This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization

Research on the menopause

Report of a WHO Scientific Group

World Health Organization
Technical Report Series
670

World Health Organization, Geneva 1981

ISBN 92 4 120670 5

PRINTED IN SWITZERLAND

81/5042 – Schüler SA – 8500

WORLD HEALTH ORGANIZATION
TECHNICAL REPORT SERIES

No. 670

RESEARCH ON THE MENOPAUSE

Report of a WHO Scientific Group

CORRIGENDA

Page 8, line 14:

Delete (2)
Insert (2*a*)

Page 81, lines 11, 17:

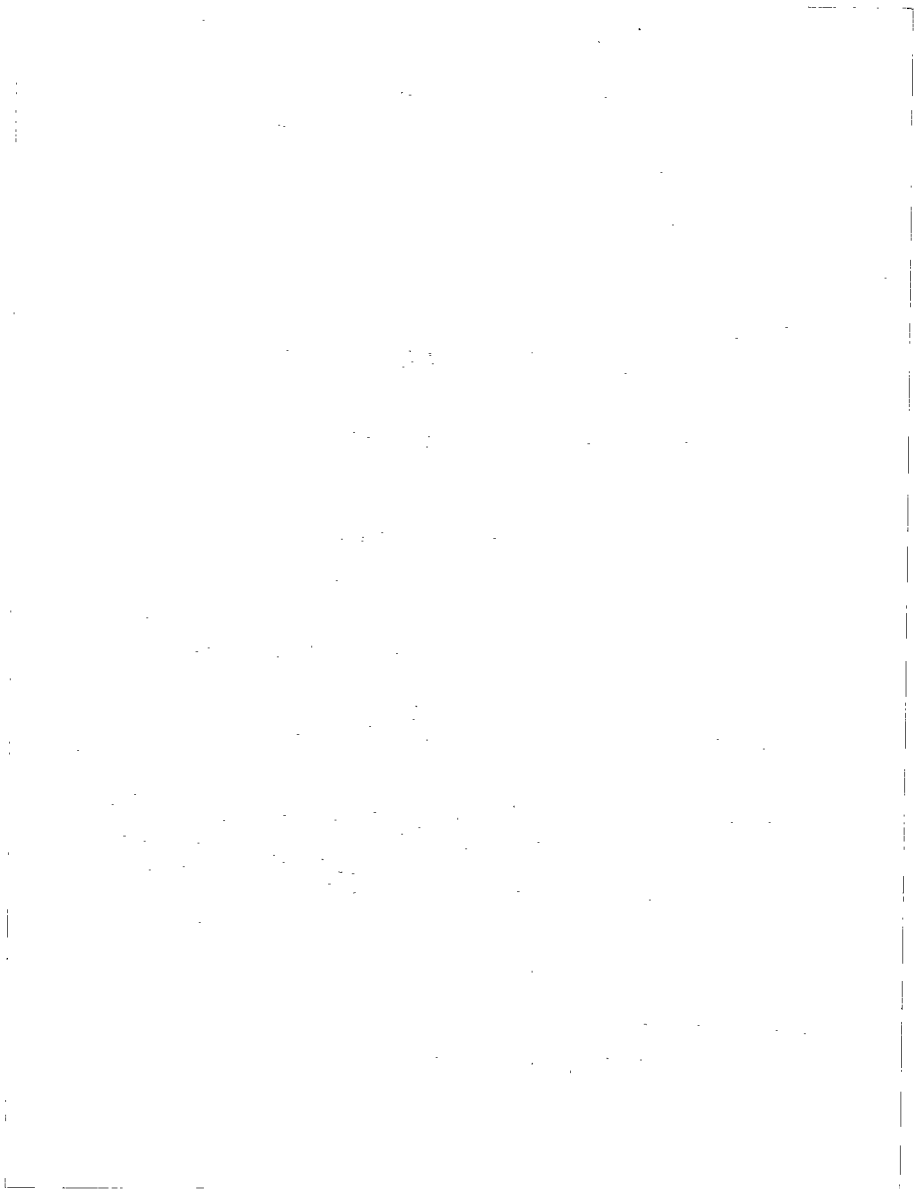
Delete (2)
Insert (2*a*)

Page 102, REFERENCES: *Add the following between* 2. *and* 3.

2a. SHERMAN, B. M., WALLACE, R. B. & TRELOAR, A. E. The menopausal transition: endocrinological and epidemiological considerations. *Journal of biosocial science,* Supplement **6**: 19–35 (1979)

Page 110, reference 168:

Delete Ageing, steroid hormones and bone.
Insert Steroid hormones, ageing and bone.



CONTENTS

WHO SCIENTIFIC GROUP ON RESEARCH ON THE MENOPAUSE

Geneva, 8–12 December 1980

Members

Dr J. Bancroft, MRC Reproductive Biology Unit, Centre for Reproductive Biology, Edinburgh, Scotland

Dr H. G. Burger, Prince Henry's Hospital Medical Research Centre, Melbourne, Australia (*Rapporteur*)

Dr P. K. Devi, Upjohn International Inc., New Delhi, India (*Vice-Chairman*)

Dr T. M. Mack, Department of Community and Family Medicine, University of Southern California, Los Angeles, CA, USA

Dr B. E. C. Nordin, MRC Mineral Metabolism Unit, The General Infirmary, Leeds, England*

Dr P. Nylander, University College Hospital, Ibadan, Nigeria

Dr K. J. Ryan, Boston Hospital for Women, Harvard Medical School, Boston, MA, USA (*Chairman*)

Dr M. Sas, Department of Obstetrics and Gynaecology, University Medical School, Szeged, Hungary

Dr T. A. Sinnathuray, Department of Obstetrics and Gynaecology, University of Malaya, Kuala Lumpur, Malaysia

Secretariat

Dr K. Edström, Medical Officer, Maternal and Child Health, WHO, Geneva, Switzerland

Dr A. Kessler, Director, Special Programme of Research, Development and Research Training in Human Reproduction, WHO, Geneva, Switzerland (*Secretary*)

---

* Present address: Royal Adelaide Hospital, Adelaide, S. Australia 5000.

RESEARCH ON THE MENOPAUSE

Report of a WHO Scientific Group

A WHO Scientific Group on Research on the Menopause met in Geneva from 8 to 12 December 1980. The meeting was opened by Dr A. Kessler, Director, Special Programme of Research, Development and Research Training in Human Reproduction, on behalf of the Director-General of WHO.

1. INTRODUCTION

All women who live beyond the age of 55 to 60 years and many of a younger age experience a period of transition from the reproductive to the nonreproductive stage of life, of which the most striking feature is the cessation of menstruation, i.e., the menopause. At present, there is controversy about whether there is a menopausal syndrome of somatic and psychological symptoms and illness, and there are virtually no data on the age distribution of the menopause and no information on its sociocultural significance in the developing countries. The subject of risks and benefits of estrogen therapy in peri- and postmenopausal women is of considerable importance in view of the large number of prescriptions issued for such medicaments in developed countries, which indicates their frequent use, and the different interpretations and opinions among epidemiologists and clinicians on both past and current studies on this subject. The choice of family planning methods presents particular problems for women who are approaching the menopause. The health repercussions of cessation of reproductive function and those caused by the agents used to treat the accompanying symptoms are additional reasons for initiating this review of the present state of knowledge regarding the menopause and the postmenopausal period. By the year 2000, the average life expectancy for women in developed countries is expected to be 75 to 80, and in developing countries 65 to 70 years (*1*). The proportion of those reaching the age of 65 can be estimated at close to 90% in the developed and 70% in the developing countries; in the latter, one out of three of this group of over-65s can be expected to celebrate her eightieth birthday, compared with one out of seven under the mortality conditions of 1975. Life expectancy for women averages six years more than for men, at least in the developed countries. If it is assumed

that reproductive function in women generally ceases at about the age of 50 years, it may be calculated that—by the year 2000—one in every two to three of these women can expect about 30 years of postmenopausal life.

2. DEFINITION OF TERMS

The Scientific Group considered that there was confusion in the medical literature regarding the use of terms such as menopause, climacteric, premenopause, perimenopause, and postmenopause.

Taken literally, the term menopause signifies the permanent cessation of menstruation. Spontaneous menopause is the result of loss of ovarian follicular function. Because the permanent cessation of mentruation in over 90% of Caucasian women aged more than 45 years is preceded by the occurrence of amenorrhea for 12 months (*2*), this interval is customarily used to indicate the fact that the menopause has occurred. Vaginal bleeding after more than 12 months of amenorrhea calls for investigation to exclude a possible malignancy.

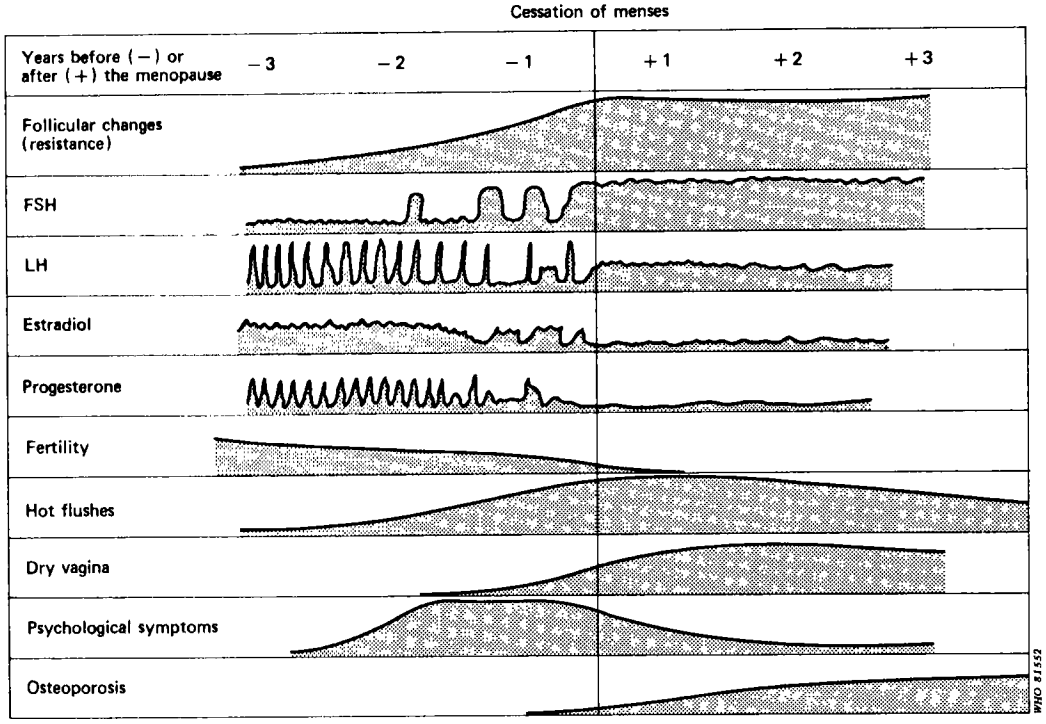
The Group recognized that the term menopause (or climacteric) is used widely in clinical practice and in the medical literature to describe a period of time during which spontaneous menstruation normally ceases. This period is characterized endocrinologically by evidence of decreasing ovarian activity, biologically by decreasing fertility, and clinically by alterations in menstrual cycle intervals and by a variety of symptoms (Fig. 1).

The term menopause is also used to describe the cessation of menstruation which follows surgical hysterectomy and iatrogenic abolition of ovarian function. The Group considered that the term should not be used to describe the cessation of menstruation which follows simple hysterectomy, because normal ovarian function may persist for a variable period after the operation. Loss of ovarian function is an essential characteristic of the concept of menopause so that the term surgical menopause should be confined to the procedure of bilateral oophorectomy, with or without hysterectomy. After simple hysterectomy, the level of ovarian function may sometimes be inferred clinically from the patient's symptoms. Objective assessment requires the measurement of gonadotrophin and/or estrogen concentrations in blood or urine.

