations (including customary law and traditional practices) related to reproductive health. Examples of issues to be examined included laws directly affecting reproductive health as well as laws that indirectly affect women’s reproductive health such as those that limit women’s decision-making power. Building on that proposal, the Scientific and Technical Advisory Group (STAG) recommended last year that HRP initiate an inventory of discriminatory laws and policies affecting reproductive health with the aim of increasing visibility with respect to the importance of laws and policies in protecting or negatively affecting reproductive health and rights.

During the course of the year, the Department held both internal and external consultations, beginning with GAP in March 1999, in order to understand how best to go about such a task. Outside experts consulted included the Center for Reproductive Law and Policy (New York, NY, USA), the François Xavier Bagnoud Center for Health and Human Rights at Harvard University (Boston, MA, USA), the Reproductive Health Law Programme of Toronto University (Toronto, Canada), the International Planned Parenthood Federation (IPPF, London, United Kingdom) and UNFPA. The Department also reviewed the work of other organizations in the field, and this revealed that there have been many initiatives in the area of cataloguing laws that affect reproductive health. Examples include the Harvard Law School’s Annual review of population law, published since 1974, which reviews national legislation affecting women’s health and population issues; and the reviews of legislation and policy affecting reproductive health undertaken by the Center for Reproductive Law and Policy in collaboration with country-based NGOs in anglophone and francophone Africa, Latin America and the Caribbean, Eastern Europe and the former Soviet Union.

Two key points emerged from this consultation and review process: (i) that a considerable amount of work has already been done in terms of documenting laws and policies affecting reproductive health in different parts of the world, and (ii) the issue of assessing the role played by laws and policies in protecting or negatively affecting reproductive health is extremely complex. Determinants of reproductive health are interlinked and range from elements such as women’s status in society (inheritance rights, property rights, education), to questions of access to and quality of health services. In addition, the actual legal and policy environments that affect reproductive health vary from one country to another, depending upon the country's history, colonial legacy, specific customary laws and a host of other factors. Our conclusion, therefore, was twofold. First, it will be more useful to draw on what has already been done in the area rather than create a new inventory of laws and policies. Second, that in order to tackle the whole domain of law and policy and its impact on reproductive health and rights, a more detailed analysis has to be made as to what is feasible and appropriate to undertake, to what purpose, and what WHO’s comparative advantage would be. The Department has therefore begun drafting a strategy for work on human rights, of which some attention to laws and policies would be a part, and which can serve as a basis for consultation. This is described in the section on “Planned activities for 2000–2001”.

Rights-based approaches

Manual on Human Rights and Safe Motherhood

The University of Toronto Faculty of Law approached the Department to help in the elaboration of a manual for health workers for Applying human rights to advance safe motherhood. As a result, an intern from the University of Toronto Faculty of Law came to work with the Department for eight weeks during 1999 to ensure that the health and rights information was easily understandable by an audience of health professionals. The publication aims to explain how a human rights approach can be used at the country level to improve maternal health. The manual presents a practical framework within which organizations can begin writing reports, working with governments and structuring litigation to address urgent problems facing safe motherhood. The draft document is now being revised and is likely to be published initially as an occasional paper of the Department so that it can be field-tested. It is hoped that this can be built upon and contribute to the overall rights-based approach of the Department, and perhaps serve as a basis for additional manuals on other aspects of reproductive health (see section on “Planned activities for 2000–2001”).

Exploring country experiences

In order to document first-hand how a rights-based approach to reproductive health services is being implemented, an exploratory visit was made to Nairobi, Kenya, in November 1999. Preliminary contacts were established with approximately 20 NGOs providing services with an explicitly rights-based approach. The results of this initial “case study” will be used in the design of a proposed series of case studies in different countries/regions.

Collaboration with UN Human Rights Treaty and Charter Bodies

Over the past year, the Department has started to work with a number of United Nations Human Rights Bodies. For instance, the Department reported on aspects of reproductive health (particularly maternal mortality and morbidity) relating to human rights to both the Human Rights Commission and the Committee on Economic, Social and Cultural Rights. With the help of another intern from the University of Toronto Faculty of Law, the Department
is drafting standardized reports, using a selection of indicators based on the Department’s databases, for the monitoring of reproductive rights as they relate to the two Committees. This is being done in close collaboration with other departments and the acting Focal Point for Human Rights. This work is intended to increase the attention given to reproductive health and rights by the Committees as well as helping Committees clarify States’ obligations in relation to reproductive rights through the provision of information on reproductive health.

The Department made a statement on reproductive rights at the 55th session of the Human Rights Commission and assisted a number of the Special Rapporteurs with mandates that relate to reproductive health, such as the Special Rapporteur on Violence Against Women.

Collaboration with ILO and other partners

The Department has been providing inputs into the revision process of the International Labour Office (ILO) Convention 103 and Recommendation No. 95 on Maternity Protection at Work. It has commissioned a background paper on the women’s health dimensions of maternity leave, and it will continue its involvement during the second reading of the revision at the ILO Conference in June 2000.

The Department is building up collaborative relationships with a number of NGO partners at the national and global levels, promoting a dialogue as well as increasing knowledge on sexual and reproductive rights through, for instance, participation in seminars and courses. Among many others, partners include the FIGO Study Group on Sexual and Reproductive Rights, the Center for Reproductive Law and Policy, the Commonwealth Medical Association, the International Federation for Medical Students Associations, and Physicians for Human Rights.

Understanding the informed consent process in research

In 1997–1998, HRP supported two qualitative, descriptive studies in Brazil and Chile, to throw light on what both research subjects and investigators understand by the process of informed consent in contraceptive research (see Annual technical report 1998 for a summary of findings). The aim was to provide the basis for creating an optimal informed consent process in this area of research. A further study of informed decision-making in a health service setting is being carried out in Mexico. Final results from this study, which was considerably delayed in starting, will be available during 2000. Results from the Brazil and Chile studies are being published in those countries, and a paper reflecting on the results from both countries is in preparation for publication in Reproductive health matters.

Informed consent in research involving human subjects has been of central concern to ethicists and researchers since the Nuremberg Code of 1947. HRP has paid particular attention to the stringent application of ethical standards in all the research it has supported over the years, and has elaborated and refined ethical guidelines on issues of specific application to reproductive health research, such as research with adolescents, partner notification, and social science research. However, HRP’s series of dialogues with women’s health advocacy groups in different regions and at the international level (the “Creating Common Ground” series) revealed the critical importance that women attach to this process, since it is through an adequate application of the principle of informed consent in research (amongst other things) that their reproductive rights will be protected.

The studies in Brazil and Chile were pilot projects in the area, and HRP’s Scientific and Ethical Review Group (SERG) proposed that this research should be extended to other countries/regions and should be conducted in the context of research projects being supported by HRP. Because of budgetary restrictions in 1999 it has not been possible to proceed with this area of work. However, in the next biennium it is hoped that it will move forward again (see section on “Planned activities for 2000–2001”).

Barrier methods

Because of the importance given by women’s health advocacy groups to barrier methods that will protect against both pregnancy and sexually transmitted infections (STIs), HRP has supported research and informational activities relating to both the diaphragm with spermicide and the female condom over the past few years.

Diaphragm with spermicide

Results from the study of acceptability, effectiveness of use and service delivery requirements of the diaphragm with spermicide in three developing country settings have now been written up and presented for publication. A paper from the study in Turkey (supported by HRP) has been accepted for publication in International family planning perspectives (see Annual technical report 1998 for a summary of results). The Woman and Child Health Center, Istanbul, which coordinated the study in Turkey, has been asked by the Ministry of Health to prepare a training programme so that the diaphragm can be provided in different parts of the country. The development of this kind of outreach is being held up, however, because of the difficulty of obtaining adequate supplies of spermicide. A local company has requested importation rights for both diaphragms and spermicides, and it is hoped that an agreement will be reached in the very near future.
The pooled results from the three countries involved in the study (Colombia, the Philippines and Turkey) have been written and a paper submitted for publication to *Contraception*. Overall, the studies indicate that the diaphragm does have a small niche in developing country settings, since 57.2% of those enrolled in the study were still using the diaphragm after 12 months. The findings also indicate that training health workers to provide the diaphragm can contribute to improvements in the overall quality of care, and that positive support to women from providers increases satisfied use of the method. The cumulative pregnancy rate at the end of 12 months was 10.1%, which is well within the broad range reported for this method (2.0%–22.0%).

In the continuing search for alternative methods of protection against sexually transmitted infections (STIs), including HIV/AIDS, the results of this study are particularly timely. There is evidence that the diaphragm with spermicide protects against upper genital tract infections. The Contraceptive Research and Development (CONRAD) Program (Arlington, VA, USA), and the US Centers for Disease Control and Prevention (Atlanta, GA, USA) are currently conducting a prospective study in Africa to establish more rigorous data. If this protective association is confirmed, the diaphragm will be an important additional measure in protecting against factors predisposing to HIV infection. The present study, a collaborative effort of HRP, Family Health International (FHI), Research Triangle Park, NC, USA, and the Population Council, New York, NY, USA, provides important information about the usability of the diaphragm in a variety of developing country settings.

**Female condom**

In collaboration with UNAIDS and the WHO HIV/STI Initiative, the Women’s Desk has continued to convene the in-house Condom Working Group to sustain coordinated attention to work on both female and male condoms. This year the Group oversaw the development and finalization of the *Planning and programming guide for the female condom*, which will be published and disseminated in early 2000. The guide, whose elaboration involved close collaboration with the only current manufacturer of the female condom—the Female Health Company—is intended for use with governments and NGOs in countries thinking about introducing the product. Follow-up work will be conducted by the Department (see section on “Planning and programming for reproductive health” for details). Other issues taken up by the Group have been: studies on re-use of the female condom, social marketing of male and female condoms, a multicountry study to compare the use-effectiveness of male and female condoms and new products in the pipeline. All of these are discussed in other sections of this report.

The Condom Working Group is an excellent example of collaboration with UNAIDS, and it will continue over the next year to ensure full coordination of efforts in this field.

**Gender Advisory Panel**

GAP, now in its fifth year, continues to be convened by the Technical Officer for Women’s Perspectives and Gender Issues. The Panel has 12 members from all WHO regions, who work in the area of reproductive health and have a demonstrated concern for gender equality issues (see Annex 1).

**PLANNED ACTIVITIES**

**Integrating gender concerns into the Department’s work**

**Gender tools**

Dependent upon the advice of GAP, the Department will pursue the development of additional “tools” for ensuring that gender equality issues are taken into account in all aspects of its work, as feasible and appropriate.

**Training initiative on gender and reproductive health**

A Regional Evaluation Workshop will be held in March 2000 involving members of the International Coordinating Committee and representatives from each of the four regional sites where the Gender and Reproductive Health Course was run in 1999. Following this evaluation, the core curriculum will be revised to reflect regional adaptation and diversity and field-tested again in some of the sites. It will then be revised yet again and a final curriculum prepared. The curriculum is expected to be published in July 2001. There is already considerable interest in the course from both academic and training institutions as well as NGOs in different parts of the world (Central Asia, Eastern Europe, Sudan and other Arabic-speaking countries) concerned with gender and reproductive health issues. For the time being, the Department is encouraging those interested in applying for the courses that are already being offered in the centres involved in the Initiative, but as soon as the curriculum is ready, it will be available for all these institutions to run their own courses.

During 2000, the Department, now acting as a full coordinator for the project, will explore the possibility of putting the course on CD ROM or on the Web. It is also hoped that, in collaboration with CEDES in Argentina and the Yunnan Reproductive Health Research Association in China, Spanish and Mandarin versions of the curriculum will be produced. Additional funding will have to be sought for all these activities.
Once the curriculum is made available, it is expected that more and more the Department collaborators and others will benefit from one or the other of the regional courses, thus making the concepts of gender equality and human rights as they apply to reproductive health widely accessible and put into practice.

**Reproductive rights, law and policy**

Over the past few years, reproductive rights have been made more explicit as human rights through internationally agreed documents such as the International Conference on Population and Development Programme of Action (1994) and the Fourth World Conference on Women’s Platform for Action (1995). These rights include, for instance, the right of all couples and individuals to decide freely and responsibly the number and spacing of their children, and to have the information, education and means to do so; the right to attain the highest standard of sexual and reproductive health; and the right to make decisions concerning reproduction free of discrimination, coercion and violence.

Reproductive rights embrace other human rights already embodied in international, legally binding Covenants, such as those on Civil and Political Rights (1966) and on Economic, Social and Cultural Rights (1966). These Covenants create obligations for States that have signed them (“States Parties”) to respect, protect and fulfil the rights of their citizens. Thus, national laws and policies represent an important way in which human rights may be protected or, if they are discriminatory, violated. The Treaty Bodies monitoring the implementation of the Covenants may consider the absence of specific laws or policies—for instance, to protect women from domestic violence, or from death due to childbirth—to be a failure on the part of States Parties to protect the rights of citizens. There is, therefore, a considerable amount of work to be done to assist States Parties in reviewing laws and policies that help or hinder the fulfilment of the reproductive rights of people, and particularly those of women who bear the brunt of the burden of reproductive ill-health. National and international NGOs in many parts of the world are working to ensure that their governments fulfil and report on their obligations under internationally binding Covenants and Consensus Documents.

However, reproductive rights can also be respected, fulfilled and protected through avenues other than national legal and policy frameworks. In the domain of reproductive health, all the technical support to countries that WHO undertakes can potentially be cast in a “rights-based” approach, thus ensuring that proposed interventions protect rather than negatively affect (however unwittingly) people’s rights. Training of health providers can include explicit attention to the respect for people’s rights, and research can contribute to highlighting areas where specific attention should be paid to resolving a problem of rights’ violations (for instance, lack of adolescents’ access to reproductive and sexual health information and services).

Over the next biennium, the Department proposes to undertake activities in the area of reproductive rights that focus on two or three specific fields of work where WHO has a comparative advantage and is likely to make the most impact. As an initial step to mapping out this work, the Department is elaborating a draft strategy for addressing human rights in reproductive health. The strategy touches upon three interlinked areas of work: integrating a rights-based approach into programmatic activities of the Department; continued collaboration with the United Nations Human Rights Treaty and Charter Bodies; and assisting countries to respect, protect and fulfill reproductive rights. Briefly, these areas involve the following.

**Integrating a rights-based approach into all programmatic activities of the Department**

This involves focusing on selected the Department projects to ensure that reproductive rights are respected, protected and fulfilled. It entails working with staff members to train them in human rights so that they could define and explore what a rights-based approach means in practical terms in the Department’s work. Eventually this would result in the “mainstreaming” of reproductive rights in the Department’s work.

**Collaboration with UN Treaty and Charter Bodies**

The aim of these activities is not only to assist these Bodies (that is, the Committees that monitor Covenants and the Special Rapporteurs) with information about reproductive health in order to facilitate their discussions with States Parties, but also to increase the attention paid to reproductive rights in all Treaty and Charter Bodies. The activities will build on the work carried out in 1999.

**Assisting countries to respect, protect and fulfil reproductive rights**

Following from the review of work done to date by others on the impact of laws and policies on reproductive health, a number of avenues could be explored. One possibility is to document successful, rights-based approaches to, say, reproductive health service delivery in particular countries or regions, with the aim of proposing overall guidance on rights-based reproductive health services. This work would build on the *Manual for promoting human rights in safe motherhood*, and the case study already carried out in Kenya. Another approach would be to conduct an analysis of the legislative frameworks in selected countries for reproductive health to highlight legislative obstacles and provide examples of
legal frameworks (or model legislation) that promote reproductive health and rights. This work is probably best done in partnership with other organizations already active in the field, and with the relevant Regional Offices.

To help the Department clearly focus its work in this area, it is proposed to convene a technical consultation with representatives of groups with experience in the field, including service providers, human rights advocates and lawyers. The consultation would provide further inputs to the strategy by making recommendations, based on background papers and presentations, as to the best way forward for WHO in this area. The consultation is planned for mid-2000.

**Research on informed consent**

As described earlier in this report, understanding the informed consent procedure in reproductive health research is vital to ensuring that such procedures are carried out optimally, so that people’s reproductive rights are both fulfilled and promoted. Over the next biennium, the Department proposes to build on the lessons learned in the pilot projects in Brazil and Chile, when expanding the research into other geographical regions.

It is proposed to carry out a study of informed consent procedures in a minimum of three countries (if possible, in different regions), so that results are available by the end of the biennium. This will involve identifying an appropriate multicountry study supported by the Department, onto which this research can be “grafted”. It is foreseen that a small (4- or 5-person) technical advisory group consisting of researchers who have been involved in similar research will be asked to help elaborate an appropriate research protocol and give advice during the running of the project.

**Regional workshop on ethical standards in research**

Under the auspices of SERG, the Advocacy and Rights Team will work with the Convenor of SERG to organize, in the African region, a workshop on ethical aspects of reproductive health research involving human subjects. This will be the third in a series of such regional workshops, the first having been held in Bangkok, Thailand, in 1997 and the second in Viña del Mar, Chile, in 1998.

**Gender Advisory Panel (GAP)**

The Women’s Desk will continue to convene GAP, and to follow up on recommendations made during meetings. Over the next biennium, GAP will be considering elements of the entire work of the Department and not just the research activities.
Annex 1

MEMBERS OF THE GENDER ADVISORY PANEL IN 1999

M. Berer, Reproductive Health Matters, London, United Kingdom (*Chairwoman*)
A. Faundes, Campinas Research Centre for the Control of Maternal and Childhood Diseases (CEMICAMP), Sao Paulo, Brazil
N. Huq, Naripokkho, Dhaka, Bangladesh
Kaining Zhang, Yunnan Reproductive Health Research Association, Kunming, China
W. Nowicka, Federation for Women and Family Planning, Warsaw, Poland
M.-I. Plata, PROFAMILIA, Bogotá, Colombia
K. Rogo, Centre for the Study of Adolescence, Nairobi, Kenya
R. Sanchez, Ateneo de Davao University, Davao City, Philippines
A. Faye Schrater, Smith College, Northampton, MA, USA
Thein Thein Htay, Ministry of Health, Department of Health, Yangon, Myanmar
K. Xaba, Women’s Health Project, Witwatersrand University, Johannesburg, South Africa
M. Zulficar, Shalakany Law Office, Cairo, Egypt

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Annex 2

PUBLICATIONS IN 1999


Part 2: Research, Development and Technical Activities
Planning and programming for reproductive health

A.M. Gülmezoglu, P. Fajans, M.Q Islam, M.K. Usher-Patel, E. Ahman
RESEARCH AND EVIDENCE

INTRODUCTION

Evidence-based health care requires that policies and practices employed in the prevention and treatment of health care problems should be based on principles which have been proven through appropriate scientific methods. A variety of problems may arise when clinical practices not based on sound scientific evidence find their way into medical/health care practice. Removing an entrenched practice is much more difficult than introducing a new one. Not only do valuable resources continue to be (mis)used for practices of unknown effectiveness but further research is also required to challenge the usefulness of these practices. There are many examples of such practices in the field of reproductive health. For example, large trials had to be conducted to show that routine episiotomy is not beneficial. Routine electronic fetal monitoring during labour and routine ultrasound assessment during pregnancy have not been shown to decrease morbidity and mortality. Yet these two practices are widely used, including in some developing countries. A more effective resource allocation, complemented by efforts to implement only those practices that are effective, should be a priority in order to improve reproductive health services in developing countries.

In the past decade, systematic reviewing has become widely accepted as the gold-standard to evaluate the effectiveness of medical and non-medical health care interventions. Irwig et al. (Bulletin of the World Health Organization, 1998, 76:17–24) recommended that a systematic review be conducted before introducing an intervention into practice and to select interventions for research. A systematic review is the starting point in the decision-making process. First, it should be established that the benefits of the intervention outweigh the risks. Next, before the intervention is implemented, differences in the epidemiology of the problem, costs, biological differences, cultural and ethical factors should be considered. After implementation, continuous audit will guide further decision-making and indicate if implementing the practice has given the intended results. Systematic reviews also help in selecting research priorities. This fact is already acknowledged by some funding agencies (for example, the Medical Research Council in the United Kingdom) which do not consider applications for funding unless they are accompanied by a systematic review.

Recommendations often need to be made without the backing of adequate evidence. In such cases, the recommendation should make it clear that the evidence base is weak. A commonly used approach in assessing recommendations is “grading of evidence and strength of the recommendations” (see box). For each recommenda-

tion, the users should be able to clearly see the evidence base and the quality for that recommendation. As indicated in the box, the use of expert panels to make recommendations should be very limited. By using the classification shown in the box, the recommendations will be transparent and hence have more credibility, and scarce resources will not be wasted on ineffective interventions. Countries can base their choice of practice depending on the strength of evidence.

The past decade has witnessed a transformation in the world of medical literature and informatics. With increasing use of the Internet and other electronic media it has become possible to access easily huge amounts of information. Many journals are now available online and there is a proliferation of electronic databases where information on ongoing studies or those published in the grey literature are also indexed. Consequently, it has become a problem to cope with excess information, and how to find the most reliable information in the available time. However, many developing countries still lack access to good quality information, and Internet access is erratic and prohibitively expensive. Nevertheless, the technological revolution will eventually reach the places where it is needed most. It is important for WHO to continue filling this information gap by making the highest quality, up-to-date and relevant information accessible to health workers in under-resourced settings.

The Department maintains databases on important reproductive health indicators such as maternal and perinatal mortality. Data on the prevalence of these conditions are collected through electronic and manual search of bibliographic databases and from surveys conducted by other agencies and governments. During 1999, new maternal mortality, skilled attendant at delivery, perinatal and neonatal mortality estimates were produced. Databases are also used in the production of estimates for use in the “Global Burden of Disease Study” and by staff for research and programmatic purposes. These activities enable the Department to take on a clear leadership role in generating and synthesizing data on reproductive health problems that are relevant to developing countries.

MAPPING BEST REPRODUCTIVE HEALTH PRACTICES

The “Mapping Best Reproductive Health Practices” initiative is now in its third year. Started in 1997, this initiative has been gradually expanding and contributing to the pool of evidence on the effectiveness of reproductive health interventions. The initiative has four components:

—preparation of systematic reviews of the effectiveness of reproductive health care interventions
—capacity building in developing countries for the preparation of systematic reviews
—dissemination of evidence-based reproductive health care recommendations
—promotion of rigorous evaluation of care and products promoted by the Department.

It is expected that the selection and recommendation of effective practices and their incorporation into services will allow developing countries to maximize their resources and utilize them in the most rational and effective way. Furthermore, these efforts will strengthen the leading role of the Department and WHO in developing reproductive health programmes both within the UN system and globally.

OBJECTIVES

Activities are conducted to ensure that the Organization’s efforts in recommending reproductive health practices are supported by the best scientific evidence. The objectives are to provide:

— the scientific basis upon which recommendations for norms and standards for reproductive health practices are made;
— access to up-to-date, high-quality information for clinical practice in under-resourced settings;
— the evidence base for setting priorities in future reproductive health research.

ACTIVITIES

Activities include: (i) preparation of systematic reviews; (ii) dissemination of evidence-based reproductive health information; (iii) capacity building in systematic reviews; and (iv) promotion of rigorous evaluation of medical and non-medical forms of care. Activities feed into other areas of the Department for both research and practice.

Preparation of systematic reviews

Systematic reviews locate, appraise and synthesize evidence from scientific studies to provide informative empirical answers to scientific research questions. In addition, by identifying what is known and not known, they are an invaluable first step before carrying out new primary research. Systematic reviews differ from traditional reviews in various aspects. The main characteristic of a systematic review is the use of an a priori protocol, including an explicit and comprehensive strategy to search, identify and select studies for inclusion. Identified studies are then evaluated for methodological quality before being included in the review.

A question often asked when systematic reviews are discussed is how the Department selects the topics for review. Topics are selected by health professionals working in the countries, the editorial group of The WHO reproductive health library and the Secretariat working with these groups. Mechanisms for selection of topics are based on three principles:

• All protocols of randomized controlled trials supported by HRP should be supported by a systematic review.
• All substantial recommendations in reproductive health (medical or non-medical) should incorporate the strength of evidence behind the recommendation. Recommendations should be based on evidence synthesized through systematic reviews whenever possible.
• Developing country scientists and health professionals are encouraged to propose topics and participate in the preparation of systematic reviews contributing to mapping the best reproductive health practices.

In addition to the preparation of systemic reviews, HRP conducts methodological studies on systematic reviews and meta-analysis to contribute to the development of these research tools.

Cochrane Reviews are prepared by the Cochrane Collaboration Collaborative Review Groups (CRGs). These systematic review groups aim to ensure quality through editorial and external peer review and also assist in retrieval of studies, identification of unpublished studies and in translation of papers published in languages other than English. Cochrane Collaboration is an international non-profit organization that prepares, maintains and disseminates systematic up-to-date reviews of health care interventions. Importantly, Cochrane Reviews are peer-reviewed, both after the completion of the protocol and the full review. Thus, completing a systematic review is a time-consuming process which usually takes 6–9 months, depending on the topic and number of studies. In addition
to the advantages mentioned above, Cochrane Reviews are unique in that they are published electronically, allowing for easy updates. CRGs are responsible for preparing reviews in specific areas. The Department is actively collaborating with the following CRGs:

1. Pregnancy and childbirth
2. Fertility regulation
3. Infectious diseases
4. Neonatal disorders
5. Gynaecological cancers
6. Sexually transmitted diseases
7. Effective practice and organization of care

Systematic review activities conducted during 1999 are summarized below according to thematic area:

**Maternal health**

The Cochrane Pregnancy and Childbirth Group (CPCG) is the main group within the Cochrane Collaboration which focuses on systematic reviews in maternal health. This group was the first review group of the Cochrane Collaboration. It has been active since 1992 and produced a large number of reviews to date.

The reviews in maternal health published, updated or in preparation during 1999 with substantive contribution from the Department are:

**Reviews published**
1. Antibiotic prophylaxis for caesarean section
2. Episiotomy for vaginal birth
3. Umbilical vein injection for management of retained placenta
4. Topical umbilical cord care at birth

**Protocols published**
5. Vitamin A supplementation during pregnancy (in press)
6. Treatments for iron deficiency anaemia in pregnancy
7. Partogram use in the management of labour

**Reviews updated**
8. Routine antenatal care for low-risk pregnancy
9. Misoprostol vaginally for labour induction
10. Calcium supplementation during pregnancy
11. Drugs for the treatment of asymptomatic bacteriuria during pregnancy
12. Anticonvulsants for pre-eclampsia
13. Prostaglandins in third stage of labour
14. Amnioinfusion prophylactically versus therapeutically
15. Bedrest for impaired fetal growth
16. Betamimetics for suspected impaired fetal growth
17. Calcium channel blockers for impaired fetal growth
18. Electrostimulation in placental insufficiency
19. External cephalic version at term
20. External cephalic version before term
21. External cephalic version facilitation at term
22. Hormone therapy for impaired fetal growth
23. Malaria in pregnancy
24. Maternal oxygen therapy in impaired fetal growth
25. Nutrients for impaired fetal growth
26. Plasma volume expansion for impaired fetal growth
27. Trichomoniasis treatment during pregnancy
28. Cephalic version by postural management
29. Maternal iodine supplementation in areas of deficiency
30. Maternal hydration for increasing amniotic fluid volume in oligohydramnios and normal amniotic fluid volume
31. Vitamin D supplementation in pregnancy

**Fertility regulation**

The Cochrane Fertility Regulation Review Group addresses the processes by which people manage their sexuality and fertility. The field of interest includes how people inform themselves, make decisions regarding sexual activity, and act on their family size and birth spacing intentions. The group addresses issues relating to decision/policy-making processes, sex education, and access to counselling and contraceptive services. It aims to review efficacy and safety of fertility regulation methods as well as the knowledge and skills of providers and how these latter two issues influence the former two.

The Cochrane Fertility Regulation Review Group is a relatively new group, which started its work in 1997, as compared to the group on maternal health. It takes considerable time for a review group to establish itself and start producing reviews. The Programme has been supporting this Group since its inception. These include financial support for the editorial base as well as representation in the Editorial Board.

During 1999, reviewing activities in fertility regulation have gained momentum as a result of the collaboration with the Department of Obstetrics and Gynaecology of the University of Geneva, Geneva, Switzerland, and Family Health International (FHI), Research Triangle Park, NC, USA.
Systematic reviews in fertility regulation in 1999

Reviews published
1. Interventions for emergency contraception

Protocols published
2. Acceptability of low-dose estrogen oral contraceptives containing levonorgestrel, norethindrone, desogestrel, gestodene and norgestimate (in press)

Reviews under preparation
3. Medical versus surgical methods of pregnancy termination
4. Surgical methods for first trimester pregnancy termination
5. Medical methods for first trimester pregnancy termination
6. Cervical ripening methods before first trimester pregnancy termination

Unsafe abortion

Abortion-related issues are handled by both the Fertility Regulation and the Pregnancy and Childbirth Groups. In general, pregnancy termination falls under the Fertility Regulation Group whereas treatments for miscarriage and its complications are handled by the Pregnancy and Childbirth Group. The outputs of review activities related to abortion during 1999 are:

Review published
1. Antibiotics for incomplete abortion

Reviews under preparation
2. Medical treatments for early pregnancy failure
3. Surgical management of incomplete abortion

Reproductive tract infections (including STIs and HIV/AIDS)

Review groups on sexually transmitted Infections and HIV/AIDS have been formed recently within the Cochrane Collaboration. There is also a group on infectious diseases. So far, one review on treatments for trichomoniasis has been published in The Cochrane library through the “Mapping Best Reproductive Health Practices” activity. This review has been substantially updated in 1999.

Currently, no systematic reviews have been completed by the HIV/AIDS Group. The review on interventions to reduce mother-to-child transmission, prepared through the Pregnancy and Childbirth Group has been updated twice this year with support from the Department.

Effective Practice and Organization of Care (EPOC)

During 1999, an interdepartmental project entitled “Strengthening the Evidence Base for Cost-Effectiveness of Integrated Interventions” was initiated. The Department took a leading role in this project. The main activity of the project has been to develop a protocol for a systematic review of “Integration in the Health Sector”. This work has been conducted in collaboration with WHO’s Department of Organization of Health Services Delivery (OSD), the International Health Division of the Liverpool School of Tropical Medicine, Liverpool, UK, and the Cochrane Effective Practice and Organization of Care Group (EPOC). A master’s student from the Liverpool School of Tropical Medicine has worked intensively on the project and a background paper and draft protocol for a systematic review is complete. It is anticipated that the full review will be completed by the end of 2000.

Dissemination of evidence-based reproductive health care information: The WHO reproductive health library

Dissemination of information cannot be conducted in isolation. The dissemination of evidence generated and synthesized within the “Mapping Reproductive Health Practices” initiative is a planned and structured activity. The WHO reproductive health library (RHL) is the main dissemination tool of this initiative. Individuals working on systematic reviews are also actively involved in the presentation and dissemination of RHL.

RHL is the product of the collaboration between the Department, research centres in developing countries and the Cochrane Collaboration. RHL is a yearly-updated, electronic review journal focusing on reproductive health problems of high priority for developing countries.

The objective of RHL is to provide health care workers in developing countries with an affordable, efficiently-distributed and user-friendly source of up-to-date systematic reviews in reproductive health. Systematic reviews included in RHL are Cochrane Reviews selected from The Cochrane Database of Systematic Reviews (CDSR) published in The Cochrane library. The Cochrane Reviews are supplemented with expert commentaries and practice implications of interventions in these reviews which are prepared by researchers from developing countries, or individuals with extensive knowledge of the conditions of practice in those countries.

The preparation and production of RHL follows the format of The Cochrane library, which is available to a limited number of subscribers mostly in Europe, North America and Australia, and contains systematic reviews in all areas of health care including reproductive health.

RHL is the first specialist database project for the Cochrane Collaboration as well as for WHO. In 1999, the visibility and acknowledgement of RHL as a valuable
resource increased substantially.

**RHL highlights in 1999**

- The review preparation and maintenance mechanism followed by RHL has been recommended as an example that should be followed by the Cochrane Collaboration (Chalmers I, presentation at the Annual Cochrane Colloquium, Rome, 5–9 October, 1999).
- RHL is now recommended by the Royal Thai College of Obstetricians and Gynaecologists for use by all obstetricians and gynaecologists, and trainees. Following this development the Secretariat has written to the Overseas Department of the Royal College of Obstetricians and Gynaecologists in the United Kingdom for a similar endorsement.
- RHL is now included in the undergraduate obstetrics and gynaecology curriculum of fourth-year students at the Department of Obstetrics and Gynaecology, University of Pretoria, South Africa. Efforts are continuing within WHO to develop a programme for this purpose.
- The Brazilian Society of Obstetrics and Gynaecology, through the Brazilian Cochrane Centre, is planning to distribute RHL to all its members (approximately 14 000).
- RHL has now formal representatives in Argentina, China, Cuba, India, Indonesia, Mexico, the Philippines, South Africa and Thailand. In 1999, RHL editors have presented and distributed copies of RHL in meetings, workshops and conferences in Argentina, Cuba, Egypt, El Salvador, India, Mexico, Namibia, South Africa, Thailand, United Kingdom, Uruguay, the USA and Zimbabwe.
- The WHO Regional Offices for South-East Asia (SEARO) and Latin America (PAHO/AMRO) are actively collaborating in RHL dissemination as well as recruiting individuals for the preparation of systematic reviews and commentaries.
- A Spanish translation of RHL was published in August 1999 (see below).

**Translations of RHL**

A complete Spanish translation of RHL No. 2 was published in 1999. Translation of Cochrane Reviews to other widely spoken languages has been under consideration by the Cochrane Collaboration for some time and the translation of RHL to Spanish, the first non-English publication of full Cochrane Reviews, has been welcomed. The Spanish RHL has provided access to 2500 users in Latin America and distribution will be increased to 5000 for the forthcoming RHL No. 3. One of the WHO centres in Latin America, the Latin American Center for Perinatology and Human Development (WHO/PAHO/CLAP), has assumed the responsibility for dissemination of the Spanish RHL. This includes mailing to subscribers as well as presentations in meetings and symposia throughout the continent. It is anticipated that this decentralization will improve efficiency and reduce distribution costs.

A collaborative activity has been established with the Shanghai Institute of Planned Parenthood Research, and the Shanghai Population Information Centre, Shanghai, China to prepare a Chinese version in the year 2000, to be published in 2001.

**Incorporating RHL into the medical curriculum**

Following the STAG 1999 recommendation, a link has been established with the WHO department involved in medical curriculum development. Several activities were suggested, such as raising awareness about RHL in the medical education community, and at the same time, mobilizing RHL regional editors about possible activities in their settings. Accordingly, an editorial is being prepared for the WHO newsletter Changing medical education and practice to be published in 2000. The regional editor in South Africa will present RHL at the Ninth Ottawa International Conference on Medical Education in March 2000.

**RHL programme contents**

RHL contents are organized in four sections. The contents of RHL No. 2 which have been published and distributed in 1999 are the following:

*Editorials relevant to reproductive health in developing countries*

This section includes editorial articles giving background information and authoritative statements regarding evidence-based medicine and important issues in developing countries. In RHL No. 2, an editorial entitled Evidence-based reproductive health in developing countries prepared by the Editorial Group has been published. RHL No. 3 will include an editorial by Dr David Grimes of FHI, entitled The need for systematic reviews in family planning.

*Effectiveness summaries*

These contain concise statements summarizing evidence from the systematic reviews. A new, updated set of these is created in each issue, using the information from the systematic reviews included in RHL. The interventions are categorized according to the level of effectiveness as outlined below:

- Beneficial forms of care
- Forms of care likely to be beneficial
- Forms of care with a trade-off
- Forms of care of unknown effectiveness
• Forms of care likely to be ineffective
• Forms of care likely to be harmful.

At a glance, users are able to see those interventions that are recommended and those that should be abandoned. RHL recommendations on maternal health are presented in the chapter on “Maternal health” and those on other areas of reproductive health in Annex 1d of this chapter.

Reproductive Health Database

Reproductive Health Database is the main section containing data. The section runs into a few hundred pages and increases every year. The following types of documents are included in this section.

Systematic reviews. Systematic reviews are taken in their entirety from the CDSR published in the last issue of The Cochrane library for that year. In the first issue of RHL, 27 Cochrane reviews were included. In RHL No. 2, 13 new reviews were added and about a third of the reviews included in No. 1 were updated—a total of 40 reviews. RHL No. 3 will be published in early 2000 and will include 12 new reviews. As explained the number of reviews addressing issues related to fertility regulation and unsafe abortion is gradually increasing through the strengthening of these components. One review has been taken out because it has not been updated despite the presence of new evidence (review on breastfeeding technique). RHL No. 3 will therefore include 51 Cochrane Reviews.

Commentaries. Commentaries are a unique feature of RHL. Each commentary is prepared by an individual with knowledge of the conditions and constraints in developing countries, with priority given to commentators from such countries. The commentaries aim to make the findings of systematic reviews relevant to developing countries. Authors of the commentaries are asked to summarize the review findings and comment on the feasibility of implementing the intervention if the review indicates beneficial effects. Commentaries are published after internal and external peer review.

Practical aspects. These are recommendations for managing the specific health problem discussed in the systematic review and commentary. A single, strict management guideline for all under-resourced settings is unrealistic, as there are many variations in the resources, logistics and traditions around the world between different countries and even between areas within countries. Thus, this section lists general principles of management in the light of the evidence emanating from the systematic review and the issues discussed in the commentary to provide a yardstick for users. Documents related to practical aspects are also peer reviewed together with the commentaries.

Editorial notes. A single commentary cannot always address the relevance of the intervention in all regions. In some cases, the prevalence of the disease may be different or there may be cultural factors that may make certain interventions irrelevant. A disagreement between the commentary author and the reviewer on the interpretation of the results of the review may lead to a confusing commentary. In such cases a clarifying note is added by the coordinating editors.

Useful information. A comprehensive register of funding agencies in maternal health and information on non-governmental organizations (NGOs) involved in the reproductive health field are listed. Information contained in this section aims to assist health workers in developing countries in approaching donor agencies for funding and collaborating in multicentre, randomized controlled trials. This section has been updated for RHL No. 3.

RHL subscriber status

Efficient dissemination of RHL has been a primary objective since the beginning of the project. The first issue of RHL was distributed widely using the mailing lists of WHO. The main objective of the dissemination strategy is to create a subscribers’ list which would include primarily individuals and institutions interested in receiving and using RHL. Thus, RHL is promoted through as many ways as possible to encourage subscriptions. National and international conferences provide an ideal opportunity and in 1999, RHL was presented at conferences worldwide by Department staff and regional editors.

The initial objective of the dissemination was to improve coverage in developing countries where most health workers are able to speak or read English. Currently, there are more than 4500 subscribers of RHL worldwide. This number is likely to increase substantially in the coming years. The print run for RHL No. 2 (1999) has been 12 500 copies in English and 2500 copies in Spanish. This number has already been increased to 5000 for the Spanish version and 13 000 for the English version of RHL No. 3 (2000).

Capacity building in systematic reviews

Preparation and training activity for systematic reviews is conducted jointly between HRP Secretariat and its collaborating institutions. The objective is that scientists from developing countries take responsibility for the preparation and maintenance of reviews of priority topics for their settings. This is very important because most reviews to date have been prepared by health workers in developed countries and thus reflect their priorities. Training support is provided through several mechanisms.
**RHL fellowships**

Systematic reviews are prepared by individuals from developing countries who take on responsibility for the preparation and maintenance of the review with support from the Secretariat. The process is operationalized as follows:

1. The main (responsible) reviewer is either from a developing country or has extensive knowledge of conditions in those settings. The RHL editorial team usually identifies individuals through contacts in collaborating institutions in developing countries but individuals can also approach the regional editors or the Secretariat with topics.

2. The review topic should be of sufficient interest for inclusion in RHL. Topics are generally interventions addressing treatments or preventive measures for major causes of reproductive morbidity and mortality.

3. The reviewer, by taking on the responsibility of preparing the systematic review, makes a commitment to complete the review for publication in The Cochrane library, and update the review as new data become available after publication of the review. Reviews that are not updated within one year of new evidence becoming available are excluded from The Cochrane library and RHL.

4. Currently, the main focus is on reviews of “effectiveness” of interventions which can be prepared through the Cochrane Collaboration review process. Systematic reviews of screening and diagnostic tests and prognosis are considered on an individual basis. That is, if the individual has the epidemiological and methodological expertise to conduct such a review, these can be undertaken.

5. If both the topic and individual are considered suitable, then the Secretariat provides technical and financial support to the preparation of the review.

The nature of the support depends on the experience and geographic location of the reviewer. Usually, the reviewer starts the work in his/her environment. Once the work has progressed sufficiently, support is provided for the reviewer to have one to two months of uninterrupted time to work on the review at the editorial bases of the relevant Cochrane Review Groups. For inexperienced reviewers, attendance at workshops, which are usually conducted by Cochrane Centres worldwide, are necessary.

**Training workshops and courses**

In addition to supporting individuals for the preparation of reviews, training workshops on review preparation, Cochrane Collaboration and Evidence-Based Medicine are conducted. During 1999, such training workshops were conducted in Argentina, South Africa, Switzerland and Thailand by the editors of RHL.

**Promotion of rigorous evaluation and tools recommended by the Department**

A randomized controlled trial to evaluate a programme promoting evidence-based medicine based on The WHO reproductive health library

The response to RHL in the first year has been overwhelming, indicating the need for a product that provides up-to-date, good quality information. The ultimate objective of RHL is to aid health workers in developing countries to adopt and implement practices that are based on firm scientific evidence. However, it is unlikely that simply having access to RHL or written medical information will cause a shift towards evidence-based clinical practice. In order to evaluate the change in practices recommended in RHL, an intervention study of RHL in maternity departments is proposed.

The study will be a randomized controlled trial conducted in three different geographic settings. The randomization unit will be maternity departments (cluster randomization) in Mexico, South Africa and Thailand. The units will be matched for country, size, baseline practice rates and randomized in pairs. The study will begin by identifying barriers to the utilization of evidence-based information. During this pre-intervention phase, the baseline rates of marker practices and the feasibility of data collection on all recommended practices in the trial sites will also be investigated. The marker practices will be interventions reviewed and clearly recommended in RHL.

Introduction of RHL through an “active” dissemination strategy will be compared to “control” of standard in-service training and continuing medical education methods. Active dissemination will consist of three RHL-focused workshops conducted by an obstetrician/gynaecologist in

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<th>Reviewer origin/location</th>
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<td>Argentina</td>
<td>Treatments for mild-to-moderate hypertension in pregnancy</td>
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<td>Treatments for symptomatic urinary tract infections</td>
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<td>Nigeria</td>
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<td>Surgical methods of managing incomplete abortion</td>
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the maternity department. The focus will be on the use of evidence derived from systematic reviews of controlled trials and the information included in RHL. The workshops will be informal and problem-oriented but will also include basic information on evidence-based medicine, Cochrane Reviews, RHL and patterns of behavioural change. As part of the intervention, participating units will receive a computer with RHL installed, and a printer which will be accessible to both doctors and midwives working in antenatal care and labour wards. In the control group, the baseline pilot phase and the outcome assessments will be the same. These units will not receive the active intervention but will be asked to continue with their standard training and education activities.

Main outcome measures will be markers of change in practice in selected interventions, as measured from patient records or other means of objective assessment (e.g. pharmacy records) of the use of the intervention. For each outcome, the difference in per cent change in practices will be compared. In addition, the number of times each file on RHL is accessed during the period of intervention will be counted on each of the study site computers as a process indicator. Qualitative evaluation of the experiences of staff and RHL coordinators will be conducted. Outcome assessments will be made 10–12 months after the intervention.

This trial will determine whether electronically presented up-to-date information on the effectiveness of health care interventions provided through an active dissemination strategy will change clinical practices. Both the methodology and results of this trial will have important implications for similar projects to evaluate the impact of health policy programmes and, therefore, will provide valuable information for future health sciences research.

The first steering committee meeting of the principal investigators was held in Geneva and site visits have been made to Mexico, South Africa and Thailand. The protocol for the trial has been completed and approved by the Scientific and Ethical Review Group (SERG). Data collection will start in year 2000 and the trial is expected to be completed by the end of 2001.

**Evaluation of the RHL programme**

RHL is a computer programme targeting a diverse group of health workers in developing countries. Users of RHL include obstetricians and gynaecologists, midwives, policymakers and managers. Hence, it is important to make RHL as user-friendly as possible. In order to achieve this objective, RHL is being evaluated independently by other groups as well as through small projects organized by the Department. Following initial evaluation by the International Health Division of the Liverpool School of Tropical Medicine, Liverpool, United Kingdom, another RHL evaluation among doctors and midwives is planned in South Africa in year 2000. The results of these evaluations will then be discussed with the coordinating editors.

**Evaluation of recommendations and tools**

Guidelines for the management of reproductive health problems need to be subjected to rigorous evaluation in terms of their scientific content, dissemination plans and intended use. The use of tools (i.e. manuals, guidelines) to promote the implementation of recommendations should be based on strategies that have been shown to be effective, and where this evidence is lacking, research is needed. Possible future activities include the evaluation of Essential care practice guides and Integrated management of pregnancy and childbirth currently under preparation by the Department.

**THE FUTURE**

The preparation of systematic reviews and their dissemination through RHL have so far been successful. RHL is gradually becoming a comprehensive source of evidence-based, up-to-date information in reproductive health. It is envisaged that RHL will be an aid to incorporating evidence-based medicine into the medical curriculum and an excellent resource for postgraduate degree and membership examinations in Obstetrical and Gynaecological Colleges. It is anticipated that RHL will become the most widely consulted resource on the effectiveness of reproductive health care interventions in the developing world in the next few years. It is, however, very important to make the information as easy to extract as possible and to make RHL accessible to non-English speaking health workers. This is being addressed by the Cochrane Collaboration, Update Software and collaborating institutions worldwide.

Future challenges for the “Mapping Best Reproductive Health Practices” initiative can be summarized as follows:

- Ensure that the Department’s recommendations for practices and implementation are based on best available evidence.
- Increase the critical mass of scientists in developing countries knowledgeable about and competent in preparing systematic reviews in reproductive health care.
- Achieve comprehensive coverage of all high-priority reproductive health issues with the best available evidence.
- Increase the use of RHL through:
  — Active and efficient dissemination
  — Rigorous evaluation of its quality and presentation
  — Translation into widely spoken languages
  — Incorporation into the health system by promoting its use in the undergraduate and postgraduate edu-
cation and training and among health workers.

REPRODUCTIVE HEALTH DATABASES

The Reproductive Health, Maternal and Newborn Database (RMN) comprises seven autonomous indicator databases that are linked to one central reference database. Data and information relevant to maternal health and safe motherhood, the newborn, and by extension, to reproductive health, are systematically collected and those specific to existing indicator databases are extracted. The RMN databases currently consist of eight distinct components: seven “indicator” databases with actively maintained data and one “reference” database maintained to allow retrieval of further quantitative and qualitative reproductive health information. The seven indicator databases are:

- Maternal mortality
- Coverage of maternity care
- Women’s anaemia
- Unsafe abortion
- Infertility
- Low birth-weight and preterm birth
- Perinatal and neonatal mortality

Estimates of reproductive health indicators are needed to plan interventions, monitor progress and for advocacy purposes. While it is important to plan reproductive health and other interventions in the context of the health status in countries, few countries are equipped to provide data on key process and outcome indicators. The rationale for the indicator databases is therefore primarily to provide source material for WHO estimates of maternal and newborn health indicators. It operates:

- to fill the information gap. The indicator databases bring together data from vital registration, community and hospital studies on both national and subnational levels available from published literature, and a substantial amount of unpublished literature.

- to aggregate incidence data relevant to maternal and newborn health to provide the evidence base for making WHO estimates. The emphasis is on assembling data from developing countries. The methodologies used to make estimates depend on the indicator as well as on the type and quality of data available. Estimates are usually generated intermittently, as meaningful information for evaluation becomes available.

The reproductive health estimates are calculated within the global framework of UN demographic estimates, thereby increasing comparability. It should also be kept in mind that estimates are imprecise substitutes for good health reporting and are precisely what their name connotes: estimates.

Indicator databases

Currently, all databases except the infertility database are updated continuously.

1. Maternal mortality: It lists data on maternal mortality ratio and rates, and percentage of reproductive age mortality due to maternal causes. New maternal mortality estimates for 1995 were calculated in December 1999, indicating approximately 530,000 maternal deaths annually. Checks are currently in progress and it is expected that the new country, regional and global estimates will be jointly published by WHO, UNICEF and UNFPA in 2000.

2. Coverage of maternity care: It lists data for two antenatal care indicators (at least one visit and four or more visits), deliveries in health institutions, skilled attendant at delivery and postpartum care. Some recent developments are:

- Country and global estimates for all above indicators were last released in 1996. The first round of biannual estimates of skilled attendant (for 1998) were calculated and projections made in 1999. Only the Latin American region is expected to reach near full coverage by the year 2005, while other regions, in particular Africa, are lagging behind. The data indicate a high correlation between high maternal mortality and lack of skilled attendant at delivery.

- At the ICPD+5 review, skilled attendant at delivery was identified as the proxy indicator to monitor improvements in maternal mortality.

- The maternity care indicator database contains other useful data extracted from the studies included, such as comparisons of maternity care coverage in rural and urban areas.

3. Unsafe abortion: Unsafe abortion is a sensitive and elusive area, and to be able to capture as much information as possible, it allows for a variety of incidence and mortality ratios and rates.

- Global and regional estimates for the incidence of unsafe abortion and its associated mortality were last released in 1998. The estimates were incorporated in a recent publication by the Alan Guttmacher Institute to show that globally an estimated 45 million abortions occur each year, over 40% of which are estimated to be unsafe, the latter contributing to 13% of maternal deaths. Such collaborations are particularly beneficial to highlight the total context of abortion.

- An update of mortality due to abortion will be carried out in 2000 to take into account the new set of mater-
4. **Perinatal and neonatal mortality**: It lists mortality rates up to one year of age. New country and global perinatal mortality estimates were made. In 1999, 50 perinatal deaths per 1000 births occurred worldwide, which corresponds to 6.7 million deaths, nearly 3 million in the first week after birth and 3.7 million stillbirths. Improvements in perinatal mortality take place at an exceedingly slow pace—only a reduction from 58 per 1000 in 1983 to 53 per 1000 in 1995. The projections for the year 2000 is 49 per 1000 births.

New country and global neonatal mortality estimates were made. There were an estimated 32 deaths per 1000 live births in the four weeks after birth, a total of 4.2 million. This is close to 60% of all deaths that occur in the first year. First-week deaths correspond to two-thirds of neonatal deaths and 40% of infant deaths.

5. **Low-birth-weight and preterm birth**: This database is updated continuously. It lists the weight distributions up to 3000 g, percentage preterm births and preterm birth low-birth-weight infants. Preparations are under way towards making the third global evaluation of data and prepare estimates in the year 2000.

6. **Anaemia in women**: This database is continuously updated. It lists available data on haemoglobin concentrations for pregnant and non-pregnant women. In addition, data on haemoglobin distributions is collected to evaluate the severity of the condition. It also contains a section on serum levels of some essential micronutrients.

   - Country, regional and global estimates have been made. Anaemia, as measured by haemoglobin levels, particularly in pregnant women is severe in many regions in the world. Approximately one in every two pregnant women is estimated to have a haemoglobin level below 110 g/L during all or part of her pregnancy.

7. **Infertility**: This database is maintained passively and no substantial updates are planned because of resource constraints and the relatively low level of priority.

**Reproductive health country profile**

In a separate database, WHO country estimates relevant to reproductive health are presented together with UN demographic estimates, and UNESCO estimates on literacy in a one-page summary, mainly for internal reference and use. This database will be enhanced in the coming year and made available for easy electronic access and print-out.

**Software developments in 1999**

During 1999, an important review and enhancement of the database software took place, including enhancement of several of the indicator databases. The main improvements are listed below.

   - The upgrade and redesign in the Windows/NT environment optimizes data entry and retrieval, offering a robust tool for analysis and review.
   - An expansion in early 2000 to allow multiple active users, which introduces an effective system for data maintenance and specialization.
   - A version for information sharing within WHO will permit any staff member to search and print from the databases. Sharing data over the Internet will also be possible. However, to ensure appropriate use and interpretation of the information in the databases, the Internet site is foreseen to be password protected, limiting access to authorized and competent users.
   - The structure of the database system allows additional relevant indicator databases to link up to the existing system, should this be desired.
   - Another aim of the software development has been to create a generic tool for indicator databases. Its structure has already been used outside the Department and plans are under way for others.

**The reference database**

This database allows retrieval of additional reproductive health information. The source material in the reference database offers a range of options for data analysis and support to ongoing activities of the Department. Information for further study can be retrieved to meet the demand for other reproductive health estimates, including global burden of disease (GBD) updates. Such data may include incidence of caesarean section, ectopic pregnancy, contraceptive method mix, or relate to pregnancy complications, case-fatality and long-term disabilities.

During 1999, an evaluation of the current status and future of reproductive health databases was initiated. The extent of use of the various indicator databases and the reference database, and the options of continuing all or focusing on some of them are being explored. The possibility of bringing a systematic search and quality assessment to be applied to one or two selected highest priority indicator databases is being considered as part of this evaluation.

**DALYS AND REPRODUCTIVE HEALTH**

In 1994, the World Bank, in collaboration with WHO, undertook a study to quantify the global burden of disease (GBD) and injury in human populations. The GBD study
was conducted in response to the need for a clear assessment of the relative magnitude of diseases and injuries, and the proportion of these attributable to major risk factors or socioeconomic determinants. This information was needed for a variety of purposes including the identification of major health problems and their relative magnitude, the recognition of patterns of health problems and the search for explanations of these patterns, the prioritization of health research investments, and along with other information, the allocation of health resources across different health interventions.

The GBD study set out to address three primary goals:

- to infuse information about non-fatal health outcomes into debates on international and national health policies;
- to disentangle epidemiology from advocacy in order to produce consistent assessments of the disease burden; and
- to measure disease and injury burden in a way that can also be used to assess the cost-effectiveness of interventions. The DALY (disability-adjusted life year) was proposed for this purpose.

DALYs are time-based indicators of health outcome—composite measures of the overall burden of disease due to losses from premature death and non-fatal disability. With regard to reproductive health, concern has been expressed regarding the assumptions and value judgements underlying the DALY methodology. With a revision of the GBD study planned for 2000, and the application of DALYs in national burden of disease studies in a number of developing and developed countries, continued debate and refinement of the approach, as well as clear recommendations to better capture the burden of reproductive ill-health are essential.

To address these concerns, the Department started an informal, international consultative process of information sharing and review of the DALY methodology and its use in the GBD exercise. During a first consultation on DALYs and Reproductive Health held in Geneva from 27–28 April 1998, the DALYs approach was critically evaluated and ways of improving the calculations proposed (World Health Organization. DALYs and Reproductive Health: Report of an informal consultation, 27–28 April 1998. WHO/RHT/98.28). Among the many issues identified as requiring further research and evaluation, one emerged as a particular concern, namely, the decision-making process whereby values are assigned to a variety of health states. A second informal consultation, planned for January 2000, is intended to stimulate debate on the values that different people give to different health conditions and to undertake, in a transparent and inclusive manner, the process of calculating disability weights associated with them. Specifically, the objectives are:

- to identify and define, according to a number of dimensions, a broad range of reproductive health conditions appropriate for analysis within the DALY framework;
- to reach a consensus on internationally applicable disability weights for the major conditions identified and on approaches for ascribing disability weights at the local level.

The outcome of the consultation will serve as an input to the GBD 2000 exercise. In addition, the consultation will identify information gaps and research needs that will help prioritize research and development work over the coming years.

**DEVELOPMENT OF NORMS AND TOOLS**

**INTRODUCTION**

The development of norms and tools is an area mostly covered by the technical support component of the Department. Several diverse activities have been conducted in 1999. Indicators of reproductive ill-health is an important area that is closely linked to “evidence” activities. HRP has commissioned case studies in five countries to review issues relating to the measurement of recommended indicators at the country level. In 2000, further work in this area will be undertaken. These activities will have important implications for other related work such as the reproductive health databases.

In 1999, the Department has been involved in an interdepartmental collaborative project entitled “Family and Community Practices”. This activity aims to systematically assess healthy behaviours within communities and to identify effective practices that can promote them.

Another collaborative project has been the development of a manual to address reproductive health problems in refugee situations. This project has been conducted in collaboration with the United Nations High Commissioner for Refugees (UNHCR) and UNFPA.

An important contribution of the Team on Development of Norms and Tools to planning and programming in reproductive health is the development of Integrated management of pregnancy and childbirth (IMPAC) and the Essential care practice guides in the forthcoming years.

**REPRODUCTIVE HEALTH INDICATORS**

Since the International Conference on Population and Development (ICPD) in Cairo, Egypt, 1994, much attention
has been paid to the development of indicators for monitoring reproductive health. A short-list of 15 indicators was generated through an inter-agency consultation, organized by WHO in 1997. These indicators were proposed to monitor globally the progress in achieving goals set in the ICPD Programme of Action for reproductive health.

Most of the efforts to develop indicators have thus far focused on operationalizing the goals established by ICPD. The need for monitoring of individual countries, particularly with regard to their programmatic priorities and the capacity of their existing health information systems, has received rather less attention. For this reason, five case studies of Colombia, France, Iran, Senegal and Zimbabwe were commissioned. The objectives were to review country-level experiences regarding data gathering, programme monitoring, and the changes made in response to the recommendations of ICPD. Another objective was to assess the extent to which indicators at the country level match those recommended for the “core” set by WHO or UNFPA.

The country case studies show that not only do the reporting systems differ, but the operationalization of “reproductive health” varies across countries. The countries also differ in terms of the emphasis placed on particular types of indicators. Major implications emerge for the work on the development of indicators. During 1999, the case studies were revised and a synthesis paper was developed. The case studies will be published in 2000.

GUIDELINES ON REPRODUCTIVE HEALTH IN REFUGEE SETTINGS

Emergency situations can result from the consequences of natural disasters, such as the recent earthquakes in Turkey and floods in Central America. They can also result from the mass movement and re-settlement of people when conflict and displacement adversely affect their physical and economic security and safety.

UNHCR estimates that there are presently over 22 million refugees (internally displaced persons, asylum seekers, returnees and stateless persons) all over the world. About half of these would be female, with the majority in their reproductive years. Any emergency has a profound negative impact on the health of women, men and adolescents. Poverty, loss of livelihood, disruption of services, breakdown of social support systems and acts of violence combine to destroy health. Within any population facing the trauma of natural disasters or conflict and displacement, the social and physical vulnerability of women, particularly pregnant women, increases. Basic services can be disrupted, particularly transportation, food, clean water and sanitation. Pregnant women and adolescent girls may find themselves without the necessary support to cope with pregnancy and childbirth. Families may become separated, and traumatized women may have no practical or emotional support during pregnancy and lactation. Access to health care facilities, medication, equipment and trained personnel is often lacking.

In 1995, UN agencies, NGOs and more than 50 governments attended an Inter-Agency Symposium on Reproductive Health in Refugee Situations. All parties committed themselves to strengthening reproductive health services for refugees. The Department has been a member of the Inter-Agency Working Group on Reproductive Health in Refugee Situations which has supported the development and publication of the Inter-agency field manual on reproductive health in refugee situations. This manual is based on WHO norms and standards and it has been tested by 50 agencies working in refugee situations in 17 countries over a period of two years before being finalized and published this year. The main purpose of this manual is to facilitate discussion and decision making in the planning, implementation, monitoring and evaluation of reproductive health interventions. The main components of reproductive health described in this manual are:

- Minimum initial service package
- Safe motherhood
- Sexual violence
- Sexually transmitted diseases, including HIV/AIDS
- Family planning
- Other reproductive health concerns
- Reproductive health of young people

This Inter-agency field manual addresses technical issues related to reproductive health. To address the mechanics of actually developing and managing reproductive health services in any man-made and/or natural disaster, the Department—in collaboration with the Women’s Health and Development and the new Cluster of Social Change and Mental Health—has built upon the technical norms and guiding principles outlined in the Inter-agency field manual to develop a complementary manual entitled Reproductive health in conflict and displacement: a guide for programme managers. This manual focuses on the managerial and service delivery aspects of reproductive health care in conflict and displacement and is presented in the following five sections.

Section 1 outlines the issues to be considered before responding to reproductive health needs during the different phases of conflict and displacement. It describes the different phases of conflict and displacement; the reproductive health needs that are likely to arise in each phase; and the guiding principles that should govern the provision of reproductive health in these settings.
Section 2 addresses the programmatic issues to be considered during conflict and emergency situations. It provides a brief overview of what is meant by “emergency preparedness” and defines the measures that can be taken to lessen the negative impacts of conflict and displacement on reproductive health, with special consideration being given to the plight of individuals facing armed conflict. The manual defines a core package of reproductive health interventions and describes how these can be adapted and implemented in emergency situations.

Section 3 describes the management tools for the effective assessment of needs, and the implementation, monitoring and evaluation of reproductive health in stabilized refugee and displacement settings as well as protracted low-grade conflict.

Section 4 describes the reproductive health implications of the post-conflict period. It addresses the reproductive health needs during the “return” and re-integration of refugees and displaced communities and the rehabilitation of the health sector in a war-torn country.

Section 5 provides guidance on how to respond to the gender-based and sexual violence that permeates each phase of conflict and displacement. Although prevention and treatment are cross-cutting themes throughout the manual, this section describes in more detail the physical, psychological and social consequences; the importance of a multisectoral response; the implementation of a medical and psychological response; and issues involved in responding to human rights violations.

The next phase of activities for the year 2000 is to support the dissemination, adaptation and use of both of these manuals by developing a training curriculum and training tools for programme managers who will potentially manage reproductive health programmes in each phase of conflict and displacement. The curriculum will be developed in collaboration with a number of institutions. It will be designed to provide managers with the necessary skills, not only in management but also for training others to judge how to meet reproductive health needs in populations facing any phase of conflict and displacement.

HEALTH PROMOTION AND COMMUNITY INVOLVEMENT

Family and community practices

During 1999, the Department has worked in an inter-cluster Working Group for Family and Community Practices, together with the Departments of Child and Adolescent Health, OSD, Women’s Health, and the HIV/AIDS/STIs Initiative. A consensus was reached on how to systematically assess the healthiest behaviours as well as interventions that can promote and support them. The following elements for the framework have been agreed upon as the context in which future work will be conducted:

- Desired health outcomes defined by health indicators
- Desired behaviours (or key practices) that will have the greatest impact on attaining the desired health outcomes
- Existing practices and their link to health outcomes
- Supports and barriers to practices with healthy outcomes
- Effective interventions to strengthen positive practices and/or reduce barriers.

These interventions can be directed at individuals, families, communities and health care providers. They can also be designed to create an enabling environment for people to make healthy choices for the promotion and protection of their health. Interventions to reinforce and change practices need to address prevailing supports and barriers.

The Department has begun a process to identify the above elements related to maternal and newborn health and a document should be ready by July 2000. Additionally, suggestions for service provisions will be included, and links will be drawn to the guidelines and tools being developed for IMPAC and the Essential Care Practice Guides. There are plans to extend this initiative to the areas of family planning and reproductive tract infections in 2000.

Training material on health promotion and IEC in reproductive health

The methodology, called “A Framework for Action Planning in Health Promotion and Education”, was designed to focus health promotion and information, education and communication (IEC) efforts on objectives that could be achievable, and emphasize the need for effective ways to establish and maintain partnerships with others working towards the same objectives. This is a WHO methodology to help policy-makers and programme managers, implementers and evaluators plan action-oriented and participatory health promotion and IEC interventions with measurable outcomes and impact. It promotes an innovative planning process that can be used in many different settings to integrate health promotion and education into existing reproductive health initiatives with no extra programme expenditures. It is based on the premise that advocates for reproductive health initiatives can use an action-planning process to induce collaboration among policy-makers and programme managers; health and education services personnel; and consumers and their families, peers, and community organizations. All these players must become involved and committed in order to have an impact on the reproductive health situation.
of the population. Jointly, these groups can create priorities and action plans that will move forward a reproductive health agenda on national, regional and local levels.

The collaborative relationships resulting from "Framework" activities carried out over the past years have laid the foundation for a larger international partnership that has been maintained through an electronic discussion list, originating in Argentina. The discussion list has enabled countries to share their experiences in applying the Framework within local settings, and create a knowledge base which helped in developing training sessions on the Framework for the XVI World Conference of the International Union for Health Promotion and Education, Paris, France.

People have been trained in 1999 to apply the methodology in Argentina, Chile, Nepal and the USA including Puerto Rico. Training materials were developed in 1999 (a trainers' guide as well as materials for participants), which were field-tested in Nepal. Based on this field test, the materials will be modified and printed in English and possibly in Spanish in 2000. Additionally, it is hoped that some of the people already trained in the use of this methodology will become training focal points for the Framework in their geographical areas and will offer technical assistance to others choosing to apply it.

TECHNICAL SUPPORT TO COUNTRIES

INTRODUCTION

Country support activities were conducted both by HRP and the Technical Support to Countries Team of the Department during 1999. HRP activities focused on the "Strategic Approach to Technology Introduction and Transfer". The details are presented in the report of that follows. The technical support component of the Department conducted a series of activities on the planning and programming aspects of specific reproductive health issues, which are described within the chapters on specific thematic areas. The Department collaborates with and provides support to other UN agencies, NGOs and WHO Regional Offices to assist in planning and programming activities at the country level.

Documents on health promotion and IEC, gender and human resource development were developed in collaboration with UNFPA Country Support Team (CST) advisors and Regional Offices. A number of field visits were carried out at the request of CSTs providing support to UNFPA country projects and programmes. The Department collaborated with UNICEF in their various activities in maternal health and contributed to the “Mother Friendly Initiative” and the “Neonatal Tetanus Elimination Initiative”. In Pakistan, a review of UNICEF activities in reproductive health and planning of future programme activities was conducted together with UNICEF. Technical support to World Bank programme reviews in Pakistan, Morocco and Bangladesh have been provided. The Department is also collaborating with the World Bank on the development of a life cycle approach to improving reproductive health.

The technical support activities of the Department cover a wide range, from capacity building in research to planning and implementing reproductive health programmes. Furthermore, many international agencies and NGOs are active in this field. One challenge for the future is to develop a coherent approach to planning and programming as well as partnerships with major players in this field. To this end, the Team on Technical Support to Countries has been organized to facilitate, among other things, the development of national reproductive health plans and programmes. This work will include the introduction of reproductive health technologies in collaboration with WHO Regional and Country Offices, governments and other partners. It will also assist in the adaptation and adoption of norms and standards essential for enhancing reproductive health care delivery.

THE STRATEGIC APPROACH TO THE INTRODUCTION OF FERTILITY REGULATION AND OTHER REPRODUCTIVE HEALTH TECHNOLOGIES

HRP has been developing, testing and refining a "strategic approach" to the introduction of fertility regulation and other reproductive health technologies with the following objectives:

- to improve the range of appropriate methods of fertility regulation and other reproductive health technologies available to individuals and couples, based on the identification of users’ needs and service delivery capabilities;
- to improve the quality of care in provision of reproductive health services through the introductory process;
- to create awareness of the need, and develop national capacity for a systematic approach to the introduction of new or underused technologies;
- to ensure that incorporation of the needs and perspectives of the potential clients, as well as consideration of the capacities of the service delivery system become integral to the decision-making process for consideration of options to improve the quality of reproductive health services.

The “strategic approach” takes an expanded view of introduction. It asks not only whether there is a need to introduce new or underutilized fertility regulation methods and/or other reproductive health programme activities, but
also whether there is a need to withdraw methods that are inappropriate or unsafe, and how the overall quality of the services can be improved. The approach has three stages.

Stage I is an assessment from a “systems” perspective of: (i) the contraceptive method mix, other options for fertility regulation and potentially, other reproductive health interventions; (ii) the extent of the coverage, quality of care and capabilities of the service delivery system; and (iii) the needs and perspectives of current and potential users. With its systems perspective, it also focuses on the interactions that exist between users of services, available technologies and the service delivery system. The assessments are designed to assist programmes in deciding on whether there is a need to introduce one or more new methods, to expand the use of existing and perhaps underutilized methods, or to withdraw any inappropriate methods, and on how the overall quality of care could be improved. The assessments use a qualitative methodology and a participatory approach, involving programme managers, service providers, researchers, and others interested in improving reproductive health, including women’s and youth organizations and other NGOs.

The principal focus of the Stage I assessments undertaken up to the end of 1996 was on contraceptive introduction, although this was always addressed in a reproductive health context. Other reproductive health issues received varying degrees of in-depth attention. Simmons et al. *Studies in family planning*, 1997, 28:79-94 have published a summary of the strategic approach to contraceptive introduction and the Component’s activities through the end of 1996. In anticipation of the broadening of HRP’s research agenda beyond fertility regulation, work began to broaden also the use of the approach to other reproductive health issues. This has included utilizing the process and framework of the strategic assessment to focus on other specific reproductive health issues, as well as to address simultaneously a broad range of issues. Since 1997, assessments have focused on questions other than contraceptive introduction, including abortion-related issues in Viet Nam and broader areas of reproductive health in Ethiopia, Myanmar and most recently in the Lao People’s Democratic Republic. This adaptation of the strategic approach and its methodology to address a broader range of reproductive health issues is discussed later.

A variety of recommendations concerning reproductive health policies, the strengthening of the quality of care in service delivery, service delivery infrastructure and management of programmes and activities emerge from the Stage I “strategic assessment”. Stage II research is a means of testing, on a limited scale, the recommendations concerning the introduction of technologies or other interventions to improve the quality of care in service delivery. A variety of research methodologies may be utilized, but the focus remains on clients’ needs and perspectives; the quality of care, including both managerial and technical aspects, of the services; as well as the interaction between providers, clients and the technologies or services. Stage II research continues to involve, in a participatory manner, programme managers and other relevant groups in the implementation and evaluation of the research activities, as well as in the dissemination of the research findings.

In 1999, Stage II introductory research projects were completed in South Africa and were in progress in Bolivia, Myanmar and Zambia.

The purpose of Stage III is to disseminate and apply the research findings generated in the Stage II action research to policy development and planning for wider implementation. Based on an evaluation of the Stage II research experience and findings, decisions are made as to whether it is appropriate to expand method introduction and/or replicate other tested interventions to strengthen quality of care on a larger scale. A strategic plan to support expansion of selected activities is developed which can include implementation of provider training, establishing other necessary infrastructure for services, provision of IEC materials, support for various necessary managerial adaptations, upgrading logistics systems, and organizing sources of supply.

An evaluation of the Stage III project in Brazil commenced in 1999 and a Stage III project in Viet Nam began implementation. It is anticipated that, during 2000, Stage III activities will arise from the Stage II projects which have been ongoing in Bolivia, South Africa and Zambia.

**ONGOING ACTIVITIES IN ASIA DURING 1999**

**Viet Nam**

The Stage I assessment of family planning services was conducted in late 1994. A Stage II study designed to assist the Government of Viet Nam to develop a strategy for introducing depot medroxyprogesterone acetate (DMPA), while at the same time strengthening the quality of family planning and reproductive health service delivery, began in mid-1996 and was completed in 1998.

Initially, the project developed training curricula and materials for providers, improved family planning IEC materials, and trained providers and community level workers, emphasizing counselling and provision of balanced information, in addition to technical information on all available contraceptive methods. The project also worked on approaches to strengthen management and particularly supervision of services, including the
development of supervision tools.

The research components of the project examined the introduction of DMPA, as well as the quality of family planning services from multiple perspectives. Users’ perspectives were examined using both quantitative and qualitative methods and service delivery research, including observations of service delivery. In-depth interviews with providers investigated the technical and managerial adaptations necessary to provide improved quality of care in the service delivery of DMPA and all other methods.

Following the mid-project workshop in 1997, the National Committee for Population and Family Planning (NCPFP) began to expand service delivery of DMPA to selected districts in eight additional provinces. However, implementation was based upon the experience gained during the Stage II project and used, (with minor adaptations) the training curricula IEC materials and other supporting materials developed by the project.

Stage II activities formally concluded at the end of 1998 with the final national “Lessons Learnt” workshop. The Stage II research showed that introduction of DMPA can enhance choices for women in Viet Nam and that good counselling and follow-up care increases the continuation rates for DMPA, if quality of care for all methods is improved. Furthermore, the study demonstrated that the introduction of a new method can be used as an opportunity to improve quality of care for all methods.

During early 1999, team members worked on the development and finalization of a proposal for a Stage III project. The objectives of the Stage III project are to implement a strategy for wider DMPA introduction while strengthening the health system to improve quality of care for all methods based on the research findings from Stage II research. The project is packaging approaches and findings of the Stage II project as a “tool kit” which includes: (i) an overview of the strategy for introduction of DMPA; (ii) training modules emphasizing quality of care for all contraceptive methods; (iii) refined IEC materials based on the community feedback on the previous versions; and (iv) revisions to the Management and Information System to support provision of DMPA and other logistics requirements. The project is providing orientation training for provincial level managers and senior Maternal and Child Health and Family Planning (MCH/FP) providers on the strategy and use of the tool kit, emphasizing DMPA introduction as an opportunity to improve quality of care for all contraceptive methods. It is also providing training for local researchers in users’ perspectives and service delivery research related to contraceptive introduction.

Wider introduction of DMPA is being implemented by programme managers utilizing the tool kit in 34 of the 53 provinces in Viet Nam where Government or donor support for strengthening health service delivery is already available. The Stage III project will document the process of dissemination of results and of adaptations from the introductory research to wider introduction and will identify strengths and weaknesses from the wider Government introduction experience and its impact on improving quality of care. As in Stage II, the Stage III project is being undertaken as a collaborative effort between the Ministry of Health, the NCPFP and the Viet Nam Women’s Union. It is jointly funded, primarily by the German Gesellschaft für Technische Zusammenarbeit (GTZ) and UNFPA, with HRP providing technical support to the activities through the International Council on Management of Population Programmes (ICOMP).

Myanmar

An assessment of the contraceptive method mix and the need for contraceptive introduction was conducted in late 1996. The Stage II research project, entitled “A Township Model for Quality of Care in Reproductive Health Services in Myanmar” began in late 1998 and will continue through the end of 2000. Based on the recommendations of the initial assessment, it focuses on developing a district level model for improving the quality of care of family planning and other reproductive health services. The major objectives of the project include: improving the public and private sector provision of available hormonal contraceptives, including both combined oral contraceptives and injectable contraceptives; discouraging the use of available hormonal contraceptives which are of low efficacy or unproven safety, including monthly oral pills, high-dose combined oral contraceptives and several available monthly injectable preparations; undertaking a controlled reintroduction of the intrauterine device (IUD); streamlining the process of obtaining tubal ligation for women desiring sterilization; promoting the concept of dual protection against pregnancy and sexually transmitted infections; strengthening the management of reproductive tract infections (RTIs) by both public and private providers; increasing male involvement in reproductive health; and increasing community involvement and advocacy for birth spacing and reproductive health more generally.

Major activities of the project include the improvement of existing and the development of new IEC materials and activities; training for public-sector basic health staff, and for private general practitioners, private drug shop staff, township and community level members of a national NGO, the Myanmar Maternal and Child Welfare Association (MCWA); a community advocacy component; and efforts to strengthen township level and health centre staff’s management capabilities related to planning, supervision and logistics. The project is being implemented in two
districts with differing geographic conditions, ethnic composition and reproductive health needs.

Research and evaluation activities include rapid qualitative assessments, modified “situation analyses” including facility inventories and observations of service delivery conducted at the beginning, middle and end of the project, complemented by quantitative surveys of women at the beginning and near the end of the project. The surveys collect data concerning women’s perspectives on and patterns of use of contraceptive methods, their knowledge and use of dual protection, men’s involvement in reproductive health issues, women’s health-care seeking behaviour focusing on both contraception and RTIs, and other related issues including abortion in the community. Qualitative user perspective research will address similar reproductive health issues, as well as include additional emphasis on client and community perspectives on the quality of reproductive health services, counselling and the new IEC materials developed by the project.

The project experienced considerable delays in commencing implementation, but activities are now progressing. The baseline provider and community-based rapid assessments and modified situation analyses at service delivery sites were completed in early 1999, with the results used in the development of the intervention activities. Data collection for the survey of women in the two districts was conducted in mid-1999 and data are currently being analysed.

A revised participatory training curriculum, which emphasizes client counselling, particularly on the full range of contraceptive methods and RTIs, has been developed for the training of district Basic Health Staff (BHS include midwives, nurses, male health assistants and assistant midwives). Training of trainers has commenced and training of staff will take place in January 2000. The technical service delivery manual on reproductive health for BHS has also been updated and revised. The training curriculum has been adapted for shorter training courses planned for private practitioners and private drug store staff in the districts. The components of the project that focus on community advocacy activities are planned to commence after the training of providers has been completed.

A major focus of preparatory activities has been the revision and development of IEC materials. Working with the staff of the Government Department of Health/Health Education, the project has updated and revised existing pamphlets on individual contraceptive methods, including oral contraceptives, injectables, IUDs and condoms and has developed a new pamphlet on men’s role in reproductive health, as well as a pamphlet and poster which provide information about the entire range of contraceptive methods. Each pamphlet now includes a message about dual protection. The pamphlets are also being translated into Shan and Pa’o, ethnic minority languages which are spoken widely in eastern Myanmar. This is the first time that IEC materials have been available in these languages. A complementary flipchart for use by BHS for client education and counselling has also been revised and is being reprinted.

In addition to pamphlets and posters, the project has developed a video script on contraceptive methods which is being submitted for approval to the Ministry of Health (MOH), the National Censor Board and the Ministry of Information. If approved, this video will be produced in a ten-minute version for the national television health education time slot while a slightly longer version will be distributed to the widely popular village video parlours and at health clinics.

As in the original assessment, the Stage II project is being conducted by a team that includes programme managers, reproductive health researchers from several different departments of the MOH and representatives from the MCWA. Intensive technical support for this project is being provided by staff from the Population Council Bangkok Office under contract to HRP.

In late 1998, the MOH requested support from UNFPA to undertake a more general assessment of reproductive health needs, utilizing the WHO strategic approach with technical assistance from the ICOMP, The Population Council Bangkok Office and the Department Secretariat. This reproductive health needs assessment built on the findings and recommendations of the earlier assessment, but gave greater attention to issues of maternal health, RTIs, unsafe abortion and adolescent health issues. The report included recommendations for policy change, programme development and research; and laid out an approach for operationalizing an essential service package for the national reproductive health programme. The report is currently being utilized by UNFPA as an input to the development of their next country programme. In addition, in 1999, The Population Council Bangkok office obtained a grant of over US$ 4 00 000 from the Packard Foundation to assist the MOH and NGOs in Myanmar to focus on research and programme development activities identified in the assessment report, including activities addressing the epidemiology and management of RTIs, unsafe abortion and activities to help in meeting adolescent health needs.

Lao People’s Democratic Republic (Lao PDR)

Following initial visits to discuss the MOH’s interest in conducting an assessment of the contraceptive method mix, assistance was provided to the MCH Institute to implement a more comprehensive assessment of reproductive health needs. Following the compilation of a
background paper reviewing the reproductive health situation in Lao PDR and a national planning workshop, the field work for the strategic assessment was conducted in March and April 1999. After completion of the draft report, the findings and recommendations of the assessment were discussed at a national dissemination workshop in June.

The assessment focused on issues related to contraception, maternal health, RTIs including HIV, and adolescent reproductive health needs. It documented a general reproductive health situation characterized by a high level of need of individuals and communities, in part reflecting a lack of availability of adequate reproductive health services. For example, in many locations, despite high levels of interest and demand for contraception, services and/or a range of methods are often unavailable and high rates of method discontinuation result from poor management of side-effects and inadequate information provided to clients. As a result, unsafe abortion appears common and contributes to the very high rates of maternal mortality. This high mortality also reflects extremely low rates of utilization of maternal health services, resulting from both a lack of availability of adequate prenatal, delivery and postpartum care in many districts, as well as a low awareness on the part of the community of the potential dangers associated with pregnancy and childbirth. The assessment found that most community members and even frontline health providers lacked critical information concerning RTIs, despite a situation where behavioural patterns of many men are likely to contribute to increased risk for RTIs including HIV infection. Access to appropriate treatment for symptomatic infection was seriously limited in many areas and, where available, was highly variable in content and quality. In the Lao PDR, adolescents often marry and commence childbearing, yet the team found that there was little awareness among community members or providers of the different reproductive health needs of adolescents. Adolescents were found to have little access to information or services including condoms or other contraception, and unwanted pregnancy and RTIs among unmarried youth were reported to be growing problems.

The assessment report made a variety of specific recommendations concerning policy, programme and research needs to assist in developing comprehensive reproductive health policies, strengthening existing reproductive health programmes and moving towards integrated quality reproductive health services to address the problems and needs identified.

A proposal is currently being developed for a Stage II action research project addressing some of the recommendations of the assessment. The activities are expected to focus on strengthening the availability and utilization of essential obstetric care at the district and community levels, as well as testing approaches to strengthening outreach by health staff from the district level to support health centre and community level reproductive health services. This will complement the new UNFPA project activities that will emphasize community level training for village health workers in reproductive health and develop a community-based system of contraceptive distribution throughout the country. The planned Stage II project is expected to be jointly funded by UNFPA, Vientianne and the Department. Technical assistance to activities in the Lao PDR have been provided by The Population Council Bangkok Office, ICOMP, Family Care International, New York, NY, USA, and the Department.

China

Officials from the Department of Science and Technology of the State Family Planning Commission (SFPC) had previously expressed interest in utilizing the Department’s strategic approach to contraceptive introduction to address the issue of introduction of IUD technologies in the national family planning programme. In October 1998, HRP organized a one-week workshop on the strategic approach in Chong Qing. A proposal for a strategic assessment was subsequently submitted by the IUD Introduction Working Group of the SFPC and, following revisions, has been approved by the Scientific Review Committee of the Component. It is anticipated that the assessment will be conducted in the second quarter of 2000, following the preparation of a background paper and the conducting of a planning workshop.

Indonesia

The Department’s key role as a technical resource to the Consortium on Emergency Contraception is discussed elsewhere in this report. One aspect of this work has been technical support for the research and evaluation components of the Consortium’s emergency contraception introductory efforts in Indonesia. Following a baseline assessment in 1997, the local branch of Pathfinder International began implementing introductory activities in 12 Indonesia Planned Parenthood Association (IPPA) clinics in Java. However, due to the slow uptake of emergency contraception in these clinics, ICOMP staff providing technical assistance to the activities on behalf of WHO, together with staff from the Program for Appropriate Technology in Health (PATH) Indonesia, have expanded introductory efforts during 1999 to a variety of other service delivery channels. This has included involving private midwives affiliated with the Indonesian Midwives Association in central Java and Bali, other NGO clinics in Jakarta, Central and East Java, including the network of health facilities run by a large, prominent Islamic organization, and public sector providers in Jakarta health centres. Efforts to facilitate the registration of Postinor-2...
have also been actively pursued.

Planning and implementation of an evaluation to review the Indonesian experience and identify future courses of action for the introduction of emergency contraception in Indonesia began in mid-1999. The evaluation has six primary components which are: (i) evaluation of the process of introduction; (ii) review of activities carried out and outputs achieved; (iii) assessment of service delivery; (iv) assessment of client perspectives and behaviours; (v) assessment of the programme and policy environment; and (vi) review of the registration process of Postinor-2 and of the efforts to promote its wider availability. In addition to a review of project progress reports and provider screening forms and other records, the evaluation will utilize in-depth interviews with clinic managers, providers who have received formal training through project activities, as well as their colleagues who have not been formally trained; interviews with users of emergency contraception; focus group discussions with non-users, including youth and men; and observations of the quality of care of service delivery through the use of “mystery clients”. Data collection will take place between December 1999 and February 2000.

The evaluation is being implemented by ICOMP Indonesia and PATH Indonesia staff, with technical support from ICOMP and the Secretariat. Funding for the evaluation field work is being provided by the Packard Foundation through PATH.

ONGOING ACTIVITIES IN AFRICA
DURING 1999

South Africa

The Stage II project entitled “Expanding Contraceptive Choice” began in late 1997, based on the results of the earlier strategic assessment. In addition to improving the quality of care in the provision of available contraceptives, the project is expanding choice through the introduction of female condoms and emergency contraception, the re-introduction of male condoms for both contraception and the prevention of sexually transmitted infections (STIs), including HIV transmission and the development of an improved referral mechanism for sterilization services. The project has been implemented by the Reproductive Health Research Unit (RHRU) of Chris Hani-Baragwanath Hospital in Soweto, Johannesburg, in collaboration with the Ministry of Health.

Activities are being undertaken in 16 clinics in three provinces. The project began with baseline studies at the intervention sites, followed by the development of a range of IEC materials, including pamphlets, posters, and a flip chart for use by providers to counsel clients. Staff at these sites received training in the provision of contraceptives and counselling. In addition, sites implemented COPE, a process for self-diagnosis and quality improvement in family planning services, developed by AVSC International.

In early 1998, the project developed messages and materials to support community education campaigns, which were conducted prior to the actual introduction of the female condom and emergency contraception. Service provision has been ongoing, with data for a mid-term evaluation collected in late 1998. This included information on users’ and providers’ perspectives on family planning methods and services, as well as observations of client–provider interactions. Analysis of the data in 1999 revealed that although many improvements in the organization of services had been achieved, frequent staff turnover often resulted in some providers not having adequate knowledge about contraceptive methods. Many clients were not being provided with adequate information about the range of available contraceptive methods, and particularly about the importance of dual protection strategies and the availability of barrier methods and emergency contraception. It was noted that there was a need for further policy and technical guidelines and protocols on reproductive health services.

Based on these findings, discussions were initiated with provincial health staff to decrease staff rotations, and the development of national policy and technical guidelines, with assistance from the Department, was undertaken. A package for training in reproductive health for health staff was developed and staff at the study sites received refresher training. In addition, checklists were developed to assist providers in ensuring that clients receive adequate information about contraceptive methods are appropriately screened prior to receiving methods, and are given other necessary information on reproductive health issues including prevention and care of STIs and HIV/AIDS. Discussions have also been held with responsible individuals to utilize the training materials developed to modify the basic training curriculae of midwives and nurses, so that barrier methods, emergency contraception, the concept of dual protection, manual vacuum aspiration (MVA) and other reproductive health issues are included in basic training. In addition, it is planned to make these curriculae available as a continuing education package for which midwives and nurses can get accreditation.

The Stage II project will end in early 2000 and a final report is in preparation, prior to implementation of national and provincial dissemination workshops. A formal evaluation of the project will be conducted by staff from the Population Council, Nairobi, Kenya, with funding through their US Agency for International Development (USAID)-supported “Expanding Contraceptive Choice” project. However, the RHRU and the MOH have already
begun planning the expansion and replication of activities to all provinces in the country. This will be centered around the dissemination of the newly developed national family planning policy and service delivery guidelines. The RHRU will provide technical support to the provinces to implement training and other interventions and will utilize IEC materials and tools developed by the Stage II project. These activities will be supported by the Kaiser Foundation and the United Kingdom Department for International Development (DFID).

As implementation of the Stage II activities was getting under way, the seriousness of the HIV/AIDS situation in South Africa, coupled with the provision by DFID of over one million female condoms, led the Department of Health, the National Barrier Methods Task Force and the RHRU, to propose an expansion of the efforts to introduce the female condom throughout the country. The resulting National Female Condom Introduction Strategy project has been implemented in 20 sites, including 18 family planning clinics and two sex-worker clinics in eight provinces. In addition, 11 community-based distribution outlets of the Planned Parenthood Association of South Africa have been participating. Although intended to support the introduction of both the female condom and emergency contraception, in practice, the project has focused on the introduction of the female condom, as purchase of emergency contraceptives was left to the responsibility of each province and as a result, in a number of sites, emergency contraceptives are not available.

With financial support from HRP, the RHRU conducted baseline assessments in all the sites, trained seven providers per province in three-day regional training workshops, provided IEC materials to participating sites and has been providing supervision to the provincial coordinators, as well as to the project sites. The project also involves collaboration with Family Health International (FHI), Nairobi, Kenya, which is supporting the research components of the project. The team has developed monitoring forms for female condom users, the principal investigator and staff of the RHRU; and individual clinics. As of mid-1999, the participating family planning clinics had reported approximately 4650 visits in which female condoms were provided, of which about 86% have been first visits and 14% or about 650 have been by repeat users. Six clinics had had less than 100 visits in which female condoms had been provided, eight clinics have had between 100 and 500 and three clinics had had more than 500 visits. RHRU staff attribute this to differences in providers’ attitudes towards female condoms and to the fact that rapid turnover of staff has limited the number of trained providers at the study sites. As each province selected the sites for inclusion in the study, not all providers had interest in the project and some have not been supportive of the provision of female condoms and/or emergency contraception.

Providers report that most users of female condoms are women who are using them primarily for protection from STIs/HIV, while using a hormonal method for contraception. About 10% clients are reported to be using the female condom for dual protection. Outreach to local communities has been identified by project staff as a key element of success in promoting use of the female condom and barrier methods. Some sites have engaged their communities by providing information and education to potential clients through youth clubs, church programmes and other community channels.

In an effort to reduce the relatively high cost of the female condom to users and because it has been documented in a number of countries that women are washing and reusing them, the Department, in conjunction with UNAIDS, has continued to support the RHRU, to undertake a series of studies on the feasibility and safety of reuse of the female condom.

In October 1999, a meeting was held at the RHRU to discuss the preliminary research results and other issues relating to the safety and feasibility of reuse of the female condom. This meeting was attended by staff of FHI who are involved in similar research; a representative of the Female Health Company, the manufacturers of the female condom; the principal investigator and staff of the RHRU; responsible staff from UNAIDS Headquarters and the Regional Office and from the HRP Secretariat.

Further analysis of the data is ongoing, but the following points summarize the results and conclusions drawn by the participants in the meeting. As noted above, reuse of the female condom by some women has been documented in a number of countries. In a small study conducted by the RHRU in a peri-urban setting, the concept of washing and reusing the female condom was found to be acceptable to the majority of respondents. Water (not necessarily running), bar soap and liquid household detergent were available to nearly all respondents, as was sunflower oil for relubricating a washed condom before reuse.
In studies of structural integrity coordinated by the RHRU, both in vitro testing in up to ten cycles of washing and in vivo testing of up to eight cycles of washing and reuse showed that despite some changes in the physical properties of the condoms, they remained within Food and Drug Authority (FDA) standards on the water leak, air burst and tensile seam strength tests. However, in both in vivo and in vitro tests, a few small holes were noted which were thought to occur during the process of washing of the condoms. The frequency of holes appeared to be highest in the initial and later cycles of washes and reuse, although the relatively small number of condoms tested in each cycle (50) preclude drawing firm conclusions about the relationship between these holes and the frequency of reuse. Use of chlorine bleach to disinfect the condoms appeared to lead to increased physical deterioration. Similar results were found after single wash and reuse in the FHI study. Intact, rewashed condoms remain impermeable to HIV virus. It was recommended that a small study be conducted to assess the ability of users to detect small holes or tears through visual examination.

Studies of microbial retention on the female condoms following use and washing were conducted in vitro and in vivo. Testing demonstrated that washing of the female condom in cold water with either soap or household liquid detergent removes both inoculated pathogens and lactobacillus in vitro, and STI organisms and vaginal flora in in vivo tests. Handling of female condoms, whether unused or those that have been washed and reused for up to eight cycles, results in microbial contamination with common skin flora and environmental microbial contaminants which can be cultured from the device. These were considered to pose no risk to women or men if the washed condoms were reused. Similar results were obtained when new male condoms were handled and then cultured. Further testing for post-wash retention of protozoan cysts was recommended.

With regard to safety of reuse of the condoms, no adverse events or effects were reported with up to eight cycles of washing and reuse. FHI is commencing a study to examine safety through colposcopic examination of women reusing the condom five times over a period of 10 days (in comparison with a control group using new female condoms five times in 10 days).

It was decided to pursue the following next steps. First, the currently available data and tentative conclusions will be reviewed by additional experts in FHI, South Africa, RHR/WHO and UNAIDS. Input from experts on the physical properties of polyurethane is also being sought. The FHI and RHRU investigators will finalize their respective reports by early 2000. One or more outside experts will be commissioned to review the data and conclusions from the two studies, as well as any other relevant literature, and prepare a technical briefing document on the feasibility and safety of multiple washing and reuse of the female condom. This document will form the basis of a technical consultation on the topic to be sponsored by UNAIDS and WHO and held in Geneva in May/June 2000. The outcomes of this consultation are expected to include a policy statement on the issue of reuse of the female condom, as well as practical guidelines for users on the safe washing and reuse of the device. Policy recommendations emerging from this consultation will be presented at the International Conference on HIV/AIDS to be held in Durban, South Africa in July 2000.

Zambia

In late 1996, a Stage II study was launched to enhance contraceptive choice and quality of care in Zambia. The study is being implemented by the Central Board of Health and CARE International, Zambia. After reviewing lessons learned from experience in strengthening service delivery and introducing new contraceptive methods at urban health facilities, a package of training, IEC and other technical support materials were refined and then utilized for training and service delivery in 11 rural health centres located in three districts in the rural Copperbelt region of Zambia.

Following baseline situation analyses at the centres, the project has supported broadening of method choice by introducing DMPA and emergency contraception and by training providers in the provision of all available methods. Referral mechanisms for methods not available at every health centre have been developed, field-based training for IUD insertion has been implemented and distance learning tools have been developed. The project has also successfully mobilized local communities to play an active role in the delivery and management of reproductive health services.

During 1999, the project supported a training course for health care providers in the syndromic management of STIs and has begun to produce and distribute a series of short newsletters for health providers. The first two issues focused on community outreach and training of providers in the context of high staff turnover. Future issues will address injectable contraception in a high STI context, injectable contraception and return to fertility, as well as other technical and programmatic issues in the field of reproductive health. The project has also continued to play an important role in efforts by the Zambia Central Board of Health (CBOH) and donor community to seek national regulatory approval of DMPA.

As the intervention phase completes its third and final year, the study’s implementing agencies are documenting the results and impact of the project and refining the strategies, tools, and action plans needed to replicate the strategy on a national scale. This will require that the intervention strategies change to reflect changes in the
economic and political environment and that effective mechanisms are promoted to enhance local demand for the interventions and quality of care.

Although the project review is ongoing, preliminary results reveal that the study has expanded the availability and quality of family planning services. They document substantial increases in the number of new contraceptive users; and the widespread acceptance of new contraceptive methods, particularly injectables. Following the beginning of the intervention phase, the average number of new acceptors per quarter has more than doubled in intervention sites.

In addition to increased utilization levels, the method mix has changed dramatically. Prior to the study, oral contraceptives and condoms accounted for almost 90% of all new acceptors. A year later, that percentage had dropped significantly as the percentage of injectable users more than tripled from 9% to over 30%. Continuation rates among users of injectables have been high, suggesting improvements in the quality of client counselling and the management of side-effects. At the smaller health centres, where outreach programmes, community involvement, and provider counselling of clients have not been especially strong, one-year continuation rates have remained as high as 90%. Early in the study, concerns were raised that the introduction of DMPA might have a negative effect on the utilization of other contraceptives, particularly condoms. However, this has not been the case as condom use has remained fairly constant at 30% of the method mix, while the percentage of new oral contraceptive acceptors (which initially accounted for over two-thirds of method use) has declined.

Overall, community members and health care providers report that the quality health care services has improved dramatically during the project. Communication between the neighbourhood in health committees and District Health Management Teams has expanded as a result of more frequent meetings and broader dissemination of information. Many providers also express greater pride in the quality of their services, and report not only providing a wider range of family planning methods with greater technical competence, but also having an increased number of male clients.

A second set of Stage II activities in Zambia involves a series of research studies on the introduction of emergency contraception, conducted by investigators at Lusaka’s University Teaching Hospital. Following training for over 80 providers in more than 21 health care facilities across Lusaka and the rural Copperbelt, the investigators collected service statistics and data from surveys, in-depth interviews and focus group discussions with both potential and actual users of emergency contraception services. This led to two further operations research studies to test strategies for improving the quality of emergency contraception services.

The first study compared the effectiveness of prophylactic distribution of PC-4, the Yuzpe method product already registered and available in Zambia, with the provision of pre-printed prescriptions. Providing emergency contraception pills to women in advance improved access and reduced the time gap between unprotected intercourse and the taking of emergency contraception. Eighty per cent of the women who received the pills ahead of time took their first emergency contraception dose within 24 hours of intercourse, as compared to only 40% of those women using emergency contraception who had received the printed prescription. The women given emergency contraception in advance were over three times more likely to use it. Although poor patterns of routine contraceptive use among many of the study participants suggested that some of the frequent use of emergency contraception had little to do with prophylactic provision, it was clear from interviews and focus group discussions that advance provision of emergency contraceptions sometimes changed the context within which contraceptive decisions were made. In some cases, it enhanced men’s or women’s ability to negotiate condom use, while in others it made it easier to abandon routine methods such as the condom in favour of emergency contraception. Prophylactic provision seemed to draw increased attention to the perceived inconveniences of other hormonal methods—particularly routine OC, and in some of these cases, led to non-use of routine contraception.

The second study was designed to provide experience in Zambia with the use of Postinor-2 (levonorgestrel 750 µg x 2 tablets). The study demonstrated that as expected, the use of Postinor-2 greatly reduced the level of nausea and vomiting as compared to PC-4. However, the study found that both products were used at similar rates, and users did not differ in their subsequent decisions to adopt a routine family planning method or in their choice of the method itself. From the service delivery perspective, there were few if any differences, other than the fact that in the context of what are sometimes poorly functioning logistics systems, it was noted that the combined oral regimen (Yuzpe regimen) could be substituted for by cutting up regular packages of contraceptives.

An important finding of the initial work was the reluctance of young women to obtain emergency contraception from traditional service delivery outlets. In late 1999, a third operations research intervention was launched to test the feasibility of and youths’ preferences for alternative sources of emergency contraception information and services. The study is training peer counsellors, existing community-based distribution workers, pharmacists and community sales agents to provide young
women with information on emergency contraception, as well as, in most cases, emergency contraception pills. The project will compare the effectiveness of these different providers in terms of the both the quantity and quality of services provided.

Ethiopia

A Stage I assessment was undertaken in Ethiopia in May 1997 to assist the MOH in identifying reproductive health needs, to prepare for the UNFPA Programme Review and Strategy Development exercise and develop a reproductive health research agenda. After the dissemination workshop in August 1998, the final assessment report was completed and planning for Stage II research began in early 1999, but has experienced delays due to regional conflict. The MOH has recently requested technical assistance from the Department and The Population Council, Nairobi, Kenya, in implementation of the reproductive health research component of its new UNFPA country programme. It is anticipated that the Stage II research will be undertaken in collaboration with the UNFPA and the FRONTIERS Project, financed by USAID.

ONGOING ACTIVITIES IN LATIN AMERICA DURING 1999

Bolivia

A Stage II study intended to strengthen family planning and related reproductive health service delivery, while simultaneously introducing DMPA and Cyclofem, was initiated in the Departments of La Paz and Santa Cruz, Bolivia in 1997. After initial baseline diagnoses in the seven study clinics, a series of interventions with special emphasis on training, introduction of injectable contraceptives, and development of appropriate record-keeping systems and monitoring were introduced. In each Department, a project executive committee has been instituted with participation from health authorities, service providers and community groups. In order to improve relationships between clinics and the community, a series of “community dialogues” have been implemented which engage providers, managers and local people in discussions about community health issues and community concerns.

Throughout the project, continuing political and administrative uncertainties have resulted in extensive delays and difficulties in implementation of project activities. Frequent replacement of staff at all levels has required reorienting several new principal investigators and retraining of staff in the participating clinics. However, the continued efforts of the project coordinator and medical director have enabled the project to make significant achievements, particularly in La Paz. Here the participatory nature of the project executive committee has been recognized as a strength of the project and the committee has assumed a stronger role in guiding health services, independent of project activities. The community dialogues have also contributed to greatly increased community interest and utilization of services and, taken together, are considered by community representatives to have been instrumental in improving the quality of services provided. Family planning services have become more accessible and the number of new acceptors is dramatically higher in participating health centres as compared to those not involved in the project. The more comprehensive reproductive health approach promoted by the project is reported to have also resulted in higher levels of provision of other reproductive health services. Another success has been the new management information system which has improved data collection and allowed for better monitoring of services and planning of supplies. The MOH is currently preparing for the expansion of this system to other areas.

The project has introduced DMPA and Cyclofem in a context of informed choice in the participating health centres. Although initial acceptance of DMPA has been considerable, the project has documented substantial rates of discontinuation. This is thought to be related to continuing inadequacies in the IEC and counseling provided to DMPA acceptors, as well as considerable resistance on the part of providers to DMPA. This experience is critical as the Bolivian MOH, with support from DFID and the World Bank, is currently planning the process of introducing DMPA on a national scale. This has created an opportunity to feed lessons from the project experience into the national introduction process. The project coordinator has become a key link between departments involved in the process. The MOH has adopted the injectable contraceptive service protocols and standards, and the injectable training curriculum developed by the project as the national standards. Acceptance of Cyclofem has been more limited, resulting to a great extent from problems of availability.

Although the Stage II project is officially coming to an end, activities are expected to continue with remaining funds yet to be released by the MOH, as well as through funds from other sources. Despite the success of the community dialogues, project staff thought that increased efforts to provide IEC directly to communities would substantially increase utilization of services. They have developed a proposal for further operations research to test the effect of adding an intensive community IEC component in communities served by two of the project health centres, as compared to two “control” communities also served by project centres. The USAID-supported FRONTIERS project has agreed to fund this supplementary study by providing US$ 75 000 over an 18-month period.

In 2000 HRP will continue to work with those involved
with nationwide introduction of injectables, so as to ensure that this takes place within a broader context of improving quality of care and a philosophy of reproductive health. The MOH and DFID have expressed interest in continued involvement of the project’s technical support team of Campinas Research Centre for the Control of Maternal and Childhood Diseases (CEMICAMP), the Population Council Campinas Office in Brazil and the University of Michigan, Ann Arbor, MI, USA, in supporting the broader national introduction of injectables, and have requested assistance in developing a proposal for the national expansion.

Brazil

Brazil is the first country where the use of the strategic approach has progressed through all three stages and where a Stage III project has been completed. A comprehensive evaluation of these activities was planned for early 1999 but was delayed in the last quarter of the year. The Stage II project in Brazil was a participatory action research project organized in one municipality, Santo Barbara, in the State of São Paulo. The project was implemented in collaboration with CEMICAMP, with technical assistance from the University of Michigan, USA and the Population Council’s Campinas Office. The project’s primary interventions initially consisted of:

- training health providers;
- restructuring the roles of providers and service delivery patterns; creation of a referral centre for reproductive health; the introduction of DMPA;
- institution of a new management information system and a system of supportive supervision; and
- development of community women’s groups to participate in the planning and management of reproductive health services.

In subsequent years, vasectomy and related reproductive health services for men were added and over 530 vasectomies have been carried out, demonstrating the feasibility of organizing such services for men within the public sector. In addition, reproductive health services for adolescents were developed. An adolescent centre was created as part of the reproductive health referral centre to provide services in counselling, gynaecology, family planning and prenatal care, as well as a support group for pregnant adolescents. In addition, youth peer educators received ongoing training and are providing peer education and counselling at the centre and in local schools.

Evaluation of the Stage II project demonstrated considerable improvements in service availability, reproductive health orientation and quality of care. The project had demonstrated that expansion of reproductive choice can occur at the municipal level within existing resource constraints. The challenge for the Stage III project was to test whether and how results achieved within one municipality were transferable to other parts of the country. Such scaling-up of service innovations to other regions poses particular challenges in Brazil, where the process of decentralization has left few resources and little authority for programme development at federal and state levels. This process of decentralization suggested a Stage III project design which was primarily focused on testing replicability of activities in other municipalities and was accompanied by a set of initiatives directed at dissemination to national- and state-level health authorities and other relevant stakeholders. These included ongoing policy dialogues with these health authorities, as well as a workshop designed to familiarize a broader audience with the lessons of the Stage II project.

The central principle guiding the Stage II project had been that organizational development can occur if programme managers undertake a process of diagnosis, intervention and evaluation, facilitated through the involvement of outside catalysts. Although the Stage III project could not repeat the high degree of support for interventions associated with the Stage II project, it sought to generate a similar process of organizational development in additional participating municipalities, allowing them to benefit from the lessons and findings of the Stage II project. Following a dissemination workshop during which key results and lessons from the Stage II project were presented, three municipalities chose to participate in the replication process.

A moderate level of technical support and training with the organizational development process of baseline diagnosis, development of interventions and stimulation of community participation was provided to two municipalities, while the third received a lower level of support. A fourth municipality joined the project at a later point, stimulated by observation of the significant changes under way in one of the initial three municipalities.

In addition to technical assistance with the replication process, other interventions included the development of a set of briefing papers summarizing key findings and lessons from the Stage II project, and a series of policy dialogues and workshops with national-level policy-makers and other stakeholders, including donors.

Municipalities responded enthusiastically to the new approach to programme planning and at times progressed faster than was possible in the original Stage II project. Baseline diagnostic activities and subsequent interventions revealed that deficiencies in reproductive health care and barriers to improvements are fundamentally similar in all municipalities involved and many of the lessons learned in Stage II have been directly applicable.

As noted earlier, the evaluation of the process of replication and the impact on service availability and quality
of care is currently ongoing. This evaluation is utilizing both quantitative and qualitative methods, including analysis of service statistics and in-depth interviews and focus group discussions with health and civil authorities, providers, clients and other community members in the participating municipalities. In addition to a focus on Stage III, the evaluation is also focusing on the vasectomy programme and the adolescent and youth services and activities, as these were not covered in the previous evaluation.

Although data collection is ongoing, the success of activities has been demonstrated in many other ways. Although the funding for the Stage II and Stage III activities ceased over a year ago, the community groups, executive committees and changes in service delivery have continued. In fact, in all of the municipalities, the “Project” is seen as an ongoing activity. Service statistics demonstrate increased utilization of services and numbers of new acceptors, and expanded contraceptive choice. The success of interventions has been disseminated in national workshops and a number of states and municipalities have requested technical support from the principal investigator and CEMICAMP to assist in utilizing this approach in their locations. In addition, USAID has requested the Population Council Campinas Office and CEMICAMP to collaborate on a project to utilize the approach to improve the quality of reproductive health services in three additional states. Interest has also been expressed in utilizing the approach to specifically address other reproductive health issues, including planning and programming in the areas of STI/HIV/AIDS and adolescent health services.

Interest in the application of the approach to address adolescent health needs has been particularly strong, resulting from the success of initial activities in Santa Barbara, as well as their subsequent replication in additional municipalities. In Santa Barbara, more than 20 peer educators continue to be active in their schools and work as counsellors in the adolescent referral centre which serves over 100 clients per month. This group has produced a local radio programme that addresses reproductive health issues and has established a website for youth with information on reproductive health. One of the members has been appointed to participate in a working group guiding the MOH in the development of national services for adolescents.

A further measure of success has been the capacity of the participating individuals and institutions to mobilize financial support for continuing replication and expansion of activities in Brazil and more widely in Latin America. Realizing that it was important to both build on the project accomplishments and scale-up nationwide, as well as provide regional support to the approach, the technical support team of the University of Michigan, together with the Population Council Campinas Office and “Reprotatina”, a reproductive health NGO founded by the principal investigator submitted a project proposal to the Bill and Melinda Gates Foundation for continuing support. The project, approved at a budget of five million UD dollars over a period of five years, will emphasize technical training in the strategic approach and the process of organizational development for reproductive health services for additional municipalities in Brazil, as well as similar training and technical support for utilization of the strategic approach in Bolivia and other countries (yet to be decided), in Latin America. In addition, the grant will support the development of electronic communication between participating municipalities and a reproductive health website with links to other regional and international reproductive health sites.

ONGOING ACTIVITIES IN EASTERN EUROPE DURING 1999

Romania

A study of clients’ and providers’ perspectives and the implications for service delivery of adding non-surgical abortion to the currently available surgical abortion services began in 1999 and is described more fully in the chapter on “Unsafe abortion” of this report. This study was implemented as a precursor to a future strategic assessment of abortion issues in Romania, which among other issues will address the potential for wider introduction of non-surgical abortion services.

RESPONSES TO THE 1998 EVALUATION OF THE STRATEGIC APPROACH

In 1998, a formal evaluation of the strategic approach to the introduction of fertility regulation technology was conducted:

- to assess the strategy in terms of its impact and utility in improving quality of care;
- to refine the design and implementation of the strategy to enhance its utility and impact and its application to other reproductive health products; and
- to provide guidance for future activities of the Department in the area of technology introduction and transfer.

It was recommended that in the future the Department and its partners should take steps to disseminate more widely and facilitate the utilization of the strategy, including: (i) the development of a field guide which explains the strategic approach and provides guidance for the implementation of the Stage I assessments; (ii) the training of regional resource people for the facilitation of the
strategy; and (iii) the further promotion and advocacy for the strategy among international, NGO and donor agencies. The Department was advised to continue to refine approaches to Stage III activities and to investigate and refine the application of the strategy to other areas of reproductive health.

During 1999, work on a draft field guide targeted at reproductive health programme managers and other key stakeholders has continued, with extensive reviews and revisions. An initial field test was conducted in Kyrgyzstan where Reproductive Health Alliance Europe (RHAE) translated the draft guide into Russian for use in strategic assessment issues in adolescent reproductive health. Following review by an sub-committee of the Strategic Review Committee in November, the field guide, entitled Making decisions about contraceptive introduction: a guide for conducting assessments to broaden contraceptive choice and improve quality of care is currently being finalized for field testing in several countries. It has also been translated into Chinese in preparation for the assessment in China described above. It is anticipated that this revised draft will be utilized in two or more regional workshops which will be held during 2000 to promote the use of the strategic approach and train regional technical facilitators in the strategy and assessment methodology.

Activities to promote the use of the strategy in the past have included briefings for various WHO Regional Office staff, UNFPA Country Support Teams (CSTs) and presentations at various international workshops and conferences. In 1999, presentations on the approach were made at: (i) an International Planned Parenthood Federation (IPPF) regional workshop in Kuala Lumpur; (ii) a workshop in Beijing on the topic of reproductive health technologies and quality of care, sponsored by the State Family Planning Commission; (iii) a conference in London entitled Male Contraception: Planning for the Future, sponsored by AVSC International and RHAE; (iv) a Nordic Academy for Advanced Study (NORFA) regional workshop on reproductive health research; and (v) to IPAS International.

Country experiences with implementation of the strategic approach were the featured topic of issue No. 49 of HRP’s Progress in human reproduction research. Experience with the strategy was also the topic of articles during 1999 in Studies in family planning, the Journal of women’s health, The development studies network of the Australian National University and Feedback, the newsletter of the ICOMP. A case study of experience with assessments in Myanmar and Viet Nam appeared in the publication Meeting the Cairo challenge: progress in sexual and reproductive health published by Family Care International and presentations on and discussion of the strategic approach featured prominently in the publication of the report of the 1998 conference on “Innovations in Technology Introduction” sponsored by the Population Council and the Center for Health and Gender Equity and held in New York, NY, USA. An issue devoted to the use of the strategic approach for programming and planning is being planned for the Asia-Pacific journal of population for 2000.

A process to review and refine alternative frameworks for Stage III activities began during 1999. This has included the development of a paper to review the literature on: (i) scaling-up of interventions in the health sector; (ii) research utilization and its impact on policy; (iii) the diffusion of innovations; and (iv) bench-marking; and to synthesize the implications of this knowledge for the design of Stage III expansion activities. A preliminary draft has been submitted and further work on this task is ongoing. The initial lessons learned will be disseminated to those developing Stage III activities in 2000.

Work is continuing on the adaptation of the strategic approach and particularly the use of the assessment methodology, to address other reproductive health issues. As mentioned earlier, an assessment of abortion-related issues is planned for Romania and further collaboration with Ipas is anticipated for the implementation of strategic assessments to address issues related to the prevention of unsafe abortion. The Department has been working with the Population Council’s USAID-funded Horizons Project on an adaptation of the strategic approach to address issues related to STIs and other RTIs. It will be used to assist countries in the assessment of needs and the planning and implementation of comprehensive packages of interventions. The preparatory phases are under way and initial assessments are expected to take place in early 2000 in Brazil, Cambodia, Ghana and Latvia. As noted earlier, the assessment methodology has been utilized for an assessment of adolescent reproductive health needs in Kyrgyzstan and there is also interest in using the approach for this purpose in Brazil. Discussions have taken place with UNAIDS and AFRO staff concerning the adaptation and utilization of the strategy for planning national strategies for the prevention of maternal-to-child transmission of HIV and it is possible that such an assessment may be conducted in the coming year.

There is a growing recognition of the need for a methodology and tools to assist countries in strategic planning and programming for comprehensive reproductive health services. In recent years, experience with the adaptation of the strategic assessments to broadly address reproductive health has been gained in Ethiopia, Myanmar, and most recently in Laos as described above. However, those involved with facilitating these assessments have felt that there is a need to review these experiences and to develop and test more formally specific guidelines and instruments for strategic reproductive health assessments if wider utilization is to be successful. ICOMP,
in collaboration with the Population Council Bangkok Office and the RHR Secretariat, has submitted a proposal to the Rockefeller Foundation for funding a series of activities over the next 18 months to develop these tools and test them in three countries. The Rockefeller Foundation has agreed to provide US$ 125 000 in support of these activities, with additional support for one or two in-country field tests to be provided by WHO.

Product management

The Programme has continued to work on aspects of product management that are essential for ensuring appropriate quality of contraceptive products within the overall concept of quality of care. Increasingly, more national family planning programmes are or will be purchasing some or all of their contraceptive supplies. The procurement process is a critical component of a contraceptive quality assurance programme. To support the national programme managers responsible for contraceptive procurement, PATH was commissioned to develop a practical guide that highlights key elements of the procurement process with an emphasis on those which influence product quality. The document provides practical advice, sample forms and tools to support the procurement process so as to achieve the goal of obtaining high-quality contraceptive commodities. This draft guide has been under review by external agencies and it is anticipated that it will be published and disseminated in 2000.

STRATEGIC FRAMEWORK TO SUPPORT THE DISSEMINATION, ADAPTATION AND UTILIZATION OF TECHNICAL GUIDANCE DOCUMENTS

An issue currently being addressed in WHO and one which is of particular concern to the Department is how to ensure that the evidence-based technical norms and standards generated by this Department are appropriately disseminated, adapted and utilized. Although WHO has a system for the distribution of technical documents, this mainly relies on distribution lists that may not have been systematically updated for a number of years. Where documents are sent is known. But what is not known is

—who needs this information but does not receive it;
—who is using it, for what purpose; and
—whether the documents meet the information needs of countries.

In order to improve the current process for developing and disseminating documents, key collaborative partners were requested to review the very successful system used to disseminate, adapt and utilize the document Improving access to quality care in family planning: medical eligibility criteria for contraceptive use in over 50 countries. During this task, which included two consultative meetings, it became evident that, although the Department can act as the catalyst to initiate action at the national level for this purpose, rarely is there the capacity to follow through this process in a structured manner in more than just a few countries.

The outcome of the above meetings resulted in the development of a draft strategy framework that examines the relevant principles, approaches and actions that can be used to develop country-specific strategies to ensure the effective dissemination, adaptation and utilization of technical documents. It is planned to introduce this strategy in the WHO South-East Asia Region during 2000.

REGIONAL CENTRES

The work on the “Strategic Approach” has been supported and assisted by several regional technical support centres. CEMICAMP in Campinas, Brazil, and the University of Michigan, Ann Arbor, MI, USA, have continued providing assistance to countries in Latin America. The group has continued to assist in the implementation of the Bolivian Stage II research study. CEMICAMP continued to manage the Stage II research project conducted in Santa Barbara d’Oeste, Brazil, as well as the Stage III expansion and evaluation activities in Brazil, with technical assistance provided by the University of Michigan.

In Africa, assistance with the implementation of the Strategy is being provided by the Population Council’s Regional Office for Eastern and Southern Africa in Nairobi, Kenya. Both financial and technical support have been provided to the Stage II research activities in Zambia. The Population Council staff have also provided assistance to investigators in the follow-up of the Ethiopia Stage I assessment.

In Asia, assistance is being provided by ICOMP, Kuala Lumpur, Malaysia and the Population Council’s Office in Bangkok, Thailand. ICOMP continued to provide support to activities in Viet Nam and to the reproductive health assessment in the Lao PDR. It is also providing assistance to the evaluation of the emergency contraception introductory activities in Indonesia, The Population Council, Bangkok, Thailand, is providing technical support for the Stage II research activities in Myanmar, as well as to the assessment conducted in the Lao PDR and follow-up activities to develop a Stage II proposal.
Annex 1a

MAPPING BEST REPRODUCTIVE HEALTH PRACTICES

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Annex 1b

MAPPING BEST REPRODUCTIVE HEALTH PRACTICES

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K. Mahomed, University of Zimbabwe, Harare, Zimbabwe
N. Maitra, Baroda Medical College, Baroda, India
M. Mathai, Christian Medical College, Vellore, India
W. May, WHO Regional Office for South-East Asia, New Delhi, India
J. McIntyre, University of Witwatersrand, Johannesburg, South Africa
J. Melnikow, University of Southern California, Davis, CA, USA
S. Mittal, All India Institute of Medical Sciences, New Delhi, India
J. Moodley, University of Durban, Durban, South Africa
S. Munjanja, University of Zimbabwe, Harare, Zimbabwe
D. Neeloufer-Khan, University of Geneva, Geneva, Switzerland
J. Neilson, University of Liverpool, Liverpool, United Kingdom
C. Nikodem, University of Witwatersrand, Johannesburg, South Africa
R. Pattinson, Pretoria University, Pretoria, South Africa
S. Ramji, Maulana Azad Medical College, New Delhi, India
L. Say, Istanbul University, Istanbul, Turkey
Annex 1b (continued)

MAPPING BEST REPRODUCTIVE HEALTH PRACTICES

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C. Van Gelderen, University of Witwatersrand, Johannesburg, South Africa
V. Vatanasapt, Khon Kaen University, Khon Kaen, Thailand
J.C. Vazquez, America Arias Hospital, Havana, Cuba
C. Williams, Oxford University, Oxford, United Kingdom
R. Yip, UNICEF, Beijing, China

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Annex 1c

PUBLICATIONS IN 1999

Publications in print media


Electronic publications (Systematic reviews and protocols published in The Cochrane library)


Full reviews

Smaill F, Hofmeyr GJ. Antibiotic prophylaxis versus no antibiotics for women undergoing cesarean section.
Carroli G, Bergel E. Umbilical vein injection for management of retained placenta.
Cheng L, Gülmezoglu AM, Ezcurra E, Van Look PFA. Interventions for emergency contraception.
May W, Gülmezoglu AM, Ba Thike K. Antibiotics for incomplete abortion.

Protocols

Buchmann E, Gülmezoglu AM, Nikodem VC. Partogram use in the management of labour.
Kulier R, Gülmezoglu AM, de Onis M, Villar J. Vitamin A supplementation in pregnancy (in press).
Cuervo LG, Mahomed K. Treatments for iron deficiency anaemia in pregnancy.

Reviews updated

Hofmeyr GJ, Gülmezoglu AM. Misoprostol vaginally for labour induction.
Atallah AN, Hofmeyr GJ, Duley L. Calcium supplementation during pregnancy.
Duley L, Gülmezoglu AM, Henderson-Śmart D. Anticonvulsants for pre-eclampsia.
Gülmezoglu AM. Prostaglandins in third stage of labour.
Hofmeyr GJ. Amnioinfusion prophylactically versus therapeutically.
Gülmezoglu AM. Trichomoniasis treatment during pregnancy.
Gülmezoglu AM, Garner P. Malaria in pregnancy.
Gülmezoglu AM, Hofmeyr GJ. Hormone therapy for impaired fetal growth.
Gülmezoglu AM, Hofmeyr GJ. Maternal oxygen therapy in impaired fetal growth.
Gülmezoglu AM, Hofmeyr GJ. Nutrients for impaired fetal growth.
Gülmezoglu AM, Hofmeyr GJ. Plasma volume expansion for impaired fetal growth.
Gülmezoglu AM, Hofmeyr GJ. Bedrest for impaired fetal growth.
Gülmezoglu AM, Hofmeyr GJ. Betamimetics for suspected impaired fetal growth.
Gülmezoglu AM, Hofmeyr GJ. Calcium channel blockers for impaired fetal growth.
Gülmezoglu AM, Hofmeyr GJ. Electrostimulation in placental insufficiency.
Hofmeyr GJ, Kulier R. External cephalic version at term.
Hofmeyr GJ. External cephalic version before term.
Hofmeyr GJ. External cephalic version facilitation at term.
Hofmeyr GJ, Kulier R. Cephalic version by postural management.
Hofmeyr GJ, Gülmezoglu AM. Maternal hydration for increasing amniotic fluid volume in oligohydramnios and normal amniotic fluid volume.
Mahomed K, Gülmezoglu AM. Maternal iodine supplementation in areas of deficiency.
Mahomed K, Gülmezoglu AM. Vitamin D supplementation in pregnancy.
Annex 1d

EFFECTIVENESS SUMMARIES OF NON-MATERNAL HEALTH TOPICS IN RHL

Beneficial forms of care

- Emergency contraception to prevent pregnancy following unprotected intercourse
- Extended tip cervical smear spatulas to detect endocervical cells, dyskaryosis and high overall rate of adequate smears
- Laparoscopic surgery for conservative management of uncomplicated, early tubal pregnancy when compared to open surgery, systemic methotrexate and local methotrexate under laparoscopic guidance
- Trichomoniasis treatment in women with short (single dose to 48 h) or long courses (5–7 days) of orally used nitroimidazoles to achieve immediate parasitological and clinical cure

Forms of care likely to be beneficial

- Levonorgestrel or mifepristone for emergency contraception when compared to the Yuzpe regimen, danazol and others
- Vitamin A supplementation to very-low-birth-weight infants to reduce death and oxygen-treatment at one month of age

Forms of care of unknown effectiveness

- Antibiotic prophylaxis for uncomplicated incomplete abortion to reduce postabortion complications
- Routine intubation at birth in vigorous term meconium-stained babies to prevent meconium aspiration syndrome
- Routine topical antiseptic or antibiotic application to the umbilical cord to prevent sepsis and other illness in the neonate

Forms of care likely to be ineffective

- Antibiotic prophylaxis at the time of intrauterine device insertion to prevent postinsertion infections
- Short (single dose to 48 h) or long (5–7 days) courses of nitroimidazoles for trichomoniasis without effective partner treatment to decrease the prevalence of *Trichomonas vaginalis* infections
Annex 2a

STRATEGIC REVIEW COMMITTEE IN 1999

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S. Ray, South Staffordshire Health Authority, Stafford, United Kingdom (On leave from Harare, Zimbabwe)
M. Whittaker, University of Queensland, Brisbane, Australia

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Collaborating agency scientists

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L. Salinas, Ministry of Health, La Paz, Bolivia  
R. Simmons, University of Michigan, Ann Arbor, MI, USA  
Thein Thein Htay, Department of Health, Yangon, Myanmar

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STRATEGIC COMPONENT SCIENTISTS IN 1999

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M. Gardner, The Population Council, Bangkok, Thailand
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S. Phamixay Lao, Youth Union, Vientiane, Lao People’s Democratic Republic
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Annex 2c

PUBLICATIONS IN 1999


Sexual and reproductive health of adolescents

S.J. Jejeebhoy, I.H. Shah, K.M. Yount
OBJECTIVES

Over one billion young people between the ages of 10 and 24 years live in developing countries. Yet, there continues to be a dearth of information on their sexual and reproductive health needs, and on the best strategies to tailor services and programmes to address these needs. The first of HRP’s four goals concentrates on addressing these gaps: “To enable people to experience healthy sexual development and maturation and enhance the capacity for equitable and responsible relationships and sexual fulfilment.” During 1999, HRP pursued two research priorities: (i) documentation of the context of adolescent reproductive and sexual health, including the magnitude, determinants and consequences for adolescents’ lives; and (ii) identification, through intervention research, and evaluation of ongoing interventions and programmes, of optimal provision of health and information services, and the best practices that respond effectively to the needs of adolescents.

PROGRESS

The Department has undertaken three main activities in the area of adolescent sexual and reproductive health. First, a synthesis was completed of ongoing or recently concluded social science research focusing on youth, with regard to abortion, sexual behaviour and men’s roles, which was supported by HRP’s Social Science Research Group on Reproductive Health. Second, support was provided under the social science research initiative launched in 1998 by HRP, for formative and intervention research studies on adolescent sexual and reproductive health. Third, a focused operations research project on improving reproductive health services for adolescents has been in progress, supported by HRP’s component on National Reproductive Health Research and Research Capability Strengthening. Besides the activities described below, HRP is engaged in other activities pertaining to adolescents which are reported in more detail in other sections of this report. These activities are briefly mentioned in this chapter to provide a complete profile of HRP’s activities relating to the sexual and reproductive health needs of youth.

Documentation of the context of adolescent reproductive and sexual health: magnitude, determinants and consequences for adolescents’ lives

Synthesis of social science research findings on the sexual and reproductive health of adolescents and youth

Under research initiatives on sexual behaviour and the role of men within the context of abortion, the Social Science Research Group on Reproductive Health has been supporting several studies that focus explicitly on the situations faced by adolescents and youth. In 1999, with support from the FRONTIERS Project, a review was undertaken of the findings of research supported over the 1990s that address the situation of adolescents and youth. This review synthesizes findings from some 34 case studies in 20 developing countries. Substantial proportions of youth in all regions are sexually active, and the evidence suggests that this sexual activity is not free from the risks of unwanted pregnancy, disease or coercion. Case studies consistently point to gender imbalances in sexual partnerships which increase the risks faced by young females, and highlight the challenges posed to interventions designed to enhance decision-making with respect to sexual and reproductive health among adolescents. Examples of some findings from this synthesis are described below.

Acceptance of gender-based double standards

Quantitative and qualitative case-study findings suggest that young females and males accept, and sometimes justify, double sexual standards and constraints imposed on the sexual behaviour of females. Young males, for example, are widely perceived to need premarital sexual experience and a variety of partners; females are not so perceived. A case study of adolescents attending reproductive health services in two hospitals in Argentina reports the widespread belief that male “sexual urges” are uncontrollable, and consequently explain the greater “need” that men have for casual sexual relations. Adolescent schoolgirls and factory workers in Bangkok, Thailand, concur that “all men are just like that. I think they have a lot of sex urge”. University students in a case study in the Philippines argued that “men should have experience...women do not need experience”, and justify this assertion with the view that “if a man does not get quite a lot of experience before marriage he’ll want even more after...”. Young females recognize the ways in which these double standards constrain their behaviour relative to that of males. Adolescent female factory workers and students in Bangkok, Thailand, for example, state that: “We cannot do whatever we want, roaming, smoking, drinking...”; “we are brought up this way”; “it’s social expectations, they will look down on you if you go loose”; “men can go anywhere, do whatever they like, even trying sex...”; but “no one wants a woman who has had sexual experience”. Similarly, low-income young women in Buenos Aires, Argentina, argue that the “the man can go with many women and not lose his reputation, but if the woman does the same thing with men, they will always say bad things about her”.

Fear of disclosure

The need to conform to these double standards may cause young females to fear disclosing their sexual activity,
and may result in a reluctance among them to report sexual experience. This fear may also inhibit sexually active adolescents from seeking contraception and other reproductive health services. For example, the leading reason cited by pregnant young women in Shanghai, China, for non-use of contraception was fear of disclosure or embarrassment. Students and factory workers in Bangkok, Thailand, cited pharmacies and department stores as preferred sources of contraceptive supplies, because of the privacy and anonymity of these sources.

Fear of disclosure can also inhibit pregnant adolescents from seeking family support and a safe resolution of pregnancy. Evidence regarding young women’s reluctance to disclose their pregnancy status to their families was attested to by diverse groups: abortion seekers in Sichuan province, China (40% were “too shy” to confide in parents), young women working in an export promotion zone in Republic of Korea (33%), and adolescents attending night school in Peru (fewer than 10%). Fear of disclosure to the family can also limit access to resources needed for a safe abortion. A case study in Mexico City, Mexico, reports that several pregnant adolescents who would have preferred abortion, continued with the pregnancy for want of financial resources and a reluctance to approach families for the necessary resources.

Constraints on sexual negotiation

Case studies suggest that the woman’s fear of losing her partner or incurring his anger appear to be important factors inhibiting young females from exercising choice in the timing of sexual activity or negotiating for the use of contraceptives or condoms. For example, adolescent female students and factory workers in Bangkok, Thailand, point out, that “women have less power to bargain, they think that if they have sex with their boyfriends they will get them forever and that is a big mistake…”.

Almost two in five adolescent females in a case study in Botswana responded that they were not certain that they could decline sex if their partner refused to use a condom. Young unmarried females working in export promotion zones in the Republic of Korea were reluctant to seek or insist on the use of condoms for fear of being labelled “bad quality girls” with “loose morals”. Even after the experience of an unwanted pregnancy, young females in a case study in Mexico City, Mexico, continued to leave contraceptive decisions to the male partner: “He looks after me” was a typical justification. Even those who chose to undergo an abortion without informing their partners were not necessarily exercising informed choice: they did so out of a fear that “I was going to lose my boyfriend”, or that “he would abandon me”.

Case studies provide only scattered evidence of young females refusing unprotected sex. In Botswana, for example, over two in five adolescent females reported that they would refuse sex without contraception. Similarly, in a qualitative study in Argentina, responses included: “As much as I would like children or the pleasure of being with him… how it is today is that I have to put myself first… use the condom, or, if not, nothing will happen”; and “he can go wherever he wants (to sleep), as long as he uses a condom and does not bring any disease home to me”.

Sexual coercion

Although force and sexual coercion were not the exclusive topics of any of the studies reviewed, some 13 studies were able to explore these issues through surveys and/or in-depth interviews. These case studies were conducted in diverse settings among school- and college-going and out-of-school youth (Argentina, Botswana, Peru, the Philippines and Thailand); youth attending night schools (Peru); working youth (Republic of Korea); youth in reproductive health facilities (Argentina), and young females experiencing pregnancy and abortion (Mexico, Panama, Philippines, United Republic of Tanzania). Their findings dispel the notion that sexual activity among young females is always consensual: between 5% and 20% of young females in these case studies report a forced or coerced sexual experience. Several case studies report that perpetrators documented in these studies were authority figures: workplace supervisors (Republic of Korea), “sugar daddies”, and older male teachers, policemen, priests and relatives (Botswana, Tanzania). Sexual coercion is also experienced by males, though fewer case studies explored this issue: findings suggest that between one and five percent of young males have experienced non-consensual sexual debut.

The synthesis highlights these and other findings and draws from them recommendations for programmes and research. Findings underscore the need for youth-friendly sexual and reproductive health services; and counselling on sexuality, pregnancy, postabortion issues and family planning. They also argue for sex education programmes which: (i) are age-appropriate, acceptable and recognize and address the unique misconceptions held by adolescents in different settings; (ii) build life and negotiation skills that will enable safe and informed choices; (iii) raise awareness of sexual coercion and equip youth to counter it; and (iv) confront existing double standards in what is acceptable for females and males. Programmes also need to address parents and enable them to overcome inhibitions in communicating with and counselling their adolescent children. Finally, if services are to be truly youth-friendly, youth must be involved in their design and content.

Research priorities are diverse and context-specific but include the need to investigate: (i) the determinants of positive outcomes (for example, gender-balanced relationships, successful negotiation skills and exercise of
informed sexual and reproductive choices); (ii) the ways in which sexual partnerships are formed among youth, and the respective social meanings that females and males attribute to relationships; (iii) the ways in which sexually active youth deal with the dual risks of unwanted pregnancy and sexually transmitted infections (STIs); (iv) young people’s access to health care, and the constraints they face in the pursuit of good health; (v) gender roles and life skills and their influence on sexual and reproductive choices; and (vi) sexual coercion, force, and violence, in the case of both married and unmarried youth.

**Research initiative on adolescent sexual and reproductive health**

The evidence accumulated from the above studies has both documented data on adolescent sexual and reproductive health, and indicated directions for programmatic efforts. It has highlighted the need to expand research geographically to a broader range of countries. It has also suggested substantive gaps that need to be addressed. Furthermore, there is a need for in-depth exploration of a range of issues, including the ways in which young people form relationships, their expectations of these relationships, the choices they make concerning their sexual and reproductive lives, the constraints they face in seeking care and information and the scope of available services. Also, the synthesis has highlighted the methodological need to use different and adolescent-friendly approaches of eliciting perspectives and needs.

With these needs in mind, since 1998, HRP’s Social Science Research on Reproductive Health has undertaken a research initiative that focuses on adolescent sexual and reproductive health. The aim is to support research that addresses factors that contribute to positive sexual and reproductive health outcomes, especially those that can be influenced by appropriate interventions in developing countries. Topics of interest include: (i) formation of partnerships, sexual relationships, gender influences, and how adolescents deal with the dual risks of unwanted pregnancy and STIs; (ii) risk behaviours and perceptions; (iii) correlates and consequences of early and unwanted pregnancy; (iv) sexual coercion, especially of female adolescents; (v) health-seeking behaviour patterns and constraints that adolescents face in acquiring sexual and reproductive health care and information; and (vi) provider perspectives on the provision of sexual and reproductive health services and information to adolescents. Also of interest in this research initiative are pilot intervention studies that build life skills among adolescents, cater to their sexual and reproductive health information and service needs, address provider perspectives and constraints and evaluate ongoing programmes designed to improve their health.

The original Call for Proposals resulted in over 240 submissions in 1998. At its 1998 meeting, the Scientific Review Committee approved three of these, and encouraged 70 investigators to develop their research proposals further. Three proposal development workshops were held in 1998–99. Participants included 55 investigators whose submissions had been positively appraised by the Scientific Review Committee. The objectives of these workshops were to build research capacity, assist in proposal development and improve the overall quality of the research supported under the initiative. The second and third of these workshops were held in Nairobi (Kenya) and Gramado (Brazil) in early 1999. The Nairobi workshop was attended by 12 investigators from sub-Saharan Africa and two from Turkey, along with a team of 11 resource persons. The Gramado workshop included 14 investigators from Latin America, one from Cape Verde and 10 resource persons. Both workshops combined substantive and methodological presentations with one-on-one consultations in respect of individual research agendas and proposals. Evaluation of the workshops by participants was extremely encouraging, and almost all investigators attending the three proposal development workshops submitted a revised proposal for review in 1999.

A total of 82 revised and new proposals were reviewed at the 1999 meeting of the Scientific Review Committee. Of these, 24 projects were approved by both the Scientific Review Committee and the Scientific and Ethical Review Group. (Of these, two are intervention-based studies, discussed in more detail below.) Including the three projects that were approved in 1998, a total of 27 research projects on the topic of adolescent sexual and reproductive health have been supported in 1998–99 under this initiative. Research for the majority of these will continue in 2000. Though all the projects are single-centre projects, efforts are under way to adopt common elements of study design and content for all the studies falling under the various thematic areas described below.

Also falling under the broad mandate of this initiative are two multicentric projects that were supported earlier and are being conducted in China. The first addresses the reproductive health status and needs of young female migrant workers. Migrant females in urban China are clearly vulnerable: they come from less developed rural areas, are mostly young (40%–50% below the age of 25 years) and unmarried. Sexual activity has tended to be restrained in their areas of origin; family and community pressures have restricted opportunities for premarital sexual activity; and knowledge of sexuality and reproduction is limited. In urban areas, significant proportions of these unmarried young women experience unprotected sex, unwanted pregnancy and STIs. Access to reproductive health services, however, is limited: government MCH and family planning services do not cater to unmarried women on the one hand, and the work environment, usually small factories or businesses, rarely provide health...
services or insurance on the other. The study is largely exploratory, and is being conducted in urban sites in Beijing, Guangzhou, Guiyang, Shanghai and Taiyuan. As reported in 1998, the objectives are: (i) to investigate the reproductive health status of young migrant workers under 25 years of age; (ii) to identify high-risk behaviour and its determinants among them; (iii) to assess perceived reproductive health needs; and (iv) to collect information that would help investigators recommend ways to improve the provision of reproductive health services to this large and growing group.

Findings reveal varying sexual activity rates among young migrant women in these sites: from 10%–20% in Beijing and Taiyuan to 50%–80% among certain groups of working adolescents in Guangzhou, Guiyang and Shanghai; and from low levels among young women working in factories to very high levels among those in the service and entertainment sectors. Unwanted pregnancy, abortion, repeat abortion and infection were not unknown. Despite a recognition of widespread sexual activity, misperceptions about safe sex characterized a majority of migrant adolescents. A 20-year-old unmarried woman who had had an abortion mentioned that it was “just bad luck that made her pregnant”. Many thought that contraception was for “older” women. A 21-year-old unmarried woman was unaware of contraception even though she had been sexually active for two years and had had one abortion. Results generally confirm that contraception was rarely practised.

The findings also show that, although good family planning services exist in urban areas, these are inaccessible for a majority of the growing number of migrant workers. Few young women were able to access family planning information or services, and the unmet need for contraception remains extremely high. The final results of this project are expected in 2000.

The second ongoing research activity in China investigates the unmet needs for and barriers to acquiring sexual and reproductive health services among sexually active unmarried young adults. This is a multisite study, conducted in seven provinces and eight cities, namely, Chengdu, Chongqing, Fuzhou, Hangzhou, Nanjing, Shanghai, Shijiazhuang and Zhengzhou. The study involves a survey of contraceptive providers and distributors; focus group discussions with sexually active unmarried young men and women, family planning programme staff, contraceptive providers and parents; and in-depth interviews with leaders of family planning programmes.

Findings related to the knowledge gaps and service needs expressed by unmarried young adults were reported in 1998. In 1999, findings became available on the perspectives of providers on the delivery of reproductive health services to adolescents, and these show a remarkable willingness among providers to expand services to include unmarried youth. Overall, 92% of providers and distributors of contraceptives were willing to provide family planning information, and 70% were willing to provide contraceptives to unmarried young men and women. In most sites, providers identified mothers, teachers and family planning workers as the most appropriate persons to provide information. Except in Hebei, over 40% of providers and distributors indicated that the government should provide contraceptive services to young unmarried adults. Overall, 78% agreed with the need to have special clinics to provide information and services to young unmarried men and women. The family planning service station was identified as the best place to provide such services. Finally, providers expressed the need for a standardized and consistent policy for information and services to young people, and a preference for the delivery of family planning services to youth through public health facilities rather than through educational institutions.

As of the year 2000, therefore, there are a total of 29 research projects supported under the social science research initiative on adolescent sexual and reproductive health. These projects cover a wide range of topics, and include the following formative, descriptive and intervention studies:

1. Sexual risk behaviour patterns: 10 (Brazil, China, Cuba, Guatemala, India, Mexico [2], Paraguay, Peru, Tanzania).
2. Socialization on gender roles, sexual attitudes: 1 (Ghana)
3. Provider perspectives: 2 (Lao People's Democratic Republic [Lao PDR], Myanmar
4. Dual protection: 3 (Colombia, Indonesia, Kenya)
5. Health-seeking behaviour and quality of care: 5 (Argentina, China [2, including one multicentric], Myanmar, Nepal).
6. Sexual coercion: 3 (Indonesia, Nigeria, the Philippines)
7. Risk behaviour of vulnerable groups (refugees, migrants): 2 (Cap Verde, China, multicentric)
8. Consequences of adolescent pregnancy: 1 (Brazil)
9. Interventions: 2 (Chile, China)

While all these projects address under-researched and sensitive issues, some are especially noteworthy for the newness of their subject matter or their unique data. Three projects—in Indonesia, Nigeria and the Philippines—will focus on perceptions and experiences of sexual coercion among adolescent females and males aged 15 to 19 years. All three studies adopt a common design, comprising an initial qualitative phase addressing adolescents and key adult informants; an exploratory survey of female and male adolescents; and in-depth interviews with selected respondents, including those who have and have not experienced coercion. Referral information and assistance will be provided to those in need.
Three studies—in Colombia, Indonesia and Kenya—will identify and explore strategies used by sexually active adolescent females and males to confront the dual risks of unplanned pregnancy and STIs, the constraints they face in changing behaviour, and the ways in which youth negotiate safe sexual relations.

Two studies in Brazil provide a unique opportunity to explore adolescent development prospectively. One of these builds on an existing study that has been following a cohort since birth in 1982 and has accumulated information on the developmental milestones, perceptions and experiences of this cohort. The objectives of this study are to explore sexual maturation, the formation of sexual unions and sexual and reproductive health issues among this cohort as it reaches the age of 17–18 years, to understand their experiences, and to explore their risk behaviour, reproductive health outcomes and health-seeking behaviour patterns. The second study will conduct a second follow-up of a cohort of pregnant adolescents who had attended the clinics of an NGO. Some of these adolescents had opted for abortion while others chose to carry the pregnancy to term. The objectives of the study are to explore the consequences of teenage pregnancy and its outcome on young women’s lives. The proposed study intends to revisit those young women three to four years after initial contact, and to interview the current partner and/or mother, if the young woman consents.

Identification, through intervention research in various national settings, of optimal provision of health and information services, and best practices that respond effectively to the needs of adolescents

Research initiative on adolescent sexual and reproductive health

The social science research initiative (described above) also supports pilot intervention studies which build life skills among adolescents, cater to their sexual and reproductive health information and service needs, address the constraints faced by providers in the provision of sexual and reproductive health services to adolescents and evaluate ongoing programmes for adolescents. A number of promising proposals for intervention studies have been received. The Scientific Review Committee has approved two such projects, subsequently cleared by the Scientific and Ethical Review Group. One such study, located in China, will implement and test the impact of youth-friendly services on youth attitudes and practices. A second study, in Chile, proposes to assess the extent to which the risk behaviour of youth can be changed through a programme involving peer leaders.

Operations research on improving reproductive health services for adolescents in French-speaking African countries

An operations research project to evaluate and improve the reproductive health services for adolescents has been in progress in six French-speaking sub-Saharan countries: Benin, Burkina Faso, Cameroon, Côte d'Ivoire, Guinea and Senegal. The project, supported by HRP’s Strategic Programme Component on National Reproductive Health Research and Research Capability Strengthening, is designed to include three phases: (i) a pilot study and a baseline survey to define the profile of the adolescent users of health services and the quality of services offered; (ii) an intervention to be developed for each country depending on the results of the baseline survey (this will address either the need for increasing the information to adolescents by training service providers or the modification of existing services to make them more youth-friendly); and (iii) a post-intervention survey to evaluate the intervention. The Programme is facilitating and coordinating this regional initiative and providing support for aspects that strengthen the research capacity of the project, but funding for each country project is being raised locally. A unique feature of the project is the constitution of multidisciplinary research teams and the active participation of youth representatives in each team. In 1999, activities were concentrated in Côte d'Ivoire and Senegal and funded, respectively, by UNFPA and the USAID-funded Frontiers in Reproductive Health project.

In Côte d'Ivoire, the first phase of the study has been completed. The study was conducted in two rural and two urban health districts with a total population of about 160 000, including about 24 000 adolescents. Data were collected through a household survey of 1470 adolescents aged 13–19 years, a facility-based survey of 789 adolescents, in-depth interviews with 56 key informants and 82 health care providers, and a total of 32 focus group discussions, 16 conducted among adolescent females and males, and another 16 with mothers and fathers. Registers maintained at health facilities were also perused.

Several interesting findings have emerged. Adolescents clearly need sexual and reproductive health services: half of all adolescents attending general health facilities reported that they were sexually experienced, with an average age of sexual debut of 15 years; and 33% of all women requiring delivery services were adolescents. Yet, there is considerable underutilization of reproductive health services, and a major obstacle to the use of health centres is the poor quality of care that adolescents receive at these centres. Major concerns expressed by adolescents included persistent absenteeism of staff, a long waiting period, high costs of consultation and care, unfriendly treatment by staff and lack of privacy at the facility. As many as 18% of adolescent males and 13% of females reported uncaring
treatment by providers, and 28% of those interviewed at a health centre reported that they had hesitated to visit the centre. Consistent with these perceptions, only 43% of adolescents reported that they would visit a health centre if they suspected that they had contracted an STI, and only 58% said that they would obtain contraceptives from health centre personnel. In focus group discussions, moreover, adolescents rarely mentioned health providers as sources of sexual and reproductive health information. In fact, peers, family and traditional providers were cited as the most likely people to be consulted in case of sexual and reproductive health concerns, and health centres were perceived as a last resort.

To some extent, providers are aware of these facility-level constraints. Long waiting periods, judgemental attitudes of providers, irregular supplies and a generally uninviting environment were cited as factors underlying the reluctance of adolescents to avail of reproductive health services. In contrast to the perceptions of the lack of privacy reported by adolescents, as many as 91% of providers reported that they offer privacy during consultation.

Parents too are not regarded as a major source of support to adolescents. In focus group discussions, parents revealed an inability to communicate with their adolescent children on topics relating to sexual health. Parents cited the lack of opportunities for youth, such as work or sports, as a major factor underlying the risky sexual behaviour patterns of adolescents. Conflict between the norms conveyed by parents to their children and those portrayed in the mass media were observed by both parents and key informants. Finally, both parents and key informants recognized that services for adolescents remained inadequate.

Four priority areas for intervention have been identified. These include: (i) provision of information and communication skills to parents and influential community members; (ii) reduction or waiver of fees for services to adolescents; (iii) development of youth-friendly services: (activities might include reorientation of existing providers and efforts to recruit young providers, counsellors and those well qualified to address adolescent concerns; provision of separate and private waiting areas for adolescents; ensuring the availability of supplies, including contraceptives); and (iv) provision of useful and acceptable messages to adolescents via the mass media.

A report of the main qualitative and quantitative findings is available, and findings were presented at a dissemination seminar. Plans are now under way for the design of the intervention, also to be funded by UNFPA.

The study in Senegal has not yet been initiated. However, during 1999, the USAID-funded Frontiers in Reproductive Health project has agreed, in collaboration with HRP, to include Senegal in its operations research on youth in four countries (including Bangladesh, Kenya and Mexico). The resulting study, to be implemented in 2000, is largely similar in objectives and design to the French-speaking Africa project. As such, the Senegal project, and others supported under the “Frontiers” project, will draw upon the experience of and technical support provided by HRP’s French-speaking African study. Findings from research conducted in Senegal will contribute to the overall profile of adolescents in French-speaking countries.

Other work of the Department relating to adolescents

Activities concerning adolescent sexual and reproductive health cut across several thematic priority areas of the Department and are briefly described here. Detailed reports are provided in other chapters.

Study on bone mass and hormonal contraception

The results of the multicentre study on hormonal contraception and bone mineral density conducted by HRP’s Surveillance and Evaluation Research Group will be published shortly in Obstetrics and gynaecology. A cross-sectional study of women, aged 30–34 years, was conducted in seven centres, one in each of the following countries: Bangladesh, Brazil, China, Egypt, Mexico, Thailand and Zimbabwe. The findings showed that hormonal contraceptive use by young adult women is associated with small, but reversible, changes in bone mineral density that occur soon after initiation of use. Use of hormonal contraception in the age range of 16–20 years, critical for bone mass acquisition, may influence the peak bone mass achieved. If young women do not reach their optimal bone mass, they may face greater risk of osteoporosis later in life. HRP is launching a five-year follow-up study measuring bone mineral density every six months in young women commencing with the use of depot medroxyprogesterone acetate (DMPA), norethisterone enantate (NET-EN) or combined oral contraceptives, and is comparing the data with that of a group of young women using no hormonal contraception. The study is being initiated in South Africa, and will be expanded to cover other population groups (for details, see the section on “Safety and efficacy of existing methods of fertility regulation”).

Essential care practice guides

Work relating to maternal and newborn health includes the development of a set of “Essential Care Practice Guides” which describe and aim to facilitate the availability of the minimum interventions required in antenatal, delivery, newborn, postpartum and postabortion care. These encompass both the normal situation and the most common complications. As this material (chart booklets,
job aids and eventually, manuals and training material) targets all women who are pregnant and new mothers, they also give extra attention to maternal health care in adolescents. The guides draw on inputs from WHO’s Department of Child and Adolescent Health and Development (CAH), and include reviews of papers produced by this group (for additional details, see the chapter on “Maternal and perinatal health”).

**Links with the Department of Child and Adolescent Health and Development**

The Department has continued to interact with the CAH Department in several activities. First, there has been close collaboration with CAH on the operations research project intended to assess reproductive health services for adolescents in French-speaking sub-Saharan African countries. Second, staff have jointly participated in meetings and workshops. For example, staff of CAH were invited to attend the meeting of the Scientific Review Committee of the Social Science Research Group on Reproductive Health and to comment on proposals under review. Programme staff have participated in meetings organized by CAH, including one that focused on the need to work with adolescent boys, and another that briefed donors, researchers and programme implementers on the work of the cluster in the area of adolescent health. Third, the staff of the Department have provided extensive comments on a range of documents and articles prepared by the staff of CAH.

In the development of norms and tools, there has been close collaboration between the two departments not only on the Essential Care Practice Guidelines, but also, recently, on incorporating into guidelines for the Integrated Management of Pregnancy and Childbirth the special measures that health workers need to take in the diagnosis, management and care of adolescents. There has also been cooperation in the development of review papers on family planning, STIs and other aspects of maternal health among adolescents. These reviews are expected to assist countries in developing appropriate interventions for adolescents.

**DISSEMINATION OF INFORMATION**

As described earlier, a synthesis paper has been completed of findings pertaining to youth drawn from earlier research supported by HRP. A paper highlighting the importance of social science research in the protection of sexual and reproductive choice of adolescents was published in *Medicine and law*. The list of publications is given in Annex 3.

An edited volume is under preparation of articles giving the results of case studies on the topic of sexual behaviour, supported by HRP over the course of the 1990s in Africa, Asia and Latin America. Though intended for publication in 1999, scheduling difficulties encountered by some authors and reviewers have postponed publication of this volume to the year 2000.

A meeting was held to disseminate findings from the operations research conducted in Côte d’Ivoire to evaluate and improve reproductive health services for adolescents.

**WORKSHOPS AND MEETINGS**

Two workshops were held in Nairobi (Kenya) and Gramado (Brazil) to strengthen social science research proposals on adolescent sexual and reproductive health. Participants at these workshops are listed in Annex 2. A research workshop was also held in Shanghai (China) to discuss the results from the two multicentre studies described above.

Staff attended a meeting organized by the Commonwealth Medical Association (CMA) with input from WHO’s CAH on incorporating the rights of adolescents into national programmes. The meeting discussed ways in which the CMA may integrate the Convention on the Rights of the Child (CRC) and other human rights instruments into its work on adolescent health; and the kinds of strategies that might be developed to promote the use of the CRC by national medical associations and other professional associations. The meeting also discussed ways in which CMA could provide input for the reporting process to the Committee on the Rights of the Child and other relevant monitoring bodies of the human rights treaty.

In collaboration with WHO’s Eastern Mediterranean Regional Office (EMRO), the National Reproductive Health Research Group for the African and Eastern Mediterranean region organized an Intercountry Workshop on Adolescents’ Needs and Perspectives in Reproductive Health in Beirut, Lebanon. The objective of this workshop was to identify priority areas of research in the region. Three areas were identified for possible multicountry study: (i) improving reproductive health services for adolescents; (ii) adolescents’ knowledge of and attitudes to reproductive health and their sources of information; and (iii) the role of the mass media in influencing adolescent sexual and reproductive health. Concept papers for possible research support were drafted.

**FUTURE ACTIVITIES**

During 2000, the Department generally and the Component of Social Science Research on Reproductive Health in particular will continue research, capacity building and dissemination activities relating to adolescent sexual
and reproductive health. Recognizing that research on adolescents poses several difficulties in various settings and requires methodologies different from those used in studies of adults, the intention is to provide ongoing assistance to the 29 researchers whose projects are supported under the social science research initiative on adolescent sexual and reproductive health. As proposed at the launch of this research initiative, the aim is to develop a network of researchers through means such as (i) e-mail networking of participants; (ii) production of an electronic newsletter; (iii) establishment of a documentation centre and circulation of relevant materials and literature to investigators; and (iv) conducting research training workshops at critical stages in the implementation of research projects (design, analysis, reporting and dissemination). These activities will commence as soon as projects become operational; supplementary support for such activities is being sought. A few additional studies may be supported in 2000.

The Programme expects to finalize an edited volume of data from developing countries on the sexual behaviour of young people.

The operations research project in French-speaking African countries to evaluate and improve reproductive health services for adolescents will continue with technical support from HRP staff. In 2000, Senegal, Burkina Faso and Guinea will complete the first phase of the study. Plans for the intervention phase will be drawn up in these three countries and Côte d’Ivoire. The Programme will continue to assist the remaining two countries—Benin and Cameroon—to secure funds for their projects.

Concept papers drafted during the EMRO workshop will be further developed and presented to the Regional Advisory Panel in February. The intention is to facilitate, through support for research on at least one of the identified priority areas, an EMRO network on adolescent reproductive health research. The Programme will provide technical support to this activity and assist researchers in securing funding for this activity during the next biennium.

A study is to be conducted in Mongolia involving pre-adolescent females with vaginal symptoms who attend an outpatient clinic. This study responds to reports from providers in Mongolia of unusually high prevalence of lower genital tract infection among Mongolian pre-adolescents. Symptoms may have been observed by the adolescents themselves, or perceived by their mothers who bring their daughters to the clinic. Mothers of these pre-adolescents will be interviewed, and vaginal specimens will be collected from the pre-adolescents. Specimens will be screened for *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis*, *Candida* spp. and anaerobes. About 250 adolescents are to be recruited for this study.

A regional research initiative is to be launched in five countries of the Greater Mekong region—China (Yunnan Province), Lao PDR, Myanmar, Thailand and Viet Nam—to assess the reproductive health needs of a growing but vulnerable and marginalized subpopulation, i.e. young migrants. Studies will be conducted in a major city in each of these settings and will address risk behaviour, health-seeking behaviour and obstacles faced, and service and information needs. Qualitative and quantitative phases of the study are envisaged. Apart from enhancing what is known about young migrants in this setting, this initiative is intended to strengthen the research capacity through intraregional networking mechanisms in the Asia–Pacific region (for details, see the report on “Technical Support to Countries: Asia and the Western Pacific region”).
Annex 1

SCIENTIFIC REVIEW COMMITTEE ON SOCIAL SCIENCE RESEARCH ON REPRODUCTIVE HEALTH IN 1999

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C. Nzioka, University of Nairobi, Nairobi, Kenya  
O.A. Ojengbede, University of Ibadan, Ibadan, Nigeria  
A. Otieno, International Institute for Population Sciences, Mumbai, India  
C. Turaman, Training and Research Unit for Women and Child Health, University of Istanbul, Istanbul, Turkey  

**Resource persons**

A. Ajayi, The Population Council, Nairobi, Kenya  
K. Awusabo-Asare, Department of Geography and Tourism, University of Cape Coast, Cape Coast, Ghana  
A. Erulkar, The Population Council, Nairobi, Kenya  
S. Harbison, Agency for International Development (USAID), Washington, DC, USA  
N. Maggwa, The Population Council, Nairobi, Kenya  
P. Mbatia, Department of Sociology, University of Nairobi, Nairobi, Kenya  
M. Mhloyi, University of Zimbabwe, Centre for Population Studies, Zimbabwe  
G. Mpagile, Family Planning Association of Kenya (FPAK), Nairobi, Kenya  
S. Neema, Makerere Institute of Social Research, Makerere University, Kampala, Uganda  
W. Njau, Centre for the Study of Adolescence, Nairobi, Kenya  
K. Rogo, Centre for the Study of Adolescence, Nairobi, Kenya  

**Research Workshop on Adolescent Sexual and Reproductive Health, Gramado, Brazil (1–5 February 1999)**

A. González, PROFAMILIA, Bogotá, Colombia  
C. McCallum, Federal University of Bahia, Bahia, Brazil  
A.A. Moyano, Centre for Population Studies (CENEP), Buenos Aires, Argentina  
H. Munita, Corporation for Education and Prevention in Social Health and AIDS, Santiago, Chile  
B. Padin, Women’s Institute, Santiago, Chile  
S. Peres, Institute for Social Medicine, State University of Rio de Janeiro, Rio de Janeiro, Brazil
Annex 2 (continued)

Research Workshop on Adolescent Sexual and Reproductive Health, Gramado, Brazil (1–5 February 1999)

M. de la Peña M, Multidisciplinary Association for Research and Training in Population (AMIDEP), Lima, Peru
T. de Armas-Pedraza, National Institute of Endocrinology, Havana, Cuba
J. dos Anjos, Federal University of Rio Grande do Sul, Porto Alegre, Brazil
T. García-Alvarez, National Institute of Endocrinology, Havana, Cuba
G. Guajardo, Latin American Faculty of Social Sciences, FLASCO-CHILE, Santiago, Chile
E. Lucich, Maternal and Perinatal Institute, Lima, Peru
C. Pereda Feliu, School of Public Health, Faculty of Medicine, University of Chile, Santiago, Chile
J.A. Valle, Tegucigalpa, Honduras
A.M. Worbiej, Center for Interdisciplinary Rural Studies, Asunción, Paraguay

Resource persons

W. Baldwin, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA
L. Coser, Ministry of Health, Brasilia, Brazil
J. Espinaldo, Office of WHO Representative, Brasilia, Brazil
A. Fort, Director of Evaluation and Research, PRIME Project, Chapel Hill, NC, USA
R. Geldstein, Centre for Population Studies (CENEP), Buenos Aires, Argentina
D. Knauth, University of Porto Alegre, Porto Alegre, Brazil
O. Leal, University of Porto Alegre, Porto Alegre, Brazil
M. Maddaleno, Pan-American Health Organization, Washington, DC, USA
E. Pantelides, Centre for Population Studies (CENEP), Buenos Aires, Argentina
T. Pullum, Department of Sociology, University of Texas at Austin, Austin, TX, USA

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Annex 3

PUBLICATIONS IN 1999


Fertility regulation

Overview of the Department’s work

P. D. Griffin
INTRODUCTION

All four of the Department’s Teams namely, Research and Evidence, Development of Norms and Tools, Technical Support to Countries, and Advocacy and Human Rights, contribute to studies on fertility regulation, in one form or another. However, to avoid unnecessary duplication, this chapter focuses on the work carried out and planned in the Teams for Research and Evidence and Development of Norms and Tools.

RESEARCH AND EVIDENCE

In the area of work of the Team for Research and Evidence, activities have been carried out and are planned in the three broad disciplines of:

— social science research,
— epidemiological research, in the context of surveillance and evaluation of the safety and efficacy of existing fertility regulating methods, and
— biomedical research, in the context of development and evaluation of improved and new methods of fertility regulation.

Social science research

The ongoing and planned research in social science aspects of fertility regulation is focused on determining the perspectives of users and potential users in respect of different types of fertility regulation; the perspectives and preferences of men with regard to fertility regulation; the needs and perspectives of adolescents concerning fertility regulation; and strategies used for the selection and use of fertility-regulating methods to prevent unwanted pregnancies and sexually transmitted infections (STIs). This is presented in the chapter on “Users’ perspectives in the context of reproductive health”.

In 1999, findings from the qualitative research on Family Planning and Sexual Behaviour in the Era of HIV/STIs became available from Zimbabwe. Several studies on the Role of Men in Reproductive Health were also completed, and a new series of briefs highlighting policy and programmatic implications of social science research was launched. Studies were completed on the acceptability of emergency contraception, the condom and medical abortion, and a study on men’s and women’s perspectives of contraception in Pakistan was approved and will be implemented in early 2000.

Despite a high level of knowledge on the prophylactic nature of the condom, its acceptability and use remain low in many settings and among married couples. An exception is Jamaica, where men (particularly unmarried men in unstable relationships) express a preference for condoms to prevent infection. Men in Turkey are also willing to assume responsibility in family planning. However, misperceptions of modern methods and concerns regarding the potential side-effects of hormonal methods and the IUD partly explain why men and women in Turkey rely on withdrawal as a contraceptive method.

Emergency contraception was found to be acceptable to people, including adolescents who are sexually active, in Brazil, Chile, China and Mexico. A clinical trial to ascertain the acceptability of medical abortion, its administration in the home rather than at the clinic, and its provision without medical supervision is under way in 15 centres and 12 countries.

Plans for a new research initiative on the quality of care in reproductive health are well advanced, and the widespread dissemination of research findings through Social Science Research Policy Briefs will continue.

New and improved methods

The studies being carried out in the area of Technology Development and Assessment are focused on the development of improved and new methods of fertility regulation for use by women and men. This work is presented in the chapter on “Development of improved and new methods of fertility regulation”. Research has continued over the past year on emergency contraception, long-acting injectable hormonal preparations for use by women and men, immunocontraceptives and non-surgical methods of pregnancy termination. In addition, basic research has been carried out to identify new leads for male contraception and to investigate the mechanism and control of progestogen-induced endometrial bleeding. The past year also has marked the first year of funding of the joint WHO/ Rockefeller Foundation Initiative on Implantation Research.

At the request of the Scientific and Technical Advisory Group (STAG) at its meeting in 1999, the use of misoprostol alone for the termination of first-trimester pregnancies was reviewed by the Strategic Committee on Technology Development and Assessment and the Specialist Panel on Post-ovulatory Methods for Fertility Regulation. The information provided to these two groups, and the recommendations they made on the role of HRP in this area are presented in the section on “Development of improved and new methods of fertility regulation” of the report.

Safety and efficacy of existing methods

The work carried out during the past year by the Surveillance and Evaluation component of HRP is described in the chapter on “Safety and efficacy of existing methods of fertility regulation”. Most of the work of this component
relates to the safety of steroidal hormonal contraceptives in healthy women and, recently, in women infected with HIV. In addition, this component is continuing to investigate the safety and efficacy of long-term use of IUDs, the safety of vasectomy and the optimal conditions for use of the female condom.

During 1999, reports resulting from the secondary analyses of data from the WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception were published. These reports included: (i) information on migraine and combined oral contraceptive use; (ii) risk of stroke associated with the use of different oral contraceptive formulations; and (iii) cardiovascular risks associated with the use of progestogens for therapeutic purposes. The two latter reports were published simultaneously with complementary analyses commissioned by HRP from the United Kingdom General Practice Research Database (GPRD). A further commissioned analysis from the GPRD revealed no cases of venous thromboembolism occurring within 45 days, in over 100 000 episodes of use of the Yuzpe regimen of emergency contraception (incidence less than 31 per 100 000 woman–years).

The results obtained in a multicentre study to investigate the possible interaction between hormonal contraceptive use and bone mass were published in 1999. A five-year, prospective study of bone mass in young women (age 15–19 years) and of those near the menopause (age 45–49 years) has been launched in Durban, South Africa and this project will be extended, as a multicentre study, to Asia and Latin America in 2000.

Two papers reporting the outcome of the main analysis of data obtained in the study on post-marketing surveillance of Norplant have been prepared and will be submitted for publication in Contraception in early 2000. A short paper providing a summary of these results will be published at the same time.

A study is being conducted to evaluate the safety of use of hormonal contraceptives by women with systemic lupus erythematosus and a multicentre study is under way in China to evaluate the effect of mifepristone-induced abortion on a subsequent wanted pregnancy.

Studies on the long-term safety and efficacy of the Multiload 375 and the 20 μg levonorgestrel-releasing IUDs, compared to the TCu380A device, continued throughout 1999, marking the ninth and fifth years, respectively, of the ongoing study of these two devices.

As part of HRP’s research on factors affecting the transmission of HIV, a study on the effect of hormonal contraceptives on the vaginal epithelium was completed during the past year and a report is expected shortly. The research instruments and logistics of the multicentre studies to compare the effects of different contraceptives used by HIV-1 seropositive women on the clinical course of HIV-1 infection and cervical/vaginal shedding of HIV-1, were revised during the past year after a pilot phase evaluation. Data collection will start in early 2000.

A study on the contraceptive effectiveness of the female condom, compared to the male condom, will be launched in four countries in early 2000, and a consultation on the safety of female condom reuse is planned for the first half of 2000.

A study is under way in New Zealand to determine if there is any relationship between prostate cancer and vasectomy.

DEVELOPMENT OF NORMS AND GUIDELINES FOR FERTILITY REGULATION

The work carried out by the Department during the past year on the development of norms and tools relevant to fertility regulation is presented in the section on “Norms and guidelines for use of methods of fertility regulation”. This work has focused on: (i) increasing data on contraceptive options; (ii) the development and updating of technical guidelines and training materials on family planning methods; (iii) the development and updating of technical guidelines and training materials on family planning services; and (iv) creating a collaborative process to support effective dissemination, adaptation and utilization of the documents generated by the Department. This last activity is being carried out as an inter-agency exercise and is focusing on structuring the manner in which technical documents are distributed in order to assist countries in using these documents to improve access to, and the quality of, family planning and reproductive health services (for more detail of this activity, see the section on page 212 entitled “Inter-agency collaboration: development of a strategy to support the dissemination, adaptation and utilization of the Department’s technical guidance documents”). As such, this activity also provides an important linkage between the Department’s strategic operational objectives of developing norms and tools and of technical support to countries.
Fertility regulation

Development of improved and new methods of fertility regulation

C. d'Arcangues, P.D. Griffin, H. von Hertzen, M.Q. Islam, M.K. Mbizvo
INTRODUCTION

Funding constraints have restricted the research supported during the past year to certain high-priority leads identified by the Strategic Committee on Technology Development and Assessment at its meeting in November 1997 (Table I). These include emergency contraception, injectable hormonal preparations for use by women and men, immunocontraceptives and non-surgical methods of pregnancy termination. Progress on some of these high-priority leads has been slower than anticipated because of unexpected technical difficulties or delays caused by prolonged discussions with potential industrial partners.

The research completed, under way and planned on these leads is reviewed at two-yearly intervals by the Strategic Committee, which assigns each lead to either a high-priority, medium-priority or low-priority category on the basis of criteria such as: (i) technical feasibility of their development into safe, effective and acceptable methods for use by women and men; (ii) expressed need and preference of users; and (iii) the likelihood of industry involvement in their future development and manufacture.

At its meeting in Geneva on 1–3 December 1999, the Strategic Committee reviewed the progress made on each of these leads and the work plans for the biennium 2000–2001. It discussed the need for work on those leads in the medium-priority and low-priority categories on which research had not been carried out during the past year, as well as other research areas that warranted attention by HRP but which were not currently part of its research portfolio. Each member of the Strategic Committee was requested, from their perception of public health needs in the area of fertility regulation and associated reproductive health technologies, to score the various leads, approaches and research needs in order of importance. As not all members voted on each lead, and some leads showed a wide variation in votes, the means of the assigned scores were used to compile a revised priority listing (Table II).

The following lead-specific sections of the report follow the priority sequence of leads selected at the November

Table I. Product lead priorities—November 1997

<table>
<thead>
<tr>
<th>High-priority leads</th>
<th>Medium-priority leads</th>
<th>Low-priority leads</th>
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<tbody>
<tr>
<td><strong>For women</strong></td>
<td></td>
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<tr>
<td>Antiprogesterone-only emergency contraception (mifepristone)</td>
<td>Contraceptive vaginal ring (levonorgestrel-releasing)</td>
<td>An estrogen-free daily pill (sequential mifepristone and progestogen)</td>
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<tr>
<td>Progestogen-only emergency contraception (levonorgestrel)</td>
<td>Calendar method of Natural Family Planning</td>
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<tr>
<td>Orally-active abortion regimen (mifepristone plus misoprostol)</td>
<td>Postpartum contraception (Lactational Amenorrhoea Method)</td>
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<td>A three-monthly injectable (levonorgestrel butanoate)</td>
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<tr>
<td>A six/twelve-monthly injectable (hCG immunocontraceptive)</td>
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<td><strong>For men</strong></td>
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<tr>
<td>Three-monthly injectables (testosterone buciclate alone or levonorgestrel butanoate plus testosterone buciclate)</td>
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<td>Non-surgical vas occlusion (silicone plugs)</td>
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<tr>
<td><strong>High-priority leads</strong></td>
<td><strong>Medium-priority leads</strong></td>
<td><strong>Low-priority leads</strong></td>
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<td><strong>For women</strong></td>
<td><strong>For men</strong></td>
<td><strong>For women</strong></td>
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<tr>
<td>Dual-protection methods</td>
<td>Combined contraceptive vaginal ring</td>
<td>An estrogen-free daily pill (sequential mifepristone and progestogen)</td>
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<tr>
<td>Three-monthly injectable (levonorgestrel butanoate)</td>
<td>Non-surgical abortion (see also medium-priority leads)</td>
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<tr>
<td>Emergency contraception (see also medium-priority leads)</td>
<td>Lactational Amenorrhoea Method</td>
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<tr>
<td>Combined contraceptive vaginal ring</td>
<td>Natural family planning—calendar method</td>
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<tr>
<td>Non-surgical abortion (see also medium-priority and low-priority leads)</td>
<td>Current hCG immunocontraceptive (see also medium-priority leads)</td>
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<tr>
<td>Lactational Amenorrhoea Method</td>
<td>Basic research on implantation (WHO/Rockefeller Foundation)</td>
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<tr>
<td>Natural family planning—calendar method</td>
<td>Basic research on mechanisms of endometrial bleeding</td>
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<tr>
<td>Current hCG immunocontraceptive (see also medium-priority leads)</td>
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<tr>
<td>Basic research on spermatogenesis and spermiogenesis</td>
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<td>Six/twelve-monthly injectable for women: optimized hCG formulation</td>
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<td>Emergency contraception: comparison of mifepristone and gestrinone</td>
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<td>Non-surgical abortion: mifepristone plus misoprostol for late first-trimester abortion</td>
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<td>Non-surgical abortion: mifepristone plus misoprostol for second-trimester abortion</td>
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Table II. Product lead priorities—December 1999
1997 meeting of the Strategic Committee and not the revised priority sequence recommended for future work by that Committee in December 1999. There is no report on two leads: non-surgical vas occlusion with silicone plugs, and the sequential use of mifepristone and a progestogen as an estrogen-free daily pill, as these were subsequently discontinued in 1998 (refer to Annual technical report 1998). With regard to the items on the revised list, it should be noted that HRP has not yet funded any research on new dual protection methods, such as microbicides/spermicides. However, HRP is expecting funds, through the Joint United Nations Programme for HIV/AIDS (UNAIDS) unified work plan and budget, for the 2000-2001 biennium to investigate promising preparations with these properties, and will collaborate with other agencies by supporting some of the centers participating in multicentre clinical trials of such preparations.

**EMERGENCY CONTRACEPTION (LEVONORGESTREL; MIFEPRISTONE)**

**Rationale for the product**

The Yuzpe regimen of combined oral contraceptives (100 µg ethinylestradiol plus 500 µg levonorgestrel, repeated after 12 hours) was, until recently, the only hormonal method for emergency contraception. However, mainly due to its side-effects, this method is not fully satisfactory for this purpose HRP, therefore, has been looking for new approaches and has investigated the potential of two compounds, levonorgestrel and mifepristone, for this indication.

**Current stage of development and assessment**

**Levonorgestrel**

HRP’s Annual technical report 1998 draws attention to the results published in August 1998 (The lancet, 352:428–433), of a large randomized, double-blind, multinational study comparing the efficacy and side-effects of levonorgestrel, given as two 0.75 mg doses 12 hours apart, with the Yuzpe regimen in emergency contraception.

The total number of women in the study was 1998. The pregnancy rate was 3.2% (95% CI 2.2–4.5) among the 997 women randomized to the Yuzpe regimen whereas it was 1.1% (0.6–2.0) among those assigned to the levonorgestrel treatment. In both groups, treatment was given within 72 hours after a single act of unprotected intercourse.

This trial produced several findings of public health importance which have major implications for emergency contraception services and counselling of women: (i) the levonorgestrel regimen was better tolerated than the Yuzpe regimen; (ii) the efficacy of the levonorgestrel regimen was greater, in terms of both crude and adjusted pregnancy rates and pregnancies prevented; and (iii) for both methods combined, efficacy was significantly greater the sooner the treatment was started after unprotected coitus. The overall pregnancy rate increased from 0.5% (treatment within 12 hours) to 4.1% (treatment between 61–72 hours). Postponement of the first dose by 12 hours raised the odds of pregnancy by almost 50%.

These findings had a major impact on the communities of family planning providers, decision-makers and researchers. There were requests from all corners of the world for further details of the study especially in respect of the rather low efficacy of the Yuzpe regimen, as suggested by the study. The results were discussed in The lancet and other journals, and additional analyses were carried out on the effect of treatment delay on efficacy of the treatment (The lancet, 1998, 352:1939–1940; The lancet, 1999, 353:721).

The study has also had a major impact on emergency contraception services. Drug regulatory authorities in several countries have expressed interest in registering the levonorgestrel-only method, and guidelines for providers are being updated. The International Consortium for Emergency Contraception had already selected levonorgestrel as the method of emergency contraception for introduction in family planning services through model programmes in Indonesia, Kenya, Mexico and Sri Lanka, on the basis of interim results in 1996. A two-pill pack of 0.75 mg levonorgestrel has now been registered for emergency contraception in Brazil, Canada, China, France, Hungary, Jamaica, Kenya, Nigeria, Sri Lanka, Thailand, the United Kingdom, the USA, Viet Nam and Yemen. Negotiations are ongoing with regard to registration in several additional countries. This study has contributed in a major way to making emergency contraception better known and more available to women in several parts of the world.

**Mifepristone**

Antiprogestogens such as mifepristone appear to have a great potential for emergency contraception as their administration either blocks or delays ovulation when administered prior to ovulation, or retards endometrial development when administered shortly after ovulation. This was confirmed in two studies with a 600 mg dose, as reported in the HRP’s Annual technical report 1992. HRP then compared in a randomized, multinational trial the efficacy and side-effects of three doses (600 mg, 50 mg and 10 mg) of mifepristone when administered up to 120 hours (five days) after unprotected coitus. The results of this study were published in February 1999 (The lancet, 1999, 353:697–702).

A total of 1717 women in 11 family planning clinics in six countries (Australia, China, Finland, Georgia, the United...
Kingdom and the USA) participated in the study. In all, 21 women were found to be pregnant after treatment, including one woman who was found retrospectively to have been pregnant at the time of treatment. It appeared that six women may have conceived two weeks or more after the act of intercourse that prompted treatment. These were probably not method failures; however, they were left in the analysis. Two pregnancies were tubal, both in the 50 mg group. Pregnancy risks were similar in all three treatment groups (seven [1.3%] of 559 in the 600 mg group; six [1.1%] of 560 in the 50 mg group, and seven [1.2%] of 565 in the 10 mg group). A comparison of the numbers of expected and current pregnancies (136 vs 20) revealed that the treatment appeared to have prevented 85% of pregnancies. Women with no further acts of intercourse had lower pregnancy rates (one [0.3%] of 328 in the 600 mg group; three [1.0%] of 308 in the 50 mg group; and one [0.3%] of 307 in the 10 mg group).

One of the secondary aims of the study had also been to see whether the effectiveness was related to the timing of the treatment. There were, however, too few pregnancies to draw any conclusion on this. Despite the 60-fold difference between the doses used, there was no significant difference in other side-effects, except for the onset of the next menses, which was significantly (p<0.01) related to the dose of mifepristone (36%, 23% and 18% of women had menses delay after 600 mg, 50 mg and 10 mg, respectively).

The results of the study have several practical implications. A lower dose of mifepristone would be substantially cheaper and would make a delay in the onset of the next menses less likely. Such a delay not only adds to anxiety that the treat may have failed, but a delay in ovulation also exposes the woman to the risk of pregnancy, should she have further acts of unprotected intercourse during the treatment cycles.

HRP is participating, in a technical capacity, in a collaborative three-year initiative in China, which aims at developing mifepristone for indications to reduce unwanted pregnancies and recourse to abortion. This work is funded by the Rockefeller Foundation, and the HRP Secretariat is assisting the State Family Planning Commission of China in the clinical research programme which will, among other things, develop a locally produced mifepristone for emergency contraception. Under this initiative, the clinical phase has recently completed a randomized, double-blind study involving 10 Chinese centres to compare the efficacy and side-effects of the 10 mg and 25 mg doses of mifepristone manufactured in China. The study included 3002 women, and the final results are expected to be available during 2000. The study protocol and the forms for data collection were developed by HRP in collaboration with the National Research Institute for Family Planning, Beijing. This research provided the opportunity for the implementation of Good Clinical Practice (GCP), including the auditing of centres as well as guidance in data management and analysis.

An important question that remains to be answered is whether mifepristone is a better choice than levonorgestrel. The levonorgestrel regimen that has been used so far shares one of the disadvantages of the Yuzpe regimen, namely, the 12-hour interval between the administration of the two doses of the drug. The method would be more practical if the two doses could be administered at the same time. To determine if this would be effective, HRP is currently carrying out a large multinational, randomized double-blind study comparing the efficacy and side-effects of 10 mg of mifepristone and two treatments of levonorgestrel, i.e. two doses of 0.75 mg of levonorgestrel administered at 12-hour intervals, and a single dose of 1.5 mg, when used for emergency contraception, up to 120 hours after unprotected intercourse. The trial, which started in mid-1998, is being carried out in 15 centres in nine countries (China, Finland, Georgia, Hungary, India, Mongolia, Sweden, Switzerland and the United Kingdom). The target is to enrol 4200 women in the study, and over 3600 of them had been recruited by the end of 1999. It is expected that the clinical phase will be completed by mid-2000 and the results will be available later in 2000.