The Scientific Group recommended:

(1) that the term *menopause* be defined as the permanent cessation of menstruation resulting from loss of ovarian follicular activity;

Fig. 1. Schematic representation of some clinical, biological and endocrinological features of the peri- and postmenopausal phases



(2) that the term *perimenopause* (or *climacteric*) be used to include the period immediately prior to the menopause (when the endocrinological, biological and clinical features of approaching menopause commence) and at least the first year after the menopause;

(3) that the *postmenopause* be defined as dating from the menopause, although it cannot be determined until after a period of 12 months of spontaneous amenorrhea has been observed.

The Scientific Group recognized that the term *premenopause* is widely used in an ambiguous manner, either to refer to the one to two years immediately before the menopause or to refer to the whole of the reproductive period prior to the menopause. In the present report the term will be used in the latter sense. The Group recommended that users of the term should define it specifically.

3. THE ENDOCRINOLOGY OF THE MENOPAUSE AND THE POSTMENOPAUSAL PERIOD

3.1 Changes in gonadotrophins and estrogens immediately prior to the menopause

The transition from regular menstrual cycles (characteristic of the reproductive phase) to amenorrhoea following the menopause may be marked by a period of menstrual cycle irregularity (*3, 4*). The duration of the transition, and the nature of the irregularity vary widely among women. In population studies, in which the basal body temperature was used to determine the relative lengths of the follicular and luteal phases of the cycle, or to diagnose anovulation by the presence of a monophasic rather than a biphasic temperature record, it has been demonstrated that the length of the follicular phase gradually declined over the two decades prior to the menopause (*4*) and that anovulatory cycles became more prevalent, e.g., there were 3–7% of anovulatory cycles between the ages of 26 and 40 years, and 12–15% between 41 and 50 years (*5*). Menstrual cycle variability persists for a longer time in women whose menopause starts at a later age (*3*) and is characterized by unusually short and unusually long intermenstrual periods, although the mean cycle length increases markedly in the one to two years immediately before the menopause.

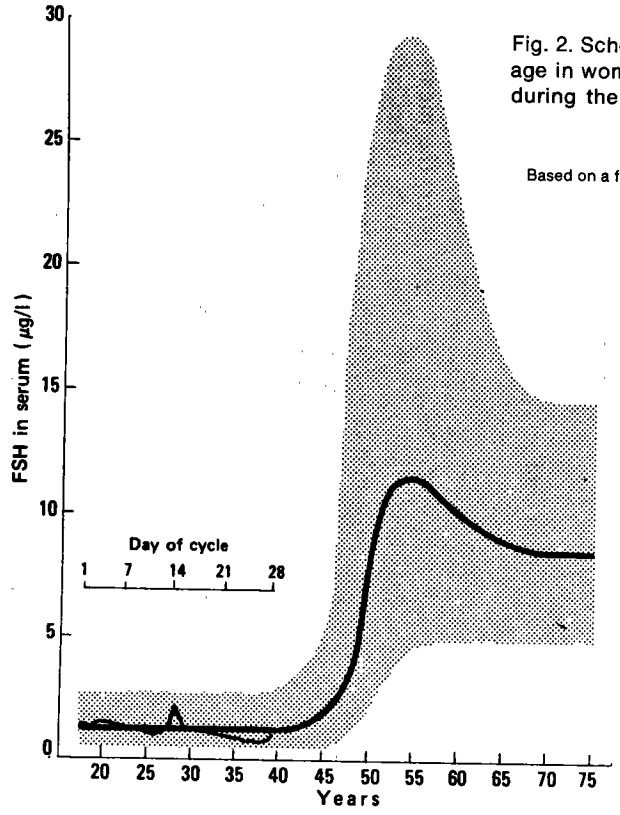
Several recent studies (*6–8*) have described the endocrine characteristics of menstrual cycles in perimenopausal women. In normal

regularly menstruating subjects over the age of 45 years (compared with younger women), the cycle length was significantly shorter, estradiol levels in the blood were lower (mean values: 50–120 ng/l (50–120 pg/ml) against 150 ng/l in the younger subjects), and FSH (follicle-stimulating hormone) levels were elevated up to twice the level found in younger women, during the early follicular phase, with some elevation also during the remainder of the cycle (*6*). In contrast, there was no change in LH (luteinizing hormone) levels in comparison with those in younger women. In subjects in whom menstrual irregularity developed, a variety of hormonal patterns has been observed (*6, 8*), including the presence of elevated levels of FSH alone, or FSH and LH, and phases of rising and falling estradiol concentrations with or without elevations in progesterone. The data have been interpreted to indicate the irregular maturation of ovarian follicles with or without hormonal evidence of ovulation. The frequent dissociation between the concentrations of FSH and LH, and the observation of elevations of FSH in the presence of normal early-to-mid-follicular phase levels of estradiol suggest either that there is a change in hypothalamic pituitary sensitivity to the feedback effects of estrogen or that another ovarian factor, similar to testicular inhibin (*9, 10*), may be involved in the modulation of FSH levels and may be secreted in diminished amounts as follicular function declines.

3.2 Changes in gonadotrophin and steroid hormone levels after the menopause

After the menopause, the levels of FSH and LH increase several fold and show marked pulsatility (*11*) and, one year later, the mean FSH concentrations are 10–15 times higher than early-follicular phase levels in young women, while LH is about three times higher (*12, 13*) (Fig. 2). Maximum LH levels are found 2–3 years after the menopause (*13*) and there is subsequently a decline in mean values with increasing age (12, 13). Previously it was shown that an elevated level of serum FSH could indicate the absence of ovarian follicles in patients with primary or secondary amenorrhoea prior to surgery (*14*). The elevated FSH levels after the menopause are thus interpreted as resulting from the gradual loss of ovarian follicular function.

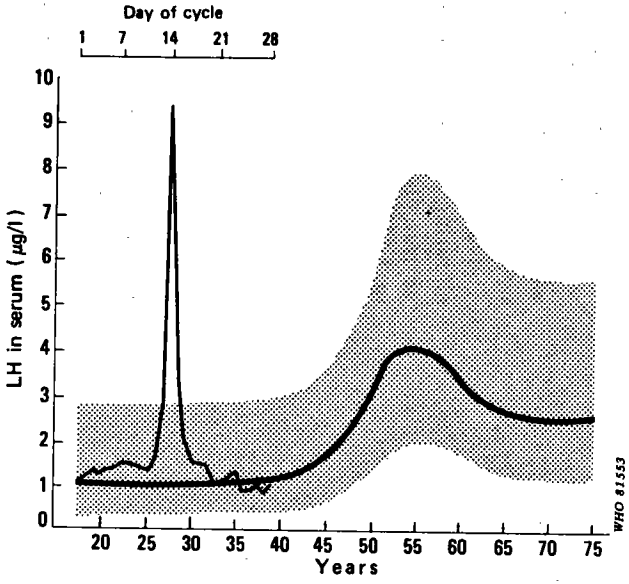
In the postmenopausal period, a change occurs in the source and nature of circulating estrogens. The normal ovary virtually ceases to secrete estrogens, although very low estradiol levels (less than 20 ng/l) may not occur until some months after the menopause (*15*).



The changes in the serum levels of FSH during the menstrual cycle in relation to the change with age in women

Fig. 2. Schematic representation of the serum FSH and LH levels as a function of age in women. Postmenopausal FSH levels are markedly higher than those seen during the menstrual cycle, while midcycle peak LH levels often exceed those of the peri- and postmenopausal period

Based on a figure from Wide, L. et al. (12); redrawn and reproduced here with permission.



The changes in the serum levels of LH during the menstrual cycle in relation to the change with age in women

Quantitatively the most important circulating estrogen in postmenopausal women is estrone, with basal levels averaging 30 ng/l (range 18–50 ng/l, see Table 1) compared with 12 ng/l estradiol (range 5–25 ng/l). Most of the circulating estrogens are derived from the extraglandular conversion of adrenal androgen precursors, notably androstenedione (*16*). The major determinant of plasma estrone has been demonstrated to be the level or rate of production of plasma androstenedione (*17, 18*). The degree of conversion to estrone is

Table 1. Plasma or serum concentrations of relevant estrogens and androgens in pre- and postmenopausal women [a]

Steroid	Mean plasma or serum concentrations in ng/l (range)		
	basal	after oophorectomy	ovarian vein
Estradiol			
premenopausal	170 (30–400)	14 (5–30)	8000 (70–40 000)
postmenopausal	12 (5–25)	14 (6–25)	31 (14–54)
Estrone			
premenopausal	120 (40–200)		880 (90–3800)
postmenopausal	30 (18–50)	39 (17–60)	72 (40–120)
Androstenedione			
premenopausal	1800 (1100–2500)	900 (300–2200)	70 000 (1000–300 000)
postmenopausal	900 (400–1300)	700 (200–1200)	3450 (450–13 000)
Testosterone			
premenopausal	300 (180–500)	130 (40–270)	3950 (740–20 000)
postmenopausal	230 (70–400)	100 (40–200)	3030 (600–8700)

	Mean plasma or serum concentrations (ng/l ± SD)		
	premenopausal	postmenopausal	oophorectomized
Dihydrotestosterone	250 ± 60	120 ± 30	50
Dehydroepiandrosterone	5000 ± 1500	1600 ± 500	1260 ± 360
Dehydroepiandrosterone sulfate	$2000 \pm 500 \times 10^3$	$400 \pm 100 \times 10^3$	

[a] Based on data from Table 6, reference *304*.

increased after the menopause (*19*); the ratio of androstenedione to estrone concentration is inversely related to the androstenedione level (*17*), which falls after the menopause (*20*). The degree of conversion is also a function of excess body fat (*16*). While the adrenal is

the major source of circulating estrogens, the postmenopausal ovarian stroma also continues to produce steroids. A steroid concentration gradient across the ovary was found in 65% of 42 postmenopausal women and was calculated to result in a major contribution to the blood production rate of estradiol in 20% of them (*21*); the ovary makes a major contribution to the circulating androgens, being responsible for about 50% of testosterone production (*22*). Plasma testosterone falls only slightly after the menopause, from approximately 300 ng/l (range, 180–500) to 230 ng/l (range 70–400); oophorectomy in the postmenopause leads to a further fall to levels of about 100 ng/l (*22*) (Table 1). Although relatively minor, the changes in steroid levels which follow oophorectomy should be borne in mind when possible endocrine factors contributing to morbidity and mortality after oophorectomy (as compared with natural menopause) are under consideration. Ovarian androstenedione production decreases by about 40% when measured after the menopause, although the adrenal contribution shows no significant change (*23*). A few years after the menopause the levels of adrenal androgens gradually decline further (*24*). It is noteworthy that the plasma concentrations of both androgens and estrogens show circadian and day-to-day variations in addition to short-term fluctuations (*22, 24, 25*). Such variations have been observed in pre- and postmenopausal women both with and without endometrial cancer and before and after oophorectomy. The variations are as great between serial samples from the same individual as between individuals. The phenomenon resembles that reported for hydrocortisone and dehydroepiandrosterone, two steroids that are secreted episodically by the adrenals in the same circadian pattern (*26*). During the normal menstrual cycle, androstenedione and testosterone levels show a periovulatory increase which is no longer seen after the menopause (*27, 28*).

These considerable variations and different factors create serious difficulties for obtaining representative values of blood concentrations of hormones in postmenopausal women and thus for correlating hormone levels to symptoms.

In the light of the endocrine fluctuations that occur prior to final loss of responsive follicles, the Scientific Group considered that objective assessment of ovarian function during the perimenopausal period can be based on the measurement of serum FSH and/or estradiol. However, in women continuing to menstruate or in those who have undergone simple hysterectomy, such measurements reflect only the situation at the time of blood sampling. When FSH levels are clearly

within the normal range for postmenopausal women and estradiol levels are less than the lowest value found during the normal menstrual cycle, loss of ovarian follicular function can be diagnosed. However, it is noteworthy that such a combination can be found in some subjects who are approaching the menopause but are still menstruating (*6*). As hormonal changes suggestive of ovulation can still occur, following the finding of elevated FSH and lowered estradiol in such subjects, the determination of the endocrine and fertility status must take account of all information available, both symptomatic and hormonal. Measurement of FSH and estradiol on a single blood sample provides supportive evidence but, by itself, cannot give a diagnosis of the postmenopausal state.

The Scientific Group considered that research was necessary to develop guidelines for adequate endocrinological characterization of peri- and postmenopausal women with regard to the hormones to be measured and the number of samples required. The aim of such studies would be to determine the usefulness of hormone measurements in predicting the occurrence of postmenopausal disorders such as osteoporosis and urogenital atrophy. For example, although estrone is the major circulating estrogen in postmenopausal women, the biological importance of estradiol is uncertain and requires further study.

The Group recommended that WHO should coordinate research in this area by convening meetings of investigators studying the menopause in order to develop standardized methods of hormonal assessment, including the use of matched assay reagents to allow comparability of results between laboratories.

4. THE AGE DISTRIBUTION OF THE MENOPAUSE

4.1 Determining the age at menopause

There is a paucity of descriptive information about the age distribution of natural menopause in populations, and, in particular, very little is known concerning populations of non-European origin. Moreover, the interpretation of existing data must be qualified because of both evident and implied limitations (*29*).

The age at menopause in individuals may be obtained by periodically asking them about the presence or absence of menstrual cycles (*30–33*), or it may be determined in retrospect from postmenopausal subjects by asking them to recall their age at the time of the last men-

strual period (*34–36*). The success of both methods depends on accurate knowledge and unbiased reporting of age. The accuracy of the first method depends upon the frequency of interviews and the completeness of final follow-up. The accuracy of the second depends on the quality of recall, which in turn reflects the interval of time since menopause, the alertness and motivation of the respondent, and the availability of useful milestones.

When the goal is determination of the age at menopause in a whole population, serious sampling errors may occur. Prospectively followed-up cohorts may be subject to large nonrandom losses (*37, 38*). Women who are questioned in retrospect constitute groups of survivors, a sizeable number of whom may not choose to participate. Two samples, drawn from different populations for purposes of comparison, may not be comparable on the basis of such things as age and birth cohort unless sufficient attention is paid to ensure that they are. Moreover, even large studies may yield relatively small groups of similar age, and therefore be subject to considerable random error.

When the goal is simply to produce an estimate of the age at menopause in a population, a simple method with little bias is to record the current menstrual situation (or *status quo*) of individuals at various ages, without attention to the remembered age at menopause in those who are postmenopausal (*30–32*).

In order to summarize data from women of various ages, to take advantage of all data, and to de-emphasize atypical and extreme observations, it has been found useful to estimate the median age as the typical age at menopause by transforming each age-specific prevalence of the postmenopausal state to a probit scale, and to plot these probits against age. Under the assumption that the distribution of menopausal age in an unselected cohort of women conforms to a normal distribution (*39*), this relationship will be linear. Thus the median age at menopause, like the LD_{50} of a dose–response curve, can be measured or calculated from a linear interpolation.

While probit analysis using such *status quo* measurements may provide a safe and simple estimate of the median menopausal age for a population, the resultant bivariate information is not optimum for purposes of quantitating the relationship between age at menopause and other characteristics such as parity or age at menarche. Such information, to the extent that it is available, has been obtained mostly from slightly biased, but internally comparable, retrospective inquiries. Comparisons over a period of time or between populations are especially liable to error, no matter what methods are used, because

separate field studies, in practice, inevitably entail differences in methodology.

4.2 Factors influencing the age at menopause

4.2.1 *Geography and race*

Table 2 (adapted from reference *29*) summarizes the estimates of menopausal age derived from studies judged to be least subject to the errors described. There is a noteworthy consistency in these estimates from the developed countries (from Australia, England, Finland, Federal Republic of Germany, Israel, Netherlands, New Zealand, Scotland, South Africa, Sweden, Switzerland and the USA), giving a median age of about 50 years for women of European origin. As for other

Table 2. Estimates of the age at menopause from selected studies[a]

Country and year of study	Race	Mean or median age at menopause in years		Study design	Source (reference)
Scotland, 1970	Caucasian	50.1	median	cross-sectional	(*31*)
England, 1965	Caucasian	50.78	median	cross-sectional	(*30*)
		47.49	mean		
England, 1951–61	Caucasian	49.82	median	cross-sectional	(*40*)
USA, 1934–74	Caucasian	49.8	median	cohort	(*37*)
		49.5	mean		
USA, 1966	Caucasian	50.02	median	cross-sectional	(*32*)
	Negro	49.31	median		
	Both races	49.8	median		
Germany, Federal Republic of, 1972	Caucasian	49.06	mean	retrospective	(*34*)
Finland, 1961	Caucasian	49.8	mean	retrospective	(*35*)
Switzerland, 1961	Caucasian	49.8	mean	retrospective	(*35*)
Israel, 1963	Caucasian	49.5	mean	retrospective	(*36*)
Netherlands, 1969	Caucasian	51.4	median	cross-sectional	(*41*)
New Zealand, 1967	Caucasian	50.7	median	cross-sectional	(*42*)
South Africa, 1971	Caucasian	50.4	median	cross-sectional	(*43*)
	Negro	49.7	median		
South Africa, 1960	Negro	48.1	median	retrospective	(*44*)
		47.7	mean		
South Africa, 1960	Caucasian	48.7	mean	retrospective	(*45*)
India (Punjab), 1966	Asian	44.0	median	cohort & cross-sectional	(*38*)
Papua New Guinea, 1973	Melanesian	47.3	median (not malnourished)	cross-sectional	(*33*)
		43.6	median (malnourished)		
Australia, 1978	Caucasian	50.4	median	cross-sectional	(*46*)
Sweden, 1968–69; 1974–75	Caucasian	49.6–50.4	median	retrospective & cross-sectional	(*47*)

[a] Adapted from R. H. Gray (*29*).

racial groups, only the Bantu in South Africa, the Punjabis in India, and the Bundi in Papua New Guinea have been studied. Because of the paucity of data and the methodological differences, strict evaluation of possible ethnic differences in the menopausal age cannot be made, but the available data (*32, 37*) do describe a somewhat lower age in these groups. Most of the methodological bias would tend to push the estimate in the same direction, however.

4.2.2 *Secular trends*

The possibility that the age of menopause has risen over the past 100 years has been put forward strongly, but there appears to be no solid evidence for a consistent secular change indicating a rise among European populations (*29*). There is, however, evidence of some fluctuations over time (*47*).

4.2.3 *Age at menarche*

Although it has been proposed that an early age of menarche might lead to a late menopause, few data to support this view are available and even these studies may be criticized on methodological grounds (*47*). Several other studies have failed to show such an association (*30, 32, 41, 45*).

4.2.4 *Marital status and occupation*

Several observers have noted that unmarried and/or employed women have a slightly earlier median age at menopause (*30, 48*), and that this cannot be accounted for by, for example, parity or age at first pregnancy.

4.2.5 *Parity*

The association between parity and menopausal age is controversial (*28, 30, 49*). While several investigators claim to have found that high parity delays menopause in women of upper but not those of lower socioeconomic status (*30, 50*), most studies show no such relationship (*32, 40*).

4.2.6 *Use of oral contraceptives*

Although it has been speculated that the suppression of ovulation by combined oral contraceptives may lead to a somewhat later age at menopause, and although such a relationship would have profound clinical, social and even biological significance, the Group could find no formal attempts to evaluate this possibility.

4.2.7 *Smoking*

Several investigations have shown that cigarette smokers have an earlier natural menopause than nonsmokers, and two recent studies review the earlier literature and add to the evidence (*51, 52*). In a group of women interviewed in hospitals in nine metropolitan areas in developed countries, there was a difference of 1.8 years in the age of menopause between women who had never smoked (mean: 49.4 years) and those who had smoked at least 15 cigarettes per day (mean: 47.6 years, $P < 0.02$) (*52*).

4.2.8 *Weather and altitude*

The effect of climate and altitude on menopausal age has been studied to a limited degree. No consensus exists on the effects of climate. There is a single report (*49*) indicating that women who live at high altitudes (greater than 2000–3000 m) appear to have experienced menopause about 1–1.5 years earlier than those living below 1000 m.

4.2.9 *Socioeconomic factors*

Much of the variation in age at menarche, including the secular trend, is thought to be related to socioeconomic factors, most notably those reflecting nutritional differences. Income (*32*), education (*41*), and the husband's occupational category (*30*) have not been found to be associated with age at menopause, although there are reports suggesting a relationship with the women's height (*48*) and weight (*32*). The previously described effect of race might have its origin in nutritional differences.

4.3 The range of ages at menopause and the definition of premature and delayed menopause

The Scientific Group noted that while estimates of the median age at menopause in populations of European origin were remarkably consistent, there was a considerable range in the individual age at menopause within a given population. For example, in one study (*30*) of English women aged 45–54 years, 4.3% of those aged 45 years and 96.4% of those aged 54 years were postmenopausal (i.e., their menses had ceased at least one year previously). The Group recognized that there is no agreed normal range for the age at menopause. The age distribution within a population is negatively skewed with a wider scatter of women reaching menopause at younger than at older ages (*29*), and the use of the median to describe the age at menopause requires arbitrary definitions of the upper and lower limits of normality. The description of a normal range is of practical importance, in order to establish appropriate definitions for the terms premature menopause and delayed menopause. These have been defined variously in the literature—for example, premature menopause has been taken to mean primary ovarian failure occurring before the age of 45 years (*53*) or before the age of 30 (*54*). The Scientific Group therefore recommended that epidemiological studies were required to determine appropriate lower and upper limits of normality for the age at menopause in different populations so that patients experiencing primary ovarian failure outside those age limits could be investigated and treated.

The Scientific Group also recommended that:

(1) The age of menopause should be characterized[1] among further populations of non-European origin.

(2) Variations in the range of ages at menopause should be investigated fully with the aim of drawing up arbitrary but useful limits for the purpose of defining premature or delayed menopause.

(3) Studies should be encouraged which might shed additional light on the factors that determine the consistency of estimates of the

[1] Such studies should be undertaken only when extreme care has been put into the study's design. It is recommended that both the current status of menstrual cycles and the age at the last menstrual period be determined, that any retrospective and prospective studies be performed on cohorts at ages as close to the expected age at menopause as possible, that the effect of each recognized bias be anticipated, and that the sample size in relation to the expected hypothesis under test should be an important consideration at the outset.

median age of menopause in different populations. Such studies might investigate the possible secular trends in a population that has undergone extreme change in some pertinent characteristic.

(4) Studies should be undertaken to ascertain whether long-term oral (or other) contraceptive usage affects the age at menopause.

5. SOCIOCULTURAL SIGNIFICANCE OF THE MENOPAUSE IN DIFFERENT SETTINGS

The occurrence and the severity of perimenopausal symptoms may well be affected by cultural and socioeconomic factors. The following factors are of possible relevance:

(*a*) the social significance of menstruation and the escape from the stigma of menstruation that follows menopause in some cultures;

(*b*) the social significance of childlessness;

(*c*) the social status of the postmenopausal woman;

(*d*) attitudes of husbands to their postmenopausal wives (e.g., as a sexual partner);

(*e*) the level of socioeconomic deprivation experienced at the time;

(*f*) the degree of change in a woman's role at this time and the availability of new or alternative roles;

(*g*) the availability of medical help for perimenopausal problems.

As yet, there are few studies comparing attitudes and reactions to the menopause in different cultures. Those that are available indicate that while the differences may be striking, their origins may be complex. Thus, women from a particular (and relatively affluent) Indian caste reported fewer perimenopausal complaints than women in the USA (*55*). The investigator attributed this to the contrast in the status of postmenopausal women in the two cultures, the Indian women escaping from many earlier limitations and gaining higher social status, the American women anticipating loss of status in a "youth-oriented" society. Differences were also noted (*56*) between middle-class Jewish and Cuban women in the USA, the latter experiencing more problems in association with the menopause. The Cuban women were, moreover, less well integrated into United States society and the explanation of these apparent ethnic differences may be complex.

Similarly, five ethnic groups of women in Israel (4 Jewish—of Central European, Persian, Turkish and North African origins respec-

tively—and 1 Arab) exhibited differences in attitudes towards the menopause, although they were similar in their reporting of somatic symptoms, including hot flushes and sweats (*57*). The Arab women were the most positive towards "the crisis of the climacteric", and the Europeans were least concerned, while the Persians had the most negative attitudes and the most complaints. The husband-wife relationship was the area of most significant differences, with the Arab woman hoping that her husband would show more interest in her after the menopause, while the Persian Jews were the most pessimistic about their husband's future attitudes. The authors concluded that their study "clearly indicates the importance of ethnic considerations in shaping psychic and psychosomatic symptomatology and the perception of the climacteric. While there are differences between modern and traditional women in this regard, often the juxtaposition is rather between the extreme ends of this spectrum against the middle".