Ancillary studies

Effectiveness, acceptability and side-effects of IUD insertion

The copper intrauterine device (IUD) can, in certain cases, be used as an alternative to hormonal methods of emergency contraception. A meta-analysis of 19 studies of postcoital insertion of IUDs revealed a failure rate of at least 0.1%, which suggests that the efficacy of this method is some 15 times higher than that of the Yuzpe regimen. An IUD can be inserted up to the estimated time of implantation, i.e. some five days after ovulation (or five days after unprotected intercourse if the day of ovulation is difficult to estimate). The IUD is effective as soon as it is inserted, i.e. some five days after ovulation (or five days after unprotected intercourse if the day of ovulation is difficult to estimate). The IUD is effective as soon as it is inserted and therefore not only provides immediate protection in subsequent acts of intercourse in the same cycle but also up to 10 years of subsequent contraceptive protection.

Side-effects or morbidity after insertion of the IUD for emergency contraception have not been studied prospectively. In standard practice, IUDs are inserted early in the cycle, which is not usually the case when they are used for emergency contraception. In terms of efficacy, all previous studies, except one, did not compare the observed with the expected numbers of pregnancies. In countries where the prevalence of IUD use is high, and where women who seek emergency contraception are already parous, the IUD could be an excellent method for emergency...
contraception for many women. Therefore, it is important to look at the efficacy, acceptability, side-effects and possible complications of this method in a prospective study.

Thus, HRP, in collaboration with the National Research Institute for Family Planning, Beijing, China, launched a study on the use of TCu380A in emergency contraception in 16 Chinese centres. The aim is to recruit a total of 2000 women for the study and follow them up for one year after IUD insertion to observe the continuation rate and late side-effects, if any. By November 1999, a total of 1713 women had been enrolled and some 900 women had completed the study. It is estimated that the recruitment for the study will be completed in early 2000 and, after the one-year follow-up of the volunteers, the final results should be available in 2001.

The interim results of the study look very promising: until now no woman has become pregnant in the treatment cycle. Two women conceived, however, with an IUD in situ, one after eight and the other after 12 months of use. No serious adverse effects or complications have been reported so far. Pelvic inflammatory disease has been a special concern when using an IUD for emergency contraception, but until now no such cases have occurred among study participants. The results of life-table analysis at three months, including over 1500 women, showed an expulsion rate of 1.5 (26 cases) per 100 woman-years and a rate for medical removals of 2.5 (42 cases). A total of 40 of the 42 removals were because of pain and/or bleeding. The total use-related discontinuation rate was 4.0 per 100 woman-years. The rate of medical removals is comparable with the studies of interval insertion of copper IUDs.

**Planned studies**

*Mechanism of action studies*

Despite the fact that the regimens used in emergency contraception may simply consist of altered doses of widely-available contraceptive pills, women may hesitate to use them because of religious or other reasons as they may think that the mode of action of the regimen is either abortifacient or that the method acts by preventing implantation of a fertilized egg. It is therefore important to clarify the mechanism of action of emergency contraceptives so that women can decide if these methods are acceptable to them and choose between the methods in case their mode of action is different. Depending on the stage of the cycle when the treatment is given, emergency contraceptives may affect follicular development, ovulation or corpus luteum function, and there is also evidence suggesting influence on the endometrium. They may also perhaps interfere with fertilization or affect the characteristics of cervical mucus, thereby trapping sperm.

As no information exists on the mode of action of the levonorgestrel regimen of two tablets of 0.75 mg given at a 12-hour interval, research is being carried out to investigate the effects of this regimen on various events leading to fertilization and the establishment of pregnancy. To this end, several new research initiatives have been planned together with HRP’s collaborating centres. For example, four collaborating centres (one in Argentina, two in Chile and one in Mexico) have established a “Latin-American Network for Research on the Mechanisms of Action of Hormonal Preparations used for Emergency Contraception” with technical and financial assistance from HRP. Several research projects are planned to be launched in 2000 with this network (see the section on “Technical Support to Countries—The Americas”).

Three centres in Nigeria participated in the previous multicentre study on levonorgestrel and the Yuzpe regimen, and the two-pill levonorgestrel regimen of emergency contraception has now been registered there. HRP will provide technical and financial assistance to these centres in their effort to launch a multicentre study to investigate the efficacy and side-effects of the one-dose regimen of 1.5 mg of levonorgestrel as compared with the standard two-pill regimen in their population.

**NON-SURGICAL ABORTION**

*Rationale for the product*

HRP’s research on non-surgical abortion started more than 20 years ago. For a number of reasons, WHO has been the only international organization able to consistently pursue research and development activities in this highly sensitive area. HRP was the first to test the sequential regimen of mifepristone and a prostaglandin analogue for the termination of an early pregnancy. This approach resulted in a viable alternative to surgical abortion, and was first registered and used in France, followed by the China, Sweden and United Kingdom. More recently, the method has been launched in nine additional countries—Austria, Belgium, Denmark, Finland, Germany, Israel, the Netherlands, Russia and Switzerland. The registered treatment regimen, to be used in pregnancies of up to 49 days’ gestation, is 600 mg of mifepristone followed 48 hours later by two tablets of 0.4 mg of oral misoprostol or 1 mg of vaginal gemeprost. In Sweden and the United Kingdom, mifepristone with gemeprost is also registered for use up to 63 days of gestation.

Although the non-surgical abortion regimen is already in routine use, several improvements were regarded as necessary for the method to be practical in developing countries. First, in many settings, the 600 mg dose of mifepristone was likely to be beyond the financial means of many people. Therefore, if lower doses of the drug...
could be used, it would lessen the costs of the treatment, making it available to a larger number of women.

Second, women in many countries did not seek abortion until after the second missed menses and, therefore, a method that could be administered only up to seven weeks of pregnancy would not have much use in such settings. It was, therefore, important to identify ways for increasing the efficacy in pregnancies of up to nine weeks. The vaginal prostaglandin gemeprost, which has been registered in Sweden and the United Kingdom for use in combination with mifepristone in pregnancies of up to nine weeks’ gestation, is expensive and unstable at room temperature, whereas misoprostol, which is a less expensive and more stable prostaglandin, would be more suitable for developing countries. Results from efficacy studies suggested, however, that 0.4 mg of oral misoprostol was not effective in amenorrhoea of more than seven weeks. Thus, there is a need to identify effective regimens that could also be used in amenorrhoea of more than seven weeks.

Finally, the duration and amount of vaginal bleeding could be a concern, especially in countries with high prevalence of anaemia, as the bleeding tended to be longer and its amount greater after medically-induced as compared with surgically-induced abortion. The method would be safer to use if ways could be identified for the reduction of postabortion bleeding.

When the final regimen has been identified, its acceptability needs to be investigated in various settings in comparison to surgical abortion. It was also important to establish what service delivery requirements was necessary for the provision of non-surgical abortion technology.

**Current stage of development and assessment**

**First-trimester abortion**

The efficacy of various mifepristone and misoprostol treatment regimens in terminating pregnancies of up to nine weeks (63 days) of gestation

**Dose of mifepristone.** As reported in previous Annual technical reports, all three randomized double-blind studies carried out by HRP comparing the 600 mg and 200 mg doses of mifepristone, followed by different prostaglandin analogues (gemeprost or misoprostol), suggest that the 200 mg dose is equally effective as the 600 mg dose and that the efficacy of the regimen is not improved by increasing the dose of mifepristone.

A recent randomized double-blind study carried out by HRP clearly shows that, with advancing gestation, the role of prostaglandin becomes more important. This trial, carried out in 17 centres involving 1589 women, compared the efficacy and side-effects of 200 mg versus 600 mg of mifepristone followed, 48 hours later, by an oral dose of 0.4 mg of misoprostol. The participants in the study were randomly assigned within gestational age strata to receive either of the two mifepristone doses.

In addition to the finding that the two doses of mifepristone had equal efficacy, this study showed that oral misoprostol is not effective in pregnancies beyond seven weeks’ gestation: the complete abortion rates for the 200 mg and the 600 mg mifepristone groups combined declined from 92.2% at the earliest gestational ages to 80.3% at the latest. A worrying finding was that the rate of continuing live pregnancies increased from 1.4% and 1.2% in the two earliest gestational age groups to 9.0% in the women with four to five weeks’ delay (p<0.01) (British journal of obstetrics and gynaecology, 2000, 107:524-530). These findings are consistent with the results from a similar study carried out by the Population Council (New England journal of medicine, 1998, 338:1241–1247) and stress the importance of accurate estimation of the length of gestation before treatment, especially if oral misoprostol is used, as well as the need for follow-up of the women after treatment.

Softening and dilatation of the cervix becomes progressively more important as the length of gestation increases, as does the contractility of the myometrium. HRP, therefore, together with the investigators in Stockholm, designed a study to compare the pharmacokinetics of misoprostol and uterine contractility after oral and vaginal administration.

Repeated administration of misoprostol may also improve clinical efficacy. However, before testing the effects of repeated administration on efficacy, HRP supported a small study to investigate the extent of side-effects, following mifepristone pretreatment of a vaginal dose of 0.4 mg of misoprostol, followed by a two-week course of daily oral intake (0.4 mg twice daily) of misoprostol. The comparison group received mifepristone followed by the vaginal dose of 0.4 mg only. All the women in this pilot study had complete abortions, and the prolonged treatment regimen was well tolerated.

Information from the abovementioned studies was used to design a randomized, double-blind study, launched in late 1998/early 1999 in 15 centres, to compare the efficacy and side-effects—including the duration of bleeding—of different regimens of misoprostol, when administered after 200 mg mifepristone in pregnancies of up to 63 days of amenorrhoea. One of the aims is to try to maximize the efficacy of medical abortion and to observe whether continued administration of misoprostol has any advantage in terms of efficacy and the duration and amount of bleeding.
**Second-trimester abortion**

HRP has not provided financial support for research on the termination of second-trimester pregnancies. It has, however, given technical advice and has procured mifepristone and placebo tablets for such studies. This research has examined ways for improving the efficacy of the procedure by using mifepristone treatment prior to the induction of abortion with prostaglandins as well as by testing different prostaglandin regimens.

It is clear from these studies that pretreatment with mifepristone followed by prostaglandin is superior to any of the currently-used alternatives (natural or synthetic hydrophilic dilators or prostaglandin preparations alone) in the efficacy and the induction-to-abortion interval as well as in the amount of prostaglandin needed. These trials also suggest that the prostaglandin analogue misoprostol is as effective as gemeprost in inducing second-trimester abortion (Annual technical report 1996). Also, after mifepristone pretreatment, misoprostol was more effective when administered vaginally than orally in terms of induction-to-abortion time, the percentage of women aborting within 24 hours and the median amount of misoprostol required for terminating pregnancies of 14–20 weeks of gestation (Annual technical report 1998).

**Ancillary studies**

**Cervical priming with misoprostol**

In spite of the advantages offered by medical, noninvasive approaches, surgical termination of pregnancy is likely to remain the choice of many women. In addition, surgical termination may continue to be the preferred method in certain situations, such as in late first-trimester and early second-trimester pregnancies, because a medical abortion method is likely to result in a high proportion of incomplete abortions, necessitating subsequent surgical intervention to avoid complications such as excessive bleeding or infection.

The Scientific Group Meeting on Medical Methods for Termination of Pregnancy, convened in April 1994, stated that “there is a need for a large randomized trial to investigate the cost-effectiveness of cervical preparation”. With the advent of misoprostol, a cheap and stable prostaglandin analogue for cervical priming could be carried out as a routine practice before surgical abortion, as it could make the procedure even more safe, especially in developing countries.

Before a study can be launched to investigate whether routine priming of the cervix with misoprostol will improve surgical methods of abortion, HRP carried out research to identify the lowest effective dose and the shortest time interval that is needed between administration of misoprostol and surgery.

**Progress made during the past year**

**First-trimester abortion**

**Efficacy of various misoprostol regimens after pretreatment with mifepristone in terminating pregnancies of up to nine weeks (63 days) of gestation**

A randomized, double-blind study was launched in late 1998/early 1999 in 15 centres: Beijing, Hong Kong SAR and Shanghai in China; Chandigarh, Mumbai and New Delhi in India; Helsinki in Finland; Ho Chi Minh City in Viet Nam; Ljubljana in Slovenia; Oslo in Norway; Singapore; Stockholm in Sweden; Szeged in Hungary; Targu-Mures in Romania; and Ulaanbaatar in Mongolia. This study involves three misoprostol regimens: (i) initial oral dose of 0.8 mg continued with oral dose of 0.4 mg twice daily for 7 days; (ii) initial vaginal dose of 0.8 mg continued with oral dose of 0.4 mg twice daily for 7 days; and (iii) the vaginal dose of 0.8 mg only. The recruitment target is 2250 women, 750 women for each of the three amenorrhoea categories of: (i) up to 49 days; (ii) 50–56 days; and (iii) 57–63 days.

By the end of 1999, a total of 1896 women had been enrolled for this trial, which is likely to be completed during the first few months of 2000. In addition to assessing efficacy and side-effects, a brief questionnaire is included in the study to find out women’s opinion on the regimen as well as whether they would feel confident to use the regimen at home, and whether home use is their preference should they be given the choice.

In connection with this multicentre trial, the participating centre in Romania carried out a study, in collaboration with HRP’s Research Group on Technology Introduction and Transfer, to investigate the impact on service delivery of the introduction of mifepristone and misoprostol for early termination of pregnancy. This project involved the collection of baseline data on current abortion services followed by the introduction of medical technology for pregnancy termination. The study also assessed acceptability of this new technology to clients and providers as well as its impact on service delivery. The data are currently being analysed, and the results should be available by mid-2000.

HRP procured the mifepristone tablets for a randomized multicentre study carried out by the Indian Council for Medical Research in 10 Indian centres, comparing the efficacy and side-effects of two prostaglandin analogues, vaginal meteneprost (5 mg) and oral misoprostol (0.6 mg) after pretreatment with 200 mg of mifepristone. The study, which was completed in 1999, included a total of 887 women who requested pregnancy termination within 28 days of missed menses. The efficacy of the two regimens was
similar, with complete abortion rates of 85.3% among 449 women in the meteneprost group and 88.1% among 438 in the misoprostol group. A somewhat higher percentage of all side-effects was reported in the oral misoprostol group. Due to excessive bleeding, a total of six women in each group required intravenous fluids. In addition, blood transfusion was necessary for two women, one in each prostaglandin group (Contraception, 2000, in press).

Second-trimester abortion

HRP has provided the mifepristone tablets for a study that aimed to compare the efficacy and side-effects of vaginal administration of 0.2 mg of misoprostol and the oral dose of 0.4 mg misoprostol after pretreatment with 200 mg of mifepristone in pregnancies of 14–20 weeks’ gestation. The study was carried out in Hong Kong SAR, and the results have been submitted for publication.

There was no significant difference in complete abortion rates between the groups: 81.4% of the women in the oral group and 75.4% in the vaginal group aborted within 24 hours. In the oral group, the incidence of diarrhoea (40% vs 23%) and the amount of drug used (1.734 mg vs 0.812 mg) were significantly higher than in the vaginal group. Overall, 82% of women preferred the oral route. The conclusion from the study was that the two regimens had similar efficacy and that the oral regimen could be offered to women who found repeated vaginal administration of the drug unacceptable.

Control and management of postabortion bleeding

During the past year, the results were published of a randomized double-blind placebo-controlled study assessing the effects of oral contraceptive pills on the outcome of medical abortion and the duration of postabortion bleeding (Human reproduction, 1999, 14:722–725). This study, which was supported by HRP and carried out in Hong Kong SAR and Shanghai, included, in each centre, a total of 100 women in the first 49 days of pregnancy. The women were treated with 200 mg mifepristone, followed two days later by the administration of 0.4 mg misoprostol vaginally. A day later they were randomized to receive either oral contraceptive (OC) pills (30 µg of ethinylestradiol and 0.15 mg levonorgestrel per tablet) or placebo for 21 days.

The complete abortion rates were 98% in the OC group and 99% in the placebo group. The median duration of bleeding was similar, but there was a significant fall in haemoglobin concentration by two weeks (5.3 g/dl) in the OC group. The indirect finding from the study that OC pills might, in fact, increase the amount of bleeding after medical abortion, was unexpected, and required further investigation. To this end, a study was launched in late 1999 in Hong Kong and Shanghai to measure the actual blood loss among 50 women at each centre following medical termination of pregnancies of up to 63 days’ duration.

The effect of repeated administration of misoprostol on the duration and amount of bleeding following termination of pregnancies of up to 63 days’ gestation is also being investigated in connection with the multicentre study of three misoprostol regimens following pretreatment with mifepristone. While all 15 centres collect information on the duration of bleeding in the three treatment groups, one centre (Hong Kong SAR) is also measuring the actual blood loss for all 150 women enrolled in the trial by that centre to determine if differences can be seen between the three prostaglandin regimens in this respect.

Ancillary studies

During the past year, a study comparing uterine contractility after oral and vaginal administration of misoprostol was completed and the results published (Obstetrics and gynecology, 1999, 93:275–280). The oral administration of misoprostol did not induce regular contractility in most of the women studied. In contrast, when misoprostol was given vaginally, it resulted in a gradually rising uterine tonus and regular contractility which continued beyond the four-hour observation period of the study. These findings explain why the clinical efficacy of misoprostol is low after oral administration in more advanced pregnancies as well as why the use of vaginal administration produces so much better results.

Cervical priming with misoprostol

Previous studies suggested that misoprostol was effective for cervical priming, but the optimal dose and route of administration needed to be defined. Therefore, a double-blind, placebo-controlled study was designed, together with investigators in Hong Kong SAR, to compare oral and vaginal doses of 0.2 mg and 0.4 mg of misoprostol administered three hours prior to suction evacuation in pregnancies of 8–12 weeks’ duration. This study was completed and the results published during the past year (Human reproduction, 1999, 14:2139–2142).

The project involved 225 nulliparous women who were randomized to five treatment groups (0.2 mg or 0.4 mg misoprostol, given either orally or vaginally, and placebo). The baseline cervical dilatation was significantly increased in misoprostol-treated groups as compared to the placebo group and this effect was dose-related in the oral but not in the vaginal group. The cumulative force required to pass through the cervix and blood loss during the aspiration procedure were significantly decreased in misoprostol-treated groups. The incidence of side-effects in the misoprostol groups was not related to the route or dose of medication.
As women preferred oral administration of the drug, the investigators recommended that the oral dose of 0.4 mg be used for cervical dilatation given three hours prior to vacuum aspiration.

**Planned studies**

**First-trimester abortion**

The 15-centre study comparing three misoprostol regimens after pretreatment with mifepristone will be completed in early 2000 and the results analysed during the first half of the year. It is expected that the outcome of the study will indicate whether there is a need to improve further the efficacy of the non-surgical abortion regimen and, if so, how this may be done. It is also hoped that the results will suggest possible ways on how to influence postabortion bleeding.

If an effective regimen is identified among those tested in the study, there are plans to collaborate with the Social Science Unit of HRP to investigate the acceptability of the regimen as compared with surgical abortion in different settings. Service delivery-related aspects of this medical regimen will be investigated in collaboration with HRP’s Unit for Technology Introduction and Transfer.

The wide availability and reasonably low price of misoprostol, as compared with other prostaglandin analogues, have contributed to its use and to a renaissance of research on a prostaglandin-only method of pregnancy termination with this compound in countries where mifepristone has not been available. To date, published data consist of case-series reports, in which the definition for successful treatment sometimes includes incomplete abortions. An as yet unpublished study of 80 women, carried out by a collaborating centre in Hong Kong SAR, suggests complete abortion rates of up to 90% in pregnancies of less than seven weeks’ gestation, but the efficacy decreases with increasing length of gestation.

Some providers of the method have suggested that WHO carry out studies on the efficacy and safety of the use of misoprostol alone for termination of early pregnancy in order to provide information and establish guidelines for its use. The involvement of HRP in the development of a misoprostol-only regimen for pregnancy termination was discussed at the meeting of the Strategic Committee for Technology Development and Assessment in December 1999. The Committee felt that a comparative study could be carried out in countries and centres where abortion is legal but where mifepristone is not available. This would enable the safety, effectiveness and acceptability of the misoprostol-alone regimen to be compared with the routine first-trimester termination method in use in those centres and would ensure access to safe back-up abortion services in those cases where the misoprostol treatment was not effective. The feasibility of undertaking such a study is under consideration.

**Second-trimester abortion**

Some treatment regimens involving repeated vaginal administration of misoprostol alone without mifepristone pretreatment, have been claimed to have a high success rate in terminating second-trimester pregnancies. As mifepristone is expensive and not widely available, it was proposed to carry out a randomized study to compare the efficacy and side-effects of vaginal misoprostol, with and without mifepristone pretreatment, in terminating second-trimester pregnancies. The protocol for such a study has been developed and approved by the review committees. However, as research on second-trimester abortion is not a high-priority area, the commencement of the study will depend on the availability of funds.

**Control and management of postabortion bleeding**

The two-centre study launched in late 1999 to investigate the effect of OCs on measured blood loss in medical termination of pregnancy by mifepristone and misoprostol will continue during 2000. This study will include 100 women who request medical termination of pregnancy of up to 63 days’ duration.

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**A THREE-MONTHLY INJECTABLE (LEVONORGESTREL BUTANOATE)**

**Rationale for the product**

It is estimated that about 16 million women worldwide use injectable contraceptives to regulate their fertility. The most widely-used injectable contraceptive is the three-monthly preparation depot medroxyprogesterone acetate (DMPA), which is used by about 13 million women. The high contraceptive efficacy of DMPA is offset by the high prevalence of amenorrhoea associated with its use, and the slow return of fertility following its discontinuation. Thus, HRP has been investigating alternative injectable preparations which might offer significant clinical improvements over DMPA.

**Current stage of development and assessment**

In collaboration with the Contraceptive Development Branch of the National Institute of Child Health and Human Development (NICHD), Bethesda, MD, USA, HRP supported the synthesis of derivatives of known progestogens as potential injectable contraceptives. More than 230 esters, ester oximes and ethers of norethisterone and levonorgestrel were prepared. After screening,
toxicological and clinical testing, one compound, levonorgestrel butanoate (LNg-B), was selected for further development.

Research to date indicates that LNg-B would provide contraceptive protection at a dose of 5–10 mg every three months. Such a preparation would impose a lower body burden of synthetic steroid than DMPA, which is used at a dose of 150 mg for contraceptive purposes, and may therefore result in less ovarian suppression, less amenorrhoea and a more rapid return of fertility after it is discontinued. Another advantage of LNg-B is that the parent compound, levonorgestrel, has a long safety record as an oral contraceptives and as the active ingredient in Norplant implant devices. Because LNg-B is easy to synthesize, it is anticipated that production costs will be low, and since HRP, together with NICHD, has generated a substantial amount of data on the product, which would be of value to a commercial partner, a favourable public sector price could be negotiated.

Based on the results of pharmacokinetic and pharmacodynamic studies, a comparative clinical trial was carried out with a 12.5 mg dose of a micronized formulation of LNg-B and the standard 200 mg dose of norethisterone enantate (NET-EN), a registered two-monthly injectable contraceptive; both preparations were given in a two-monthly regimen in this study. Both drugs had the same high contraceptive efficacy and both induced steroid-related side-effects. However, after one year of use, the average weight gain and the observed disturbance of vaginal bleeding patterns were more pronounced in the NET-EN users than in the women using LNg-B.

Subsequently, studies were undertaken in cynomolgus monkeys to test the effect of LNg-B particle size on the pharmacokinetics of the preparation. These studies demonstrated that, with larger particles, peak blood levels of the steroid are reduced, the duration of action is increased, and the overall steroid dosage required for three months of contraceptive coverage is reduced. An optimal particle size range was determined and a manufacturing process was established. Pharmacokinetic/pharmacodynamic studies in women with this larger particle size preparation suggested that the final dosage required for three months of contraceptive coverage will be 10 mg or less. One-year toxicology studies on the use of this preparation in rats and monkeys did not reveal any unexpected side-effects. An Investigational New Drug application was filed with the United States Food and Drug Administration (FDA) for this compound.

In addition to developing this product as a contraceptive for women, HRP is also investigating its potential, in combination with an androgen ester, as a male method of contraception (see the section on “Hormonal contraceptives for use by men”).

Stability studies of LNg-B, conducted concurrently with the clinical studies mentioned above, showed good chemical stability of the compound. However, they also revealed that, with prolonged storage, crystal particles tended to aggregate, to deposit out, and adhere to the ampoule glass, making the preparation difficult to re-suspend and administer in a reliable manner. Thus, since 1996, work has focused on the investigation and resolution of this issue. This work has been carried out at a custom formulation facility in the USA; and the Contraceptive Research and Development Program (CONRAD), Arlington, VA, USA, has provided major technical input and advice to these studies which have included identification of the deposits, assessment of the solubility of the steroid in the suspending vehicle, assessment of the effects of the different vehicle components and of the container/closure system of the compound, and evaluation of the formulation procedure. Preliminary results indicated that improvements could be achieved by changing from a glass-seal ampoule to a pre-filled syringe, modifying the manufacturing process to improve wetting of the steroid, and modifying the formula by adding a flocculating agent to alter the hydrophil–lipophil balance and thereby produce a well flocculated and easily resuspendable preparation.

**Progress made during the past year**

During the past year, studies have been carried out to define conditions required for the preparation of particles of LNg-B of a size range shown previously to generate the required pharmacokinetic profile. Wet-milling studies, using monomorphic crystals of LNg-B obtained by recrystallization, were successful up to the maximum concentration tested, 100 mg/ml. Even at this relatively high concentration, the crystals milled easily and flowed freely through the homogenizer head. By adjusting milling time and speed, samples were obtained with a particle size distribution similar to that of a previously-manufactured batch.

Other studies were carried out to evaluate the efficiency of different solvents in solubilizing LNg-B, to determine the percentage recovery of the solubilized material in crystalline form, and to estimate the susceptibility of the crystalline material to chemical breakdown during exposure to varying sterilizing doses of irradiation. These studies have been carried out to identify the most efficient, clinically-acceptable LNg-B synthesis procedures and to determine if irradiation can be used as a terminal sterilization procedure, thus obviating the need for a more costly and logistically more difficult aseptic preparation and formulation process.

A preliminary study was carried out with seven solvents: acetone, ethanol, ethyl acetate, hexane, isopropyl alcohol, methanol and tetrahydrofuran. In this study, the volume of each solvent required to fully dissolve 10 mg of LNg-B at
60 °C was found to range between 160 µL for tetrahydrofuran to 2200 µL for methanol. LNG-B proved to be insoluble in hexane. A subsequent study was then carried out to determine the solubility and recovery rates, using the five solvents that were found to be most efficient in the preliminary study and are considered to be clinically acceptable in terms of residual solvent contamination of the crystalline LNG-B. This study showed recovery rates for the solubilized LNG-B that ranged between 51% with ethyl acetate and 95% with methanol. With the exclusion of ethyl acetate, the remaining four solvents yielded recovery rates ranging between 89% and 95%.

The crystalline materials derived from these four solvents were dried thoroughly and then subjected to electron beam irradiation at three sterilizing dose levels—1 Mrad, 1.5 Mrad and 2.5 Mrad. Electron beam irradiation was preferred, as this is easier to use and control than gamma-irradiation and has been shown previously to be as efficient as gamma-irradiation. A sample of LNG-B from a previously-manufactured batch was included as a control preparation. The subsequent purity of the irradiated samples was estimated in comparison with a standard of 99.7% purity. The results obtained for LNG-B derived from the four solvents ranged between 97.0% and 98.8% after 1 Mrad, between 97.0% and 97.9% after 1.5 Mrad, and between 95.8% and 97.4% after 2.5 Mrad, indicating a decrease in purity with an increasing irradiation dose. The control sample fared the worst, yielding purity values of 96.4%, 96.1% and 95.1%, after the three dose levels of irradiation. Visual inspection of the samples revealed yellow discoloration of the irradiated samples, the intensity of which was proportional to the irradiation dose. This discoloration was found to be due to the presence of more than 10 impurities, of which free levonorgestrel is one of the most abundant.

Studies were also carried out to determine if autoclaving could be used as an alternative to irradiation as a sterilizing procedure. Samples of LNG-B were suspended in different versions of the modified vehicle and subjected to a standard 20-minute autoclave cycle. The samples were then tested for changes in particle size range and degradation. All but one of the samples showed a twofold increase in particle size after autoclaving; the sample that did not show any increase in particle size after autoclaving had been formulated in the modified suspending medium, together with Tween 80 and water. Subsequent HPLC evaluation of autoclaved and non-autoclaved versions of this sample showed no difference in composition.

A number of companies with experience in the synthesis of steroids and/or the formulation of steroid-containing preparations, and which have expressed an interest in synthesizing and/or formulating LNG-B, have been contacted during the latter part of the year. Each of these companies has been advised of the need to provide material prepared under Good Manufacturing Practices (GMP) conditions and with all of the documentation required to permit its use in preclinical studies and preliminary clinical trials of safety and contraceptive efficacy in women and, in combination with a suitable androgen, in men. Subject to confirmation by these companies of their willingness to prepare this material, under these conditions, for these purposes, and to reaching agreement on the time and cost estimates for this work, a company will be selected and a contract issued. It is estimated that a total of 1 kg will be needed to carry out confirmatory pharmacokinetics and local tolerance studies in appropriate animal models, and to initiate Phase I and Phase II clinical trials in women (and men) volunteers.

Ancillary studies

Initiation of Cyclofem treatment

The once-a-month injectable contraceptive, Cyclofem (which contains 25 mg of DMPA and 5 mg of estradiol cypionate), has been in use in national family planning programmes for the past eight years. The current recommendation for its use is to administer the first injection during the first five days of a menstrual cycle and give subsequent injections every 30±3 days. However, with other injectable contraceptives such as DMPA, the first injection is given during the first seven days of the cycle and it would be of benefit to programmes to harmonize the administration schedule of all injectable methods.

There is a theoretical concern that giving the first injection of Cyclofem later in the follicular phase may jeopardize its high level of efficacy. Indeed, whereas DMPA is a progestin-only method which acts by inhibiting ovulation but also by thickening the cervical mucus, thus creating a barrier to sperm within hours of administration, Cyclofem is an estrogen/progestin combination which relies essentially on ovulation inhibition. Previous studies have shown that this effect is highly dependent on the estrogen/progestogen ratio and there is a possibility that administering the first injection later in the follicular phase might jeopardize its efficacy. Furthermore, no data are available on the effect of Cyclofem on cervical mucus. In Phase III clinical trials of Cyclofem and of Mesigyna (a similar product containing 50 mg NET-EN and 5 mg estradiol valerate), very few pregnancies occurred but in half of the cases, conception was estimated to have taken place during the first injection interval.

To address this issue, a multicentre study was initiated by Family Health International to describe the ovarian activity and the cervical mucus changes in women who received a first injection of Cyclofem administered on day 7 of their menstrual cycle and to compare these changes with a control group having the first injection of Cyclofem on day 5 of their menstrual cycle. As the three participating
centres were selected in Brazil, Chile and Santo Domingo, it was considered important to address possible ethnic differences by including a centre in China, with support from HRP. A total of 160 women were enrolled, randomized to one of the treatment schedules and followed over 14 days, with monitoring of follicular size, occurrence of ovulation, mucus quality and sperm penetration. Data collection was completed in all centres in December 1999 and data analysis is in progress.

Planned studies

During the early part 2000, consultations will be carried out with all interested and involved parties to finalize the synthesis and manufacturing specifications for the required dosage form of LNG-B. The issues to be addressed and resolved include: (i) what solvent should be used in the final crystallization step of the synthesis; (ii) whether wet-milling of dry-milling should be used to obtain the required particle size distribution; (iii) what should be the composition of the suspending medium; (iv) what method of sterilization should be used and when this should be carried out; and (v) how sterility should be determined and at what stage(s) this should be carried out.

A contract will be issued to a selected company with the necessary experience and facilities to prepare material to the required specifications and under full GMP conditions. In collaboration with NICHD, animal pharmacokinetics and local tolerance studies will be initiated with this material.

Subject to a successful outcome to the animal pharmacokinetics and local tolerance studies, approval to restart clinical testing will be sought from the regulatory authorities. A Phase I clinical trial of the pharmacokinetics and pharmacodynamics of the new formulation will be undertaken to confirm the dose necessary to obtain contraceptive coverage for three months in women volunteers. This will be followed by a multicentre contraceptive efficacy study to compare LNG-B with DMPA, in which the side-effects and acceptability of both preparations will also be assessed.

A SIX/TWELVE-MONTHLY INJECTABLE (hCG IMMUNOCONTRACEPTIVE)

Rationale for the product

The hCG immunocontraceptive being developed by HRP is designed to provide protection against pregnancy for a period of at least six months, and perhaps as long as 12 months, depending on its composition and formulation. It is envisaged that this method of family planning could be used at all stages of reproductive life: for postponing first pregnancies, for spacing pregnancies, and for providing a long-acting, and naturally reversing, alternative to sterilization on attainment of the desired family size. Furthermore, this particular immunocontraceptive may be of particular interest to women seeking a systemic contraceptive method that: (i) is free of the side-effects and contraindications associated with currently-available hormonal contraceptives (such as pills, injections and implants); (ii) does not require the insertion of a device (such as the IUD); and (iii) has a relatively long, but not permanent, duration of action.

Current stage of development and assessment

HRP has been supporting exploratory and applied research on hCG immunocontraception since the mid-1970s and has been instrumental in developing novel techniques and procedures for immunogen design and engineering. This resulted, in the mid-1980s, in the development, preclinical evaluation and clinical testing of the first synthetic peptide-based immunogen in this area. It is estimated that a further five to seven years of clinical testing and product improvement will be required before a first-generation product will be available. A second-generation, totally-synthetic, bioengineered product is also under development, in collaboration with industry, and could become available within a similar, or slightly more-extended, time-frame.

Following successful completion of a Phase I clinical trial with a prototype hCG immunocontraceptive in 1986, a Phase II trial with an improved version of this preparation was initiated in early 1994 but was interrupted when unexpectedly high levels of injection-site pain and tissue reactions were encountered in the first few volunteers to receive the preparation. The research carried out since then has involved a systematic evaluation of each of the components of the preparation used in the interrupted Phase II trial in order to determine the cause of these unexpected side-effects so that they can be eliminated or reduced to acceptable levels in future preparations. A successful outcome to these studies is considered central to ensuring that the composition and formulation of this advanced prototype version of the hCG immunocontraceptive to be used in future clinical trials will be clinically acceptable. The source of the problem encountered in the Phase II clinical trial has been identified and a new formulation, the advanced prototype hCG immunocontraceptive, has been prepared. Preclinical animal studies with this preparation started in 1998 and continued through 1999.
Progress made during the past year

Advanced prototype hCG immunocontraceptive development

As indicated in Annual technical report 1998, a composition and formulation of the advanced prototype hCG immunocontraceptive had been selected. This preparation was capable of eliciting a putatively protective level of immunity to hCG in rabbits, but did not produce the unacceptable local injection-site reactions that were encountered with the prototype version. During the past year, in a pre-Phase I toxicity study, this “standard” preparation has been evaluated to determine the duration of the immune response elicited by various immunization regimens, and for long-term stability. The ongoing preclinical safety studies, due to finish in early 2000, will determine if this preparation is suitable for clinical testing.

Pre-Phase I toxicity study

The local tolerance (muscle irritancy) and subacute toxicity of the standard preparation in rabbits was carried out by a custom toxicology facility in the United Kingdom. The highest dose (0.8 ml) intended for evaluation in a Phase I clinical trial was used in this study. A total of 22 rabbits (11 male and 11 female) were given the test preparation by deep intramuscular injection at weeks 0, 4 and 14. Based on previous experience, groups of the animals were autopsied at the time of expected peak immune responses, namely two weeks after each injection, at weeks 2, 6 and 16, respectively. Although only one of the 22 rabbits, autopsied at 16 weeks, exhibited a level of muscle reaction that is considered, on the basis of preclinical and clinical studies with a similar preparation, to be unacceptable clinically, several others exhibited evidence of chronic inflammatory reactions.

These unexpected findings may have been due to the fact that the test preparation used in the toxicity study was found to contain twice the specified level of the nor-muramyl dipeptide (nor-MDP) immunostimulant. A repeat toxicity study with a new batch of material, of the correct composition, is under way and the results should be available in May 2000. If these results are considered acceptable, a new application for a Phase I clinical trial will be made to the regulatory authorities.

The duration of the immune response elicited by various immunization regimens

In order to make the primary immunization regimen as acceptable and manageable as possible, studies have been carried out to evaluate the number and timing of the injections that are needed to ensure an adequate level and duration of immunity to hCG. In one study, a group of eight rabbits was immunized with 1.0 mg of the standard preparation at 0 and 4 weeks. After 12 weeks, antibody levels had declined below those believed to be adequate for preventing pregnancy. These data indicated that a minimum of three injections is needed to elicit a protective level of immunity of more than 12 weeks’ duration. These same animals were given a third injection at week 24 and this resulted in a prompt and significant rise in antibody levels which were maintained until week 48. Another booster injection was given at week 48, and antibody levels again rose and lasted another 24 weeks, until week 72. A similar response was found when a further booster injection was given at week 72. There was a slight increase in the peak antibody levels attained after each successive booster injection.

An additional study was carried out to determine if reducing the overall time-frame for the three injections needed for the primary immunization would markedly affect the magnitude or duration of the elicited antibody levels. In this study, the first two injections were given at weeks 0 and 4 as before, but the third injection was given at week 14, instead of week 24. In these animals, elevated antibody levels have been maintained for at least 16 weeks, suggesting that the primary immunization might be completed in 14 weeks and that effective antibody levels can be maintained thereafter with injections given at 16-week intervals at least, and possibly at 24-week intervals. Further studies are in progress to determine whether the primary immunization time can be further shortened without reducing the magnitude or duration of the immune response to an unacceptable level. These include three-injection regimens of: 0, 4 and 8 weeks; 0, 2 and 6 weeks; and 0, 2 and 4 weeks.

These encouraging preliminary data suggest that: (i) repeated immunizations with the hCG peptide:diphtheria toxoid conjugates does not lead to diphtheria toxoid carrier-induced suppression of the desired immune response to the peptides; and (ii) putatively protective levels of immunity can be maintained with booster injections given at intervals of six months, or perhaps longer. However, clinical studies are needed to determine if the standard preparation represents a viable six-monthly, non-hormonal, injectable contraceptive suitable for human use.

Immunogenicity of a GMP batch of the standard preparation

While the stability of laboratory-prepared batches of the standard preparation, as assessed by the accepted criteria of visual appearance and immunogenicity, has been demonstrated, similar tests had not been carried out on a batch prepared by a manufacturer under the rigorous conditions demanded by GMP requirements. The first GMP lot of the standard preparation was manufactured in the United Kingdom in October 1998 and was used in the local tolerance and subacute toxicity study in rabbits, as
described above.

Visual observation of this material at intervals up to 12 months post-manufacture has revealed no evidence of breakdown of the emulsion. The potency of this batch of material was determined on samples stored for 8, 20 and 30 weeks by injecting rabbits with this material at weeks 0 and 4, and measuring antibody levels at weekly intervals, from weeks 2–8. Although some variation was seen in the antibody levels of individual rabbits at 2 weeks and 3 weeks in this study, mean levels at all times after 4 weeks were nearly identical. These data indicate that the potency of the standard preparation is not diminished after storage for at least 8 months at 4°C. The evaluation of the potency of this batch after storage for one year post-manufacture is currently under way.

Optimized hCG immunocontraceptive development

The advanced prototype hCG immunocontraceptive is considered less than optimal in that: (i) the diphtheria toxoid carrier molecule for the hCG peptides is not a well-defined component in terms of composition and chemical structure; and (ii) the standard water-in-oil emulsion delivery system means that two or three injections are needed to elicit an immune response of the required magnitude and duration. Studies have continued during the past year, therefore, to develop an optimized hCG immunocontraceptive containing totally synthetic immunogens that do not need a diphtheria toxoid carrier, and improved delivery systems that will permit the desired duration of protection to be achieved following a single injection.

Synthetic immunogens

The objective of these studies is to identify B-cell stimulating and T-cell stimulating peptide sequences and constructs which are promiscuous, in the sense that they are able to elicit a safe and effective immune response, irrespective of the genetic background of the immunocontraceptive recipient. Work in this area has focused on the CTP and loop B-cell peptides and T-cell peptides representing known sequences in tetanus toxoid, measles virus protein F, and malaria proteins.

Two approaches to the production of these novel immunogens are being followed. The first involves the total chemical synthesis of the constructs using classical solid-phase peptide synthesis procedures; the other is investigating the feasibility of producing these peptide constructs using bioengineering techniques. The relative advantages and disadvantages of these two approaches, in terms of ease and cost of production, and quality and yield of product, will be assessed in parallel, so that a decision can be made on which of these two approaches should be used for scale-up production and eventual manufacture.

Chemically-synthesized immunogen. During the past year, three additional 38–57 loop:T-cell epitope peptide constructs have been prepared, and one of these has been tested for immunogenicity. This peptide construct comprises a T-cell epitope derived from tetanus toxoid linked to the N-terminus of the cyclized 38–57 loop peptide. Preliminary data obtained in rabbit studies suggest that this totally synthetic peptide construct is as immunogenic as a conjugate of the loop peptide with DT. It is intended to compare the immuno-genicity of this loop:T-cell construct with other such constructs when injected together with one or more CTP: T-cell epitope peptide constructs. This will include assessing the MH C restriction of various mixtures of these synthetic immunogens in order to select a combination which shows the least amount of genetically-determined nonresponsiveness.

Bioengineered immunogens. Collaboration between HRP and the industrial licensee of this novel technology continued during 1999. The focus of the research ongoing within the company is to develop and optimize expression systems using both prokaryotic (E. coli) and eukaryotic (Baculovirus) vectors, the objective being to develop a high-yield and low-cost biotechnological method for production of the desired immunogen constructs. Solubility problems, manifested by inclusion bodies and reduced expression, have been encountered with the constructs containing hydrophobic promiscuous T-cell epitopes. Longer and more hydrophilic minigene spacers have been designed for insertion between the B-cell and T-cell nucleotide sequences in an effort to overcome the solubility problem, and promoters have been incorporated into the vector to improve yields. These modifications of the vector have resulted in increased expression of the constructs in the E. coli system with no evidence of intracellular toxicity. However, in the Baculovirus system, although these sequence modifications have increased the solubilities of certain multiple promiscuous epitope products, they exhibit varying levels of intracellular toxicities for this eukaryotic system. Additional T-cell epitopes (from malarial and HBV surface antigen proteins) are being investigated in various combinations to determine if they exhibit reduced intracellular toxicity. The production and subsequent purification of the constructs from both expression systems are being examined in order to identify and select those capable of producing the high yield of the appropriate product that is needed for biological applications in vitro and in vivo.

Improved immunostimulants and delivery systems

Since 1980, the hCG immunocontraceptive preparations developed and evaluated by HRP have involved the use of nor-MDP as the immunostimulant and water-in-oil emulsion vehicles as the delivery system. Although not optimal for
inducing antibodies for a prolonged duration, and not totally devoid of local reactions, this “standard” formulation has proven useful for testing the safety and efficacy of the hCG immunocontraceptive and might even be suitable for initial product development. However, part of the ongoing development work includes comparing additional immunostimulant compounds and delivery systems that have been described by other investigators, in order to determine if they might constitute improved alternatives to nor-MDP and to the water-in-oil emulsions.

**Phosphazine polymer**

This compound, provided by the Virus Research Institute, Boston, MA, USA, has been further evaluated as an adjuvant when added, together with nor-MDP, to the aqueous phase of a water-in-oil emulsion. Two lots of the polymer have been tested during the past year. Although significant antibody levels were elicited, neither the magnitude nor duration of the response was considered sufficient to justify further studies with this compound.

**Non-ionic block polymer**

Preliminary studies, reported in the *Annual technical report 1998*, indicated that a non-ionic block polymer was a strong adjuvant when added to the aqueous phase of the standard emulsion. These data, obtained from immunizing rabbits twice, at 0 and 4 weeks, showed that such formulations induced antibody levels that remained elevated for several months. Further, it was shown that the immune response could be augmented even more when nor-MDP is added to the non-ionic block polymer and formulated in the standard emulsion. Unfortunately, unacceptable levels of tissue reactivity were observed at the injection site following the administration of both of these preparations.

Further studies were carried out, therefore, with single and lower doses of the non-ionic block polymer. The antibody levels that were induced were nearly the same as those in the higher dose groups, but the tissue reactivity was only slightly lower and was considered still unacceptable. However, the prompt elevation in antibody levels (even before the second injection at 4 weeks), and the sustained duration of the immune response, suggested that this polymer–emulsion mixture was worth pursuing further. It was, therefore, decided that a more extensive study should be conducted using single injections of formulations comprising a fixed lower dose of polymer and a varying dose of the immunogen. It was found that the dose of non-ionic block polymer could be reduced by a factor of 10 before a significant reduction in the level or duration of the antibody response was observed. Moreover, at the lowest dose, the tissue reactivity dropped to a level that was considered clinically acceptable.

The results of these studies suggest that inclusion of the non-ionic block polymer in the standard emulsion elicits a putatively effective level of immunity that is sustained for at least four months without inducing an unacceptable level of local reactivity at the injection site. These responses can be obtained by using much lower doses of immunogen than the standard nor-MDP-containing emulsion, and this preparation represents a slight improvement over the standard delivery system for the advanced prototype immunocontraceptive.

**Microparticle delivery system**

During the past year, studies have been carried out with a proprietary new technology in which immunogens are incorporated into an inorganic/biopolymer composite, resulting in particulate material with slow-release characteristics.

Conjugate-containing particles, 25–50 µM in diameter, were suspended in the standard emulsion containing nor-MDP. Antibodies rose quickly after a single injection of this material, reaching a peak at 8 weeks, after which a slow decline in antibody levels was observed until week 26 when the study was terminated. Although no muscle pathology was seen in the rabbits at the end of the study, interim autopsies were not carried out. These data indicate that a protracted immune response can be achieved with a single injection.

A further study has been initiated with a mixture of the particles used in the previous experiment, and another lot of particles formulated for even slower release of the entrapped immunogen. This mixture was also administered in an emulsion vehicle containing nor-MDP. This study is still under way, but preliminary data indicate that the duration of elevated antibody levels may have been prolonged by about 6–8 weeks with the use of this mixed-particle preparation.

**Ancillary studies**

In preparation for evaluation of the immune response elicited in clinical trials, further studies have been carried out to develop a rapid *in vitro* bioassay for the bioneutralization capacity of antibodies raised to the hCG immunocontraceptive. The results obtained in these studies are compared to those obtained by using the mouse uterine weight inhibition (MUWI) assay, a reliable and predictive bioassay, but one that takes 96–120 hours to conduct. These studies have included further evaluation of pooled antisera, using the rat testicular receptor binding, mouse interstitial cell testosterone production and rat ovarian receptor binding inhibition assays.

Problems of sensitivity encountered with the development of the mouse interstitial cell testosterone
(MICT) production assay have been attributed to the strain and age of the mice. Three strains of mice, and five age groups have been investigated, and the results show that the outbred ND4 Swiss Webster mouse was the most sensitive to hCG stimulation and that cells from 6–8 week-old mice appear to respond more than those from younger or older animals. Because of this age-dependent effect, the number of mouse testes pooled for each assay was increased in order to reduce the variations in responsiveness caused by age differences in the mice. A total of 27 MICT assays have been conducted in this way during the past year. Unfortunately, in spite of these precautions, almost fourfold differences were observed in the degree of inhibition caused by control sera, and it was concluded that the MICT assay is not suitable as a replacement for the MUWI assay.

Further studies have also been carried out over the past year with the rat ovarian and rat testicular receptor binding inhibition assays, again using the MUWI for comparison. Using pooled sera from rabbits immunized with the standard preparation, or with the individual conjugates thereof, it was found that the rat ovarian receptor assay neutralization values correlated the most closely with those of the MUWI. The rat ovarian receptor binding assay thus appears to be the only relatively rapid bioassay method found so far that can be replicated with adequate sensitivity and precision to be recommended for use in evaluating the bioneutralization capacity of antisera raised to the hCG immunocontraceptive. The relevance of this assay for this purpose, in terms of the secondary biological events associated with receptor binding, remains to be elucidated.

Planned studies

Advanced prototype hCG immunocontraceptive

The results of the repeat pre-Phase I toxicity study will be available during the second quarter of 2000. Assuming a satisfactory outcome of these studies, a resubmission will be made to the regulatory authorities to initiate a Phase I clinical trial with this preparation later in the year.

It is anticipated that the Phase I clinical trial with the selected emulsion formulation of the advanced prototype hCG immunocontraceptive will be initiated during 2000 and could continue into 2001. Assuming satisfactory progress in this study in terms of safety and performance characteristics, pre-Phase II teratology studies will be carried out and permission sought to initiate a Phase II clinical trial with this preparation in 2001.

Optimized hCG immunocontraceptive

Further research will be carried out during the 2000–2001 biennium to develop an optimized hCG immunocontraceptive preparation. These studies will include the continued comparative assessment of selected synthetic or bioengineered B-cell:T-cell constructs and improved delivery systems to identify a preparation that will produce the desired specificity, and level and duration of putatively effective immunity following a single injection.

Batches of the optimized hCG immunocontraceptive, comprising the selected B-cell:T-cell constructs and delivery system, will be prepared in sufficient quantity and under the relevant GMP conditions for preclinical efficacy and safety studies and subsequent clinical testing.

Ancillary studies

Studies will be continued during the coming biennium to assess further in vitro bioassays to establish how well they correlate with reference assays such as radioimmunoassay (RIA) and the MUWI and to determine the correction factors that need to be applied to ensure that they can be used as reliable and rapid predictors of a protective level of immunity in future clinical trial volunteers.

HORMONAL CONTRACEPTIVES FOR USE BY MEN

Rationale for the product

Although there are currently no systemic methods of contraception for use by men, the development of male counterparts of the oral, injectable and implantable female steroid hormone methods of contraception has been the subject of research for the past 30 years or more. A number of studies in animals and men have shown that the administration of androgens alone, combinations of gonadotrophin-releasing hormone analogues and androgens, and progestogen and androgen combinations can suppress gonadotrophin secretion and spermatogenesis either completely to azoospermia or to a sufficiently low level of oligozoospermia to render the treated individuals infertile. Furthermore, discontinuation of the treatment leads to full recovery of gonadotrophin secretion and spermatogenesis and to restoration of fertility.

The advent of a safe, effective and reversible systemic method of contraception for men is expected to provide a valuable addition to the range of methods to be offered to users of family planning and an attractive alternative to the limited options of the condom, vasectomy and withdrawal, which are the only methods currently available to men. In fact, in two earlier multicentre clinical trials carried out by HRP together with CONRAD (Arlington, VA, USA) to investigate the contraceptive efficacy of azoospermia and oligozoospermia induced by injections of an androgen ester, testosterone enantate (TE), a high level of acceptability was found among both the recipients and
their partners, in spite of the need for weekly injections with this particular, relatively short-acting, test compound. Many of the men who took part in these TE trials indicated that a longer-acting preparation, which could be used at intervals of two or three months, would be more attractive and a distinct improvement over TE.

It is possible that an androgen-alone approach to male contraception may prove to be a safe and effective option in certain population groups. However, it is generally agreed that a male hormonal contraceptive for wide-scale use in different parts of the world will probably need to be a progestogen–androgen combination in which spermatogenic suppression is achieved mainly by the progestogen, with the androgen given primarily for replacement purposes, and therefore at lower doses than would be needed in an androgen-alone contraceptive. In addition, the combination approach is expected to reduce the potential for any physiological, psychological and pathological changes that might arise from the continued exposure to supra-physiological levels of exogenous androgen.

HRP is investigating, or planning to investigate, a variety of oral and injectable androgen-alone and androgen–progestogen combinations, which can be taken at intervals of six weeks, two months or three months, to suppress sperm production.

**Current stage of development and assessment**

**Six-weekly injectable preparations**

The results of a dose-finding study, cofunded by HRP in China in 1997, indicated that there was no significant difference between 500 mg and 1000 mg of testosterone undecanoate (TU) given at six-week intervals, in terms of the number of men achieving azoospermia and the time taken to achieve azoospermia. TU is a testosterone ester which, in an injectable formulation, has a pharmaco-kinetic profile that is capable of maintaining blood levels of testosterone within the physiological range when injected at intervals of six weeks and perhaps longer. No adverse behavioural or other side-effects were reported by the trial participants, and no unacceptable changes were observed in any of the clinical chemistry parameters examined.

An earlier study funded by HRP in Indonesia had demonstrated the ability of 250 mg DMPA given by injection every six weeks, in combination with either 200 mg TE or 200 mg 19-nortestosterone (19NT) given by injection every three weeks, to suppress spermatogenesis in men completely or to a level that renders them infertile. These data have been used as the basis for proposing a possible six-weekly injectable combination, using 250 mg DMPA in combination with 500 mg TU.

**Three-monthly injectable preparations**

Pharmacokinetic studies with testosterone buciclate (TB), a long-acting ester resulting from the joint WHO/NICHD Chemical Synthesis Programme of the early 1980s, have shown that this compound is capable of maintaining serum testosterone levels within the normal range for a period of approximately 100 days in hypogonadal men. Furthermore, in contrast to short-acting testosterone esters, such as TE, TB is not associated with a peak of testosterone release soon after injection, and its release rate more closely approximates zero-order kinetics. In addition, the side chain is metabolized to products that are normal body constituents. These attributes make it an attractive option for development as a three-monthly androgen-alone injectable or as the androgen component of a three-monthly combined injectable contraceptive.

Preliminary data obtained in an earlier clinical trial involving a small number of normal men demonstrated the ability of TB to suppress gonadotrophin levels and reduce spermatogenesis. Further clinical studies of this type had to be postponed because of the need to resolve formulation problems that had become apparent with the most recent batch of material prepared for clinical testing. The formulation problems were manifested by clumping of the steroid particles, making it difficult to resuspend the material, and adhesion of the steroid to the inner surface of the glass container. These formulation and packaging problems raised concerns about the composition and dose of the injected material, and much of the effort during the past few years has been directed at solving these problems.

**Progress made during the past year**

**Six-weekly injectable preparations**

A multicentre contraceptive efficacy study has been carried out in six centres in China, in which TU was given at a dose of 1000 mg during the suppression phase and at 500 mg dose during the efficacy phase of the trial. Although sperm reappeared in the ejaculates of some men during the efficacy phase, necessitating the reduction of the injection interval from six weeks to four weeks in one centre, the sperm concentrations did not exceed 1 million/ml and no pregnancies have been reported during the six-month exposure phase of the trial. Currently, various hormonal and blood chemistry measurements are being performed, and data entry and analysis are continuing. Acceptability studies, involving both the trial participants and their partners, have been undertaken concurrently with the contraceptive efficacy study, and the data obtained in these studies are also being analysed.
Three-monthly injectable preparations

During the past year, HRP has been involved, with NIH, in protracted discussions with a potential industrial partner concerning the licensing of TB and its subsequent development as a product for male contraception (either alone or in combination with a progestogen), and for androgen replacement therapy in hypogonadal men. Such an arrangement will involve the preparation of a mutually-agreed product development plan, indicating the respective financial and technical inputs of the various parties. As a consequence of these discussions and in order to avoid unnecessary or irrelevant expenditures, HRP has not carried out significant work with TB during the past year.

Previous studies had shown that levels of gamma irradiation required to ensure sterility of TB also caused unacceptably high levels of degradation, resulting in a large number of breakdown products of unknown composition. Some additional work has been carried out to see if TB can be exposed to a putatively sterilizing dose of gamma irradiation without being degraded to a point that would make it unacceptable for use in a pharmaceutical product intended for human use. Samples of TB were subjected to irradiation doses of 1.5, 2.0 or 2.5 Mrad. Subsequent HPLC analysis of these samples revealed less than 1% degradation, which was considerably lower than that seen before at these doses, suggesting that it may prove possible to use gamma irradiation for the sterilization of TB preparations to be used in clinical trials and in eventual product manufacture.

Other combinations and clinical studies

It is thought that the low level of spermatogenesis that persists in some men taking part in clinical trials of androgen-alone and progestogen–androgen combinations as male contraceptives may be due to a persisting, low level of production of dihydrotestosterone (DHT). A study was carried out in Australia to observe whether the administration of a 5α-reductase inhibitor, finasteride, which would prevent the conversion of testosterone to DHT, would completely suppress the severe oligozoospermia induced by exogenous testosterone to azoosperma.

In this study, finasteride was administered to men in whom testosterone-releasing rods (pellets) had been inserted to suppress gonadotrophin secretion and subsequent spermatogenesis. The levels of DHT and residual sperm production in these men were assessed and compared to those in a control group of men receiving the testosterone-releasing rods only. The present study demonstrated that the use of testosterone implants, at doses of 800–1200 mg every three months, achieves spermatogenic suppression in at least 60% of Caucasian men, with minimal side-effects. However, no evidence of improved efficacy of the treatment was found in the men also receiving finasteride, although the number of men who completed the study in both treatment and control arms was small. It has been suggested that finasteride selectively inhibits the type 2 enzyme and, at least in rats, the type 1 enzyme predominates in the adult testis. Thus it will be relevant to investigate the effects of dual inhibitors of both type 1 and type 2 5α-reductases.

Acceptability and behavioural studies related to male contraception

HRP considers it important to carry out acceptability and user perspective studies for the assessment of sexual function and possible behaviour changes during the course of clinical trials of male hormonal contraceptives. An acceptability and behavioural study was carried out as part of the six-centre TU contraceptive efficacy study conducted in China, as described above. Both qualitative and quantitative approaches were used to collect information on the acceptability of male contraceptive use, family size preferences, contraceptive decision-making and perceptions on access and mode of contraceptive delivery.

In another study, which is being supported in the United Kingdom, a range of psychometric tools are being developed for adaptation and validation, for the assessment of sexual and behavioural changes associated with male hormonal contraceptive use. The data being obtained in these studies should provide information regarding the ability of this methodology, and user perspectives and needs in the development of male fertility regulation.

Planned studies

Oral and injectable combination preparations

Preliminary, non-HRP supported studies carried out some time ago indicated that daily doses of cyproterone acetate (CPA) given orally, daily, in combination with TE given by weekly injections, had an antispermatogenic effect in normal men. These results have recently been confirmed, using CPA plus TU. An advantage of this particular treatment regimen is that the anti-androgenic effect of CPA appears to counteract the potentially adverse effect of TU on lipid metabolism, thereby largely eliminating the androgen-induced reduction in high-density lipoprotein (HDL) levels. HRP had planned to carry out a multicentre study, in six centres in both developing and developed countries, to evaluate the effects on spermato-genesis of a treatment regimen consisting of a daily oral dose of 20 mg CPA in combination with injections of 1000 mg of TU given every eight weeks. This study was to have been carried out as a collaborative project with CONRAD and industry. However, the industrial partner has elected not to collaborate in this study but to contribute to the planned evaluation of a two-monthly injectable combination, norethisterone enantate (NET-EN) and TU (see below).
**Six-weekly injectable preparations**

In view of the encouraging preliminary information on the safety, efficacy and acceptability resulting from the TU-alone study in China, it has been proposed that a larger-scale study, Phase III, may need to be carried out, using the same treatment regimen. Such a study would require a major financial input which is currently beyond the capabilities of HRP to provide. However, HRP could assist with developing the protocol and with data collection and analysis, if required.

A Phase II study to assess the contraceptive efficacy of a six-weekly DMPA and TU injectable combination regimen to be carried out in Indonesia has been planned for some time but has been delayed, pending the supply of TU. This study may be started during the coming biennium. During the six months’ efficacy phase, fertility and metabolic effects would be assessed, and a separate study would assess acceptability among users and their partners.

**Two-monthly injectable preparations**

The pharmacokinetic profile of TU suggests that it may be possible to use it, in combination with a suitable progestogen such as NET-EN, as an eight-weekly injectable. In view of the past experience with various progestogen–androgen combination regimens, albeit involving small numbers of men, it may prove possible to move rapidly from a Phase I to a Phase II clinical trial of an NET-EN plus TU combination. Protocols for such studies have been developed, and the possibility of obtaining the required quantities of the two preparations from the manufacturer is currently being investigated.

**Three-monthly injectable preparations**

HRP is planning to move ahead with formulation, animal safety and pharmacokinetic studies in order to resolve remaining issues concerning the suitability of TB for clinical use. The primary objective of this work will be to use TB in combination with levonorgestrel butanoate (LNG-B), a long-acting progestogen resulting from the joint WHO/NICHD Chemical Synthesis Programme and which has similar pharmacokinetics to TB. It is expected that this work will form a major part of HRP’s activities in the development and assessment of male hormonal contraceptives during the next biennium.

**LEVONORGESTREL-RELEASING CONTRACEPTIVE VAGINAL RING**

**Rationale for the product**

Women’s health advocates have argued that women need methods that are long-acting and effective but which remain under their control. The vaginal ring meets these needs in that it can be easily inserted, checked, removed and replaced by the woman herself. It also has other advantages, namely, it can be worn continuously for a number of weeks; its use is not coitally related; it provides a constant rate of drug release resulting in a steady plasma level of the minimum dose required for contraception; and in the case of accidental pregnancy or if protection is no longer required, plasma levels fall rapidly to zero and fertility returns following removal of the ring. Thus, it is currently the only form of long-acting contraception which is user-controlled.

**Current stage of development and assessment**

HRP first collaborated with industry in 1974 in testing a series of different progestogens released from vaginal rings. On the basis of these tests, levonorgestrel, delivered at the rate of 20 µg/24 hours, was selected as the product of choice. At that point, all activities were taken over by HRP, including safety, efficacy and acceptability testing, and development of manufacturing equipment. Eventually, in 1990, a license agreement was concluded with a company in the United Kingdom for the manufacture and distribution of this product.

To fulfil the requirements of the licensing authorities in the United Kingdom, the company undertook a Phase III clinical trial of the ring. This study confirmed the results obtained in previous WHO-supported clinical trials, except that vaginal lesions were reported in a proportion of the users. As it was hypothesized that these lesions could be due to a combined effect of pressure from the ring and thinning of the vaginal wall due to local exposure to levonorgestrel, the ring was redesigned into a thinner, more flexible device.

A multicentre clinical trial was initiated to test the pressure effect of the redesigned ring by comparing the vaginal effects of a placebo vaginal ring with corresponding observations in a control group of women using a non-vaginal, non-hormonal method of contraception. The results suggested that the new ring design did not induce lesions on the cervix or vaginal wall and that the geometry of the new ring could be considered suitable for future development of the device.

In 1997, the pharmaceutical company decided to withdraw from the project, preferring to focus on the development of a combined contraceptive ring releasing progestogen and estrogen, and agreed to return the licence to WHO. Subsequently, CONRAD indicated their interest in collaborating with HRP on this project.

**Progress made during the past year**

Because of concerns over the limited efficacy of the
ring releasing 20 µg/24 hours of levonorgestrel, particularly in heavier women, the plan was to develop, as a final product, a higher-dose version of the redesigned vaginal ring releasing 35 µg/24 hours of levonorgestrel. In 1998–1999, negotiations were initiated with potential industrial partners for the production of a batch of rings suitable for clinical testing. Several options were compared, based on different manufacturing techniques. However, in 1999, CONRAD withdrew its support because of the difficulties encountered in obtaining a ring for dose-titration studies, at a reasonable cost.

**Planned studies**

At its December 1999 meeting, the Strategic Committee for Technology Development and Assessment recommended that no further work be carried out on this product. They re-emphasized the unique potential of the vaginal ring as a long-acting method of fertility regulation under the user’s control and recommended that HRP investigate possible collaboration with other groups with promising leads in this area.

**NATURAL FAMILY PLANNING**

**Rationale for the product**

Survey data show that the “rhythm” or “calendar” method for determining the fertile period is the most commonly used method of natural family planning worldwide. However, there has been little or no scientific evaluation of any of the suggested calendar-based rules for determining the period of abstinence. Although this method is already established and in wide use, its reliability would be improved, and its utilization increased by the provision of simpler and more precise rules on the timing and duration of the fertile period.

**Current stage of development and assessment**

HRP and the Institute for Reproductive Health (IRH) of Georgetown University, Washington, DC, USA, have agreed to a research strategy in this area. IRH, in collaboration with HRP, conducted focus group discussions with calendar method users to investigate how couples actually identify the fertile period. This preliminary work, conducted in four countries, indicated a high demand in certain populations for a simplified calendar method. To meet this need, IRH conducted studies on the optimization of calendar rules, based on a re-analysis of the large data set of women’s menstrual cycles obtained in HRP’s study of the Ovulation Method. This analysis showed that a “standard rule” method, based on a fixed period of abstinence from day eight to day 19 of the cycle, would result in a very high theoretical reduction in the probability of pregnancy and have the advantage of simplicity over the traditional “calendar rule” method.

Subsequently, IRH, with some input from HRP, planned a prospective multicentre study of the effectiveness and acceptability of a standard rule method. IRH conducted a pilot study in Bolivia and in the Philippines to test the study instruments, including a mnemonic device in the form of a necklace for teaching the method. Based on this study, IRH is now initiating the main study of the 8–19-day standard rule among women whose cycles are 26–32 days long, each woman being followed over 13 cycles. The study is being launched in Bolivia and the Philippines, where the pilot study was conducted, and additional sites are being considered in El Salvador, Kenya and Peru. It is anticipated that each study site will recruit 100 women.

**Planned studies**

HRP is exploring the possibility of supporting two sub-Saharan African centres to contribute to the above-mentioned multicentre study.

**RESEARCH ON LACTATIONAL AMENORRHOEA**

**Rationale**

The aim of HRP’s research on lactation and its role in the natural suppression of fertility has been to identify: (i) the determinants of the duration of lactational infertility; and (ii) ways for optimal linkage of the contraceptive effect of lactational amenorrhea and the introduction of other methods of family planning. The outcome of this research would be of particular benefit to those women who have no other means to regulate their fertility as well as to countries that have limited resources for family planning methods and services. It is also in line with the Programme of Action adopted at the International Conference on Population and Development (ICPD) in Cairo in September 1994 which includes in its list of objectives in the area of family planning: “to promote breastfeeding to enhance birth spacing”.

**Current stage of development and assessment**

To implement the use of the birth-spacing effect of breastfeeding in family planning programmes, scientifically valid information is required on the conditions under which breastfeeding provides protection against unplanned pregnancy. HRP’s main undertaking in this area was a large, prospective, multinational study on the duration of lactational amenorrhea in relation to breastfeeding practices. The first two papers from this study were published in September 1998 in *Fertility and sterility*, and two additional papers were published in September 1999 (*Fertility and sterility*, 1999, 72:431–440; *Fertility and sterility*, 1999, 72:441–447).
The study was carried out in seven countries—Australia, Chile, China, Guatemala, India, Nigeria and Sweden. The objectives of the study were: (i) to describe the duration of lactational amenorrhoea in relation to breastfeeding practices in different populations; (ii) to establish whether, with similar breastfeeding practices, there are real differences in the duration of lactational amenorrhoea between the study populations; and (iii) to gain information on factors that may contribute to any differences observed.

A total of 4118 mother–infant pairs were recruited for the study. Recruitment was effected during the first week after delivery, and follow-up was maintained until the second normal menstruation, or pregnancy. Mothers were instructed to fill in a card on which they recorded the daily number of breastfeeding episodes and manual breast expressions, the number and type of any supplementary feeds, and vaginal bleeding and spotting. A detailed day-chart was completed over a period of 24 hours every two weeks, in which the timing and duration of each breastfeeding episode was recorded. The type of supplementary food and when (in relation to a breastfeed) and how (cup, spoon, bottle) it was given were also noted. This study, the largest of its kind ever undertaken, yielded a wealth of detailed information on breastfeeding practices, patterns of supplementation, infant growth, maternal and infant morbidity, etc.

As reported in the Annual technical report 1998, the first two papers resulting from this study published in 1998, described the infant-feeding patterns and the return of menses (Paper I) and factors associated with the length of amenorrhoea (Paper II). Two additional papers were published in 1999 on the results obtained from further analyses of the data.

The objective of the analysis reported in Paper III (Fertility and sterility, 1999, 72:431–440) was to determine the risk of pregnancy during lactational amenorrhoea, relative to infant-feeding status. In all, 3422 women completed the study with a recognized fertility outcome: 3337 were regarded as having had two menstrual bleeding episodes and 85 became pregnant. The remaining 696 women had only one (i.e. unconfirmed) menstrual bleeding episode before leaving the study (n=150) or left the study before they had even one bleeding episode. One-third of all pregnancies occurred in one centre (Chengdu). Twenty-one women conceived after the infant had been totally weaned, and 64 women became pregnant during breastfeeding. A quarter of these 64 women (n=16) conceived during full breastfeeding and the remaining three-quarters (n=48) conceived when the infant was receiving caloric food supplements of varying amounts (i.e. during partial breastfeeding). Nearly all the pregnancies that occurred during full breastfeeding (15 of the 16) were in one centre (Chengdu).

Of the 64 women who conceived while breastfeeding, 18 reported using a family planning method during the estimated time of conception, and the remaining 46 who became pregnant used no method of contraception. Contraceptive failure was associated with the use of withdrawal, natural family planning, barrier methods, an IUD and vasectomy. About half the contraceptive failures occurred when the women were clearly menstruating.

Cumulative pregnancy rates at six months after childbirth during lactational amenorrhoea up to the end of full and partial breastfeeding ranged from 0.9%–1.2% depending on the definition of the end of amenorrhoea, whereas at the end of 12 months the rates were 3.7%–5.2%. The cumulative pregnancy rates calculated from delivery until the end of full breastfeeding and from delivery until the end of partial breastfeeding were not significantly different (p<0.05) at either time limit (six or 12 months). However, for each breastfeeding status, the pregnancy rate at 12 months postpartum was substantially higher than at six months postpartum.

There were no pregnancies during amenorrhoea and full breastfeeding among women not using any contraceptive method in any centre other than Chengdu. Thus, the pregnancy rates during full breastfeeding are due to data from one centre. The Bellagio Consensus (Consensus statement, The lancet, 1988, ii:1204–1205) states that women who are not using family planning but who are fully or nearly fully breastfeeding and amenorrhoeic, have a cumulative risk of pregnancy of <2% as long as the infant is still ≤6 months old. In this study, the highest 6-month cumulative pregnancy rate among women under these conditions was 1.2% (95% CI=0%–2.4%). Thus, the conclusion from the study was that the results support the Bellagio Consensus on the use of lactational amenorrhoea for family planning and confirm that the Lactational Amenorrhoea Method (LAM) of contraception is a viable approach to postpartum contraception.

Detailed information was collected on vaginal bleeding during the study, which allowed analyses of patterns of menstrual return during breastfeeding, including characteristics of bleeding episodes that occurred during the first few weeks after delivery. These results were published in Paper IV (Fertility and sterility, 1999, 72: 441–447.) The objectives were: (i) to describe and compare the duration of lochia in the women participating in the study from seven countries; (ii) to investigate the occurrence of a possible ‘end-of-puerperium’ bleeding episode; and (iii) to determine the frequency of bleeding episodes before postpartum day 56, which applies to the practice of LAM.

Although postpartum lochia is experienced by all women, it has received very little attention in the medical
literature, and only two previous studies can be found on this issue, one on women in London, whose median duration of lochia was 33 days, and the other on breastfeeding women in the Philippines with a median duration of 27 days. Of the 4118 women admitted into HRP’s study, 3955 (96%) reported a date on which lochia ended. One woman who started using hormonal contraception and 73 others who had an IUD inserted before the end of lochia were excluded from the analysis. Among the remaining 3881 women, the median duration of lochia was 27 days, ranging from 22 days in Chengdu to 34 days in Uppsala. In 11% of the women, lochia persisted for >40 days. The duration of lochia did not vary significantly according to the woman’s age or number of live births, or to the 24-hour breastfeeding frequency. The infant’s weight was significantly related to the duration of lochia in only two centres: Guatemala (risk ratio 0.78) and Melbourne/Sydney (0.82).

Of the 2694 women who had finished lochia by postpartum day 33, a total of 20.3% experienced a postlochial bleeding episode within a week of postpartum day 40 (between days 33 and 47), ranging from 3.1% in Chengdu to 51% in Santiago. In this two-week period, most of the women who experienced this bleeding reported only one episode of mean length 3.2 days.

A total of 3792 women had both a reported date for the end of lochia and a menstrual diary through to the end of the eighth postpartum week (56 days). Of these women, 1.5% still reported lochia at 56 days, and of the remaining 3737 women, 25.4% reported at least one bleeding episode between the end of lochia and the 56th day, ranging from 5.4% in Chengdu to 63.3% in Santiago. The mean duration of such bleeding episodes was 3.6 days. These data show that lochia usually stops and then starts again at least once in breastfeeding women before it stops completely.

The main conclusion was that the duration of lochia varied significantly among the study populations and that long durations were not unusual. The significance of end-of-puerperium bleeding is unknown. Most users of LAM will not experience a postlochial bleeding episode before postpartum day 56.

Progress made during the past year

No new initiatives have been started by HRP in this low-priority area during the last five years and, therefore, no projects were conducted in 1999. The study investigating the relationship between physical activity and lactational amenorrhoea was completed in 1998 and its results, which were analysed in 1999, will be available in 2000.

Planned activities

The Strategic Committee of Technology Development and Assessment suggested, at its meeting in December 1999, that HRP should make efforts to improve knowledge about LAM in order to increase its use, especially in countries where the choice of contraceptive methods is limited. The Committee also recommended, subject to the availability of funds, that the planned study on the use of LAM over an extended period of 6-12 months should be carried out.

BASIC RESEARCH

Exploratory, goal-oriented research is being carried out by HRP to identify new leads: (i) for the development of methods that could be used to regulate male fertility; (ii) for methods that could be used by women as once-a-month methods or menses inducers; and (iii) to further investigate the mechanism of progestogen-induced endometrial bleeding with a view to improving the performance and acceptability of such methods.

Male methods

Background

The research being promoted in this area is focusing on the molecular and cellular aspects of spermatogenesis/spermiogenesis, and the acquisition of sperm-fertilizing capacity. The purpose of these studies is to identify potential new approaches to male fertility regulation which are based on factors involved in, or required for, spermatogenesis and spermiogenesis, acrosome and flagellar formation, and other unique properties of developing spermatids and spermatozoa. Investigators are encouraged to consider the feasibility of subsequent development of their research leads into acceptable contraceptive products.

Progress in 1999

All of the studies supported by HRP in this area during the past year are concerned with various aspects of spermatogenesis and spermiogenesis.

Role of adenosine deaminase in the field of male reproduction and its histological localization

Adenosine is able to alter intracellular cAMP levels and to affect the physiological functions of sperm. Adenosine deaminase (ADA), an enzyme regulating adenosine levels, exists in the plasma membrane of spermatozoa. Funding was provided towards the screening of cDNA libraries and isolating testis-specific cDNA for ADA. The results obtained demonstrated, for the first time, the presence of a major testis-specific ADA mRNA and a weaker ADA transcript. Expression of the testis-specific ADA mRNA may be related to specific proliferation and differentiation
events of spermatogenesis. Monoclonal antibodies specific for testicular ADA are being evaluated for their ability to disrupt fertility.

*Study of the control mechanisms of spermatogenesis: physiological significance in spermiogenesis of a truncated form of the proto-oncogene c-kit specifically expressed in mouse spermatids*

HRP supported a study to establish the role of the tr-kit product in fertilization and pre-implantation development in order to determine if the inhibition of tr-kit expression or function would have any effect on the fertilizing capacity of sperm. Results obtained so far are relevant for the understanding of egg activation following sperm penetration. Published data resulting from this study indicate that the tr-kit is specifically localized in the residual sperm cytoplasm, with maximum accumulation in the flagellum, suggesting that it can enter the egg during fertilization. Further findings demonstrated tr-kit as a putative sperm factor required for triggering activation of mouse eggs at fertilization. This ongoing research should further define the functional significance of tr-kit in spermiogenesis as well as the fertilizing ability of knockout mice lacking the tr-kit promoter.

*Biochemistry of sperm capacitation and acrosome reaction*

Phospholipases A₂ are enzymes believed to play important roles in numerous physiological systems, including sperm cell maturation. In this project, it was possible to purify and characterize proteins that cross-react with antibovine serum protein (anti-BSP)-A₃ and, like antigens from seminal fluid, isolate phospholipase A₂, and study the effects of BSP on the activity of the enzyme. Mechanisms of inhibition of seminal phospholipase A₂ (PLA₂) activity by BSP have been further amplified in these studies, resulting in several publications.

*Gabaergic neurotransmitter mechanisms involved in the control of sperm function*

Using GABA-A receptor-binding antagonists and agonists, the results from this study suggested the presence of GABA-A receptors on human sperm membrane. The effects of GABA-A on sperm motility, including hyperactivation, were also demonstrated in capacitating medium. The results suggest that GABA appears to be one of the factors that modulate testicular function and motility and could play a role in male fertility.

*Underlying mechanism of triptolide’s anti-spermatogenic and antifertility effects*

Previous studies have shown that extracts of the Chinese medicinal plant *Tripterygium wilfordii* contain compounds which cause infertility in male rats. One of these compounds, triptolide, has been tested for mutagenicity/genotoxicity in a mouse bone marrow cytogenetic assay. The test results were negative.

Current findings suggest that the antifertility effects of triptolide seem to be due to a reduction in the epididymal sperm number and almost complete loss of sperm motility. It is also speculated that a longer duration of treatment with triptolide affects spermatogenesis and both the maturing and mature germ cells.

Tissue-specific accumulation of triptolide at a dose that exerts both antispermatogenic and antifertility effects and their reversibility are also being studied to elaborate further the underlying mechanisms of this compound’s antifertility effects.

*Post-testicular antifertility effects of triptolide in adult rats*

*In situ* 3’-end labelling of apoptotic DNA fragmentation, which permits recognition of very early stages of degeneration or dying cells, had confirmed that triptolide induces infertility in the male without suppressing spermatogenesis. The investigators have submitted a new proposal to study further the mechanisms underlying the antifertility effects of triptolide as part of ongoing collaboration between institutes in China and Thailand.

*Infertility-related human monoclonal antibody study*

In this study, funded in 1996 and 1997 and extended until December 1999, monoclonal antibodies (MAB) are raised against sperm-specific and epididymis-specific proteins, using hybridomas formed from lymphocytes of infertile men. The goal is to determine the tissue specificity and improve the production of these anti-epididymis MAB. Current studies involve the purification of the specific MAB and establishment of their effect on epididymal function.

*Evaluation of the effects of a high-potency androgen on mouse testis and prostate*

The study, funded since 1997, is aimed at assessing the effects of a high-potency, non 17-α alkylated androgen on mouse testis, prostate and liver. The rationale is that although androgens are central to any hormonal regimen for male contraception, there are limitations posed by the large mass of steroid that is needed either to suppress gonadotrophin secretion or to provide androgen replacement. High-potency, synthetic androgens lacking the 17-α alkyl substitution have been little considered despite potentially few side-effects.

The studies are evaluating the biological effects of the
Inhibition of sperm–zona pellucida binding in humans by GnRH antagonists

This work is focusing on recent and original results that indicate the existence of a mechanism of regulation of sperm–zona pellucida (ZP) binding by gonadotrophin-releasing hormone (GnRH) in humans. While GnRH increases sperm–ZP binding, preliminary evidence indicates that this effect is inhibited by GnRH antagonists.

The aims of the project are: (i) to study the mechanisms by which the GnRH antagonists inhibit sperm–ZP binding in humans; (ii) to study the expression of GnRH receptor in human testicular germ cells; and (iii) to test the in vivo effect of GnRH antagonists in rats.

Delivery of antibodies to the male reproductive ducts to achieve immunocontraception

In this project, the investigators are determining the mechanisms of entry of antibodies into the lumen of the male reproductive tract in order to identify factors that maximize the delivery of antibodies. Although the main aim of this project is to develop a method of immunization which could lead to achieving contraception in males, it would also provide a basis for treating STIs.

The study will concentrate mainly on the mouse as preliminary work in this animal model has established methods to collect uncontaminated luminal fluid by micropuncture. In those cases in which the collection of fluid in the mouse proves technically impossible, the experiments will be performed in the rat. The sperm surface antigen (PH20), coupled to tetanus toxoid, will be used as the immunogen in these studies.

Future plans

The advertisement that is placed in scientific journals by HRP to solicit proposals for basic research in this area, is being revised to encourage partnerships and twinning between and among institutions in developing and developed countries. The focus of the research will be on those unique aspects of sperm development in the male reproductive tract that have potential for male contraceptive development. Such events include sperm-specific gene expression, acrosome formation, and the development and properties of sperm cell membranes in the post-meiotic stages of spermatogenesis and spermiogenesis.

The WHO/Rockefeller Foundation Initiative on Implantation Research

Background

Anti-implantation and menses-inducing agents have long been seen as attractive options for methods of fertility regulation. The main advantages of these agents are that they could be self-administered, they need be taken only on an “as needed” basis or as a backup method, would be used at most on only one occasion in any menstrual cycle, and should be comparatively inexpensive. As such, they would not need continuous medication or use and would avoid many of the logistical problems and side-effects associated with the use of continuous methods such as oral contraceptives, and yet would still be accessible to women with lower incomes. Provided such methods prove to be safe, effective and acceptable—both in their mode of action and in terms of the side-effects, if any, of their use—they are likely to be an attractive new option for women worldwide and especially in developing countries.

A large number of studies have been carried out in recent years on the structure, function and molecular composition of the normal endometrium. Studies have also been carried out on the volume and chemical composition of endometrial secretions at different times in the cycle, and the effects these changes have on the receptivity of the uterine epithelium and the surface of the trophectoderm of the preimplantation blastocyst. Other studies have focused on differences in the endometrium of fertile and infertile women and have reported the presence of aberrant morphology, function and molecular expression in certain infertile states. An area of active investigation is the cyclical processes of controlled tissue breakdown and angiogenesis (and the role therein of angiogenic factors and their regulators) that occur in the endometrium during the fertile years.

It is far from clear which of these many cellular and molecular factors that appear to be part of normal endometrial physiology are essential for implantation. Nor is it clear which of these could be suitable targets for an anti-implantation agent. At its November 1997 meeting, the Strategic Committee for Technology Development and Assessment identified the implantation window in the primate as one of the more promising areas for goal-oriented basic research with a view to developing novel anti-implantation agents.

As the result of discussions that took place towards the end of 1997 between HRP and the Rockefeller Foundation, a joint, goal-oriented basic research initiative in the area of implantation was established, with HRP taking primary responsibility for the scientific, technical and ethical oversight of the research, and the Foundation providing the financial and administrative support.
The primary objectives of this Initiative are: (i) to identify promising leads in this area that can be developed into products in collaboration with industry; and, eventually, (ii) to develop novel anti-implantation or menses-inducing agents which are woman-controlled, effective, safe and acceptable in their mode of administration and mechanism of action. Three broad areas have been identified as being particularly important in this context and form the primary foci of the research being carried out under the Initiative:

— the implantation window in the primate, at the endometrial level;
— the development and demise of the primate corpus luteum; and

Proposals were solicited from more than 30 investigators known to be active in the field and, from the 29 proposals received and reviewed, six were selected for support. The following criteria were used in the review and selection process: (i) relevance of the work to the main objectives of the Initiative; (ii) feasibility of development into a safe, effective intervention for clinical use; (iii) lack of duplication or substantial overlap with other proposals or with known work ongoing elsewhere; and (iv) likelihood of industry interest and involvement. The six centres involved are located in Australia, China, Germany, India, the United Kingdom and the USA.

**Progress in 1999**

The six proposals currently being supported cover the three broad areas of: (i) in vitro and in vivo basic research, mainly at the molecular level; (ii) research in appropriate animal models; and (iii) clinical research on mechanisms of action of alleged anti-implantation agents and menses inducers, and on infertility due to endometrial or ovarian factors. More specifically, the research being carried out is focusing on:

— the specificity of action of anti-angiogenic factors in the pre-ovulatory follicle in the primate;
— the effect of anti-angiogenic factors in follicular development, ovulation and the development and function of the primate corpus luteum;
— angiogenesis in the endometrium and at the site of implantation;
— the role of angiogenic growth factors and the effect of their inhibition on implantation;
— the contraceptive potential of anti-angiogenic agents;
— angiogenesis and trophoblast invasion in the monkey;
— receptive-stage gene expression in the endometrium and the molecular basis of the development of uterine receptivity;
— the identification and comparison of animal and human homologues of implantation site genes and their products;
— factors involved in syncytial fusion and trophoblast attachment to, and invasion of, the endometrium and the development and evaluation of immunological or chemical inhibitors of these mechanisms;
— the molecular and cellular basis of implantation and placentaion in the rhesus monkey;
— the action of mifepristone in emergency contraception at the endometrial level;
— the effect of mifepristone and cytokines on implantation and demise of the primate corpus luteum.

An important part of this Initiative is the exchange of research materials, information, experience and expertise, and the interinstitutional training of researchers, especially those from developing country institutions, in specialized techniques needed for this work. In this context, supplementary funding has been provided by the Rockefeller Foundation during the past year to enable a clinical research fellow from one of the centres to set up required techniques in another centre.

A meeting of the six principal investigators and the project review committee was held in May 1999 in Geneva. The primary objective of this first meeting was to discuss the individual projects and the overall objectives of the Initiative to determine if there is any overlap in the proposed work or any gaps that need to be covered. In addition, the opportunity was taken to further foster collaboration among the investigators and promote close integration of the work, leading to the establishment and efficient functioning of a comprehensive, interactive research programme of complementary projects.

**Future plans**

It is intended to hold annual meetings of principal investigators and the project review committee towards the end of each year, to enable evaluation of progress and discussion on the content of future work, as well as modifications to be made to the research planned for the subsequent year. To facilitate interaction among the research teams, these meetings will be held in each centre in turn.

**Endometrial bleeding**

A large proportion of the more than 15 million women using progestogen-only methods of contraception endures the irregularities in vaginal bleeding that these methods induce. This has significant implications on their sexual life as well as impact on the sociocultural, economic and, for some, religious dimensions of their lives. The options offered to them to alleviate this problem are few. The addition of estrogens is only moderately beneficial and negates some of the benefits of a progestogen-only method.
Non-steroidal anti-inflammatory drugs have positive effects but are often too expensive or not available locally. As a result, counselling is the main resource that women experiencing bleeding irregularities can expect from providers. Clearly, there is a need to better understand the mechanisms of menstruation and how these are affected by contraceptive steroids, particularly progestogens. This will provide the necessary knowledge to formulate appropriate treatments and develop new methods free of these side-effects.

Mechanism of normal menstruation

Through research supported by HRP and other institutions, the mechanisms of normal menstruation are beginning to be defined under a new concept. Classically, menstrual bleeding was seen as resulting from ischaemic necrosis of the endometrium, following arterial spasm and thrombosis mediated by prostaglandins and involving autolysis by lysosomal enzymes. Currently, the triggering mechanism of menstruation is seen as an inflammatory response to the withdrawal of progesterone, in which cells of the immune system invade the endometrium and/or are activated and release regulatory molecules which increase the production and activation of matrix metalloproteinases (MMPs) but not of their inhibitors (tissue inhibitors of metalloproteinases, TIMPs). This imbalance leads to destruction of the endometrial connective tissue and degeneration of the functionalis layer with exposure of open blood vessels and endometrial glands. In this new scheme, active tissue destruction becomes the primary event initiating menstruation. This provides a molecular explanation for the observation made decades ago that menstruation was preceded by tissue shrinkage and disappearance of collagen fibres.

Mechanism of progestogen-induced endometrial bleeding

Progestogen-induced endometrial bleeding differs from menstruation in that bleeding is intermittent, unpredictable in its onset and cessation, and occurs from small superficial veins and capillaries. Previous studies provided evidence of vascular fragility, abnormal angiogenesis and disturbed mechanisms of menstruation associated with progestogen treatment. Further support for these events is provided by the following recent findings derived from research supported by HRP.

The study was undertaken in Brussels (Belgium) in 23 Norplant implant users, and compared their endometrium at the onset of a vaginal bleeding episode and during non-bleeding times. The analysis of biopsies showed that abnormal endometrial bleeding is associated with focal stromal breakdown and collagen fibre lysis. This was found to be related to the local expression and activation of MMP-1 (interstitial collagenase-1), activation of MMP-9 (gelatinase B), increased expression of MMP-2 (gelatinase A) and decreased production of TIMP-1. Further observations suggested that these events were initiated by the local expression and activation of MMP-3 (stromelysin-1) in stromal cells. These are some of the strongest data establishing links between specific mechanisms and breakthrough bleeding, although direct causality remains to be proven.