Variations in the extent of perimenopausal problems within specific cultures have also been shown to be related to socioeconomic status. Swiss women from a lower social class were found to have more difficulty in coping with the perimenopause than those from a higher social class (*58*). The postmenopausal decline in sexuality was more marked in lower than in higher social-class Swedish women (*59*).

Prior to the meeting of the Scientific Group, senior clinicians at WHO Collaborating Centres for Clinical Research in Human Reproduction in Argentina, Brazil, Chile, Cuba, Egypt, Hungary, India, Kenya, Nigeria, Philippines, Singapore and Thailand were asked to complete a questionnaire about the clinical importance of perimenopausal problems in their setting. The replies confirmed the impression that very few reliable data are available regarding the nature and prevalence of problems related to the menopause outside Europe and the USA. The comment was repeatedly made that the proportion of women, among those attending hospital-based clinics, who presented with such problems was very low (1–5%) and that affluent women were more likely to be involved. In a few centres, it was considered likely that more women from both higher and lower social classes would seek such help if it was known to be available.

It remains probable that important cultural differences exist, some of which (if better understood) may throw light on the determinants of perimenopausal symptoms.

Further cross-cultural research on this issue is needed before the health care priorities of women in the perimenopausal period can be properly evaluated.

The Scientific Group recommended that:

(1) Further studies should be undertaken to establish whether the apparent differences in the incidence and characteristics of menopausal symptoms in different cultures are real, and if so, to what extent they can be attributed to cultural, socioeconomic or biological (e.g., nutritional) factors.

(2) Suitable instruments for the assessment of symptoms, especially psychological symptoms, should be developed for studies in different cultures.

6. SYMPTOMS ASSOCIATED WITH THE MENOPAUSE

6.1 Incidence of different symptoms in perimenopausal women

A number of studies have reported the frequencies of the different complaints of perimenopausal women attending clinics (*60–62*). Such information is of some interest but surveys of nonclinical population samples are needed to establish the true incidence of perimenopausal symptoms.

A number of such surveys have been reported from Australia (*63*), the Federal Republic of Germany (*64*), the Netherlands (*65*), Sweden (*59*), Switzerland (*58*), the United Kingdom (*31, 66–68*) and the USA (*69*). The comparability of these various studies is limited by a variety of methodological factors, particularly a very variable approach to the elicitation of symptoms and, in several studies, a failure to distinguish between the perimenopausal and postmenopausal phases. Some findings, however, are sufficiently consistent to deserve comment, as described below.

6.1.1 *Vasomotor symptoms*

All studies demonstrated an increase in vasomotor symptoms, such as hot flushes and night sweats, about the time of the menopause. In several studies it was concluded that this was the only characteristic feature of the perimenopause. The time relationship with the menopause was variable: in the Netherlands study (*65*) of women aged 42–62 years, 17% with regular cycles were already experiencing flushes; the figure rose to 40% in women with irregular cycles, was 65% at 1–2 years after the menopause, and was still 35% some 5–10 years after the menopause. The severity of this symptom is difficult

to grade; however, 21% of subjects reporting on the frequency of flushes in one study (*31*) experienced them every few hours, and almost half of the subjects in another study (*30*) felt "acute physical discomfort".

6.1.2 *Psychological symptoms*

A variety of psychological and psychosomatic complaints have been recorded but little attention has been paid to their interrelationships. Thus, it is not clear to what extent these "symptom descriptions" reflect some general factor of "wellbeing" or more discrete psychological states such as depression, fatigue, or irritability. With allowance for this conceptual vagueness, a number of studies have found an increase in psychological complaints in the period preceding the cessation of menses, their frequency declining in the one to two years following the menopause (*59, 65, 67, 68*).

Thus, psychological symptoms tend to be maximal before and vasomotor symptoms after the cessation of menses. This pattern of psychological disturbance does not appear to be associated with an increased incidence of serious psychiatric illness (*59, 70, 71*). However, there is other evidence (from general practice studies) of an increase in consultation for emotional problems by women in the perimenopausal and early postmenopausal age group and an increase in the prescription of psychotropic drugs for them (*72, 73*).

6.1.3 *Disturbances of sexuality*

Very few of the surveys have enquired about sexuality. The best information comes from a Swedish study (*59*), showing a decline in sexual interest in women after the menopause which could not be accounted for simply as an age effect or as a consequence of decline in the husband's interest. Other evidence consistent with this finding has been reported (*74*).

Women attending clinics with perimenopausal or postmenopausal complaints commonly report vaginal dryness and associated dyspareunia (*60*). This can lead to a secondary decline in sexual enjoyment and interest. In one study (*75*), this problem was found frequently to occur in 3% and occasionally in 5% of the subjects, and the decline in interest following the menopause persisted when control for this variable was made.

6.1.4 *Insomnia*

The findings concerning insomnia have been inconsistent, partly because of the disruptive effect that vasomotor symptoms have on sleep. However, some studies report a continuing increase in insomnia with advancing age among postmenopausal women (*76*).

6.2 The physiological and hormonal basis of perimenopausal symptoms and the response to hormone therapy

The psychological and social significance of the menopause and its consequent effects on symptomatology have already been alluded to (section 5). It therefore remains important to establish to what extent the accompanying symptoms are a result of the biological and, in particular, the hormonal changes that underlie the menopause.

An important source of information is to be found in studies in which the effects of hormone treatment have been compared with placebo in a suitably controlled manner, the treatment consisting in the administration of estrogens, estrogen-progestogen combinations, or progestogens alone (*60, 77–91*). Once again, methodological shortcomings have been common, particularly a failure to distinguish between different stages of the menopausal process or between natural and surgical menopause. The best evidence from these studies will be considered briefly in relation to the important symptoms described above.

6.2.1 *Vasomotor symptoms*

Vasomotor instability or menopausal hot flushes are characterized by a rise in skin temperature, peripheral vasodilatation, transient increase in heart rate, and changes in electrodermal activity (*92–95*). The symptom complex may include sweats, chills, nervousness, irritability and headache.

The hot flush is believed to be due to a sympathetic discharge (*93*) but its hormonal basis remains obscure. The flush is synchronous with a pulsatile release of LH from the pituitary (*96, 97*) but does not appear to be a direct consequence of the raised LH levels (*98, 99*); thus, flushes may occur after hypophysectomy (*98*) or after treatment with danazol which lowers gonadotrophin levels (*99*). The precipitating event may be a central hypothalamic discharge which is associated with but is not the same as the pulsatile release of luteinizing hormone releasing hormone (LHRH) (*96*). Experimentally, a number of changes in hypothalamic amine and prostaglandin levels have been

observed following castration (*100–105*) but the precise mechanisms involved have not been defined. It is of interest that the administration of a central alpha-adrenergic agonist drug (clonidine), as compared with placebo, significantly reduces the frequency of hot flushes (*106*). It is unusual for hot flushes to occur in prepuberal castrates or persons with primary gonadal failure, but they are observed in such patients after withdrawal of long-term estrogen therapy.

Hot flushes also have a psychosomatic aspect. They can be triggered by emotional events and in several studies have responded to placebo treatment to some extent. However, a series of studies have shown better control of hot flushes by estrogens or progestogens in comparison with placebo (*60, 78, 82, 83, 85, 91*), though estrogen may be more effective than progestogen (*87*). Only one study failed to find a significant difference between estrogen and placebo in this respect (*84*). The therapeutic effect of sex steroids is believed to be indirect, by acting on some intermediate hypothalamic mechanisms. There is no evidence that the vasomotor symptoms are a consequence of estrogen deprivation *per se* (*107*). It is of interest, however, that clomifene, an anti-estrogen which has a direct action on the hypothalamic estradiol receptors, induces hot flushes which disappear on discontinuation of the drug (*108*).

The "natural history" of vasomotor symptoms, starting as they often do before the cessation of the menses and continuing for a variable but limited period after the menopause, suggests that they are a manifestation of some transitional state of hypothalamic functioning. The Scientific Group considered that the important advances in the understanding of the physiology of hot flushes, as recorded above, provide a basis for objective monitoring of the efficacy of treatment (*109*).

6.2.2 *Psychological symptoms*

The fact that most of the psychological symptoms occur in the period preceding the cessation of menses, when the menstrual cycles are irregular or abnormal, raises the possibility that fluctuations in hormone levels are responsible rather than hormone deficiency (*65*). This situation might have similarities to the premenstrual syndrome, the hormonal basis of which is still disputed and which does not respond in a predictable fashion to any specific hormone therapy. Several workers have commented that women who report psychological symptoms in the perimenopause tend to have had psychological dis-

turbances earlier in their lives (reviewed in *110*). This evidence has been used to attribute perimenopausal problems to a "neurotic disposition". No systematic attempt has been made to see if women with a history of the premenstrual syndrome, which tends to get worse with age (*111*), are at a greater risk of perimenopausal problems. If they are, this would suggest some common underlying mechanism. Research is needed on this point.

After the menopause, the fluctuation in the steroid levels ceases and a more stable low-estrogen state prevails. If fluctuating steroid levels are in any way related to mood disturbances, it may be expected that there would be a different pattern of psychological symptoms at this later stage. Unfortunately, in many of the treatment-based studies, the women in these two endocrine categories were not clearly distinguished and the inconsistent finding of beneficial effects of estrogen on mood is therefore not surprising. Surgical menopause, though possibly different from natural menopause in important ways, does provide a more homogeneous endocrine picture. Three treatment-based studies of oophorectomized women have been reported (*79, 80, 88*). In the first study (*79*), a "mental tonic" effect of estrogen (in comparison with placebo) was reported, though the study was only "single blind". In the second study by the same group (*80*), a "double-blind" procedure was used and no "mental tonic" effect was found, but the number of women involved was very small. In the third study (*88*), a beneficial effect on mood was reported with estrogen and a lesser effect with progestogen. Part (but not all) of this benefit was probably secondary to relief of the hot flushes; these women were not clinically depressed at the outset.

The mood-elevating effect of estrogen in the postmenopausal woman remains a possibility, but further research is required to confirm this before estrogen can be recommended for this purpose. It has been suggested that lack of estrogen leads to a reduction of free tryptophan in the blood and a consequent reduction of 5-hydroxytryptamine (5HT) synthesis (*112*). Impaired 5HT synthesis may lead to depression. Hence a therapeutic effect of estrogen on depressed mood has been atrributed to a consequent rise in free tryptophan in the plasma (*113*). Tryptophan itself has been shown to have antidepressant properties (*114*), but the earlier findings of a relationship between the level of free tryptophan in the plasma and depressed mood (*112*) have not been confirmed (*115, 116*). The validity of this biochemical hypothesis to explain depression in the postmenopausal woman therefore remains very uncertain.

6.2.3 *Disturbances of sexuality*

Although the available evidence indicates a postmenopausal decline in sexual interest (for example, 72% of a group of 54-year-old postmenopausal women in a Swedish study reported some or great decrease in sexual interest (*59*)), women may also report an apparent increase in sexual interest or enjoyment—at least temporarily, after the menopause (*117, 118*). Obviously nonhormonal factors, such as freedom from fear of pregnancy, may operate, but a consideration of the possible hormonal factors suggests a complex rather than a simple pattern of change in women's sexuality at this time.

Mood disturbance has an adverse effect on sexual interest or response in both men and women. If a woman experiences mood symptoms in the perimenopausal phase, the improvement of mood that occurs when she enters the more stable postmenopausal phase may be associated with some enhancement of her sexuality.

There is some reason to believe that progesterone may have an inhibitory effect on sexuality (*119*). Progestogens have been used in both men and women to inhibit sexual desire (reviewed in *120*). If normal luteal levels of progesterone do have a negative sexual effect, then the postmenopausal woman will be free from this effect.