The control of MMP-3 expression remains unclear. No difference was found in serum levels of levonorgestrel and progesterone between bleeding and non-bleeding times in this study. In contrast, the average concentration of estradiol was lower at the start of bleeding episodes than during non-bleeding intervals (yet this was not confirmed in paired samples), and the total release of MMP-3 was inversely correlated with serum concentration of estradiol. Estrogen and progesterone receptors were generally not detected in areas of endometrial breakdown and this could be responsible for a weakened inhibition of MMP-3 expression. Other factors, such as paracrine interactions, may also play a role.

In 1997, a study was launched to compare the endometrium of Norplant users and women not using contraceptive methods in terms of:

- the expression and distribution of cellular markers that may contribute to vascular fragility;
- the binding capacity of progesterone receptors and the expression of progesterone-regulated proteins, to explain the previous finding of an increased immunostaining of stromal progesterone receptor;
- the regulation of MMPs;
- the epithelial integrity in the endometrium;
- the rates of endometrial and vascular apoptosis in Norplant users with and without breakthrough bleeding and the expression and distribution of factors known to influence apoptosis;
- the types of lymphomyeloid cells and their apparent link with the bleeding process; and
- the role of chemokines in the trafficking of endometrial leukocytes.

This study is based on a twinning arrangement between the University of Indonesia in Jakarta (Indonesia) and Monash University and the Prince Henry’s Institute of Medical Research, both in Clayton (Australia), which allows for institution strengthening with transfer of technology to Indonesia. Initially, the study was delayed by the effects of the economic crisis on the Indonesian research centre but, to date, over 300 subjects have been enrolled, and the aim is to reach the full recruitment target of 420 subjects by mid-2000.

Analyses of the biopsies obtained so far have provided the following preliminary findings:
Alpha-smooth muscle actin was found to be reduced around the blood vessels in the endometrium of Norplant users who experienced breakthrough bleeding, as compared with those who did not have this side-effect. This is the first time that a structural vascular feature that contributes to vascular fragility is found to correlate with breakthrough bleeding.

Studies of endometrial apoptosis did not provide support for a role for altered apoptosis in either the endometrium or the blood vessels of Norplant® users with or without breakthrough bleeding.

Mast cell activation was observed in the endometrium of Norplant and DMPA users, similar to premenstrual and menstrual controls but not at other times of the normal cycle. These mast cells were of the phenotype usually found in the functionalis layer of the normal endometrium. They produce a myriad of mediators which can trigger endometrial breakdown, for example, by activating latent MMPs.

Two studies were launched to assess the effects of different treatments on progestogen-induced prolonged bleeding. One is a double-blind, placebo-controlled trial conducted in Santiago (Chile) to test the efficacy of mifepristone in improving the vaginal bleeding pattern of Norplant® users. After Norplant® insertion, 120 volunteers received 100 mg of mifepristone on two consecutive days at intervals of 30 days over a period of six months, and were followed for a total of 13 months. The clinical trial ended in October 1999, with 109 volunteers having completed the full period of follow-up, and data analysis is currently in progress.

In 1998, a double-blind, randomized, placebo-controlled clinical trial was initiated to test the effect of vitamin E as an antioxidant, and of low-dose aspirin as an anti-inflammatory agent, alone and in combination, on Norplant-induced prolonged bleeding. This study is being conducted in Beijing (China), Jakarta (Indonesia), Santiago (Chile), Santo Domingo (Dominican Republic) and Tunis (Tunisia). Recruitment began in September 1998 in all centres except Tunis, where the study was launched in January 1999. A total of 290 subjects have been enrolled to date, and it is anticipated that the target enrolment of 500 volunteers will be reached by mid-2000, allowing the follow-up to be completed by mid-2001.

A meeting cosponsored by HRP and NICHD on “Steroids and endometrial breakthrough bleeding” was held at Monash University, Clayton, Australia, on 4–5 May 1999. It brought together leading scientists in the field to review the state of knowledge and plan future research in this area. The proceedings of the meeting will be published as a supplement of the journal Human reproduction in 2000.

Three broad areas of research were considered important for future studies. First, there is a need for a better understanding of the attitudes of women towards vaginal bleeding in diverse multicultural situations. This concerns a broader constituency now that there is increasing use of continuous combined regimens of postmenopausal hormonal replacement therapies which also affect endometrial bleeding. Second, studies are needed to explore the interplay between the endometrial vasculature and its environment, more specifically: factors that regulate focal expression of MMPs; regulation of endometrial angiogenic growth factor expression; traffic of immunocompetent cells from the vascular compartment into the endometrial stroma and their effects on angiogenesis; nature of steroid receptors expressed on endometrial endothelial cells; direct effects of steroids on endothelial cell function. Third, clinical studies are needed to investigate the effect of MMP inhibitors and oral TIMPs on vaginal bleeding in progestogen users and in women using hormonal replacement therapy; to determine the effect of selective estrogen receptor modulators on endometrial bleeding; and to evaluate the potential role of low-dose antiprogestogen treatment in progestogen users.

**DUAL-PROTECTION METHODS**

The Department’s work on barrier methods is summarized in the section on “Reproductive tract infections, cervical cancer and infertility”. In addition, HRP is planning to initiate studies on microbicides/spermicides as part of its technology development and assessment activities. Until now, HRP had intended to maintain only a watching brief in this area, because of the substantial investments being made by other public sector agencies, especially UNAIDS, NICHD and NIAID, and CONRAD, and by the private sector.

However, with the withdrawal of UNAIDS from this area of research and the expectation that WHO would take on this responsibility, HRP had included the assessment of the effectiveness of a dual-protection preparation, with microbicidal and spermicidal properties, in the proposal it had prepared and submitted to UNAIDS. The approved unified workload and budget of UNAIDS for the 2000–2001 biennium includes the provision to HRP of US$ 400 000 for this purpose, on the understanding that HRP will also contribute an amount to this activity. The first priority of this new research line will be collaboration in the Phase II clinical evaluation of preparations and formulations that have shown microbicidal activity in vitro, and appear to be safe for use in vivo, as evidenced by data obtained in Phase I clinical trials.
Annex 1a

STRATEGIC COMMITTEE TECHNOLOGY DEVELOPMENT AND ASSESSMENT IN 1999

Committee members

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M.J. Free, Program for Appropriate Technology in Health (PATH), Seattle, WA, USA
B.T. Nasah, Buea, South West Province, Cameroon
N. Ortayli, Institute of Child Health, University of Istanbul, Istanbul, Turkey
A.F. Schrater, Smith College Foundation, Project on Women and Social Change, Northampton, MA, USA
R. Snow, University of Heidelberg Medical School, Heidelberg, Germany
C.C.L. Wang, Harbor-University of California at Los Angeles Medical Center, Torrance, CA, USA
Xiao Bilian, National Research Institute for Family Planning, Beijing, China

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Annex 1b

RESEARCH GROUP ON POST-OVULATORY METHODS FOR FERTILITY REGULATION IN 1999

Committee members

G. Bártfai, Albert Szent-Györgyi Medical University, Szeged, Hungary
Cheng Linan, Shanghai Institute of Family Planning Technical Instruction, Shanghai, China
K. Gemzell-Danielsson, Karolinska Hospital, Stockholm, Sweden
P.C. Ho, University of Hong Kong, Hong Kong, Special Administrative Region of China (Chairman)
J. Sengupta, All India Institute of Medical Sciences, New Delhi, India
Wang Jie-dong, National Research Institute for Family Planning, Beijing, China

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Collaborating agency scientists

T. MacKay, Contraceptive and Reproductive Health Branch, National Institute of Child Health and Human Development, Rockville, MD, USA
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### Annex 1c

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**Committee members**

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M.R. Massai, Chilean Institute of Reproductive Medicine (ICMER), Santiago, Chile  
Wisut Boonkasemsanti, Chulalongkorn University, Bangkok, Thailand

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**Collaborating agency scientists**

L. Dorflinger, Family Health International, Research Triangle Park, NC, USA  
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S. Sehgal, Postgraduate Institute of Medical Education and Research, Chandigarh, India
G. Sukhikh, International Institute of Biological Medicine, Moscow, Russian Federation

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Collaborating agency scientists

D. Colvard, Contraceptive Research and Development Program (CONRAD), Arlington, VA, USA
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Annex 1e

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M.A. Isahakia, National Museums of Kenya, Nairobi, Kenya
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S. Roy, Reproductive Health Foundation, New Delhi, India
C.C.L. Wang, Harbor-University of California at Los Angeles Medical Center, Torrance, CA, USA (Chairwoman)
F.C.W. Wu, University of Manchester, Manchester, United Kingdom

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Sub-Committee members for the review of Male Basic Science research

S. Campo, Endocrinology Research Centre (CEDIE), Buenos Aires, Argentina
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J. Spieler, Agency for International Development, Washington, DC, USA
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K.H. Tennekoon, University of Colombo, Colombo, Sri Lanka
J.-C. Thalabard, University of Paris, Paris, France

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EMRO
EURO
SEARO
WPRO

Collaborating agency scientists

V. Jennings, Institute for Reproductive Health, Washington, DC, USA
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R.J.B. King, Esher, Surrey, United Kingdom
S. Tabacova, National Centre of Hygiene, Ecology and Nutrition, Sofia, Bulgaria
J. White, Hammersmith Hospital, London, United Kingdom

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Rockefeller Foundation representatives

M. Fathalla, The Rockefeller Foundation, Assiut, Egypt
E. Majidi, The Rockefeller Foundation, New York, NY, USA
Annex 2b

RESEARCH GROUP ON POST-OVULATORY METHODS FOR FERTILITY REGULATION

SCIENTISTS IN 1999

Principal investigators

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M. Bygdeman, Karolinska Institute, Stockholm, Sweden
Yong-Qing, Institute of Zoology, Beijing, China
Cheng Li-cun, Shanghai Changning Obstetrics and Gynaecology Hospital, Shanghai, China
Cheng Linan, Shanghai Institute of Family Planning Technical Instruction, Shanghai, China
Cheng Wei-yu, Tianjin Municipal Research Institute for Family Planning, Tianjin, China
M. Condrea, University of Geneva, Geneva, Switzerland
H. Croxatto, Chilean Institute of Reproductive Medicine, Santiago, Chile
Ding Ju-hong, Jiangsu Family Planning Research Institute, Nanjing, China
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D. Ghosh, All India Institute of Medical Sciences, New Delhi, India
S. Gopalan, Postgraduate Institute of Medical Education and Research, Chandigarh, India
P.C. Ho, University of Hong Kong, Hong Kong, Special Administrative Region of China
H. Honkanen, Helsinki University Central Hospital, Helsinki, Finland
M. Horga, Medical Research Centre, Targu-Mures, Romania
F. Jerve, Ulleval Hospital, Oslo, Norway
A.G. Khomassuridze, Zhordania Institute of Human Reproduction, Tbilisi, Georgia
R.J. Kirkman, University Hospital of South Manchester, Manchester, United Kingdom
L. Kovacs, Albert Szent-Györgyi Medical University, Szeged, Hungary
Liu Yinkun, Liver Cancer Institute, Zhong Shan Hospital, Shanghai, China
Liu Yi-xun, Institute of Zoology, Academia Sinica, Beijing, China
F. Lüdicke, University of Geneva, Geneva, Switzerland
S. Mittal, All India Institute of Medical Sciences, New Delhi, India
E. Ng, University of Hong Kong, Hong Kong, Special Administrative Region of China
C. Ngai, University of Hong Kong, Hong Kong, Special Administrative Region of China
Nguyen thi Nhu Ngoc, Hung Vuong Hospital, Ho Chi Minh City, Viet Nam
R.N.V. Prasad, National University of Singapore, Singapore
A. Pretnar-Darovec, University Medical Centre, Ljubljana, Slovenia
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B.N. Saxena, Indian Council of Medical Research, New Delhi, India
J. Sengupta, All India Institute of Medical Sciences, New Delhi, India
R.S. Shah, Institute for Research in Reproduction, Mumbai, India
Song Si, Shanghai Institute of Planned Parenthood Research, Shanghai, China
O.S. Tang, University of Hong Kong, Hong Kong, Special Administrative Region of China
Wang Jie-dong, National Research Institute for Family Planning, Beijing, China
Wang Yi-fang, Wuxi Maternal and Child Health Hospital, Wuxi, China
Wei Fei-ying, Shanghai Changning Obstetrics and Gynaecology Hospital, Shanghai, China
Wu Shang-chun, National Research Institute for Family Planning, Beijing, China
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Annex 2b

RESEARCH GROUP ON POST-OVULATORY METHODS FOR FERTILITY REGULATION

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Wu Er-ruo, National Research Institute for Family Planning, Beijing, China
Xiao Bilian, National Research Institute for Family Planning, Beijing, China
Zhu Peng-di, National Research Institute for Family Planning, Beijing, China

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145
Annex 2c

RESEARCH GROUP ON LONG-ACTING SYSTEMIC AGENTS FOR FERTILITY REGULATION

SCIENTISTS IN 1999

Principal investigators

Biran Affandi, University of Indonesia, Jakarta, Indonesia
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V. Brache, PROFAMILIA, Santo Domingo, Dominican Republic
A.L. Fites, Cook Imaging, Bloomington, IN, USA
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Gu Sujuan, Beijing Municipal Research Institute for Family Planning, Beijing, China
R. Hamzaoui, Research Centre for Human Reproduction, Tunis, Tunisia
S. Killick, The Princess Royal Hospital, Hull, United Kingdom
B.-M. Landgren, Karolinska Hospital, Stockholm, Sweden
E. Marbaix, International Institute of Cellular and Molecular Pathology, Brussels, Belgium
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A. Rodger, University of Warwick, Coventry, United Kingdom
P. Rogers, Monash Medical Centre, Clayton, Australia
J. Ruminjo, University of Nairobi, Nairobi, Kenya
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Sang Guo-wei, Family Planning Research Institute of Zhejiang, Hangzhou, China
S.B. Subakir, University of Indonesia, Jakarta, Indonesia
Julianto Witjaksono, University of Indonesia, Jakarta, Indonesia
S. Wonodirekso, University of Indonesia, Jakarta, Indonesia

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Annex 2c (continued)

RESEARCH GROUP ON LONG-ACTING SYSTEMIC AGENTS FOR FERTILITY REGULATION

SCIENTISTS IN 1999 (continued)

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Yang Hua, Family Planning Research Institute of Zhejiang, Hangzhou, China
E. Weisberg, Queen Elizabeth II Research Institute for Mothers and Infants, Sydney, NSW, Australia

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147
### Annex 2d

**RESEARCH GROUP ON IMMUNOCONTRACEPTIVES**

**SCIENTISTS IN 1999**

**Principal investigators**

R. Ascione, Aphton Corporation, Woodland, CA, USA  
B. Fong, Peninsula Laboratories, San Carlos, CA, USA  
V. Stevens, Ohio State University, Columbus, OH, USA

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RESEARCH GROUP ON IMMUNOCONTRACEPTIVES

SCIENTISTS IN 1999 (continued)

Other scientists

R. Ascione, Aphton Corporation, Miami, FL, USA
S. Åström, Hylae Clinical Research AB, Lund, Sweden
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T. de Roij, Aphton Corporation, Tervuren, Belgium
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P. White, Nova Laboratories Limited, Leicester, United Kingdom

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Annex 2e

RESEARCH GROUP ON METHODS FOR THE REGULATION OF MALE FERTILITY

SCIENTISTS IN 1999

Principal investigators

K.M. Arsyad, Sriwijaya University, Palembang, Indonesia
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P. Morales, University of Antofagasta, Antofagasta, Chile
A. Tan, University of Indonesia, Jakarta, Indonesia
F.C.W. Wu, University of Manchester, Manchester, United Kingdom
Zhang Gui-Yuan, National Research Institute for Family Planning, Beijing, China
Zhang Li-ying, National Research Institute for Family Planning, Beijing, China

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Annex 2e (continued)

RESEARCH GROUP ON METHODS FOR THE REGULATION OF MALE FERTILITY

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R.J. Aitken, The University of Newcastle, Newcastle, NSW, Australia
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D.M. Soebadi, Airlangga University, Surabaya, Indonesia
J. Suominen, University of Turku, Turku, Finland
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J. Zhang, National Institute of Child Health and Human Development, Bethesda, MD, USA
M. Zitzmann, Institute for Reproductive Medicine of the University, Münster, Germany
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Annex 2f

RESEARCH GROUP ON NATURAL REGULATION OF FERTILITY

SCIENTISTS IN 1999

Principal investigators

S. Becker, Johns Hopkins University, Baltimore, MD, USA
L.F. Blackwell, Massey University, Palmerston North, New Zealand
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O.A. Dada, Ogun State University Teaching Hospital, Sagamu, Nigeria
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Y. Hofvander, Uppsala University, Uppsala, Sweden
Cui Nian, Sichuan Family Planning Research Institute, Chengdu, China
M. de Rosas-Valera, Health & Management Information System, Manila, Philippines
M. Serón-Ferré, Catholic University of Chile, Santiago, Chile
C. Subasinghe, The Family Planning Association of Sri Lanka, Colombo, Sri Lanka
K.H. Tennekoon, University of Colombo, Colombo, Sri Lanka

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Annex 2f (continued)

RESEARCH GROUP ON NATURAL REGULATION OF FERTILITY

SCIENTISTS IN 1999 (continued)

Other scientists

Kumkum Amin, John Snow Inc., Boston, MA, USA
H. Burger, Prince Henry’s Institute of Medical Research, Melbourne, Australia
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K. Kennedy, Denver, CO, USA
E. Kylberg, Uppsala University, Uppsala, Sweden
P. Royston, Royal Postgraduate Medical School, London, United Kingdom
R. Snow, University of Heidelberg Medical School, Heidelberg, Germany

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**Annex 2g**

**WHO/ROCKEFELLER FOUNDATION INITIATIVE ON IMPLANTATION RESEARCH**

**Principal investigators**

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J. Sengupta, All India Institute of Medical Sciences, New Delhi, India  
S. Smith, The Rosie Maternity Hospital, Cambridge, United Kingdom  
R.L. Stouffer, Oregon Regional Primate Research Center, Beaverton, OR, USA

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Annex 3b

RESEARCH GROUP ON POST-OVULATORY METHODS FOR FERTILITY REGULATION

Publications in 1999


Chen YJ, Gao HJ, Liu YX. Ovarian follicles in pregnant rat do not have ability of steroidogenesis. *Chinese science bulletin* (in press).


Hu ZY, Liu YX, Zou RJ, Ockleford CD. Expression of tissue type and urokinase type plasminogen activators as well as their inhibitors type-1 and type-2 in the placenta of human and rhesus monkey. *Journal of anatomy*, 1999, 194:183–195.

Liu YX. Regulation of the plasminogen activator system in the ovary. (Review). *Biological signals and receptors*, 1999, 8:160–177.


Annex 3b (continued)

RESEARCH GROUP ON POST-OVULATORY METHODS FOR FERTILITY REGULATION

Publications in 1999 (continued)


Tao YX, Cao YQ. Interferon gamma in early pregnant trophoblast tissue. *Chinese science bulletin* (submitted).


Annex 3c

RESEARCH GROUP ON LONG-ACTING SYSTEMIC AGENTS FOR FERTILITY REGULATION

Publications in 1999


d’Arcangues C. Treatment of vaginal bleeding irregularities induced by progestogen-only contraceptives. Human reproduction supplement (in press).


Dennerstein L. Psychosexual effects of hormonal contraception. Gynaecology forum, 1999, 4:13–16


Grow DR, Reece MT. The role of selective estrogen receptor modulators (SERMs) in the treatment of endometrial bleeding in women using long-acting progestin contraception. Human reproduction supplement (in press).


Hampton AL, Rogers PAW, Affandi B, Salamonsen LA. Expression of the chemokines, monocyte chemotactic protein (MCP)-1 and MCP-2 in endometrium of normal women and Norplant users does not support a central role in macrophage infiltration into endometrium. Molecular human reproduction (submitted).


Hickey M, Fraser IS. The structure of endometrial microvessels. Human reproduction supplement (in press).


Annex 3c (continued)

RESEARCH GROUP ON LONG-ACTING SYSTEMIC AGENTS FOR FERTILITY REGULATION

Publications in 1999 (continued)

Le Sy-Q, Casey LM. Regulation of the levels of urokinase plasminogen activator receptor mRNA in human endometrial stromal cells. *Human reproduction supplement* (in press).


Rogers PAW, Plunkett D, Affandi B. Perivascular smooth muscle α-actin is reduced in the endometrium of women with progestin-only contraceptive breakthrough bleeding. *Human reproduction supplement* (in press).


Thomas AM, Hickey M, Fraser IS. Disturbances of bleeding with hormone replacement therapy. *Human reproduction supplement* (in press).


Annex 3d

RESEARCH GROUP ON IMMUNOCONEPTIVES

Publications in 1999


Annex 3e

RESEARCH GROUP ON METHODS FOR THE REGULATION OF MALE FERTILITY

Publications in 1999


Annex 3f

RESEARCH GROUP ON NATURAL REGULATION OF FERTILITY

Publications in 1999


Vásquez K, Vergara M, Recabarren M, Brandeis A, Serón Ferré M. Development of a radioimmunoassay for *Cebus apella* PRL. *Biolological research*, 1997, **30**:75–84.


Fertility regulation

Users’ perspectives in the context of reproductive health

INTRODUCTION AND OBJECTIVES

The fertility regulation needs of more than 400 million individuals remain under-served, despite the expansion of family planning programmes globally. Furthermore, over 40% of those using a contraceptive method to space births discontinue the practice either because of side-effects or method failure. The strong association between these unmet needs and the dual risks of sexually transmitted infections (STIs)/HIV and unwanted pregnancy make even more relevant the call to reorient existing services to meet the demands for dual protection and sexual health. A reorientation that incorporates the perspectives of women and men and enables couples to attain safely their sexual and reproductive goals is a widely supported strategy.

To this end, HRP has supported focused research initiatives in three areas: (i) women’s and men’s perceptions and behaviours regarding the dual risks of unplanned pregnancy and STIs; (ii) the role of men in reproductive health; and (iii) the acceptability of fertility regulation methods. This research is generating the evidence necessary for national authorities to make informed decisions regarding the provision of services and methods of fertility regulation that are acceptable to current users, meet their needs, and have the potential to attract new users.

PROGRESS

During 1999, HRP continued to support research that promotes evidence-based policy-making and programmatic development. During the year, fieldwork was undertaken and preliminary results made available for several studies relating to the dual risks of HIV/STIs and unwanted pregnancy, the role of men in reproductive health, and the acceptability of certain fertility regulation methods. In addition, a new research project on the perceptions and acceptability of fertility regulation methods was initiated among couples in Lahore, Pakistan. Dissemination activities were strengthened through the launching of a new series entitled Social Science Research Policy Briefs, and preparations were made for a new research initiative on the quality of care in reproductive health.

Family planning and sexual behaviour in the era of HIV/STIs: a multicountry study in six African countries

The rise in the prevalence of HIV and AIDS has rendered even more urgent the need to achieve dual protection in men and women exposed to the risks of STIs/HIV and unplanned pregnancy. A multicountry research project was undertaken in six African countries—Kenya, South Africa, Tanzania, Uganda, Zambia, and Zimbabwe to: (i) ascertain the perspectives of sexually active individuals about the dual risks of STIs (including HIV/AIDS) and unwanted pregnancy; (ii) investigate strategies that sexually active individuals would consider appropriate, practical, and effective for coping with these risks; and (iii) explore opportunities for and constraints to behavioural change, with particular emphasis on communication between partners.

The study involves three phases. The first phase, begun in 1997–1998, consisted of 12 or more focus group discussions (FGDs) in each setting. The second phase, which is currently under way, involves the conduct of a survey, and the third phase will consist of follow-up in-depth interviews. At the end of 1998, findings from phase I were available for five of the six countries and these were reported in the Annual technical report 1998. In Zimbabwe, phase I research was initiated in 1998, and the available findings are reported here: 24 FGDs were held in four districts, as shown in the table below.

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FP= family planning

Findings from Zimbabwe are broadly consistent with those from other settings in five countries. Though there appears to be considerable knowledge and awareness of STIs/HIV and their modes of transmission, various misconceptions persist. For example, nearly all male and female groups reported that menstruation, which is perceived to be a cleansing process, reduces the risk of women getting infected with STIs/HIV. Men were, however, perceived to be more at risk of HIV infection than menstruating women. Such perceptions are coupled by a notable proportion of individuals who do not consistently practise safe sex. On the one hand, men in the sample reported that condoms are well known and easily available, and male and female participants viewed condoms as an appropriate method to prevent infection in casual relationships. On the other hand, participants considered condoms to be an unacceptable method to use within marriage, and generally ineffective in preventing pregnancy:

“Condoms are used mostly by commercial sex workers,”
“You cannot use the condom in the home as a family planning method. The husband would not agree to use it for such a long time,” (female user, Harare).

“I do not agree with the idea of relying only on the condom for family planning. It might break,” (male, Harare).

In the study areas, many participants expressed the belief that contraceptive use is a woman’s responsibility but a man’s decision. For example, a male participant stated that “women are the ones who use family planning because they are the ones who do not want to get pregnant”, and a female participant noted that only “those men who are educated are the ones who allow their wives to use family planning”.

Participants’ attitudes toward the use of family planning among youth were generally negative. Both covert contraceptive use and unwanted pregnancy are sources of stigma for young, sexually active girls:

“That the young are turning to family planning services for advice. The nurses are just dishing out the pills …” (female user, Harare).

“Young girls are especially affected (by unwanted pregnancy) because boys refuse responsibility and parents will not be ready to have grandchildren,” (female user, Harare).

The continued spread of HIV/AIDS was attributed mainly to the continued existence of untreated STIs, multiple sex partners among infected men, and the use of traditional medicine with incomplete treatment. For example, one participant said “our husbands are not satisfied with one wife, they want to ‘test’ all women”, (female non-user).

In general, the participants feared the consequences of being HIV positive. As one man from Mtoko put it: “There is no sick person who admits to having AIDS— for fear of alienation and rejection by society and family members.” Another man from Harare said: “If you are a lodger, the landlord will chuck you out. Some think your going to the toilet will leave the virus on the seat and they will also get it.”

Whereas communication between spouses on family planning was generally reported, discussion on sexual matters and STIs/HIV was uncommon. As one woman from Mtoko who practised family planning said: “… husbands are afraid of being accused of promiscuity so you cannot talk about AIDS”.

People in the focus groups also discussed strategies to promote protective behaviours, including: (i) self control for men; (ii) use of condoms; (iii) counselling on the consequences of unsafe sex; (iv) going to church; and (v) peer education. Based on these findings, the investigator outlined several policy implications. First, educational campaigns are needed to correct misperceptions regarding STIs/HIV infection which are major constraints to behavioural change. Second, families and friends of those with AIDS should be counselled about the provision of support and care. Third, information on the prevalence of HIV and AIDS should be disseminated widely to inform people about the risks and consequences of unsafe sex. Fourth, condom use should be encouraged both within and outside marriage. Finally, more efforts should be made to promote communication between spouses on HIV/AIDS and related issues.

In 2000, results from the surveys are expected to be available. It is planned to release Social Science Research Policy Briefs as soon as the results become available and hold local and regional meetings on information dissemination.

Role of men in reproductive health: opportunities and constraints

Researchers, policy-makers and programme planners have increasingly acknowledged the need to involve men in programmes intended to reduce the unmet need for contraception and improve sexual and reproductive health. The scarcity of social science research on men’s roles and perspectives in developing countries led HRP to launch a focused initiative in 1995. Among others, the objectives of this initiative were: (i) to document men’s knowledge of and experiences with STIs and contraception; (ii) to assess the perceived acceptability of various male and female contraceptive methods among men; and (iii) to understand men’s influence on contraceptive decision-making within the family. A total of 17 studies were supported under this initiative, and seven others that were supported under different initiatives also focused on men and reproductive health. Results from six studies related to men were presented in earlier Annual technical reports. Studies on men that highlight opportunities for and constraints to male involvement in reproductive health were completed in 1999. Key findings from these studies are discussed below.

One study conducted in Jamaica and another conducted in Turkey suggest that men from widely different cultural settings view favourably certain male methods of contraception and are willing to assume responsibility for preventing pregnancy and decreasing STI transmission. At the same time, men in these studies expressed attitudes
and concerns that may constrain their full, positive participation in reproductive health.

The study in Jamaica gathered information on knowledge and attitudes relating to contraception, contraceptive practices, reactions to pregnancy and union formation among 714 men aged 15-40 who resided in Kingston, rural St. Andrew, and Hanover. A subsample of these men participated in FGDs on related topics. Findings suggest high overall levels of awareness, approval and use of contraception. Although method-specific awareness ranged from 36% for tubal ligation to 96% for condoms, 99% of men in the sample knew of at least one method of contraception, 94% approved of family planning, and 55% practised contraception to prevent unwanted pregnancy.

Despite high approval of contraception in general, men expressed concerns about the side-effects and low effectiveness of certain female methods, such as the oral contraceptive:

“…she can get fat, her belly hang over, breast drop out of shape. She nuh look good again. Dem time deh, a man a go waan flee,” (39 years, common-law relationship with one child).

“It can give the female cancer and it can give the male rash,” (20 years, casual relationship with two children).

Men also expressed ambivalence about condoms. A substantial minority (30%) of men in the sample, particularly younger men in unstable relationships, favoured condom use for disease prevention, whereas men in “bonafide” relationships with a trusted partner viewed female methods as more appropriate. “When yuh settle down with a girl, yuh nuh need to use a condom cause yuh a look forward to establishing a family.” Even men in bonafide relationships tend to view condoms favourably when they doubt the fidelity of their partner: “You have your bonafide girlfriend an she might have all ten odda man…so yuh have to use it (condom) with yuh bonafide girl too;” (26 years, common-law relationship with two children). Instability of sexual relationships and cultural pressure to prove one’s virility are cited as reasons for irregular use.

In contrast to their ambivalence toward condoms, most men in this study expressed a clear disapproval of permanent methods: 89% of the men disapproved of tubal ligation for themselves, and 96% would not consider vasectomy for themselves; 36% of men in the sample provided no justification for their opposition to permanent methods: “Mi nah cut nuting!” (34 years, common-law relationship with two children). The uncertainty of interpersonal relationships made 27% of men feel that vasectomy was too final: “You might do it today and tomorrow you see a girl and you want her to get pregnant for you and you can’t get her pregnant;” (35 years, common-law relationship with two children). One-fourth of the men stated that permanent methods were against God’s will, and 8% attributed their disapproval of male sterilization to a perceived loss of pleasure: “Not for me. I won’t be di one to contradict God’s work,” (38 years, married, three children). Negative attitudes toward permanent methods also stemmed from uncertainty about desired completed family size.

Therefore, overall high approval of family planning and relatively high use of condoms among Jamaican men (17% among all married men or men in union, as reported in another survey conducted in 1993) is coupled with persistent fears of the side-effects of certain methods, an ambivalent attitude to condoms that is rooted in cultural beliefs and gender roles, and disapproval of permanent methods that threaten family formation strategies and valued aspects of male identity.

In Turkey, the methods accepted by men and those causing ambivalence are somewhat different from those in Jamaica. Investigators in Turkey conducted an exploratory study of the perceptions of men and women toward various contraceptive methods, including withdrawal and condoms. Nine in-depth interviews with selected key informants and ten FGDs each with married women and men, respectively, were conducted in neighbourhoods in Umranicy, one of the most densely populated districts in Istanbul. The results indicate a sustained willingness among men in Turkey to use certain types of male methods. According to another survey, almost one in four couples using contraceptives in Turkey relies on withdrawal (26% in 1988 and 24% in 1998). Far fewer, however, use condoms (7% in 1988 and 8% in 1998). Otherwise, the most commonly used modern method in Turkey has been the IUD (14% in 1988 and 20% in 1998).

Findings suggest that withdrawal is widely known and accepted among men. The most common phrase that participants used for withdrawal was “men’s protection”. Other terms included “pulling back”, “spilling out”, “emptying out”, “self defence”, and “own method”. These local terms squarely define withdrawal as a contraceptive method that is the responsibility of and under the control of men.

Although both women and men in the study favoured voluntary use of withdrawal, reasons sometimes varied. Women tended to favour withdrawal because it has no health risks and is natural, clean and free.

“Although it (withdrawal) is not hundred per cent guarantee, it has no health risks for me…”

“At least we don’t get any foreign material, coil inserted, not getting pills, meaning it’s quite natural…”

Women also viewed withdrawal as a means for men to
assume responsibility for contraception:

“It is the most wonderful method since it is used by the other side…”

“…since I have used a few different methods … I am expecting a method of contraception from him now… I want the other part to make some effort…”

Additional reasons underlying men’s reliance on withdrawal in Turkey included poor knowledge of other methods, negative experiences with modern methods, and rumours about the side-effects of modern methods. These have led couples to use withdrawal by default.

“…on the outskirts of Istanbul those people who live in squatter areas probably don’t know the variety of methods … so still use some traditional methods like withdrawal…”

“Pills … are bad for health. They disturb the hormones, create things like irritability… it’s better that men use protection…”

“…I think pills are troublesome. Why? It is my lady’s health and … the IUD … makes an allergy… in my self defence (withdrawal) I have nothing wrong though I’m married for twenty-five years… I’m continuing as it is since then.”

“A man … how can he take his wife for an IUD insertion? He would be too shy… Hence, withdrawal is practised…”

While withdrawal is commonly used and is acceptable to a high percentage of men and women in Turkey, other contraceptive methods are less accepted and used. For example, the perceived advantages of condoms, namely, that they “don’t have any health hazards”, “also please the woman”, are “good for neatness” and “prevent disease”, may be outweighed by their perceived disadvantages. Almost all study participants said they would be embarrassed to buy condoms in public. One male participant explained: “I feel ashamed … to go and get the condom from the pharmacy.” Both men and women stated that condoms interrupt sexual pleasure: “When he uses a condom I feel uncomfortable … it makes a very strange sound. You cannot get any pleasure.” These disadvantages, as well as the possible perception that condoms are intended for disease prevention, may explain the relatively low use of condoms compared to withdrawal by men in Turkey.

Fears of side-effects may to some extent inhibit the acceptance and continued use of IUDs and oral contraceptives. Regarding IUDs, men and women commonly expressed the concern that couples engaged in intercourse could become “stuck”.

“Excuse me for being so open, but I have heard that in different positions used during intercourse it gets stuck,” (man).

Men and women expressed fears of perceived side-effects of oral contraceptives on the kidneys and liver, and of pill-induced sequelae such as cancer, addiction and infertility.

“Pills have many side-effects … they cause overweight or nervousness … In addition, they … develop cancers,” (woman).

“Doesn’t it discharge by the kidneys? I mean as a medicine…If it’s used continuously, …the body would have immunity and be worn out,” (man).

“We know some live examples of using pills for two years…I have relatives who are infertile now because of this,” (man).

“…Sometimes it causes hormonal irregularities or even worse as other diseases resulting in cancers,” (man).

Further expansion of the family planning and reproductive health programme in Turkey requires a better understanding of the factors motivating couples’ persistent use of withdrawal and their relatively slow acceptance of modern methods, including condoms.

Studies conducted elsewhere corroborate the expressed ambivalence of men and their partners toward certain contraceptive methods, and underscore the importance of men’s roles in determining whether or not fertility regulation is practised at all. In a study conducted in urban squatter settlements in Karachi, Pakistan, the dynamics of contraceptive use were explored by interviewing women (404 contraceptive users and 313 non-users), their husbands, and their mothers-in-law. Findings suggest that women’s educational status and discussion with the mother-in-law on family planning have an important bearing on whether or not a woman uses a contraceptive method. The investigators suggest that, for the short term, family planning information campaigns should include husbands and mothers-in-law. In the long run, increased female literacy is likely to improve the acceptance of family planning.

Acceptability of condoms

Acceptability of condoms has been the focus of four studies. Two studies conducted in Shanghai, China, examined the acceptability and use of condoms among patients with STIs.

A study conducted at the Shanghai Centre for STD Control and Prevention explored the impact of an
educational and motivational intervention on men’s attitudes toward condoms and condom use. A total of 2266 male clinic attendees diagnosed with an STI were recruited and randomly assigned to one of three groups: (i) a control group receiving routine clinical services (n=842); (ii) a group receiving routine services and an educational video (n=716); and (iii) a group receiving routine services, an educational video and the opportunity to participate in facilitated group sessions to discuss the video (n=708). The 20-minute long video provided men with correct information on STIs and their prevention, portrayed positive attitudes about condom use, and provided culturally and gender-appropriate messages to encourage condom use. A second interview was requested 2–3 weeks after the first, at which time knowledge of STIs and correct condom use and attitudes toward condoms were ascertained. Results suggest that men in the video and video-plus-discussion groups more frequently answered questions on knowledge correctly and more often expressed favourable attitudes toward condoms.

In a second study, FGDs were held with male and female providers to understand providers’ perspectives of clients, counselling and condom promotion in STI clinics. In addition, 203 clinic attendees were interviewed in-depth, an intervention to improve counselling skills was introduced, and follow-up interviews were conducted with clients using a structured questionnaire.

Most notably, results highlight the extent to which men’s risky sexual behaviours place their wives or regular partners at risk of infection. Fifty-nine per cent reported having had at least one casual partner in the month before interview. Some 14% claimed that their infections had come from a spouse or stable partner. However, of the 70% of clients who reported having had sex at least once between the first and second interviews, only 80% used a condom consistently. The reason stated for not using a condom was embarrassment in telling one’s spouse about the infection.

“My wife has already been inserted with an IUD. I cannot find an excuse to propose using condom,” (38-year-old married male public servant).

With regard to clients’ perceptions of sources of care, some 80% of clients stated that they feared visiting public STI clinics because they expected providers to express negative attitudes.

“...I cannot stand when they kept asking ‘where did the disease come from’?... I just lied that my husband went to Hainan a few weeks ago, this is why I get it,” (21-year-old bar girl, unmarried resident).

Instead, clients expressed a preference for untrained private providers because “they have … warm attitudes, are less expensive, and … are more friendly”.

Physicians in public clinics did not always understand clients’ fears about seeking public-sector STI care.

“Our attitudes to the STI clients have been good enough, much better to than other clients, they (the clients) should feel happy,” (29-year-old female physician).

However, most physicians (14 out of 18) appreciated the need to distribute condoms at STI clinics, and all agreed that STI clinics are the best places to promote condom use. The appropriate mechanism for distribution was unclear because: (i) free distribution was often financially difficult for clinics to sustain; (ii) sale of condoms violated local health policy; and (iii) installation of condom vending machines required a permit from the local health authority.

All physicians recognized that counselling is important to prevent STIs/HIV. However, counselling is still uncommon in most clinics because: (i) doctors reportedly lack the time to counsel clients, and (ii) STI clinics in China rely on practices that generate income: “I know that counselling is important to STI/HIV prevention, but I have no time to do it and providing counselling gets no economic profit, so there is no point to do so,” (34-year-old male physician).

The investigator recommends that public STI clinic services should be improved by incorporating clients’ perspectives and needs into the service delivery process. Changes in health-seeking and sexual behaviour rely on good counselling, condom promotion, demonstration of correct condom use, and distribution of condoms along with a guide for their use. Outreach programmes that include health education and condom promotion should be encouraged, since vulnerable groups such as commercial sex workers are sometimes difficult to access.

HRP is also supporting a study in South Africa and Thailand, entitled Acceptability of a Non-latex Male Condom: A Cross-national Study, to ascertain the acceptability of a non-latex condom. This study, which has a comparative randomized crossover study design, will also provide information on the background characteristics of men and women who are more or less likely to accept the latex or a non-latex condom. In addition, information on the reasons for accepting or discontinuing use during the study period is ascertained. Data collection has been completed in both countries, and the analysis is under way.

Assessing the acceptability of male hormonal contraception

An interest in obtaining the perspectives of men and
women on fertility regulating methods as early as possible in the contraceptive development process has spurred efforts to develop the necessary research tools and mechanisms. Participants in a clinical trial are uniquely positioned to offer their perspectives regarding a method’s ability to meet their needs, the appropriate steps to improve its marketability, and the factors motivating and constraining the successful introduction of a hormonal contraceptive method for men.

Efforts to develop an acceptability protocol that could be applied to the study of any male hormonal contraceptive under development are based on the needs: (i) to pool data on a small sample of men who are participating in a standard clinical trial at different centres; (ii) to measure changes over time in mood, sexual function, behaviour and consequent acceptability of the method; and (iii) to assess other user and partner perspectives at the individual level.

In 1999, HRP developed a protocol and set of instruments to be used in a six-centre clinical trial of cyproterone acetate (CPA) and testosterone undecanoate (TU) in normal men. Participating centres are located in Australia, Canada, Germany, India, Italy and the United Kingdom. The primary aims of this study are: (i) to pilot instruments that assess whether or not there are any adverse effects on mood, sexual function and behaviour of participants receiving either CPA plus TU or placebo plus TU, and (ii) to pilot instruments that assess users’ perspectives and any perceived benefits or disadvantages of either of the two regimens.

The acceptability component includes forms to document: (i) the sociodemographic and economic profile of all men expressing interest in participating in the trial; (ii) factors motivating participation in a study to test the ability of a hormone to suppress sperm production; (iii) contraceptive history of participants and attitudes toward contraception; (iv) side-effects, if any, that participants experience during the study which are attributable to treatment; (v) changes, if any, experienced in the level of energy, physical activity, aggression and mood during the study; (vi) changes, if any, experienced in sexual function during the study; (vii) perceived advantages/disadvantages of a contraceptive method that resembles prototype(s) in this study; and (viii) the potential for use of a similar method of contraception, were one to be made available.

The Social Science Research on Reproductive Health Group also extended technical support to develop a very similar protocol and set of instruments to assess sexual function, users’ perspectives, and method acceptability among 40 normal Indonesian men participating in a Phase III clinical trial of TU alone or combined with depot medroxyprogesterone acetate (DMPA). The acceptability component of this clinical trial also includes instruments to assess the perspectives of partners of the male subjects. This study will be initiated in early 2000.

**Perspectives of users on emergency contraception**

HRP continues to acknowledge the importance of understanding the perspectives of users and potential users of new contraceptive technologies before their introduction into existing services. To this end, HRP has supported two studies in China that explored the acceptability of emergency contraception among women seeking termination of pregnancy. One study of the knowledge, attitudes, needs and availability of emergency contraception among women aged 18 to 50 who sought to terminate a pregnancy was conducted in three maternal and child health centres in Shanghai, China. After women were informed about the usage and possible side-effects of the emergency pill and IUD, they were asked about their willingness to use either method: 86% of all the women interviewed said that they would be willing to use either method in the future, if necessary. Young, well-educated and professional women were more often willing to use emergency contraception than older, uneducated women. Also, unmarried women and married women without children were more likely to express a willingness to use emergency contraception than married women with children. Finally, women who had known about emergency contraception before the study were more willing to use the method than those who learned of it from the study.

Among those women who were willing to use emergency contraception, the overwhelming majority (83%) preferred the emergency pill, 8% preferred the IUD, and 9% had no preference. The main reasons for selecting the pill were its convenience (40%) and painless administration (21%). The main reasons for selecting the IUD were its high efficacy (33%), few side-effects (31%) and its potential to be used as a regular contraceptive method. Fear of side-effects was a commonly expressed reason for women’s unwillingness to use the method (20%). Sixty per cent of all women interviewed thought the drug store was the best place to obtain emergency contraception, 30% selected hospitals, 5% selected the workplace, 3% selected other places, and 1% did not express a preference. The main reason for choosing the drug store was its convenience (87%), and for choosing the hospital was its reliability (86%).

HRP has also supported a project on the “Acceptability of emergency contraception in Latin America”. The objectives of the study were: (i) to assess the acceptability of emergency contraception among potential users, possible providers, authorities and other influential persons in service provision; and (ii) to design introductory strategies for emergency contraception according to the perceptions of these persons, and in keeping with the political, cultural and socioeconomic context and the health service conditions prevalent in each country. The study was carried out in Campinas, Brazil; Santiago, Chile; and
Durango, Mexico. The research team at each site included biomedical and social scientists.

Two types of data were collected. First, background documents containing information on the sociocultural, political, legal and religious context, the status of reproductive and sexual health and rights, and the situation of health services were prepared upon reviewing existing official documents, reports from other studies, academic publications and information in the mass media. Second, the opinions of potential users, possible providers, authorities and influential persons were collected both through individual/collective interviews and a series of FGDs.

In all three countries, the acceptability of emergency contraception was high among potential users and among the majority of health care providers, schoolteachers and authorities. More cautious opinions were found in Chile than in Brazil and Mexico. In general, emergency contraception was perceived as an important component of the solution to major personal and public health problems such as pregnancy among adolescents, unsafe abortion or suffering derived from unwanted children.

The investigators concluded that the acceptability of emergency contraception in the general population would be higher if it is introduced in the broader context of responsible fertility regulation, prevention of induced abortion and reproductive and sexual health and rights. Important components of a common introductory strategy would be the training of providers, inclusion of emergency contraception in the family planning services, improved accessibility and quality of services, and the provision of accurate and clear information materials that would prevent misuse of the method. Information about emergency contraception should be given together with information on other contraceptives and in the context of responsible and safe sexual behaviour. The tailoring of services to meet adolescents’ needs and the provision of sex education to adolescents and their parents were recommended in all three countries.

Acceptability of medical abortion

During 1999, HRP also implemented a study entitled “A double-blind, randomized, controlled multicentre trial of three misoprostol regimens after pretreatment with mifepristone for termination of early pregnancy” in 15 centres in 12 countries. As a part of this study, information on the acceptability of surgical or medical abortion is being collected. Information is also being sought from subjects on: (i) their assessment of the feasibility of use of abortion-inducing medicaments without supervision of medical professionals; and (ii) their preferences for undergoing a medical abortion at home or at a health facility. Data collection is currently under way.

Another study entitled “A comparative study of surgical and medical abortion in China” examines the acceptability of the two methods of abortion among women seeking abortion in Tianjin (China). The project is in the final phase of data collection and results are expected in 2000.

Impact of improved quality of care on contraceptive acceptability and client satisfaction

HRP recognizes that users’ perspectives and the acceptability of fertility regulation methods are likely to be associated with the quality of service delivery systems. Two studies have explored the extent to which interventions to improve the quality of family planning and other reproductive health services can improve clients’ knowledge of and attitudes towards contraception, contraceptive use and reproductive health outcomes.

An intervention study conducted in Southern and Northern Jiangsu Province, China, explored the impact of improved family planning services on client satisfaction, contraceptive continuation and other reproductive health outcomes. An experimental (intervention) programme was initiated in selected areas in the early 1990s to provide better information, improved counselling and a wider range of reversible contraceptive methods. The four villages in which the intervention programme was introduced were matched with four control villages which had comparable socioeconomic and health characteristics. In each village, 350–450 healthy, sexually active and unsterilized couples were recruited and followed for three years. Preliminary results suggest that client satisfaction was higher, contraceptive discontinuation was lower, and rates of induced abortion were lower in the experimental than in the control villages. For example, the five-year discontinuation rate for the pill was 29% in the intervention areas versus 55% in the control areas (Figure 1).

![Figure 1. Percentage of women who discontinue contraceptive use within 60 months, by type of method and area, Jiangsui, China](image-url)
Regional and international workshops, as well as new dissemination activities initiated by HRP, have enhanced the local and global impact of social science research on users’ perspectives.

As Phase I of the multicountry study “Family Planning and Sexual Behaviour in the Era of STDs and HIV/AIDS” comes to a close, investigators from participating countries have begun to disseminate their findings at the grassroots and international levels. In November 1998, results from Phase I FGDs conducted in Nakuru, Kenya, were disseminated in the urban and rural communities in Nakuru district, where the research was conducted. The audience of this presentation included local community members, community leaders and health service providers. A presentation was also made at a UNFPA workshop in Dakar (Thematic Workshop on HIV/AIDS, Dakar, 15–19 July 1999), and the background paper for the presentation will appear in the proceedings. A paper entitled “Family Planning and Sexual Behaviour in the Era of STDs and HIV/AIDS: A Case of Nakuru District, Kenya” is intended for publication in the African Policy and Health Research Centre working paper series, and was presented at the Third African Population Conference, Durban, 6–10 December 1999.

At the International Symposium on Quality of Care in Family Planning in China, held in Beijing (17–19 November 1999), an investigator presented preliminary results of the intervention study conducted in Jiangsu Province, China. The symposium was designed to examine the impact of improved family planning service delivery on client satisfaction, contraceptive continuation and other reproductive health outcomes. The same investigators gave a presentation on data analysis for field experiments at a workshop on Reproductive Health Epidemiology held this year in Nanjing, China, with the sponsorship of the Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA.

Presentations were also made by the Secretariat at national and international meetings in Beijing, Shanghai, and Urumqi, China, and in Cairo, Egypt.

To disseminate more widely findings from social science research, a new series of fact-sheets entitled Social Science Research Policy Briefs was launched in 1999. Each brief consists of a two-page summary of research findings, policy implications and programmatic recommendations. The goals of these briefs are threefold: (i) to disseminate widely the findings of research supported by HRP; (ii) to build the analytical capacity and technical writing skills of in-country investigators through extensive collaboration during the development of this publication; and (iii) to highlight the policy relevance and programmatic impact of social science research. Briefs are widely disseminated to over 3000 individuals and institutions. The briefs are also targeted at governmental and nongovernmental organizations in the countries where the research is conducted. Finally, the briefs are distributed to the entire network of social science investigators who have received support from HRP.

The Social Science Research Policy Briefs are to be divided into series that highlight the research of focused initiatives. The first series of briefs focuses on men’s attitudes and role in reproductive health. The first two briefs summarize findings from two studies that were described in the Annual technical report 1998: (i) men’s role in family planning in Kenya; and (ii) sexual risk behaviour among men in five border towns in Nepal. To date, responses from recipients of the brief have been extremely positive, and distribution of the first brief spurred several investigators to submit draft briefs of their own research.

PLANNED ACTIVITIES FOR 2000

Research on users’ perspectives and the acceptability of fertility regulation methods will continue in several countries, including Brazil (2), China (3), Iran (1), Kenya (2), South Africa (2), Tanzania (1), Thailand (1), Uganda (1), Zambia (1) and Zimbabwe (1). At its June 1999 meeting, the Scientific Review Committee of the Strategic Component for Social Science Research in Reproductive Health approved a new study, which will focus on the perceptions of couples toward contraceptive use in Pakistan. The objective of this study is to ascertain the reasons why the majority of eligible men and women in Pakistan do not use contraception, even when it is accessible and free in Maternity and Child Welfare Association (MCWAP) project areas where door-to-door family planning services are provided. The investigators will explore people’s needs, concerns and preferences regarding contraception, choice of method, and discontinuation patterns. Quantitative and qualitative research methods will be used, and urban and rural areas will be included in the study.

HRP will continue to produce and disseminate Social Science Research Policy Briefs by expanding the series on “Men and reproductive health” and by producing briefs that focus on other thematic areas. Briefs may be made even more accessible by placing them on the Department’s web site.

Finally, HRP intends to launch a new social science research initiative on the quality of care in reproductive health. Preliminary ideas on this initiative were discussed at the 1999 meetings of the Scientific and Technical Advisory Group (STAG) and Gender Advisory Panel (GAP).
Taking into consideration the recommendations of STAG, GAP and the Scientific Review Committee, and in view of the gaps in what is known about quality of care in different aspects of reproductive health, HRP envisages a dual approach in this initiative. The first will focus on the development of process indicators and measurement of quality of care in the areas of abortion/postabortion, RTIs/STIs and maternal/safe pregnancy care in both the private and public sectors. Research in these areas might focus on the measurement of quality of care from the client’s, provider’s and community’s (including non-users’) perspectives. For this prong of the initiative, an open Call for Proposals is to be disseminated, and proposals would be sought from the wider research community.

Considerable attention has already been devoted to the development of process indicators in the area of family planning. Thus, a second aspect of this initiative is intended to support research that will employ various study designs, such as areal comparisons, longitudinal study designs, or before–after case–control study designs to explore the influence of quality of care on understudied dimensions of contraceptive use (e.g. contraceptive uptake, continuation, and method failure). Recognizing that it may not be feasible to fund major interventions in this area, HRP will explore ongoing interventions or “natural experiments”. By its nature, the family planning aspect of the initiative would consist of selected studies to be developed more centrally in consultation with the Scientific Review Committee.

In response to a recommendation made by HRP’s STAG, GAP, and the Scientific Review Committee, a background paper has been prepared. The paper highlights, for potential investigators, the priority thematic areas, and introduces to potential investigators:

— relevant definitions and concepts;
— methods to measure quality of care;
— examples of studies exploring non-users’, users’, and providers’ perspectives on quality of care in different areas of reproductive health; and
— studies demonstrating the impact of improved services on users’ perspectives/client satisfaction and other reproductive health outcomes.

HRP intends to disseminate this document, a summary concept paper, and a call for proposals in the spring of 2000. Submitted concept papers and proposals will be at its meeting of the Scientific Review Committee at its meeting in 2000.
Annex 1

SCIENTIFIC REVIEW COMMITTEE ON SOCIAL SCIENCE RESEARCH ON REPRODUCTIVE HEALTH IN 1999

Members

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Annex 2

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Annex 3

PUBLICATIONS IN 1999


Guo You-ning, Man-lun Ng. Factors related to the marital satisfaction of couples at five years after wedding in Shanghai. 14th World congress of sexology, 23–27 August 1999, Hong Kong, China.


Fertility regulation

Safety and efficacy of existing methods of fertility regulation

T.T.M. Farley, O. Meirik, P.J. Rowe
OBJECTIVES

The Programme’s research on the safety and efficacy of existing methods of fertility regulation is concerned with the identification and incidence of adverse and non-contraceptive beneficial side-effects of currently available fertility regulating methods, and evaluation of the contraceptive efficacy of these methods when this is not well known. The research methodologies employed for these evaluations include observational epidemiological research, as well as randomized and non-randomized clinical trials.

STEROID HORMONE CONTRACEPTION AND CARDIOVASCULAR DISEASE

The WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception (the WHO CVD Study) was initiated by HRP in the mid-1980s. At that time, most information available on adverse cardiovascular effects (acute myocardial infarction, stroke and venous thromboembolism [VTE]) of hormonal contraception referred to pills containing higher dosages of estrogens and progestogens than those currently available. In addition, there was almost no knowledge about adverse cardiovascular effects from developing countries where most of the hormonal contraceptives are used. Furthermore, the potential impact of changed prescribing patterns had not been evaluated.

The methodology and major findings from the WHO CVD Study have been described in previous Annual technical reports. Additional analyses of the data have been published in the past year, and HRP has sponsored studies based on the United Kingdom General Practice Research Database (GPRD).

Migraine and OC use

Migraine has been reported to be a risk factor for ischaemic stroke and a previous case–control study showed a substantially increased risk of ischaemic stroke in women with migraine who had used oral contraceptives (OCs) (Tzourio et al., British medical journal, 1995, 310:830–833). Bickerstaff (Neurological complications of oral contraceptives, Oxford University Press, 1975) cited examples of changed patterns of migraine heralding a stroke in women starting OC use and advised that women should stop taking OCs if their migraine changed from simple (without aura) to classical (with aura). However, no formal epidemiological studies had been conducted to address this issue, and investigators from the five European centres participating in the WHO CVD Study used an additional questionnaire to collect information from all cases of stroke and their matched controls about migraine history (Chang et al., British medical journal, 1999, 318:13–18).

These data contained information on the nature and frequency of past and current headaches, accompanying aura, family history of migraine, changes in the frequency and characteristics of headache associated with the use of OCs, and whether headache with migrainous features had occurred within three days of onset of the stroke. Simple migraine was defined as a severe headache lasting more than four hours but less than three days, on one or both sides of the head, associated with feeling sick and finding loud noises and/or bright lights unpleasant (Headache Classification Committee of the International Headache Society, Cephalgia, 1988, 8 (suppl 7):1–96). Simple migraine symptoms accompanied by an initial aura consisting of visual disturbance or abnormalities of speech, skin sensation or muscle power were defined as classical migraine.

The supplementary questionnaire was completed in the European centres by 291 women who had suffered a stroke (94% of all stroke cases) and 736 matched controls: 25% of cases and 13% of controls reported a personal history of migraine. Migraine was associated with ischaemic, but not haemorrhagic, stroke (odds ratios [ORs] 3.54 [95% confidence interval 1.30–9.61] and 1.10 [0.63–1.94], respectively). Odds ratios for ischaemic stroke were similar for classical (3.81 [1.26–11.5]) and simple migraine (2.97 [0.66–13.5]). A family history of migraine, irrespective of personal history, was associated with an increased risk of both ischaemic and haemorrhagic stroke (5-fold and 2.3-fold, respectively). There was no association between OC use and haemorrhagic stroke, whether or not women reported a history of migraine. In contrast, the overall risk of ischaemic stroke associated with the use of low estrogen dose OCs was 1.88 (0.63–5.64). It was 1.19 (0.33–4.29) in women with no history of migraine, and 6.59 (0.79–54.8) in those with a history of migraine. There was a strong interaction between migraine and the presence of other risk factors for ischaemic stroke, in particular smoking and a history of hypertension. There was no evidence that a change in the frequency or type of migraine on starting OC use predicted a subsequent risk of stroke.

The observation that there was no increase in the risk of ischaemic stroke in users of low estrogen dose OCs who had no history of migraine underlines the conclusion from the data of the full study that women without cardiovascular risk factors (no history of hypertension, diabetes or hyperlipidaemia) who do not smoke and who reported that their blood pressure had been checked prior to OC use do not have an increased risk of ischaemic stroke associated with the use of low estrogen dose OCs (WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception, The lancet, 1996, 348:498–510).
Stroke and type of progestogen in combined OCs

Two further reports of secondary analyses of data from the WHO CVD Study were published during 1999. The first concerned potential differences in the risk of stroke among users of low estrogen dose OCs containing levonorgestrel or the so-called “third-generation” progestogens, desogestrel or gestodene (Poulter et al., *The lancet*, 1999, 354:301–302). This report was prepared to complement the previous analyses of risk of VTE and myocardial infarction in relation to the type of OC (WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception, *The lancet*, 1995, 346:1575–1582 and 1582–1588, and *The lancet*, 1997, 349:1202–1209).

Restricting the analysis to the 11 centres where stroke cases or their matched controls used any third-generation OCs, the risk of ischaemic stroke was higher in users of levonorgestrel-containing OCs (2.70 [1.77–4.14]) than in those using third-generation OCs (1.75 [0.59–5.16]). However, the difference in risk was lower among users who reported that their blood pressure had been checked prior to use, particularly users of levonorgestrel-containing OCs. The ORs were reduced to 1.95 (1.06–3.58) for users of levonorgestrel-containing OCs and 1.63 (0.43–6.61) for users of third-generation OCs.

The impact of blood pressure checking had been previously shown to be important when interpreting apparent differences in the risk of myocardial infarction associated with the use of different types of OCs. There was no difference in the risk of haemorrhagic stroke for users of third-generation OCs compared with levonorgestrel-containing OCs, but a surprising observation was that users of gestodene-containing OCs had higher risk than users of desogestrel- or levonorgestrel-containing OCs. The ORs were 6.84 (1.73–27.1), 0.64 (0.20–2.07) and 1.73 (1.19–2.53), for the three types of OCs, respectively. The interpretation of this observation was difficult, and a study on the UK GPRD specifically addressing the risk of haemorrhagic stroke among users of desogestrel-, gestodene- or levonorgestrel-containing OCs was commissioned and published at the same time (Jick et al., *The lancet*, 1999, 354:302–303). This analysis showed no difference in risk between the OC types, suggesting that the observation of higher risk with gestodene-containing OCs from the WHO CVD Study could have been due to chance. Neither of the two reports suggested that there was a substantially reduced risk of stroke for third-generation OCs compared with levonorgestrel-containing OCs.

Progestogens used for therapeutic indications

The other secondary analysis from the WHO CVD Study (WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception, *The lancet*, 1999, 354:1610) was prompted by the report published in 1998 on cardiovascular risks associated with the use of progestogen-only contraceptives (*Contraception*, 1998, 57:315–324). A small number of cases and controls had used progestogens for therapeutic (non-contraceptive) purposes, primarily for the management of dysfunctional bleeding. Some of the progestogens used for this purpose are the same as those in progestogen-only or combined hormonal OCs, but in considerably higher dosages, closer to the dosages used in the combined OCs. There was no increased risk of stroke or myocardial infarction associated with the use of these products (ORs 1.13 [0.18–7.13] and 0.85 [0.05–15.3], respectively), but the risk of VTE was significantly elevated (OR 5.92 [1.16–30.1]). These observations mirrored the previous results which showed that progestogen-only hormonal contraceptives were associated with a modest (2-fold) increased risk of VTE but no increased risk of stroke or myocardial infarction (*Contraception*, 1998, 57:315–324).

Since this was the first study to report on the cardiovascular risks associated with the use of progestogens for therapeutic purposes, independent confirmation was sought from the GPRD prior to publication. This study showed that women who used progestogens for contraceptive purposes were not at increased risk of VTE (OR 0.8 [0.2–4.4] as compared with unexposed women), but those exposed to progestogens for therapeutic purposes (primarily menstrual disorders) were at significantly elevated risk (OR 7.6 [1.5–38.0]) (Vasilakis et al., *The lancet*, 1999, 354:1610–1612). The clinical importance of these results is unclear, but they suggest that progestogens in dosages found in combined OCs can be associated with VTE, adding support for a difference in VTE risk between OC types. This analysis also confirmed the previous findings from the WHO CVD study of no increased VTE risk for users of progestogen-only pills, and provided further data on the previously observed higher VTE risk with combined OCs containing third-generation progestogens.

Emergency contraception and VTE

One exposure not addressed in the WHO CVD study was emergency contraception. The use of the Yuzpe regimen is rapidly becoming more widespread in Europe and the USA, yet no epidemiological data on cardiovascular safety are available. Since the Yuzpe regimen involves an estrogen dose comparable with that in the old “high estrogen dose” combined OCs, an increased risk of VTE might be expected, in parallel with the known effects of combined OCs. Moreover, as emergency contraception becomes more widely used, the coincidence of VTE and recent exposure to emergency contraception is more likely to occur, generating either spontaneous case reports or attracting media attention. In order to quantify the risk of VTE associated with emergency contraception, HRP sponsored a study using the GPRD (Vasilakis et al.,...
A total of 100,615 emergency contraception prescriptions to 73,302 women below the age of 50 years were identified in the database between 1 January 1989 and 31 October 1996. The database was searched for all cases of idiopathic VTE that occurred in the cohort of women who had ever received emergency contraception. A total of 19 cases were identified, none of which occurred within 45 days of the emergency contraception prescription (upper 95% confidence limit 3.7 per 100,000 prescriptions). Two cases were exposed to second-generation OCs, six to third-generation OCs, five cases were pregnant or postpartum, and six cases were neither pregnant nor exposed to any hormonal contraception. The incidence rates and confidence intervals for the different exposures are shown in Table I.

These results on the possible association between emergency contraception and VTE are reassuring, despite the wide confidence interval. Although covering over 100,000 prescriptions, the information on the safety of emergency contraception is limited. Computerized databases assembled for other purposes are one of the few cost-effective and practical mechanisms to collect information on such rare diseases as idiopathic VTE. As the use of emergency contraception increases, it will be possible to derive more precise estimates of risk.

### Overall cardiovascular risks and type of progestogen

The debate on whether third-generation combined OCs are truly associated with a higher VTE risk than second-generation products continued through 1999, with various claims and counter-claims by different authors. The editors of a special issue of Human reproduction update devoted to the controversy of third-generation OCs, requested a review of the most recent information on potential biases and the implications of any differences in cardiovascular risk between products. We concluded (Farley et al., Human reproduction update, 1999, 5:721–735) that the arguments claiming that differences in VTE risk resulted from bias and/or confounding either lacked empirical support or could not account for a 2-fold increased risk. Applying the most recent risk estimates to previously developed models of OC-attributable events and deaths, we estimated that OC-attributable cardiovascular mortality in women <35 years was <3 per million users annually, rising to about 10 per million users annually among smokers. In the context of external cause mortality (about 90 per million women of reproductive age annually in the United Kingdom), such risks appeared small. In women over 35 years of age, OC-attributable cardiovascular mortality was a more important concern, particularly among smokers (in the range of 20–40 deaths per million users annually). In the absence of any appreciable OC-attributable mortality in young healthy women, the additional VTE risk for third-, compared with second-generation OCs, was a factor that should be considered when women choose which OC to use.

A recent report of a randomized cross-over study of women using desogestrel- or levonorgestrel-containing OCs showed that resistance to activated protein C (APC) was increased during cycles of pill use compared with pill-free cycles, and the increase was greater in the desogestrel as compared with the levonorgestrel cycles (Rosing et al., The lancet, 1999, 354:2036–2040). This study confirmed the results of a previous cross-sectional study of users of different OC types (Rosing et al., British journal of haematology, 1997, 97:233–238). Since hereditary APC resistance, caused by a mutation in the Leiden factor V gene, is associated with an increased risk of VTE, these observations point to a mechanism whereby OC users are at increased risk of VTE. The risk is highest in users of third- compared with second-generation OCs.

### Future work

HRP is not planning any further research work on the relationship between hormonal contraception and cardiovascular disease at present. The WHO CVD Study has provided valuable new information on the risks of cardiovascular diseases associated with the use of steroid hormonal contraception, particularly in women from developing countries. A total of 13 papers describing the methodology, key results according to disease and/or

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Table I. Incidence of venous thromboembolism according to current exposure

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<th>Exposure</th>
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exposure, or assessing the overall impact of the increased risks have been published to date. Further use and analysis of this large dataset, which represents a wealth of information on the risk factors for cardiovascular disease in women of reproductive age, will be encouraged.

**POST-MARKETING SURVEILLANCE OF NORPLANT**

Post-Marketing Surveillance of Norplant was a multi-centre study involving 32 family planning clinics in eight developing countries. Three international agencies working in contraceptive research (Family Health International [FHI], Research Triangle Park, NC, USA; the Population Council, New York, NY, and HRP) participated in launching, funding, monitoring and conducting the study.

The main objective of the study was to discover possible major short- to medium-term side-effects of Norplant use that may not have been identified in clinical trials. The design was a concurrent cohort study. Rates of complications and diseases among women accepting Norplant were compared with those of control subjects choosing the intrauterine device (IUD) or sterilization. The Norplant acceptors and control subjects were followed up for five years, irrespective of change in contraceptive method. The focus was on side-effects of public health importance, defined as a doubling of a background incidence of one per 1000 woman-years. Based on these considerations, it was necessary to observe 25 000 woman-years of Norplant use for the study. It was further estimated that 8000 Norplant acceptors would have to be recruited for follow-up, taking into account discontinuation of the method during the course of the study. HRP was the principal coordinator of the project. Centres in Chile, Egypt, Indonesia, Sri Lanka and Thailand were monitored and financially supported by HRP. FHI monitored and supported clinics in Bangladesh, while the Population Council had the primary monitoring and funding responsibilities for China and Colombia.

As reported in previous *Annual technical reports*, the main phase started in January–February 1989 in Bangladesh, Chile, China, Sri Lanka and Thailand, but was delayed in Indonesia until December 1989. In Colombia, the main phase was launched in January 1990, while enrolment in Egypt commenced in October 1990. By the end of 1991, 7977 Norplant acceptors and 8044 control subjects (6625 IUD and 1419 sterilization acceptors) had been admitted to the study.

In 1997, data collection was completed in all participating countries. The overall follow-up rate of the 16 000 women was 94.6%, much higher than anticipated at the outset of the study. Some countries were more successful than others in achieving low rates of loss to follow-up; in China, for example, the overall rate of follow-up was 99.9%, whereas in Sri Lanka and Thailand the rates were 89.0% and 89.3%, respectively. A total of 78 323 woman–years of follow-up were accumulated in the study.

More than 99% of the women in the study were married, cohabiting, or parous. The mean age of Norplant, IUD and sterilization initiators was 28.5, 28.5 and 29.6 years, respectively. Three hundred and seven (1.9%) women were not followed up after the end of six months, because they had either changed the initial method or become pregnant in the interval, and 553 (3.5%) women discontinued follow-up. By the end of five years, the mean duration of first-segment use (i.e. continuous use of the device inserted at admission to the study) per initiator was 4.16 years for Norplant, 4.10 years for the IUD and 4.96 years for sterilization. The study accumulated 78 323 woman-years of observation, of which 39 337 were in initiators of Norplant, 31 915 in initiators of IUD, and 7071 initiators of sterilization. Overall Pearl pregnancy rates for Norplant, copper IUDs and female sterilization were 0.27, 0.88, and 0.17 per 100 woman-years, respectively. Users of Norplant, copper IUDs and sterilization had rates of ectopic pregnancy of 0.30, 0.68 and 0.13 per 1000 woman-years, respectively. Major health events related to the reproductive system were rare. The incidence of breast and cervical cancer was below 1 per 1000 woman-years in the three groups. Rates of acute pelvic inflammatory disease (PID) were significantly lower among Norplant users than in the IUD group (p=0.004). The rate of ovarian enlargement was significantly higher in Norplant users (p<0.001), but hospitalization for this condition was rare and did not differ significantly between contraceptive groups. Signs and symptoms of vaginitis and discharge, and gynaecological pain were significantly less frequent in Norplant users than in the other groups. Bleeding disturbances were much more frequent among Norplant users, but not anaemia. Rates of other reproductive health events were not significantly different in the three groups.

Twenty-two of the 34 deaths recorded were due to accidents, suicide or homicide. Few deaths or major health events were due to cancer or cardiovascular diseases, and these were not associated with the contraceptive method used. Among the more frequent non-reproductive major health events were gallbladder disease and hypertension. Among Norplant users, the incidence of gallbladder disease was 1.5 per 1000 woman-years, and was weakly associated with the use of Norplant, with a rate ratio of 1.52 (1.02–2.27) in Norplant users compared with controls. The incidence rate of hypertension in current users of Norplant was 0.7 per 1000 woman-years (rate ratio 1.78 [0.93–3.40]) in current Norplant users compared with controls. The incidences of headache and/or migraine, weight gain, mood disturbances, pruritus, eczema and acne among Norplant users were 11.5, 4.5, 2.8, 1.5, 1.4 and 0.9 per 1000 woman–years,
respectively, all significantly elevated compared with the incidence in controls. Respiratory problems, non-specific symptoms, and ill-defined conditions were reported significantly more often by Norplant users.

This large, longer-term controlled surveillance study of initiators of Norplant, IUD and sterilization in developing countries confirmed that Norplant is a safe and highly effective contraceptive method. The incidence of major reproductive health problems was low. Similarly, the incidence of major non-reproductive health events was low and, apart from gallbladder disease, did not differ significantly between the contraceptive groups. There was no significant excess of serious morbidity among users of Norplant. The occurrence of other less serious health events was also low, and several of them were significantly more often reported among Norplant users. Reporting and surveillance bias may, however, have been the reasons for several of the differences in less serious diseases.

Three papers describing the results from the study will be submitted for publication in 2000. The first paper summarizes the overall findings of the study and will be submitted to a high-impact, general medical journal. It reports on reproductive health events, including contraceptive efficacy and continuation rates for Norplant, copper IUDs and non-copper IUDs. The other two papers describe results of the study in considerable detail, and will be submitted together to Contraception.

**CANCER**

**Cervical cancer**

HRP collaborates with the Unit for Field and Intervention Studies at the International Agency for Research on Cancer (IARC), Lyon, France, on the possible interaction between oncogenic strains of the human papilloma virus (HPV) and combined OCs with respect to invasive cervical cancer. The community-based study, conducted in Bogotá, Colombia, involved repeat cervical cytology and assessment of samples for HPV presence and strain-specific evaluation. The study has been monitored by staff at IARC and was completed in 1999. The report from the study is awaited.

A further collaboration with IARC concerns a secondary analysis of HPV cofactors, including herpes simplex virus-2 and *Chlamydia trachomatis* in the etiology of cervical cancer, together with their potential interaction with the use of hormonal contraception and smoking. The final results from the study are awaited.

Although cervical cancer is a larger public health problem than breast cancer, it has received considerably less attention. Cancer of the uterine cervix is the leading cause of cancer among women in almost all developing countries. In 1995, it accounted for about 323 000 new cases out of the world total of an estimated 406 500 cases. Of the 210 000 projected deaths from cervical cancer, 168 000 will have occurred in developing countries (Ferlay et al., *IARC cancer base* no. 3, IARC 1998). Though organized cervical cytology programmes are effective in reducing the incidence and mortality from cervical cancer, these are not feasible in many developing countries. Even low-intensity screening with cervical cytology every 10 years or once in a lifetime for women aged 30 years or more is not feasible (World Health Organization, *Bulletin of the WHO*, 1986, 64:607–618).

Currently HRP is not funding any further research into cervical cancer and its relationship, if any, with the use of different contraceptive methods. A small consultation is planned to consider whether there are any issues in this area where HRP can contribute with the limited funds available.

**Prostate cancer and vasectomy**


A meeting convened by the National Institutes of Health (NIH) in Bethesda, MD, USA, in 1993 concluded that no known biological mechanism existed to explain any possible association between vasectomy and prostate cancer, and that any causal relationship between the two was unlikely (Healy, *Journal of the American Medical Association*, 1993, 269:1303–1307).
1993, 269:2620). The panel recommended that providers should continue to offer vasectomy and perform the procedure; that vasectomy reversal is not warranted to prevent prostate cancer; and that screening for prostate cancer should not be any different for men who have had a vasectomy than for those who have not. Since the NIH meeting, several new studies have been published in developed countries, indicating no relationship between vasectomy and prostate cancer (Hiatt et al., Cancer causes and control, 1994, 5:66–72; Rosenberg et al., American journal of epidemiology, 1994, 140:431–438; Möller et al., British medical journal, 1994, 309:295–299; John et al., Journal of the National Cancer Institute, 1995, 87:662–669; Zhu et al., American journal of epidemiology, 1996, 144:717–722). Two studies from developing countries indicated a weak elevated relationship similar to that seen in the early US studies (Hsing, Wang and Gu, Cancer epidemiology, biomarkers and prevention, 1994, 3:285–288; Platz et al., International journal of epidemiology, 1997, 26:933–938).

Since the risk factors for prostate cancer are poorly understood and the incidence rates and screening practices vary widely between countries, it may not be justified to extrapolate the results on vasectomy and prostate cancer from the USA to countries with low incidence rates of prostate cancer and different health care practices. Because information was needed on the relationship between vasectomy and prostate cancer in those developing countries where vasectomy was prevalent, HRP, in collaboration with FHI, undertook a multicentre, hospital-based case–control study in China, Korea and Nepal. The data collection was completed in February 1997, and histopathological review of tissue samples (slides) by reference pathologists was completed in May 1998. The study involved 353 cases of prostate cancer, of which 294 had histopathologically confirmed cancer, as determined by the study reference pathologist. A total of 879 controls were matched to these cases. The final manuscript is undergoing review prior to submission for publication.

Also in collaboration with FHI, HRP is jointly funding a national multicentre case–control study of prostate cancer and vasectomy, coordinated by the Department of Preventive and Social Medicine, University of Otago, Dunedin, New Zealand. The main phase of this study was launched in 1997 and data collection completed by the end of 1999. The final report is awaited.

**SAFETY OF HORMONAL CONTRACEPTION**

**Oral contraception and gestational diabetes**

The use of OCs is associated with some alterations in carbohydrate metabolism. Increases in blood glucose as well as in the circulating levels of insulin and glucagon have been reported in women using OCs (Runnebaum et al., American journal of obstetrics and gynecology, 1987, 157:1059–1063; Spellacy et al., Fertility and sterility, 1989, 51:71–74; Peterson et al., Obstetrics and gynecology, 1991, 78:666–672). Scant information is available on the effects of combined OC use on carbohydrate metabolism in women with a history of gestational glucose intolerance. HRP is supporting a study in eight hospitals in Caracas, Venezuela, to evaluate if there are any differential effects on carbohydrate metabolism of the use of a standard preparation OC (ethinyl estradiol 30 µg, levonorgestrel 150 µg) and use of a non-hormonal contraceptive method in women with a history of gestational diabetes mellitus in their most recent pregnancy. Women in the study are being monitored to evaluate possible clinical effects and alterations in carbohydrate and lipid metabolism during a period of one year of method use.

The enrolment of women into the study was much slower than anticipated. A total of 121 women (54 OC users and 67 controls) have been enrolled, and preliminary results on the first 45 to complete the study showed no differences between the two groups with respect to glucose and lipid metabolism. Final results are expected in 2000.

**Bone mineral density and contraception**

Osteoporosis is a disease characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and consequent increase in fracture risk (WHO Technical report series, 1994, No. 843). Osteoporosis and associated fractures are a major cause of mortality, morbidity and medical expense worldwide. For example, osteoporosis affects an estimated 75 million people in Europe, Japan and the USA, including one in three postmenopausal women and most elderly people. The prevalence of both osteoporosis and associated fractures varies by country and by population group within countries. Osteoporosis is rare in African countries, frequent in India and most common in Europe and North America.

The probability of developing osteoporosis in later life is dependent on both the peak bone mass achieved at maturity and the rate of bone loss over the subsequent years. Previous cross-sectional studies had suggested that peak bone mass in women is achieved at about 30 years of age; more recent cross-sectional and longitudinal data indicate that bone accretion is essentially complete by the late teenage years (Theintz et al., Journal of clinical endocrinology and metabolism, 1992, 75:1060–1065; Rizzolli and Bonjour, The lancet, 1997, 349:s120–s123). Although bone mass in women is less than in men at all ages and at all body sites (after correction is made for body size), the peak bone density achieved by women at maturity is equivalent to that in men. In the subsequent years, bone density is lost at a rate of about 0.5%–1% per
year at most sites in both sexes. In women, the rate of bone loss increases in the 5–10 years after the menopause, resulting in an average total loss of approximately 15% in the first few postmenopausal years. Thereafter, the rate of loss decreases to a much slower pace (WHO Technical report series, 1996, No. 866).

To further evaluate the effect of the use of hormonal contraceptives on bone mass, a cross-sectional study was undertaken in 2474 women aged 30–34 years from Bangladesh, Brazil, China, Egypt, Mexico, Thailand and Zimbabwe (Pettiti et al., Obstetrics and gynecology, 2000, 95:736-744). Among current users of combined oral contraceptives, bone mineral density (BMD) was significantly higher for short-term users (two–three years) as compared with never-users. Among short-term users of the progestogen-only methods, DMPA and Norplant, BMD was significantly lower compared with never-users. Among long-term users (four or more years) of all three hormonal methods, there were no significant differences as compared with never-users. Equally, past users showed no significant differences compared with never-users. The magnitude of the changes in BMD were small and within 1 standard deviation of the mean of never-users of steroid contraceptives. The study suggests that the use of hormonal contraceptives by young adult women is associated with small changes in BMD that occur early after initiation of use and are reversible.

In view of these findings and other data indicating that progestogen-only contraceptives have a small but unfavourable effect on bone mass (Scholes et al., Obstetrics and gynecology 1999, 93:233–238), HRP has initiated a study in Durban, South Africa, with investigators from the Reproductive Health Research Unit, Baragwanath Hospital, Johannesburg. It is a five-year longitudinal study in young (16–20 years) and older women (45–49 years) of the impact of depot medroxyprogesterone acetate (DMPA), norethisterone enantate (NET-EN) and combined OCs on BMD, with a comparison group of women not using any hormonal contraception. The young age group was chosen because recent data indicate that peak bone mass may be reached around the age of 20 years (Theintz et al., Journal of clinical endocrinology and metabolism, 1992, 75:1060–1065; Rizzolli and Bonjour, The lancet, 1997, 349:s120–s123) and peak bone mass is regarded as a determinant of osteoporosis in later life (WHO Technical report series, 1996, No. 866).

If hormonal contraceptives adversely affect peak bone mass, they may also influence the risk of osteoporosis at a more advanced age. For older women, a high level of bone mass at the age of menopause would reduce the risk of postmenopausal osteoporosis at all ages after menopause (WHO Technical report series, 1996, No. 866). Therefore, it is an advantage for women approaching the menopause to use contraceptive methods that maintain bone mass or do not accelerate the physiological reduction of bone mass which occurs in the decade or so before menopause. At present, there is no information on the effect of hormonal contraceptive use on bone mass in women nearing the menopause.

Since the effects of hormonal contraption on bone mass may differ between population groups or according to dietary factors, it is planned to expand this research to other countries in 2000.

**Hepatitis B and steroid hormone contraception**

In some countries, family planning programmes recommend the assessment of liver function before prescribing combined OCs or caution against the use of them among women with a history of jaundice, since some studies have shown that OCs affect liver function. These recommendations are based on findings involving mainly a higher dose of combined OCs (Dickerson et al., Contraception, 1980, 22:597–603; Shaaban et al., Contraception, 1982, 26:65–74). A recent analysis of two large cohort studies in the United Kingdom, with up to 27 years of follow-up, reported that there was no evidence of an increased risk of serious liver disease overall among current or former pill users. In one of these cohort studies, there was a modest increased risk of mild liver disease associated with the use of OCs containing ≥50 µg estrogen. This risk declined after four years of use and after cessation of use (Hannaford et al., Contraception, 1997, 55:145–151). In developing countries where hepatitis B infection is prevalent, the recommendations to test liver function result in high costs to clients and programmes, and may unnecessarily disqualify some women from using OCs. The rationale for this recommendation is being investigated further by HRP.

Studies were undertaken in Bangkok (Thailand) and Tianjin (China) on liver function during the use of combined OCs or IUDs by women with chronic asymptomatic hepatitis B virus (HBV) infection. Liver function in such women is potentially impaired, and they are most likely to be at risk should hormonal contraceptives adversely affect liver function. The study involved women who were HBV surface antigen (HBsAg) positive and chose to use low-dose combined OCs or IUDs. The women were followed for six months with regular blood sampling and clinical assessment. The Thai study included 53 users of OCs (30 µg ethinyl estradiol, 150 µg levonorgestrel) and 59 IUD users who were all asymptomatic and HBsAg positive and had normal liver function tests. Liver function tests were taken at three and six months. One user of OCs had slightly increased bilirubin at three months. However, at six months, the liver function tests were similar and showed no increase in either of the two groups. The authors concluded that low-dose combined OCs do not affect liver function in hepatitis B carriers who have normal liver function or show...

A further study of OC users and users of non-hormonal methods is being conducted in Yaoundé, Cameroon, an area with a high prevalence of hepatitis B infection. From a total of 225 hormonal contraceptive users and 172 users of non-hormonal methods, 38 (17%) and 29 (17%) women, respectively, were HBsAg positive. None had any clinical signs of acute liver infection, but they were not required to have normal liver function tests as in the Thai study. All volunteers are being followed after six and twelve months. Preliminary results show that those using the hormonal methods had on average a decrease in albumin levels and a small increase in liver enzymes during the period of follow-up, with very little change in the non-hormonal group. However, the proportion of women with at least one abnormal liver function test after six months was similar in the hormonal and non-hormonal groups (59% and 53%, respectively). These results suggest that in HBsAg carriers with no clinical signs of disease there is no increased risk of liver disease in users of hormonal methods, and thus the practice of requiring normal liver function tests is unnecessary. The final results from the 12-month follow-up are expected in 2000.

Systemic lupus erythematosus and steroid hormone contraception

Over the years, HRP has evaluated the potential interaction between fertility regulating methods and several prevalent diseases, particularly in developing countries. Systemic lupus erythematosus (SLE) is a chronic disease aggravated by pregnancy, and women with SLE require effective contraception. Women with SLE have been cautioned against the use of hormonal contraceptives as it is believed that these drugs carry increased risk of lupus flares, and women with SLE are already at high risk of VTE.

The caution against the use of hormonal contraceptives among women with SLE is based on scant information, most of it from case reports and case series. The few controlled studies which have been conducted included small numbers of SLE cases and relate to higher-dose OCs (Garowich et al., American journal of obstetrics and gynecology, 1971, 110:366–369; Gill, Journal of chronic diseases, 1968, 21:435–444; Dubois et al., The lancet, 1968, ii:679; Tarzy et al. The lancet, 1972, ii:501–503). There may, nevertheless, be a relationship between female sex steroids and SLE: SLE is eight times more prevalent in women than men; lupus flares are associated with puberty, menses, pregnancy and the postpartum period; and estrogen therapy in postmenopausal women is associated with increased risk of SLE (Silman and Hochberg, Epidemiology of the rheumatic diseases, Oxford University Press, Oxford, 1993; Sanchez-Guerrero et al., Annals of internal medicine, 1995, 122:430–433; Rose and Pillsbury, Annals of internal medicine, 1944, 21:1022–1034; Mund et al., Journal of the American Medical Association, 1963, 183:917–920; Jungers et al., Arthritis and rheumatology, 1982, 25:618–623; Barret et al., British journal of rheumatology, 1986, 25:300–301). HRP is supporting a randomized trial of combined OCs (30 µg ethinyl estradiol, 150 µg levonorgestrel), prostegsten-only pills (30 µg levonorgestrel) and IUDs (TCu380A) with one-year follow-up. The study is being conducted by gynaecologists/endocrinologists and immunologists/rheumatologists at the National Institute of Nutrition, Salvador Zubiran, Mexico City, Mexico, a tertiary care centre with a large number of registered SLE patients. Those women invited to participate in the study who declined to be randomized to one of the three study groups will be followed up to provide further information on the natural history of SLE against which the incidence of adverse events in the study can be compared. The study is to be completed in 2000.

Planned studies

In 2000–2001, HRP will expand its research into the relationship between hormonal contraceptives and BMD in young women. The first study, to be conducted in different regions of the world, will examine the relationship between past use of progestogen-only methods and current BMD status in women aged 55-64 years. This age range was selected in order to measure BMD as close as possible to the age when the incidence of fractures becomes appreciable, but also to ensure that women would have had the opportunity to use progestogen-only methods. A second study will assess BMD in women who are currently participating in the randomized trial of levonorgestrel-releasing IUD compared with the TCu380A IUD. The women included in the study will be those who have now reached their fourth or fifth year of use.

IMPACT OF FAMILY PLANNING SERVICES ON SAFETY AND EFFECTIVENESS

Research undertaken by HRP and others has documented the generic safety of currently available contraceptives (WHO Technical eport series, 1992, No. 817; WHO Technical report series, 1998, No. 877). This research has also uncovered an interaction between specific contraceptives and medical conditions, certain individual characteristics of women and lifestyle factors which, in combination, substantially increase the risk of severe adverse effects of contraceptive methods. It is important to evaluate thoroughly the impact of quality of family planning services on the safety of fertility regulating methods, and to consider whether enhancing the quality of family planning services will make contraceptive use safer.

The review on “The impact of family planning services of the safety and efficacy of contraceptive use” by K
Paine, M Thorogood and K Wellings, London School of Hygiene and Tropical Medicine, London, United Kingdom, commissioned by HRP, was discussed at the Strategic Review Committee on Surveillance and Evaluation in August 1999, together with the report of a workshop held in September 1998. Although research into the impact of quality of services on contraceptive safety was needed, the Review Committee felt that many of the issues were being addressed by other groups, such as the FRONTIERS project and HRP’s Social Science Research Group. In view of the funding and staffing constraints on the Surveillance and Evaluation Research Group, it was considered not appropriate to launch a major new initiative at this stage, but rather to provide technical support, where required, to these other groups. Progress in this area will be reviewed at future meetings, and consideration will be given to a more active involvement in the future.

**INTRAUTERINE DEVICES**

Intrauterine devices are used by more than 120 million women worldwide as their preferred method of family planning. They have the advantages of being long-acting and also of being relatively easy to remove with a rapid return of fertility. An important aspect of the acceptability and more widespread use of the currently available IUDs for interval insertion is the demonstration of their long-term safety and efficacy, especially in developing countries.

The objective of this line of research is the long-term evaluation of the safety and efficacy of the copper IUDs that are most commonly used in national family planning programmes in developing countries and of the newly marketed IUDs that are being introduced.

Between 1978 and 1982, HRP initiated three large-scale, randomized multicentre studies on three IUDs that, at that time, were being introduced into family planning programmes. The objectives were to evaluate their safety and efficacy in large studies, primarily in developing countries, and to establish their efficacy beyond the two years that was the life span of the devices then approved by regulatory authorities.

**Long-term safety and efficacy of the Multiload 375 and TCu380A devices**

The randomized, multicentre comparative trial of the TCu380A and Multiload 375 started in 1989 with participation from 19 centres in eight countries (10 in China). A total of 3684 subjects were recruited. The summary results from the interim analysis of the nine-year data are given in Table II.

The Multiload 375 had a significantly higher intrauterine pregnancy and expulsion rate than the TCu380A at nine years of use. This difference in pregnancy rates is seen from the second year of use, but the difference in expulsion rates becomes statistically significant only from the fourth year of use until the eighth. This study will continue until ten years of use have been achieved at the end of 2001, provided that adequate numbers of subjects remain in the trial.

**Frameless IUD (FlexiGard)**

Two of the major reasons for discontinuation of use of an IUD are the side-effects of pain and bleeding and expulsion of the device. These are thought to be related to the size of the frame or shape of the IUD relative to the dimensions of the uterine cavity. Thus it would be expected that if a “frameless” IUD could be inserted, these reasons for discontinuation would be minimized. Results from preliminary clinical trials with such devices have been encouraging (Batar, *Contraception*, 1992, 46:307–312; Wildemeersch, *British journal of family planning*, 1994, 20:2–5; Rosenberg, *Contraception*, 1996, 53:197–203; Van

| Table II. Cumulative net probabilities of discontinuations and standard error per 100 women at nine years of use |
|-----------------------------------------------------|-----------------|-----------------|
| TCu380A                                             | Multiload 375   |
| Total pregnancy                                     | 3.2 (0.5)       | 5.0 (0.7)*      |
| — Ectopic                                          | 0.8 (0.3)       | 0.1 (0.1)*      |
| — Intrauterine                                     | 2.5 (0.4)       | 5.0 (0.7)***    |
| Expulsions                                          | 11.7 (1.4)      | 14.5 (1.4)      |
| Total medical removals                              | 30.2 (1.8)      | 29.3 (1.9)      |
| Pelvic inflammatory disease                         | 0.2 (0.1)       | 0.5 (0.2)       |
| Loss to follow-up                                   | 9.8 (0.9)       | 8.2 (0.8)       |
| Continuation rate                                   | 40.9 (1.5)      | 39.3 (1.6)      |
| Woman-years                                        | 9253.0          | 9128.8          |
| Number of women completing interval                 | 343             | 317             |

*p<0.05   **p<0.01   ***p<0.001
The frameless IUD—the FlexiGard—consists of six copper sleeves with a surface area of 330 mm² crimped onto nylon suture material. The device is inserted to a maximal depth of one centimetre in the fundal myometrium by means of a needle inserter rod and retained in the myometrium by means of a knot in the suture material.

In the ongoing study in which the FlexiGard device is being compared to the TCu380A, 2104 women have been recruited to the FlexiGard device and 2184 to the TCu380A. The final data obtained after eight years of use are provided in Table III.

Compared with the TCu380A, the pregnancy rate for the FlexiGard was significantly higher at one year of use but not thereafter. The cumulative expulsion rate for the FlexiGard was significantly higher at all intervals when compared with the TCu380A, but the second- to eighth-year annual rates were similar. Removals for bleeding disturbances were significantly higher with the FlexiGard device from the sixth year of use.

The TCu380A annual pregnancy rate remains between 0.1 and 0.6 per 100 women, whereas the FlexiGard rate is highest in the first year (1.2 per 100 women), principally due to pregnancy occurring after an unnoticed expulsion. Thereafter, in the second and subsequent years of use, the rates are comparable to those of the TCu380A. The cumulative rate for ectopic pregnancy at eight years was higher for the TCu380A, and the removal rate for complaints of bleeding was significantly higher for the FlexiGard device. The provisional conclusion from this study is that the version of the FlexiGard tested by HRP, whilst a novel approach to the problems of expulsion and removals for pain and/or bleeding, does not fulfil the expectations of lower expulsion and removal rates because of the less-than-optimal inserter and insertion technique. The TCu380A subjects continue to be followed in order to increase the database on the long-term safety and efficacy of this IUD.

**Levonorgestrel-releasing IUD**

Previous studies have shown that the intrauterine administration of progestational steroids is effective in preventing pregnancy and reducing menstrual blood loss (Gallegos et al., *Contraception*, 1978, 17:153–161). The drawback to intrauterine progesterone administration is that the effective life span of 12–18 months for the device is too short for most family planning programmes. HRP developed and tested a 2 µg/day levonorgestrel-releasing device, but this was abandoned because of an unacceptably high level of ectopic pregnancies. In parallel with this research, the Population Council sponsored the development and clinical testing of an IUD that releases 20 µg/day levonorgestrel. This device has been reported, in a randomized study, as having a pregnancy rate at five years of 1.1 per 100 woman-years but a removal rate for amenorrhoea of nearly 20% (Sivin, *Contraception*, 1990, 42:361–378). To date, there have been more than 70 publications on this device but few on the long term safety and efficacy of the device in developing countries, where the side-effect of amenorrhoea may not be as acceptable as it is in some developed countries.

HRP initiated a study to compare the 20 µg/day levonorgestrel-releasing IUD with the TCu380A device in four centres in late 1993, in another 14 centres in 1994/1995, and a further two centres in 1997. The interim results obtained in this study are summarized in Table IV.

A total of 1914 subjects have been admitted to the TCu380A group and 1922 to the levonorgestrel-releasing IUD group. The principal differences between the two

**Table III. Cumulative net discontinuation rates (standard error) per 100 women at eight years of use**

<table>
<thead>
<tr>
<th></th>
<th>TCu380A</th>
<th>FlexiGard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total pregnancy</td>
<td>2.9 (0.4)</td>
<td>2.5 (0.4)</td>
</tr>
<tr>
<td>Expulsions</td>
<td>7.7 (0.8)</td>
<td>9.6 (0.8)</td>
</tr>
<tr>
<td>Total medical removals</td>
<td>21.6 (1.3)</td>
<td>24.3 (1.8)</td>
</tr>
<tr>
<td>—Bleeding</td>
<td>12.0 (1.0)</td>
<td>16.4 (1.6)*</td>
</tr>
<tr>
<td>—Pain and/or bleeding</td>
<td>18.7 (1.2)</td>
<td>20.9 (1.7)</td>
</tr>
<tr>
<td>PID</td>
<td>0.6 (0.2)</td>
<td>0.4 (0.2)</td>
</tr>
<tr>
<td>Total incidental medical and personal reasons</td>
<td>18.6 (1.2)</td>
<td>17.0 (1.2)</td>
</tr>
<tr>
<td>Loss to follow-up</td>
<td>14.2 (1.0)</td>
<td>13.2 (1.0)</td>
</tr>
<tr>
<td>Number of women completing interval</td>
<td>331</td>
<td>97</td>
</tr>
<tr>
<td>Woman-years experience</td>
<td>10791.3</td>
<td>9702.0</td>
</tr>
</tbody>
</table>

*p<0.05*
devices were removals for amenorrhoea, reduced bleeding and hormone-related reasons being higher in the levonorgestrel IUD group. The expulsion and removal rates for increased bleeding were higher in the TCu380A group but not significantly so.

Greater differences between the devices were seen when the Chinese centres were compared with the non-Chinese centres. The total pregnancy rate for the TCu380A was significantly higher in the Chinese centres, but the removal rates for menstrual-related reasons were higher in the non-Chinese centres. Conversely, these rates in the Chinese centres were significantly higher with the levonorgestrel IUD. It would appear that Chinese subjects do not tolerate menstrual disturbances, especially amenorrhoea, as well as non-Chinese subjects.

Comparison of the two devices within the Chinese centres showed significantly higher pregnancy rates (2.10 vs 0.0) and removal rates for increased menstrual bleeding (5.70 vs 0.0) and for pain alone (2.10 vs 0.0) for the TCu380A. On the other hand, the discontinuation rates for the levonorgestrel IUD were significantly higher for expulsion (4.6 vs 0.0), total menstrual-related reasons (43.71 vs 8.2), amenorrhoea (12.82 vs 2.41) and hormone-related reasons (5.4 vs 0.0).

Similar but less marked differences between the two devices were seen in the non-Chinese centres. The removal rate for amenorrhoea in the Chinese centres was more than twice that seen in the non-Chinese centres, whereas the removal rate for increased bleeding and pain alone for the TCu380A in the non-Chinese centres was 2–3 times that seen in the Chinese centres.

Significant differences between the Chinese and non-Chinese centres have been observed and published in other WHO multicentre randomized IUD trials. No immediate explanation has been forthcoming for these differences.

**Planned studies**

No new research on IUDs is envisaged during the 2000–2001 biennium.

**CONDOMS**

**Effectiveness of a combined regimen of condom and emergency contraception**

HRP supported a study in Shanghai and Tianjin, China, to determine the contraceptive use- and method-effectiveness of the condom and of the condom plus emergency contraception. This cluster (clinic) randomized trial compared a combined regimen (condom with back-up of emergency contraception using levonorgestrel 750 µg x 2) vs the condom only. In Tianjin a total of 1526 women from 20 clinics were enrolled, and over 98% of them were still using the method after 12 months. Preliminary results show that the overall pregnancy rate after 12 months in the condom-only clinics was 1.7%, and in the clinics where the combined regimen was used the rate was 0.5%. In Shanghai, a total of 1562 women from nine urban clusters were enrolled. After one year, the overall method continuation rate was 93%. The pregnancy rate in the women using the combined regimen was 0.2 per 100 woman-years, and in the condom-only group it was 0.1 per 100 woman-years. Such high method continuation and low contraceptive failure rates probably reflect the high motivation of the volunteers and the monthly follow-up visits by study staff to reinforce compliance. A final report from the study is expected in 2000.

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**Table IV. Cumulative net discontinuation rates (standard error) per 100 women at five years of use (all subjects)**

<table>
<thead>
<tr>
<th></th>
<th>TCu380A</th>
<th>Levonorgestrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total pregnancy</td>
<td>1.64 (0.35)</td>
<td>0.62 (0.25)*</td>
</tr>
<tr>
<td>Expulsions</td>
<td>6.95 (0.75)</td>
<td>5.82 (0.68)**</td>
</tr>
<tr>
<td>Total menstrual related reasons</td>
<td>10.36 (1.37)</td>
<td>38.79 (2.17)***</td>
</tr>
<tr>
<td>—amenorrhoea</td>
<td>0.07 (0.07)</td>
<td>27.11 (2.1)***</td>
</tr>
<tr>
<td>—reduced bleeding</td>
<td>2.99 (0.74)</td>
<td>11.32 (1.5)***</td>
</tr>
<tr>
<td>—increased bleeding</td>
<td>7.53 (1.23)</td>
<td>5.3 (1.15)**</td>
</tr>
<tr>
<td>Hormone-related reasons</td>
<td>0.13 (0.09)</td>
<td>4.7 (0.8)***</td>
</tr>
<tr>
<td>PID</td>
<td>0.0 (0.0)</td>
<td>0.3 (0.13)**</td>
</tr>
<tr>
<td>Continuation rate</td>
<td>66.12 (1.70)</td>
<td>41.76 (2.21)***</td>
</tr>
<tr>
<td>Woman-years</td>
<td>5210.2</td>
<td>4641.3</td>
</tr>
</tbody>
</table>

*** p < 0.001  * p < 0.05  ns = not significant
Planned studies during 2000–2001

The female condom is a method that provides protection against unwanted pregnancy and STDs. However, only limited information is available about its effectiveness in pregnancy prevention when used as the main method by family planning clients. HRP will conduct a multicentre study on the comparative effectiveness of male and female condoms among women attending family planning clinics in China, Nigeria, South Africa and a fourth country yet to be identified. Women who choose male or female condoms as their main method of family planning will be invited to participate in the research study and followed up at 1, 3, 6, 9 and 12 months. They will be free to discontinue from the trial and/or change from male to female condoms, or vice versa, during the study. The incidence of pregnancy and STIs during the follow-up period will be compared according to the method used. It is envisaged that a total of 1000 women (500 choosing female and 500 choosing male condoms) will be required to establish the comparative effectiveness of the female condom. HRP has supported limited research into the potential for the female condom to be washed and reused. The Research Group on Epidemiological Research will collaborate in a consultation to assess the available information on the safety and risks of washing and reusing the female condom. An anticipated outcome of that consultation is to identify whether further research into reuse is warranted. HRP will consider initiating research to address those unanswered questions that fall within its mandate.

ABORTION

Induced abortion and subsequent pregnancy outcome

In China, about 10 million legally induced abortions are performed annually, but there are no national data on possible obstetric sequelae of induced abortion. HRP is supporting a study in Shanghai which involves a cohort of women enrolled in the study before the eighth week of pregnancy with and without a history of induced abortion, and follow-up until the end of the pregnancy to examine the course of pregnancy and its outcome in terms of maternal morbidity, spontaneous abortion, preterm delivery, low-birth-weight and perinatal morbidity and mortality.

The study started in 1993 and was initially confined to eight hospitals. However, the requirement that women be recruited to the study before the end of the eighth week of pregnancy made enrolment much slower than originally anticipated, and the study was extended to involve 15 hospitals. A total of 2953 nulliparous women were recruited to the study and interviewed five times up to 42 days postpartum. Of the 1363 singleton vaginal deliveries, 703 women had never been previously pregnant (primigravida) while 660 had a history of one or more previous induced abortions. A prolonged third stage of labour (>30 minutes) was seen in 3.4% of women with a history of one or more induced abortions as compared with 1.0% in primigravid women. The risk of a prolonged third stage was higher in women who had a history of late (>50 days) first trimester abortion as compared with those with an early first trimester abortion. There was no increased risk of postpartum haemorrhage or retained placenta in those with a history of abortion (Zhou et al., Journal of obstetrics and gynaecology, 1999, 19:349-354). Further analyses of these data are expected.

Mifepristone-induced abortion

In China, early pregnancy termination by means of mifepristone and prostaglandins has become prevalent, and early pregnancy termination is increasing among young, nulliparous women. There is currently no scientific information on the effect of mifepristone-induced abortion on subsequent reproductive outcome. HRP is sponsoring a study in centres in Beijing, Chengdu and Shanghai in which women are identified during their first antenatal care visit before the 16th week of pregnancy and followed up until one month after delivery. Pregnancy outcomes in a group of 4500 women with a history of one-time mifepristone-induced abortion will be compared to outcomes in similar-size groups of women with a history of one-time surgically-induced first-trimester abortion, and with no history of abortion. The study will be completed during 2000.

CONTRACEPTION AND HIV

Steroid hormonal contraception and clinical course of HIV infection

The majority of HIV-infected women worldwide are of reproductive age. Although they have reduced fertility as compared with uninfected women, their need for reliable contraception continues. Many highly effective contraceptive methods (OCs, DMPA and Norplant) exert their effect through steroid hormones and hence may have an effect on the progression of HIV disease, either directly through an interaction with the virus itself (Soudeyns et al., Virology, 1993, 194:758–768; Rafali, Proceedings of the National Academy of Sciences USA, 1995, 92:3621–3625), or indirectly through effects on the immune system (Grossman, Science, 1985, 227:257–261). There is no firm empirical information on the effect of contraceptive steroids on the progression of HIV infection.

A prospective observational cohort study will determine the effect of steroid hormone contraceptives on the
progression of HIV infection by comparing the course of HIV infection among women taking steroid hormone contraceptives (OCs, Norplant, DMPA) with that among HIV-infected women not using hormonal contraception (sterilization, barrier methods or no contraception). HIV-infected women with and without AIDS-defining conditions will be recruited from centres in Brazil, Kenya, Thailand and Zimbabwe.

A total of 220 women will be enrolled in each of the hormonal contraceptive groups (Norplant, DMPA, OCs) and compared with a total of 340 women using non-hormonal methods. Baseline information will be collected through interview, physical examination and blood sample collection for CD4 count, HIV quantification and subtyping. The women will be followed up every six months for four years and the CD4 counts and HIV quantification will be repeated at each follow-up visit. Outcome measures include death, AIDS (CDC case definition, 1993 revision), clinical markers of severity of HIV infection using the WHO clinical staging system, and surrogate markers such as CD4 counts and viral load. The pilot study was successfully completed in the four countries and the main phase of the study will start in early 2000. Results from this study will have direct and important implications for the care and family planning practices of HIV-positive women.

Steroid hormonal contraception and cervical/vaginal shedding of HIV

HRP has initiated a study on the effect of steroid hormone contraceptives on the shedding of HIV in the cervical–vaginal secretions of HIV-infected women without AIDS-defining conditions. Few studies of genital tract shedding of HIV among women have been conducted, and factors associated with the variability observed have been incompletely described. Cross-sectional studies (Clemetson et al., Journal of the American Medical Association, 1993, 269:2860–2864; Mostad et al., The lancet, 1997, 350:922–927) have reported large increases in genital tract shedding of cell-bound HIV (viral DNA) in women using oral and other hormonal contraceptives. Although the magnitude of these associations may be partly due to incomplete correction for bias and to the statistical methods used, these findings have potentially important implications for heterosexual HIV transmission.

A total of 115 women will be enrolled into each of four groups: current users of Norplant, DMPA, OCs, and non-hormonal methods. Endpoints include prevalence of HIV shedding and quantification of the amount of virus shed, using molecular biology techniques to measure viral RNA. Although HIV has been found in genital tract secretions during each phase of the menstrual cycle, the probability of isolating the virus appears highest during the first 10 days of the cycle. Therefore, cervicovaginal specimens will be collected in the follicular and luteal phases of regularly cycling women using non-hormonal contraception. Blood samples will be collected for assessment of CD4 count, plasma viraemia and measurement of hormone levels. The pilot study was completed in 1999, and the main phase of the study will start in early 2000 in Brazil, Thailand and Zimbabwe.

The vaginal epithelium and steroid hormone contraception

Recent data show that progesterone administration in monkeys leads to thinning of the vaginal epithelium and increased susceptibility to infection with simian immunodeficiency virus (SIV) (Marx et al., Nature medicine, 1996, 2:1084–1089). Almost no information is available on the effects of steroid hormone contraceptives on the vaginal epithelium in women. They may potentially affect women’s susceptibility to HIV and other sexually transmitted agents, such as HPV.

HRP sponsored a study at the Department of Obstetrics and Gynaecology and the Department of Immunology, University Hospital, Umeå, Sweden of women using combined OCs, DMPA and Norplant with a comparison group not using any hormonal contraception. The analysis of vaginal biopsy specimens included comparison of thickness, number of cell layers, amount of progesterone and estrogen receptors, and immunological markers in the vaginal epithelium. Collection and examination of vaginal biopsies has been completed and results from the study are expected in early 2000.
Annex 1a

STRATEGIC COMMITTEE FOR SURVEILLANCE AND EVALUATION IN 1999

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J. Olsen, Aarhus University, Aarhus, Denmark
D. Skegg, University of Otago, Dunedin, New Zealand (Chairman)
F.E. Skjeldstad, University of Trondheim, Trondheim, Norway

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Collaborating agency scientists

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Annex 1b

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Annex 2a

SURVEILLANCE AND EVALUATION

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Unnop Jaisamrarn, Chulalongkorn University, Bangkok, Thailand

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Annex 2a (continued)

SURVEILLANCE AND EVALUATION

SCIENTISTS IN 1999 (continued)

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Annex 2b

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Zhuang Liu-qi, International Peace Maternity and Child Health Hospital, Shanghai, China

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199
Annex 2b

RESEARCH GROUP ON IUDs

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Annex 2b (continued)

RESEARCH GROUP ON IUDs

SCIENTISTS IN 1999

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Annex 3b

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Annex 3a

SURVEILLANCE AND EVALUATION

Publications in 1999


Annex 3a (continued)

SURVEILLANCE AND EVALUATION

Publications in 1999 (continued)


RESEARCH GROUP ON IUDs

Publication in 1999

Fertility regulation

Norms and guidelines for use of methods of fertility regulation

Q.M. Islam, M.K. Usher-Patel, H.Peterson
INTRODUCTION

The work carried out during 1999 on the development of norms and guidelines relevant to fertility regulation has focused on: (i) increasing information about contraceptive options; (ii) developing and updating technical guidelines and training materials on family planning methods; (iii) developing and updating technical guidelines and training materials on family planning services; and (iv) developing a collaborative process to support effective dissemination, adaptation and utilization of the documents generated by the Department. The last of these activities is being carried out as an interagency exercise and focuses on structuring the distribution of technical documents so as to assist countries in using these documents to improve access to, and quality of, family planning and reproductive health services. As such, this activity also provides an important linkage between the Department’s strategic operational objectives of developing norms and tools and of providing technical support to countries.

INCREASING INFORMATION ABOUT CONTRACEPTIVE OPTIONS

Emergency contraception

In 1997, guidelines were prepared for service providers, policy-makers and programme managers as part of an effort to increase awareness and disseminate accurate information about the emergency use of combined oral contraceptives and copper-releasing IUDs. For service providers, these guidelines give complete technical information on the two methods and how they work, their safety and efficacy, medical eligibility, counselling and screening of clients and side-effects and their management. For decision-makers and programme managers, the document contains a discussion of the role of emergency contraception in family planning/reproductive health programmes, clarification of the mode of action of emergency contraceptives in order to dispel misunderstanding about the methods being abortifacients, and strategies for introducing emergency contraception in various programmes and services, as well as economic concerns.

The English version of the guidelines was finalized and printed towards the end of 1998 and work was under way in 1999 on the French and Spanish translations.

Information package: update on family planning methods

The Department is working with Family Health International (FHI), Research Triangle Park, NC, USA, to develop a series of fact sheets on family planning methods and their use by different age groups across the life span. The draft documents are currently undergoing review for technical accuracy and will be further revised and discussed at a meeting of experts before being finalized for printing.

During 1999, the Department collaborated with the Johns Hopkins University, Baltimore, MD, USA, in publishing the Population Report Family planning methods: new guidance (Series J, Number 44, 1999).

Technical guidance on contraception and HIV

As part of the ongoing debate on whether steroid hormone contraceptives affect the risk of HIV transmission or the progression of AIDS, a review of all information and study results on HIV and contraceptive methods was prepared to assist the Department in developing technical guidelines in this area. The paper will be assessed by WHO and UNAIDS staff and will be used as background information in the planned revision of WHO’s document Improving access to quality care in family planning: medical eligibility criteria for contraceptive use (see also the next section “Medical eligibility criteria for contraceptive use”).

Medical eligibility criteria for contraceptive use

To reach an agreement on appropriate eligibility criteria for widely used contraceptive methods, a number of agencies and organizations have collaborated with WHO in carrying out an in-depth review of the epidemiological and clinical evidence relevant to the medical eligibility of well-established contraceptive methods.

Two scientific working group meetings were organized by the Department to formulate recommendations for revising the medical eligibility criteria for each contraceptive method. A report of the two meetings was prepared and distributed to policy-makers, family planning programme managers and the scientific community. It aims at providing guidance to national family planning/reproductive health programmes in the preparation and revision of national medical and service provision guidelines based on new recommendations for initiating and continuing the use of each contraceptive method. The French, Spanish, Russian, Chinese, Vietnamese and Indonesian versions of the report were printed in the 1998–1999 biennium.

In an effort to strengthen further the inter-agency collaborative work undertaken for reviewing the medical eligibility criteria for contraceptive use, active support has been given to follow-up work on programme guidelines that a number of agencies initiated in 1998–1999. This has helped to maintain WHO’s continued coordinating role in this initiative by ensuring that the programmatic and service delivery guidance being provided to countries by various groups is consistent and reflects adequately the international consensus on medical issues. Examples of this support are as follows.
• Assistance, with either technical review or development of materials for programme managers and service providers (based on WHO recommendations), was given to: the International Planned Parenthood Federation (IPPF), London, United Kingdom; the Johns Hopkins University Center for Communications Programs (JHUCCP), Baltimore, MD, USA; the Program for International Training in Health (INTRAH), Chapel Hill, NC, USA; FHI; and the Program for Appropriate Technology in Health (PATH), Seattle, WA, USA. This resulted in the following four joint publications:

—The essentials of contraceptive technology
—Medical and service delivery guidelines for family planning
—Recommendations for updating selected practices in contraceptive use, Volumes I+II
—Family planning methods: new guidance, a special issue of Population Reports, Series J, Number 44.

• Technical support was provided by the Department to assist regional teams and countries in using the recommendations through the presentation and introduction of the document to relevant staff in the African, American, South-East Asian and Western Pacific regions, the leaders of UNFPA Country Support Teams (CST), all Technical Support Services (TSS)/CST reproductive health specialists, Departments of Health as requested and as feasible, nongovernmental organizations (NGOs) and country project staff in India, the Philippines, South Africa, Turkmenistan and Zambia.

• Intensive support was provided to the Ministry of Health of South Africa in initiating the process of building a national consensus and developing national policy and service delivery guidelines for family planning in line with the latest WHO recommendations.

• Discussions were held with relevant experts to review and carry out the necessary revisions of WHO’s medical eligibility criteria for initiating and continuing use of different contraceptive methods. Preparations were underway for an expert committee meeting to be convened on 8–10 March 2000 to revise the document Improving access to quality care in family planning: medical eligibility criteria for contraceptive use.

### TECHNICAL GUIDELINES AND TRAINING MATERIALS ON FAMILY PLANNING METHODS

The prevention of unwanted pregnancy and STI/HIV/AIDS

**The male latex condom**

During 1998–1999, as part of the joint programme of work, UNAIDS and WHO, in collaboration with the private sector and with scientific, technical and programmatic experts published and disseminated a package of materials designed to summarize the latest scientific evidence and principles of best practice in the key areas of condom programming (see the flow-chart below).

This compendium of materials is entitled *The male latex condom* and contains the following publications.
Specification and guidelines for condom procurement focuses primarily on procurement issues related to condom quality, since these differ significantly from those used to procure other health products. Section 1 provides a step-by-step guide to the procurement process and the different quality assurance measures that are applied to ensure the manufacture, procurement and distribution of good quality condoms. Section 2 details the essential components of a good purchase specification, laboratory tests and requirements that must be met as part of a quality assurance process to ensure that a good quality product is manufactured. This is important since poorly manufactured and packaged condoms will deteriorate rapidly and will not withstand harsh conditions of storage and distribution.

Ten Condom programming fact sheets are designed to review the latest scientific evidence and best practices regarding key elements of condom programming. The fact sheets can be used for generating a higher level of confidence in promoting condom use, improving levels of competence in major areas of condom programming, improving the quality of ongoing condom programmes, and increasing public awareness of the effectiveness of condoms to prevent both unwanted pregnancy and the transmission of sexually transmitted infections (STI), including HIV/AIDS.

The monograph The latex condom—recent advances and future directions is produced by FHI and published in collaboration with WHO and USAID. The monograph supports the information provided in the fact sheets by reviewing the large number of published studies and articles concerning multiple aspects of condom quality, performance in use, acceptability and user behaviour.

JHUCCP has undertaken an extensive review of the literature published over the last decade on a wide variety of issues related to condom research, production, quality and programming. The Department has collaborated with JHUCCP on receiving different aspects of the literature and publication of the Popline report entitled Closing the gap on condom use. Information from this literature review has also been incorporated into a CD-ROM produced by JHUCCP and UNFPA. This provides an interactive review of literature and materials that have been used around the world for condom promotion.

A designated Technical Officer from the Department participates in the biannual meetings convened by the Organization of International Standardization, Technical Working Group 157 for Mechanical Contraceptives (ISO/TC/157). This Group is currently working on the revision of the International standard for male latex condom 4074. The meetings involve delegates representing condom manufacturers, testing laboratories, consumer groups, national regulatory boards and scientific experts from around the world in the process of analysing and agreeing upon the quality assurance tests and procedures that should be incorporated into the 4074 Standard. The WHO document, Specification and guidelines for condom procurement is used as a technical reference document at these meetings. It is expected that the new 4074 Standard will be published by the end of 2000. WHO and UNAIDS will then undertake a scientific review of the WHO specification to ensure consistency with the published standard.

The work undertaken by the Department in relation to the male latex condom is the first phase in a series of activities designed to support national family planning and STI/HIV/AIDS prevention programmes. So far, these activities have generated accurate evidence-based technical guidance materials. The next phase, due to start in the year 2000, will focus on providing technical assistance to countries to help disseminate, adapt and operationalize the technical guidelines to improve the quality of condom programming activities. This will form part of an integrated programmatic approach to support the prevention of STIs and HIV/AIDS and unwanted pregnancies.

Towards the end of 1999, UNAIDS approved funding for the Department to assess country-specific managerial and technical needs required to sustain improved quality assurance measures for the procurement and distribution of good quality condoms. This assessment will help to focus country support activities designed to improve the quality of male and female condom programming. Already technical support has been provided to South Africa to update national regulatory standards for condom procurement and improve the quality assurance measures applied to condom procurement and distribution.

To offer a cohesive approach to condom programming activities, the Department has worked closely with UNAIDS and WHO’s HIV/AIDS/STI Initiative to submit a proposal for inclusion in the UNAIDS unified workplan for the biennium 2000–2001. This proposal encompasses not only the programmatic and quality assurance issues related to male and female condom procurement, promotion, distribution and use, it also covers the Department’s work in social marketing and dual protection. A team from the Department and UNAIDS meets on a regular basis to formulate and monitor a detailed workplan for this biennium.

Female condom

The development of the female condom has introduced into the market a viable barrier method against unwanted pregnancy and the transmission of STI/HIV that is under the control of women. The Department maintains a Condom Working Group which collaborates closely with UNAIDS, Population Services International (PSI), Washington, DC, USA, and the Female Health Company, London, United Kingdom. The Department and UNAIDS have:
— developed and widely disseminated a Female condom information pack;
— negotiated a special public sector price with the manufacturer;
— expanded the briefing package to include components addressing such issues as: Information, education and communication (IEC) that are required to promote the use of the female condom; Social marketing and the female condom; and Going to scale— introduction to development of national programmes;
— worked with countries in eastern and southern Africa to explore different IEC strategies that can be used to ensure the successful introduction and sustained use of the female condom;
— worked with a national project in South Africa to introduce the female condom into the public sector and conduct research to determine the feasibility, acceptability and safety of female condom reuse;
— supported biomedical research to generate additional information and evidence regarding the efficacy of the female condom as a method of contraception and as a barrier to the transmission of STI/HIV.

Social marketing

The Department collaborates with UNAIDS in developing a comprehensive strategy to support condom programming activities for the prevention of STI/HIV/AIDS and unwanted pregnancy. Social marketing of products, services and behaviour-change communication will be part of this package of strategies designed to improve reproductive health. As part of this strategy, UNAIDS, WHO and UNFPA are planning to hold a “Social Marketing Forum”. This Forum will be designed to bring together donor agencies, collaborating partners and country representatives in order to explore the comparative advantages and potential of social marketing in improving access to reproductive health services and technologies, particularly the prevention of STIs/HIV/AIDS and unwanted pregnancies.

To initiate activities in the area of social marketing and develop a framework for the Social Marketing Forum, UNAIDS convened a two-day meeting in October 1998 with WHO, UNFPA, IPPF, MSI, PSI, Futures Group, HORIZONS/Population Council, United Kingdom Department for International Development (DFID) and the US Agency for International Development (USAID). Another planning meeting was held in July 1999 to include a broader range of partners in the discussions required to finalize the framework for the Forum. At that meeting, it was decided that the primary focus of the Forum would be advocacy, in order to raise the profile of social marketing and to define clearly how it can contribute to the provision of reproductive health care in general, and in particular, the prevention of STI/HIV/AIDS and unwanted pregnancy. It was agreed that the Forum would first seek to clarify the definition of social marketing and address misconceptions through a series of papers that will examine and provide evidence on:

— the effectiveness of social marketing—does it work? does it affect behaviour?
— equity—does social marketing really reach the poor?
— cost-effectiveness—is it cost-effective and how does it compare with other approaches?
— sustainability—is social marketing sustainable financially, institutionally and in terms of impact?
— public sector roles—how can the public sector adjust to and work with social marketing?

The Forum is being designed to analyse and make recommendations on how best to go forward. It will identify a common research agenda and explore the best means of utilizing social marketing approaches to strengthen efforts already under way to prevent STI/HIV/AIDS and unwanted pregnancy.

During the last quarter of 1999, individuals were identified to prepare background papers and to act as keynote speakers at the Forum, scheduled for the end of 2000.

Introduction to integration: the management and prevention of STIs/HIV/AIDS in maternal health and family planning services

The provision of health care services is challenged by new problems and concerns caused by increasing levels of transmission of STIs, including HIV. A review of the literature regarding the treatment of STI has determined that many of the STI control programmes remain under-resourced and are located in specialized clinics in large towns which often reach only a small proportion of those in need. It is reported that an estimated 90% of patients are male, and services assisting women in treatment or prevention of future infections are virtually non-existent.

Maternal and Child Health/Family Planning (MCH/FP) services are well placed to help prevent and control STI/HIV, since sexually active women often seek health information and care from these facilities. These services can make STI/HIV prevention, education, risk assessment, counselling and motivation a regular part of client care. In addition, MCH/FP service providers are expected to deal with issues of sexuality, methods of contraception, care during pregnancy, childbirth and breastfeeding, all of which relate closely to the prevention of STI/HIV.

The integration of STI/HIV prevention and control measures in MCH/FP programmes is intended to increase the coverage, primarily by reaching women who might not otherwise have access to STI/HIV prevention and clinical services. Women are, in many ways, particularly vulnerable to STI/HIV and yet, for some women, MCH/FP programmes represent their only source of information and
health care. Integration is also intended to improve the quality of care by responding in a concerted manner to a broader set of reproductive health concerns of women who seek services, minimizing missed opportunities for dealing with health problems such as STIs, and addressing areas of technical overlap between services, such as in the case of dual protection.

It is often claimed that there is insufficient evidence to formulate a guideline on managing integration. However, in response to requests from countries, donor interest and a recognized need, the Department has produced an initial draft of a document intended for national- and district-level programme managers who are responsible for the planning and implementation of reproductive health care programmes. This draft, produced through a wide consultative process, has been reviewed internally at WHO and externally by an expert panel to develop principles of best practice into specific guidance on technical and managerial issues involved in the partial or full integration of these various programmes. The draft will be revised to reflect the outcome of the review process and the work that the Department has undertaken to review the current literature that exists on issues related to integration. It is expected that this document will be finalized and published in 2000.

**TECHNICAL GUIDELINES AND TRAINING MATERIALS ON QUALITY FAMILY PLANNING SERVICES**

A consortium of a number of international agencies and organizations, together with the Department, has developed an information package and training guidelines concerned with the provision of quality family planning services.

**Preparing practical materials**

Work has been under way during the past biennium on the preparation of sets of practical materials for clinic- and community-based service providers. These have included counselling guides, revised screening procedures and algorithms for contraceptive method choice, and a handbook to adapt these materials.

In 1998, preparatory work was carried out by the Department on the formulation of WHO’s new recommendations for medical eligibility criteria for contraceptive use into practical materials for family planning service providers.

A booklet entitled *WHO call to action: standardizing contraceptive eligibility criteria*, is being produced as a companion volume to *Improving access to quality care in family planning: medical eligibility criteria for contraceptive use*. This volume is being prepared to provide suggestions to decision-makers for updating national family planning counselling and prescription practices. In particular, it discusses the programmatic implications of the new WHO criteria in terms of policy modification, service delivery, personnel, training, logistics and evaluation. In addition, it outlines a step-by-step process that the programme decision-makers can follow to adapt the criteria to the often diverse situations in which contraceptive services are provided.

A separate document, *Improving access to quality care in family planning: a guide for providers*, is also under development and will provide method-by-method summaries of the service delivery implications of the WHO medical eligibility criteria. This guide deals with all the widely used modern and traditional contraceptive methods and will also offer synthesized information to providers on cross-cutting reproductive health issues and how they can be addressed. These issues include: clients’ rights, effective counselling, infection prevention, gender sensitivity and domestic violence, encouraging men’s involvement in sharing responsibility for reproductive health, and controlling STDs. A section addressing the special needs of women (especially in terms of contraceptive/STI information and care) as they pass through different vulnerable stages of their reproductive life span is being researched and developed. A final section addresses some of the most common chronic health conditions faced by women, for example, anaemia, diabetes, severe dysmenorrhoea, headache/migraine, tuberculosis, etc. and classifies the suitability of different contraceptive methods in the presence of any of these conditions.

It is envisaged that all of these materials will be published, in English, during 2000.

**Completion of the WHO series of technical and managerial guidelines on contraceptive methods**

Over the past several years, WHO’s family planning and population activities have included a focus on responding to countries’ needs for technical and managerial support in setting up and/or strengthening the family planning component of their reproductive health programmes on the basis of WHO’s latest norms and standards for safe health care practices. A series of managerial and technical guidelines has been developed to synthesize and translate the results of the large amount of clinical and operational research in family planning into practical applications that will help improve contraceptive safety, choice and quality. These guidelines are intended for use, particularly by the national- and district-level family planning programme manager or administrator.

In 1997, work on two sets of guidelines was given priority because of the urgent need to update the guidance
provided to countries on two of the most widely used contraceptive methods, namely, IUDs and oral contraceptives. The publication *Intrauterine devices: guidelines for programme managers*, was finalized as per WHO’s new recommendations for medical screening and counselling for IUD use, and was printed in English in 1997. This book was widely disseminated through WHO and UNFPA channels. French and Spanish versions of the document were printed during 1998–1999. Work on the finalization of the technical and managerial guidelines on oral contraceptives was completed during 1999 and the document has been thoroughly revised according to the recommendations of the expert group meeting on revised medical eligibility criteria for contraceptive use. The document has also been reviewed extensively by numerous experts and it now incorporates, for instance, the latest data on oral contraceptive use and the risk of myocardial infarction; the guide will be printed during 2000.

### Development of simple information/education materials on contraceptive methods

Simplified companion volumes, to each of the technical and managerial guidelines, that address the needs of various levels of providers in a user-friendly format and presentation have been developed. These aim at improving counselling by health care providers by increasing their knowledge on how the method works, its safety and efficacy, and the comparative benefits and disadvantages of each method. These simple materials also include an assessment of the efficacy of each method in providing adequate protection against STIs, including HIV, and its suitability for women at various stages in their reproductive lives.

New brochures that were prepared, reviewed and edited during 1998–1999 include:

- **Injectable contraceptives: what health workers need to know**
- **Intrauterine devices: what health workers need to know**
- **Oral contraceptives: what health workers need to know.**

These documents were all revised to reflect the new recommendations concerning medical eligibility criteria for counselling, screening and method provision. The first two have been printed in English and are currently being widely distributed. The third will be printed in English during 2000, as will other language versions of all three brochures.

Simplified guidelines for *Postpartum and post-abortion family planning: what health workers need to know* are also being prepared and will be submitted for external review and publication in 2000.

French and Spanish translations of the following brochures were completed in 1998–1999:

- Health benefits of family planning
- Providing an appropriate contraceptive method choice
- Vasectomy: what health workers need to know
- Natural family planning: what health workers need to know
- Female sterilization: what health workers need to know

All have been printed and are being distributed through WHO and UNFPA channels.

### Quality of care in family planning/reproductive health services

Work on the development of a guidance document and a facilitators’ guide has been initiated to assist countries in addressing issues related to the improvement of quality of reproductive health services. This is a collaborative effort between WHO, AVSC, IPPF, and The Population Council, with WHO as the technical lead agency. Since each of these agencies/organizations has carried out extensive work, both conceptually and programmatically, it is important that all the experience gained and the lessons learnt in this area are pooled, analysed and synthesized for the formulation of guidelines for national programme staff. Moreover, this collaboration will be instrumental in maximizing the use of resources since it will avoid duplication and support the harmonization of technical and programmatic guidance. This approach is particularly important as it takes into consideration programmatic needs and the minimal resources often available for improvement of quality of care.

The Department has collaborated with IPPF, AVSC International, PATH and The Population Council in the development of various guidelines and training materials on quality family planning service delivery. Outlines of various documents that have been developed and responsibilities assigned in meetings in the United Kingdom, USA and Geneva are as follows:

— through contact with country offices, WHO and IPPF gathered information from 70 countries on common myths and misconceptions related to family planning methods. This information is being analysed and assigned to different categories so that evidence-based answers can be provided for each misconception. WHO and IPPF will then develop these findings into a manual on how health workers can provide the correct information to clients in order to overcome rumours and misconceptions (see also the section on “Myths and misconceptions”);
— WHO collaborated with the Population Reference Bureau to develop an information package "Contraceptive
safety: rumours and realities;
— WHO is working with AVSC International to develop a Guide to facilitative supervision to improve quality of services. A draft document has been developed and is currently being reviewed by WHO staff;
— WHO is working with FHI in evaluating the impact of WHO’s guidelines on quality of service delivery;
— WHO collaborated with the Johns Hopkins University in publishing the Population Report GATHER guide to counselling (Series J, Number 48).

Myths and misconceptions

While some of the more common myths and misconceptions surrounding family planning and contraceptive use are known and are being addressed by various organizations, there are a large number of diverse issues prevalent among health workers and clients that have not been systematically reviewed and answered. These misconceptions contribute to the cultural, behavioural and information obstacles that prevent family planning providers from providing accurate information and appropriate levels of quality care. It also prohibits users from seeking timely care.

The Department, in collaboration with IPPF, approached 70 family planning associations, WHO country representatives, institutes and NGOs, to complete an international survey to determine the common myths and misconceptions prevalent in each country. The response rate has been very high and the data are currently being analysed. A systematic review of the latest research findings and principles of best practice will be undertaken to provide evidence-based answers to correct the myths and misconceptions. A technical consultation will be convened in 2000 to review the evidence that has been used to answer the common myths and misconceptions and reach a consensus on areas where no definitive evidence exists. A manual will then be developed that addresses both the information and training needs of health care providers so as to answer accurately common myths and misconceptions. It is anticipated that this manual will be published by the end of 2000.

Multiagency collaboration to improve the quality of family planning services

WHO, IPPF, AVSC International, PATH and The Population Council have initiated discussions to develop and produce a joint publication for supervisors, managers and trainers to improve the quality of family planning services. The agencies will then develop a strategy to introduce these materials, which have been designed to assist health care providers to improve the quality of service delivery, and to monitor the impact of this strategy. To date, AVSC International has produced a draft Guide to facilitative supervision. This document is currently under review.

Essential Care Practice Guide for family planning

This manual encompasses guidelines on family planning as one of the essential components of maternal health. This information has since been developed into a series of algorithmic flow charts designed to assist health care providers to make the appropriate decisions based on individual need and the types of care women require. It also contains sections on counselling and the giving of advice on choice of method and follow-up. The process of developing an Essential care practice guide for family planning was initiated by staff, and discussions were held with FHI, John Hopkins University, PATH, The Population Council, IPPF and others. An informal meeting of the relevant groups took place in 1999. This guide is due to be issued in 2000.

An interagency group, involving IPPF, FHI, AVSC International, JHPIEGO, Futures Group, Population Council and JHU/CCP, has offered its full support in the development of the Essential care practice guide for family planning, and a consultant will be hired to finalize it in early 2000.

INTER-AGENCY COLLABORATION: DEVELOPMENT OF A STRATEGY TO SUPPORT THE DISSEMINATION, ADAPTATION AND UTILIZATION OF THE DEPARTMENT’S TECHNICAL GUIDANCE DOCUMENTS

An issue being currently addressed in WHO, and which is of particular concern to the Department, is how to ensure that the evidence-based technical norms and standards generated by WHO are appropriately disseminated, adapted and utilized. The strategy that is currently being developed by the Department to support country adaptation and utilization of technical documents is based on a multi-agency review of the USAID-supported strategy that has been used to introduce the medical eligibility criteria in over 50 countries, and is known as the Maximizing Access to Quality of Care Initiative (MAQ Initiative).

The Department convened a two-day meeting in May 1999, with representatives from FHI, JHPIEGO, and JHU/CCP, to review lessons learnt from the successful dissemination of the medical eligibility criteria and identify how the agencies can collaborate to develop a strategic approach to ensure the effective dissemination, adaptation and utilization of technical guidelines at the policy and programmatic levels.

A second meeting, involving the Department, JHPIEGO, FHI, JHU/CCP, and additional collaborators (UNFPA, AVSC International, The Population Council, and IPPF) was convened in Geneva, Switzerland, in August 1999. Full reports of both meetings are available on request from the Department.
The strategic approach being developed will enable WHO and its partners to translate evidence-based results (reflected in the WHO guidance documents and related materials) into improved services (reflected by the adaptation and utilization of the guidance documents). The participants in the meetings pledged the support of their agencies and organizations to this strategy and noted that its principles could be applied to the dissemination and use of any technical document.

In the year 2000, it is planned to field test this strategy using recently published family planning documents. The Department, in collaboration with WHO Regional Offices and partner agencies, will convene a series of intercountry meetings to review the strategy and foster commitment to implement country-specific strategies to adapt and utilize technical documents pertaining to reproductive health.
Maternal and perinatal health

Generating and summarizing evidence

J. Villar and E. Hoff
INTRODUCTION

The average maternal mortality ratio is approximately 27 maternal deaths for every 100,000 live births in the more developed regions, and 480 for the less developed regions of the world. Deaths are concentrated in some regions—approximately 55% of them occur in seven developing countries and one country contributes 20% of all deaths. A few direct causes of mortality (abortion, hypertensive disorders, haemorrhage, obstructed labour and infections) account for 80% of maternal deaths, although poverty is, in most instances, the underlying cause of all the suffering.

Although there is a great deal of knowledge about general medical and surgical practices to prevent many maternal deaths, and considerable progress has been made in the field of infectious diseases, the challenge ahead is the transfer of this knowledge into practice in developing populations. Nevertheless, there is still a considerable gap in the understanding of most of the specific pregnancy-related conditions. For pre-eclampsia/eclampsia, which affects 4%–8% of all pregnant women, the pathophysiology remains largely unknown and there are no effective preventive and curative strategies other than delivery. For postpartum haemorrhage, although delivery by a skilled attendant and the use of active management of the third stage of labour are advocated, approximately 3%–5% of all women still experience postpartum blood loss of more than 1000 ml with the recommended management. Obstructed labour, mostly related to factors affecting the women during childhood, is very difficult to predict and ante- and intrapartum referral strategies need to be evaluated rigorously for their effectiveness. It is paradoxical that for some populations the problem is underutilization of Caesarean section, while for others the overutilization of this surgical procedure has become a public health problem. Although routine iron and folic acid supplementation are recommended as an effective preventive strategy for anaemia, a very large proportion of women start pregnancy with severe anaemia for which the effective treatment remains unclear. The best strategy for pregnant women living in malaria-prevalent regions is still unsettled.

Severe morbidity such as that caused by chronic anaemia, fistulae, gynaecological infections, pyelonephritis, chronic renal disease, chronic pelvic pain, uterine prolapse and depression affect large numbers of women. Some of these conditions can be prevented or treated effectively while for others considerable etiological, therapeutic or health service research is needed. For example, although 10%–15% of women are thought to be suffering from depression, there is controversy about whether there is an entity such as postpartum depression. The same percentage of mothers is found to be depressed, regardless of the age of their children or length of time since giving birth. To date, trials of preventive strategies for postpartum depression have not shown significant benefits. Finally, there are no effective preventive measures for preterm labour and prelabour rupture of membranes—two pregnancy-specific conditions that are leading causes of maternal and newborn morbidity and mortality. These conditions are related to infections in most epidemiological studies, but randomized controlled trials have failed to demonstrate the effectiveness of antibiotic treatment in their prevention.

Recent evidence from developed and developing countries suggests intra- and intergenerational effects of pregnancy-related events. For example, there is an association between impaired fetal growth in female fetuses and obstructed labour later in life due to short stature, as well as impaired fetal growth and chronic disease during adulthood. The latter effects, if confirmed in populations from developing countries, could have great importance for those countries in their epidemiological transition, where ischaemic heart disease is already the second most common cause of death. This is in addition to the strong evidence that impaired fetal growth is associated with poor mental and neurological development and school performance, as well as neonatal morbidity and mortality.

This short review of research gaps demonstrates that although health services can incorporate effective medical and surgical strategies to reduce maternal mortality and morbidity, and morbidity, there is an alarming lack of scientific understanding of pregnancy-specific conditions, particularly those related to the prevention of leading causes of morbidity. This is an overt contradiction to the major progress made in other areas of medicine in the last decade, including some related disciplines such as human genetics.

THE RIGOROUS EVALUATION OF MATERNAL HEALTH PROGRAMMES

Over the last few decades, there has been a dramatic growth of new medical practices and technologies in the field of reproductive health care. Many of these practices have been introduced before their benefits and safety were established in terms of improved health outcomes. In some instances, they were based on randomized trials, but a large proportion of these studies was of questionable quality. Experience shows that once a practice is introduced and accepted by the medical community, it becomes difficult to assess or change.

HRP should play a leading role to ensure that maternal health interventions recommended for developing countries undergo critical evaluation in terms of the best available scientific evidence. In this way, not only will women be ensured of receiving good care, but also scarce resources will not be wasted on ineffective interventions.
HRP’S COMPARATIVE ADVANTAGE IN MATERNAL HEALTH RESEARCH

At the end of 1998, a Technical Consultation Group discussed, at the request of the Scientific and Technical Advisory Group (STAG), the priority research areas taking into account HRP’s comparative advantage in undertaking maternal health research. It was felt that HRP has the credibility and neutrality at the international level and is in a strong position to make an impact through implementation of evidence-based programmes. The capacity building efforts of HRP have created a network of collaborating institutions in the majority of developing countries. In collaboration with this network, HRP possesses the skills and resources to conduct high-priority research that is unlikely to be conducted individually by research initiatives in developing countries.

HRP has demonstrated its capacity by implementing and successfully completing several multicentre trials exploring the effect of medical and non-medical interventions (Table I) in a relatively short period of time. When the last trials of this series are completed, a total of 239 178 women/newborns will have been studied over a period of less than five years.

AIM AND STRATEGIES FOR IMPLEMENTATION OF THE PROGRAMME OF WORK

The aim of this programme is to reduce maternal morbidity and mortality through the development of acceptable and affordable evidence-based health programmes.

The implementation of the maternal health research programme is achieved by: (i) evaluating effectiveness of practices, including conducting systematic reviews of the literature; (ii) improving understanding of the sociocultural factors influencing maternal health care; (iii) reviewing methodological issues related to maternal health research; (iv) conducting follow-up studies of the populations included in pregnancy-related research; (v) evaluating the implementation strategies of research results; and (vi) stimulating fundamental research on outstanding obstetric problems of global importance. In addition, during 1999, activities were initiated that aimed at minimizing the risk of mother-to-child transmission (MTCT) of HIV infection.

The report of the activities is presented below.

PROGRESS

Evaluate effectiveness of practices

The WHO randomized controlled trial for the evaluation of a new antenatal care programme

In collaboration with four institutions in developing countries, during 1999, HRP completed a large multicentre randomized controlled trial to evaluate the impact of a new antenatal care programme on the health of mothers and newborns. This new programme limits the antenatal tests, clinical procedures and follow-up actions to those scientifically demonstrated to be effective in improving maternal and newborn outcomes. The selected antenatal care activities are distributed over four visits during the course of pregnancy.

The study was conducted in three cities (Rosario, Argentina; Havana, Cuba; Jeddah, Saudi Arabia) and the province of Khon Kaen in Thailand. There were 53 antenatal care units randomly allocated to provide either the new programme of antenatal care or the traditional programme presently in use. A total of 24 678 women presenting for antenatal care at the clinics over an average period of 18 months were recruited by April 1998. Since

Table I. Maternal health interventions evaluated during 1999 with leading/active participation of the Programme

<table>
<thead>
<tr>
<th>Countries</th>
<th>Women</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antenatal care</td>
<td>5</td>
<td>24 678</td>
</tr>
<tr>
<td>Caesarean section*</td>
<td>5</td>
<td>142 000</td>
</tr>
<tr>
<td>Postpartum haemorrhage</td>
<td>9</td>
<td>18 530</td>
</tr>
<tr>
<td>Treatment of pre-eclampsia**</td>
<td>28</td>
<td>14 000</td>
</tr>
<tr>
<td>Reproductive health library evaluation</td>
<td>3</td>
<td>30 000</td>
</tr>
<tr>
<td>Prevention of pre-eclampsia</td>
<td>6</td>
<td>8 500</td>
</tr>
<tr>
<td>TOTAL(***)</td>
<td>56</td>
<td>233 728</td>
</tr>
</tbody>
</table>

* In collaboration with PAHO/CLAP
** The Programme is not responsible for the implementation
*** Some countries participate in more than one evaluation
women attending the control clinics receive the “best standard treatment” as presently offered in these clinics, individual informed consent was requested only from women attending the intervention clinics. Authorities of the corresponding health districts and all participating clinics provided written institutional informed consent before randomization.

The primary outcomes of the trial in relation to maternal conditions were proteinuric pre-eclampsia or eclampsia during pregnancy or within 24 hours of delivery; severe postpartum anaemia (<90 g/L of haemoglobin); and treated urinary tract infection or pyelonephritis, defined as an episode requiring antibiotic treatment and/or hospitalization. The primary fetal outcome was the rate of low birth weight (<2500 g). Several secondary maternal and perinatal outcomes were also considered. The trial included a comprehensive cost-effectiveness analysis and a women’s and providers’ evaluation, which are described under a separate title.

Before randomization, a comprehensive baseline survey of 2913 women was conducted which described in detail the antenatal care services available in the participating clinics. A similar survey, and a patient satisfaction evaluation were conducted during the implementation of the trial. A series of methodological papers discussing the study design and its characteristics was published during 1998.

All data obtained during the study were analysed in Geneva during 1999. The final data analysis of the three components of the study (clinical evaluation, women/provider satisfaction and economical evaluation) was completed in October 1999 and several papers are under preparation for publication during 2000. An extensive dissemination effort is being planned, including presentations at meetings and symposia, and medical and non-medical publications.

*The WHO multicentre randomized trial of misoprostol in the management of the third stage of labour*

Postpartum haemorrhage is a leading cause of maternal death, in both developing and industrialized countries. The use of oxytocics (oxytocin and ergometrine preparations) in the management of the third stage of labour reduces the amount of bleeding and the need for blood transfusion, but it is associated with side-effects when ergometrine preparations are used. Furthermore, these agents are administered by injection, and syntometrine requires refrigeration to preserve its effectiveness. Some prostaglandin preparations have been found to be potentially effective in the prevention of postpartum haemorrhage during the third stage but they are expensive and also need to be administered by injection. There is a need for a cheap, effective oral agent which could be used during the routine management of the third stage of labour in places where refrigeration and personnel are not readily available.

Misoprostol, a prostaglandin E1 analogue registered for the treatment of peptic ulcer disease, has attracted widespread attention because of its uterotonic effects. Clinical trials have found it effective for priming the cervix prior to surgical abortion and for medical induction of abortion in combination with mifepristone. There have also been promising reports on its use in cervical ripening and induction of labour. Misoprostol retains its activity for a long period when stored at room temperature and is absorbed rapidly after oral ingestion, making it a promising agent for the management of the third stage of labour.

A multicentre, double-blind, randomized controlled trial launched by HRP in 1997 was completed in November 1999. The objective was to evaluate the overall efficacy of oral misoprostol when used routinely for the management of the third stage of labour. The primary question was, how effective is a single oral dose of 600 µg of misoprostol in reducing severe postpartum blood loss and the need for additional treatment in the third stage when compared with an intramuscular or intravenous 10 IU dose of oxytocin.

The trial was double-blind with each woman receiving a placebo and active treatment. The primary outcome was postpartum haemorrhage (≥1000 ml) which was assessed by measurement of blood loss after delivery. Data on adverse events were also collected.

Overall trial coordination was done by HRP with collaborating centres in Argentina, China, Egypt, Ireland, Nigeria, South Africa, Switzerland, Thailand and Viet Nam. A total of 18 530 women were enrolled in these countries. Data analyses are in progress in Geneva and the first report is expected to be available by April 2000. This protocol has been provisionally approved by *The lancet* for publication in 2000.

*The Latin American randomized controlled trial of mandatory second opinion for reduction of the rate of Caesarean section*

This trial is implemented in Latin America in collaboration with the Latin American Center of Perinatology and Human Development (CLAP), Montevideo, Uruguay. It is mostly funded with a grant from the European Community and contributions from The Population Council, New York, NY, USA, and HRP. Within the framework of cluster randomization, the trial is evaluating an intervention aimed at reducing Caesarean section rates in Latin America. The intervention consists of a systematic second opinion requested before every non-emergency Caesarean section. The intervention applies a process of decision-making based on the best
available evidence about effective and safe management of childbirth.

In the maternity units assigned to the intervention, the objective is to achieve a 25% reduction in Caesarean sections without increasing the rates of fetal, neonatal, and maternal morbidity and mortality. Thirty-six hospitals from five Latin American countries are participating in the trial—Argentina (18), Brazil (8), Cuba (4), Guatemala (2) and Mexico (4). A special research component aimed at evaluating women’s and providers’ perceptions with the second opinion process is supported by HRP, and data collection was started during 1999 in Argentina, Cuba, Guatemala and Mexico. Similar evaluations will be conducted in Brazil during 2000.

All participating hospitals began six months of baseline data collection between January and October 1998, which was completed during 1999. The intervention started in Cuba on 1 July 1999. By March 2000, 28 hospitals expect to complete recruitment, including a total of 110,000 deliveries. The hospitals in the last study site, Brazil, will complete the study in June 2000, adding 32,000 women to the study population. Results are expected to be ready for publication by September 2000.

The trial of magnesium sulfate for the prevention of eclampsia: reducing the human and health service burden of pre-eclampsia

This trial, known as the “Magpie Trial”, is being conducted in collaboration with the Institute of Health Sciences, Oxford University, Oxford, United Kingdom, which is coordinating the trial.

Pre-eclampsia is an important cause of morbidity and mortality for the woman and her infant. Eclampsia, the occurrence of seizures superimposed on pre-eclampsia, is rare but associated with a far worse outcome than pre-eclampsia. Anticonvulsants are used for women with pre-eclampsia in the belief that they reduce the risk of eclampsia, and so improve outcome. Internationally, there is controversy about whether an anticonvulsant should be given to women with pre-eclampsia. If one is used, however, magnesium sulphate seems to be the best choice, even though there is little reliable evidence about the overall benefits and hazards of such treatment.

The Magpie Trial is comparing magnesium sulphate with placebo for treatment of women with pre-eclampsia. The primary measures of outcome are eclampsia and death of the baby. The effects on other measures of serious maternal and neonatal morbidity will also be assessed, as will the use of health service resources.

Following a pilot trial in South Africa, recruitment to the main study began in July 1998 and already involves women and clinicians from 120 hospitals in 28 countries, with 30 more hospitals waiting for ethical approval. By December 1999, over 2500 women had already been recruited, making this the biggest ever trial of anti-convulsants for the treatment of pre-eclampsia. It is expected that a total sample of 13,990 women will be achieved.

A randomized double-blind controlled trial of calcium supplementation during pregnancy provided to women with deficient calcium intake for the prevention of pre-eclampsia

Calcium supplementation during pregnancy has been provided either to increase the intake among those with deficiency or to obtain a pharmacological, perhaps non-nutritional effect, among individuals with an adequate calcium intake. A systematic review including only randomized double-blind controlled trials of calcium supplementation during pregnancy has been independently prepared and published in The Cochrane library. In view of the heterogeneity of results, stratified analyses were conducted by level of baseline dietary calcium intake (mean calcium intake in the population above or below 900 mg/day). The risk of high blood pressure was reduced among women with low baseline dietary calcium intake (relative risk [RR]=0.49; 95% Confidence Interval [CI] 0.38–0.62). Among those with an adequate calcium diet, the risk of high blood pressure was RR=0.89; 95% CI 0.81–0.99. The risk of pre-eclampsia was considerably reduced in trials conducted in low calcium diet populations (RR=0.32; 95% CI 0.21–0.49) but not among women with adequate calcium diet.

Based on these results, the protective effect of calcium supplementation during pregnancy provided to women with deficient calcium intake is a promising preventive strategy for pre-eclampsia. A definitive evaluation in an adequately-sized trial deserves to be conducted in populations with low calcium intake—the most likely to benefit from such a nutritional intervention. Long-term health benefits for the offspring are also an attractive possibility. This recommendation was supported by the 1999 publication entitled Reduction of maternal mortality: a joint WHO/UNFPA/UNICEF/World Bank statement, and at the 1999 STAG meeting, which has identified that calcium supplementation “may be an important option where diets are deficient in calcium” and that “women whose diets are low in calcium appear to be at increased risk of developing pre-eclampsia and eclampsia during pregnancy”.

The trial is ready to start recruitment of patients in Argentina, Colombia, Egypt, India, South Africa and Viet Nam. A survey of calcium intake of the pregnant population served by selected hospitals in these countries demonstrated that the mean calcium intake is less than 600 mg/day. The total sample size is expected to be 8500 women and the primary outcome of the trial is the rate of pre-
eclampsia. Data collection is expected to start in the selected centres during the later part of 2000.

The economic evaluation of a rational package for antenatal care conducted alongside a multicentre randomized controlled trial

This economic evaluation was completed in collaboration with the University of East Anglia, Norwich, United Kingdom, and the London School of Hygiene and Tropical Medicine, London, United Kingdom. The overall aim was to assess whether the new programme of antenatal care tested in the WHO antenatal care trial was more cost-effective than the existing level of service, both for women using the service and for health care providers.

A further aim was to examine the factors that may lead to differences between the cost–effectiveness estimates for the countries that took part in the economic study, and to assess transferability of the results. To this end, data were also collected in an additional centre in KwaZulu Natal, South Africa and combined with data from the WHO trial centres.

Data collection was completed in Argentina, Cuba and Thailand, including monthly cost data over one year in Cuba and Thailand from each clinic and hospital in the study. Cost to the health care system and women’s costs were combined with data from the WHO trial on the use of services in each arm of the trial and in each country, to estimate cost differences and cost-effectiveness. A thesis on the question of generalizing cost data between and beyond the centres taking part in the WHO trial was conducted in parallel with the main study. Final data analysis will be conducted for the preparation of the main publication of the study, as well as for the publication of reports on specific components of the trial.

Systematic reviews of the literature

Systematic reviews are conducted within the framework of the “Mapping Best Reproductive Health Practices” activity. Review topics are selected on the basis of their importance for developing countries; and scientists from these countries take the responsibility of preparing and maintaining these reviews. During 1999, three scientists from Argentina, Cuba and Nigeria were provided support to work on maternal health systematic reviews.

As part of this effort to synthesize evidence for effectiveness of maternal health care interventions, 28 systematic reviews and three protocols were conducted or maintained following The Cochrane Library requirements, by staff of HRP or by scientists from developing countries supported by HRP. These systematic reviews were published in the 1999 issue of The Cochrane Database of systematic reviews which is updated quarterly, and will be included in The WHO reproductive health library (RHL), No. 3, 2000. The main areas in which systematic reviews have been prepared through this effort are:

- Prevention of breech delivery by external cephalic version
- Anaemia treatment during pregnancy
- Management of fetal distress during labour
- Prevention of postpartum haemorrhage by prostaglandins
- Antenatal care
- Alternative treatments for asymptomatic and symptomatic bacteriuria
- Calcium supplementation to prevent pre-eclampsia
- Vaginal misoprostol for induction of labour

New recommendations based on the systematic reviews prepared or updated during 1999 with support from HRP are presented in Annex 1. These recommendations are added to the table of effectives summaries of forms of care, which are updated annually and distributed through RHL.

Vitamin A supplementation during pregnancy

The review was initiated as a response to the publication of a large randomized controlled trial of vitamin A supplementation during pregnancy, which demonstrated a very strong effect in reducing maternal mortality.

Anaemia has been associated with vitamin A deficiency, especially in developing countries. Other manifestations of vitamin A deficiency are scaliness of the skin, failure of reproduction and keratinization of the cornea. Damaged epithelial structures can become infected (e.g. respiratory tract, eye) and vitamin A has been shown to have an important role in preventing infection during childhood. Vitamin A deficiency occurs commonly in developing countries and its supplementation, especially together with iron, has led to improvement in haemoglobin levels in different studies.

Safe doses of vitamin A that can be given to pregnant women are not exactly known. For example, severe vitamin A overload might be associated with possible teratogenic effects in early pregnancy and with neuropsychological effects during later stages of pregnancy. An expert group consultation concluded that doses of 10 000 IU daily or 25 000 IU weekly after day 60 are probably safe. Currently, WHO recommends routine vitamin A supplementation during pregnancy or after delivery at any time during lactation (before menstruation resumes) in areas with endemic vitamin A deficiency (where night blindness occurs). Data from controlled trials suggest possible improvements in haematological and clinical indices.

This review includes trials of vitamin A supplementation
during pregnancy with vitamin A alone or in combination with other micronutrients on maternal and newborn clinical and laboratory outcomes. Trials to assess supplementation for HIV-positive pregnant women will not be considered, as they are already included in another Cochrane review. The review protocol has been accepted for publication and will be published in the first issue of *The Cochrane Library* in 2000. The full review will be completed by the end of 2000.

**Improve understanding of sociocultural factors influencing maternal health care**

**Women’s and providers’ perceptions of the quality of antenatal care**

Women’s and providers’ perceptions of the quality of antenatal care were ascertained alongside the WHO Antenatal Care trial in collaboration with the Latin American office of The Population Council, Mexico City, Mexico, and the National Perinatal Epidemiology Unit, Oxford University, Oxford, United Kingdom. During this study, information was obtained by applying both qualitative and quantitative research methodologies. Focus group discussions and in-depth interviews contributed useful insights into the cultural milieu in which care is provided, users’ and providers’ expectations, and their concept of quality. Based on these findings, two standardized questionnaires were developed. One was administered to a representative sample of 1600 pregnant women and the other to all antenatal care providers participating in the trial.

Women expressed their points of view concerning a reduced number of visits, type of provider, information that they get during clinical encounters and interpersonal relations with health professionals. The qualitative information, together with data from the surveys, identified aspects such as resistance to change by providers and the expected type of care that was not completely fulfilled to women. These issues will have to be considered during the introduction of the new model of care on a routine basis. The qualitative component of the study has been completed and reports are being prepared. The data analysis of the quantitative part was completed during late 1999 and will be incorporated in the full set of publications of the WHO Antenatal Care trial.

**Women’s needs and perspectives: insights from social science research on maternal health**

There is a scarcity of behavioural research in developing countries that explores the context of pregnancy and maternal care, and the constraints that women face in accessing and acquiring appropriate and acceptable care during pregnancy, delivery and the postpartum period. Recognizing this gap, the HRP has supported studies that explore these issues. Findings from three projects conducted in India and Sri Lanka that became available in 1999 point to high levels of morbidity and limited health care-seeking practice.

Obstetric morbidity in India, although probably high, is not well documented. Few rural or urban slum women use existing health services and most deliveries occur at home. Under these circumstances, gathering data about obstetric morbidity and its sociocultural context requires community-based studies. Two such studies are ongoing, one in rural south India, with the objective of exploring sociocultural determinants of obstetric care, and a second in an urban slum in New Delhi, India. Both studies are following up a cohort of pregnant women through the postpartum stage, and combine qualitative and quantitative research methods; in the New Delhi study, clinical and laboratory testing is also being undertaken.

Initial findings from both studies highlight continuing traditional health practices and high rates of self-reported morbidity. In rural south India, preliminary findings suggest that despite the fact that two-fifths of the cohort had six or more years of schooling, and a large proportion had received some antenatal care from government or private practitioners, the majority (90%) had planned to deliver at home, only half of these (56%) with trained assistance. It is only the experience of complications that prompted one-third of these women to deliver at a health centre.

Results suggest that few women and families plan ahead for delivery; awareness of danger signals is limited; and loss of family support and traditional practices are major reasons underlying the reluctance to deliver institutionally. Large percentages of women whose deliveries were conducted by an auxiliary nurse-midwife (ANM) or in an institution report the use of “injections to increase pains” (reference to oxytocics) (53% and 90%, respectively). Morbidity (abnormal presentation, premature rupture of membranes, prolonged labour, heavy bleeding, retained placenta, perineal tear, loss of consciousness) is reported by about one-fifth of the women in the sample.

Furthermore, findings from the New Delhi study report high rates of morbidity including laboratory-detected reproductive tract infections (RTIs) (35%), and anaemia (12%, ≤8 g/L haemoglobin). In addition, 13% reported serious obstetric morbidity during pregnancy (bleeding, hypertension and premature rupture of membranes); yet, of these, only a third recognized the severity of the condition, and about one-third of these sought no care. A similar profile characterizes postpartum care as well.

Sri Lanka presents a different picture. Relatively low levels of maternal mortality have already been achieved, and the overwhelming majority of women receive antenatal care and skilled attendance at birth. Yet, a case study
expanding sociocultural and economic aspects of postpartum care in Sri Lanka suggests that women in the postpartum period are relatively neglected unless major complications are experienced. The study consisted of a prospective survey of 600 women who had newly delivered; the women were interviewed within one week and at 43–50 days postpartum. Findings confirm higher-than-expected levels of reported morbidity in the postpartum period, particularly among low-income groups, along with a tendency among women themselves to disregard these complications as a “normal” consequence of pregnancy. Despite these experiences of postpartum morbidity, and the fact that several visits to women in the postpartum period are stipulated as part of the Maternal and Child Health Programme in Sri Lanka, almost three-quarters of women did not receive adequate postpartum care.

Review research methodology related to maternal health

Statistical methods for meta-analysis of randomized controlled trials

This is a follow-up of previous work evaluating the predictability of meta-analysis of randomized controlled trials of the results of large trials in perinatology. There has been limited empirical work comparing the random effect model with the fixed effect model in the calculation of a pooled estimator in meta-analysis of randomized controlled trials. This is of importance particularly when there is heterogeneity in trial results. A total of 84 independent meta-analyses in which each trial included a set of different women/newborns were evaluated. These meta-analyses were published in The Cochrane library, Issue 3, 1998.

Pregnancy and childbirth module. Twenty-one of these 84 meta-analyses demonstrated statistical heterogeneity at p<0.10. The random effect model estimates showed wider confidence intervals, particularly in meta-analyses with heterogeneity of trial results. The summary relative risk for the random effect model tends to show larger protective treatment effect than the fixed effect model when there is heterogeneity in the meta-analysis. Therefore, there may be opposing effects if the random effect model is used in meta-analyses of clinical trials with heterogeneity—less conservative estimation of the summary relative risk, but wider, more conservative confidence intervals with this summary measure.

Considerations for the design of stratified cluster randomization trials

This activity is conducted in collaboration with the Department of Epidemiology and Biostatistics, University of Western Ontario, London, Canada. Utilizing the experience gained from the WHO Antenatal Care trial, the statistical issues related to trial design, sample size and power calculations, including stratification and clustering in the design, were reviewed. The ethical considerations of the Zelen design and the role of intent-to-treat principle and efficacy analysis are also considered in two publications. In the field of software development, sample size and analysis formulae for the cluster randomized design that are not available in standard statistical packages, were programmed and are now available in a software developed by HRP staff.

Follow-up studies of populations included in pregnancy-related research

The possibility of an intrauterine programming of diseases later in life, including various chronic conditions, has recently attracted considerable interest. This hypothesis is supported by a growing number of observational studies; most of them conducted in populations from developed countries. Concerns have been raised about the methodological limitations of these epidemiological studies, which used data from decades-old hospital records and included small numbers of intrauterine growth-retarded newborns. There are also several important inconsistencies among the reports. It is very important to confirm these results in populations in developing countries, where the incidence of intrauterine growth retardation is approximately 20% of all births, and with some of the most populated developing countries in the phase of epidemiological transition to high prevalence of chronic diseases. HRP has collaborated with two institutions in Latin America to test these hypotheses, using prospectively collected perinatal and childhood/adolescent data, in large cohorts of children.

The effect of high calcium exposure in utero on blood pressure during late childhood: long-term follow-up of subjects enrolled in a randomized controlled trial

HRP has provided technical support to the preparation of this protocol which has obtained complete funding from an external donor and is now being implemented in Argentina by the Rosario Centre for Perinatal Studies (CREP), a WHO Collaborating Centre. This is a prospective follow-up study of children, aged 10–12 years, born to pregnant women enrolled in a double-blind, randomized, placebo-controlled trial of calcium supplementation during pregnancy. It is exploring the long-term effect of calcium supplementation during pregnancy on the offspring’s blood pressure during pre-adolescence, particularly among children with high body–mass index. The possibility of an amplification effect with age in the blood pressure of these children will also be explored by comparing the new data with the previous follow-up evaluation.
The study will enrol 298 children whose mothers received calcium supplementation during pregnancy (2 g/day) and 292 children whose mothers were in the placebo arm of the original trial conducted between 1987 and 1989.

Standardized blood pressure, clinical anthropometric measures, and morbidity history is obtained at follow-up for the children and mothers. Because of the randomized nature of the original trial and the blinded-to-treatment status of all participants in this follow-up, it is expected that groups will remain comparable in terms of baseline and follow-up characteristics except calcium exposure, blood pressure and biochemical indicators. (Nurses blinded to treatment status will take blood pressure measurements.) The impact of calcium exposure in utero will be evaluated in terms of blood pressure levels of children and mothers. If the long-term effect of calcium supplementation during pregnancy is confirmed, strong support for the fetal “programming” theory will be available. Furthermore, additional evidence for recommending calcium supplementation to pregnant women, particularly to those with low calcium intake, could be justified.

The Guatemalan perinatal follow-up study

This study is conducted within the context of a Long-term Institutional Development (LID) grant provided by HRP. The study is a long-term follow-up of a subsample of 14,847 newborns originally included in the Guatemalan Perinatal Study conducted between April 1984 and January 1986. The present follow-up includes a sample of newborns that were intrauterine growth-retarded at birth and a corresponding control group of normal birth-weight infants. These children were between 12 and 14 years of age when contacted for the follow-up study. The objective is to compare the cognitive and behavioural development, attained growth by anthropometric measures, blood pressure levels, and morbidity experiences. Blood samples are taken in a subsample of the children. There is a maternal component of the study that explores the reproductive patterns of the mothers after the index pregnancy and the socioeconomic characteristics of these women at the time of the follow-up. Data collection, including data on school performance, was completed during 1999, with a total sample size of 935 children. Plans for analysis and publication were prepared and will be implemented during 2000.

Evaluation of the implementation strategies of research results

A randomized controlled trial to evaluate a programme promoting evidence-based medicine based on The WHO reproductive health library (RHL)

To evaluate the uptake of information from RHL with subsequent changes in health care practices, a randomized controlled trial of an educational outreach strategy will be undertaken. The trial will be conducted in Mexico, South Africa and Thailand using maternity departments as the unit of randomization (cluster randomization). The objective of the trial is to change or increase the use of obstetric practices as recommended in RHL. The protocol for the trial has been completed and approved by the Scientific and Ethical Review Group (SERG) of HRP. Data collection will start in 2000 and the trial is expected to be completed by the end of 2001.

Stimulate fundamental research on outstanding obstetric problems of global importance

There are two highly prevalent maternal morbidities for which there is very little concrete pathophysiological knowledge on which to base preventive and therapeutic interventions. These are responsible for a large proportion of morbidity/mortality costs to services in developing countries. Hypertensive disorders of pregnancy affect approximately 10% of all pregnancies and are a significant contributor to severe maternal morbidity and mortality. Impaired fetal growth is another major problem affecting up to 20% of all pregnancies and is responsible for a significant proportion of perinatal and long-term morbidity in both developing and developed countries. Currently available interventions consist largely of symptomatic treatments for the mother and intensive care of a preterm or growth-impaired infant. It is unlikely that morbidity indicators and costs can be reduced without preventing these two conditions. Moreover, because severe pre-eclampsia and impaired fetal growth are relatively rare, they are not research priorities in developed countries.

HRP has established contacts with researchers and funding agencies already active in these research areas and reviewed opportunities for collaborative research, including the network of HRP’s collaborating centres. There has been discussion of possible protocols for biochemical markers that can predict pre-eclampsia, the effect of amino acids such as L-arginine on fetal growth, and the effect of antioxidants for the prevention of pre-eclampsia. It is expected that during 2000 a meeting to review and identify promising areas will be organized in collaboration with funding agencies. The feasibility of HRP’s participation in these protocols will be evaluated.

Prevention of mother-to-child transmission of HIV infection (MTCT)

A detailed evaluation of the activities performed by other (more active) players in the crowded field of MTCT of HIV infection vis-à-vis the available resources in the Department was conducted during 1999 by HRP’s staff. It was decided to concentrate on a few areas for which the
Department is best qualified. These are as follows.

**Update and maintain evidence-based recommendations for MTCT**

*Complete and publish “HIV in pregnancy” review*

This document includes an updated review of most of the main topics in the area and represents a good background for MTCT activities. Because of the noticeably changing field, the document will require continued updating and an electronic version will therefore be produced.

**Update systematic reviews of randomized controlled trials of MTCT interventions**

This was included in RHL No.2 and disseminated in 1999 in English and Spanish. HRP will support its continuous update and the follow-up of ongoing trials.

An external consultation was organized on 10–11 August 1999 and a joint WHO/UNICEF/UNFPA statement was produced on the use of nevirapine for prevention of MTCT in public health programmes, particularly in Africa. An update of the new information on short-course antiretrovirals for the reduction of MTCT has been drafted and is currently under review. It is to be published shortly in the *WHO Weekly epidemiological record*.

**Provide support to MTCT pilot projects**

In collaboration with UNAIDS, UNICEF and UNFPA, WHO is providing support to MTCT pilot projects in Africa aimed at the introduction of voluntary counselling and testing for HIV infection, and of antiretroviral therapy for the reduction of MTCT. The protocols, which were prepared in the countries undertaking pilot projects, were reviewed, amalgamated, and a common, generic protocol describing the basic components of the interventions was prepared and reviewed by the AIDS Theme Groups and MTCT task forces at country level. It will be distributed to the pilot countries and other agencies and will be the baseline for future programmatic evaluations.

The following countries have developed implementation plans: Botswana, Burkina Faso, Côte d’Ivoire, Kenya, Rwanda, Tanzania, Uganda, Zambia and Zimbabwe. Botswana, Côte d’Ivoire, Rwanda and Zimbabwe have already started implementation. A funding of US$ 3 million has been secured from the United Nations Foundation through UNICEF for seven of the pilot projects. As more and more countries express interest in joining the pilot initiative, additional funding needs to be sought by the Inter-Agency Steering Group of WHO, UNICEF, UNFPA and UNAIDS.

**Preliminary evaluation of pilot projects**

The pilot projects show the need to focus on uptake and acceptance of voluntary counselling and testing (VCT), and on counselling and support of HIV-positive mothers with respect to infant feeding options. This could be achieved through greater community mobilization, and involvement of those who are HIV-infected in the planning, design and implementation of MTCT activities, as well as by developing strategies for the provision of psychosocial support to HIV-affected families. The Division of Family and Reproductive Health in WHO’s Regional Office for Africa, in collaboration with WHO Headquarters, has decided to integrate within the initiative, work on the psychosocial aspects of support to HIV-infected pregnant women and their families. Demonstration projects are being planned in four African countries following completion of focused needs-assessment exercises.

In the process of pilot project development, countries are developing MTCT policy frameworks that will be crucial in the move towards nationwide programming and implementation. At the same time, pilot projects need to build the technical capacity required to train and supervise MTCT implementers during the national programming phase. It is estimated that a pilot phase of six months is required before proceeding to a carefully planned implementation phase of MTCT prevention.

Pilot projects are slowly moving towards a more holistic approach to the prevention of MTCT. Often starting as a set of limited technical interventions for reducing MTCT, they are beginning to include a broader set of interventions and enabling measures aimed at preventing MTCT. These include primary prevention of HIV among young men and women, providing access to family planning for women with HIV, involving partners in VCT, and providing care and support to women with HIV. This underlines the need to assess and improve the quality of reproductive health services, so as to enable them to provide high-quality MTCT prevention and care. It also points to the need for greater integration of prevention, management and care strategies in the area of MTCT within reproductive health/family planning/STD programmes. Furthermore, there is a need to step up efforts to reduce the price of antiretrovirals and breastmilk substitutes.

**Develop supporting documents and tools**

The following documents were produced for introduction into the MTCT programmes:

- HIV and infant-feeding
  —*A review of HIV transmission through breastfeeding* (developed in partnership with UNICEF and UNAIDS)
  —*HIV and infant-feeding: guidelines for decision-makers*
___HIV and infant-feeding: a guide for health care managers and supervisors__

- WHO/UNAIDS recommendations on the safe and effective use of short-course zidovudine for prevention of HIV transmission
- Clinical guides for HIV management in maternity settings (draft)
- Local monitoring and evaluation of the integrated prevention of MTCT projects in low-income countries (developed jointly with the partners of the Inter-Agency Task Team on MTCT)

**Coordinate global research into MTCT on behalf of the Inter-Agency MTCT Task Team**

The objective is to maintain a register of ongoing and planned research by different groups and agencies, identify gaps in the research relevant to current and foreseen needs of developing countries, and stimulate research by WHO and other agencies to address these gaps.

This activity has been identified as one of WHO’s key contributions to the Inter-Agency MTCT Task Team. This work will build on the published reviews mentioned above, and will formalize the inventory of country-specific MTCT activities. The inventories of research and other activities will be disseminated to all agencies involved in MTCT and a consultation will be held to identify gaps in the research relevant to the needs of resource-poor and middle-income countries.

**Conduct MTCT-related research: optimal infant feeding practices for minimizing risk of MTCT of HIV**

Work was undertaken by the Department staff in consultation with policy-makers, scientists and staff from other agencies to identify inadequately addressed priority research questions which the Department was best positioned and qualified to address. This led to a proposal submitted jointly with the Department on Child and Adolescent Health Development in September to the UN Foundation for research on optimal infant-feeding practices for minimizing risk of MTCT of HIV. This proposal has the following objectives:

- Develop and test common tools to assess breast- and infant-feeding patterns and practices in HIV-positive women;
- Use existing cohorts of HIV-positive mothers and their infants who have received antiretroviral therapy, pre-, intra- and/or postpartum to determine the impact of different feeding patterns on the risk of postnatal HIV transmission from mother to child;
- Study the preventive effect on HIV transmission rates of introducing the UNICEF/WHO breastfeeding counselling and training courses;
- Quantify the impact on HIV transmission, overall infant morbidity and mortality rates of different infant-feeding policies for HIV-positive women.

Funds are actively being sought for this proposal.

**THE FUTURE**

HRP and its network of collaborating centres have completed the initial phase of the implementation of the maternal health research programme focused on selected, priority maternal/pregnancy outcomes. After the consultation process and the preparation of the programme of work, which was approved by STAG in 1999, implementation of the planned activities was initiated. The multidisciplinary nature of the programme of work, the importance of the selected topics, plus HRP’s previous capacity-building efforts, make this research an important addition to HRP’s research portfolio. The year 2000 will focus on: (i) publishing the extensive material collected during 1997–1999 in leading medical journals and disseminating results at country and regional levels to the medical and public health communities; (ii) implementing the research projects that are in preparation; and (iii) exploring new research priority areas such as the prevention of MTCT of HIV infection. Finally, it is clear that there will not be any major breakthrough in the prevention of pregnancy-specific maternal morbidity such as pre-eclampsia, preterm delivery and prelabour rupture of membranes without new advances in knowledge on the pathophysiology of these conditions. Although it is not expected that HRP will provide substantial funding for this more basic research, it should take a leading role in the promotion of these needs to the scientific and funding communities. All new evidence from this research will be incorporated into the Department’s programmatic work, and contribute to improving health services and health conditions of populations in greatest need.
Annex 1

Recommendations based on systematic reviews prepared and updated during 1999 with support from HRP

**Beneficial forms of care**

— Zidovudine, nevirapine and/or delivery by elective Caesarean section in decreasing the risk of mother-to-child transmission of HIV infection.
— Antibiotic prophylaxis for women undergoing Caesarean section to reduce postoperative infectious complications.
— Vitamin A supplementation to very low-birth-weight babies to reduce intensive care stay and mortality.
— Routine iron and folate supplementation to prevent maternal anaemia at delivery or six weeks postpartum.
— Social support during labour in busy, technology-oriented settings on the need for pain relief and a positive labour experience.

**Forms of care likely to be beneficial**

— Antimalarial prophylaxis during pregnancy to primigravidae in endemic malarious areas to increase birth weight and reduce the incidence of low-birth-weight.
— Antimalarial prophylaxis during pregnancy in endemic malarious areas to reduce subsequent fever and sickness episodes.
— Antimalarial prophylaxis during pregnancy in endemic malarious areas to reduce maternal anaemia in late pregnancy.
— Balanced protein/energy supplementation during pregnancy to women with malnutrition or low calorie intake on reducing the number of low-birth-weight babies and increasing birth weight.
— Calcium supplementation to nulliparous women living in low calcium intake areas to reduce the rate of pre-eclampsia.
— Midwife/general practitioner-led antenatal care for low-risk women compared to specialist-led care, by lower costs without any increase in adverse events.
— Reduced number of antenatal care visits compared to higher number of visits in traditional antenatal care, by having no increase in adverse events.
— Social support during labour in busy, technology-oriented settings on lowering Caesarean section rates, number of infants with low Apgar scores (< 7 at 5 min) and duration of labour (shorter).
— Vitamin A supplementation to very low-birth-weight infants to reduce death and oxygen-treatment at one month of age.

**Forms of care with a trade-off**

— Vaginal misoprostol administration for induction of labour in doses of 25 µg (3-hourly) or more is more effective than oxytocin or other prostaglandins, but it is associated with increased fetal heart rate abnormalities and uterine hyperstimulation.
— Antimalarial prophylaxis during pregnancy in endemic malarious areas on preterm delivery and perinatal mortality.
— Screening and treatment for bacterial vaginosis to reduce preterm birth.
— Balanced protein/energy supplementation during pregnancy to women with malnutrition or low calorie intake on reducing preterm delivery, perinatal mortality and improving long-term neurocognitive development.

**Forms of care likely to be ineffective**

— Early amniotomy during labour in reducing Caesarean section rates.
— External cephalic version before term to reduce the incidence of breech presentation at delivery.
— Ketanserin for rapid lowering of very high blood pressure during pregnancy.

**Forms of care likely to be harmful**

— A policy of routine episiotomy to prevent perineal/vaginal tears compared to restricted use of episiotomy.
— Diazoxide for rapid lowering of severe high blood pressure during pregnancy because of severe hypotension.
— Forceps extraction instead of vacuum extraction for assisted vaginal delivery when both are applicable is associated with increased incidence of trauma to the maternal genital tract.
### Annex 2

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Annex 2 (continued)

RESEARCH GROUP ON MATERNAL HEALTH

Scientists in 1999

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Annex 3

RESEARCH GROUP ON MATERNAL HEALTH

Publications in 1999


Annex 3

RESEARCH GROUP ON MATERNAL HEALTH

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Gülmezoglu AM, Hofmeyr GJ. Nutrients for impaired fetal growth.
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Mahomed K, Gülmezoglu AM. Vitamin D supplementation in pregnancy.
Villar J, Lydon-Rochelle MT, Gülmezoglu AM. Drugs for the treatment of asymptomatic bacteriuria during pregnancy.
Maternal and perinatal health

Implementation of evidence-based programmes

M.K. Usher-Patel, J. Zupan, R. Guidotti, L. de Bernes, M.Q. Islam
INTRODUCTION

Since 1987, the Safe Motherhood Initiative has contributed to an increased emphasis on clinical and operational research in the area of maternal and perinatal health. There is greater knowledge today than there was in 1987 as to what works and what does not in improving maternal and newborn health. WHO has contributed both to research and promotion of research results via advocacy and to the development of guidelines.

The Department and its collaborating partners have been responding to the conclusions and recommendations of the Inter-Agency conference, held in Colombo, Sri Lanka, in November 1997 that reviewed lessons learnt from implementing safe motherhood over the last decade. In addition, to give greater emphasis to safe motherhood, the ICPD+5 session of the United Nations General Assembly in June 1999 urged “WHO to fulfil its leadership role within the United Nations system in assisting countries, in particular developing countries, to put in place standards for the care and treatment for women and girls ....to reduce the risks associated with pregnancy.....”

The approaches currently being developed build on the Mother–baby package (WHO, 1994) and provide a set of guidelines, adaptation guides and training material, with a clear strategy for implementation. The following pages describe current efforts: (i) to strengthen evidence for programmes; (ii) to improve and increase services through Integrated Management of Pregnancy and Childbirth (IMPAC); and (iii) to collaborate with other agencies to increase the application of existing knowledge globally.

PROGRESS

Strengthening evidence for programmes

During the 1990s, WHO has organized a consecutive series of Technical Working Group meetings on programmatic aspects of maternal and neonatal health care. A group of experts would analyse the outcome of an extensive literature review to arrive at conclusions and make recommendations regarding the type of care that should be provided for specific technical interventions. The outcome of these meetings are normally published as a practical guide in 1999. The Department continued this process of technical consultations to address the following issues.