The role of estrogens in female sexuality also remains uncertain. They undoubtedly are essential for maintaining a normal vaginal epithelium (*121*). In the postmenopausal and sometimes the perimenopausal woman, vaginal dryness is not unusual. Whether this is due to an impaired transudate mechanism in response to erotic stimulation or more generally to deficient vascularity of the vaginal wall is not yet clear, but such dryness is reversed by either systemic or local estrogen treatment (*60, 85*). With more prolonged estrogen deficiency, the vaginal epithelium becomes atrophic and the cellular pattern changes. This may lead to narrowing or even fibrosis and shortening of the vaginal barrel and the thinned epithelium is particularly susceptible to trauma and further fibrosis (*122, 123*). These changes are also reversed by estrogen (*60*). Symptoms of dry vagina and dyspareunia have been correlated with circulating estradiol levels (*107, 124*). Thus, the importance of estrogen for normal vaginal function in the postmenopausal woman is undisputed, though it should be emphasized that probably in a majority (75–80%) of postmenopausal women, the level of circulating estrogen is sufficient for this particular purpose (*61*).

The importance of estrogens for other aspects of female sexuality is far less clear. In women with normal menstrual periods, no correlation between estradiol and sexual interest or response has yet been found (*125*). However, in female rhesus monkeys (*126*) a small amount of estrogen may be necessary for normal female sexual interest and response. Controlled studies of estrogen treatment in perimenopausal women have so far failed to find any significant sexual effect other than on vaginal dryness (*85*), but the mixed endocrine status of the women involved in these studies may have obscured such an effect. Two studies of oophorectomized women have produced conflicting results in this respect—in one (*60*), no effect of estrogens on "libido" was found, whereas in the other (*90*) estrogen was found to enhance the woman's sexual interest and enjoyment, an effect that was somewhat reduced by combining the estrogen with progestogen.

It thus remains possible that some postmenopausal women will experience a decline in sexual interest as well as vaginal response as a result of lack of estrogen, but further research is needed to clarify this point. In such studies of sexuality, the distinction between changes in spontaneous levels of sexual appetite and the ability to enjoy sexual activity when it occurs deserves attention.

Testosterone is widely believed to be the "libido hormone" in women as it is in men, though so far the evidence in support of this is very limited (*127, 128*). There is a modest reduction in circulating testosterone following the menopause (see section 3), and this could contribute to a sexual decline. As yet, evidence of the therapeutic benefits of testosterone in the postmenopausal woman is very limited (*121*) and properly controlled studies are needed to clarify this issue. It should be remembered that testosterone is an important source of estrogen in the postmenopausal woman, and therefore any study of testosterone treatment should be controlled for possible estrogenic effects.

6.2.4 *Insomnia*

The progressive deterioration in sleep patterns with age, that has been described could be related to estrogen deficiency. Two studies have shown that, in response to estrogen, there were subtle but significant increases in the amount of sleeping time which were not attributable to a reduction in night sweats (*84, 129*).

6.2.5 *Other symptoms associated with the perimenopause*

Some other problems, which have not been considered in the various surveys and which are of clinical importance and deserve consideration, are described below.

6.2.5.1 *Urinary problems in the perimenopausal period.* In view of the embryological relationships between the bladder trigone, the urethra and the vagina, it is not surprising that the lower urinary tract shows responses to estrogen deficiency and replacement which resemble those of the vagina. Cytological changes in the urinary sediment are statistically correlated with those in the vaginal smear (*130*) and provide a useful and convenient parameter to assess the estrogen status in the perimenopausal period (*131*). Various urinary symptoms have been described in the postmenopausal period (*132*), but little objective evidence is available of the precise relationship of such symptoms to the hormonal changes occurring at the menopause. A recent population survey showed that frequency and urgency of micturition were not symptoms that could be related to the mean age at menopause (*64*). The relationship of stress incontinence with prolapse (seen commonly in the postmenopausal period) to estrogen deprivation is uncertain, and other factors (such as the number and type of deliveries) are important. The Scientific Group considered that, since urinary symptoms are common in postmenopausal women, complete work-up and identification of those who can benefit by hormonal therapy and the type of therapy itself constitute important areas for future research (*130–132*).

6.2.5.2 *Skin changes in the perimenopausal period.* The skin normally ages as a result of physical and ultraviolet-light effects; it is a major target organ for estrogenic action (*133*), contains estrogen receptors (*383*), and can metabolize estrogens actively (*134*). The estrogens affect the hyaluronic-acid and water content in the sexual skin areas (reviewed in *133*) and appear to increase the skin's thickness and to enhance tritiated-thymidine uptake in skin explants (*133, 135*). The Scientific Group considered that, despite these considerations, the role and clinical utility of estrogen therapy for the skin in ageing women are not well established.

6.2.5.3 *Peri- and postmenopausal bleeding.* The Scientific Group recognized that vaginal bleeding that occurs after 12 months of

amenorrhoea in women of perimenopausal age (postmenopausal bleeding) is an important symptom requiring investigation and treatment, specifically with a view to excluding the possibility of endometrial cancer, which may occur in as many as 13% of patients (*136*). However, the Group believed that a detailed consideration of this topic was beyond the scope of this report and attention is therefore given only briefly to certain aspects. The Scientific Group also recognized that there are wide variations in menstrual bleeding patterns in perimenopausal women; in some, previously regular menses cease abruptly while in others, patterns of irregular bleeding may continue for months or years and may be associated with ovulation or anovulation with constant or changing estrogen levels (*137*); such irregular bleeding, which is not due to local or systemic disease, is called dysfunctional uterine bleeding and various mechanisms are involved in its production (*138*). The histopathology of the endometrium is variable and includes conditions described as proliferative, secretory, atrophic, adenomatous, hyperplasia, endometrial polyp or carcinoma (*139, 140*).

Patients with postmenopausal bleeding associated with estrogen therapy may show endometrial histology generally similar to that of untreated patients (*141*), although high-dose unopposed estrogen (given either cyclically or continuously) gives rise to endometrial hyperplasia and abnormal bleeding (*142, 143*). Small doses of estrogen are less likely to cause bleeding problems and hence it has been recommended that, when estrogen therapy is indicated, treatment should be initiated with small doses (*144*).

Progestins, administered to patients with postmenopausal bleeding associated with endometrial hyperplasia, have been shown to cause reversion to normal endometrium in the majority, whether or not the hyperplasia was associated with exogenous estrogen therapy (*145*). Addition of cyclic progestins to regimens of estrogen therapy has also been shown to reduce the frequency of endometrial hyperplasia, but the efficacy depends on the dosage and particularly the duration of progestin therapy (*145–147*), 7–13 days' duration being effective in preventing hyperplasia (*147, 148*). A biochemical basis for the effect of progestins on endometrial hyperplasia has been demonstrated and includes a decrease in the number of uterine receptors for estradiol 17β and an increase in the ability of the endometrium to inactivate estradiol 17β by increasing the dehydrogenase activity (*149*). The possible effects of progestins in preventing the occurrence of endometrial carcinoma in estrogen-treated postmenopausal women will be considered in section 8.2.

The occurrence of bleeding associated with estrogen therapy is a problem causing anxiety to both physician and patient and may necessitate frequent diagnostic procedures to rule out the possibility of malignancy. The Scientific Group therefore concluded that the administration of estrogens for the control of menopausal symptoms should not be undertaken lightly in women with an intact uterus. The Group considered that the following areas merit further study:

(1) the endocrine basis of abnormal perimenopausal bleeding from different types of endometrium;

(2) the endometrial response to different agents and modalities of therapy;

(3) the medical management of abnormal bleeding due to endocrine causes in the perimenopausal and postmenopausal period.

6.3 Conclusions and recommendations

The Scientific Group concluded that vasomotor symptoms and vaginal dryness are the symptoms which are convincingly related to the hormonal changes during the perimenopause. The first is a "transitional" symptom which, although responding to estrogen (or progestogen) treatment, will disappear spontaneously in time. The second (i.e., vaginal dryness) is more akin to an estrogen-deprivation symptom and may require, in certain cases, more prolonged estrogen replacement. Urinary symptoms may be similar in this respect, but more work on their response to estrogen therapy is needed.

The psychological disturbances associated with the perimenopause have a very uncertain hormonal basis and, so far, do not predictably respond to hormonal therapy. The relationship between postmenopausal mood change and estrogen lack remains to be demonstrated. Estrogen deficiency may contribute to the insomnia that accompanies ageing in postmenopausal women.

The endocrine basis of perimenopausal and postmenopausal bleeding, particularly that which occurs from an atrophic endometrium, requires further elucidation, although many of the mechanisms involved in dysfunctional uterine bleeding have been clarified in recent years.

Sexual decline following the menopause is, in part, due to the vaginal impairment that accompanies severe estrogen lack. The association between loss of sexual interest and a deficiency of estrogen and/or testosterone requires to be established before therapeutic use of these hormones for this purpose can be justified.

The Scientific Group made the following recommendations:

(1) Methods that are scientifically sound and suitable (and are adaptable for use in different cultural settings) should be developed for determining the perimenopausal symptoms.

(2) In the assessment of the effects of the menopause on female sexuality, a distinction should be made between the various aspects of female sexuality (e.g., vaginal physiology, orgasm, spontaneous interest), each of which may be differently affected by hormonal factors.

(3) Epidemiological studies are required in order to identify even earlier characteristics, such as a tendency to premenstrual tension, which may predispose women to perimenopausal problems.

(4) Further research is required to:

(*a*) establish the cause of vasomotor symptoms so that alternative methods of control can be introduced, which will make it possible to avoid the use of sex hormones when these are contraindicated;

(*b*) increase our understanding of the endocrine determinants of the irregularities and abnormalities of uterine bleeding in the perimenopausal and postmenopausal periods, and hence to improve the methods of control;

(*c*) increase our understanding of the relationship between estrogen lack and the impairment of vaginal and bladder function.

(5) Further controlled studies of the effects of estrogen, progestogen and testosterone on mood and sexuality in the perimenopausal woman are required, involving adequate control of the initial endocrine status and the use of appropriate methods for measuring change in psychological variables.

7. DISORDERS RESULTING FROM, OR POSSIBLY ACCELERATED BY, THE MENOPAUSE

The Scientific Group considered in detail the problem of postmenopausal osteoporosis and the evidence linking accelerated atherosclerotic cardiovascular disease with the menopause. Brief consideration was given to arthritic disorders.

7.1 Osteoporosis

7.1.1 *Introduction*

Postmenopausal osteoporosis was first described 40 years ago (*150*) and is now a well-recognized disorder. The Scientific Group therefore considered it appropriate to review present understanding of the nature of the relationship between osteoporosis and the menopause, bearing in mind that most of the available data are derived from Caucasian populations.

7.1.2 *Definition of osteoporosis*

Although it is generally agreed that osteoporosis constitutes a reduction in the mass of bony tissue relative to the volume of the anatomical bone, the precise point at which such a reduction should be regarded as abnormal and justify the appellation "osteoporotic" has not been defined. Much confusion in the research literature stems from this lack of agreement. Since the importance of osteoporosis arises mainly from the increased risk of fractures which it entails, the term should clearly be applied when an increased fracture risk can be identified. It has been suggested, on the basis of epidemiological data and X-ray appearances, that a "fracture threshold" can be identified at bone mass values that are 1 standard deviation (SD) below the young normal mean in respect of distal forearm fractures and 2.5 SD below the young normal mean in respect of femoral neck fractures (*151*), and that the age- and sex-related rises in the incidence of these fractures can be attributed to the progressive increase in the proportion of the population falling below these thresholds with advancing age.

Although this concept is a useful one, there is inevitable uncertainty about the precise location of these boundaries and since it is clear that the fracture rates rise with age *pari passu* with the decline in bone mass, it has recently been proposed that the postulated threshold should be equated with the young normal lower limit (mean value minus 2 SD) of relative bone mass and that values below this should constitute osteoporosis (*152*). The reference bone and method used must, of course, be defined in any particular case and a distinction should be made between cortical and trabecular osteoporosis, which may be present separately or together. This concept implies that reduced bone mass increases the fracture risk regardless of the age and

sex of the individual. However, from the point of view of *pathogenesis,* a distinction needs to be made between a degree of osteoporosis appropriate to the age and sex of the subject, which it is suggested should be termed "simple osteoporosis" (previously called osteopenia (*153*)), and a degree of osteoporosis that is excessive for the person's sex and age, which it is suggested should be called "accelerated osteoporosis" (*152*). Here too the bone may be trabecular, cortical or both. The Scientific Group recommended that this terminology be adopted.

7.1.3 *Methodology*

The determination of bone mass required for the recognition of osteoporosis can be performed in a variety of ways (*154*). These include gamma-ray and X-ray absorptiometry (*155, 156*), X-ray film densitometry (*157, 158*), and neutron activation analysis of the whole (*159*) or part of the skeleton (*160*). All these procedures are equally applicable to cortical and trabecular bone, but the favoured sites are the distal radius (*155*) and, more recently, the vertebrae (*161*), which are largely sites of trabecular bone. A simpler procedure, applicable to cortical bone only, is measurement of the width of cortical and total bone on plain radiographs. This can be applied to any long bone but the favoured site of measurement is the midpoint of the second metacarpal of the right hand (*162*), which has been used in a number of population studies (*163*). Another simple method depends on visual assessment of the trabecular pattern in the proximal femur on X-ray films (*164*). An alternative procedure is iliac crest biopsy, which is mainly used for the estimation of trabecular bone status (*165, 166*). Whatever method is used, cross-sectional measurements of bone mass should be corrected for, or related to some function or measurement of total bone volume, since the agreed definition of osteoporosis is a reduction in relative bone mass (see sections 7.1.2 and 7.1.8). If this is not done, all small individuals with small bones will appear to be "osteoporotic".

All these procedures can be employed for cross-sectional or longitudinal measurements, but their value for the latter purpose depends critically on their precision since the annual rate of bone loss in the ageing population, though clinically very significant, is relatively small. Generally speaking, the error in measurement of trabecular bone, which is the most labile component of the skeleton, is greater than that of cortical bone, which changes less. It should be noted that cor-

rection for bone volume is not necessary in longitudinal studies since it changes little within individuals.

7.1.4 *Effects of the menopause on the skeleton*

The hormonal changes which accompany the menopause are associated with the onset of bone loss, which then proceeds at an average rate of about 1% per annum. This loss of bone is not uniformly distributed throughout the skeleton, the relative loss of trabecular bone (which comprises 20% of the skeleton) being greater than the relative loss of cortical bone (which comprises 80% of the skeleton). However, although trabecular bone loses proportionately more of its tissue than cortical bone, this loss tends to be self-limiting in the normal population, whereas cortical bone loss continues to the end of life (*152, 166*).

The onset of bone loss is associated with small but significant changes in calcium metabolism. There are slight rises in the plasma calcium and phosphate concentrations and the plasma alkaline phosphatase, as well as in the urinary calcium and hydroxyproline (*167, 168*), which reflect a net transfer of bone mineral and collagen from the skeleton to the plasma and urine. This net loss of skeletal tissue could be due to a decrease in the rate of bone formation or an increase in the rate of bone resorption, or a combination of the two. The histological evidence required to resolve this issue is somewhat conflicting, but the prevailing view is probably that bone turnover increases rather than decreases at the menopause (*165*) (which is compatible with the rise in urine hydroxyproline and plasma alkaline phosphatase), in which case the loss of bone must be due primarily to an acceleration of the resorption process. The cause of this acceleration is not fully understood, but a widely accepted hypothesis is that estrogens have a protective effect on bone and that the fall in plasma estrogen levels at the menopause makes the bone more sensitive to the resorbing action of parathyroid hormone and/or the 1,25-dihydroxy derivative of cholecalciferol (vitamin D_3) (*169, 170*). More recently it has been suggested that this protective effect of estrogen on bone may be mediated by calcitonin, the secretion of which appears to be stimulated by estrogens (*171*). Whatever the explanation, the net effect of the menopause is to increase the mean calcium requirement (i.e., the amount required to preserve calcium balance) from about 500 to 1500 mg daily, because of the rise in urine calcium coupled (possibly) with a fall in calcium absorption (*172*).

As already indicated, postmenopausal bone loss is associated with a steep rise in the rates of fractures, particularly of the distal radius, the vertebrae and the proximal femur (*165, 173*); 25% of Western women have sustained one or more of these fractures by the age of 80 (*152*). There is no corresponding rise in wrist fracture rates in men (*173, 174*) and the lower age-specific incidence of spine and femoral neck fractures in males appears to be compatible with the fact that their age-related loss of bone starts later and progresses more slowly than in women.

If the fracture risk is a function of relative bone mass, it follows that fracture cases should be more osteoporotic—either at the fracture site or in the skeleton as a whole—than age-matched controls. This has, in fact, been confirmed. In wrist fracture cases, a bone deficit in the distal radius of about 10% has been reported (*175*). In vertebral crush fracture cases, a very significant deficit of trabecular bone (measured on iliac crest biopsy) is well documented (*166, 176*). In femoral neck fracture cases, there is a significant deficit of both cortical and trabecular bone which is most significant when determined on the femur itself, but remains significant when determined at sites distant from the fracture (*152*).

The question of whether the bone deficit in fracture cases is due to a low initial bone mass or results from accelerated bone loss has not been fully resolved but the weight of opinion is probably moving in favour of the latter (for reasons discussed below); conclusive evidence, in the sense of sequential bone measurement in fracture and non-fracture cases, is not yet forthcoming.

Indirect evidence that the bone deficit in fracture cases is due to accelerated bone loss is derived from metabolic data. There is general agreement that malabsorption of calcium is frequently present in patients with vertebral compression fractures (*176, 177*), but there is a difference of opinion as to its pathogenesis. Some workers report low plasma levels of 1,25-dihydroxycholecalciferol in these cases (*178*), but others have failed to confirm this (*179*). There is also evidence of malabsorption of calcium in femoral neck fracture cases (*180*) but, in this population, true vitamin D deficiency may be present to account for it (*181*). It should be noted in this connexion that the femoral neck fracture rate is lower in blacks than whites within the same country (*182, 183*) and—to judge by mortality from falls in the elderly—is a positive function of latitude and a negative function of sunlight exposure (*184, 185*). The latter is supported by a recent case-control study (*186*).

There is also disagreement as to the role of estrogens in regulating postmenopausal bone loss. In the postmenopausal woman, the predominant circulating estrogen is estrone (*186*), but the plasma estrone varies widely and is inversely related to the fasting urinary calcium (*187*) and hydroxyproline (*168*); this suggests that the degree of estrogen deficiency may be an important determinant of the rate of bone loss. However, evidence on endogenous estrogen status in fracture cases is conflicting. Low androstenedione and estrone levels in osteoporotic patients, particularly those with low cortical bone mass, have been reported by one group (*179*) but denied by others (*188*).

7.1.5 *Estrogen administration and the prevention of osteoporosis*

There is general agreement that estrogen administration in the doses normally used for the control of menopausal symptoms lowers urine calcium and prevents bone loss (see Table 3) (*189–193*), but there is a suggestion that when estrogen therapy is stopped, a phase of accelerated bone loss occurs which largely negates the benefit (*194*). However, it is hard to reconcile this with the reduced fracture risk in estrogen-treated subjects (described below). Two studies have reported that bone loss can also be delayed (if not prevented) in normal postmenopausal women by the administration of large calcium supplements (1–1.5 g daily) (*189, 192*).

As far as the long-term benefit of hormone therapy is concerned, three case control studies, summarized in Table 4, have now shown a fracture risk ratio of about 2–3 in favour of estrogen therapy (*186, 195, 196*). The benefits from estrogens for women of a given age were greater for those who had been oophorectomized than for those undergoing spontaneous menopause (*186*). In the same study (*186*), smoking, diabetes and alcohol were identified as positive risk factors for fracture. There is also a retrospective study showing significantly fewer wrist fractures among estrogen-treated patients than would be expected in the normal population (*197*).

Other prophylactic treatments that have been tried in normal postmenopausal women include vitamin D, a thiazide diuretic, and sodium fluoride; no significant preventive effect was observed with any of them (*193*).

Table 3. Annual rate of bone change in control and treated subjects

Authors	Therapy	Method	Controls (N)	Treated (N)	Significance
Lindsay et al. (1980) (*190*)	mestranol	metacarpal X-ray densitometry	–0.87% (42)	–0.35% (58)	$P < 0.01$
		radial photon absorptiometry	–1.02% (42)	–0.23% (58)	$P < 0.01$
Horsman et al. (1977) (*189*)	ethinyl estradiol	metacarpal morphometry	–1.7% (18)	–0.64% (19)	$P < 0.01$
		ulnar photon absorptiometry	–3.5% (18)	–1.45% (19)	$P < 0.001$
	calcium	metacarpal morphometry	–1.7% (18)	–1.13% (19)	N.S.
		ulnar photon absorptiometry	–3.5% (18)	–0.52% (19)	$P < 0.05$
Recker et al. (1977) (*192*)	conjugated estrogens + methyltestosterone	metacarpal morphometry	–1.18% (20)	–0.15% (18)	$P < 0.05$
		radial photon absorptiometry	–2.88% (20)	–0.73% (18)	N.S.
	calcium	metacarpal morphometry	–1.18% (20)	–0.22% (22)	$P < 0.05$
		radial photon absorptiometry	–2.88% (20)	–1.83% (22)	N.S.
Nachtigall et al. (1979) (*191*)	conjugated estrogens + medroxyprogesterone	metacarpal photon absorptiometry	–1.1% (41)	–0.05% (37)	$P < 0.001$
Christiansen et al. (1980) (*193*)	estradiol + estriol + norethisterone	radial photon absorptiometry	–1.65% (103)	–1.25% (21)	$P < 0.01$

Table 4. Case-control fracture studies

Authors	No. of fracture cases	No. of controls	Risk ratios		
			Diabetes	Alcohol	Estrogens
Hutchinson et al. (1979) (*195*)	157	157	1.2 (N.S.)	3.6 (P <0.01)	0.26–0.33 (P <0.01)
Weiss et al. (1980) (*196*)	327	567			0.38 (P <0.05) (⩾6 yrs use)
Paganini-Hill et al. (1981) (*186*)	91	166	4.6 (P <0.01)	1.3 (N.S.)	0.42 (P <0.03) (⩾6 yrs use)

7.1.6 *Treatment of established osteoporosis*

The treatment of established osteoporosis is more controversial. In most studies, patients with vertebral compression have been classified as osteoporotic; they probably comprise cases of simple and accelerated trabecular osteoporosis as defined above. From these studies it may be concluded that estrogens inhibit bone resorption in most osteoporotic (as in normal) postmenopausal women, but there is a suggestion that this treatment may be inadequate in the presence of malabsorption of calcium and should perhaps be supplemented by some form of vitamin D in such cases (*198, 199*). Vitamin D and its metabolites are not successful when given alone, possibly because of their bone-resorbing action, but there may be a place for this treatment when combined with estrogen. Calcium supplements (given to those with normal absorption) or a combination of calcium with vitamin D (given to those with malabsorption) appear to inhibit bone loss (*199*). There is a serious lack of data on the effectiveness of all these therapies in osteoporotic subjects.

Much the same can be said of other forms of therapy. It has been suggested that small doses of calcitonin are effective in osteoporosis (*200*) but a careful histological study failed to confirm this (*201*). However, larger doses have been reported to increase total body calcium (*202*). Sodium fluoride may increase trabecular bone volume (*203*) and possibly reduce the vertebral fracture rate (*201, 204*), but it has generally been given in combination with large doses of vitamin D and calcium which makes the benefit of fluoride itself difficult to assess. Anabolic steroids have been widely used on the assumption that osteoporosis is due to a failure of collagen synthesis, but in most reports the benefits are confined to subjective symptoms. However, in at least one controlled study, a significant gain in total body cal-

cium has been reported with an anabolic steroid (*202*). Another study, still in progress, relies on the anabolic effects of parathyroid hormone (*205*). There is virtually no information on the treatment of corticosteroid-induced osteoporosis in postmenopausal women who may be particularly at risk for this disease because adrenal suppression virtually deprives them of estrogens (*206*).

7.1.7 *Conclusions*

The Scientific Group concluded that there is no doubt that estrogen deficiency is associated with loss of bone and that this can be prevented in normal subjects by estrogen therapy. It is probable that large calcium supplements have a similar effect but the evidence is sparse.