Health care for adolescents mothers

Jointly with the former WHO Division of Reproductive Health (Technical Support), the former WHO Unit of Adolescent Health had commissioned four background papers to review the evidence for modifying the health care provisions for adolescents. Areas included maternal–newborn health, family planning, abortion and sexually transmitted infections (STIs). With the exception of the paper on family planning, the other three were completed in 1999, and were issued by the WHO Department of Child and Adolescent Health and Development.

In the area of adolescent maternal health, the review revealed gaps in published information from developing countries, necessitating the need to contact experts from developing countries; this helped to retrieve unpublished research data from those countries. These efforts assisted in the development of the Essential Care Practice Guides which outline the special features required to provide appropriate reproductive health services for adolescents.

Micronutrient supplementation in pregnancy and postpartum

A meeting was held in 1998 to discuss the possibility of introducing multimicronutrient supplementation in pregnancy. The meeting concluded that in addition to iron, folic acid and vitamin A, research efforts should consider other micronutrients as well. A second workshop, sponsored by WHO and UNICEF, was held to present data on a multimicronutrient supplement and to debate the feasibility of recommending it during pregnancy. The issues discussed focused on existing evidence regarding the different elements that would go into such a preparation together with their dosages and the required composition of such a supplement. The panel of experts suggested various combinations of multimicronutrient supplementation in pregnancy, and recommended that both WHO and UNICEF conduct research in this area.

In November 1999, a technical consultation reviewed the evidence on the efficacy and effectiveness of intermittent iron supplementation (weekly) in the control of iron-deficiency anaemia in pregnant women, concluding that daily rather than weekly iron supplementation should still be promoted during pregnancy. The Department, together with the Departments of Nutrition, Child and Adolescent Health and Development, and the WHO Team for Vaccine Assessment and Monitoring is planning to hold a consultation in early 2000 to review the evidence on vitamin A supplementation in pregnancy, the postpartum period and infancy, particularly with respect to new issues related to HIV transmission and safety concerns.

Postpartum care

A literature review was prepared and presented as a background paper for a Technical Working Group meeting convened to define essential interventions that should be provided to women and newborn infants during the postpartum period. The report of this meeting was published as a practical guide in 1999.
The postpartum period (up to seven days after giving birth) has been neglected with regard to operations research, in spite of the fact that a majority of maternal deaths resulting from complications during labour and delivery taking place within this time-frame. The evidence on which to base programmatic recommendations for the first critical week after birth is quite limited. Further evidence is needed in this area, including testing different approaches that can be used to reach postpartum women who have complications such as anaemia, haemorrhage, sepsis or eclampsia. Recommendations are being made in the Essential Care Practice Guides, and will eventually be validated and evaluated in that context.

**Active management of the third stage of labour**

Studies in the developed world have proved that the active management of the third stage of labour reduces postpartum bleeding. However, research is needed on how best to introduce this intervention in developing countries.

To address the question in a resource-poor setting and at the same time analyse the potential of using a prefilled device to deliver a specific dose of oxytocin, the Department is supporting a study on the routine use of oxytocin in prefilled injection devices (Uniject) for the active management of the third stage of labour in Luanda, Angola. The study is expected to be completed during 2000.

**Improve and increase services through Integrated Management of Pregnancy and Childbirth (IMPAC)**

The Department’s new initiative entitled Integrated Management of Pregnancy and Childbirth (IMPAC), represents an innovative and far-reaching strategy for reducing maternal and perinatal mortality and morbidity, and improving maternal and newborn health. IMPAC’s approach is designed to apply evidence to support technical and clinical interventions.

The overall aim of the strategy is to provide countries with a cohesive management plan to help local health systems, families and communities improve their practices and responses with respect to pregnancy and delivery. It does so by (i) setting norms and standards of care, (ii) helping countries evaluate health systems requirements and community practices and (iii) providing an implementation strategy.

The strategy focuses on three areas: (i) improving the skills of health workers through locally adapted guidelines and standards for the management of pregnancy and childbirth at different levels of the health system, and activities to promote their use; (ii) interventions to improve the response of the health systems and district level management of health services, including the provision of adequate staffing, logistics, supplies and equipment; and (iii) health education and promotion activities to improve family and community practices and responses in relation to pregnancy and childbirth.

A key element of Step I of the IMPAC strategy is to develop standards and norms which will improve the skills of health workers. To achieve this objective, two Essential Care Practice Guides have been prepared:

- **Essential practice guide for maternal and newborn care**
- **Management of complications in pregnancy and childbirth.**

These guides have their origins in the *Mother-baby package* launched by WHO in 1994 as one of the first attempts to bring together in one conceptual framework the interventions necessary to improve the quality of maternal and neonatal health care. The Guides are a synthesis of the latest information on essential interventions that appear to have the greatest impact on reducing maternal and neonatal mortality. The Essential Care Practice Guides aim to provide a set of tools that will facilitate the implementation of the *Mother-baby package* from peripheral health units upwards. They are targeted at an audience with at least one year of pre-service training.

The document **Essential practice guide for maternal and newborn care** is a comprehensive manual defining optimum clinical practice. As a cornerstone of the Department’s work on raising standards, it enables health care providers to make the most appropriate decisions for women during pregnancy, delivery and the postpartum period. It also covers counselling and advice and linkages to other interventions at the first level of health care. Work on the *Essential practice guide for maternal and newborn care* has been progressing steadily since 1997. Task lists for essential care in health posts and health centres were developed in late 1997 and, throughout 1998-1998, the scientific evidence was reviewed in order to resolve technical questions in a number of critical areas such as prevention and treatment of malaria, treatment of intestinal parasites, screening and treatment of STIs and anaemia, and prevention and treatment of pre-eclampsia/eclampsia. Consecutive drafts of comprehensive charts and algorithms for the pregnancy, delivery and post-pregnancy components of the guides have been produced. They deal with obstetric first aid, antenatal care, postnatal care and post-abortion care, as well as delivery and newborn care.

The document **Management of complications in pregnancy and childbirth** has been developed for use by doctors, midwives and other senior health workers responsible for the inpatient care of pregnant women. Its approach is symptom-based and focuses on the emergency care of women and newborns suffering complications during pregnancy, delivery or in the immediate postpartum period.
Thus, the manual is targeted for use in district hospitals, which are defined as facilities that can provide comprehensive obstetric care, including operative delivery and blood transfusion. Work on the manual began in 1997 and since 1998 has involved close collaboration with JHPIEGO. A meeting hosted by JHPIEGO in 1999 reviewed the manual and discussed the most effective way to distribute it to health workers in district hospitals. An Internet working group was set up to provide feedback on changes suggested during the review meeting. The final stages will involve a thorough outside review and an initial print run of 10,000 copies in English. Plans include translation of the manual into other languages and the development of accompanying reference and training materials. The Management of complications in pregnancy and childbirth will be actively disseminated through, among others, WHO’s Regional and Country offices, professional organizations, United Nations agencies and NGOs with safe motherhood programmes in countries, and via partners in the Safe Motherhood Initiative.

A package to improve health systems’ capacities for implementing these norms is being developed simultaneously with the preparation of materials to improve family and community practices relating to pregnancy and childbirth.

The three-stage IMPAC strategy is designed to be adapted to local situations and to be implemented in countries by governments in collaboration with United Nations and bilateral agencies, professional bodies, NGOs, and other organizations within the context of prevailing needs and priorities in the country.

Midwifery training modules

To help improve midwifery skills of nurses and midwives, and in turn to enable countries to improve the quality of, and access to, maternal and newborn health care services, a set of six midwifery training modules (five training modules and a foundation module) were issued by WHO in 1996. The need for these modules was identified by midwives and teachers of midwives from around the world who attended the Pre-Congress Workshop on Midwifery Education held in Kobe, Japan, in 1990, under the joint sponsorship of WHO, the International Confederation of Midwives (ICM) and UNICEF (see also “Guidelines for strengthening midwifery”).

The modules address the skills needed to deal with the major causes of maternal mortality, such as haemorrhage, obstructed labour, puerperal sepsis and eclampsia. Each module is self-contained and can, if necessary, be taught independently of the other modules. In 1998, in response to a request from countries, the Department developed a set of student notes to accompany the modules. In 1999, the Department initiated a revision of the manuals in accordance with the feedback received from the end-users. The ongoing technical updating of the modules will ensure that they are consistent with the Essential Care Practice Guides and the manual on the Management of complications in pregnancy and childbirth.

An new module on postabortion care is being prepared. During 1999, this module was being reviewed in response to feedback received from internal and external reviews. Field-testing of this module is planned in Uganda in 2000. In addition, during 1999, the Department developed a Procedural guide on vacuum extraction that is currently under external review. In 2000, revised editions of the six midwifery modules will be issued, along with the revised module on Post-abortion care and the Procedural guide on vacuum extraction.

Managerial tools to strengthen the capacity of the health care system

To operationalize IMPAC, it will be necessary to develop tools that support the formulation of national policies, and programmatic guidelines and the overall strengthening of the health care system. These tools will include the following:

District managers’ planning process

The development of a planning tool for use by district health management teams was started in 1997. The purpose of this tool is to support the process of decentralization by providing a framework for problem-solving and planning that enables managers to work with other stakeholders to prioritize and seek solutions to operational problems.

The tool, developed by the Department during 1998–1999, is currently in the form of two mini-workshops in which a group of local senior managers are first trained as facilitators and supportive supervisors of the district management team. These senior managers then act as the facilitators for a five-day problem-solving workshop for the district management team, the outcome of which is an action-oriented plan of work. This is then reviewed at specific intervals and periodically followed-up by the facilitators.

The tool has been field-tested in two districts in Uganda. After field-testing it was found that there had been an improvement in the capacity of the district management team to generate and sustain the implementation of realistic district plans.

In 2000, it is planned to undertake final field-testing of this tool in the WHO South-East Asia Region. Since similar management tools are also being developed in other WHO Departments close contact is maintained for sharing information. This has led to the identification of key
principles for developing managerial tools and a generic "toolbox" that is designed to build capacity within the health care system to support priority health interventions.

Guidelines on conducting case reviews of maternal deaths

A key challenge for safe motherhood programmes is to improve the quality of obstetric care provided at health care facilities. Achieving high quality care depends on many factors, including the availability of sound information upon which to base decisions and an understanding of factors—clinical, socioeconomic and cultural—that adversely affect the quality of care women receive. In developing the Guidelines on conducting case reviews of maternal deaths, the aim is to assist decision-making and improve quality of care by enhancing information flow within health care facilities and strengthening outreach to the community. The project tests two approaches to meet these information needs, namely, the maternal death case review and sentinel events reporting.

In 1999, at the request of the WHO Regional Office for the Western Pacific, technical support on the maternal death audit was provided to China and Mongolia. In China, a three-day workshop was held in August 1999, at the Obstetric and Gynaecology Hospital, Beijing. The field-tested English version of the guidelines on maternal death review was translated into Chinese and it was decided at the workshop that the WHO module would be adapted to the present reporting system of maternal deaths in China. Field-testing of the adapted guidelines would be undertaken in selected municipalities. Likewise, in Mongolia, a workshop was held in Ulaanbaatar in 1999 to present the WHO guidelines on maternal death audit and to discuss how best to adapt them to the local situation. A review of the national maternal mortality information card was carried out during the workshop and participants suggested adding community factors, delays in referral, and coding for computer analysis. The new information card will be field tested before being formally adopted.

In coordination with the WHO Regional Offices for Europe and South-East Asia, a meeting was held to plan the development of comprehensive guidelines for investigating maternal mortality. The objectives of the meeting were to define both the structure as well as the contents of the guidelines. Participants developed a detailed annotated workplan and agreed on responsibilities for developing the various sections of the guidelines. In 2000, it is planned to hold a meeting in the WHO Regional Office for South-East Asia to finalize these guidelines.

Sentinel events reporting is an innovative approach, which has not yet been field tested. Uganda will be the first country participating in its assessment during 2000. One of the outputs from the assessment will be a manual to complement the maternal deaths case review manual.

Guidelines for strengthening midwifery

Evidence suggests that the presence of a skilled attendant at birth is one of the most important ways of reducing maternal and neonatal mortality and morbidity. This means that strengthening midwifery services and increasing access to staff with midwifery skills is a vital intervention in the battle to reduce maternal and neonatal mortality and morbidity. Yet, during the last decade, the presence of a skilled attendant at birth has only increased marginally, from 51% to 53%.

To assist countries in strengthening their midwifery programmes by defining or redefining the role of the midwife, determining the required levels of competency and proficiency and identifying the regulatory, legislative and training requirements, the Department, in close collaboration with ICM, is producing the following package of materials:

- a generic midwifery curriculum
- a teachers’ training programme
- a standard-setting process to establish standards of practice and specify levels of competency
- guidelines on regulation and legislation.

These are presently being edited for an external review. The final products will be made available to all partners in the Safe Motherhood Initiative and will also be distributed at major international meetings on reproductive health as well as through normal WHO distribution channels.

Mother–baby package costing spreadsheet

WHO developed the Mother–baby package costing spreadsheet to assist in estimating the cost of implementing a set of interventions at the district level.

The Ugandan Government is implementing a comprehensive safe motherhood programme based on the Mother–baby package in an effort to reduce the high levels of maternal and neonatal morbidity and mortality in the country. In order to provide programme planners with a better appreciation of the costs of implementing the package, a costing study was carried out by the Ministry of Health using the Mother–baby package costing spreadsheet.

The spreadsheet proved very useful to national authorities, donor governments, and other partners at the national level in considering and addressing the substantial cost implications of providing higher-quality maternal and newborn care. For example, the results proved invaluable in discussions in the planning group of the Ugandan Ministry of Health, in advocating an increased budget.
allocation for safe motherhood interventions. In addition, in the context of the development of a new national budget, the estimates were used to validate and in some cases increase the budget allocations for certain lines relating to maternal health. The results of the costing spreadsheet also served as a key input into the Uganda National Health Strategy and its “minimum package” cost estimates. Finally, when decentralized district-level budgets are developed, the estimates will be used again to advocate an increased allocation for maternal health.

A dissemination workshop was held in Uganda with the participation of national parliamentarians, the Director-General of Health Services and other staff of the Ministry of Health, senior district health personnel, and major partners in maternal and newborn health at the national level. Results were presented and discussed, along with strategies for addressing the identified resource “shortfall” of US$ 1.30 per capita. Draft recommendations were developed.

The spreadsheet and its application in Uganda proved invaluable in facilitating an important dialogue on maternal and newborn health care financing and sustainability issues. In 1999, the results of the Uganda study were published as a WHO document, Mother–baby package costing study in Uganda, as well as in the Safe motherhood initiatives: critical issues, published by Reproductive Health Matters, London, United Kingdom.

Community issues in reproductive health

Guidelines are currently under development which form the community component of the Essential Care Practice Guides. This foundation document will present key steps for creating/strengthening linkages between health care service providers and community members to improve reproductive health outcomes. The following general principles that are common to creating these linkages for obstetric care, the care of reproductive tract infections, and family planning services will be included:

- Getting to know the community (exercises for learning about various aspects of community life, i.e. identifying community leaders, various committees and groups, food availability, sources of income, etc.)
- Improving quality and access to care (exercises for improving provider–client interaction and community expectation for quality services)
- Learning about informal options for health care
- Establishing an emergency transport system (including advice on what steps a health care provider can take to facilitate this process)
- Establishing a community-based financial scheme for obstetric emergencies (including advice on the steps a health care provider can take to facilitate this process)
- Establishing linkages with the informal health care sys-

The guidelines will be prepared and ready for field-testing by the end of 2000.

Collaboration with other agencies and professional organizations

The Department has close ties with partners participating in the Inter-Agency Group for Safe Motherhood. In addition, the Department has a close collaboration with two key professional organizations, ICM and FIGO, which have now also become members of the Inter-Agency Group for Safe Motherhood.

Collaboration with ICM includes: regular information sharing on ongoing projects; representation at ICM Executive Board meetings, pre-congress workshops and congresses. In 1999, ICM held their Triennial Congress in Manila, Philippines, where WHO was a key partner and co-hosted the Pre-Congress Workshop on the Midwife’s Role in the Management and Prevention of STI/HIV/AIDS.

Planning for the development of global WHO–ICM–FIGO standards for midwifery competencies, based on the standards established by the WHO Regional Office for South-East Asia, is under way. A WHO/ICM session on skilled birth attendants is planned for the FIGO 2000 Congress.

WHO co-chairs the WHO/FIGO Task Force on maternal Health, which meets regularly with representatives of the other major United Nations agencies dealing with reproductive health. WHO has contributed to the planning of several sessions of the FIGO Congress in 2000, as well as to the planning of the Pre-Congress Workshop which will focus on emergency obstetrics care.

WHO is also represented on the Steering Committee of FIGO’s “Save the Mothers Fund” project, which is attempting to improve care of obstetric emergencies in selected district hospitals of a number of developing countries under the auspices of twinning projects (a developing country obstetric–gynaecology society working with a sister society in a developed country). Even though the project is limited in scope, it is hoped that it will be strategically significant in helping to draw increased global attention of professionals to the huge unmet need in this area.

In 1999, WHO published Reduction of maternal mortality: a joint WHO/UNFPA/UNICEF/World Bank statement. The heads of these United Nations agencies launched the document at a press conference in October 1999. The Statement synthesizes the understanding of
what is needed to reduce maternal and newborn mortality, based on lessons learned over many years of work. It provides the contextual framework for United Nations agencies to collaborate in maternal and newborn health, especially at the country level. Plans for such work are being developed in the context of WHO’s accelerated efforts reflected in WHO’s new initiative on Making Pregnancy Safer.

THE FUTURE

The merging of HRP and the former WHO Division of Reproductive Health (Technical Support) has provided the opportunity to review the validity of the process used to promote “best practices” in reproductive health. It has been agreed to review present recommendations and ensure that all future consultations and publications are based on systematic reviews of the literature, including meta-analysis when appropriate. Depending on the strength of the evidence, a grade will be provided for major recommendations.

The Department is currently organizing an extensive external and internal review of the Essential Care Practice Guides, in which reviewers are being requested to address a series of generic issues, such as applicability, clarity and consistency of the approach used in the diagnostic chart booklets. In addition, departments within WHO and over 80 external reviewers have been asked to review specific components of the chart booklets which pertain to their particular area of technical expertise. The feedback received will be collated and the chart booklets revised in areas where consensus has been reached by the reviewers. A technical consultation will then be held to discuss the outcome of the review and take decisions on areas where no agreement could be reached during the review process. Simultaneously, work will continue on the development of the Essential Care Practice Guides for other components of reproductive health care, such as family planning, adolescent health needs, nutrition and the management and prevention of STIs/HIV/AIDS in pregnancy.

During the process of revising the chart booklets, the Department will work together with several collaborating research centres to develop the protocol and procedures to undertake validation studies of specific algorithmic flowcharts contained in the chart booklets. The purpose of the validation studies is to determine the sensitivity, specificity and likelihood ratios of the diagnostic flowchart. The Essential Care Practice Guides will be revised in the light of the outcome of these studies.

In addition to the validation studies, the Essential Care Practice Guides will be field tested in countries to determine what processes must be used to ensure that the Guides are appropriately introduced, adapted and utilized. The selection of countries and preparation for the field tests will be undertaken in collaboration with WHO Regional Offices and partner agencies during 2000. These field tests are, however, dependent on the completion of the validation studies, technical basis papers and the adaptation guidelines.

Work will commence on the development of a detailed training strategy and materials for each level of the health care system. It is envisaged that the generic training process will be competency-based and aimed at changing the existing standards of practice, where needed. Since this strategy is a generic tool, it will be designed to be flexible so that it can be adapted to meet specific priority-training needs of individual countries. The strategy will incorporate a wide spectrum of training approaches so that countries can use it in a variety of different ways, such as for developing continuous educational programmes, distance learning, upgrade programmes, in-service and post-basic training programmes, and pre-service training.

In 2000, WHO will start, in collaboration with partner agencies, Regional Offices and WHO Country Representatives the detailed planning process for implementation of the IMPAC strategy.
Unsafe abortion

OBJECTIVES

The 1994 International Conference on Population and Development (ICPD) described unsafe abortion as a “major public health concern” (ICPD Programme of Action, paragraph 8.25). Approximately 45 million abortions occur globally each year, over 40% of which are estimated to be unsafe. Unsafe abortions are estimated to account for 13% of all maternal deaths and, in some countries, as many as 40% of all maternal deaths. WHO has long advocated for attention to the issue of unsafe abortion, including focused efforts to investigate the determinants and consequences of abortion; establish norms and standards for the effective management of complications due to unsafe abortion; develop technical, managerial and clinical guidelines for abortion services; provide guidance for postabortion family planning services; and prevent unsafe abortion through research and development in the area of fertility regulation and non-surgical abortion.

The Department has identified unsafe abortion as a thematic area for renewed and consolidated efforts, with the ultimate goal of eliminating its occurrence. This goal is to be achieved by undertaking, in a systematic manner, activities that involve all Departmental Teams. In the area of unsafe abortion, the objectives of the Research and Evidence Team are: (i) to document the global dimensions of unsafe abortion by gathering, analysing and disseminating information on the magnitude of unsafe abortion, its determinants and the groups of women most affected; (ii) to develop improved methods of non-surgical abortion and fertility regulation; (iii) to investigate ways to improve services that address women’s needs for abortion-related care; and (iv) to implement, monitor and evaluate a range of programmatic activities related to unsafe abortion. The Team for Development of Norms and Tools aims to develop guidelines for the safe use of non-surgical methods of pregnancy termination with mifepristone and misoprostol. The Team for Technical Support to Countries aims to build capacity for research and promote national and multicountry studies. The Department intends to convene a technical consultation on preventing and addressing unsafe abortion and will continue to disseminate relevant resource materials.

PROGRESS

The Department’s work on unsafe abortion is summarized below by contribution of each of the Teams.

Research and evidence

Estimating the magnitude of unsafe abortion

The number of abortions, abortion-related morbidities, and deaths due to abortion are among the most difficult reproductive health indicators to estimate. The Department, through its Reproductive Health, Maternal and Newborn (RMN) database, compiles data to generate such estimates at the global and regional levels. Global and regional estimates for the incidence of unsafe abortion and associated mortality were last released in 1998: 45 million abortions occur globally each year, over 40% of which are estimated to be unsafe. In 1999, these estimates were incorporated in a publication by the Alan Guttmacher Institute entitled Sharing responsibility: women, society and abortion world-wide.

The primary rationale for the indicator databases is to provide source material for WHO estimates of maternal and newborn health indicators. The details of these databases and the methodologies used to generate these estimates are given in the chapter on “Planning and programming for reproductive health”. Information on unsafe abortion is routinely collated, reviewed and analysed and the database on unsafe abortion is continuously updated. Because of the sensitive nature of the information, every effort is made to locate as much information as possible to generate various estimates of incidence, mortality ratios and rates. Updated estimates of abortion-related mortality will be completed in 2000 to account for new estimates of maternal mortality. Efforts are under way to develop global estimates of unsafe abortion during adolescence. Collaboration with the Alan Guttmacher Institute has been particularly helpful in documenting the overall context of abortion.

Documenting abortion-related morbidity and mortality

HRP has conducted a series of hospital-based studies in Bangladesh, Benin, Brazil, Cameroon, Chile, Ethiopia, Guatemala, Senegal, Thailand and Uganda to document the morbidity and mortality caused by unsafe abortion and the cost to health care services. Following a workshop intended to promote scientific writing and preparation of manuscript(s) on these studies in West Africa, a paper was written by the investigators from Benin, Cameroon and Senegal with assistance from INSERM, Paris, France. Results from these three countries that participated in the prospective hospital-based study on complications of abortion showed that, of the 1957 women admitted, 988 had experienced a miscarriage and 969 had an induced abortion. Significant differences were observed according to the gestational age in cases of miscarriage. Differentials, by use of contraception and educational level, were also observed in cases of induced abortion. A total of 26 maternal deaths were recorded, of which 22 were associated with unsafe abortion. Signs of infection were the largest risk factor for death.

Understanding the context of abortion

As early as 1989, HRP launched a pioneering effort to
understand the determinants of a woman’s decision to abort a pregnancy in various cultural, social, programmatic and legal contexts. Twenty-three studies were supported in 15 developing countries (Brazil, Chile, China, Colombia, Cuba, Dominican Republic, Indonesia, Republic of Korea, Mauritius, Mexico, Nepal, Philippines, Sri Lanka, Tanzania and Turkey). The studies dealt with issues such as the relationship between abortion and contraception, the quality of abortion care from women’s and providers’ perspectives, adolescent sexuality and abortion, research methods to understand factors leading to induced abortion, issues for future research, and implications for policy.

The studies were published in 1999 in a book entitled *Abortion in the developing world* (Mundigo AI, Indriso C, eds.). The book has been published simultaneously in India, the United Kingdom and the USA and presents the best available scientific evidence to date on the determinants of induced abortion in a variety of developing countries. In its final chapter, the book also contains a discussion on policy implications, public debate and the provision of family planning services to women who had undergone an abortion. A Press Release issued by WHO in May 1999 highlights the main findings. Research supported under this initiative was instrumental in understanding the context of abortion. In Myanmar, the recently completed project entitled “Factors Determining Induced Abortion” aimed: (i) to compare, among women who have had an unplanned/unwanted pregnancy, characteristics of women who have an induced abortion with those who continue the pregnancy to term; and (ii) assess factors underlying the decision to opt for induced abortion.

The study compared 600 women seeking treatment for abortion complications with 900 women delivering “unplanned” pregnancies. Study participants were residents of North Okkalapa and other townships within the Yangon City Development area. Findings shed light on a number of issues related to unintended pregnancy in the context of highly restrictive access to abortion. A comparison of the background characteristics of the two groups of women revealed that abortion-seekers are more often unmarried (10% vs 1%), more often have had five or more pregnancies (28% vs 18%), and are more likely to be repeat abortion-seekers (26% vs 6% had two or more abortions). Abortion-seekers are also less often dependent on others for financial support (52% vs 71%).

Although between one-sixth and one-fifth of women in both groups maintain that abortion is widespread in their communities, their attitudes toward abortion and contraception vary. Generally, abortion-seekers report more favourable attitudes to abortion than women who deliver. For example, they are more likely than the group of women who deliver to accept women resorting to abortion in cases of untimely pregnancies (44% among abortion-seekers vs 3% among women who delivered), economic difficulties (52% vs 12%), pregnancy among the unmarried (24% vs 19%), and contraceptive failure (15% vs 4%). Moreover, women who sought abortion were more likely than women who delivered to perceive that abortion procedures were easy to procure (13% vs 2%), were not dangerous (10% vs 2%), cost less than a normal delivery (37% vs 11%), and did not violate religious tenets (93% vs 86%). The experience of abortion also raises concerns: all abortion-seekers in the study had been hospitalized with major complications of abortion, yet 14% supported the widespread use of abortion to regulate fertility (compared to 11% of women who delivered), around one-fourth of abortion-seekers had experienced two or more abortions in the past, and a considerable percentage (17%) viewed abortion as an appropriate method of contraception (compared to less than 1% of women who delivered). The study highlights the need to provide contraceptive information and services to all women, including the unmarried.

Induced abortion is permitted in Sri Lanka “only when the act is done in good faith for the specific purpose of saving the life of the mother”. A study, currently ongoing in the Colombo district, is intended to explore the abortion situation as experienced by both providers and women themselves. In the first phase of study, 119 health professionals responded to a self-administered questionnaire that ascertained their experiences. All providers stated having had experience in dealing with complicated cases of abortion or having provided postabortion counselling and services. Providers reported, moreover, that a significant minority of abortion-seekers are unmarried (16%), the majority are in their twenties (54%), and over half are unemployed (53%). The second phase, comprising a household survey of 1500 married women, will be fielded in early 2000 and will provide information on the incidence and experience of abortion among women living in the Colombo district.

Despite the fact that abortion is widely practised in Eastern Europe, few studies have systematically explored the experiences and motivations of women undergoing abortion in these countries. A multicountry study,
“Determinants of the Choice and Use of Fertility-Regulating Methods in East European Countries” explored the context of induced abortion, including the characteristics of women who seek abortion, factors underlying abortion, perceptions of contraceptives, and service- and provider-level constraints. The study, jointly supported by the Scientific Working Group (SWG) on Reproductive Health in Eastern Europe and HRP’s Group on Social Science Research on Reproductive Health, was conducted in five settings: Armenia (Yerevan), Georgia (Tbilisi), Lithuania (Kaunas), Romania (Targu-Mures) and Russia (Moscow, Djukovsk, Smolensk). Samples were drawn from various health facilities providing obstetric and gynaecological services. Study populations included: (i) 1496 women opting for abortion; (ii) 1123 women using a modern contraceptive method; and (iii) all (43) providers of abortion and contraceptive services in the centres included in the study. Abortion-seekers and contraceptive users were selected randomly from the list of daily appointments.

The study describes the context of induced abortion in participating countries. Abortion on demand has been legal in all participating countries since 1955 (except in Romania), and abortion rates (per 1000 women) in the late 1990s ranged from 22 to 33; rates among adolescents were higher (for example, 44 per 1000 women in Russia). Findings confirm that abortion is common in all centres, among women who had currently sought abortion and those who were currently practising contraception. Repeat abortions were not unusual: 40%–50% of current abortion-seekers, and 33%–60% of those currently practising contraception had experienced an earlier abortion. Socioeconomic and demographic characteristics of the two groups were similar in terms of age, parity, education, marital status and religion. Notably, 25% of abortion-seekers are nulliparous, about 16% are adolescents (aged 10–19 years), and 43% are aged 25 years or less.

Reliance on abortion as a method of fertility regulation in this region is evident from the reported contraceptive patterns. Over half (54%) of the abortion-seekers were not using any contraceptive method prior to experiencing the unintended pregnancy; and three in four of those who were practising contraception were using a traditional method (largely rhythm). Even among those who had previously experienced an abortion, about one-third (ranging from 27% in Moscow to 57% in Targu-Mures) did not practice contraception consistently. Abortion is, moreover, used both to limit and to space births. Finally, almost half underwent abortion as a consequence of contraceptive failure (46% of the sample reported using a method at the time they became pregnant).

Awareness of the range of contraceptives, their advantages and disadvantages, and sources of supply is incomplete. Although women seem to be aware of the IUD, oral contraceptives and condoms (less so in Yerevan), two-thirds of all respondents indicated that they had insufficient knowledge about contraception, and one-third did not know where to obtain more information. Only 45% (ranging from 24% in Yerevan to 69% in Moscow) had ever received information on contraception from a provider. Of these, 28% were dissatisfied with the information received (ranging from 5% in Yerevan and Tbilisi to 51% in Moscow). A large percentage of women (38%) reported discontinuation of modern methods in the past as a result of side-effects.

Women reported a variety of reasons for the non-use of modern contraceptives, including: (i) reliance on the husband to use the method (34% of abortion-seekers stated that they relied on the husband to use a method to avoid pregnancy); (ii) the belief that they would not become pregnant (31%); (iii) unanticipated or infrequent sexual relations (24%); (iv) fear and/or experience of complications, and preference for traditional methods (15%); (v) dislike of the condom, oral contraceptives and the IUD; (vi) cost, distance to source, and lack of supplies at the facility (8%); and (vii) indecision or not fully appreciating the risk of unprotected sex (19%).

Assessing the impact of interventions

A study is ongoing in the Matlab district of Bangladesh in which a comprehensive Maternal and Child Health–Family Planning (MCH–FP) project has been in existence since 1977 in half of the area (MCH–FP Project area), and the usual governmental family planning and MCH services have been provided in the other half (Comparison area). The MCH–FP Project initially provided menstrual regulation services, but discontinued them in 1984. Menstrual regulation services are routinely provided at the government clinics in the Comparison area.

This study is based on an analysis of primary and secondary data. Secondary data were obtained from the Matlab Demographic Surveillance System (DSS) and the Record Keeping System (RKS) of the Centre for Health and Population Research of the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) Centre for Health and Population Research. In the DSS, data on births and other pregnancy outcomes including abortions (since 1978), deaths, marriages (since 1974), and migration have been collected since 1966 for 2 00 000 residents. The investigators collected primary data from 194 women who had undergone an abortion in 1997 in the DSS area to gain information on postabortion complications, and conducted in-depth qualitative case studies to understand the community’s perception of abortion.

Findings suggest that, at the beginning of the MCH–FP Project in 1977, the demographic and socioeconomic conditions of the two areas were similar. Between 1989 and 1997, 2206 abortions were reported in both the MCH–FP
Project and Comparison areas. Nearly half (975) of these were performed using traditional, mostly unsafe, methods. The mean length of pregnancy at abortion was significantly shorter (2.8 months) in the MCH–FP Project area than in the Comparison area (3.0 months).

Trends of abortion rate, contraceptive prevalence rate and the total fertility rate in the MCH–FP Project clearly suggested that rates of induced abortion are consistently lower and contraceptive prevalence consistently higher in the integrated MCH–FP Project area than in the Comparison area. The investigators contend that the MCH–FP Project influenced fertility norms and promoted contraceptive use.

The number of abortions per 1000 live births was also higher in the MCH–FP area than in the Comparison area at the beginning of the MCH–FP project. However, this abortion ratio started to decline in the MCH–FP area and soon became significantly lower than that in the Comparison area, where it continued to rise. There was a substantial increase in the level of contraceptive use in the MCH–FP Project area as compared to the Comparison area. By 1996, the prevalence of contraceptive use had reached almost 70% in the MCH–FP Project area as compared to about 50% in the Comparison area. The use of modern methods of abortion, including menstrual regulation, was slightly higher in the MCH–FP Project area than the Comparison area. The investigators concluded that the MCH–FP Project reduced abortions by reducing unwanted need for contraception and unwanted pregnancy. Frequent contact with MCH–FP workers may help women who opt for abortion or menstrual regulation to obtain services earlier in the pregnancy. However, in the absence of abortion or menstrual regulation services, the MCH–FP Project may not significantly reduce the proportion of unsafe abortions, even if abortions are fewer than in the Comparison area. As stated earlier, in the MCH–FP Project area, menstrual regulation services were not provided after 1984, whereas they are routinely available at government family planning clinics in the Comparison area. Results from interviews with 194 women who had an abortion and qualitative case studies are expected to shed light on postabortion complications and community perceptions of abortion.

In China, an intervention study examined the effect on unintended pregnancies of introducing emergency contraception among young workers. The study was carried out among young women below the age of 30 years who were working in six supermarkets in Zhengzhou city of Henan province. The six supermarkets were randomly divided into intervention (3) and control (3) groups. The package of interventions was developed on the basis of in-depth interviews and focus group discussions among the workers and health personnel of the three supermarkets in the treatment group. Female medical workers of the existing health and family planning services in the supermarkets of the treatment group were trained to provide information, counselling and emergency contraceptive services. Interventions were introduced over a period of two years and included: (i) a 24-hour telephone hotline and 24-hour emergency contraception services at the Henan Research Institute of Family Planning (HRIFP); (ii) “over-the-counter” provision of specially packed emergency contraception pills through designated pharmacies; and (iii) on-site (at the supermarket) counselling, dissemination of printed material, lectures, and playing of video cassettes. The address, telephone numbers and working hours of the pharmacies and HRIFP were widely distributed among workers in the intervention group.

Prior to the implementation of the intervention, a baseline survey was conducted among 1550 women each in the intervention and control supermarkets. A follow-up survey was undertaken in August 1999. Preliminary findings suggest that women’s attitudes toward emergency contraception became more positive, availability of emergency contraception for young women expanded and their use increased significantly in the intervention group (from 3% using at baseline to 14% using at last follow-up). The use of emergency contraception remained low and was 3% at follow-up in the control group. In the follow-up survey, a lower percentage of women reported contraceptive failures in the intervention group (18%) than in the control group (27%). Analysis of unintended pregnancies and the incidence of induced abortion is underway. Preliminary findings suggest that in the year prior to the last follow-up, abortion was experienced by a lower percentage of women in the intervention group (2.1%) than in the control group (3.7%) and the decline in the incidence of abortion between baseline (1997) and last follow-up (1999) was greater in the intervention group than in the control group (7.6% to 2.1% vs 4.9% to 3.7%).

The successful implementation of the project and the qualitative assessment of the feasibility, acceptability and effectiveness of introducing emergency contraception have led the supermarket and HRIFP authorities to continue intervention services in the three treatment supermarkets. The staff of HRIFP also continue to provide reproductive health services, including gynaecological examinations and contraceptive services, to women in the intervention group.

An ongoing project in Tianjin, China, compared the acceptability of medical (mifepristone and prostaglandin) and surgical abortion among 400 women who have used medical and surgical methods of abortion. This study also ascertains the perspectives of providers on medical abortion and its regular provision. Analysis of data is in progress.

Prevention of unsafe abortion through contraception

The most effective intervention to prevent unsafe abortion is contraception. The 1994 ICPD agreed that abortion should not be promoted as a method of family
planning. It also agreed that expanding and improving family planning services was the key to reducing recourse to abortion and that, in countries where abortion is not against the law, it should be safe. Yet, unsafe abortions occur both in countries where abortion on demand is permitted and in countries where it is restricted by law.

The Department has continued its efforts to improve existing contraceptive technologies and expand method choice by developing new methods. However, because of non-use, improper use or method failure, many women become pregnant each year. Unwanted pregnancy continues to be a major tragedy for millions of women worldwide and results from events such as condom rupture, unplanned intercourse (particularly in the case of young adults), incidental misuse of regular contraceptives or rape.

In such situations, the use of emergency contraception could significantly reduce the risk of pregnancy. Biomedical research conducted by the Research Group on Post-ovulatory Methods has focused on the development of improved methods for emergency contraception. This work has led to the development of two new methods, namely, the levonorgestrel-only regimen and low-dose mifepristone regimen, both of which cause fewer side-effects and have higher efficacy than the combined oral contraceptives (Yuzpe regimen) used until now. These results are described in detail in the section on “Development of improved and new methods of fertility regulation” and are briefly summarized below.

Results of a large randomized double-blind study published in August 1998 suggested that levonorgestrel (one tablet of 0.75 mg levonorgestrel taken within 72 hours after unprotected intercourse and another tablet taken 12 hours later) was more acceptable and more effective than the Yuzpe regimen (The lancet, 1998, 352:428–433). Following this publication, the levonorgestrel regimen was registered in a number of countries (Brazil, Canada, China, Estonia, France, Hungary, Jamaica, Kenya, Nigeria, Russia, Singapore, Sri Lanka, Thailand, United Kingdom, USA, Viet Nam and Yemen) and will soon be available in the European Union and additional developing countries. The regimen was also included in the main list of essential drugs by a WHO expert committee at its recent meeting. Further, the study has stimulated efforts among nongovernmental organizations (NGOs) to build awareness and a positive climate towards emergency contraception at country level. These efforts have included research on the attitudes of providers, potential clients and other community members (e.g. lawyers, teachers).

In addition to levonorgestrel, HRP tested different doses of the antiprogestogen mifepristone for emergency contraception. Interestingly, a dose as low as 10 mg (which is one-sixtieth of the registered dose to induce abortion) was effective in emergency contraception and caused very few, if any, side-effects (The lancet, 1999, 353:697–702). Subsequently, the 10 mg dose of mifepristone was registered for emergency contraception in China.

Research is also under way to test whether mifepristone is preferable to levonorgestrel. The levonorgestrel regimen, like the Yuzpe regimen, has the disadvantage of a 12-hour interval between administration of the two doses of the drug. Simultaneous administration of the two tablets would be more practical. To this end, a multinational double-blind study including 4000 women is under way to compare the 10 mg dose of mifepristone and two regimens of levonorgestrel. Results of the study will be available around mid-2000.

Research that will investigate the mechanisms of action of emergency contraception is also planned, so that women can decide if these methods are acceptable and they have a choice of methods in the event that modes of action differ.

The development of non-surgical methods of abortion

Whereas timely and appropriate use of emergency contraception assists in preventing unintended pregnancies suspected within 72 hours (120 hours in the case of mifepristone) of unprotected sexual relations, many women remain in need of pregnancy termination services. Invasive procedures for pregnancy termination are not without risk, especially when carried out by untrained providers under unhygienic conditions. Understandably, non-surgical alternatives have substantial appeal. Studies have observed that non-surgical abortion is not only more acceptable to some women than surgical abortion, but also to providers, since it can be administered safely and effectively without, in most cases, resort to surgical intervention. This feature would especially benefit countries where abortion is legal but trained staff in short supply.

The regimen of the antiprogestogen mifepristone and a prostaglandin, first tested by HRP, is being used clinically as an alternative to surgical termination of pregnancy in China and several European countries. In developing countries, the only feasible prostaglandin for this regimen is misoprostol, because other currently available prostaglandins are expensive and require refrigeration. Although misoprostol is widely used for medical abortion, it is only registered for this indication in France and China, to be used in pregnancies of up to seven weeks’ gestation following mifepristone pretreatment.

Now that HRP has established the minimum dose of mifepristone required in this regimen, current aims for research are: (i) to find the minimal dose and optimal route of administration of misoprostol which, after pretreatment with mifepristone, is effective up to nine weeks’ gestation (for example, after two missed periods), that is, the time by
which most women in developing countries seek termination of pregnancy; and (ii) to identify ways of reducing the lengthy duration of bleeding that is often experienced after medical abortion. To this end, a large multinational study was launched to compare an oral, repeated regimen with two vaginal regimens of misoprostol in pregnancies of up to nine weeks. The study is nearing completion, and results will be available by mid-2000. Also, various approaches are being tested to shorten the duration of postabortion bleeding. Future research needs will be discussed at the meeting of the Research Group in January 2000.

The oral prostaglandin misoprostol, which is marketed for the prevention and treatment of peptic ulcer in over 70 countries, is being used to induce abortion by clinicians in several countries as an inexpensive and practical option. This drug is also used by women themselves in countries in which abortion services are unavailable or restricted. Reports from a number of countries suggest that, as a consequence of clandestine use of misoprostol, the occurrence of septic abortions has decreased in many areas. Studies exploring the use of misoprostol alone suggest reasonably good results in the first trimester. However, the procedure is long and requires repeated administrations of the drug. The regimens used vary, and there appears to be no agreement on the most suitable dose(s) or interval between doses. Research to address these issues is being planned by the Research Group, as detailed in the section on “Development of improved and new methods of fertility regulation”.

Development of norms and tools

A number of guidelines and tools in the area of abortion are under preparation in the Department. To support the upgrading of midwifery skills for nurses and midwives so that countries can improve the quality of and access to maternal and newborn health care services, a set of midwifery modules has been developed by the Department. The need for such modules is indisputable. Although WHO defines a “skilled attendant” as a person (for example, doctor, nurse, midwife) who has been trained to proficiency in the skills necessary to manage normal deliveries and to diagnose or refer obstetric complications, midwives in developing countries are not necessarily trained to proficiency of a midwife. The midwifery modules aim to enable midwives to become skilled practitioners, to think critically and to make clinical decisions on the basis of sound knowledge and understanding of obstetric issues. One of the six modules developed deals exclusively with postabortion care.

While each of the modules can, if necessary, be used independently of the others, they are intended to be complementary, since together they present a comprehensive approach to deal with the major causes of maternal mortality and morbidity. A set of notes for students accompanies the modules.

The module on postabortion care follows a common framework including: (i) an introduction to the problem of abortion, (ii) avoidable factors, (iii) identifying the problem, (iv) managing incomplete abortion, (v) learning clinical skills, (vi) manual vacuum aspiration, (vii) post-abortion family planning; and finally (viii) case studies. In 1999, work on this module continued, especially in developing countries for field testing. The module will be tested in Uganda in early 2000.

Technical support to countries

The Team for Technical Support to Countries undertook two major activities in the area of unsafe abortion.

As described earlier in the chapter on “Planning and programming for reproductive health”, HRP has begun adaptation of the process and methods of the “Strategic Approach” to technology introduction to reduce recourse to abortion by broadening contraceptive choices and improve the quality of service delivery in countries where abortion is legal. Following initial testing of a strategic assessment of issues related to abortion in Viet Nam, discussions have continued with International Projects Assistance Services (Ipas), Chapel Hill, NC, USA, an NGO providing technical assistance in reproductive health, on the development of guidelines for national strategic assessments of abortion-related issues.

Following the submission of a proposal from Romania for the introduction of mifepristone and misoprostol for medical termination of pregnancy, it was recommended that an assessment of abortion issues in a broader reproductive health context be conducted first. Prior to initiating such an assessment, it was thought that the planned Romanian component of a HRP-supported multicentre clinical trial of mifepristone and misoprostol for medical abortion could provide an opportunity to collect useful information on users’ perspectives and implications of adding medical abortion to the available abortion services.

This study, entitled “The Provision of Mifepristone and Misoprostol for Termination of Early Pregnancy in Romania: Acceptability and Impact on Service Delivery”, was begun in 1999. It aims to assess the acceptability of surgical (vacuum aspiration) and medical (mifepristone plus misoprostol) abortion services among clients and providers, and to determine whether and how the addition of a medical alternative would affect the overall delivery of abortion services.
The study examines the current provision of surgical abortion and documents the managerial and resource changes required when medical abortion is added to existing surgical abortion services. Baseline data collection included a comprehensive assessment of existing surgical abortion services (infrastructure, flow of services, training, quality of care, human and material resource requirements, and hospital-based family planning services). Resource use and quality of care were also assessed after the introduction of medical abortion services. Study participants were interviewed pre- and postprocedure and at follow-up about their reasons for choosing medical or surgical abortion and their perspectives on the procedures and related services.

During preliminary screening, 435 women were invited to join the study and choose between medical and surgical abortion. Of these, 188 chose medical abortion, 147 chose surgical abortion, and 100 declined to participate. Upon further screening, 43 of the 188 women who chose medical abortion were considered to be ineligible for the medical procedure. Out of these, 31 chose to have surgical abortion and remained in the study while 12 chose the same but decided not to participate in the study. Thus, out of 323 study participants, 145 women received medical abortion and 178 received the surgical procedure. The data are currently being analysed, and reports will be written during the first half of 2000. Results are expected to provide useful information for an assessment of abortion issues, likely to take place in Romania during 2000. Results will also be useful to other countries considering the introduction of medical abortion services. The study is funded by the Scientific Working Group on Reproductive Health Research in Eastern Europe, and technical support for the study has been provided by HRP Secretariat and Ipas.

The Team for Technical Support to Countries has also supported a project on the “Acceptability of emergency contraception in Latin America”, which is described in detail in the section on “Users’ perspectives in the context of reproductive health”. The study, carried out in Campinas, Brazil, Santiago, Chile; and Durango, Mexico, revealed that emergency contraception was acceptable to potential users, health care providers, schoolteachers, and authorities. However, attitudes expressed in Chile tended to be more cautious than those expressed in Brazil or Mexico.

INFORMATION DISSEMINATION

Findings from the book Abortion in the developing world were disseminated globally. WHO issued a related Press Release (WHO/28) on 17 May 1999. The Press Release was placed on the WHO web site, and information was further disseminated through the e-mail newsletter UNWIRE, the electronic news service of the United Nations Foundation Inc., and through other international professional meetings. Publications resulting from research supported by HRP are listed in Annex 3.

FUTURE ACTIVITIES

The work to collate and document data on abortion, research on the determinants and consequences of induced abortion, emergency contraception and non-surgical abortion as well as the development of the modules on postabortion care will continue over the next two years. Abortion-related morbidity and mortality will also be documented. In addition, scientific evidence will be collected on the incidence of unsafe abortion. Systematic reviews will be conducted and updated, when necessary, on the management of abortion complications. An assessment of the feasibility of providing abortion services, where permitted by law, by non-physicians is also anticipated.

The Department plans to organize a Technical Consultation on Reducing Unsafe Abortion and Improving Access to Safe Abortion Services. The ICPD+5 key actions document provides the context for the Consultation, more specifically:

In recognizing and implementing the above, and in circumstances where abortion is not against the law, health systems should train and equip health service providers and should take other measures to ensure that such abortion is safe and accessible. Additional measures should be taken to safeguard women’s health. (Para 63.iii)

In addition to the technical and managerial guidelines, the Consultation will generate an easily used resource package, which will provide evidence-based guidance on reducing unsafe abortion and improving access to safe abortion services. The package will be accessible to a wide range of users and will contain, for example, information on training and equipping health providers and systems; identification of key gaps in knowledge, practice and policy; and a practical agenda for continuing action at global, regional and national levels.

The Consultation will be prepared with input from a range of groups and individuals, particularly from developing countries. Approximately 35 participants will represent different regional actors including policy-makers, service providers, researchers and NGOs. The Consultation is scheduled to take place in September 2000.

Two additional meetings are planned for 2000. First, a meeting will be organized to review available evidence and to identify priority areas of research, needs for technical support, and the development of guidelines on issues
related to abortion and postabortion care. This meeting will guide the identification of specific priority issues. Second, a consultation will be organized to review experience in the provision of abortion services by non-physicians and to assess and develop operations research projects to improve quality of care and the skills of non-physicians in the provision of abortion services, where permitted.
Annex 1

SCIENTIFIC REVIEW COMMITTEE ON SOCIAL SCIENCE RESEARCH ON REPRODUCTIVE HEALTH IN 1999

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Annex 3

Publications in 1999


Li Ying, Wu Yu-lin, Sun, Zhi-ming, Gu Xiao-ping, Ren nai-xiu, Zhang Jin. Impact of improved quality of care on the


Reproductive tract infections, cervical cancer and infertility

K.R. O'Reilly and P.J. Rowe
OBJECTIVES

The thematic group on reproductive tract infections (RTIs) focuses on the integration of RTI issues and concerns into other reproductive health services. It attempts to accomplish this through: (i) a better understanding of the epidemiology of RTI and hence the need for integration in different country settings; (ii) reviews of previous attempts at programmatic integration of RTI/sexually transmitted infection (STI) management into other reproductive services; (iii) advocacy for more feasible integrated approaches; and (iv) direct assistance to countries.

INTRODUCTION

RTIs include: STIs, endogenous infections (such as bacterial vaginosis); and iatrogenic infections. In most parts of the world, it is now well accepted that control of RTIs, especially STIs, is an urgent health need. The highest public health priority is for primary prevention of infection. However, primary prevention efforts are not 100% successful, resulting in a need for additional interventions to address the problem of established infection of the reproductive tract. Failure to treat RTIs leads to severe consequences for both women and men. Presently, there is also substantial evidence linking the presence of these infections to an increased risk of HIV transmission.


More than 30 bacterial, viral and parasitic diseases that can be spread by sexual contact have now been identified; however, only a minority have sexual transmission as their dominant route of spread (Gerbase A, et al. The lancet, 1998, 351:S112–S114). Sexually transmitted RTIs receive the most attention. However, the causative organisms in postabortal and puerperal pelvic infections are most commonly not sexually transmitted but result in pelvic infection following ascent from the lower genital tract.

PROGRESS

Research and evidence on sexually transmitted infections

Prevalence of sexually transmitted disease

All activities in this area are conducted by HRP. Progress in 1999 was hampered during the initial part of the year owing to a lack of funds. In lieu of funding, much of the activity in this area in the past year was devoted to planning and proposal development.

Only about 20 studies on chlamydial antibody detection have been carried out in developing countries. These suggest that the relative contributions of chlamydial and gonococcal infection to tubal disease may be different from those in developed countries, with a higher proportion of tubal disease possibly attributable to past gonococcal disease (Wasserheit J, International journal of gynecology and obstetrics, 1989, 3 (suppl):145–168). Further data on the prevalence of chlamydial lower genital tract infection in women are needed, with particular emphasis on developing countries in Asia and Latin America. HRP is planning to conduct such studies in selected populations and as a component of gynaecological health surveys in the next biennium.

Chlamydia trachomatis and Neisseria gonorrhoeae are not the sole causative organisms of acute salpingitis. In a study involving 50 women with acute pelvic inflammatory disease (PID), Neisseria gonorrhoeae was isolated in 12%, Chlamydia trachomatis in 4%, and other pathogens in 20% (no pathogens were detected in the remainder) (Brunham R, et al., Journal of infectious diseases, 1988, 158:510–517). Many of these other pathogens are also implicated in bacterial vaginosis but, to date, there is very little information available on the prevalence of bacterial vaginosis in developing countries. Further research is needed to establish the role of bacterial vaginosis in upper genital tract infection as well as the risk factors for lower genital tract infection. The objectives of this research line include studies on the prevalence of genital tract infection in selected populations and epidemiological studies on lower genital tract infection. Prevalence rates of RTIs are a vital indicator of the general population’s reproductive health and the susceptibility of a population to the spread of HIV infection. Research studies on the prevalence of lower genital tract infections in different populations are planned for implementation in China, Indonesia and the Lao People’s Democratic Republic (Lao PDR) in 2000–2001.

Epidemiology of lower genital tract infection in selected populations

Information on the epidemiology of STIs in developing
countries is scarce. Most hypotheses depend upon few observations from small samples in differing population groups in geographically disparate regions (Brunham R and Ronald A. In: Wasserheit J et al., eds. Research issues in human behavior and STIs in the AIDS era. Washington, DC, American Society for Microbiology, 1991:61–80). Despite these caveats, prevalence studies on active chlamydial and gonococcal lower genital tract infections in selected populations, both high-risk and low-risk, can point towards epidemiological patterns. As an important element in its research efforts in the coming year, HRP will attempt to obtain good quality data on the prevalence of chlamydial, gonococcal and, in some cases, trichomonal infection.

A study of the epidemiology of STI is planned for the year 2000, in which a cross-sectional survey of approximately 2000 married women of reproductive age living in a rural area of Sichuan province, China will be clinically examined and tested for the prevalence of chlamydial and gonococcal lower genital tract infection.

In another similar multicentre study in Shanghai and Hefei, China, rates of STIs including Chlamydia trachomatis and Neisseria gonorrhoeae in women attending family planning clinics, commercial sex workers and their clients will be measured. The estimated sample sizes will be 1225, 368 and 195, respectively. The study will start in 2000 and take one year to complete.

In Nanjing, China, the Jiangsu Family Planning Research Institute will collaborate with the National Center for STD Control and Research on a study of a mobile population working in two construction companies. Eight hundred and forty subjects will be recruited and screened for chlamydial and gonococcal infection as well as syphilis and trichomoniasis. In a parallel study, the same population of men will be randomly allocated to an intervention group who will receive intensive education every three months on health care and STI prevention including condom use. The intervention is planned to last one year. The control group will receive routine counselling on STI prevention, the standard that is currently offered. At one year, the men will be re-examined for STIs and the two groups compared for re-infection rates.

Rates of STIs are thought to be rapidly increasing in other developing countries in the Asia–Pacific region. Through the Long-term Institutional Development (LID) Grant mechanism, the Department of Medical Research, Yangon, Myanmar will undertake a cross-sectional prevalence study of lower genital tract infections in approximately 600 women attending antenatal clinics at the Central Women’s Hospital, Yangon.

Also in Myanmar, 150 women with ectopic pregnancy will have a portion of tubal tissue tested for chlamydial antigen by ELISA. In a similar study starting in 2000, 130 cases of ectopic pregnancy and 65 women undergoing tubal ligation will be tested for chlamydial antigen in the excised tubal tissue.

In Mongolia, vaginal discharge is a common reason for prepubertal girls to be brought by their mothers to the gynaecological clinic. Why so many cases should be attending, the mother’s reasons for attending, and her attitude and perceptions concerning both vaginal discharge and STIs, will be examined in approximately 800 prepubertal girls and their mothers. As an adjunct to this research, microbiological samples will be obtained from approximately 400 prepubertal girls and examined for sexually transmitted organisms.

A sample of 500 antenatal patients attending maternity hospitals in Vientiane, Lao PDR will be screened for syphilis, gonorrhoea, chlamydial infection and bacterial vaginosis. This will be the first such study in the Lao PDR.

Five hundred adolescent males in Surabaya, Indonesia, will be screened for occult chlamydial urethritis in a LID Grant-supported project in the year 2000. In Ho Chi Minh City, Viet Nam, the prevalence of RTIs will be estimated in a population of antenatal subjects and a study will be initiated on the relationship between lower genital tract infection in pregnant women and adverse pregnancy outcome.

As one of the Regional Research Initiatives developed by the Asia–Pacific region within the framework of Technical Support to Countries, a joint study between centres in Bangkok, Thailand, and Shanghai, China, will examine STIs and other reproductive health concerns in migrant populations.

In China, termination of pregnancy is usually undertaken without screening the subjects for STIs or providing antibiotic cover. In 2000, a study will start in Beijing with the following objectives: (i) to determine the incidence of postabortal complications; (ii) to study the infectious causes of these complications; and (iii) to establish the risk predictors. An estimated 2000 subjects will be recruited.

**Simple STI diagnostic tests**

In 1999, HRP was active in the area of simple diagnostic tests. Effective screening and intervention for STIs require close-to-care testing. Ideally, a suitable test would be simple to perform, heat-stable, capable of detecting multiple pathogens (e.g. gonococci, Chlamydia and Haemophilus ducreyi) with high levels of specificity and sensitivity, and affordable in developing countries.
The rates of chlamydial isolation in men with recent onset of non-gonococcal urethritis, men with no symptoms or signs of urethritis, and men with gonococcal urethritis have been remarkably consistent from study to study, despite differences in patient population and methodology. Urethral infection in men due to Chlamydia trachomatis is more often asymptomatic than gonococcal urethral infection and many men with asymptomatic chlamydial urethral infection exhibit persistent urethral leukocytosis on Gram stains of urethral secretions, indicating ongoing inflammation.

In the absence of antigen detection or culture techniques, many STI clinics use the “two-glass” test to observe any turbidity in male urine samples and thus presume an infection. The comparative study in Hat Yai, Thailand, of the predictive value of this test compared to the predictive value of the leukocyte esterase (LE) test was completed in 1999. One hundred and twenty-nine men attending two STI clinics were recruited to the study. Dysuria was a symptom in 78% of men. Urethral discharge was a symptom in 68% but was evident on examination in 95% of the men. The prevalences of infection were 32.6% for N. gonorrhoeae, 23.3% for C. trachomatis, 1.6% for T. vaginalis and 51.9% for any infection. The sensitivities and specificities of urethral discharge on examination, two-glass test and LE test of first-voided urine specimens as indicators of infection with either or both N. gonorrhoeae or C. trachomatis were 97% and 8%; 57% and 83%; and 59% and 78%, respectively. Combinations of urethral discharge on examination and one of the other indicators were more specific but much less sensitive than the presence of discharge alone. Culture for N. gonorrhoeae was found to be only 43% sensitive compared to an expanded gold standard involving a polymerase chain reaction (PCR) test.

In another study in Hat Yai, Thailand, to assess how effectively the pH test can detect infectious vaginitis, vaginal specimens were tested in 422 women. The pH of vaginal fluid as a screening test showed a sensitivity of 49.7%. When combined with clinical symptoms and signs, the sensitivity increased to 67.5%. When used to screen for bacterial vaginosis, the pH test alone had 73.4% sensitivity. When combined with signs and symptoms, the sensitivity increased to 81.3%.

The Department plans to be active on the issue of RTI/STI testing in 2000. Rapid diagnostic tests for STI already exist and are in use in developed countries. Conventional wisdom, however, dictates that these tests are too expensive for consideration in developing countries. A comparison of all costs incurred in the use of rapid tests, standard tests currently in use in reference laboratories in developing countries and in the use of WHO’s Syndromic management for sexually transmitted diseases is required to determine if conventional wisdom is correct. A comprehensive costing would include: (i) expenditures for test kits and reagents; (ii) transport of specimens to reference laboratories; (iii) labour for conducting conventional laboratory tests; and (iv) the costs of misdiagnosis, overtreatment and loss to follow-up (with the possibility of continued spread of infection and sequelae of untreated infections) with both conventional tests and Syndromic management. In 2000, the Department will conduct such a costing study to determine if advances in rapid diagnostic techniques for STI that are already available have any application in the developing world. Should these rapid diagnostic tests prove to be within the realm of possibility for use in developing countries, a second stage to this process will be the development of algorithms to guide the use of these tests to maximize their benefit while diminishing unnecessary costs.

Guidelines for research on reproductive tract infections or gynaecological morbidity

In 1999, HRP addressed the issue of social and behavioural research on RTIs and made substantial progress in a project that will continue into the coming biennium.

Over the last decade, several studies in developing countries have highlighted the widespread prevalence of RTIs or gynaecological morbidities in community settings. These findings have spurred a great deal of interest among researchers and nongovernmental organizations (NGOs) in the prevalence, correlates and consequences of RTIs, or gynaecological morbidity more generally, using both self-reported, as well as clinically-diagnosed and laboratory-detected measures of morbidity. The experience of studies conducted thus far has also raised a variety of methodological concerns, and offers a rich source of methodological lessons for future work. These lessons are important to document, in light of the expanding number of ongoing or planned research studies on the prevalence and correlates of RTIs, or gynaecological morbidity. Documentation of research approaches becomes especially important because of the need to avoid repeating the methodological weaknesses of earlier studies, the complexities of undertaking these surveys and the relative lack of attention thus far on the behavioural determinants and consequences of gynaecological morbidity.

HRP, along with the Ford and Rockefeller Foundations, has undertaken a project that draws upon the existing experience in the area of social and biomedical research on RTIs and other gynaecological morbidity. The intention is to develop a set of guidelines or research approaches on how to plan and implement rigorous studies on the prevalence of RTIs, and gynaecological morbidity such as prolapse, vesico-vaginal fistulae and menstrual disorders, as well as on their behavioural determinants and consequences for women’s lives. The goal is to publish
and disseminate widely the recommendations on research approaches to the study of RTIs and other gynaecological disorders. A few studies may be launched following the publication of this document.

When completed, the guidelines will address both biomedical and women’s perspectives. They will include:

— an overall framework for exploring gynaecological morbidity, including its correlates and consequences for women’s lives;
— the ways in which men’s roles and behaviours impinge on women’s gynaecological morbidity; and
— a discussion of design and methodological issues.

They will also include a presentation of important issues in the clinical diagnosis of morbidity, and standards of laboratory tests, including field-based tests using new low-cost technologies for detecting morbidity. A discussion of ways to address and analyse women’s perceptions and experiences through quantitative and qualitative data-gathering methods will also be included.

To prepare these research approaches, a multidisciplinary, international consultative group has been formed, with representation from the social, biomedical and biostatistical spheres. The Group met in mid-1999 and presented work-in-progress on their individual contributions. Finalization of chapters is under way and will be completed in 2000.

Case studies on integrating STI prevention and care into other reproductive health services

In 1999, the Department has been active in reviewing the evidence and experience on integration in the context of reproductive health services.

Integration of services in reproductive health has been in existence since family planning services and maternal/child health (MCH) services were integrated in many countries decades ago. The issue received new impetus from concerns regarding infection, especially HIV, and the need to protect women from these infections. This concern motivated the 1994 International Conference on Population and Development (ICPD) in Cairo to call for expanded attention to infections, their prevention and treatment, through usual sources of reproductive health care for women, primarily family planning or family planning/MCH clinics. While the idea of integration has an intuitive logic, it was not clear how much was known factually about how it worked. In 1998, WHO commissioned a review of everything known on the topic of integrating STI management into family planning services. This review, released in its entirety as Occasional Paper No. 1 from the Department in 1999, concluded, among other things, that relatively little evidence exists on this topic. The issue is compounded by differing definitions, differing expectations, differing levels and types of services into which STI management is integrated and altogether too little evaluation. Clearly, more must be known and understood about integration, its costs and benefits in general, as well as the different operational models in use before guidance on the topic can be developed.

Following the development of the review on the topic, in 1999 the Department formed a partnership with UNAIDS and THE FRONTIERS Project, which is The Population Council’s operational research programme in reproductive health. The purpose of this partnership has been to develop additional case studies on integration to broaden the available information base about the topic. Some of the case studies would, in addition, serve an important function in the implementation of FRONTIERS agenda of research by providing an initial assessment of the services that exist in the sites where subsequent larger-scale intervention studies on integration are planned.

In 1999, proposals for case studies were developed and three were funded through the UNAIDS partnership. All three focus on antenatal syphilis screening, an important element of research planned by FRONTIERS and a key area in integration as well. These describe the various operational models that have been used to integrate antenatal syphilis screening into MCH services or the factors that have influenced whether or not a successful research trial on antenatal syphilis screening resulted in programmatic change following its completion. The studies are short in their duration and descriptive, not evaluative. Others on additional topics, such as the integration of Syndromic management of sexually transmitted diseases into reproductive health services or the integration of the logistics systems for family planning and STI, will be developed in 2000 or have been developed and will be evaluated for funding by the Department early in 2000.

When complete, these studies will expand by a substantial amount both the number of studies available on integration and the types of integration documented. They will be useful evidence in the preparation of guidelines for countries on the best approaches for the integration of RTI/STI management into other reproductive health services.

Development of norms and tools

Improved flow-chart for syndromic diagnosis and management of vaginal discharge

This area has involved substantial work in the Department in 1999 and will continue into the next biennium.

When WHO introduced the Syndromic management for sexually transmitted diseases in 1992, it had the
potential to revolutionize the way STIs were diagnosed and treated throughout the world. Shortly thereafter, when ICPD called for an expanded mandate for reproductive health services, particularly with an emphasis on the management of women’s RTIs, Syndromic management was embraced as a way to detect and treat RTIs in reproductive health services. What has followed since in the literature is a fierce debate about the utility of Syndromic management for vaginal discharge in areas or settings of low prevalence and even debate about the utility of the entire Syndromic approach. Much of this debate stems from a misunderstanding of the intended purpose of the Syndromic approach; it was designed to be a case management tool, not a case detection tool. Some of this debate also stems from a failure to provide a means for countries to alter or modify the approach to Syndromic management for vaginal discharge to suit specific needs. In all, however, the debate has succeeded in focusing attention on the clinical interaction once a woman recognizes symptoms and seeks treatment for those symptoms. Conversely, this debate has distracted attention from the broader context in which these clinical activities must be placed for meaningful progress to occur against RTIs.

In an attempt to assess whether it was possible to improve the sensitivity and specificity of the vaginal discharge flow-chart contained in Syndromic management for sexually transmitted diseases, a variety of additional tests or alternative logic was evaluated. Unfortunately, none of the methods or alterations investigated represented an improvement over what was already recommended. It was obvious, however, that the debate over the best clinical procedures for the diagnosis of cervical infection in women with vaginal discharge distracted attention from the fuller range of interventions possible and usually not employed in the effort to manage RTIs among women.

Determining the most appropriate set of interventions for a public health programme to meet the needs of both men and women with established RTIs, including STIs, has been problematic. Emphasis has been placed primarily on selecting approaches for the case management of symptomatic individuals. Companion interventions that should be included in a comprehensive public health programme have been inadequately considered, and insufficient attention has been paid to identifying the appropriate mix of interventions for different epidemiological, social and health delivery settings. In this context, a process to prioritize the development of locally relevant interventions for addressing established RTIs is urgently needed.

A comprehensive mix of interventions should focus on enhanced symptom recognition and health care seeking behaviour, effective outreach programmes to identify symptomatic individuals and their sexual partners, and improved quality of clinical services for women and men. The appropriate mix of interventions for each local and/or national programme is determined by a number of interrelated factors:

- Prevalence and incidence of RTIs
- Cultural and social norms of sexual and health behaviours
- Local perceptions and beliefs concerning reproductive morbidity
- Patterns of health care seeking behaviour
- Utilization of public and private sector health services
- Resources available at country level
- Existing structure of public health programmes
- Patterns of antimicrobial use and resistance

Typically, programme managers have imperfect data on many or all of the above factors. Furthermore, when data do exist, programme managers rarely have a clear process for deciding what actions might be indicated. To address this problem, the Department and the Population Council’s HORIZONS Project have formed a collaboration to evaluate a process for making decisions about programme goals and directions and the key steps in implementing those decisions to address the problem of established RTIs. This programme guidance tool is designed to allow programme managers to assess the nature of the particular RTI problem they face and to design interventions that address it. To accomplish this, a procedure that has been developed and field tested by HRP in a number of countries, the Strategic Approach to Contraceptive Technology Introduction (see description in the section on “Planning and programming for reproductive health: development of norms and tools”) has been brought to bear on a new problem. This method forms the basis for the assessment of the nature of the RTI problem in a country.

The work proceeds in phases. In the first phase, a background paper reviewing the state-of-the-art knowledge on RTIs and programmes to address them is drafted. The paper identifies gaps and ambiguities and sets the stage for the development of key strategic questions to be explored in the field assessment stage. This stage, a period of rapidly conducted qualitative fieldwork, enables an appropriate team of experts to assess the nature of the problem first-hand, thus facilitating consensus development and decision-making about actions to be taken following field work. The next phase consists of getting agreement on the priorities for action to address the problems identified and implement those decisions. The final step is the evaluation of the process to see if the improved direction and re-prioritized interventions have been implemented and are indeed more effective.

In 1999, the Department and HORIZONS developed the key components of the Programme Guidance Tool and reviewed these with outside experts in a meeting in Geneva,
Switzerland, in March 1999. At that time, the consensus was that no further development should take place until after the approach was field-tested. Following that meeting, four sites were identified for field tests, proposals were developed and funded in three. These sites, Latvia, Cambodia and the state of Ceara in north-east Brazil, all became active in the field test in 1999.

In the coming biennium, these activities will be continued. Following the completion of the first phase of these field tests (the assessment phase) in 2000, the information gathered and evaluated will be used to develop new, or confirm existing, priorities and interventions in the management of RTIs. Subsequently, new proposals will be developed to cover the evaluation phase. In all sites, evaluation will consist of assessing changes in priorities assigned to different interventions following the field test of the Programme Guidance Tool. In two sites, chosen for their ability to conduct more sophisticated research and laboratory tests, evaluation is also planned to address the impact of those changed priorities. Details of these evaluations can only be developed following successful completion of the assessment phase, now under way.

At the completion of this exercise, it is hoped that WHO and its partners can make available to countries a flexible approach to assess their own RTI problems and their capacity for finding solutions.

**Update of STI treatment guidelines**

WHO plays a key role in the development and distribution of guidelines for the treatment of STIs. Updated every four years or as needed, these guidelines are important in forming the basis for national guidelines for treatment of STIs and in influencing essential drug policies in countries.

In 1999, the Department participated with WHO’s Initiative on HIV/AIDS/Sexually Transmitted Infections (HSI) and UNAIDS, in convening a consultation to review the existing guidelines, assess their adequacy in the light of changing patterns of epidemiology, patterns of antimicrobial resistance and the development of new antibiotics. This process often follows a similar process of development for treatment guidelines in the USA, under the auspices of the US Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA, which addressed the development of new STI treatment guidelines in 1999. In developing its guidelines, CDC undertook a review of the evidence to support the decisions that are made about the choice of antibiotic regimens. WHO can often profit from this review and it is therefore cost-effective for WHO to wait until the US guideline update is complete before updating its existing guidelines. The recommendation for antimicrobial agents must, of course, be adjusted to accommodate health budgets that are less capable of large expenditures for drug supplies.

The review of STI treatment guidelines was conducted in the spring of 1999 and the new guidelines will soon be ready. In addition to some modifications in the recommended drugs for STIs, this revision will also alter the way in which vaginal discharge as a symptom is interpreted and treated. A key component of WHO’s Syndromic management, the treatment of this symptom has proved problematic under the previous treatment guidelines and may now be improved. Previously, in Syndromic management, vaginal discharge was taken as a symptom of cervical infection. In the revision, vaginal discharge will be taken as an indication of vaginal infection only. Treatment for cervical infection will not be routinely recommended as initial treatment for women with vaginal discharge alone, in the absence of obvious risk factors for infection. In 2000, the Department will be active with HSI and UNAIDS in finalizing and distributing these new guidelines.

**Female condom programming guide**

During 1999, the Department worked with UNAIDS and the Female Health Company to develop a Planning and programming guide on the female condom. Input has also been provided by many programme managers who have been working with the female condom in the field. The Guide is composed of the following elements:

- What the female condom is
- What we know about the female condom
- Cost-effectiveness of the female condom
- Planning strategically for the female condom
- Steps to integrate the female condom into existing programmes and services training
- Samples of educational materials
- Contacts for further information and assistance

It is expected that the document will be printed by mid-2000.

**Technical support to countries**

HRP has continued to be active in its support to countries in 1999. WHO has estimated that more than 333 million new cases of treatable STIs occurred in 1995 in people aged 15–43 years. These included 12.2 million cases of syphilis, 62.2 million cases of gonorrhoea, 89.1 million cases of chlamydial infection and 167.2 million cases of trichomoniasis. The vast majority of these occurred in developing countries with the largest number of new infections in South and South-Eastern Asia (47%), sub-Saharan Africa (20%), and Latin America and the Caribbean (11%).
These estimates, although based upon a comprehensive survey of available information, are limited by the quantity and quality of prevalence data available (Gerbase et al., *Sexually transmitted infections*, 1998, 74:S12–S16). The quantity and quality of data, in turn, are limited by a lack of professionals trained in STI epidemiology, inadequate sampling techniques, inappropriate choice of study populations and inadequate microbiological facilities for the diagnosis of STI. HRP has, over the past ten years, addressed some of these issues by convening training workshops in STI epidemiology which have trained more than 50 health care professionals in China, Fiji, Mexico, Thailand and Zimbabwe. In addition, HRP has assisted in strengthening microbiological facilities by providing equipment, reagents and supplies as well as training in more than 27 centres in 17 countries. These efforts have resulted in a variety of prevalence studies including research on previous chlamydial and gonococcal infection in groups such as commercial sex workers and their clients, antenatal patients and subjects with infertility. Prevalence studies of current chlamydial and gonococcal infection in commercial sex workers, antenatal subjects, military personnel, sexually active adolescents and young adults have been conducted in ten centres. The focus has now shifted to studies of STI prevalence in migrant populations. These are often characterized by having most, if not all, of the risk factors for STIs, such as being young, unmarried, changing partners frequently and not using condoms for STI prevention.

In conjunction with the strengthening of microbiological facilities, provision of equipment, reagents and supplies, HRP will provide technical assistance to Indonesia, Lao PDR, Mongolia and Myanmar in initiating STI prevalence studies in selected populations in 2000.

As a component of the LID Grants, prevalence studies on ectopic pregnancy, PID and STIs will be started in Ulaanbaatar, Mongolia and Yangon, Myanmar in 2000. The LID Grant for 1999 and 2000 for the Maternal and Child Health Institute, Vientiane, Lao PDR includes studies on septic abortion and on women with symptoms of lower genital tract infection. A workshop was held in 1999 to finalize the research proposals.

**Advocacy**

**Review of the interface between STI and family planning**

In 1999, the Department was active in the area of dual protection. ICPD was successful in facilitating change in the language that guides the activities of many of the major agencies working in reproductive health. To date, however, it may have been less successful in changing the thinking and approaches that are actually used on the ground in reproductive health programmes. An example of this is the issue of dual protection. Dual protection is the prevention of two undesired and undesirable outcomes, unintended pregnancy and STI, including HIV. As such, it is a goal with which all can agree. At the service-delivery level, however, how to provide dual protection to a client is a contentious issue. Dual protection can be provided by the simultaneous use of two methods, a barrier method (particularly a condom) to prevent infection and another contraceptive method to prevent pregnancy. Evidence shows, however, that this approach presents difficulties. Among these difficulties are: (i) the added cost of using two methods; (ii) reluctance of many women to use two methods; (iii) apparent difficulty of maintaining consistent condom use to prevent against infection alone; and (iv) the seemingly higher value placed on protection against pregnancy. Another approach to dual protection is the consistent use of condoms to prevent against both pregnancy and infection. This approach facilitates condom use in relationships, as protection against pregnancy is apparently a more acceptable issue for couples to discuss than protection against infection which may raise suspicion and distrust. However, for this approach to work, family planning providers must change their views that the condom is not an effective method of contraception.

Many factors may influence the decision about which approach to dual protection is adopted. At a regional or national level, maternal mortality rates and availability of legal safe abortion are of course important, as are rates of STIs including HIV. Birth rates and the history of family planning efforts in a country are also important, as are data on the effectiveness of different available methods of contraception, including the condom. While the perception exists in family planning circles that the condom is far inferior to oral contraceptives in protecting against pregnancy, evidence to the contrary exists and this evidence is either unknown or ignored by many family planning service providers. It is also clear that only one method—the condom—affords any protection against infection. If family planning service providers become equally concerned about all unplanned or undesirable consequences of sexual activity, not just unintended pregnancy, then the role of the condom in providing family planning services in the absence of other methods such as surgical sterilization must be reappraised.

In 1999, the Department hosted a five-day consultation on this topic. This consultation was cofunded and coorganized by WHO, UNFPA and UNAIDS. In the first three days, the issue of dual protection was addressed at a global level, with representatives of family planning organizations and STI/HIV prevention efforts from countries in all the regions represented. The results of this initial part of the consultation were a strong endorsement of a single-method approach to dual protection where appropriate, and a call for guidance and assistance from international agencies in helping countries adopt this new
approach. A joint policy statement of the sponsoring agencies was specifically requested and is under development. In the next two days, representatives from eastern European countries and the newly independent states addressed dual protection from their particular regional perspective. This region is characterized by low birth rates, high rates of abortion, rapidly evolving local HIV epidemics and a regionwide epidemic of other STIs, especially syphilis. At the same time, the modernization of health services following the end of the Soviet Union has included the establishment of modern family planning activities, with an emphasis on hormonal contraception in an attempt to decrease the rate of abortion use. The results of this second part of the consultation were a plea for assistance from international agencies to address not only the high rate of abortions through expanded family planning efforts but also the rapid spread of STIs including HIV through the promotion of condoms as a single method effective against both unintended pregnancy and infections.

In 2000, additional cosponsored, cofunded region-specific consultations are planned, to assess the nature of the problems each region faces in attempting to address the issue of dual protection and to discuss and recommend the best course of action.

**PLANNED ACTIVITIES**

**Research and evidence**

In the coming biennium, the Department will continue to collect information in the form of case studies on the operational aspects and, where possible, the benefits of integrating STI management into other reproductive health services, as planned in 1999 and described earlier in this report. This information will be essential for compiling an empirical database for subsequent evaluation studies, trials and meta-analyses of the topic.

HRP will continue to pursue studies on the prevalence and incidence of RTIs in selected developing countries and will complete the production of guidelines for studying gynaecological morbidities among women in developing countries, as described earlier.

In the area of STI diagnostic techniques, the Department will undertake a costing study to assess the feasibility and affordability of currently available rapid tests, described above, and will follow this activity with the development of algorithms to guide their use, if proven useful.

The Department will also cooperate with HSI in focusing on the role of the private sector in the provision of STI care in the developing world. This stems from a concern that, while WHO and other agencies focus their attention on assisting public sector sources of health care, the portion of health care delivered by the private sector is growing in most developing countries. The private sector can include physicians in private practice, pharmacists and even informal sources of health care. A review of what is known and what is being done to improve the quality of care provided through these sources or to involve these providers in a partnership with the more traditional public sector approaches is being planned. A consultation to disseminate the findings of the activity and enlist the support and agreement of all parties in developing countries is anticipated.

The Department will also be active in a number of areas related to condoms and their promotion. A review of the approaches used for the promotion of condoms is planned, as a way to identify more successful strategies for dissemination to countries. Studies of non-latex condoms are also planned. One, a comparative study of latex and non-latex condoms, will be initiated in four countries in the next biennium and will assess the equivalency of the two in terms of reinfection rates. In another, users’ perspectives on non-latex condoms will be assessed in two countries (see the chapter on “Users’ perspectives in the context of reproductive health”). Studies on the acceptability of the female condom are also planned. Though many studies on the acceptability of this device have been carried out and the results have been generally favourable, government officials still seem reluctant to approve its distribution or recommend its use with the benefit of locally conducted acceptability studies. The Department will continue to play a role in this area.

The relationship between the use of steroid hormonal contraception and human papilloma virus (HPV) remains an open question. Research currently under way is refining the understanding of the viral subtypes most closely linked to cervical cancer. Until this new research is completed and the viral subtypes of HPV most likely to be linked to cervical cancer are known, HRP will not undertake anticipated epidemiological studies in developing countries.

In the coming biennium, the Department will continue to update its database on infertility.

**Development of norms and tools**

Congenital syphilis remains an important reproductive health problem in many countries, several years after the discovery of affordable prevention and treatment. In recent years, demonstration projects have been completed and have proven the feasibility of greatly reducing, if not eliminating, the threat of congenital syphilis. The technical approaches which have enabled syphilis screening to be provided to pregnant women on a “see and treat” basis have been well-described in the publications of results

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from these projects. However, real-life experience in implementing this approach to congenital syphilis control on a national or regional basis is limited and the existing experience points to managerial challenges. The Department will address this issue in the coming biennium by developing managerial guidelines for countries to use in implementing prenatal syphilis screening and congenital syphilis control.

The Department will also begin developing its companion approach to the Essential care practice guides for pregnancy and childbirth. An essential care approach for the incorporation of RTI/STI management into other reproductive health services at the peripheral level will build on what has been accomplished by WHO already with the Syndromic management for sexually transmitted diseases and will be adjusted as necessary for the reproductive health setting. The development will also include field testing which is planned to begin before the biennium concludes.

The Department will continue its collaboration with the HORIZONS Project on the Programme Guidance Tool for improved management of RTI, especially vaginal discharge, and pursue the completion of the four country field tests.

Following from its costing study, the Department will develop algorithms to guide the use of rapid diagnostic tests for STI, if proven to be cost-beneficial for developing countries.

As described above, the Department has produced the Planning and programming guide on the female condom. It is expected that the document will be printed by mid-2000 and will be distributed to countries via workshops to prepare providers for integrating this method into already existing programmes and services, as well as promoting new ones. Collaboration with other partners in the implementation phase, such as the Female Health Company and UNFPA, is anticipated.

Following completion of its current collection of additional experience and evidence on the integration of RTI/STI management into other reproductive health services (described above), the Department will undertake the development of modular training materials to facilitate the adoption of an integrated approach to reproductive health services. The completion of both the additional case studies and the field test of the RTI programme manager’s guidance tools will be used to develop these materials.

The Department is assessing the contribution that WHO can make to addressing cervical cancer through reproductive health services in resource-poor settings. A variety of low-cost approaches have been evaluated of late and found to be relatively effective at some stages of the disease. A large and well-funded Alliance is promoting an expanded view of cervical cancer control to include more than the traditional cytology approaches, especially in resource-poor settings. The Department is exploring the contribution that it can make to this collaborative effort and will be seeking a consultant capable of carrying this area forward in the next biennium.

**Technical Support to Countries**

In the next biennium, the Department will assist countries, as requested, in the implementation of congenital syphilis control by assisting them in the adoption and implementation of procedures and approaches shown to be effective in demonstration projects.

**Advocacy**

The Department will continue to promote the adoption of dual protection in additional regional consultations in 2000. The success of the first regional consultation, addressing eastern Europe and the newly independent states, has highlighted the importance of a region-specific approach to identifying the most important target groups for dual protection, as well as the potential barriers and possible solutions to the promotion of condoms for family planning in addition to disease prevention.


Annex 1

RESEARCH GROUP ON INFERTILITY

Scientists in 1999

Principal investigators

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**Annex 2**

**REPRODUCTIVE TRACT INFECTIONS**

**Publications in 1999**


Female genital mutilation and other harmful practices

E.O.A. Akande
INTRODUCTION

Female genital mutilation (FGM) encompasses a range of procedures that involve partial or total removal of the external genitalia for cultural or any other non-therapeutic reasons. It is estimated that 100-130 million girls and women have undergone some type of FGM, and two million others are at risk of FGM each year. Most of those affected live in Africa and the Middle East. It is increasingly been seen in some immigrant population groups in Europe and America.

FGM is a practice with social, cultural and economic dimensions. It is also a major cause of reproductive ill-health and a threat to safe motherhood in many parts of Africa. FGM as a public health problem has been neglected. Major gaps remain in knowledge and understanding of the extent of the problem, its health impact and the kinds of interventions that can be successful in eliminating FGM. Large-scale evidence regarding the social, psychosexual and medical consequences of FGM is lacking. The immediate health effects or long-term morbidity following FGM, and many of the health consequences of the procedure, are not clearly documented. Urinary problems, difficulty with menstruation, coital and psychosexual problems, infertility, vaginal infections and problems during labour have all been mentioned, but the frequency and severity have not been studied in depth.

Although the groundwork for action has been laid in the past 15 years by nongovernmental organizations (NGOs), so far there are no evaluated models of effective interventions for the prevention and elimination of FGM at the grassroots level. Efforts to stop the practice need to go beyond the medical model of disease elimination and need to include a multidisciplinary, multidirectional approach towards action against this and other cultural practices that inhibit the potential of women’s participation in development. WHO’s comparative advantage in this area of work is its technical expertise, its key role in advising governments and its credibility amongst the public as a non-threatening agency for health.

WHO is committed to the protection of women and girls and has emphasized the need to advance and protect the health of women and girls, including psychological, reproductive and sexual health. The Organization has adopted a number of resolutions urging Member States to establish clear national policies to end traditional practices harmful to the health of women and children and is committed to strengthening support to countries in this regard.

OBJECTIVES

Current work by the Department focuses on the obstetric sequelae of FGM, as well as the sociocultural, gender and economic contexts of the practice. The objective of this work is to increase knowledge, particularly on the frequency of the reproductive health consequences of FGM, to improve advocacy and programming as well as to develop, test and disseminate tools for research into various aspects of FGM.

PROGRESS

The proposed research will be undertaken as a multicountry, multicentre prospective cohort study, based at a number of maternity units and obstetric departments in Burkina Faso, Cameroon, Gambia, Ghana, Kenya, Nigeria and the Sudan. It aims to provide reliable information regarding the health consequences of FGM and has the following primary objectives:

— to estimate the incidence of obstetric complications among women with a history of FGM giving birth in hospital; and

— to evaluate the relationship between different types of FGM and obstetric complications.

A subsidiary objective is to obtain clinical information relevant to the prevention and treatment of obstetric complications in women with FGM.

In view of the paucity of pre-existing data regarding FGM and obstetric outcome, a pilot study is proposed prior to the finalization of the main study protocol, to establish the feasibility of the study and provide information necessary for sample size calculations and other aspects of study design. Based on the available evidence, in the absence of pilot study data, it is estimated that approximately 20 000 women will be required in order to detect a 2-fold increase in the risk of outcomes such as stillbirth/early neonatal death in women with each type of FGM, compared to women without it. The total duration of the study is expected to be approximately three years, including preparation, data collection and analysis.

As the first large controlled epidemiological study of the effects of FGM on obstetric outcome, the proposed research is expected to contribute substantially to the worldwide evidence on the subject. In so doing, it will provide a more reliable basis for advocacy, policy-making, effective interventions and future research regarding FGM.

The protocol for the study was approved by the Scientific and Ethical Review Group (SERG) in October 1999.

Research on the sociocultural, gender and economic contexts of FGM

Although there is growing information on FGM, much of it is fragmentary and from secondary sources. There is,
therefore, a need for in-depth information to understand the sociocultural diversity and complexity of FGM and its consequences, in order to design culturally meaningful and workable programmes for advocacy and intervention strategies.

Results from a pilot study in Cameroon indicate that men are not in full support of FGM and perceive FGM as interfering with male as well as female sexual pleasures. Also, there appear to be changes in parental decision-making as regards FGM and its enforcement on younger generations. Nonetheless, women indicate uncertainty on the intermediate- and long-term consequences of FGM on sexuality, health and reproduction.

To fill the above-mentioned gap in existing knowledge, the proposed study aims at investigating the sociocultural, gender, political and economic contexts of FGM, as well as the individual experiences and consequences on women’s and men’s sexual and reproductive health. The study will be descriptive and exploratory in nature and will generate a comprehensive understanding of the context of FGM, as a framework for its subsequent elimination. It is hoped that the research protocol can serve as a prototype for adoption at country levels. The specific objectives are:

- to determine the social and cultural context of FGM and its implications from the perspective of the recipients, parents, practitioners and significant others such as spouses;
- to investigate the social costs of not undergoing FGM from the perspective of the girl, parents, family, future spouse and community;
- to investigate the perceived advantages and disadvantages of FGM to sexuality and reproductive health of recipients;
- to identify the gendered attitudes and perceptions of children, women and men with regard to FGM; and
- to identify the dynamics of change as regards FGM: within and between societies, generations and different socioeconomic groups.

In July 1999, the WHO Department of Women’s Health and HRP, in collaboration with the African Midwives Research Network (AMRN), Dar-es-Salaam, Tanzania, organized a regional training workshop on Creating Awareness Among Nurses and Midwives on Female Genital Mutilation. The workshop brought together nurses and midwives from over 20 countries in the African and the Eastern Mediterranean region, where FGM is prevalent.