It is well established that postmenopausal bone loss is associated with rising fracture rates, and reasonably well established that the fractures affect those with the greatest bone deficit. It is likely that the bone deficit in some fracture cases is due to initial low bone mass and in others to accelerated bone loss, but it is not clear what roles are played by malabsorption of calcium and/or hormonal status in determining the rate of bone loss. The relative immunity of men to fractures is probably accounted for by their later and slower bone loss, but the explanation for this remains to be established. From the impressions of clinicians in Third World countries, there is an apparent relative immunity of their populations to age-related fractures and the Scientific Group considered that this observation required confirmation by systematic study. This phenomenon and the similar immunity of black populations in wealthier countries to age-related fractures are unexplained.

There is some evidence that further deterioration in osteoporotic subjects can be prevented or delayed by a variety of treatments, but there is no agreement as to what the indications may be for the different therapies or which one is the most effective. Despite the wide demand for an agent which will accelerate bone formation and replace bone that is lost, there is little evidence that such an agent is at present available.

There is evidence that hormone therapy reduces the postmenopausal fracture rates but no agreement yet as to how subjects at risk of fracture should be identified in advance.

7.1.8 *Recommendations*

The Scientific Group made the following recommendations:

(*a*) *Terminology*

Osteoporosis should be defined as a bone mass/volume ratio which is more than 2 SD below the mean for healthy young adults of the appropriate sex. The reference bone and the method of measurement should be specified, and the osteoporosis defined as trabecular or cortical accordingly. If the bone mass/volume ratio is below the young normal range, but within the normal range for the age and sex of the subject, the term "simple osteoporosis" should be used. If the bone status is below the normal range for age and sex, the term "accelerated osteoporosis" should be used.

(*b*) *Future research*

(1) The relationship between hormonal status, bone loss and fracture risk needs to be established in postmenopausal women, and measurable variables (predictive of bone loss and/or fracture) need to be identified.
(2) The role of nutritional factors (such as calcium and vitamin D) in bone loss and fractures needs to be established, particularly in older postmenopausal women.
(3) Such studies should include comparisons in different socio-economic groups and between Western and Third World countries to establish whether the age-specific fracture rates are in fact as varied as they appear to be, and if so, why.
(4) Further work is required on the indications for and value of calcium, vitamin D and estrogen in the treatment of established postmenopausal osteoporosis.

7.2 Atherosclerotic cardiovascular disease

7.2.1 *Introduction*

Cardiovascular diseases are the leading cause of death among men in developed countries, and the second or third leading cause among women; they have also emerged as a major public health concern in some less developed countries (*1*). The mortality rates per 100 000 population for ischaemic heart disease and for all diseases of the circulatory system from one developed and two developing country

Table 5. Death rates per 100 000 population from ischaemic heart disease (IHD) and from diseases of the circulatory system (CVD)[a] in one developed and two developing countries[b]

Sex	Country (year)	Age groups (years) 35–44 IHD	35–44 CVD	45–54 IHD	45–54 CVD	55–64 IHD	55–64 CVD	IHD ratios for 55–64/35–44
Male	USA (1977)	63.5	93.1	272.2	355.6	721.5	952.6	11.4
	Philippines (1976)	32.6	85.3	82.0	202.9	179.4	464.2	5.5
	Thailand (1978)	0.7	55.3	2.2	123.5	2.6	117.9	3.7
Female	USA (1977)	14.6	38.2	66.9	126.0	237.2	379.8	16.2
	Philippines (1976)	14.3	56.8	35.9	121.0	83.2	247.7	5.8
	Thailand (1978)	0.2	34.9	0.6	69.3	1.9	66.4	9.5

[a] Cardiovascular disease, including rheumatism, hypertension, ischaemic and other forms of heart disease, cerebrovascular disease, diseases of arteries, arterioles and capillaries, venous thrombosis and embolism, and other diseases of the circulatory system. Particularly in developing countries, the specific diagnosis of ischaemic heart disease as a cause of deaths may not be reliable.

[b] Based on data from *World Health Statistics Annual 1980: Vital Statistics and Causes of Death* (207).

populations, for both sexes, and for the age groups 35–44, 45–54, and 55–64 years are shown in Table 5, together with the ratios between the rates for the two age groups 35–44 years (mainly premenopausal) and 55–64 years (mainly postmenopausal). In the USA, the mortality rates for ischaemic heart disease in females rose 16.2-fold, compared with a rise of 11.4-fold in males; relative rises in the Philippines were 5.5-fold (males) and 5.8-fold (females), and in Thailand 3.7-fold (males) and 9.5-fold (females). The Scientific Group considered that a wide range of endogenous and exogenous risk factors has been described for cardiovascular diseases, specifically those of atherosclerotic origin, and that it was therefore pertinent to examine the effects of cessation of ovarian function and of treatment with exogenous estrogens on the risk factors and on the incidence of atherosclerotic (ischaemic) cardiovascular disease.

7.2.2 *Menopause and risk factors for atherosclerotic cardiovascular disease*

The Scientific Group was of the opinion that a detailed consideration of the known risk factors for atherosclerotic vascular disease was not within the scope of its deliberations, but it reviewed data on the effects of the menopause on serum levels of cholesterol and triglycerides. Some studies of population samples have demonstrated an increase in serum cholesterol (*208–210*) and of triglycerides (*208, 210*) after the menopause, while a further study of patients undergoing oophorectomy before the age of 45 years, showed that serum cholesterol, phospholipids and beta-lipoprotein cholesterol levels were higher in these patients in the fifth decade than in controls who had undergone a simple hysterectomy (*211*). A study of women subjected to oophorectomy before the age of 35 similarly showed higher levels of serum cholesterol in those who had been bilaterally oophorectomized than in those undergoing unilateral operation (*212*).

The Scientific Group concluded that there was an increase in certain risk factors for ischaemic heart disease associated with loss of ovarian function.

7.2.3 *Menopause and atherosclerotic cardiovascular disease*

Assessment of the frequency of clinical cardiovascular disease in developed countries has shown that the ratio of males to females is high, and that it is several times higher before the age of menopause

than after (*213*). To clarify the effect of loss of ovarian function, several investigators have examined the impact of castration on the degree of atheroma observed pathologically and on the risks of cardiovascular morbidity and mortality in hospital patients. One autopsy investigation (*214*) compared 80 North American women, who had had a bilateral oophorectomy before the age of 50, with 80 control patients who died from cancers of various sites or from accidental causes. The castrated patients had a significantly higher incidence of coronary atherosclerotic arterial blockage and of myocardial infarcts, and this was related to the time interval from castration to the expected menopause (taken as age 50 years or age at death prior to 50). Only those women who had been castrated 10 or more years before the age of 50 had significantly more severe coronary heart disease. In contrast, in another autopsy study (*215*) no significant differences were found between previously castrated North American women and controls, although no formal statistical analysis was undertaken. This study has been criticized on the grounds that the percentage of controls showing atherosclerosis at autopsy was high in comparison with the data reported by others.

With regard to the risks of clinical cardiovascular morbidity and mortality, one study, which has already been referred to (*212*), succeeded in following up some 87 out of 200 surgical patients, half of whom had undergone unilateral and half bilateral oophorectomy. Most of the symptomatic cardiovascular disease which was found by examination and interview after 20 years was angina pectoris, and most occurred in the castrated group, as did the increase in total serum cholesterol. A similar study, estimating the effects of oophorectomy and hysterectomy alone after up to 20 years, also found an excess of angina in the castrated group and was also limited by the inability to examine more than a minority of the groups as originally defined (*211*). A third study (*216*) compared oophorectomy with hysterectomy alone and used a more rigorous protocol, which included follow-up of about two-thirds of the 541 cases, blind assessment of groups of equal size, and the inclusion of a group of sisters of the cases as separate controls. In this study, no difference was found between the two surgically treated groups in the frequency of evidence of cardiovascular disease after 10 or more years. In order to evaluate the results further, the investigators identified the patients who had sisters who resided nearby and were able to examine 127 of 908 living sisters. The sisters were younger than the patients and fewer had hypertension. The age-specific rate of coronary disease was

consistently lower than that in the study patients, and more comparable to the rate observed in an unselected population. None of the differences between the sisters and cases was statistically significant, however. The authors of this study concluded that factors other than ovarian function account for the differences in cardiovascular morbidity and mortality between males and females, provided that it is assumed that hysterectomy has little influence on ovarian function. The Scientific Group considered that the above evidence did not permit definitive conclusions regarding the effects of castration on cardiovascular disease.

A few observations are based on defined populations. Close examination of actual age-specific morbidity curves for atherosclerotic heart disease for men and women demonstrates that the most profound influence of age on the sex ratio derives from the curve for men, which tends to flatten out in old age, rather than that for women, which continues to increase at a relatively constant rate (*213*). While such a curve does not suggest an effect at menopause, it is quite consistent with such an effect, since it is possible that, without the menopause, the curve for females might also tend to flatten.

Two groups have had the opportunity to examine the relationship between menopause and carefully defined cardiovascular disease within the context of entire populations. In Göteborg, Sweden, systematic samples from birth cohorts of women were examined and classified on the basis of past history of myocardial infarction, angina pectoris, and electrocardiographic evidence of ischaemic heart disease (*217*). Over 90% of the 1622 women selected agreed to participate. The cases found were compared to the well members of their cohort in three age strata, and those in all three categories were found on the average to have undergone earlier menopause.

In the Framingham cohort, consisting of a probability sample of residents of Framingham, MS, USA, a rise in the incidence of coronary heart disease and a dramatic increase in the severity of the presenting syndrome were noted to occur after menopause among the 2873 women who had been followed up for up to 24 years after initial characterization (*218*). No premenopausal women developed myocardial infarction or died of coronary heart disease, whereas such events were common among postmenopausal women. Within each of the age groups 40–44, 45–49 and 50–54 years, coronary heart disease was more than twice as common in postmenopausal as in premenopausal women, whether the menopause was natural or caused by surgery.

Another group (*381*) examined this question by evaluating the risk of non-fatal myocardial infarction among groups of American nurses. Risk was inversely related to age at natural menopause, and especially to age at artificial menopause, with those who had bilateral oophorectomy before the age of 35 having over seven times the risk of premenopausal women of the same age and with the same risk factors. While there was a minor increase in risk associated with hysterectomy in the absence of oophorectomy, this was not related to the age at operation. The Scientific Group was unable to provide a satisfactory explanation for any effect of hysterectomy alone, as reported (*216, 218, 381*), and considered that further investigations should be undertaken to clarify the issue, particularly with respect to careful evaluation of ovarian function after simple hysterectomy.

There has been a single clinical study of the long-term effects of castration on risks of cerebrovascular accident (*219*). More than 20 years of follow-up of 6767 young women treated for menstrual irregularities by low- or high-dose irradiation or by unilateral or bilateral oophorectomy has demonstrated that those who were castrated by either high-dose irradiation or bilateral oophorectomy suffered a nearly threefold increase in risk of cerebrovascular accident. No population-based studies of this question are available.

On the basis of these data, the Scientific Group concluded that there was strong suggestive evidence that cessation of ovarian function was associated with an increase in the risks of morbidity and mortality from atherosclerotic cardiovascular disease and that some controversy remained regarding the findings in purely pathological studies.

7.2.4 *The effects of estrogen therapy on risk factors for atherosclerotic cardiovascular disease*

As regards the possible consequences of estrogen therapy in peri- and postmenopausal women, the effects of such therapy on risk factors for atherosclerotic cardiovascular disease are important. The published literature includes studies of pre- and postmenopausal women who were given estrogens with or without progestins for varying time periods, at various doses and for various indications. With the proviso that the results of these studies may not necessarily reflect the consequences of estrogen therapy after the menopause, the Scientific Group noted that when changes in plasma lipids and lipoproteins have occurred after therapy with estrogens alone, the serum cholesterol and low-density lipoprotein levels have tended to decrease, triglycer-

ides have been variable in response, and high-density lipoprotein levels have tended to increase (*220–226*). There is some evidence that natural conjugated estrogens or natural estrogen esters (see section 10.4.1) may differ from synthetic estrogens in their effects on cholesterol and triglycerides. For example, ethinyl estrogens have been shown to increase the serum level of triglycerides (*227–231*). While most reports indicate that natural estrogens do not show such an increase (*220, 224, 228, 232–234*), conflicting findings have been reported (*235*).