Also, during the year, a Regional Steering Group was formed, bringing together United Nations agencies (WHO, UNFPA, UNICEF, UNIFEM), representatives from the Ministries of Health of the six countries (Burkina Faso, Cameroon, Gambia, Ghana, Kenya and Nigeria), regional NGOs groups, health workers and researchers to provide overall direction to the activities, and to act as a forum for disseminating information and assessing the different stages of the project supported by the UN Foundation Inc. The first meeting of the Steering Group was held in Accra, Ghana, in August 1999.

FUTURE PLANS

- Convene an Investigators’ meeting on Research on the Obstetric Sequelae of FGM and initiate the pilot study in five centres.
- Finalize protocol on the sociocultural, gender and economic context of FGM and initiate studies in at least two countries.
Part 3: Technical Support to Countries
Technical support to countries

Overview

M.T. Mbizvo
OBJECTIVES

The work of the Team on Technical Support to Countries is concerned primarily with the achievement of the second and third strategic operational objectives of the Department of Reproductive Health and Research. This includes assisting developing countries to strengthen their capacities to carry out the required research and programmatic activities in the area of reproductive health. The Team has been organized to ensure, among other things, the following:

— to facilitate the implementation of WHO’s support to national reproductive health plans and programmes;
— to assist developing countries with the identification of their needs in reproductive health, including the adaptation and application of practice guidelines essential for improving reproductive health, as well as the definition of areas where research is required to address these needs;
— to support national-level planning and programming for reproductive health, including the introduction of reproductive health technologies, in cooperation with WHO Regional and Country Offices, governments, nongovernmental organizations (NGOs) and other partners;
— to promote, nationally and regionally, the conduct of research that addresses relevant reproductive health needs;
— to assist developing countries in building their own capacity to carry out their national reproductive health programmes and participate in national, regional and global research in accordance with the highest scientific and ethical standards;
— to support developing countries in programmes to disseminate and apply the results of reproductive health research, and to adapt, adopt and utilize new and updated norms, standards, tools and other approaches towards improving reproductive health.

The Team acts as the focal point in the Department for the facilitation of activities in countries, in line with the above objectives.

INTRODUCTION

The activities of the Team are based on assessments of national and regional needs and priorities for research and the implementation of evidence-based action plans and programmes. It makes optimal use of opportunities for linking reproductive health research and technical service programmes.

For each region, the Team maintains a directory of the network of institutions collaborating with the Department in reproductive health, as well as those receiving various forms of grants. It coordinates and monitors the supported research and research capability strengthening activities.

The network of institutions, which has been developed over the years with the support of HRP, is contributing to the establishment of a critical mass of scientists in developing countries, who are playing a significant role in research and planning and programming in reproductive health. This has contributed to the capacity of developing country institutions to take part in the global research effort, and to undertake research relevant to country and regional needs.

As part of its main strategy for supporting countries, the Department, through its Team for Technical Support to Countries, provides grants for strengthening necessary research facilities and human resources in reproductive health. This includes research training and technical support activities.

The Team has also been organized to serve as the focal point for collaborative activities with WHO Regional Offices. The main activities implemented in each of the regions are highlighted in this overview, and described in detail under each of the regional sections.

PROGRESS

Support towards research capability strengthening

This strategy has been used to support developing countries in the conduct of research that promotes reproductive health not only in their communities, but also in the global effort to reduce reproductive ill-health.

Whereas HRP’s initial mandate in research was to focus on fertility regulation, the nature of support towards research capability strengthening has traditionally been broader and is based on issues and problems identified by national experts and institutions. HRP has thus assisted in the development of national capacity to respond to the prevailing reproductive ill-health issues in countries.

In the wake of the 1994 International Conference on Population and Development (ICPD), held in Cairo, Egypt, which recommended a broader reproductive health focus, the Programme is reviewing its strategy for research capability strengthening, as recommended by the Scientific and Technical Advisory Group (STAG) at its 1998 meeting.

Strategies for research capacity strengthening

The training of scientists and supporting staff has been provided by awarding Research Training Grants (RTGs). Institutions to which such support has been provided would, in the past, have had a collaborative arrangement with HRP for strengthening research capacities. Institutions
are required to provide assurance that a research trainee will, after training, return to a position where his/her contribution can continue.

During the 1998–1999 biennium, RTGs were awarded to 27 scientists (two in AFRO/EMRO, eight in the Americas and 17 in Asia and the Pacific region). The areas of training are indicated in Table I.

On return to their home institutions, trainees are encouraged to apply for Re-entry Grants (RETs). Such grants enable successful trainees to establish research activities using the new knowledge and skills acquired during their training. More comprehensive support has been awarded as Career Development Grants, on a competitive basis. These enable trainees to carry out research at home while spending some time in institutions abroad, which offer the necessary training over a period of up to three years.

In the 1998–1999 biennium, a total of six RETs were awarded (five in the Americas region and one in the Asia/Pacific Region) and one Career Development Grants was awarded in the Americas region.

Research training has also been provided through support to seminars and short-term group learning activities. These are intended to promote research, particularly through intensive, supervised formulation of research protocols, and are described under the respective regions.

**Development of research support resources**

The Long-term Institutional Development (LID) Grant is the main vehicle for strengthening research institutions.

The Grant is based on the institution’s proposed research programme, comprising all the research projects as identified through a formal assessment of research needs or other criteria. The Grant is normally awarded for a period of five years, renewable once.

In 1999, LID Grants were awarded to seven institutions in Africa and the Eastern Mediterranean region, to three institutions in the Americas Region, and to nine in the Asia/Pacific Region.

Resource Maintenance Grants (RMGs) are short-term support, not exceeding three years, to institutions at the completion of long-term support. In 1999, RMGs were ongoing or awarded to institutions in the following proportions: three in Africa and the Eastern Mediterranean Region, seven in the Americas Region, and 11 in the Asia/Pacific Region.

**Collaborating Centres**

HRP bases its activities in countries on a strong partnership with collaborating institutions from both developed and developing countries. This unique network of institutions allows the conduct of basic, biomedical, clinical, epidemiological and social science research in the full breadth of reproductive health issues.

The network of collaborating centres includes 54 officially designated WHO Collaborating Centres for Research in Human Reproduction and other centres not officially designated. The 54 officially designated research centres are distributed in 32 countries, as shown in Table II.

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**Table 1. Different areas of research training provided in 1999**

<table>
<thead>
<tr>
<th>Research area</th>
<th>Africa and Eastern Mediterranean</th>
<th>Americas</th>
<th>Asia and the Pacific</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trials</td>
<td></td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Epidemiology</td>
<td></td>
<td>3</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Molecular biology</td>
<td></td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Public health</td>
<td></td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Reproductive endocrinology</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Reproductive medicine</td>
<td>1</td>
<td>1</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Sexually transmitted diseases</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Social sciences</td>
<td></td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Statistics</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>8</td>
<td>17</td>
<td>27</td>
</tr>
</tbody>
</table>
Four principles are used in the Department as the basis for designation, re-designation and de-designation of the Collaborating Centres. These are:

**Relevance.** The relevance of the proposed workplan to the goals, objectives and strategies of the Department.

**Excellence.** The scientific and technical standing of the institution concerned at the national and international levels.

**Active collaboration.** Ongoing and planned activities carried out in collaboration with the Department.

**Potential for development and sustainability.** Evidence that the institution will develop its potential with the scientific and technical support of WHO, and evidence of potential for subsequent sustainability.

The outcome of the review on the designations of centres depends on WHO’s overall assessment of the process.

As new guidelines on WHO Collaborating Centres are being developed and expected to be adopted by the WHO Executive Board, the Department did not designate new centres during 1999.

**FUTURE PLANS**

The structural and functional reorganization that has recently taken place within the Department should provide a better link and interface between research-based evidence and activities towards technical support to countries. This approach should also ensure a strong link between the knowledge from national and global research, and action plans at country and regional levels.

**Support to action plans in countries**

Activities of the Team for Technical Support to Countries within the new structure of the Department have expanded to include:

— technical assistance to countries for the strengthening and formulation of national reproductive health plans and programmes;
— assistance to countries for the adoption and adaptation of tools and practice guidelines which are aimed at improving reproductive health;
— assistance in the utilization and implementation of recommendations of research findings for improving reproductive health.

Specific activities will take into account national reproductive health needs within the regions and will be based on advice from the expanded Regional Advisory Panels (RAPs), in collaboration with Regional Offices and other partners, NGOs and cooperating agencies.

**Regional Advisory Panels**

Regional Advisory Panels (RAPs), established in 1997, provide advice and guidance to the Team, based on their knowledge of the reproductive health problems and needs for support in the relevant region. They have a mandate to develop a strategic plan for research and capacity building, and to review proposals for research and institutional strengthening. They also promote the dissemination of research results and, within their expanded role, advise on the development of reproductive health programmatic strategies, including the adoption of norms and standards and the utilization of guidelines based on research findings.

The Terms of Reference of RAPs, including criteria for membership, have been revised to better enable the link between research and the implementation of results. This

**Table II. Distribution of WHO Collaborating Centres for Research in human reproduction**

<table>
<thead>
<tr>
<th>WHO Region</th>
<th>Country (number)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>Kenya (1), Nigeria (1), Zimbabwe (1)</td>
<td>3</td>
</tr>
<tr>
<td>Americas</td>
<td>Chile (1), Colombia (1), Cuba (1), Mexico (1), USA (3)</td>
<td>7</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>Egypt (1), Pakistan (1)</td>
<td>2</td>
</tr>
<tr>
<td>Europe</td>
<td>Armenia (1), Belgium (1), Denmark (1), Finland (1), France (1), Georgia (1),</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Germany (2), Hungary (1), Russia (3), Slovenia (1), Sweden (2), Switzerland</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1), Turkey (1), United Kingdom (3)</td>
<td></td>
</tr>
<tr>
<td>South-East Asia</td>
<td>India (4), Indonesia (1), Thailand (3)</td>
<td>8</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>Australia (3), China (7), Republic of Korea (1), Philippines (2), Singapore (1)</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>54*</td>
</tr>
</tbody>
</table>

*Recommendations were made in 1999 to terminate the designation of six of the centres
process will include a stronger need for RAPs to provide advice to the Team for Technical Support to Countries in developing consolidated plans of work with Regional Offices, including stronger collaboration with UNFPA’s multi-agency Country Support Teams.

**Normative and operations research**

It is proposed that the initial phase in supporting the new strategy should entail greater emphasis, at regional levels, on operations research based on common regional reproductive health issues to be established for each region. This will need the creation of research networks, or strengthening of existing ones, to facilitate their work on common reproductive health themes, especially those that lend themselves to operations research. Such operations research should facilitate the adoption of guidelines based on normative research findings into policies and programmes required to ensure relevant interventions for improving reproductive health.

**Review of research capability strengthening**

A review of HRP’s research capability strengthening activities started in 1999 and the final report should be ready in 2001. The results of the review will assist in re-orienting the approaches to meet the changing challenges in developing countries. The two main challenges are the broader reproductive health agenda of the post-ICPD era and the need for greater participation of scientists from developing countries in the implementation of HRP’s priority research agenda elaborated in 1997.
Technical support to countries

Africa and the Eastern Mediterranean Region

E.O. Akande, H. Bathija
OBJECTIVES

Strengthening the research capacity of institutions in Africa and the Eastern Mediterranean region was undertaken to further enhance their potential to implement reproductive health research relevant to national and regional needs and to facilitate their participation in the global research effort.

INTRODUCTION

The strategy for strengthening the research capacity in reproductive health in Africa and the Eastern Mediterranean region, which was revised in the previous biennium, continues to focus on the strengthening of selected institutions and the stimulation of interest in reproductive health in various countries.

The main elements of the strategy are:

— development of subregional “Centres of Excellence”, which are capable of assisting weaker centres, especially those in the least developed countries (LDCs);
— promotion of networks through “South-to-South” and “South-to-North” links;
— improvement of research protocol development, research management and scientific writing;
— promotion of intraregional training;
— stimulating interest in LDCs, francophone Africa and the Eastern Mediterranean region;
— promoting resource mobilization for research capability strengthening activities in the region;
— strengthening research skills in the social sciences; and
— promoting “targeted” research on major reproductive health problems and the needs of LDCs.

For francophone Africa, additional strategies for increasing the research capacity include:

— stimulating interest in research on reproductive health at the country level;
— disseminating research findings in French;
— creating or reinforcing research networks among francophone African scientists and institutions;
— organizing regional conferences for francophone African countries and improving the infrastructure for research by developing human resources, strengthening libraries and promoting good management practices.

These strategies for francophone countries are being pursued in collaboration with other agencies, groups and institutions, such as the French National Institute of Health and Medical Research (INSERM), Paris, France.

PROGRESS

REGIONAL INITIATIVES AND ACTIVITIES

Research

Research on female genital mutilation

Current work on female genital mutilation (FGM) by the Department focuses on the obstetric sequelae as well as the sociocultural, gender and economic contexts of the practice.

The objective of the work is to increase knowledge, particularly on the frequency of the reproductive health consequences of FGM, in order to improve advocacy and programming, as well as to develop, test and disseminate tools to support research into various aspects of FGM.

The proposed research on obstetric sequelae of FGM will be undertaken as a multicountry, multicentre prospective cohort study, based at a number of maternity units and obstetric departments in Burkina Faso, Cameroon, Gambia, Ghana, Kenya, Nigeria and the Sudan. It aims to provide reliable information on the health consequences of different types of FGM, specifically: (i) to estimate the incidence of obstetric complications among women with a history of FGM giving birth in hospital; and (ii) to obtain clinical information relevant to the prevention and treatment of obstetric complications in women with FGM.

Research on FGM aims at generating a comprehensive understanding of the sociocultural, gender, political and economic contexts of the practice, as well as its consequences as a framework and basis for its subsequent elimination. It is hoped that the research protocol can serve as a prototype to be adopted at country levels.

As this is the first large controlled epidemiological study of the effects of FGM on obstetric outcome, the proposed research is expected to contribute substantially to the worldwide evidence on the subject. In so doing, it will provide a more reliable basis for advocacy, policymaking and future research on FGM.

More details on this study are given in the section on “Female genital mutilation and other harmful practices”.

Operations research on improving reproductive health services for adolescents

During 1999, the operations research project to evaluate and improve reproductive health services for adolescents was further developed. Six francophone sub-Saharan countries were involved: Benin, Burkina Faso, Cameroon, Côte d’Ivoire, Guinea and Senegal. The project includes
first a pilot study and then a baseline survey to define the profile of the adolescent users of health services and the quality of services offered. Subsequently, an intervention strategy will be developed for each country, depending on the results of the baseline survey. This will address either the need for increasing information to adolescents or the modification of existing services to make them more youth-friendly. The impact of the intervention will be evaluated through a second survey. HRP is facilitating and coordinating this regional initiative and to providing support for research capacity strengthening aspects of the project, but funding for each country project is being raised locally. A unique feature of the project is the constitution of multidisciplinary research teams and the active participation of youth representatives in each team.

During the initiation phase of the project, a number of intercountry workshops were held to strengthen the capacity of the teams to carry out the project. In 1999, no further workshops took place, but certain country-specific activities were carried out. They are listed here, but more details are given in the section on “Sexual and reproductive health of adolescents”:

In Côte d’Ivoire, the project has been funded by UNFPA. In 1999, data analysis of the first phase of the study was completed. A report presenting the results of both quantitative and qualitative studies was prepared and a dissemination seminar organized. Plans for interventions are under way.

In Senegal, HRP is collaborating with the USAID-funded FRONTIERS Project. The FRONTIERS Project has assumed the entire funding for the research and interventions in Senegal. The project has a broader focus and is also being carried out in Bangladesh, Kenya and Mexico. The first phase of the Senegal project started in October 1999.

In Guinea, the analysis of the quantitative data of the first phase was completed by the end of December 1999. The Benin, Burkina Faso, and Cameroon research teams are still trying to identify funding sources for their project.

Operations research on reinforcement of the links between antenatal care and delivery care

As per the process described in Annual Technical Reports 1997 and 1998, it was agreed that the French-speaking African countries should conduct a study on maternal health that will focus on the ways in which pregnant women themselves, their communities and health personnel perceive complications and react to them. This should be followed by actions such as using antenatal care visits to prepare birth plans with women and exploring ways to ensure skilled attendance at delivery.

The project development was halted in April 1998 following the Scientific and Technical Advisory Group (STAG) recommendation that an expert group meeting be held to plan HRP strategy for research on maternal health. The expert group met in November 1998. The project got a favourable review, and it was planned that the protocol would be finalized, participating countries chosen and pilot studies carried out in 1999. Following the Regional Advisory Panel (RAP) meeting in February 1999, it was also agreed that a special feature would be to look at the role of men in maternal health care. A specific proposal on this had already been developed by the HRP component of Technology Development and Assessment. The two protocols were combined and a working group was set up between RHR and WHO’s Department of Organization of Health Services Delivery to take the project further. It has now been agreed that a feasibility study be carried out in early 2000 in three districts in Senegal, using the Safe Motherhood Needs Assessment Tools.

Research training

Workshops and short courses

A regional course on qualitative research methodologies was organized in Yaoundé, Cameroon, in September/October 1999. Participants were from Benin, Cameroon and Côte d’Ivoire, but the faculty was entirely from Cameroon. A second course on qualitative research methodologies was organized in Tunis, Tunisia, in October/November 1999 for ten persons (gynaecologists, generalists, a nurse, a demographer and a statistician) from several Tunisian centres that participate in the development of a national network on reproductive health research. The faculty included scientists from Cameroon and Tunisia, as well as Programme staff. The objective of both courses, which were for three weeks each, was to teach participants the major qualitative methods, develop a protocol and instruments for a study using qualitative methods, carry out data collection using these instruments and analyse and report the data.

The outcome of the Tunisian workshop was that data collection instruments for two studies, guidelines for in-depth interviews and focus group discussions (FGDs) on the themes “Perceptions on menopause” and “Acceptability of female condom” were developed and field tested. Some data were collected using these instruments, then transcribed and an analysis was initiated.

HRP convened two workshops on adolescent sexual and reproductive health. One was organized in December 1998, in Beirut, Lebanon in collaboration with EMRO as an Intercountry Workshop on Adolescent’s Needs and Perspectives in Reproductive Health. The other was a proposal development workshop, held in January 1999 in Nairobi, for selected investigators who had submitted promising proposals for research on adolescent sexual
and reproductive health. Both are reported in the section on “Sexual and reproductive health of adolescents”.

Courses on gender and reproductive health were held in South Africa and Kenya. Details of the courses are given in the section on “Women’s perspectives and gender issues”.

Research Training Grants

During the biennium, two new Research Training Grants (RTGs) were awarded. In 1999, a statistician from Benin presented his Ph.D. dissertation in the London School of Hygiene and Tropical Medicine, London, United Kingdom, entitled *Fertility transition in Benin: new reproductive patterns or traditional behaviour?* An obstetrician-gynaecologist from Cameroon finished his studies for the Diploma of Higher Studies in Reproductive Medicine in the University of Geneva by presenting a thesis entitled *Characteristics and outcome of pregnancy among adolescents in Yaoundé, Cameroon.*

**M.Sc. Course in Reproductive Biology, University of Nairobi, Kenya**

A Master’s Degree course (M.Sc.) in Reproductive Biology was introduced in October 1993 at the University of Nairobi with assistance from HRP. The participants were from six countries. Most of the students received University of Nairobi scholarships from grants provided by HRP under the terms of a Memorandum of Understanding between the University of Nairobi and WHO. In 1999, the Course was allocated additional space to develop a laboratory for work in cell and tissue culture. In addition to the M.Sc. students formally registered in the Course, two students completed their Ph.D. and two more students are currently registered for Ph.D. During the 1998–1999 biennium, the students published or presented 19 papers.

**COUNTRY REPORTS**

**Benin**

The Centre for Research in Human Reproduction and Demography (CERRHUD) of the Department of Obstetrics and Gynaecology, University of Benin, Cotonou, received Long-term Institutional Development (LID) Grant support between 1987 and 1996. A large part of the grant was used for training a team of scientists, including demographers, a documentalist, a social scientist, a microbiologist, a statistician and an endocrinologist. In 1999, the Centre was awarded a Small Grant.

**Research**

In 1999, the Centre had five ongoing research projects which were supported by funding sources other than HRP. For the HRP-coordinated multicountry study on improving reproductive health services for adolescents, the Centre provided the statistical coordinator for the multicountry project. In addition, studies on severe maternal morbidity (“near-miss”), follow-up of Norplant users and on clinical features and feto-maternal prognosis of eclampsia were carried out. The Centre continued an operations research project on a pilot programme for the prevention of infertility, sexually transmitted infections (STIs) and genital cancers.

**Capacity building**

One staff member completed a Ph.D. course in biostatistics. He also provided training and technical support for the national teams participating in HRP-coordinated multicountry project on improving reproductive health services for adolescents. Centre staff participated in a regional course on qualitative research methodologies organized by HRP in Cameroon.

**Other**

The microbiology and andrology laboratories were operational and provided income for the Centre.

**Cameroon**

The Centre for Human Reproduction Research at the Faculty of Medical and Biological Sciences of the University of Yaoundé received LID Grant support between 1987 and 1996. In 1999, the Centre benefited from a Resource Maintenance Grant (RMG).

**Research**

In 1999, the Centre had 20 research projects. Two of these were in the field of reproductive biology, nine on maternal and infant health, one on abortion, three on contraception, three on STIs and two on gynaecological oncology. Funding for 13 of the projects came from national sources, for four projects from HRP and for the remaining three projects from other international organizations. The research included several projects relating to adolescent
reproductive health, a survey of ectopic pregnancy, a prospective study on the prevalence of STI and HIV infections in women attending family planning clinics, and a study comparing the acid wash technique with the Pap smear in diagnosing cervical cancer.

**Capacity building**

One member from the Centre served as the international coordinator for the regional research methodology training activities organized by HRP. Another member finished his training for a Diploma in Reproductive Biology and Medicine. The Centre organized a workshop to carry out a self-evaluation of its activities and prepare future plans.

**CÔTE D'IVOIRE**

Since 1995, the National Institute of Public Health in Abidjan has hosted the National Research Cellule on Reproductive Health, which was established in 1989 as part of The African Network on Research on Reproductive Health. Currently, the Cellule has 55 members, the majority are clinical scientists, and it includes 12 social scientists. The most active members of the Cellule are the seven members of a coordination committee, and eight members of the scientific committee.

The Centre was awarded a LID Grant for the period 1998–2002.

**Research**

Five research projects were under way in 1999. Both the principal investigator and the coordinator for the national team participating in the HRP-coordinated multicountry project on improving reproductive health services for adolescents are from the Cellule. The Cellule also participated in an INSERM-coordinated multicentre project on the complications of the first trimester of pregnancy and the risk factors of unsafe abortion. A study on “Near-miss survey as a strategy to improve the quality of obstetrical care in Benin, Côte d’Ivoire and Morocco”, coordinated by the London School of Hygiene and Tropical Medicine, commenced in 1999. Also, a project on the association between HIV infection and invasive cervical carcinoma was under way.

**Capacity building**

Several members of the Research Cellule benefited from the regional course on qualitative research methodologies organized by HRP in Yaoundé, Cameroon.

**Other**

The Cellule participated in the national Task Force to elaborate and validate the documents on policies, programmes, norms and procedures for the National Programme of Reproductive Health.

**ETHIOPIA**

The Department of Obstetrics and Gynaecology, University of Addis Ababa, Addis Ababa, was awarded a LID Grant from 1990 to 1994, an RMG in 1995 and, since 1996, a Small Grant renewed annually for library support.

**Research**

Nine epidemiological and clinical studies were ongoing, mostly in the field of maternal and infant health.

**Capacity building**

A basic Clinical Epidemiology and Research Methodology course was organized.

**KENYA**

The four units collaborating with HRP in Kenya constitute the National Centre for Research in Reproduction (NCRR). These units are: (i) the Department of Obstetrics and Gynaecology, University of Nairobi; (ii) the Reproductive Biology Unit in the Department of Animal Physiology, also at the University of Nairobi; (iii) the Institute of Primate Research of the National Museums of Kenya; and (iv) the Reproductive Health Research Unit (RHRU) of the Kenya Medical Research Institute (KEMRI), which was the last to become a part of NCRR.

The various units of NCRR have continued to collaborate with HRP after LID Grants to the original three units came to an end in 1989. NCRR has proved to be a unique association which has provided opportunities for a comprehensive Human Reproduction Training and Research Programme that has been of benefit not only to Kenyans but also to scientists from other parts of Africa. Within the various units involved in NCRR research, there are well-trained scientists in various disciplines, who are producing a steady flow of research results and are actively involved in human reproduction research training activities. The establishment of a Master’s Degree programme in 1993 at the University of Nairobi, under the auspices of NCRR and with financial support from HRP, has undoubtedly widened NCRR’s role as a Regional Training Centre.

**Institute of Primate Research of the National Museums of Kenya**

HRP’s Institutional Development Support to the
Institute dates back to 1979, when the Institute received its first LID Grant. Since then, the Institute has received a grant every year. In 1999, it was a Small Grant to support animal and library facilities. The Institute continues to collaborate actively with close to 100 international institutions in research and research training.

Research

During 1999, 34 research projects were under way: 17 of these were in the area of reproductive biology, seven on maternal and infant health, three on infertility, three on STIs and four on basic sciences.

The reproductive biology projects included work on the development of HIV heterosexual transmission by means of an animal model using simian immunodeficiency virus (SIV) in the baboon, cloning, sequencing and characterization of baboon sperm protein SP17 and modulation of the uterine environment during implantation in the baboon. The Institute had 38 publications in 1999.

Capacity building

The Institute is currently offering research training to postgraduate students undertaking the M.Sc. course in Reproductive Biology which is supported by HRP at the University of Nairobi. The Institute continues to play a key role in the training of students from around the world in biomedical research using non-human primate models. A workshop was conducted on the welfare of laboratory animals and ethics. In addition, 45 persons received individual training at the Institute during the year.

Reproductive Biology Unit, University of Nairobi

The Reproductive Biology Unit (RBU) of the Department of Animal Physiology, University of Nairobi, was established in 1979 by a group of collaborating scientists from various disciplines with a common interest in reproductive biology. HRP supported the Unit from its inception because of its potential to identify animal models for research in reproduction. Institutional strengthening support ceased at the end of 1989, but since then the Unit has received an annual Small Grant for the purchase of journals and consumable laboratory supplies.

The RBU is the focal point for the M.Sc. Degree course in Reproductive Biology which was developed by the NCRR and is supported by HRP.

Department of Obstetrics and Gynaecology, University of Nairobi

HRP’s institutional support to the Department of Obstetrics and Gynaecology commenced in 1979 and was phased out in 1989, at the expiration of the second LID Grant. Since then, Small Grants have been given to maintain library resources and purchase laboratory supplies. HRP’s long-term support has enabled the Department to develop to a stage, where it is now capable of attracting funds from elsewhere to continue its research efforts successfully.

Research

Four projects were ongoing: one, a knowledge, attitude and practice (KAP) study on infertility and STIs, another on IUD use in HIV-positive women, a third on the acceptability of Cyclofem and a fourth on psychosocial aspects and pathophysiology of the menopause. There were 12 publications during the period 1998–1999.

Capacity building

Teaching for undergraduate students has continued.

Kenya Medical Research Institute (KEMRI)

During 1999, the Institute received a Small Grant for laboratory supplies and journal subscriptions.

Research

The main research focus of the RHRU at KEMRI is the adaptation and introduction, as well as long-term surveillance, of contraceptive technology in Kenya. There were seven projects under way in 1999: four on maternal and infant health, one on infertility and two on STIs.

Capacity building

No activities were reported in 1999.

MOZAMBIQUE

The Department of Obstetrics and Gynaecology, National University of Maputo, Maputo, has received a LID Grant since 1989.

Research

During 1999, the Department had six clinical projects ongoing, which included the determination of the prevalence of genital tuberculosis in infertile patients, the evaluation of the need for episiotomy in primigravidae and the audit on maternal mortality. The Department had five publications in international journals.

Capacity building

Two research methodology courses were held, one for physicians and the other for nurses. The Centre continued a programme with the Ministry of Health to support
provinces in training specialists. The staff has had an important role in formulating national policies for maternal care. The Department is planning to produce three books for national use: on gynaecological endocrinology, adolescent medicine, and obstetrics and gynaecology.

**NIGERIA**

HRP’s collaboration with Nigeria began in 1972 with the joint designation of the Departments of Chemical Pathology and Obstetrics and Gynaecology at the University of Ibadan as a WHO Collaborating Centre for Research in Human Reproduction. Since then, collaboration has been extended to other institutions in the country.

**Department of Obstetrics and Gynaecology, University of Ibadan, Ibadan**

The Programme’s long-term support to the Department ceased in 1986, but Small Grants for library facilities and laboratory support continue to be given.

**Research**

The majority of research projects are clinical, with increasing input from social science methodologies. Thirteen projects were under way, including five in the area of contraception, four on maternal health, two on STDs and two others. There were 14 publications, and 11 papers had been accepted for publication.

**Capacity building**

Ten scientists participated in a course on social science research methods and 84 in a seminar on recent advances in the clinical management of HIV/AIDS.

**SENEGAL**

The Department of Obstetrics and Gynaecology at Le Dantec Hospital, University of Dakar, Dakar, has collaborated with HRP in various projects since 1981. In November 1996, the Centre for Training and Research in Reproductive Health (CEFOREP), which is attached to the Department, started to function as a nongovernmental organization (NGO) at national level. A LID Grant was awarded in 1999 to the Department and CEFOREP together.

**Research**

In 1999, the Centre carried out an evaluation on the strategy of decentralization of emergency obstetrical care and provided the principal investigator for the national team in Senegal for the study on improving the reproductive health services for adolescents. It also participated in an INSERM-coordinated multicountry study on complications of the first trimester of pregnancy and the risk factors of unsafe abortion. The Centre had seven publications in 1999.

**Capacity building**

The Centre organized a large number of clinical training courses for doctors and midwives on various aspects of fertility regulation methods, as well as on counselling and teaching methods. The participants came from eight countries in the subregion, and seven of the training events were organized outside Senegal.

**Other**

During 1999, the Centre strengthened its collaboration with a large number of international agencies, as well as with the newly established National Service for Reproductive Health within the Ministry of Health in Senegal.
SOUTH AFRICA

Since 1992, there have been a number of initiatives within the field of reproductive health, which have brought together South African researchers and policy-makers with their counterparts from other African countries. Following the readmission of South Africa to WHO in May 1994, HRP has started to expand its links with South African researchers and institutions.

Reproductive Health Research Unit, Baragwanath Hospital, Soweto

Collaboration between HRP and the Reproductive Health Research Unit (RHRU), Baragwanath Hospital, Soweto, has steadily increased since 1993.

Research

In 1999, HRP supported four research projects of the Unit, all in the field of contraception. A collaborative project with CDC has started on the association between hormonal contraceptive use and transmission of HIV infection. A project on strengthening STI control at the district level has a major evaluation and operations research component. The Unit is in charge of evaluating a national-level adolescent health initiative known as “Love life”. The Unit had 14 publications in 1999.

Capacity building

All staff are involved in the research methodology training programme. In July 1999, the Centre held a course on reproductive health research methods which was attended by participants from the entire southern African region. The Documentation Centre is fully functional with a qualified librarian and is a national resource with the most comprehensive collection of materials on reproductive health in South Africa.

Other

The Unit continued to provide major technical support to the National Department of Health, Directorate of Maternal, Child and Woman’s Health and the AIDS Directorate. It also provided technical support to the provincial health departments. In October 1999, the Unit hosted a technical investigators’ meeting on the reuse of the female condom in collaboration with WHO, UNAIDS and Family Health International (FHI).

UGANDA

The Department of Obstetrics and Gynaecology of Makerere University, which is based in the Mulago Hospital at Kampala, has received a LID Grant since 1989.

Research

In 1999, there were six ongoing projects, including various trials to determine the efficacy of certain drugs (zidovudine and 3TC or nevirapine) for the prevention of mother-to-child transmission (MTCT) of HIV infection. The initial results, based on the study of 626 subjects, showed that a single dose of nevirapine given to HIV-1 infected women at the onset of labour and to the infant within 72 hours after birth reduced the risk of HIV transmission during the first 14–16 weeks of life by nearly 50% in the breastfeeding population in Uganda, compared to a short intrapartum/postpartum AZT regimen. This simple and relatively inexpensive regimen has the potential to significantly reduce MTCT of HIV in developing countries. The result has been hailed as a major breakthrough in the prevention of vertical transmission. The Department had seven publications at the national level and three in international journals.

Capacity building

One staff member continued Ph.D. studies in reproductive endocrinology. A workshop on cervical cancer was organized as well as a seminar on essential obstetric care at peripheral health units.

Other

The Department has joined the Ministry of Health in preparing for the implementation of a project programme for the prevention of MCTC of HIV in the preparation of guidelines for medical workers for essential reproductive health services and of guidelines for the screening and management of cervical cancer.

ZAMBIA

The Department of Obstetrics and Gynaecology of the University of Zambia, based in the Teaching Hospital in Lusaka, was designated a WHO Collaborating Centre for Research in Human Reproduction in 1973. Institution strengthening support included a LID Grant in 1987, which ceased in 1991. Since then, the Department has received Small Grants to support library facilities and the purchase of consumable laboratory supplies.

Research

About 20 projects were ongoing, including several theses in the Departments of Post Basic Nursing and Community Medicine. In partnership with the University of Alabama, Birmingham, AL, USA, the Department of Obstetrics and Gynaecology, together with the Department of Paediatrics, received a contract from FHI for studies on perinatal transmission of HIV infection. HRP’s Research
Group on Surveillance and Evaluation selected the Centre to participate in a multicountry study on the effects of hormonal contraception in HIV-positive women. Preparations for the study began in 1997 and continued during 1999.

During the year, a two-year research project on “Women Friendly—Quality of Care” was initiated in collaboration with the Institute of Child Health, University College, London, United Kingdom, with funding from the British Department for International Development (DFID), whilst an ongoing major research project on emergency contraception was expanded to include two operations research projects.

**Capacity building**

No activities were reported for 1999.

**ZIMBABWE**

The Department of Obstetrics and Gynaecology of the University of Zimbabwe in Harare received a LID Grant from 1988 to 1997 and an RMG in 1999.

**Research**

There were 19 ongoing projects, mostly in the fields of reproductive biology and maternal and infant health. The Department had four publications in international journals.

**Capacity building**

The Department organized a national Master’s Degree course in Public Health, which was attended by 90 students. Four dissemination workshops were organized on the results of various studies.

**OTHER ACTIVITIES IN THE REGION**

Several projects were supported in the African Region under a range of Social Science Research Initiatives: a study on sexual behaviour in Cameroon; projects on the role of men in reproductive health in Senegal, Kenya and Zaire; projects on STIs and family planning in Nigeria, South Africa, and Zimbabwe; projects on adolescent reproductive health in Cape Verde, Ghana, Kenya, Nigeria and Tanzania. These are reported in detail in other chapters of this report.

**EASTERN MEDITERRANEAN REGION**

**EGYPT**

**Department of Obstetrics and Gynaecology, University of Alexandria, Alexandria**

The Department of Obstetrics and Gynaecology, University of Alexandria, Alexandria was one of the earliest institutions to collaborate with HRP. It was designated a WHO Collaborating Centre for Research in Human Reproduction in 1972. HRP’s core institutional support to the Centre ceased in 1980, when it was considered to have gone through the “strengthening” phase, but other forms of support continue to be given to maintain library and laboratory facilities.

The Centre continues to collaborate actively with different organizations within the country. In particular, it interacts closely with the National Family Planning Programme and participates in the planning and supervision of activities of governmental committees on family planning. The Centre also interacts closely with the Egyptian Fertility Care Society and the Egyptian Society of Clinical Chemists.

**Research**

The Centre’s research continues to focus on maternal and infant health, infertility, as well as contraception. In 1999, there were 72 research projects under way.

**Capacity building**

In 1999, the Centre organized ten workshops and seminars with over 800 participants. The themes of these group learning activities varied from quality control in reproductive health laboratories to toxaemia in pregnancy.

**The Egyptian Fertility Care Society**

The Egyptian Fertility Care Society (EFCS) was founded in 1974 as an affiliate of the Egyptian Medical Association with a mandate to promote maternal and child health through the promotion of fertility management and family health care. EFCS research network includes all University and Ministry of Health teaching hospitals, which carry out multicentric research focused on the needs of the National Family Planning Programme. Priorities for research undertaken by EFCS are set in consultation with the national research and service-delivery institutions and are revised on a five-yearly basis.
EFCS has been receiving a LID Grant since 1992.

Research

During 1999, EFCS continued research on the prevalence of RTIs, initiated a study of intracervical misoprostol combined with manual vacuum aspiration in the management of first-trimester missed abortion, and completed the data analysis and report writing on the etiological factors of infertility in Egypt. A new project was started for the institutionalization of improved postabortion care at three major hospitals.

An extensive effort was made to disseminate the results of the completed studies. Five papers were accepted by international journals, presentations were made at four conferences, a scientific seminar was organized in connection with the meeting of HRP’s Regional Advisory Panel for Africa and the Eastern Mediterranean region, and EFCS was in charge of organizing the Third Congress of the Arab Union of Obstetrics and Gynaecology Societies. In addition, EFCS provided technical assistance to the Communication Development Centre, the official body responsible for the development of media messages on women’s health for Egyptian television and radio.

Capacity building

EFCS participated in five regional reproductive health workshops organized by the Ministry of Health to train policy- and decision-makers and programme managers, and it also participated in the development of the curriculum for training of physicians and nurses on reproductive health indicators. Several activities were undertaken to complete the training of the Centre’s library staff.

ISLAMIC REPUBLIC OF IRAN

In 1998, discussions were held between representatives of the National Research Centre for Reproductive Health, which is under the Deputy Minister of Health and Medical Education (MOHME), UNFPA/Tehran, the Shanghai Institute of Planned Parenthood Research and HRP, within the framework of the one-year extension of the UNFPA project, IRA/95/PO6, “Promoting Reproductive Health Research and Training”. These discussions led to the development of a joint plan for collaboration between Iran and China.

In 1999, the Centre was awarded a Small Grant for library support.

Research

There were eleven projects, all of them funded from national and international sources other than HRP.

Capacity building

One workshop on clinical and basic sciences for 25 participants was organized.

PAKISTAN

The National Research Institute of Fertility Control (NRIFC) in Karachi was established in 1962 to carry out research that would be useful to the Government in deciding on the introduction of contraceptive methods in Pakistan. The Institute was designated a WHO Collaborating Centre for Research in Human Reproduction in 1976, and has since participated in a number of multicentre studies. It was awarded a Small Grant in 1999 for library resources and laboratory supplies.

Research

Seven research projects were ongoing in the areas of contraception, reproductive biology and contraceptive quality control.

Capacity building

No training activities were reported in 1999.

Other

NRIFC is the only institute in the country where contraceptives are tested. It is regularly visited by members of governmental organizations and various university staff and researchers. The staff of the Institute pay regular visits to various clinics to check their functioning. A new Director in Charge, and the Director of Research, as well as a new Deputy-Director, were appointed in 1999, and they have explored a number of new possibilities for the Institute to collaborate at the international level.

SUDAN

The Department of Obstetrics and Gynaecology, University of Khartoum, Khartoum, has received a LID Grant since 1989.

Research

Two research projects were ongoing during 1999. One of these was on the prevalence of teenage pregnancy and its hazards, and the other was a hospital-based study on the complications of abortion.

Capacity building

Two research methodology courses and one computer
course were organized, as well as a six-week training course in basic sciences; these were attended by 80 persons. A workshop was held on the clinical and epidemiological aspects of STIs. The endocrine laboratory was acknowledged as an important centre for hormone assays in the country.

Other

The new Centre for Assisted Reproduction, affiliated to the Department but financed privately, is ready to function. The government is pleased with this, as the Centre is the first of its kind in the country and will reduce the quantum of travel abroad of those seeking these services.

TUNISIA

The Centre for Research in Human Reproduction, Tunis

The Centre is a large government clinic providing services for family planning and the management of infertility. It is a national reference centre for the scientific evaluation of contraceptive methods in use in the country, as well as of new methods prior to their introduction in the country. The Centre received a LID Grant from 1987 to 1991 and, since 1994, received a Small Grant annually to support library and laboratory services. In 1998, a new LID Grant was awarded for the period 1998–2002.

Research

Six research projects were ongoing in 1999: one on STIs, one on infertility, one on cervical cancer and three on contraception. Funding came mainly from national sources. Several protocols are under development as a follow-up of the training courses on research methodology held at the end of 1998 and 1999.

Capacity building

A national course on qualitative research methodology was held in November 1999 and the Centre organizes regular training sessions for midwives. The staff of the Centre participated actively in a number of international conferences organized in Tunisia in 1999.

Other

In 1999, the Centre continued its reoriented activities of building up a national and regional network of research. It received financial support from UNFPA for improving the reproductive health services it offers. Major renovation and construction work to improve the facilities for research was completed.

OTHER COUNTRIES IN THE EASTERN MEDITERRANEAN REGION

HRP is actively exploring mechanisms for expanding its collaboration to other countries in the WHO Eastern Mediterranean Region. In this regard, a collaborative research project on the evaluation of a new model of antenatal care is currently ongoing in the Kingdom of Saudi Arabia (Jeddah and Riyadh). It is also expected that the workshop on adolescent reproductive health research (reported above) will encourage the countries in the Region to create research networks.

FUTURE ACTIVITIES

Activities planned for the next biennium can be summarized under the following main lines of work:

— support and maintain institutions currently collaborating with the Department through institutional development grants, to enable them to undertake research projects relevant to their identified reproductive health needs and priorities. It is hoped that the financial situation will allow this group of institutions to be expanded by two to three institutions.
— promote and strengthen regional research networks working on key issues such as FGM, adolescent reproductive health and maternal health by providing technical support in project development, data analysis, dissemination of research results and promoting the use of research in defining programmatic activities. Many of these network support activities have until now taken place in West Africa, but it is planned that they could be extended, especially to the Eastern Mediterranean region.
— promote research training intraregionally by supporting institutions that offer courses and by collaborating closely with training initiatives in which the host institute has an active role in supporting the trainees even after their return have from training.
Annex 1

REGIONAL ADVISORY PANEL FOR AFRICA AND THE EASTERN MEDITERRANEAN REGION IN 1999

Members

M. Ba, University of Dakar, Dakar, Senegal
H. Ba’aqeel, King Khalid National Guard Hospital, Jeddah, Saudi Arabia
C. Kigondu, University of Nairobi, Nairobi, Kenya
J. Moodley, University of Natal, Congella, South Africa
B. Nasah, Buea, Cameroon (Chairman)
J. Neilson, University of Liverpool, Liverpool, United Kingdom
B. Osotimehin, University College Hospital, Ibadan, Nigeria
N.O. Simelane, University of Swaziland, Kwaluseni, Swaziland

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Collaborating agencies

Family Health International
The Population Council
French National Institute of Health and Medical Research (INSERM)
Commonwealth Regional Health Community Secretariat for East, Central and Southern Africa
Annex 2

SCIENTISTS COLLABORATING WITH HRP IN 1999

African Region

Y. Ahmed, Department of Obstetrics and Gynaecology, University of Zambia, Lusaka, Zambia
E. Alihonou, Centre of Research in Human Reproduction and Demography, National University of Benin, Cotonou, Benin
O.A. Ashiru, College of Medicine, University of Lagos, Lagos, Nigeria
M.D. Balde, University Hospital of Donka, Conakry, Guinea
C.S. Bambra, Institute of Primates Research, National Museums of Kenya, Nairobi, Kenya
A.M. Bugalho, Department of Obstetrics and Gynaecology, Maputo Central Hospital, Maputo, Mozambique
T. Chipato, Department of Obstetrics and Gynaecology, University of Zimbabwe, Harare, Zimbabwe
O.A. Dada, College of Health Sciences, Ogun State University, Sagamu, Nigeria
F. Diadhiou, Faculty of Medicine and Pharmacy, University of Dakar, Dakar, Senegal
F. Giwa-Osagie, College of Medicine, University of Lagos, Lagos, Nigeria
A. Gossa, University of Addis Ababa, Addis Ababa, Ethiopia
J.G. Karanja, Department of Obstetrics and Gynaecology, University of Nairobi, Nairobi, Kenya
J. Kasule, Department of Obstetrics and Gynaecology, University of Zimbabwe, Harare, Zimbabwe
C. Kigondu, Department of Obstetrics and Gynaecology, University of Ibadan, Ibadan, Nigeria
R. Leke, Department of Obstetrics and Gynaecology, Faculty of Medicine and Biological Sciences, Yaoundé, Cameroon
F. Mirembe, Department of Obstetrics and Gynaecology, Makerere University, Kampala, Uganda
F.A. Mmiro, Department of Obstetrics and Gynaecology, Makerere University, Kampala, Uganda
D. Oduor-Okelo, Reproductive Biology Unit, University of Nairobi, Nairobi, Kenya
A.O. Ojengbede, Department of Obstetrics and Gynaecology, University of Ibadan, Ibadan, Nigeria
A.A.E. Orhue, Department of Obstetrics and Gynaecology, University of Benin, Benin City, Nigeria
N.C. Sikazwe, Department of Obstetrics and Gynaecology, University of Zambia, Lusaka, Zambia
N.O. Simelane, University of Swaziland, Kwaluseni, Swaziland
M. Te Bonle, National Research Cellule of Reproductive Health, National Institute of Public Health, Abidjan, Côte d’Ivoire
E.O. Wango, Reproductive Biology Unit, University of Nairobi, Nairobi, Kenya

Eastern Mediterranean Region

R.K. Ali, National Research Institute of Fertility Control, Karachi, Pakistan
E. Barouti, National Research Centre in Family Planning, Ministry of Health and Medical Education, Teheran, Iran
R. Ben Aissa, Research Centre for Human Reproduction, National Office for Family and Population, Tunis, Tunisia
A.S. Gerais, Department of Obstetrics and Gynaecology, University of Khartoum, Khartoum, Sudan
E.O. Hassan, The Egyptian Fertility Care Society, Cairo, Egypt
W. Sadek, Department of Obstetrics and Gynaecology, Shatby Maternity Hospital, Alexandria, Egypt
S. Said, Department of Obstetrics and Gynaecology, Shatby Maternity Hospital, Alexandria, Egypt
M. Shaaban, Department of Obstetrics and Gynaecology, Assiut University, Assiut, Egypt
M. Shahab, Department of Biological Sciences, Quaid-i-Azam University, Islamabad, Pakistan
Technical support to countries

Region of the Americas

E. Ezcurra
OBJECTIVES

Strengthening the research capacity of institutions in the region of the Americas was undertaken to further enhance their potential to implement reproductive health research relevant to national and regional needs and to facilitate their participation in the global research effort.

INTRODUCTION

The Regional Advisory Panel (RAP) proposed that HRP-supported collaborating institutions in the Americas region strengthen research capacities in the 1998–1999 biennium by promoting and supporting the implementation of well-designed research projects in topics relevant to national and regional reproductive health problems. The following strategies were selected for attaining this goal:

- Implementation of regional and national plans for reproductive health research and participation in the global research effort
- Strengthening of regional and national research networks in basic reproductive biology, clinical/epidemiological investigations, and social sciences research relevant to reproductive health
- Increased linkage between institution strengthening support and implementation of specific research initiatives, regional or national.

The main activities implemented under these strategies are described in the following section.

PROGRESS

Regional initiatives and activities

Implementation of regional and national plans for reproductive health research and participation in the global research effort

Launching research initiatives in topics of relevance to regional needs in reproductive health has been one of the main goals during the past two years. The year 1999 witnessed considerable progress in this direction.

Three centres in Brazil, Chile and Mexico completed the multicentre research project “Acceptability of Emergency Contraception in Latin America”, funded by the Mellon Foundation; the final report was presented in June 1999. Institutions in Argentina, Bolivia, Cuba and Peru have almost completed data collection for the multicentre social science research proposal: “Reality and beliefs in the sexual and reproductive decision-making process: men’s perceptions and behaviour”. Several hospitals in Argentina, Brazil, Cuba, Guatemala and Mexico are participating in a multicentre study developed by the centres that addresses the problem of the increasing rate of caesarean sections in Latin America. Four centres in Argentina, Colombia, Cuba and Venezuela are taking part in a multicentre trial coordinated by Oxford University, Oxford, United Kingdom, that evaluates the use of magnesium sulfate for the treatment of pre-eclampsia (Magpie Trial).

The four centres in Argentina, Chile and Mexico involved in basic reproductive biology research identified the study of the mechanisms of action of hormonal methods used for emergency contraception as a common topic for a regional research initiative; they conducted a comprehensive literature review on this topic and prepared research outlines, some of which will be developed into full proposals during 2000. All these projects are based on the concept of regional networking and are focused on topics relevant to the regional needs in reproductive health problems and issues.

In addition to these regional research initiatives, the centres are involved in projects that address national priorities. During 1998, 15 projects (9%) were implemented with support from HRP capacity building grants (Long-term Institutional Development, Resource Maintenance and Re-entry Grants). Sixty-eight projects (42%) were carried out at the centres with support from national sources. These projects employ methodologies ranging from molecular biology techniques to focus group discussions (FGDs) and cover the full spectrum of reproductive health issues. Participation of the regional centres in the global research effort is exemplified by the 17 projects (10%) conducted in these collaborating institutions with support from other HRP Research Groups. HRP has used institutional strengthening efforts in its regional centres to enhance their capacities for fund-raising from other international agencies, and to address topics of global or local relevance. During 1998, 63 projects (39%) were carried out in these regional centres, with support from international agencies other than WHO. Table I summarizes the research activities of the centres in 1998 and illustrates the holistic coverage of reproductive health issues.

Strengthening of regional and national research networks in basic reproductive biology, clinical/epidemiological investigations and social sciences research relevant to reproductive health

In the Americas region, three research networks are in operation—basic reproductive biology, clinical/epidemiology research, and social sciences research. The regional network of clinical/epidemiological research comprises centres in Argentina, Brazil, Cuba, Guatemala and Mexico, and activities include both research and training programmes in reproductive epidemiology. The network is instrumental in the implementation of the
multicentre study on Caesarean section. The Master’s Degree course in Reproductive Epidemiology, which began in Cuernavaca, Mexico, in March 1991, continues to attract foreign students. In 1998–1999, eight students enrolled for the course, three of whom were supported by Research Training Grants.

HRP provides support to the Centre for Population Studies (CENEP) in Buenos Aires, Argentina, to coordinate the regional social sciences network. Its purpose is twofold. Firstly, the Centre disseminates information on social sciences research relevant to reproductive health, on training opportunities, scientific meetings, etc. The network has already published eight bulletins and 26 newsletters; the latter are circulated via e-mail to more than 250 scientists from the Americas and other parts of the world. The second task of the Centre is to coordinate the regional, multicentre research project “Reality and beliefs in the sexual and reproductive decision-making process: men’s perceptions and behaviour” which includes social science groups from Argentina, Bolivia, Cuba and Peru; the project is expected to be completed in July 2000.

With respect to the basic sciences network, as already mentioned, centres in Argentina, Chile and Mexico are involved in a regional research initiative focused on the study of the mechanism of action of hormonal preparations used for emergency contraception. Specific research proposals will be developed in 2000.

HRP continued to support the Latin American Programme of Cooperation and Research in Human Reproduction (PLACIRH), a unique regional research and research training organization active in the field of reproductive health. Resources for training grants were again awarded to PLACIRH to support its extensive intraregional training programme for young scientists from Latin American institutions.

Increased linkage between institutional strengthening support and implementation of specific research initiatives at national and regional levels

RAP has reiterated its recommendation that resources for new Long-term Institutional Development (LID) and Resource Maintenance Grants (RMGs) should be linked to specific research projects, and all budget lines such as salaries, equipment, reagents, etc. should correspond to contributions to well-defined research activities.

In 1998, 11 research projects linked to institutional strengthening grants were under way or completed. In addition, four recipients of Research Training Grants (RTGs) were carrying out their Re-entry Grant projects (see Table I for topics covered by these 15 studies supported by capacity building grants).

At the same time, centres taking part in the regional research initiatives are being strengthened through their participation in these multicentre studies which are based on proposals approved after extensive ethical and scientific review, locally and within HRP. This practical application of the concepts of “strengthening through research” and “networking” is critical to an optimal use of the limited capacity building resources centrally available. It promotes intraregional cooperation, and amplifies the impact of the efforts and resources that HRP has deployed in building up research capacities in the Americas region over the last 20 years.

Research training, the other main component of institutional strengthening, continues to be a prioritized

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activity, so that further development of research capacities at the regional level may be achieved. In 1998–1999, eight scientists were trained, seven of them in intraregional programmes in the areas of reproductive epidemiology, reproductive medicine, biostatistics, public health and molecular biology; four of these scientists were women, and the average duration of training was nine months.

**COUNTRY REPORTS**

During 1999, HRP collaborated with 19 institutions in 11 countries of Latin America: Argentina, Bolivia, Brazil, Chile, Colombia, Cuba, Guatemala, Mexico, Paraguay, Peru and Venezuela. A description of the main developments at the country level follows.

**ARGENTINA**

Support has continued to the Rosario Centre for Perinatal Studies (CREP). CREP conducts research in the areas of maternal and infant health, adolescent health and reproductive health epidemiology. It also serves as a training and research methodology referral centre for the country and the region. It was one of the four sites of the antenatal care project and is also participating in the misoprostol trial and the regional Caesarean section study, which were initiated in 1998.

The Centre for Population Studies (CENEP) in Buenos Aires is the coordinator and one of the study sites of the regional multicountry social science study on men’s perceptions and behaviour with regard to decision-making processes affecting sexual and reproductive health.

The Institute for Experimental Biology and Medicine, awarded a LID Grant in 1997, continues to develop basic sciences research in the field of male fertility.

The Centre for Studies of the State and Society (CEDES) in Buenos Aires is coordinating the social science component of the regional initiative on Caesarean section.

**BRAZIL**

The Campinas Research Centre for the Control of Maternal and Childhood Diseases (CEMICAMP) of the University of Campinas is the main recipient of HRP support in the country. Grants cover work undertaken on training in research methodology and on research dealing with clinical epidemiology and social science issues relevant to contraceptive introduction and other aspects of women’s reproductive health. CEMICAMP was one of the three study sites implementing the regional multicentre study on the acceptability of emergency contraception, which was completed in 1999. It also conducted one of the three projects being carried out in the region to explore the process of informed consent.

CEMICAMP is also taking part in the clinical and social sciences studies concerned with the regional Caesarean section trial.

**CHILE**

Two institutions in Santiago continued to receive support: the Chilean Institute of Reproductive Medicine (ICMER) and the Unit of Reproductive Biology and Development at the Catholic University of Chile. These centres also participate in HRP-supported institutional development activities and act as regional training centres.

In addition to institution-initiated research focused on the biology and physiology of reproduction of the New World monkey *Cebus apella*, the Unit of Reproductive Biology and Development is coordinating the regional basic sciences network concerned with the mechanism of action of hormonal preparations used for emergency contraception. Research at ICMER, the recipient of an RMG, is focused on projects that integrate biomedical and social sciences approaches and methodologies, and aim to improve contraceptive use and family planning services. ICMER coordinated and participated in the regional multicentre study on the acceptability of emergency contraception, which was completed in June 1999.

**COLOMBIA**

The University of Valle in Cali is involved in plans to reduce maternal mortality in the country, the main objectives being: (i) to develop operational research to improve the delivery of maternal health services; (ii) to support epidemiological studies on the development of risk models for the primary causes of maternal morbidity and mortality in Colombia; and (iii) to improve the network of maternal care research. HRP is extending support to the centre for participation in the Magpie Trial coordinated by Oxford University, Oxford, United Kingdom, which evaluates the
use of magnesium sulphate for the treatment of pre-eclampsia.

CUBA

Cuba’s research in reproductive health is conducted within the well-established national strategic plan by the National Coordinating Network for Research in Human Reproduction (comprising the National Institute of Endocrinology, the Hospital America Arias, and the Ramon Gonzalez Coro Hospital) and in concert with the other public health programmes in the country. Extensive collaboration in multicentre trials is ongoing with various HRP Research Groups. In 1998, the National Centre for Sex Education (CENESEX) was incorporated as the fourth Unit of the network.

The Institute of Endocrinology continues to conduct basic sciences research in the area of reproductive immunology. The Institute’s Social Sciences Unit is implementing the four-country regional research initiative on men’s perceptions and behaviour in respect of decision-making processes affecting sexual and reproductive health.

The America Arias Hospital took part in the multicentre antenatal care project and is currently participating in both the clinical and social sciences components of the regional caesarean section study.

GUATEMALA

The Guatemalan Research Group in Reproductive Health, based at the San Juan de Dios Hospital, Guatemala City, receives support to develop a reproductive health research unit for epidemiological and health service studies focused on the country’s research priorities. It also provides consultant assistance to institutions in the Central American subregion and coordinates a subregional study on maternal mortality supported by the International Federation of Gynecology and Obstetrics (FIGO). Research was focused on a detailed follow-up study of women and their offspring of the index pregnancy that occurred approximately 10 years previously; data collection for this study was completed in 1999. Its main objective is to assess the current situation of a subsample of intrauterine growth-retarded, preterm and normal birth-weight children from the original cohort; the main outcomes being evaluated are anthropometric variables, blood pressure, schooling and sexual maturation. The Guatemalan centre is also participating in both the clinical and social sciences components of the regional caesarean section study.

MEXICO

The Department of Reproductive Biology in the National Institute of Nutrition, Mexico City, is the main recipient of HRP support in the country. The Institute receives major support from national authorities, including the Ministry of Health, which has extensive national programmes for the improvement of reproductive health. The Institute is also actively involved with the various Strategic Programme Components and other international funding agencies. The Institute maintains a very high level of research productivity and continues to play an important role in collaboration with HRP and other research centres in the Region. In 1999, the Institute continued to receive Resource Maintenance and Basic Resources for Training Grants, which have facilitated its extensive participation in research and training. The Institute is one of the four centres constituting the regional basic sciences network, the aim of which is to explore the mechanism of action of hormonal preparations used for emergency contraception.

HRP supported activities in three other Mexican centres. One is the Reproductive Biology Department of the University of Coahuila at Torreon, which is developing programmes in the area of postpartum contraceptive methods and the relationship between reproductive health and environmental contamination. Support to this centre is focused on a study that explores the influence of adverse environmental conditions on male reproductive health.

The second grant is to the two-year M.Sc. Degree programme in Reproductive Epidemiology organized by the National Institute of Public Health at its centre in Cuernavaca. Over the past eight years, the course has had on its rolls graduate students from Programme-supported centres in Argentina, Chile, Cuba, Guatemala, Mexico, Panama, Peru and Venezuela.

The Institute for Scientific Research of the University of Durango is the third Mexican centre involved in Programme-supported activities. In conjunction with ICMER (Chile) and CEMICAMP (Brazil), Durango took part in the regional multicentre study on the acceptability of emergency contraception, completed in June 1999.

PARAGUAY

Continuation of collaborative activities between the Centre for Interdisciplinary Studies (CERI), Paraguay, and CENEP, Buenos Aires, have facilitated the strengthening of human resources for social sciences research relevant to reproductive health in this country. One of the fellows trained as part of this twinning programme was successful in getting a research project approved in the Programme’s call for proposals in the area of sexual and reproductive health of adolescents.
PERU

HRP supported two centres affiliated to the Peru University Cayetano Heredia in Lima, which serves as a resource and training centre in reproductive health. Research carried out by the Institute of Research on Altitude, currently receiving an RMG, includes studies in the areas of reproductive health of adolescents, reproduction at high altitude and reproductive immunology.

The other centre, the Institute for Population Studies in Lima, is one of the sites of the four-country, regional social science research initiative on men’s perceptions and behaviour in respect of decision-making processes affecting sexual and reproductive health.

VENEZUELA

HRP collaborates with the Foundation for the Study of Mother and Child (FUNDAMATIN), a private non-profit organization, based at the Maternity Concepción Palacios in Caracas, and with the Venezuelan Institute of Scientific Research (IVIC). The grant awarded to IVIC is utilized for research that explores basic science issues related to the pathophysiology of eclampsia. FUNDAMATIN receives support to take part in the Magpie Trial coordinated by Oxford University, UK, which evaluates the use of magnesium sulphate for the treatment of pre-eclampsia. In collaboration with IVIC, FUNDAMATIN organizes an M.Sc. postgraduate programme in human reproductive biology.

PLANNED ACTIVITIES

Activities in the Region are taking into account the reorganization that has recently taken place within HRP and the Department.

Regional activities have been included in the Technical Support to Countries (TSC) Team of the Department. These activities formerly focused on national and regional reproductive health research and research capacity-building. They have been expanded to include the provision of knowledge and tools to countries to assist in the formulation of policies and strategies required to implement appropriate interventions for the improvement of reproductive health.

At the 1999 meeting of RAP (the Americas), the integration of research and technical support activities was strongly commended. Nevertheless, it was felt that without a significant increase in financial resources for regional activities, the achievements would be negligible. Some of the regional centres are prepared to undertake technical support activities at the regional and national levels, but the need to strengthen capacities in the area of operations research was strongly emphasized. Likewise, it was felt that this new approach required an even stronger coordination and collaboration with the Regional Office and with the UNFPA Country Support Teams, both of which are strongly involved in technical support to activities in reproductive health at the country and regional levels.

In preparation for the work to be undertaken in the 2000–2001 biennium by the TSC Team, staff from the Department and from the Americas Regional Office, with the endorsement of RAP, have identified six topics on which to focus research and technical support activities: maternal mortality; adolescent reproductive health; perinatal health; men’s roles in reproductive health; emergency contraception; and reproductive health services.

The integration of research and technical support activities at the regional and country levels should undoubtedly facilitate a more effective and timely response to the reproductive health needs of populations in the developing world.
Annex 1

REGIONAL ADVISORY PANEL FOR THE AMERICAS IN 1999

Members

C. Hogue, Emory School of Public Health, Atlanta, GA, USA (Chairman)
E. Taucher, Institute of Nutrition and Food Technology, Santiago, Chile
Z. Palma, Women’s Centre, Buenos Aires, Argentina

Co-opted Members

S. Campo, Children’s Hospital, Buenos Aires, Argentina
R. Ferriani, University of Sao Paulo, Sao Paulo, Brazil
A. Diez, Hospital del Mar, Barcelona, Spain

<table>
<thead>
<tr>
<th>Region</th>
<th>Developing countries</th>
<th>Countries in transition</th>
<th>Developed countries</th>
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<tr>
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<td>Number</td>
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<td>66</td>
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</tr>
<tr>
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</table>

from:
AFRO
AMRO
EMRO
EURO
SEARO
WPRO

Collaborating agency scientists

R. Schiavon, The Population Council, Mexico City, Mexico
R. Rivera, Family Health International, Research Triangle Park, NC, USA
J. Tolosa, International Clinical Epidemiology Network, Philadelphia, PA, USA
Annex 2

REGIONAL SCIENTISTS IN 1999

Principal investigators

G. Alvarado, Institute for Scientific Investigation, Durango, Mexico
A. Andrade, Centre for Reproductive Biology (CBR), Juiz de Fora, Brazil
K. Austin, Centre for Research in Human Reproduction, Panama City, Panama
S. Bassol, University of Coahuila, Torreon, Mexico
S. Campo, Endocrinology Research Centre (CEDIE), Buenos Aires, Argentina
P. Cuasnicu, Institute for Biology and Experimental Medicine (IBYME), Buenos Aires, Argentina
G. Carroli, Rosario Centre for Perinatal Studies (CREP), Argentina
R. Deis, Reproduction and Lactation Laboratory (LARLAC), Mendoza, Argentina
L. Devoto, Institute for Maternal and Child Health Research (IDIMI), Santiago, Chile
G. Etchegoyen, Centre for Applied and Experimental Endocrinology (CENEXA), La Plata, Argentina
F. Febres, Foundation for the Study of Mother and Child (FUNDAMATIN), Caracas, Venezuela
R. Fogel, Centre for Interdisciplinary Studies (CERI), Asunción, Paraguay
F. García Pimentel, Ministry for Planning and Sustained Development, La Paz, Bolivia
G. Gonzales, Cayetano Heredia Peru University, Lima, Peru
E. Hardy, Centre for Research and Control of Maternal and Childhood Disease (CEMICAMP), Campinas, Brazil
E. Kestler, Epidemiologic Research Centre, Guatemala City, Guatemala
F. Larrea, National Institute of Nutrition, Mexico City, Mexico
E. Lazcano, National Institute of Public Health, Cuernavaca, Mexico
O. Mateo de Acosta, National Institute of Endocrinology, Havana, Cuba
G. Muñoz, Simón Bolívar University, Caracas, Venezuela
E. Pantelides, Centre for Population Studies (CENEP), Buenos Aires, Argentina
S. Quiroga, Centre for Medical Education and Clinical Investigation (CEMIC), Buenos Aires, Argentina
M. Rivarola, Growth and Development Research Laboratory, Garrahan Hospital, Buenos Aires, Argentina
O. Rojas, University of Valle, Cali, Colombia
C. Romero, J.J. Aguirre Hospital, Santiago, Chile
M. Serrón-Ferré, Pontifical Catholic University, Santiago, Chile
F. Zegers-Hochschild, Chilean Institute of Reproductive Medicine (ICMER), Santiago, Chile
Technical support to countries

Asia and the Western Pacific region

Wang Yi Fei and P.J. Rowe
OBJECTIVES

One of the major goals of HRP is to respond to the needs of developing countries. WHO’s South-East Asia and Western Pacific Regions comprise 46 countries distributed over a very broad geographic area, representing a diversity of reproductive health profiles. The challenges presented by this diversity and the huge population (about 60% of the world’s total) are daunting and an adequate response would require resources far beyond the means of HRP.

The two broad objectives of HRP in this combined region are to ensure that the needs of developing countries in Asia and the Pacific are reflected in all activities of HRP, and that they receive technical and financial support to strengthen their capacity to undertake research in reproductive health which is country-specific and, where appropriate, address global reproductive health problems.

INTRODUCTION

During the past years, collaboration between HRP and many centres in the region has been exceptionally productive and successful. HRP’s technical and financial support has resulted in significant strengthening of research capabilities and has had an impact through research, on reproductive health care and family planning policies and services in many of these countries. Collaboration between HRP and some countries of the region (e.g. China, India and Thailand) over the past two decades has significantly increased the research capacity in reproductive health of these countries. Some centres in these countries now have excellent research facilities and competent scientists who are able to determine their own research priorities, design appropriate research projects and implement them. These institutes have demonstrated their ability to participate increasingly in WHO’s global research efforts, as well as provide technical support to other countries of the region.

Reproductive health research and research capacity strengthening are major national needs in all developing countries of this region. The demands for continued institutional and human resource development in these countries remain very high. A creative approach is needed to ensure that HRP’s activities within each country would make a real difference to the people in need. One of the possible solutions may be to devote HRP’s major efforts to encouraging intraregional cooperation, including regional self-reliance in research training, regional research initiatives and regional networking mechanisms. Strengthening collaboration between HRP and the network of institutions, especially mature centres and WHO Collaborating Centres in the region, can also contribute significantly towards the development of institutional capacity to undertake research in reproductive health specific to the needs of the country or region.

PROGRESS

Regional initiatives and activities

Regional research needs and research agenda

At the Asia and Pacific Symposium on “Intraregional Cooperation in Reproductive Health Research” (Shanghai, China, 12–13 October 1998), which preceded the annual meeting of the Regional Advisory Panel (RAP), the participants identified the regional research needs, as well as recommended a regional reproductive health research agenda with the following twelve key issues, among which five topics have been recognized as high priorities (*):

- fertility regulation*
- unsafe abortion*
- maternal and perinatal health*
- adolescent reproductive health*
- RTIs/STDs/HIV/AIDS and cervical cancer*
- infertility
- reproductive ageing
- male involvement in reproductive health
- planning and programming for reproductive health
- environment and reproductive health
- goal-oriented basic research: implantation and sperm biology
- a holistic approach including the cross-cutting issues of gender, ethics and integrated reproductive health services.

The recommendations on regional reproductive health research needs and research agenda are based on the following common consensus: Asia is the region with the largest population and a great diversity of reproductive health issues. Thus, reproductive health needs and population development remain a top priority for research in the Asia/Pacific region in the coming decades.

Based on these recommendations, a document entitled “Sexual and Reproductive Health Research Needs and Research Agenda: the Asian and Pacific Perspective” has been prepared and endorsed by RAP at its 1999 meeting.

Regional research initiatives

The 1998 RAP (Asia and the Pacific) meeting recommended that one of the high-priority tasks in the coming years was to initiate several joint research programmes of regional importance. A regional joint research programme is a powerful stimulus to regional networking, as well as a cost-effective way of research capacity strengthening.
The following two regional research initiatives were being developed in 1999:

- “Collaborative Reproductive Epidemiology Research: patterns and predictors of Caesarean section in Asia”, an 11-country joint research programme (Bangladesh, China, Indonesia, Mongolia, Myanmar, Nepal, the Philippines, Republic of Korea, Sri Lanka, Thailand and Viet Nam) coordinated by the Epidemiology Unit, Faculty of Medicine, Prince of Songkla University, Hat Yai, Thailand.

- “Regional Research Initiative on Adolescent Migrants and Reproductive Health in the Greater Mekong Region”, a five-country joint research programme (China, Lao People’s Democratic Republic, Myanmar, Thailand and Viet Nam) coordinated by the Institute for Population and Social Research, Mahidol University, Nakornpathom, Thailand.

**Regional self-reliance in research training**

Research capacity building, including research training, is a vital and continuing need for the region. An important strategy is to adopt a research-based support for reproductive health capacity building. HRP will support a well-designed and objective-oriented research proposal within which a specific research training programme in skills, relevant to the project and to specific areas considered to be of national importance or in response to urgent needs of the country, is an essential component.

More research training facilities should be encouraged within the region and within the South-to-South cooperation effort. In recent years, centres in Malaysia, Singapore and Thailand have hosted an increasing number of trainees in a variety of research disciplines requiring significant understanding of local public health issues and cultural values. These include community-based studies using epidemiological or social science skills for which there is a pressing need to provide training in a similar cultural setting. Table I summarizes the Research Training Grants funded in 1998.

**National networks**

For many countries in this region, an agenda for a national reproductive health research programme, especially an agenda that takes into account the broader concept of reproductive health as well as the relevant needs and demands in the coming decade, is not yet complete. As a result, research institutes are not able to formulate effectively either their mission statement, or their goals within the context of national needs. Countries are the ultimate practitioners of reproductive health programmes and require sound information from quality and evidence-based research as the basis for planning, designing and implementing programmes addressing the needs and demands of their people. Some of this information is global in nature (e.g. best methods, best practices), but most is country-specific (e.g. the size and nature of the problem to be addressed, the sociocultural context). Most Asian countries, irrespective of their stage of development, will require to undertake their own national reproductive health research, as well as to develop their own national reproductive health policies and service programmes. To this end, the research institutions should and could play an active role in conducting high-quality research and research training, as well as acting as advisers and, in some cases, promotionalists in the policy-making process and improvement of reproductive health care services. However, there is little coordination and collaboration among institutions in many of the countries, especially in the better use of the resources that have been established. It is probable that the national research objectives cannot be met until an effective national coordination mechanism is in place.

Three national research institution networks have been established in the region.

**China**

The National Coordinating Board of China, consisting of stakeholder representatives (State Family Planning Commission, Ministry of Public Health, etc.) and its permanent Secretariat was established in May 1998. Its main functions are described below in the country report on China.

<table>
<thead>
<tr>
<th>Home country of the grantee</th>
<th>Sex of the grantee</th>
<th>Subject of training</th>
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<tbody>
<tr>
<td>China</td>
<td>Female</td>
<td>Endocrinology</td>
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<tr>
<td>Viet Nam</td>
<td>Female</td>
<td>Biostatistics</td>
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</tbody>
</table>
Sri Lanka

Research in reproductive health in Sri Lanka is carried out by four multidisciplinary Task Forces in Colombo, Galle, Jaffna and Peradeniya. The activities of these four Task Forces are coordinated by a National Coordinating Committee with its office in Colombo.

Thailand

The Ministry of Public Health is responsible for the promotion of reproductive health research in Thailand. Its research activities are carried out by seven institutions, the activities of which are coordinated by the Research Institute for Health Science, Chiang Mai University, Chiang Mai.

The ultimate aim of supporting research at the country level is to make a direct impact on the reproductive health of the population. This should be reflected in the improvement of reproductive health indices such as a decrease in infant and maternal mortality rates, a decrease in sexually transmitted infections (STIs), and an increase in the contraceptive prevalence rates. Given the broad scope and magnitude of reproductive health needs in the developing countries of Asia and the Pacific, it would be difficult for HRP to make a significant impact on reproductive health indicators; however, the indirect impact on reproductive health could be effected through national research capacity strengthening and national networking activities, which should eventually make an impact on the national health care system and facilitate the translation of research into action.

To evaluate the impact of research capacity building and national research networking activities, the following indicators are suggested by RAP for Asia and the Pacific:

- number and quality of research projects in reproductive health including total amount of financial support received
- number and quality of publications in peer-reviewed journals and other scientific/technical reports, and presentations of scientific results at national, regional and international meetings
- performance of scientific teams with an interdisciplinary approach
- number and quality of research training programmes and consultancy services the institution has provided within the country and in the region
- role in establishing national guidelines and standards for improving the scientific, gender and ethical aspects of reproductive health research and in the implementation of the national reproductive health programme
- role in building national capacity to carry out national reproductive health programmes
- role in dissemination and utilization of reproductive health and in promotion of reproductive health research collaboration within the country and the region
- role in the formation and implementation of the reproductive health policy of the country
- involvement and participation in the regional and global reproductive health research agenda.

COUNTRY REPORTS

CHINA

Collaboration between HRP and China has been one of the most successful research capacity building initiatives in the last 20 years. Both the Chinese Government and HRP agree that strengthening collaboration can significantly contribute towards the development of research capacity and the promotion of research in family planning and reproductive health in China, as well as enrich HRP’s experience and capacity to assist other developing countries to achieve the same goals.

Since 1979, total funding from HRP to these collaborative activities in China has amounted to some US$ 17 million. Total funding from UNFPA has been US$ 13 million. The Chinese Government has invested at least twice the combined WHO and UNFPA input of US$ 30 million, covering all costs for capital construction, staff salaries and other running expenses. As China’s institutional research capability has expanded, the strategy for collaboration in the future requires adjustment to remain appropriate. A review of the strategy for collaboration with China was initiated by HRP in 1996. After several in-depth discussions between the Chinese Government and HRP, a “Strategic Framework for Collaboration on Reproductive Health/Family Planning (RH/FP) Research between China and WHO (1998–2003)” and work plan for 1998–1999 were formulated in 1997.

The major components of this new strategy are:

- to review and set priorities for RH/FP research at national and institutional levels;
- to further strengthen the national and institutional capability for research in RH/FP;
- to conduct RH/FP research at national, provincial and community levels;
- to promote dissemination, transmission and utilization of RH/FP research results to policy-makers, programme managers and service providers;
- to improve the management and coordinating capacity in RH/FP research at national and institutional levels;
- to participate in the global RH/FP research effort and share experiences with other countries.

The 1997 and 1998 RAP meetings appreciated the general
strategy to be taken to promote the collaboration with China and recommended that HRP could now economize on the core support to these institutes. Instead of supporting these institutes individually, HRP should assist in developing a new national research capacity building strategy and establishing an effective national coordinating mechanism, making better use of existing resources in these institutes, as well as strengthening the links between research and reproductive health policies and services.

For these relatively mature institutes, including former UNFPA-supported institutes, further assistance should be by way of supporting some of the research programmes consisting of several research projects of national and regional importance. The research programme should provide information on the rationale, objectives and the expected outcome of the overall programme, and the experimental details of the individual research projects forming the programme. The need for equipment, research training and workshops relevant to the proposed research programme would then have to be justified. These institutions should be encouraged to participate more actively in research projects of both national and regional importance, and to undertake more effective interaction with national authorities and international agencies. The scientists of the institute will also be called upon as a resource to promote and assist with research and research capacity building of other institutions in the country and the region.

National Coordinating Board (NCB)

The NCB, consisting of stakeholder representatives (such as the State Family Planning Commission and the Ministry of Health) and its permanent Secretariat was established in May 1998. Its main functions are:

- drafting national reproductive health research programmes based on the national needs assessment and priority setting;
- coordinating the national research network comprising seven WHO Collaborating Centres and some 20 provincial research institutes;
- better utilization of the human and non-human resources that have been established;
- streamlining procedures for review and processing of research proposals;
- organizing national workshops/training courses/scientific meetings; and
- seeking national and international funding.

Regular NCB meetings were held in 1998–1999.

Several Steering Committees, including the National Ethical Review Group, National Scientific and Technical Advisory Group, Male Methods, Female Contraceptives, and IUD have been established. In addition, three working groups (social science, technology introduction and transfer, and post-marketing surveillance) were established as well.

One of the key strategies for collaboration on RH/FP research between China and WHO (1998–2003) is to assist the Chinese Government in the articulation of what is wanted in a national research programme, especially within the broader concept of reproductive health and the relevant needs as well as the demands of China in the coming century. For this purpose, a National Workshop for Institutional Leaders on National and Institutional Priorities for Reproductive Health and Family Planning Research was held in Beijing, 6–8 May 1998.

The objectives of this workshop were:

— to review and set priorities for RH/FP research at national and institutional levels; and
— to identify which of the reviewed issues require initiatives to write research proposals.

The following are considered to be high-priority research areas:

(i) Fertility regulation
— assess the safety and efficacy of existing methods of fertility regulation;
— develop approaches to broaden the choice of methods of fertility regulation and to ensure their provision through both quality and sustainable services;
— develop improved and new methods of fertility regulation, such as emergency contraception, male methods and dual protection methods.

(ii) Maternal and perinatal health
— conduct research on causes and consequences of unsafe abortion and develop tools to monitor programmes designed to reduce unsafe abortion;
— identify minimum integrated packages of reproductive health information and care, including free and informed choice in fertility regulation, appropriate for use in different settings and within the primary health care approach;
— develop simplified methods of diagnosis and treatment of selected conditions in the newborn and promote effective methods to ensure optimal fetal growth and prevent premature birth.

(iii) Reproductive tract infections (RTIs) and sexually transmitted infections (STIs)
— document the prevalence and social and behavioural determinants of STIs and non-sexually transmitted RTIs in different population groups;
— develop and promote cost-effective interventions for prevention of RTIs and STIs (including HIV).
(iv) **People’s needs and demands**

—document the extent and identify the cause of unmet needs for RH services among groups with different demographic and sociocultural characteristics;

—promote environments conducive to free and informed choice for RH services by raising awareness and knowledge, especially among the youth and underserved people and by facilitating relevant policy changes.

Four working groups were established at the workshop and each was requested to identify which of the reviewed priority issues require initiatives to write research proposals, preferably multicentre research protocols.

**Site visit to six research institutes**

HRP and NCB staff undertook joint site visits to six institutions. To build capacity for RH/FP research and to strengthen the link between research and health care, there is need to determine the role of all research institutes in contributing to the goals and objectives of the Chinese national RH/FP programme.

- Each institute should be encouraged to identify and promote its strengths in terms of the country’s needs and to define its comparative advantages.
- All the institutes require help in their strategic planning so that the research programmes give full scope to the strengths of the institutes and address priority national, provisional and local issues.
- Consideration should be given to other functions of research institutes in addition to the traditional research and training activities such as: information dissemination; communication with policy-makers, service providers and users; provision of norms, guidelines and standards of RH/FP service; community service and model setting on RH/FP; etc.

The following were recommended as the research priority areas and main collaborative activities between WHO and the institutes (1998–2001):

**National Research Institute for Family Planning (NRIFP), Beijing**

- Develop improved and new methods of fertility regulation, such as emergency contraception, male methods and immunocontraception.
- Develop new diagnostic methods for congenital malformations and birth defects.
- Document the extent and identify the causes of unmet needs for RH services among groups with different demographic and sociocultural characteristics.

**Peking Union Medical College Hospital (PUMCH), Beijing**

- Assess the safety and efficacy of existing methods of fertility regulation.
- Develop methods for perinatal diagnosis.
- Menopause: basic and clinical study.

**Institute for Population Research, Peking Union (IPRPU), Beijing**

- Social and demographic determinants of reproductive health.
- Planning and programming for RH.
- International Postgraduate Programme in Population and Development.

**Tianjin Municipal Family Planning Research Institute (TMFRI), Tianjin**

- Assess the safety and efficacy of existing methods of fertility regulation.
- Develop improved and new methods of fertility regulation.
- Planning and programming for RH.

**Shanghai Institute of Planned Parenthood Research (SIPPR), Shanghai**

- Assess the safety and efficacy of existing methods of fertility regulation.
- Develop approaches to broaden the choice of methods of fertility regulation and ensure their provision through high quality and sustainable services.
- Develop improved and new methods of fertility regulation.
- Social and demographic determinants of reproductive health.
- Prevention of and intervention for reduction of RTIs/STIs.

**National Evaluation Centre for the Toxicology of Fertility Regulating Drugs (NTC), Shanghai**

- Set up a series of standard toxicology tests and establish the Centre as one that meets international standards for toxicology testing of contraceptive drugs.

Site visits to the Family Planning Research Institutes of Zhejiang and Sichuan were undertaken in 1999.

**National research proposals**

Several research proposals have been developed:

- An assessment of the needs for contraceptive introduction in Chongqing Municipality, China
• An intervention trial for providing quality care in family planning services to decrease the incidence of adverse reactions of IUDs in Chinese women
• Promoting condom use among couples for dual protection against both pregnancy and STIs
• Semen quality and its influencing factors
• The role of men in reproductive health

National Workshops/Training Courses

During 1998–1999, six National Workshops/Training Courses were organized by NCB, with technical and financial support from HRP:

• National Workshop on “Contraceptive Adverse Reactions Reporting System”, Nanjing, 16–18 November 1998
• National Workshop on “Reproductive Health: Technology and Services”, Beijing, 1–3 September 1999
• WHO/Ford Foundation cosupported National Training Course in Gender and Reproductive Health, Kunming, 6–24 September 1999

Publications and dissemination

The English version of the Chinese journal of reproduction and contraception was published during 1998–1999.

National Research Institute for Family Planning (NRIFP), Beijing

In the late 1970s, the Chinese Government created a network of Family Planning Research Institutes that would conduct research of relevance to the national family planning programme. The National Research Institute for Family Planning, Beijing, created in 1979, was to be developed as a national institute, having a leadership role in research, research training and in providing assistance to the Government in the planning and implementation of the national research programme in reproductive health. The Institute moved to new buildings with first class research facilities in 1986.

To undertake its busy research programme, the Institute collaborates with numerous hospitals and other institutions in the Beijing municipality, with institutes of the national research network and with many international agencies. In the countryside, one-and-a-half hours from Beijing by road, the Institute has developed a Rural Study Programme that will provide access to 40,000 couples of reproductive age.

The Institute was designated a WHO Collaborating Centre in 1990.

Research activities

Research activities of the institute in 1998–1999 included more than 40 research projects, among which 14 were supported by HRP:

• A randomized comparative study of interval insertion of two IUDs: the TCu380A and FlexiGard
• A randomized comparative study of interval insertion of two IUDs: the TCu380A and the Multiload Cu375
• A prospective comparative study of three methods of male sterilization
• A randomized comparative study of interval insertion of two IUDs: the TCu380A and levonorgestrel 20 µg IUDs
• Development and evaluation of introduction of emergency contraception for reducing unintended pregnancy among young workers
• Mechanism of emergency contraception
• Multicentre clinical evaluation of contraceptive efficacy of injectable testosterone undecanoate in normal men
• The role of men in reproductive health in China
• A randomized comparative study of two IUDs: the TCu380A and the uterine-shaped steel–copper ring
• A clinical study of using IUD in emergency contraception
• The acceptability study of injectable testosterone undecanoate as a contraceptive method in China
• Effect of RU486-induced abortion on outcomes of subsequent pregnancy in China
• Double-blind, multinational study to compare mifepristone and two regimens of levonorgestrel in emergency contraception
• A double-blind, randomized multicentre trial of three misoprostol regimens after pretreatment with mifepristone for termination of early pregnancy

The main research areas of NRIFP are:

• fertility regulation including emergency contraception, IUDs, male methods and immunoc contraception;
• social science and epidemiology studies;
• diagnostic technology for birth defects;
• basic research: cell and molecular biology.

Research capacity building

During this period, eight staff members were trained abroad, of whom four have already returned. In 1998, 28
foreign experts including two members of HRP visited the Institute.

The Institute offered several postgraduate courses leading to a Master’s Degree in the following subjects: Reproductive Endocrinology, Cell Biology, Molecular Biology, Biochemistry and Pharmaceutical Chemistry. In addition, two national training courses on maternal health with 600 trainees and one symposium on reducing unwanted pregnancy were organized by the Institute in 1998. More than 2000 field workers were trained by staff of the Institute in 1998.

Supported by the Chinese Government, the research facilities, including a clinical research centre and animal house, have been greatly improved. A Chinese reproductive health research database has been created in the Institute as well.

Dissemination of information

The annual report of NRIFP included an impressive list of publications in 1998:

- 51 original articles (11 in international journals)
- two books
- two book chapters
- eight congress abstracts.

Fourteen staff members attended 24 international symposia/meetings in 1998.

The Science Information Centre at NRIFP is responsible for the collection and dissemination of scientific information, including the translation of HRP newsletter Progress in human reproduction research, Outlook, IPPF medical bulletin and Reproductive health matters, as well as the publication of the bilingual Chinese journal of reproductive medicine and Chinese journal of family planning.

Shanghai Institute of Planned Parenthood Research (SIPPR), Shanghai

The Shanghai Institute of Planned Parenthood Research (SIPPR), founded in 1979, and the National Research Institute for Family Planning in Beijing, were established as national centres with special responsibility for assisting the Government in planning and implementing the national research programme. SIPPR pursues a very broad programme of reproductive health research, covering areas from social science, synthetic and analytical chemistry, pharmacology, preclinical studies and clinical trials to large-scale epidemiological projects and increasing activities in basic research.

The Institute was designated a WHO Collaborating Centre in 1983.

Research activities

Research activities of the Institute in 1998 included 54 research projects, of which 23 were supported by HRP covering the areas of social science, fertility regulation, induced abortion, RTIs/STIs and basic research. They are:

- A randomized comparative study of interval insertion of two IUDs in parous women: the TCu380A and the FlexiGard
- A randomized comparative study of interval insertion of two IUDs: the TCu380A and the Multiload Cu375
- A randomized comparative study of interval insertion of TCu380A and the levonorgestrel 20 µg IUDs
- A cohort study of couples’ use of contraception and fertility status within five years of their marriage
- Semi-prospective study on induced abortion and outcome of subsequent pregnancy
- Contraceptive efficacy of a combined contraceptive regimen of condom and postcoital emergency contraception
- Chlamydia and gonorrhoea prevalence rates in women seeking abortion and the association between main STDs and demographic characteristics as well as sexual history data
- The effectiveness of education in promoting condom use among STD patients
- To assess the quality of sexual behaviour survey data in Shanghai
- A randomized comparative study of two IUDs: the TCu380A and the uterine-shaped steel–copper ring in parous women in rural areas of China
- Condom promotion and STD clinics in Shanghai municipality
- Study of STDs and induced abortion-related complications in women seeking abortion
- Intrauterine device TCu380A used in emergency contraception
- Trial of acceptability of three types of condoms in Shanghai
- Emergency contraception and reasons for its non-use among women
- Research on the development of a radioimmunoassay method for the new one-rod contraceptive implant containing gestodene
- A study of integrated STD/HIV services into family planning clinics
- Effect of RU486-induced abortion on outcomes of subsequent pregnancy in China
- Expression of mouse endometrial factors MEF1.6 and MEF1.7 in E. coli (Re-entry Grant)
- A randomized, multinational study to compare mifepristone and two regimens of levonorgestrel in emergency contraception
- A double-blind, randomized, controlled multicentre trial
of three misoprostol regimens after pretreatment with mifepristone for termination of early pregnancy

- Reproductive health status and needs of young migrants in urban China
- Study on the unmet needs and provision barriers for sexual and reproductive health services for sexually active unmarried young adults in China

**Research capacity building**

The Asia and Pacific symposium entitled "Intraregional Cooperation in Reproductive Health Research" was held in Shanghai on 12–13 October 1998 in conjunction with the 20th founding anniversary of the Institute. At the meeting, a new strategic plan for institutional development of SIPPR was introduced. According to this new infrastructure plan, the research arm of SIPPR would include:

- Reproductive Health Research Centre
- Drug Research Centre
- Laboratory Animal Inspection Centre.


The Institute offered several postgraduate courses leading to Ph.D. and/or Master’s Degrees in the following subjects: Medical Demography; Obstetrics and Gynaecology; Medical Genetics; Developmental Biology; Pharmacokinetics; Reproductive Immunology; and Reproductive Toxicology.

In addition, one international symposium, one workshop and one training course were organized by the Institute in 1998.

Five scientists were invited as members of the Chinese National Scientific and Technical Advisory Committee.

In undertaking research, SIPPR collaborates with a number of institutions within China (51) and many institutions overseas (35). Notable among the latter is Prince Henry’s Institute of Medical Research, Melbourne, Australia. The twinning programme between these institutes, which is supported by HRP, focuses on different aspects of fertility regulation research and has created a good opportunity for both institutes to establish close linkage in areas of mutual interest.

**Dissemination of information**

The Annual Report of SIPPR provided an impressive list of 71 professional publications for 1998:

- 44 original papers
- five review articles
- two full books
- two book chapters
- 18 congress abstracts

The Science Information Centre at SIPPR is responsible for the collection and dissemination of scientific information, including translation of HRP’s Biennial Report and other WHO publications relating to reproductive health, as well as the publication of the bilingual journal *Reproduction and Contraception*.

**Peking Union Medical College Hospital (PUMCH), Beijing**

The Peking Union Medical College Hospital (PUMCH) is a general hospital which is affiliated to the Peking Union Medical College and which has, for many years, enjoyed a reputation as the most prestigious medical university in China. In recognition of the contribution made in the field of reproductive health research, the Division of Reproductive Endocrinology and Infertility, PUMCH was designated a WHO Collaborating Centre for Research in Human Reproduction in 1993.

**Research activities**

During 1998–1999, the Division reported 19 ongoing research projects, two of which were funded by HRP:

- Comparison study of TCu380A and FlexiGard IUDs
- Comparison study of TCu380A and levonorgestrel 20 µg IUDs

The main research areas of PUMCH are:

- fertility regulation including IUDs, emergency contraception and sterilization
- menopause: basic and clinical studies
- prenatal diagnosis
- assisted reproductive technologies.

**Research capacity building**

Support through a Long-term Institutional Development (LID) Grant to the Institute began in 1990. In undertaking the research projects, the Division continued its good collaboration with many international agencies and pharmaceutical companies.

During 1998, one staff member underwent training abroad and one returned from training. Both were supported by HRP.

The Institute offered several postgraduate courses leading to Ph.D. and/or Master’s Degrees in the fields of Reproductive Biology and Reproductive Medicine. In addition, two regional symposia and four national training
courses were organized by the Institute and attended by 3250 participants.

Dissemination of information

The Institute published nine original articles, five review papers and three book chapters in 1998. The book Research on the menopause in the 1990s was translated and published. The Institute continues to publish the Journal of reproductive medicine, partly supported by HRP, which is welcomed by both Chinese and international readers.

Institute of Population Research, Peking University (IPRPU), Beijing

The Institute of Population Research, Peking University (IPRPU) is an interdisciplinary centre with expertise in population economics, economic demography, social demography and population demography. It has a broad research programme, including studies on behavioural and social determinants of fertility regulation, fertility preferences and analysis of national population census data.

The Institute was designated a WHO Collaborating Centre in 1991.

Research activities

During 1998–1999, the Institute initiated or continued eight social science research projects on reproductive health, among which two were supported by HRP:

- Study on reproductive health service in poor rural areas of China
- Reproductive health status and needs of young female migratory workers in urban China.

Research capacity building

The Institute has received a LID Grant from HRP since 1990. Central to the LID Grant proposal was support for a postgraduate course leading to a Master’s Degree (M.A.). Since 1996, the financial and technical support to this Institute has been decided on a yearly basis.

During the reported period, one staff member went abroad for post-doctoral training, and one returned from her training abroad.

The Institute provides the following postgraduate courses:

- Population and Society: Introduction
- Demographic Analysis: Methods and Application
- Social Science Research in Reproductive Health
- Computer Application in Population Science
- Research Methods of Social Science

A total of 81 students attended these courses, among whom 15 were foreigners.

During 1998, three doctoral students were admitted; seven students—six Chinese and one foreigner—started the International M.A. Degree Programme in Population Science, supported by HRP and the Chinese Government.

The Institute is in an excellent position to play a significant part in advising the Government on population policy and to help other institutions through teaching and collaborative research.

Dissemination of information

During the reporting period, 15 original papers and four books were published.

Tianjin Municipal Research Institute for Family Planning (TMRIFP), Tianjin

In 1978 and 1979, the Chinese Government created a nationwide network of Family Planning Research Institutes to meet the needs for research of the family planning programme. The Institute in Tianjin forms part of this network and was founded as a research institute of the Tianjin Medical College in 1982. In September 1984, it moved to a small campus in a science park in the suburbs of Tianjin. The Institute implements a programme of research in collaboration with 17 principal national collaborating units, of which five are in Tianjin and 12 in other provinces and municipalities. The family planning clinic attached to the Institute was officially started in a new building constructed in 1990.

The Institute was designated a WHO Collaborating Centre in 1990.

Research activities

During 1998–1999, the Institute initiated or continued 17 research projects, among which nine were supported by HRP:

- A randomized comparative study of interval insertion in parous women of two IUDs: the TCu380A and the FlexiGard IUD
- A randomized comparative study of interval insertion of two IUDs: the TCu380A and the Multiload 375 IUD
- A randomized comparative trial of interval insertion of TCu380A and levonorgestrel 20 µg IUDs
- A pilot study of the postplacental insertion of the GyneFix (CuFix) IUD
Contraceptive efficacy of a combined contraceptive regimen consisting of condom and postcoital emergency contraception

A comparative study of acceptability of surgical and medical abortion in China

A randomized comparative trial of interval insertion of the TCu380A and the uterine-shaped steel–copper IUD in parous women in rural areas of China

A multicentre clinical study of inserting the TCu380A for emergency contraception

A randomized, double-blind, multinational study to compare mifepristone and two regimens of levonorgestrel in emergency contraception

Research capacity building

The research capacity of the Institute was further enhanced in 1998.

- The Institute started its collaboration with pharmaceutical companies and international agencies. Notable among the latter is the EU–China Training Programme on HIV/AIDS and STDs.
- The Institute offered several postgraduate courses (peptide chemistry) leading to a Master’s Degree.
- Five foreign experts visited the Institute in 1998.
- In 1998, 4260 primary medical workers from grassroots units in China were trained in reproductive health and primary health care at the Institute.

Dissemination of information

Nineteen scientific papers were published in 1998.

Family Planning Research Institute of Zhejiang (FPRIZ), Hangzhou

This Institute was established in 1978 and is one of six institutes of the Zhejiang Academy of Medicine under the Ministry of Public Health. This Institute is best known for its research on long-acting methods of fertility regulation, particularly for the development of injectable steroid preparations. The Institute has also been recognized for its pharmacological work on contraceptive steroids by the Drug Regulatory Bureau of China and for the promotion of Good Clinical Practice (GCP) by the Ministry of Public Health and the Chinese Medical Society.

The Institute was designated a WHO Collaborating Centre in 1981.

Research activities

Research activities in 1998 included 11 research projects in the areas of emergency contraception, long-acting contraceptives, male methods, HIV and STIs, and basic research. Three of these were supported by HRP:

- Effect of medical abortion on outcome of next pregnancy
- Delayed injection of Cyclofem: ovarian and cervical changes
- Study on the unmet needs and provision barriers for sexual and reproductive health services of sexually active unmarried young adults in China.

A randomized multicentre study to compare different regimens of mifepristone alone or combined with anordrin in emergency postcoital contraception in Chinese women was completed. The clinical data indicated that 25 mg mifepristone used alone and 10 mg mifepristone plus 5 mg anordrin are effective and safe methods for emergency contraception. The combination regimen significantly decreased the incidence of induced bleeding.

Research capacity building

The Institute continued to be responsible for assisting the Government in planning and implementing the National Family Planning Research Programme and had special responsibility in the administrative drug regulation process.

The Director of the Institute continued his activities in the Chinese National GCP/Good Laboratory Practice (GLP) Expertise Committee, and was appointed Deputy Chairman of the Task Force of Contraceptive Drugs and Devices by the State Family Planning Commission. In addition, the Institute continued its collaboration with many international agencies and pharmaceutical companies.

After a strict evaluation process, the Institute was redesignated by the Ministry of Health as the National Clinical Pharmacology Base of Contraception, the only one from the entire network of Chinese family planning research institutes. In addition, a National Key Laboratory of Preclinical Safety Evaluation of Drugs was established in the Institute, with support from the State Commission of Science and Technology.

Dissemination of information

Fourteen scientific papers (five in international journals) were reported to have been published.

Family Planning Research Institute of Sichuan (FPRIS), Chengdu

The Family Planning Research Institute of Sichuan is located in Chengdu, the capital of China’s most populous province, Sichuan. The Institute was founded in 1978 as one of several in a national network created by the Government to address problems of family planning. The Centre has direct access, through an established network of village-level clinics in 14 counties and cities in the province, to people living in rural districts. The research in the behavioural and social determinants of fertility
regulation utilizes this network. The Institute plays a leadership role in research in family planning in western China. Its research activities are of national importance and the Institute is receiving increasing international recognition.

The Institute was designated a WHO Collaborating Centre in 1988.

**Research activities**

During 1998–1999, the Institute initiated or continued 28 research projects, among which 14 were supported by HRP.

- A randomized comparative study of interval insertion in parous women of 2 IUDs: the TCu380A and the FlexiGard IUD
- A randomized comparative study of interval insertion of two IUDs: the TCu380A and the Multiload Cu375
- A prospective comparative study of three methods of male sterilization
- A survey of fertility rate and determinants of contraceptive method choice among minority nationalities in Sichuan, China
- A cross-panel multicentre study of genital tract Chlamydia and gonorrhoeal infection in Han woman and minorities
- A randomized comparative trial of interval insertion of the TCu380A and levonorgestrel 20 µg IUDs
- Infertility-related human sperm antigen
- Contraceptive efficacy of injectable testosterone undecanoate in normal men
- A social study on the influence of breastfeeding of working and non-working mothers in Sichuan, China
- Case–control study on tubal infertility and induced abortion (Re-entry Grant)
- Study of effects of long-term administration of androgens on prostate (Re-entry Grant)
- The acceptability study of injectable testosterone undecanoate for male contraception
- Effect of RU486-induced abortion on the outcome of subsequent pregnancy in China
- Study on the unmet needs and provision barriers for sexual and reproductive health services for sexually active unmarried young adults in China.

**Research capacity building**

During restructuring in 1999, FPRIS was incorporated into the Sichuan Reproductive Health Institute (SRHI), which was established in 1980 according to the agreement reached between the Chinese Government and UNFPA.

SRHI engages in continuing education and training for senior MCH/FP professionals. Serving as an important national RH/FP training centre, SRHI has trained more than 10 000 Chinese MCH/FP professionals since its founding. Meanwhile, sponsored by UFNPA, WHO and IPPF, hundreds of senior MCH/FP professionals from 20 countries have completed SRHI training courses, especially in the field of the no-scalpel vasectomy technique.

HRP staff, accompanied by one State Family Planning Commission Officer, visited FPRIS in September 1999 to assist in drawing up implementation plans for priority research in RH/FP. The following were recommended as research priorities and main research directions for FPRIS in the coming years:

- male contraceptive technology; and
- social science and epidemiology studies on unmet needs for RH.

**Dissemination of information**

Fifty-six original articles, 13 review papers, two book chapters, and one full book were released during the reporting period.

**National Evaluation Centre for the Toxicology of Fertility Regulating Drugs (NTC), Shanghai**

The National Evaluation Centre for the Toxicology of Fertility Regulating Drugs evaluates the toxicity of new drugs. It was built to very high standards following advice from WHO consultants specializing in toxicology, animal husbandry and the design of research laboratories and breeding facilities. It also provides specific pathogen-free animals.

**Research activities**

During 1998–1999, seven research projects were ongoing, one of which was supported by HRP:

- Assessment of spermatocyte toxicity screening models in vitro for male fertility regulating drugs using seminiferous tubule culture, Sertoli–germ cell coculture and enriched germ cell culture systems.

The Institute’s research programme focused mainly on studies of the environment and human reproduction, establishment of reproductive toxicology assessment techniques, male methods and immunocontraception.

**Research capacity building**

The Institute was provided with a Resource Maintenance Grant during 1997, with emphasis on the implementation of the toxicological assessment of fertility regulating agents and for the preparatory work for GLP.

The Institute has submitted a new proposal with the
following broad objectives:
— to develop the Institute so that it is authorized for the evaluation of contraceptive drugs and devices; and
— to introduce the GLP standard and put it into practice for the evaluation of fertility regulating drugs and devices.

In undertaking reproductive toxicology research, NTC continued its collaboration with universities in Japan (Nagoya University, Nagoya, and Kumamoto University, Kumamoto) and a pharmaceutical company (Zonagen, Inc., The Woodlands, TX, USA).

A workshop on “Environment and Reproduction” was held in October 1998, partly supported by HRP.

During the reporting period, one staff member went to the Free University of Berlin, Berlin, Germany for training on toxicology, and another returned from her research training in Japan.

In 1998, Professor Ding Xuncheng, Director of NTC, was given the “National Special Achievement Scientist” award by the State Council of China.

Dissemination of information

Seven original papers (three in international journals), one review article, and three official reports were published in 1998.

INDIA

All India Institute of Medical Sciences (AIIMS), New Delhi

The All India Institute of Medical Sciences (AIIMS) has been collaborating with HRP since 1972 and has been a WHO Collaborating Centre since then. It is a well-established national research and training institute set within a large teaching hospital. The following departments at AIIMS have collaborated with HRP: Reproductive Biology, Obstetrics and Gynaecology, Central Radioimmunoassay Facility, and the Non-human Primate Research Facility. The main areas of research in reproductive health are: (i) the development of postovulatory methods for fertility regulation; (ii) the development of methods for male fertility regulation; and (iii) the study of male and female reproductive physiology.

Research activities

The ongoing research programme of AIIMS included 17 research projects, among which two were supported by HRP.

- Double-blind, multinational study to compare mifepristone and two regimens of levonorgestrel in emergency contraception
- A double-blind, randomized, multicentre trial of three misoprostol regimens after pretreatment with mifepristone for termination of early pregnancy.

Drugs were supplied by WHO for another research project entitled “The effect of a long-acting androgen in inducing and maintaining azoospermia in combination with a long-acting progestogen”.

Research capacity building

A three-year grant request, presented as a LID Grant Proposal starting in 1997, was continued as a Resource Maintenance Grant because the Institute has already received support from HRP for more than 20 years. During 1998–1999, HRP continued resource maintenance support to the Central Radioimmunoassay Facility and the Primate Research Facility. The Institute offered a postgraduate course in male reproductive biology leading to a Ph.D. Two foreign experts paid visits to AIIMS during 1998.

Dissemination of information

Seventeen scientific papers were published in 1998.

Institute for Research in Reproduction (IRR), Mumbai

The Institute for Research in Reproduction (IRR), Indian Council for Medical Research (ICMR), is located in Mumbai. It was designated a WHO Collaborating Centre in 1972 and has, in the past, actively participated in collaborative research with HRP, mainly in the area of postovulatory methods for fertility regulation. The Institute has a broad range of scientific programmes in basic and clinical research, such as: immunocontraception, gonadal peptides as contraceptives, contraceptive potential of antiprogestogens, development of diagnostic kits for infertility, RTIs, breastfeeding and lactational amenorrhoea, acceptability studies of contraceptive methods, etc.

Research activities

During 1998–1999, 39 research projects were under way at IRR, among which three were supported by HRP:

- Molecular mechanisms regulating steroidogenic enzymes in ovarian androgen-producing cells (Re-entry Grant)
- Creation and evaluation of a “model system” for predicting comparable in vivo breast milk/plasma ratio of therapeutic drugs (Re-entry Grant)
- A double-blind, randomized, controlled multicentre trial of three misoprostol regimens after pretreatment with mifepristone for termination of early pregnancy.
Another three research projects were supported by the WHO Regional Office for South-East Asia:

- Studies on the antifertility effect of active immunization with N-terminal 1–17 and C-terminal 67–94 synthetic peptide sequences of human seminal plasma inhibins in male rats and monkeys
- Resazurin test for the assessment of fertility potential in men
- Fertility intentions and family planning practices of men in a rural community of Maharashtra.

**Research capacity building**

The Institute is in the process of phasing out unproductive research areas to make institutional objectives more focused and tangible. In the coming years, the research of the Institute would concentrate on:

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- male contraception; and
- men’s involvement in reproductive health.

Staff have been encouraged to participate in national and international workshops and scientific conferences. Institutional seminars are held regularly. Five workshops/training courses/conferences were conducted in 1998.

- WHO Workshop on scientific writing
- International Conference on Reproductive Health (partly supported by HRP)
- Public debate on consultative document on *Ethical guidelines on biomedical research involving human subjects*
- Training Course on Andrology for Clinicians
- Workshop on improving contraceptive choices in the National Family Welfare Programme.

**Dissemination of information**

Twenty-three original articles, 42 congress abstracts and five official reports were released in 1998.

**INDONESIA**

**West Indonesian Reproductive Health Development Centre (WIRHDC), Faculty of Medicine, University of North Sumatra, Medan**

The WIRHDC has 16 professional staff (all part-time) who cover disciplines such as andrology, endocrinology, social science, public health, maternal and child health, perinatology and family planning. There are eight technical and nursing support staff available, of whom four are involved in the radioimmunoassay laboratory, two are midwives, one is a typist and one is involved in andrology laboratory services. The administrative and laboratory facilities of WIRHDC are situated on the campus of the Faculty of Medicine of the University of North Sumatra and the clinical facilities in the Dr Pirngadi Hospital and the Adam Malik Hospital. In total, there are 55 obstetric beds with 3500 deliveries, 32 gynaecological beds and 2000 inpatients per annum.

Yearly, there are approximately 500 new IUD acceptors, 120 users of injectables, 750 tubal ligations and 40 women who choose oral contraceptives. Medan city has a population of approximately two million. Nearby rural districts include Asahan district—a mixed farming and fishing area with a population of approximately two million; Karo district is mountainous and is located 50 kilometres from Medan. This district has one of the highest uptake rates of contraceptive use.

WIRHDC has access to radioimmunoassays, simple andrological investigations and basic microbiology, as well as computer facilities. MEDLINE, Internet and e-mail facilities have been available since early 1997.

**Research activities**

No research projects are reported as being under way in 1998.

**Research capacity building**

**Workshops/courses**

In July 1998, a “vision” meeting to plan the Centre’s priorities and future activities was held and was attended by 51 participants. In August 1998, 50 people attended a workshop on immediate response to obstetric emergencies and 51 persons attended a seminar on recent advances in the management of infertility.

**Research training**

One staff member was trained for three months at the Prince of Songkla University, Hat Yai, Thailand, in data management.

**Dissemination of information**

There were 14 presentations and congress abstracts from Centre staff in 1998.

**Reproductive Health Research Centre, Airlangga University, Surabaya**

The Medical Faculty of Airlangga University is engaged in teaching, the provision of services and the conduct of medical research. Its teaching hospital, the Dr Soetomo Hospital, is a tertiary-level hospital and the main referral centre for the East Indonesian region. It has some 2000
beds and an active family planning and infertility clinic.

The Human Reproduction Research Group itself was established in 1983, although some research projects in human reproduction and family planning had been conducted before then. The formation of the Group enabled more efficient use of scarce research resources and permitted improved coordination of research activities. The Group was also in a position to respond to the demands of the national research programme organized by BKKBN and to benefit from support provided for the build-up of research capability. Though the group comprises at least 30 members having an M.D. or Ph.D. degree, the amount of time available for research is severely limited owing to the need to give priority to teaching, service provision (including private practice) and administration. Despite these constraints, the Group has been active in a number of research areas, notably those of andrology and long-acting methods for the regulation of fertility.

At the beginning of 1998, a new management structure was introduced and the Centre was reorganized. The Centre now consists of ten units including: Animal Reproduction, Reproductive Endocrinology, Assisted Reproductive Technology, Male Infertility/Andrology, Female Infertility, Sexually Transmitted Diseases, Safe Motherhood, Adolescents, Family Planning and Social and Behavioural research. All these units function independently but their research activities are coordinated by the Research Centre.

**Research activities**

During 1998, the Centre was involved in five research projects, three of which were completed in 1998. Four projects were funded by the Indonesia Institute of Science (Risbin Iptekdok) and one by Airlangga University. Two projects were on sperm physiology, one each on mouse oocyte fertilization, immunological aspects of pre-eclampsia and the peritoneal factor in post PID cases complaining of infertility.

**Research capacity building**

A total of 18 staff (17 scientists and one support staff member) are involved in the Centre.

**Workshops/courses**

One course on reproductive health for postgraduates was attended by seven nationals.

**Research training**

There were no research training activities nor staff trained in 1998.

**Dissemination of information**

Two of the completed research projects were presented in 1998, one at a national and the other at an international congress.

**LAO PEOPLE’S DEMOCRATIC REPUBLIC**

**Maternal and Child Health Institute, Ministry of Health, Vientiane**

The Institute of Maternal and Child Health (IMCH) was established by the Ministry of Health in 1989. Initially, there were 11 staff members, today there are 33 scientists and 30 support staff (two specialists in Paediatrics, two Masters of Tropical Health, 30 Bachelors of Science and six technical staff).

The IMCH plays an important role in research. It guides studies and research on Knowledge, Attitudes and Practice (KAP), maternal and child health problems, fertility, and diseases which are the main cause of morbidity and mortality in mothers and children. It also uses the findings of the research for improving mother and child health.

There are six divisions: Training; Research; Technical—Logistics and Supervision; Information, Education, Communication (IEC); Planning; Statistics, Finance and Administration.

There are three main programmes, which include many projects whose purpose is to improve the quality of life of the population.

The **MCH Programme** works for the health of pregnant women, young mothers and babies. It promotes breastfeeding, birth-spacing, safe motherhood, control of diarrhoeal diseases (CDD), acute respiratory infections (ARI) and other health messages.

The **ARI/CDD Programme** attempts to reduce the inappropriate use of antibiotics and harmful drugs by focusing on increasing access to standard case management, home treatment, advice to mothers and improved referral of children. The ARI/CDD Programme works in collaboration with the National Committee of Cholera Control and delivers oral rehydration salts in all districts, trying to cover all villages.

The **National Birth-Spacing Programme** aims mainly to assist the Government in reducing the maternal and infant mortality rates and to provide information and services on birth-spacing to couples who wish to plan and space the births of their children. Additionally, the purpose of the National Birth-Spacing Programme is to improve the quality of life of the population.
**Research activities**

Two research projects were initiated and completed in 1998, namely:

- Strategic assessment of reproductive health needs
- Maternal mortality and women’s reproductive health

These projects were funded by WHO and ORSTOM (France), respectively.

**Research capacity building**

**Workshops/courses**

- A five-day course on clinical research methodology was attended by 32 scientists and funded from the LID Grant. Two draft research proposals were developed.
- Basic computer training was given to three graduates and three technical support staff.

**Research training**

Two staff members went for training in biostatistics (WHO-supported) and social science (UNFPA-supported) to Thailand in 1998.

**Dissemination of information**

There were no formal publications in 1998.

**MONGOLIA**

**State Research Centre on Mother and Child Health and Human Reproduction, Ulaanbaatar**

The long-term objective of collaboration with HRP is to develop the Research Centre on Maternal and Child Health and Human Reproduction as a national centre: (i) to undertake research on the assessment of contraceptive efficacy, safety and acceptability, the prevention and treatment of infertility and on maternal and child health; (ii) to provide leadership in improving the quality of family planning services; and (iii) to provide advice to the Government relating to policy in reproductive health. The Centre would be the key institution in Mongolia for research and training in this area. More specific, short-term objectives relate to the recruitment and training of staff, equipping of laboratory facilities, development of research programmes and individual research projects, and the establishment of a unit for the collection and dissemination of technical information on reproductive health.

The Institute has received a LID Grant since 1994 and its research programme comprises three broad areas:

- research on infertility, which is thought to affect as many as ten per cent of couples in Mongolia;
- research on family planning methods; and
- research in other aspects of reproductive health including RTIs and the collection of basic information on the physiology, endocrinology and biochemistry of Mongolian women throughout their reproductive life, including pregnancy, lactation and the normal menstrual cycle.

Research is being undertaken in the following areas:

- trials of safety, and efficacy and acceptability of injectables, IUDs and emergency contraception;
- infertility: epidemiological survey;
- STIs: establishment of methodologies, epidemiological survey;
- normal physiological parameters of Mongolian people.

**Research activities**

During 1998, the Institute was involved in six research projects in the area of human reproduction, five of which were supported by HRP:

- Interval insertion of the TCu 380A IUD
- A randomized comparative trial of interval insertion of the TCu380A and levonorgestrel 20µg IUDs
- Survey of contraceptive use in Mongolia
- Randomized multinational study to compare mifepristone and two regimes of levonorgestrel in emergency contraception
- The clinical patterns and major causes of infertility
- Some acid–base indices of mothers and newborns delivered on Rakhmanov’s bed.

**Research capacity building**

During the reporting period, the Centre employed 12 scientific and four technical staff.

**Workshops/courses**

Two workshops were held in 1998:

- Data management (20 participants)
- STI microbiology (17 participants from three hospitals including the MCH Centre).

**Dissemination of information**

There were six congress abstracts published by the Institute’s staff in 1998.
MYANMAR

Department of Medical Research, Ministry of Health, Yangon

The Union of Myanmar has maintained a pronatalist policy since its independence in 1948 on the grounds that the country is under-populated, endowed with rich natural resources and has a low density of population. A seminar was held in June 1992 to draft a National Population Policy which recognized for the first time that an improvement in the quality of life can result from reduced population growth. Among the objectives of the National Population Policy are: (i) to promote awareness of population issues and the impact of rapid population growth on development; (ii) to provide the necessary information and education about the benefits of a “reasonable” family size; (iii) to improve the health status of the population, especially of women and children by lowering morbidity and mortality rates; (iv) to give greater access to quality birth-spacing services for all married couples; and (v) to reduce the incidence of unsafe illegal abortions and unwanted pregnancies.

The collaboration with HRP supports five institutions:

- Department of Medical Research, Ministry of Health (DMR)
- Institute of Medicine 1, Yangon (IM1)
- Institute of Medicine 2, Yangon (IM2)
- Central Women’s Hospital, Yangon (CWH)
- Institute of Medicine, Mandalay (IMM)

IM1, IM2 and IMM are under the Department of Medical Science, Ministry of Health (MOH), while CWH is under the Department of Health, MOH. Several other institutions under the Department of Health are also involved in implementing research projects. These include hospitals and health centres in Yangon, Mandalay, and the countryside.

The focal point for collaboration with HRP is the DMR. This is one of five departments within the Ministry and is itself divided into 17 research divisions and five service divisions. There is no division designated specifically for reproductive health research, which is under the guidance of a National Committee on Reproductive Health Research chaired by the Director General of Medical Research. The DMR has an ethics committee.

Research activities

During the reporting period (1998), the Institute was involved in seven research projects, two of which were completed and the remainder were to be completed in 1999 or 2000. The studies included:

- Acceptability of modern contraceptive methods in Hlaing Tharyar township
- Factors determining induced abortion
- Quality of antenatal care at outpatient departments of health institutions in Mandalay City: time utilization and satisfaction among users
- Socioeconomic characteristics and behaviour of adolescent mothers
- A study on the safety, efficacy and acceptability of injectable preparations in Myanmar women.

Research capacity building

Workshops/courses

No workshops or courses were held in 1998; however, 36 nationals received training in laboratory techniques, eight in clinical research and two in public health.

Research training

Two staff members returned from Research Training Grants in 1998; both received three months’ training in clinical trial management and data analysis at the Prince of Songkla University, Hat Yai, Thailand.

Dissemination of information

In 1998, the Institute’s staff had six publications in national journals and two publications in international journals.

SRI LANKA

Research in reproductive health in Sri Lanka is carried out by four multidisciplinary Task Forces located in Colombo, Galle, Jaffna and Peradeniya. The activities of these four Task Forces are coordinated by a National Coordination Committee for Research on Reproductive Health with its office in Colombo. Financial support to implement the projects on reproductive health is being obtained from WHO and from national and other international agencies.

Research projects

During 1998, a total of 30 research projects (among which two were supported by HRP), were started or are in progress:

- Experience of married women on induced abortion: a case study of Colombo district in Sri Lanka (Ruhuna)
- An examination of sociocultural and economic aspects of postpuerperal maternal health care in Sri Lanka (Colombo)—completed.
Research capacity building

During 1998, the National Coordinating Committee held seven meetings, which greatly strengthened the coordination of research activities in three Task Forces. The following research topics were recognized by the National Coordinating Committee as the priority research areas for Sri Lanka:

— maternal morbidity and mortality;
— adolescent reproductive health; and
— unmet needs in fertility regulation.

During 1998, four staff members were undergoing training abroad; two were supported by HRP. In addition, eight staff members (among them, two supported by HRP) attended and made presentations at the International Conference in Reproductive Health, Mumbai, India, March 1998.

Several workshops/training courses were conducted in 1998, including a participatory workshop generating research proposals with two resource persons supported by HRP. Four proposals were developed at the workshop:

- Factors underlying adolescent programming in rural Sri Lanka
- The context of induced abortion among married and unmarried women in rural Sri Lanka
- Women’s perceptions of quality of maternal health care provided at government primary health care level
- Sexual behaviour, knowledge and perceptions among adolescents in one province of Sri Lanka.

Dissemination of information

Five original articles, 11 book chapters and 30 congress abstracts were released in 1998.

THAILAND

Family Health Division, Department of Health, Ministry of Public Health, Bangkok

The Ministry of Public Health is responsible for the promotion of reproductive health research in Thailand. Its research activities are carried out by 11 institutions, the activities of which are coordinated by the Department of Obstetrics and Gynaecology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Thailand. The research group has approximately 126 scientists and 103 supporting staff. The objective of HRP’s support has been to strengthen the capabilities of the institutions to undertake research on the development of contraceptives through field trials, including evaluation of the safety and efficacy of currently used methods. The second cycle of five-year LID Grant support expired in 1997 and 2000 is the final year of the Resource Maintenance Grant. In addition to funding received from HRP, the institutes obtained financial support from JHPIEGO, IARC, UNAIDS, UNICEF, FHI, NIAID, NICHD, CONRAD, The British Council, one foundation and four universities in the USA, the Faculty of Medicine of Khon Kaen University, the Thai Research Council, and five other national funding sources.

Research activities

The network was involved in 61 research projects in 1998. The Annual Report provides details of the research being undertaken in six of the 11 Centres in the network. A total of six projects were supported by HRP, 19 by international agencies and 36 by national funding sources.

Resource capacity building

Five staff members were trained abroad in 1998 in Japan, United Kingdom and USA. All were funded by the host institute, their university or by the Thai Government. All training was in clinical sciences. Two staff members returned from training abroad in Japan and the United Kingdom during 1998.

There were 18 expert/consultant visits funded by WHO, the Thai University, The British Council, an NGO or overseas university.

Seven workshops were held in 1998. One on “Changing trends: the way forward in childbirth and breastfeeding” involved 134 participants and another course had a total of 205 participants.

Dissemination of information

There were a total of 19 original scientific publications in national journals, 13 in international publications, and one book was published in 1998.

VIET NAM

Hung Vuong Hospital, Ho Chi Minh City

The Hung Vuong Hospital is a tertiary-level referral hospital in obstetrics and gynaecology and family planning, and serves a population of more than four million living in 18 urban and suburban districts of Ho Chi Minh City. The hospital has a total of 440 beds and 450 technical staff, of whom 72 are medical doctors and seven are pharmacists. The hospital is responsible for routine health care, teaching of medical students and midwives and for research. Health care facilities remain inadequate and the modest laboratory facilities are not able to meet the demands of the clinical services. Notwithstanding these difficulties, the Hung
Vuong Hospital has established a group interested in conducting research relating to reproductive health and has acted as a coordinating centre for several national-level studies. The 1996 Annual Report lists 20 scientists, mostly medical doctors, and 50 support staff as being involved in research. Most research, however, involves only a few of these individuals. The profile of the institution indicates research activity in gynaecology and family planning, while a research programme commencing in 1993 also includes maternal health, fertility regulation, perinatal health and STIs.

The Institute collaborates with other institutions in Viet Nam, particularly the Institute for the Protection of the Mother and Newborn in Hanoi. The Deputy Director of the hospital is the Vice Chairman of the Vietnamese Family Planning Department, and is also Vice-Director in charge of Research and International Relations, and has been the principal investigator for much of the research.

**Research activities**

During 1998, the hospital was involved in ten research projects, of which two were completed in that year. Four of these projects were funded by HRP:

**Projects completed**

- Safe motherhood demonstration project
- Mifepristone–misoprostol medical abortion: simplifying the regimen.

**Ongoing projects**

- Misoprostol in the management of the third stage of labour
- Three misoprostol regimens after pretreatment with mifepristone for termination of early pregnancy

**Research capacity building**

A total of 27 scientific and 40 support staff are employed in the Centre.

**Workshops/courses**

No workshops or courses were held in 1998.

**Research training**

One staff member received training in epidemiology and social science in 1998 and returned to the institute in 1998.

**Dissemination of information**

There were four reports and publications in national journals and two in international journals in 1998.

**PLANNED ACTIVITIES**

In line with the new goals and operational objectives of the Department of Reproductive Health and Research, the regional strategic framework for the future has required adjustment to include with the following key issues:

- to assist the developing countries of Asia and the Pacific in identifying their needs in national reproductive health programmes, including the adaptation and application of tools essential for improving reproductive health, as well as areas where research is required to address these needs;
- to support national-level planning and programming for reproductive health in cooperation with other collaborating agencies and partners;
- to assist developing countries of the region in building their own capacity to carry out their national reproductive health programmes and participate in national, regional and global research in accordance with the highest scientific and ethical standards;
- to strengthen capacity building in the region to plan, implement, monitor and evaluate national programmes and activities in reproductive health; and
- to enable developing countries in the region to disseminate and apply the results of reproductive health research and to adapt, adopt and implement new and updated norms, standards, tools and approaches.

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### Regional Advisory Panel for Asia and the Western Pacific Region in 1999

**Members**

V.H.H. Goh, Department of Obstetrics and Gynaecology, National University of Singapore, Singapore  
S. Hatmadji, Demographic Institute, Faculty of Economics, University of Indonesia, Jakarta, Indonesia  
J. Hearn, Research School of Biological Sciences, Australian National University, Canberra, Australia  
N. Huq, Naripokkho, Dhaka, Bangladesh  
R. Mra, National AIDS Prevention and Control Programme, Department of Health, Ministry of Health, Yangon, Myanmar  
M. Passey, Northern Rivers Institute of Health and Research, Lismore, Australia *(Chairwoman)*  
Wisut Boonkasemsanti, Department of Obstetrics and Gynaecology, Chulalongkorn University Hospital, Bangkok, Thailand  
Zhang De-wei, C/o Dr Fan Ke-juan, Shanghai Institute of Planned Parenthood Research, Shanghai, China

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</tbody>
</table>
Annex 2

REGIONAL SCIENTISTS

Heads of centres in 1999

Chen Hailin, National Evaluation Centre for the Toxicology of Fertility Regulating Drugs, Shanghai, China
Duong Thi Cuong, Institute for the Protection of Mother and Newborn, Hanoi, Viet Nam
Gao Ersheng, Shanghai Institute of Planned Parenthood Research, Shanghai, China
Ge Qin-Sheng, Peking Union Medical College, Beijing, China
Hou Qingchang, Tianjin Municipal Family Planning Research Institute, Tianjin, China
H.S. Juneja, Institute of Research in Reproduction, Mumbai, India
Li Weixiong, National Research Institute for Family Planning, Beijing, China
Luo Lin, Family Planning Research Institute of Sichuan, Chengdu, China
D. Lutan, University of North Sumatra, Medan, Indonesia
S. Mittal, All India Institute of Medical Sciences, New Delhi, India
Phonethep Pholsena, Maternal and Child Health Institute, Ministry of Public Health, Vientiane, Lao People’s Democratic Republic
J. Radnaabazar, State Research Centre on Mother and Child Health and Human Reproduction, Ulaanbaatar, Mongolia
Sungwal Rugpao, Ministry of Public Health Network, Chiang Mai University, Chiang Mai, Thailand
Sang Guo-wei, Family Planning Research Institute of Zhejiang, Hangzhou, China
M.P. Shrestha, Tribhuvan University, Kathmandu, Nepal
Soe Thein, Department of Medical Research, Ministry of Health, Yangon, Myanmar
Nguyen Thi Thuy, Hung Vuong Hospital, Ho Chi Minh City, Viet Nam
Virasakdi Chongsuvivatwong, Prince of Songkla University, Hat Yai, Thailand
C.N. Wijeyaratne, Faculty of Medicine, University of Colombo, Colombo, Sri Lanka
Zheng Xiaoying, Institute of Population Research, Peking University, Beijing, China
Technical support to countries

Eastern European Region

R.J. Guidotti
OBJECTIVES

The main objective of the Department is to strengthen national capacity in reproductive health research in some countries of Eastern Europe and to assist the WHO Regional Office for Europe (EURO) in providing technical support to countries to implement their programmes in reproductive health.

INTRODUCTION

The Department of Reproductive Health and Research has assisted Eastern European countries mainly towards the successful implementation of research projects. These projects are aimed at addressing some of the major problems in these countries which include: (i) high levels of maternal mortality; (ii) a large number of abortions per woman; (iii) poor availability of information and services for family planning; and (iv) the growing incidence of sexually transmitted infections (STIs).

The highest maternal mortality rates are found in the Central Asian republics and in Romania. Abortion remains a major cause of maternal mortality in these countries as a result of the absence of or limited access to affordable contraceptives.

Although HRP experienced an unexpected shortfall in funding and, as a result, had to cancel the planned joint meeting of the HRP Scientific Working Group (SWG) and the EURO Scientific Advisory Group, the research projects were able to continue. No new projects were initiated in 1999.

Following the reorganization of the Department, it is foreseen that future activities in Eastern European countries will include both research as well as technical support to countries. This support will be in the form of providing reproductive health managers with the latest evidence-based research results on specific topics, including how best to adapt and introduce them into their respective programmes. In addition, the Department will provide, as requested, technical advice on:

— the integration of the prevention and treatment of STIs into other reproductive health services such as antenatal care;
— development of policies on reproductive health; and
— reproductive health research methodologies.

PROGRESS

In response to the reproductive health issues identified in the region, a number of research projects have been supported by HRP. This support has also included the participation of centres in the Region in various multicentre studies coordinated by HRP.

Family planning

A study on the determinants of contraceptive choice and use of fertility regulating methods in Eastern European countries was initiated in Romania. The main objective of the study is to assess the characteristics of women who do not use modern contraception (abortion clients), compared to users of modern contraceptive methods, to determine specific reasons for not using a modern contraceptive method. The study also aims: (i) to establish perceptions about modern contraceptive methods; (ii) to identify sources of information on family planning; and (iii) to assess the contraceptive service delivery needs of the population.

The study is managed by the Medical Research Centre for Health and Management Services, Centre for Public Health, Targu-Mures, Romania, with four participating centres in Armenia, Georgia, Lithuania and Moscow.

Preliminary findings indicate that there is a higher rate of contraceptive discontinuation among women presenting for abortion. Furthermore, most abortion patients who had used contraception when they became pregnant had used a traditional method, especially the rhythm method, and almost all the abortion patients reported the current pregnancy as unwanted. Collection of data has been completed and a draft report was presented in 1999. A second study in this area is on “Acceptance and Follow-up of Different Contraceptive Methods in Parous Women”. The study continued through the year in Hungary and Romania.

In another study, a centre in Szeged participated in a two-centre evaluation of the efficacy of a very low daily dose of mifepristone (0.5 mg) as a method of oral contraception. A total of 20 women were recruited for the study in Szeged, who used the daily dose of 0.5 mg of mifepristone as their only method of contraception for six months. The study was stopped before completion due to an unacceptable number of pregnancies. The results of the study were published in 1999 in the journal Human reproduction.

HRP’s Research Group on Post-ovulatory Methods for Fertility Regulation currently has two multicentre studies in which centres from Eastern Europe are participating.

One is a multicentre randomized double-blind comparison of the 10 mg dose of mifepristone and two regimens of levonorgestrel (0.75 mg levonorgestrel administered in two doses at a 12-hour interval or two tablets of 0.75 mg levonorgestrel given in one dose) for emergency contraception. Treatment is started as soon as
the woman comes to the clinic, but no later than 120 hours after unprotected intercourse. The recruitment target is 4200 women. The study started in May 1998 and a total of 15 centres are participating, with three centres in Eastern Europe, namely in Szeged, Hungary; Ljubljana, Slovenia; and Tbilisi, Georgia. The centre in Tbilisi has completed recruitment whereas the study is still continuing in Ljubljana and Szeged.

The second project by the Research Group is a randomized, double-blind comparison of three regimens of misoprostol after pretreatment with mifepristone for termination of early pregnancy (see next section).

Reducing morbidity from abortion

In this study, women who ask for pregnancy termination prior to or at gestational age of 63 days and fulfill all the necessary criteria, are randomized to three groups. In all the groups, women first receive 200 mg of mifepristone orally. They return to the clinic two days later when they receive misoprostol, either orally or vaginally. The oral group and one of the two vaginal groups continue taking misoprostol orally for one week. In addition to the efficacy and side-effects, this study also compares the duration and amount (in one centre) of bleeding, after the administration of the three regimens.

There are 15 participating centres, three of them in Eastern Europe: Targu-Mures, Romania; Szeged, Hungary; and Ljubljana, Slovenia. Recruitment for the study was very quick, especially in Romania, as women wished to have a non-surgical method of abortion. A research protocol is being reviewed which addresses other issues related to the reduction of morbidity from abortion.

Perinatal audit

Support is being provided for testing a model for classification of perinatal death in four countries, Armenia, Kazakhstan Kyrgyzstan, and Russia. The study is based on the Nordic perinatal audit. A computerized version of Vitting Andersen’s dichotomizing scheme defining a single or principal cause is being used. Its nine main categories have several subgroupings resulting in 22 categories. In addition to the application of Andersen’s classification of the principal causes of death, the cases will be classified by all possible causes of death (“multiple cause” classification). The same computerized information system will be used while examining case records from all countries. This protocol includes a structured data set of all variables of interest and all possible causes of death. Data entry is performed directly from the medical record and the software is self-instructing and prevents inconsistencies between values.

Reproductive health research training

The Ninth postgraduate Course on Reproductive Medicine and Biology was held at the University of Geneva, Geneva, Switzerland. It was partly supported by HRP. Of the 30 participants, 11 were from Eastern Europe. The course was structured in eight modules, with 11 lectures and sessions on different reproductive health issues in different regions and settings. Three of the modules were conducted in the Department (family planning; safe motherhood; and epidemiology, statistics, Cochrane library). Staff in the Department continued to assist in the development of research proposals identified during the course.

EURO’S Scientific Advisory Group (SAG) on Training in Reproductive Health for Countries in Central and Eastern Europe and Newly Independent States, met to review needs for reproductive health training and receive reports on training activities. It is planned that SAG and SWG will meet jointly to view the close interaction in their respective mandates.

PLANNED ACTIVITIES

Collaboration between the Department and the EURO should strengthen the work of HRP’s SWG and EURO’s SAG on training in reproductive health. The Department will review progress and draw up new work plans. Despite limitations in funding, both research and training are set to continue actively into the coming biennium. There were joint planning meetings in 1999 between the Department and EURO to further define areas for collaboration. The Department’s Technical Support to Countries Team is collaborating with the Regional Office to support regional and national strategies and programmes for the promotion of sexual and reproductive health and the provision of reproductive health care services. Specific areas proposed for joint activities include the following.

Short course on reproductive health research methodology, including operations research

Experience in the East–West SWG showed that there is a need to strengthen knowledge on updated research methodology, especially on operations research for researchers in Central and Eastern Europe, to provide a basis for more action-oriented research for defining appropriate interventions in reproductive health care.

It is proposed to support two courses in the next biennium, of three weeks’ duration each, to be organized by the WHO Collaborating Centre, Gynaecological Faculty of the University of Debrecen, Hungary. Each course would be for no more than 15 participants, in order to allow for intensive learning. It is proposed that further support will
be provided to participants for their research projects after they complete the course.

**Meeting of the Scientific Advisory Group, 8–9 May 2000**

There are plans also for collaboration in research studies, including proposals on prevention of STIs, postabortion morbidity and strategies for prevention. The next meeting, scheduled for 8–9 May 2000, will bring together again HRP’s SWG and the EURO-supported SAG. The two Groups did not meet in 1999.

**Development of a reproductive health strategy for Eastern Europe**

Another area proposed for collaboration is to provide assistance to countries in the region in developing policy and programmes in reproductive health including the development of a regional sexual and reproductive health strategy. Reproductive health strategies being employed in other regions could serve as a model. A request for supporting a consultant and dissemination workshop has been received from EURO.

**Dissemination of antenatal care (ANC) trial results to Eastern European policy-makers**

The Department is being requested to provide technical and financial support to EURO for a dissemination workshop on HRP’s antenatal care trial. Eastern European policy-makers have requested that WHO assist them in setting the best practices for antenatal care for their countries.

**Development of a national reproductive health document for fund raising activities**

At present, many countries in Eastern Europe have information on reproductive health that is not organized in a manner that can be shared with outside funding agencies. Following on recent experience involving STI/AIDS, a WHO team visited countries and assisted nationals in collating, summarizing and organizing available information. This resulted in a national report that served to raise funds for activities in this area. EURO is planning to assist countries in producing similar reports for reproductive health and has asked the Department for assistance. Priority countries include the central Asian republics, Ukraine, and Moldova.

**Support to Bulgaria on the integration of reproductive health and STIs**

EURO has been requested to explore how best to integrate reproductive health and STIs in Bulgaria. This effort should be based on prior integration activities and adapted to the national situation. It is planned to hold a national workshop on this subject and to assist the government with implementation of the programme.
Annex 1

SCIENTIFIC WORKING GROUP ON REPRODUCTIVE HEALTH RESEARCH IN EASTERN EUROPE IN 1999

Members

S. Alexaniants, Armenian Research Centre of Maternal and Child Health Protection, Yerevan, Armenia (Chairman)
A. Campana, Clinic for Infertility and Gynaecological Endocrinology, Geneva, Switzerland
M. Horga, Institute of Public Health and Medical Research, Targu-Mures, Romania
L. Kovacs, Albert Szent-György Medical University, Szeged, Hungary
G. Lindmark, University Hospital, Uppsala, Sweden
P. Velebil, Institute for Maternal and Child Care, Prague, the Czech Republic
E. Vikhlyaeva, Research Centre of Obstetrics, Gynaecology and Perinatology, Moscow, the Russian Federation

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from:
EURO

5 71
2 29
7

327
Part 4: Other Activities
Clinical trials and informatics support

O. Ayeni, T.T.M. Farley, G. Piaggio Pareja, and A Pinol
OBJECTIVES

The section responsible for clinical trials and informatics support provides technical support in this area to the whole Department. To the Team for Research and Evidence, it provides statistical and data-processing support for the multinational clinical trials and epidemiological studies conducted by the various thematic groups. To the Team for Technical Support to Countries support is provided for strengthening biostatistical and data-processing capabilities of developing country institutions collaborating with the Department, so that they can fully support their own reproductive health research. Staff of the section contribute to the development of appropriate techniques for conducting, managing and analysing multicentre research in reproductive health in developing countries. They also provide local informatics support to the administrative management of the Department.

Technical support to research activities includes statistical advice in the review and development of research projects and responsibility for the management and analysis of some single and nearly all multicentre studies carried out by HRP. The section also coordinates the implementation of WHO Good Clinical Practice (GCP) guidelines in all of HRP’s research activities. In the area of research capability strengthening, the section assists in the formulation, execution and review of institution strengthening policies in statistics and data processing, and in the organization and conduct of workshops, seminars and training courses for scientists from collaborating centres. Staff of the section also provide on-the-project training in research data management and statistical analysis to staff of countries participating in some multicentre studies or carrying out their own single-centre trials.

The section’s strategy is to coordinate international multicentre trials from Geneva while continuing to enhance the ability of individual centres to handle their own single-centre studies as well as national multicentre studies.

PROGRESS

Support to research projects

Activities carried out by the section for clinical trials and informatics support during 1999 to support research projects included:

— technical advice on the development and review of research protocols;
— statistical design;
— assistance with project organization;
— data processing, monitoring and management;
— data analysis and preparation of statistical reports; and,
— participation in the writing of scientific papers resulting from the projects.

During 1999, 65 research projects were supported by the section, and a total of 65 000 forms were processed and entered into HRP’s database. The distribution of these projects by their stage of support at the end of 1999 is shown in Table I.

One of the multicentre projects being coordinated was on behalf of the WHO Department of Nutrition for Health and Development in the Cluster of Sustainable Development and Healthy Environment. This is the WHO Multicentre Growth Reference Study being conducted in six countries to build a set of standard growth curves for children under five years of age to be adopted as a new international growth reference. During 1999, a staff member of the section visited Oslo, Norway, to participate in the Steering Committee meeting of the project.

Among the studies completed during 1999 was the ten-year study on the Post-Marketing Surveillance of Norplant, for which data collection for the main phase had started in January 1989. Another study completed was the international multicentre WHO Antenatal Care Randomized Controlled Trial. Final analyses were completed for both studies and manuscripts are now being prepared for publication. The three-country study to assess the acceptability, service delivery requirements and use-effectiveness of the diaphragm cosponsored by HRP and two collaborating agencies, namely Family Health International, Research Triangle Park, NC, USA, and the Population Council, New York, NY, USA, also finished data collection and its final analysis is now in progress.

In addition to the technical support given to these specific projects, all of which are being coordinated in Geneva, support was provided to the Teams of the Department, in particular the Team for Research and Evidence, with the technical review of projects submitted.

Table I. Number of studies by stage of support (December 1999)

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to them for funding, and with arrangements for logistical support to projects before launching. The technical review focused mainly on the biostatistical and data processing aspects of the protocols while logistic support arrangements included site visits to the proposed study and coordinating centres to review facilities and data collection mechanisms. To this end, statisticians from the section visited London, United Kingdom, twice and Lima, Peru, once on behalf of the WHO Multicountry Study on Women’s Health and Domestic Violence. The visit to London was to review statistical and coordination issues arising in planning and implementing the study, while Lima was visited for discussions on the local implementation of the study at the centre.

Consultations were held with a clinical research organization in Lund, Sweden, regarding its suitability as a potential local monitor for the hCG immunocontraceptive Phase II study to be conducted in Stockholm, Sweden.

One of the statisticians in the section was delegated as the Organization’s focal point for the Inter-Agency Task Team for the Prevention of HIV Transmission from Mother to Child. During the year, he visited Abidjan, Côte d’Ivoire, to participate in a workshop to launch pilot studies of the prevention of mother-to-child transmission (MTCT). He also visited Montreal, Canada where he attended the Second International Conference on Global Strategies for the Prevention of HIV Transmission from Mothers to Infants, participated in a technical review meeting on the use of antiretrovirals to reduce MTCT and represented the Department in the Inter-Agency MTCT Task Team meeting.

Implementation of WHO Good Clinical Practice (GCP) guidelines in research

During 1999, efforts continued, though at a reduced pace, to formally implement WHO GCP research guidelines throughout HRP’s research activities. A consultant visited the section towards the end of the year to start the review and finalization of the draft Standard Operating Procedures (SOPs) and their consolidation into a manual.

Institution strengthening activities

Strengthening of biostatistical and data-processing capabilities of collaborating institutions continued during 1999. Some of the highlights of this work are described below.

Training courses, seminars and workshops

Staff of the section presented a seminar in Geneva on GCP requirements and implications for HRP’s clinical research to a meeting of investigators participating in the international multicentre study on sperm suppression with cypionate acetate and testosterone undecanoate in normal men.

A staff member of the section gave lectures on strategies for data analysis at the 9th Postgraduate Course for Training in Reproductive Medicine and Reproductive Biology at the WHO Collaborating Centre at the Cantonal Hospital, University of Geneva, Geneva, Switzerland.

Site visits

Staff of the section continued on-site training of staff at collaborating centres performing data management and statistical analysis of studies in their countries. The purpose of such visits included help with formulation of study protocol including sample size estimation, review of data-processing strategy, management of data queries, supervision of data collection, monitoring of progress, closure of data management, preparation of final analyses and interpretation of data.

Centres in Havana, Cuba, and Jeddah, Saudi Arabia, were visited during the year to supervise the closure of the data collection phase of the multinational WHO Antenatal Care Randomized Controlled Trial. Oxford, United Kingdom, was also visited to discuss the results of the final analysis of the quality of care component of the same study.

Development of new computing environment for statistics and data processing

During 1999, the section continued the search for a suitable alternative to the use of the International Computing Centre’s (ICC) mainframe computer. With the completion of the WHO Local Area Network (WHO LAN) renewal and the introduction of the Organization-wide Synergy System, the local computing environment has become more certain. The section for clinical trials and informatics support has identified a number of potential software and hardware solutions that would improve acquisition, review and cleaning of data. The most promising candidate was acquired on loan and extensively tested during the last quarter of the year. A report is currently being prepared.

Development of methodological tools

Cluster randomized trials have become increasingly popular in the evaluation of nontherapeutic interventions when the units of randomization are communities, hospital wards and medical practices. This type of intervention trial has particular relevance for getting evidence into practice. During 1999, staff of the section developed a computer software package for sample size determination and analysis of cluster randomization trials. This was not available till now in any standard statistical package in the market.
Attendance at professional/scientific meetings

During the year, staff of the section attended and presented scientific papers at various professional and scientific meetings. These included:

— a workshop on Cluster Randomization Trials held in Sheffield, United Kingdom;
— the International Workshop on Pharmacoepidemiology and Drug Safety held in St Paul de Vence, France;
— the meeting of the European Society for Pharmacovigilance held in Ankara, Turkey;
— the joint conference on medical statistics by the Royal Statistical Society Medical Section and the London School of Hygiene and Tropical Medicine held in London, United Kingdom;
— the SAS Swiss Users Group Conference held in Zurich, Switzerland; and
— the WHO/UNAIDS Technical Consultation on the Safety and Effectiveness of Nevirapine for the Prevention of HIV Transmission from Mother to Child held in Geneva, Switzerland.

PLANNED ACTIVITIES

Support to research projects

In 2000, statistical and data management support will continue for the 51 ongoing studies as well as for any new multicentre studies initiated by the Department. Technical support in the review and development of new projects will also continue.

The section for clinical trials and informatics support will continue to support formal implementation of WHO GCP procedures throughout all research activities. The work of reviewing and revising the SOPs initiated in 1997 and continued through 1998 and 1999, will be completed and put into operation in 2000. A training workshop on the use of the SOPs and on the duties and responsibilities of monitors will be conducted for staff later in the year. The SOPs will be made easily accessible to all staff through the WHO computer network and a system of regular review will be implemented. The SOPs will be extended to cover the research activities in centres participating in HRP-sponsored collaborative research. Assistance will be given to collaborating centres and those receiving institutional development grants to fully implement the GCP guidelines throughout their research activities.

Institution strengthening activities

Research capability strengthening support in biostatistics and data processing will continue to be given to collaborating institutions to enable them to participate in HRP’s international multicentre trials and to become self-reliant in their subject area in handling their own centre-initiated studies.

Further development of the new computing environment for statistics and data processing

The assessment of the selected candidate system for the new computing environment for HRP’s statistics and data-processing operations will be completed and installed, subject to availability of funds. Staff will be trained in its use and research projects will be transferred progressively to the new system.
Annex 1

CONSULTANTS AND TEMPORARY ADVISERS DURING 1999

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<tr>
<th>Name</th>
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<td>M. Ali</td>
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<tr>
<td>D. Machin</td>
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Annex 2

PUBLICATIONS IN 1999

Farley TMM. Current use of oral contraceptives increases the risk of ischaemic stroke but not myocardial infarction (Commentary). Evidence based obstetrics and gynaecology (accepted).

Farley TMM, Meirik O, Collins J. Cardiovascular disease and combined oral contraceptives: reviewing the evidence and balancing the risks. Human reproduction update (accepted).

International Post-Marketing Surveillance of Norplant. Analysis of the safety and effectiveness of Norplant, IUDs and sterilization in a five-year controlled cohort study. The lancet (submitted).


Short-course antiretrovirals for prevention of mother-to-child transmission of HIV. Invited review, co-authored by Farley TMM, Vincenzi I. WHO Weekly epidemiological record (accepted).


Standardization and quality control of laboratory procedures

E. Ezcurra
INTRODUCTION

Since 1976, laboratories collaborating in research and institutions in developing countries receiving support for the strengthening of research capability have been provided with matched reagents for the immunoassay of reproductive hormones through the Matched Reagents Programme (MRP). The performance of recipient laboratories in the assay of these hormones was monitored through an External Quality Assessment (EQA) scheme.

In line with the recommendations of the Scientific and Technical Advisory Group (STAG), the WHO Collaborating Centre for Research and Reference Services in the Immunoassay of Hormones in Human Reproduction (the London Centre) developed and distributed enzyme immunoassays (EIAs) as replacement for radioimmunoassays of FSH, LH, prolactin, hCG and progesterone. The development of EIAs for estradiol and testosterone was ongoing and it was anticipated that this would be completed in 1999–2000.

MATCHED REAGENTS PROGRAMME

The MRP provided collaborating laboratories with standardized assay methods and matched assay reagents for the measurement of eight analytes: FSH, LH, prolactin, hCG, estradiol, progesterone, testosterone and cortisol. In 1999, a total of 30 laboratories in 19 countries (17 developing) received matched reagents sufficient for 321 200 assay tubes (Table I). All these reagents were produced at the London Centre.

It is to be noted that, out of the grand total of 3212 kits, 1050 were provided for HRP-monitored projects without charge, while 2162 were distributed for research and patient care at a subsidized price.

ENZYME IMMUNOASSAY (EIA) REAGENTS

At its 1992 meeting, STAG stressed the importance, to both developed and developing countries, of providing EIA reagents in place of radioisotopic reagents (RIAs). The development work needed for the production of kits for the accurate measurement of reproductive hormones by EIA was continuously carried out at the London Centre. Centres of the Latin American Regional Reagent Programme (LARRP) contributed by developing some components of the EIA methodology.

Development of EIA kits

Kits for LH, FSH and prolactin were introduced in 1994, for hCG in 1995 and for progesterone in 1996. The EIA methodology was also introduced for the assays of pregnanediol glucuronide and estrone glucuronide which were requested for urinary assays.

Difficulties were encountered in the development of estradiol EIA. It was hoped, however, that the testing would be completed in 1999.

The development of a kit for testosterone EIA was accelerated by the work of a WHO research trainee from the Havana Collaborating Centre for Research in Human

Table I. Total vials (100 assay tubes per vial) for RIA and kits (100 assay tubes) for EIA distributed in 1999

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<tr>
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<tr>
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<td></td>
</tr>
<tr>
<td>Levonorgestrel</td>
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<td></td>
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<tr>
<td>Pregnanediol glucuronide</td>
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<tr>
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<td>Grand total</td>
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Reproduction (CCR), at the London Centre. Further development of the kit for testing was done in parallel in the Centres of the LARRP. It was hoped that after having sorted out the last problems the kit would be endorsed and introduced in 1999.

Due to the phasing-out of the MRP, plans to complete the development of estradiol and testosterone EIAs were not pursued in 1999.

Concurrently with the introduction of the EIA kits, production and distribution of RIA reagents diminished and ceased.

Reference limits for WHO EIA kits

Reference ranges established over the last 20 years with Matched Reagents RIAs could not be utilized with the new EIAs, particularly those for peptide hormones. Every new assay methodology, including the Matched Reagents EIA kits, is likely to produce differing values and, consequently, different reference ranges. At the same time, the knowledge of reference ranges is of great importance when the results are to be used for diagnostic or comparative purposes. Reference ranges were very often requested by the centres using the EIA kits.

A programme for establishing reference ranges for all WHO EIA kits was formulated. Following a statistical evaluation, the format used to report the reference range was determined (95% confidence limits, 2.5th and 97.5th percentiles or ranges), depending on the character of distribution of the observations.

A large number of results for dated samples from women assayed with the use of Matched Reagents EIA kits were obtained by the Singapore CCR. Measurements of FSH, LH and progesterone for various parts of the menstrual cycle, prolactin for women of fertile age, and hCG for pregnant women were carried out. These data have been processed statistically and 95% confidence limits were established for follicular phases and peaks of FSH and LH, respectively, and for prolactin. For hCG, the 2.5th and 97.5th percentiles were obtained. As the assay of progesterone encountered some methodological problems, the limits could not be established.

At the Moscow CCR, 80 samples from men were analysed for LH, FSH and prolactin. The data were processed and 95% confidence limits were established.

In 1998, the Mexico CCR analysed samples for FSH, LH and prolactin from 20 women. The data will be processed together with the data from Singapore and Nigeria, where samples from 38 women are being assayed.

Eventually, after collection and statistical evaluation of all data, a publication may be considered. Such a publication would be aimed at exploring the differences which may be apparent between African, Asian and Latin American populations, with respect to serum levels of some reproductive hormones.

Serono instruments

Serono spectrophotometers (Serozyme I) are used for reading the colour signal at the end of the EIA procedure and for calculating the results. Fifty such instruments have been distributed by HRP to collaborating laboratories and eight are still in stock in Geneva, either to be distributed or kept in reserve in case of breakdowns.

In the future, all laboratories that will use EIA kits of the same format as that of the WHO Matched Reagents kits, i.e. kits from Immunometrics or BioChem ImmunoSystems (former Serono), will be able to use the instruments. Their maintenance, notably replacement of deteriorating filter blocks, will have to be solved individually.

QUALITY ASSURANCE

Continuous review of quality assurance practices was carried out with the aim of improving assay performance and maintaining it at a high level in the laboratories receiving WHO Matched Reagents. Internal Quality Control (IQC) and External Quality Assessment (EQA) were considered to be integral parts of quality assurance.

External Quality Assessment in a biennial perspective

An evaluation was carried out of the EQA scheme as it functioned during the 1997–1998 and 1998–99 EQA cycles. A total of 35 and 27 laboratories, respectively, participated in the EQA scheme.

The discipline of participation was high, as judged from the high percentage of results returned (86% and 79%, respectively).

The performance of individual laboratories was ranked and a comparison of both the EQA cycles was presented. Most laboratories maintained the quality of their analytical performance and, in some, a marked improvement was noted.

The performance of each type of kit was evaluated with regard to comparability both in EQA cycles and between-run imprecision. The EIAs for FSH, LH and prolactin showed very satisfactory results. The EIA for hCG provided less satisfactory, but acceptable results. Progesterone EIA exhibited a low precision for levels below 10 nmol/L.
Two remaining quarterly EQA runs ending with 21/09/1999 and 21/12/1999 will be evaluated separately in January 2000.

**Laboratory manuals on EQA and IQC**

The purpose of the EQA manual, which was published in 1995, was to explain the principles and significance of the EQA scheme to the current participants and to provide guidance to those laboratories that conducted—or wished to initiate—a regional or national EQA scheme for reproductive hormones. The guidelines on IQC procedures were published by HRP in 1993. A Spanish version of the EQA manual was published in 1997 and of the IQC manual in 1998.

As of 2000, the importance of the IQC manual will increase, as the central EQA will no longer exist and the IQC will remain the main instrument for maintaining and improving the analytical quality of a laboratory.

**TRAINING AND TECHNOLOGY TRANSFER**

**Training and technical assistance**

During the phasing-out year 1999, no training or technology transfer was conducted.

**Latin American Regional Reagent Programme (LARRP)**

LARRP consisted of three centres: the Centre for Medical Education and Clinical Investigations (CEMIC), Buenos Aires, Argentina; the National Institute of Endocrinology, Havana, Cuba; and the Salvador Zubiran National Institute of Nutrition, Mexico City, Mexico.

Originally it was planned that LARRP should eventually take over the assay technology from the London Centre to be able to produce and distribute EIA kits in the Region and, possibly later, on a global scale. Organizational issues (remit of the parent institutions) prevented this in some of the centres and, instead, LARRP has been contributing with its expertise to speed up and reduce costs of method development of WHO Matched Reagents at the London Centre.

In 1999, the Havana Centre submitted a proposal for the development of testosterone EIA based on a monoclonal antibody, produced at the Buenos AiresCentre. The method, once developed, could serve national and/or regional purposes.

**PHASING OUT THE MATCHED REAGENTS PROGRAMME AND THE LONDON CENTRE**

In the first half of 1999, the staff of the London Centre distributed WHO Matched Reagents to laboratories in compliance with the requests submitted and approved in 1998 (as listed in Table I). The EQA scheme was continued and will end with reports from participating centres in January 2000.

The staff of the London Centre, after having received redundancy payments or taken early retirement, have gradually left the Centre. The Director of the Centre, Mr S. Sufi, stayed in the office until the end of 1999.

As far as the equipment and remaining reagents were concerned, HRP allowed the Director (Mr S. Sufi) and his staff to form a new enterprise called Immunometrics (UK) Ltd. under the condition that this enterprise would continue to collaborate with HRP and its centres in developing countries in the area of hormonal assays. Based on this transfer of equipment and material, the Immunometrics hopes to provide, on commercial terms, assay reagents identical with the present WHO Matched Reagents and/or corresponding assays.

Exempted from this transfer was a portion of remaining reagents for levonorgestrel, estrone and pregnanediol glucuronides (1000 kits each). These reagents would be kept by Immunometrics (UK) Ltd. on WHO’s behalf, and released upon request. This exception was motivated by the concern of HRP that these assays would otherwise be available with great difficulty or not at all, if Immunometrics ceased to exist because of financial problems. The above conditions were accepted by the new company.

**FUTURE PROVISION OF REAGENTS FOR HORMONE MEASUREMENTS**

Discontinuation of the operations of the London Centre means that HRP will have to rely upon ad hoc arrangements for the provision of commercial kits and EQA when needed for individual research projects and institution strengthening. For HRP research projects, HRP Group Leaders and Regional Managers have not identified any need for reagents in 2000. If and when the need arises, they will have three choices for reagent provision (as described below).

**Immunometrics (UK) Ltd.**

Immunometrics Ltd. has inherited the Matched Reagents Programme. It is expected that, because of their previous experience with the Matched Reagents Programme, the HRP collaborating laboratories will prefer to purchase
reagents from Immunometrics rather than another source since Immunometrics will be able to provide material identical to that which they previously received from HRP. Also, the costs may be lower than those charged by other commercial sources. Another advantage is the availability of some reagents that would otherwise be accessible with great difficulty, i.e. reagents for levonorgestrel, estrone glucuronide and pregnanediol glucuronide. Assays of samples sent to Immunometrics would be negotiable.

Individual collaborating laboratories have been informed of the conditions of ordering assay reagents from Immunometrics. The price per kit will be US$ 85, not including freight. It will mainly be orders from the laboratories that will influence the future viability of this company. As of December 1999, a total of 1186 kits were requested by individual laboratories. Out of this number, 68 kits were requested to be funded by HRP. This means that laboratories were willing to purchase 1118 kits from Immunometrics for research and patient care.

It may be expected that the year 2000 will be important for the assessment of whether or not Immunometrics will continue its activities.

BioChem ImmunoSystems

In the event that Immunometrics ceases to operate, the second choice would be the company BioChem ImmunoSystems (Germany), which sells EIA kits of a similar assay format (magnetic separation and use of Serozyme spectrophotometers) as the WHO Matched Reagents/Immunometrics reagents. The estimated costs would be US$ 130–150 per kit, not including freight. As Immunometrics would not supply EIA kits for estradiol and testosterone, it would be necessary to order these kits from BioChem ImmunoSystems. Kits for levonorgestrel, estrone glucuronide and pregnanediol glucuronide would not be available from this company.

Other sources

HRP managers will be free to choose any other reagents or assays they see fit. As mentioned above, special arrangements have been made for those assays which are currently not available commercially (levonorgestrel, glucuronides of estrone and pregnanediol) in the event that Immunometrics closes down.

FUTURE PROVISION OF EQA

The absence of a systematic EQA will make it impossible to assess continuously the quality of analytical work in individual laboratories. This is why HRP’s Research Groups will be well advised to include in projects requiring hormonal assays only those laboratories that have a proven analytical record and capability.

It is envisaged that EQA will be project-oriented and based on control samples with a known range of values; such samples are usually contained in assay kits, or can be acquired. Assay results of control samples may then be used both for IQC and for EQA, as well as for the estimation of bias, within-run and between-run imprecision, and, finally, for the assessment of reliability of results in individual laboratories. It is impossible to present a uniform and detailed EQA plan for all future projects. Therefore, an individual EQA scheme will have to be developed for each project.

It should be recommended to all participating laboratories to adhere to the IQC procedures as described in the laboratory IQC manual.

CONCLUSIONS

Although the MRP was very useful in providing HRP and its centres with support for research and institution strengthening, the shift of the HRP’s work from mainly biomedical to other areas, as well as the high costs of the MRP, made it mandatory to phase it out and replace it by a system of acquiring necessary reagents from commercial sources and organizing EQA for individual projects.
### Annex 1

**LABORATORY METHODS GROUP IN 1999**

**Members**

S.Z. Cekan, Karolinska Institute, Stockholm, Sweden (*Chairman*)
O.A. Dada, Centre for Research in Reproductive Health, Sagamu, Nigeria
V. Goh, National University Hospital, Singapore
V. Puri, P.D. Hinduja National Hospital & Medical Research Centre, Mumbai, India

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</table>
Annex 2

PARTICIPATING SCIENTISTS IN 1999

S.Z. Cekan, Karolinska Institute, Stockholm, Sweden
V. Diaz Sanchez, Salvador Zubiran National Institute of Nutrition, Mexico City, Mexico
G. Garcia, National Institute of Endocrinology, Havana, Cuba
V. Goh, National University Hospital, Singapore
R. Gonzalez-Suarez, National Institute of Endocrinology, Havana, Cuba
M. Hayes, Queen Charlotte’s & Chelsea Hospital, London, United Kingdom
A. Latif, Queen Charlotte’s & Chelsea Hospital, London, United Kingdom
J. Micallef, Queen Charlotte’s & Chelsea Hospital, London, United Kingdom
J. Millard, Queen Charlotte’s & Chelsea Hospital, London, United Kingdom
S. Quiroga, Centre for Medical Education and Clinical Investigations (CEMIC), Buenos Aires, Argentina
S. Sufi, Queen Charlotte’s & Chelsea Hospital, London, United Kingdom

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from:
AFRO
AMRO
EMRO
EURO
SEARO
WPRO

345
Communication and dissemination of information

J. Khanna and C.A. Hamill
INTRODUCTION

The creation of the Department of Reproductive Health and Research—by bringing together the previous WHO Division of Reproductive Health (Technical Support) (RHT) and HRP—necessitated reorganization of the work of the two components related to information dissemination and communication to give it a common focus and purpose. In the new structure of the Department, this work has been placed under the Team for Advocacy and Human Rights.

During 1999, with a view to increasing efficiency through better utilization of available resources, steps were taken to redistribute the work among the various staff responsible for information dissemination in the new Team. The Team also began to formulate a new set of common objectives and strategies for the Department’s information dissemination and communication work. The Team expects to start working towards the new objectives in 2000.

Much of the work done in 1999 was conducted as per the previous objectives of HRP and RHT. This report starts with those objectives.

OBJECTIVES

HRP

HRP aims to maintain effective communication with its constituencies through:

— the production of a variety of information materials on reproductive health research, especially information from HRP, and their dissemination to a range of audiences including scientists, national and international policy-makers (including donors to HRP), programme managers of reproductive health services, nongovernmental organizations including those focusing on women’s issues, regulatory agencies, representatives of consumers, special interest groups and the public at large;
— timely press releases to the international mass media on important issues of reproductive health arising from HRP’s research;
— continuing evaluation of the current use and impact of materials produced by HRP; and
— strengthening the communication capacity of HRP’s collaborating centres by conducting scientific writing workshops and communication workshops, and by providing technical assistance in setting up information dissemination/communication units.

RHT

RHT seeks to strengthen the capacity of countries to enable people to promote and protect their own health and that of their partners as it relates to sexuality and reproduction, and to have access to quality health care. To achieve this, RHT undertakes a range of activities, including among others:

— advocacy for reproductive health;
— activities to facilitate the identification of local and national needs and priorities;
— development of means for costing reproductive health interventions;
— development of ways of assessing more accurately the extent, determinants and nature of reproductive ill-health;
— identification of indicators for measuring progress towards internationally agreed targets; and
— activities to address emerging priorities.

This work results in different types of tools. The aim of the information dissemination activities of RHT is to produce these tools in the form of printed documents, posters, wall-charts, videos and information published on the RHT Internet website. They are targeted at decision-makers, scientists, health specialists and the general public, and disseminated through different channels.

PRODUCTION OF DOCUMENTS AND PUBLICATIONS

Material issued during 1999 by HRP

The following publications were produced and distributed in 1999.

Progress in human reproduction research

Progress in human reproduction research is the quarterly newsletter of HRP. The newsletter has continued to serve as the main instrument for information dissemination to policy-makers, programme managers, scientists and the general public. Four issues of the newsletter (Nos. 49–52) were published in 1999. The year 1999 marked an anniversary of sorts as the No. 50 issue of the newsletter was published in June. The four issues covered the following topics: progress in research on planning and programming, advancing reproductive health through human rights and laws, improving methods of emergency contraception, and research on endometrial bleeding. In December 1999, the print-run of the English edition of the newsletter stood at around 12 000. Almost 80% of the recipients of the newsletter live in developing countries. Progress continues to be translated into Chinese, and some 5000 copies are distributed widely in China by the National Research Institute for Family Planning, Beijing. The newsletter is also published on the Internet on HRP’s website.
Annual technical report 1998

This report, aimed primarily at scientists, documents in detail all areas of HRP’s research and technical work during 1998. More than 2500 copies of the report were distributed, primarily to scientists and national and international policymakers.

Social science methods for research in reproductive health

Aimed at both trained social scientists and biomedical and other scientists with an interest in social science research, this HRP book contains practical advice on how to plan and conduct social science research in reproductive health.

An assessment of reproductive health needs in Ethiopia

This report documents the findings of a national assessment of reproductive health needs—the first of the three stages of the WHO’s Strategic Approach. Designed as a strategic planning exercise, the assessment defines policy and research options in the reproductive health field through the involvement of a broad range of stakeholders and participants. The assessment reviewed key national reproductive health indicators, including population and fertility, utilization of antenatal, safe delivery and postnatal care services, abortion, sexually transmitted infections (STIs) including HIV/AIDS, and the availability of health care services.

An assessment of abortion services in Viet Nam

This report presents findings of a strategic assessment of abortion services conducted by HRP and partners in Viet Nam, with the goal of understanding how to reduce the recourse to abortion among Vietnamese women, and how to improve the safety and quality of abortion services being provided. The findings of this assessment are intended to assist in developing recommendations for policy change and programme modification, and to identify further research needs.

Policy briefs from social science research

A new series entitled Social Science Research Policy Briefs was launched in 1999. The aim of this series is to make available to policy-makers and scientists information on especially the policy implications of HRP’s social science research. The information in the policy briefs is presented in a user-friendly format on a single page. Two policy briefs were issued during 1999. The first (Series 1, No. 1) was entitled Kenyan men interested in family planning, but can the available services address their needs? The title of the second (Series 1, No. 2) was Men in Nepal ignoring risks from unprotected sex. Two thousand copies of each were produced and more than 1600 of each were distributed by December 1999.

Abortion in the developing world

This book contains the findings of social science research sponsored by HRP in various developing countries to increase the knowledge base on the reasons why women seek abortion, even in contexts where family planning services are widely available. The 25 chapters in the book contributed by various authors are divided into four parts, namely: The relationship between abortion and contraception, Quality of abortion care, Adolescent sexuality and abortion, and Research and its implications for policy: conclusions. This book is published on behalf of WHO by Vistaar Publications (a division of Sage Publications), New Delhi, India (with distribution rights for the Indian subcontinent), and Zed Books, London, England (with distribution rights for the rest of the world).

Printed material produced by RHT during 1999

Dispositifs intra-utérins: ce que les agents de santé doivent savoir

This is the French version of the book entitled: Intra-uterine devices: what health workers need to know. It provides an overview of intrauterine devices (IUDs) and all the essential information health workers need to know, including how IUDs work; their effectiveness; client concerns about them; their appropriate use; and the basic elements of high-quality IUD services.


This document was prepared for the Meeting of Interested Parties in 1999, and reports on the progress in activities during 1998 of the former Division of Reproductive Health (Technical Support).


This document is a financial report for 1998 of the former Division of Reproductive Health (Technical Support) and was prepared for the Meeting of Interested Parties in 1999.

HIV and pregnancy: a review

This document reviews what is known to date about HIV in pregnancy. It looks at the epidemiology of HIV, the susceptibility of women to infection and the issue of mother-to-child transmission. It also describes appropriate interventions and management of HIV-positive pregnant women and care of neonates.
Improving access to quality care in family planning. 
Medical eligibility criteria for contraceptive use  
(Arabic version)

Published in 1999 is the Arabic version of this book, which sets out detailed criteria for determining whether individual family planning clients are medically eligible to use, or continue using, a particular contraceptive method.

DALYs and reproductive health: report of an informal consultation, 27–28 April 1998

The informal consultation discussed the use of the Disability Adjusted Life Year (DALY) as a metric for the estimation of the burden of disease due to reproductive ill-health. The document is not a detailed critique of the DALY methodology but represents an analysis of the difficulties inherent in estimating the Global Burden of Disease due to reproductive health conditions using the DALY methodology.

Integrating STI management into FP services: what are the benefits?

This review was commissioned by WHO to document current experience with the integration of the management of sexually transmitted infections (STIs) into family planning services, to clarify the public health benefit of this integration, and highlight the operational challenges. Attention was given to both published and unpublished reports of empirical evidence drawn from programme experience worldwide.

Interpreting reproductive health. ICPD+5 Forum, The Hague, 8–12 February 1999
Interpréter la santé génésique. Forum CIPD+5, La Haye, 8–12 février 1999

A short paper representing WHO is contribution to the ICPD+5 discussion, produced in both English and French. It presents WHO thinking on how reproductive health evolved five years on from the ICPD meeting in Cairo.

L’avortement à risques. Axes de recherche. Guide pratique

The French version of Studying Unsafe Abortion: a practical guide. This document is aimed at all those who have an interest in research on the problems of unsafe abortion, and in developing practical, humane responses to these problems.

Midwifery module. Managing incomplete abortion (Field testing version)

This is an additional module to accompany the existing five training manuals developed to help equip midwives with essential life-saving skills. The modules were designed for the in-service training of midwives and nurse-midwives, and rely on a range of problem-based learning methods designed to maximize student involvement. As with the other modules, this module will be field tested before a final version is produced.

Mother–baby package costing spreadsheet. User guide

This document was published initially on the website in response to user demand and was followed by the printed version. The spreadsheet is designed to be used to estimate the cost of implementing a set of maternal and newborn health interventions at the district level.

Planification familiale après avortement: guide pratique à l’intention des responsables de programmes Planificación familiar postaborto: guía práctica para administradores de programas

The French and Spanish versions of Post-abortion family planning: a practical guide for programme managers. A manual, addressed to the managers of abortion care and family planning programmes, focused on the special needs of women who have undergone an abortion. Noting that such women are in critical need of family planning services, the manual offers practical advice on ways to counsel the postabortion client and provide the services needed to prevent another unwanted pregnancy. Particular attention is given to the need to adapt services to the clinical condition of the postabortion client and her special psychological and social needs.

Premiers soins de réanimation du nouveau-né: guide pratique

The French version of Basic newborn resuscitation: a practical guide. Written for health professionals responsible for the care of the newborn, this document describes a simple method for resuscitating newborn infants, even where resources are limited.

Réduire la mortalité maternelle. Déclaration commune OMS/FNUAP/UNICEF/Banque mondiale

Complications arising from pregnancy and childbirth cause the deaths of more than half a million women every year and leave many others with serious and lifelong health problems. This joint statement by WHO, UNFPA, UNICEF and the World Bank delivers key messages that draw on lessons learned and experience gained by countries worldwide in their efforts to reduce and prevent maternal deaths. The statement was published in English and French. A Spanish version is under preparation.
Reproductive health indicators: country profiles
(Available as reference)

Drawing upon a vast database of some 3000 reports and studies, the country profiles provide WHO estimates relevant to reproductive health, together with United Nations demographic estimates and UNICEF estimates of literacy.

Safe motherhood. A newsletter of worldwide activity

The Safe Motherhood Initiative is a global effort to reduce maternal mortality and morbidity. As part of its contribution to the Initiative, WHO began publishing the Safe motherhood newsletter in 1989. Now issued twice a year, the newsletter provides a news update and offers an ideal opportunity to exchange information on activities and programmes and to describe results and developments in research. It is printed and disseminated in Arabic from the Eastern Mediterranean Regional Office, in Chinese, through the Western Pacific Regional Office and in English and French from WHO Headquarters.

Soins à la mère et au nouveau-né dans le centre de santé. Deuxième révision

This is the second revision in French of the practical guide for the care of mother and baby at the health centre which defines the essential functions, tasks and skills needed for the comprehensive care of mothers and babies at the first referral level. Both normal care and life-saving emergency procedures are covered. Addressed to health planners and programme managers, the report recommends lines of action that can improve access to services and help decentralize maternal and newborn care.

Soins à la mère et au nouveau-né dans le post-partum: guide pratique

The French version of Postpartum care of mother and newborn: a practical guide. This document reports the outcomes of a technical consultation on the full range of issues relevant to the postpartum period for the mother and newborn.

(Available as reference)

The French version of the technical working group report on antenatal care which focuses attention on drawing up recommendations on antenatal care and outlining the tasks and procedures health workers are expected to perform at different levels of the health care system. It also examines how to optimize antenatal care in terms of clinical tasks and procedures with regard to the timing of visits, distance to referral centres, and frequency of attendance.

Statement by Dr Gro Harlem Brundtland, Director-General, ICPD+5 Forum, The Hague, 8–12 February 1999
Allocation du Dr Gro Harlem Brundtland, Directeur général. Forum CIPD+5, La Haye, 8–12 février 1999

This statement was produced as a booklet in English and French for distribution at the ICPD+5 conference at The Hague, The Netherlands.

Technical working group meeting to review new research findings for the prevention of MTCT of HIV. WHO and UNAIDS Secretariat in collaboration with UNICEF and UNFPA, Geneva, 10–11 August 1999

This document reports on a meeting, the objectives of which included:
— to review available data on effectiveness of short-course antiretroviral regimens;
— to review results from the HIVNET 012 study on effectiveness of Nevirapine in prevention of mother-to-child transmission (MTCT) of HIV;
— to review further research needs on short-course drug regimens for prevention of MTCT;
— to determine implications, if any, for current UN Joint recommendations on prevention of MTCT drug therapies in resource-poor settings and for conduct of inter-agency prevention of MTCT pilot projects.

Uganda Safe Motherhood Programme: costing study

The Ugandan government is implementing a comprehensive safe motherhood programme in an effort to reduce high levels of maternal and neonatal morbidity and mortality in the country. The Mother–baby package is used to set standards regarding the scope and quality of health care provided to pregnant women and newborn babies. To provide programme planners with a better appreciation of the costs entailed in implementing the Mother–baby package, a costing study was done using a standard WHO methodology and this document reports on the findings.

Dissemination of The WHO Reproductive health library (RHL) No. 2 and production of RHL No. 3

After the unequivocal success of RHL No. 1, RHL No. 2 was published in January 1999. Later in the year, a Spanish version of RHL No. 2 was also published. RHL No. 2 includes 40 Cochrane reviews and corresponding commentaries. A total of 15 000 copies were produced and by December 1999, more than 13 800 copies had been distributed. A key element of the dissemination strategy adopted for RHL has been free distribution on subscription basis. Subscriptions to RHL continue to rise rapidly. In November 1999, there were 4586 addresses in the mailing
A scientific writing workshop was also conducted in Dhaka, Bangladesh, in collaboration with the Bangladesh Institute of Research for Promotion of Essential and Reproductive Health Technologies, a centre which has collaborated with HRP for many years. Twenty-six participants from various research groups working in the area of reproductive health in the city of Dhaka participated in the workshop. The level of the participants varied from experienced researchers to those at the beginning of their research careers. All the participants said that the workshop had been very useful for them. The closing ceremony of the workshop was attended by the Minister of State for Health and Family Welfare, Dr M. Ammanullah, which helped highlight the importance of reproductive health research for Bangladesh.

**Workshops to improve communication skills and networking with the mass media**

Since the mass media play a vital role in communication, promotion of networking between local journalists and scientists is important. HRP’s collaborating institutions are HRP’s main partners at the country level and researchers in these institutions are potentially well-placed to influence public opinion and policies in their respective countries. Moreover, HRP believes that researchers have a responsibility not only to publish their findings in peer-reviewed journals, but also to make their findings known to the general public, who are investors in, and beneficiaries of, research. For these reasons, HRP supports the improvement of the scientist’s skills in communicating with the mass media.

During 1999, the Thai Medical Schools Consortium funded a communication workshop that HRP conducted at the Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand. A total of 21 scientists from various reproductive health research centres in Thailand, and two journalists participated in the workshop. All participants found the workshop to be very useful.

A second communication workshop was conducted at the Shanghai Institute of Family Planning Technical Instruction, Shanghai, China. This was the first workshop aimed at improving the communication skills of reproductive health programme managers and policy-makers. This workshop was conducted at the request of the Shanghai Family Planning Commission, which also provided funds for all local costs, except the travel of the participants. The 25 participants were largely from the Shanghai area and included six journalists. All found the workshop to be very useful. Important experience was gained in this workshop with regard to the communication skills needed by programme managers and policy-makers. This experience is helping the Department of Reproductive Health and Research to develop more focused training components in the area of advocacy and interpersonal communication.
PRESS RELEASES

Four press releases were issued in 1999. The first, issued on 17 May 1999, announced the publication of the new book *Abortion in the developing world*. The second was issued on 16 June 1999 to announce the award of a grant of US$ 10 million to HRP by the William H. Gates Foundation. Both press releases received considerable coverage in the media, earning much publicity for HRP.

The third press release was issued on 12 October 1999 to mark the day on which the world’s population touched six billion. Entitled *Meeting the reproductive health needs of six billion people: a statement by WHO*, this release made the point that half of the six billion people are under 25 years of age and meeting the reproductive health needs of these “parents of the next generation” will be a challenging task.

The final press release of the year was issued to launch a the publication *Reduction of maternal mortality: a Joint WHO/UNFPA/UNICEF/World Bank statement*. A press conference was organized at the United Nations in New York, NY, USA, to launch the book. It was attended by the Director-General of WHO, the Executive Directors of UNFPA and UNICEF and a Vice President of the World Bank. This press release generated considerable media interest. Staff of the Department also gave interviews to the press.

INTERNET WEBSITES

For historical reasons, the Department currently has two Internet websites—one for HRP (www.who.int/hrp/) and another for the RHT (www.who.int/rht/). Work started in November 1999 to create a new common site for the whole Department. This site is expected to become operational in 2000.

HRP

HRP’s Internet website, *HRP Online*, is a virtual online documentation centre, containing HRP’s main information materials. In 1999, the website was updated regularly and new material added.

RHT

As part of its information dissemination activities during 1998, the then Division of Reproductive Health (Technical Support) developed its first website. During 1999, the site ran alongside that of HRP and has a similar look and feel. The Technical Support site gives an overview of the dimensions of reproductive ill-health and WHO’s main activities in the areas of maternal and newborn health, family planning and reproductive tract infections. A comprehensive listing of resources is also available through this site, along with details of how to obtain them. Some 30 technical support documents are already available through this site (either in pdf or html format for easy printing or downloading), and work is ongoing to make further documents available. The site was designed to be user-friendly for the most basic hardware and software.

COLLABORATION

The scientific writing workshops are conducted in collaboration with the WHO Office of Publications. The Department of Communication, Cornell University, Ithaca, NY, USA, collaborates with HRP in a variety of activities including the conduct of communication workshops for scientists.

PLANNED ACTIVITIES

The first priority for 2000 is to define a common information dissemination and communication strategy for the new Department. This strategy is expected to become functional in 2000.

In 2000, the Department will continue to produce its usual serial and non-serial publications, appropriate public relations material and conduct its scientific writing and communication workshops. It is planned to conduct two scientific writing workshops in Taegu (Republic of Korea) and one each in Kampala (Uganda) and Tunis (Tunisia). Two communication workshops for scientists, programme managers and policy-makers are also planned, at least one of which will take place in Egypt. Activities to strengthen the communication capacity of collaborating centres will also continue.
Annex 1

PUBLICATION IN 1999

Appendix 1

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