In contrast, combined oral contraceptives which contain progestins have produced more variable and even opposite responses, depending on the composition, the dose of estrogen, and whether or not sequential agents were used (*221, 226*).

Other influences relate to alterations in blood coagulation factors with estrogen therapy. There is again evidence that natural conjugated estrogens or natural estrogen esters may differ from synthetic estrogens in their effects on blood clotting factors. Thus mestranol has been reported to cause a high incidence of venous thromboembolism (in 16% of 25 oophorectomized women given 20 μg daily for 120 days (*236*)), while conjugated estrogens have been reported to cause no change in the coagulation mechanism by some workers (*237*) but to produce an increase in coagulability by others (*238–240*).

7.2.5 *Effects of estrogen therapy on the course of atherosclerotic cardiovascular disease*

The Scientific Group recognized the controversy which exists with regard to the effects of estrogens on the course of atherosclerotic cardiovascular disease, and in particular the possibility that they may have a preventive effect.

The Group noted that estrogens had been used in the treatment of men who had suffered previous myocardial infarction. In a large randomized trial (*241*), high doses of conjugated estrogens (2.5 or 5 mg/day) were included as alternative treatment methods along with other drugs which could be expected to affect the lipids or lipoproteins. The higher estrogen dose was eliminated from the trial after two years because of an excess of nonfatal cardiovascular events (*241*), and three years later the lower estrogen dose was also discontinued because those men treated with a placebo had a small and statistically insignificant reduction in overall mortality due to both car-

diovascular and noncardiovascular complications (*242*). The treated group also suffered an excess of morbidity from pulmonary embolism and thrombophlebitis.

In the Framingham study (*218*), nearly 300 out of 17 000 women in the cohort had used estrogens, but only about one-half of these had used them for as long as a year. While there were no overall differences in mortality experience between nonusers and these two user groups, an increase in the frequency of coronary heart disease, especially angina, was noted in the treated group, and was of similar magnitude in those treated for less than or more than one year. Other risk factors for coronary events were not examined simultaneously within this small group.

The Scientific Group also noted several observations that long-term contraceptive use in premenopausal women appears to be associated with a high risk of myocardial infarction and other thromboembolic disease (*243, 244*) (see also section 9). The Group emphasized, however, that such preparations contain progestins and have a higher dose of estrogens than those customarily used to treat menopausal symptoms.

A study designed to test for a relationship between coronary artery disease and oral contraception also gathered data on 19 cases of myocardial infarction in women under 46 years of age who did not require contraception, usually because they were surgically or naturally postmenopausal (*245*). In comparison with control women of the same age who had been discharged in similar periods from the same highly selected hospitals, these cases reported in retrospect a higher frequency of noncontraceptive estrogen use. The same group has explicitly studied nonfatal acute myocardial infarction in postmenopausal women in relation to other hospital patients (*246*). A protective effect of estrogens (crude risk ratio = 0.39) was observed in the 328 cases and 6730 controls, but fewer than 2% of the cases were currently taking estrogens, and this effect disappeared when other risk factors for myocardial infarction were accounted for.

Investigators in North Carolina (*329*) retrospectively compared the experiences of their postmenopausal patients who had and who had not taken replacement estrogens and observed a substantial and significant reduction in the frequency of cardiovascular diseases occurring after the beginning of therapy. While the two groups differed in several other respects, and while the allocation of estrogens was not systematic, the two groups had been similar in respect of their pretreatment occurrence of cardiovascular disease.

The incidence of myocardial infarctions was studied in relation to estrogen use by examining the pharmacy records among the female residents in a community of retired people (*247*). A small protective effect was observed, again largely explained by other known risk factors. The incompleteness of the pharmacy records, and the potential bias due to the relative convenience of the pharmacy for symptomatic patients must be considered when interpreting these results. Using the more complete evidence available from medical records, a second study (*248*) in the same community examined deaths from ischaemic heart disease in relation to other community members. A strong protective effect of estrogens (risk ratio = 0.43) was observed that could not be explained by known sources of bias, including the other expected determinants of disease, namely, history of hypertension, diabetes, stroke, angina pectoris and heavy cigarette smoking. The independent effects of each of these could also be confirmed in the study.

In summary, the Scientific Group noted that there have been very few careful epidemiological studies of the relationship between estrogens and morbidity or mortality from cardiovascular disease. There are some indications that estrogens alone may eventually prove to be beneficial but the effects of estrogens plus progestins are less easy to predict in the light of recent evidence associating the progestin component of combined oral contraceptives with risk factors and deaths from stroke and ischaemic heart disease (*225, 249, 250*). Because of the overwhelming importance of this disease in comparison with all other potential effects of estrogens under consideration, the Scientific Group considered that the final cost-effectiveness of estrogen administration is likely to depend, to a very large extent, on the outcome of definitive studies with relation to cardiovascular disease.

7.2.6 *Recommendations*

The Scientific Group made the following recommendation.

Further epidemiological studies of the effects of estrogens, with or without added progestins, on atherosclerotic cardiovascular disease should be undertaken in peri- and postmenopausal women and should have the following characteristics:

(1) The settings of the studies should be such that a sufficient number of subjects is available, and that there are facilities for long-term follow-up so that a solid statistical appraisal of risk and its rela-

tionship to dosage and duration of estrogen use (with or without progestin) can be made.

(2) Other factors known to modify the risks must be accounted for and their effects assessed quantitatively.

(3) Treatment and control groups should be comparable with respect to the sensitivity and specificity of the methods used to assess the various outcomes.

(4) Reasons for treatment or nontreatment should be specified.

Because of the overwhelming size of the underlying risk, the Scientific Group believes that such studies should be assigned the highest priority.

7.3 Arthritic disorders

The Scientific Group recognized that although musculoskeletal disorders are said to be a common and troublesome feature of the menopause (*251*), little documentation is available to support this. In a study of 2232 women aged 45–55 years in Lower Franconia, Federal Republic of Germany (*252*), various generalized categories of illness were compared for four groups: group A, premenopausal (at least two menses in the preceding 6 months), comprising half of the subjects; and those up to 2 years postmenopausal (group B), 2–5 years (group C) and 5–10 years postmenopausal (group D), with equal numbers in each. While the frequencies of organic heart disease, functional circulatory disturbances, and diseases of the stomach and bowel, liver and gallbladder, and kidneys and bladder were equal in group A, and in groups B, C and D combined, there was a statistically significant (though small) difference in the frequency of rheumatic and degenerative skeletal disorders (23.5% of group A, 29.1% of groups B, C and D). When a detailed comparison was made, groups A and D showed approximately equal frequency (23.2% and 23.5%), group B had a frequency of 32.3% and group C 30.7%. It was noted that skeletal disorders were more frequent (35.1%) in women with severe hot flushes, sweating and dizziness, than in those without such symptoms (27.0%).

Osteoarthrotic changes in the finger joints were graded radiologically by standard criteria in a study of 155 Belgian women (*253*). There was a progressive increase in severity with age, although there was a sharp rise around the age of 50; the authors stated that a similar increase was observed in men, delayed by one decade. Analysis of

24 women with vertebral collapse and 34 with femoral neck fracture (i.e., two groups with osteoporosis), and 60 with primary osteoarthrosis of the hip showed that the osteoporotic subjects had a significantly lower degree of osteoarthrosis than expected, while the osteoarthrotic subjects had a higher degree than the controls, indicating the presence of a more generalized joint disease.

In population studies done in the United Kingdom, the age at onset of generalized osteoarthrosis showed a mode at about age 50; although there was a difference in magnitude of the modes for the two sexes, "there has been nothing to suggest any dissimilarity in the overall patterns in the two sexes" (*254*). The incidence of rheumatoid arthritis (seropositive) gradually rose to approximately age 50 and then declined in both sexes, while gout in the female was uncommon and reached its peak incidence over the age of 60 (*254*).

The Scientific Group concluded that the above data suggest that there is considerable doubt about the specificity of musculoskeletal disorders as a feature of the menopause. The Group did, however, take note of a recent publication (*255*) in which it was observed that there had been a decline in the secular trend of the incidence of rheumatoid arthritis in females during the period 1950 to 1974. The rates for females had declined dramatically during the last 10 years of the study and the authors believed that oral contraceptives and postmenopausal estrogens were the likely causes of the decline. The observation is in agreement with another report (*256*), which states that oral contraceptives protect against the development of rheumatoid arthritis. The Scientific Group recommended that further studies be undertaken to establish whether postmenopausal estrogen use was in fact protective against rheumatoid arthritis and considered that, if this was established, it was another factor which must be considered in weighing up the risks and benefits of estrogen therapy.

8. RISKS, WITH PARTICULAR REFERENCE TO NEOPLASIA, OF THERAPEUTIC ESTROGENS AND PROGESTINS GIVEN TO PERI- AND POSTMENOPAUSAL WOMEN

8.1 Introduction

The Scientific Group recognized that the use of estrogens with or without progestins to treat peri- and postmenopausal women has been

a subject of major controversy in the medical literature for some years. Particularly relevant to this controversy have been reports associating estrogen therapy with an increased risk of developing endometrial cancer, and recently also breast cancer. The Group therefore considered the risks of estrogen therapy with particular reference to these two neoplasms. The epidemiological approaches used to identify possible associations between drug exposure and the development of disease have been summarized in a recent report by another WHO Scientific Group (*257*).

8.2 Endometrial cancer

8.2.1 *Estrogens*

The Scientific Group noted that for decades, since about the time when ovarian steroid hormones were first recognized to induce endometrial hyperplasia, there has been speculation about the relationship between estrogens and endometrial carcinoma (*258*). Pathologists have recognized the coexistence of hyperplasia and adenocarcinoma and the apparent evolution of adenomatous hyperplasia into adenocarcinoma (*259*). Cytologists have observed the increased prevalence of well-cornified vaginal epithelium as an indication of the presence of high levels of estrogens in women with endometrial carcinoma (*260*). Clinicians began to accumulate evidence of increased risk of endometrial disease after the occurrence of theca cell tumours and polycystic ovarian disease. They also noted the appearance of endometrial adenocarcinoma in patients with gonadal dysgenesis, who had been treated with synthetic estrogens (*261, 262*).

Moreover, the association of the disease with low parity and early age at menarche suggested a relationship with estrogens (*263*). The evidence of peripheral conversion of androstenedione to estrone (aromatization) (*16, 19 264*) offered potential explanations for several hitherto unexplained epidemiological observations: the association between endometrial carcinoma and obesity, and the persistence of high risk over the decade following menopause. The observation also weakened reservations about an estrogen hypothesis which stemmed from the observation that endometrial cancer sometimes occurs in women after oophorectomy in the absence of exogenous estrogens (*265*). The absence of a strong secular trend in the incidence of endometrial cancer in the USA is hard to interpret because of the prevalence of past hysterectomy (*266*).

Table 6. Summary of three studies of

Investigator, year and country (reference)	Nature of study	Factors accounted for	Age range (years)
Jensen et al. (1954) Denmark (272)	Retrospective (hospital-based) control study of case records. Controls were postmenopausal women with diseases stated to have no influence on the outcome of the questions examined	Age, onset of menopause, abnormal uterine bleeding, marital status, fertility	31–80 (controls: not stated)
Wynder et al. (1966) USA (273)	Interview and case-record study of endometrial cancer cases and controls (hospital-based)	Excluded breast and gynaecological disease in controls. No other selection criteria given. Data on religion, education, marital status, etc.	36–78 (interviewed) (mean 59.3) 23–90 (from records) (mean 58.4) 35–70 (controls)
Dunn & Bradbury (1967) USA (274)	Interview and examination of cases of endometrial cancer and postmenopausal bleeding with atrophic endometrium (hospital-based)	Age range, race, economic status, primary reason for referral	Cases: average 63.9 Controls: average 61.3

While there are singularly few animal models of endometrial carcinoma, studies in the rabbit have shown that estrogen administration induces more frequent and earlier carcinomas (*267*). More recently a similar and more convincing induction has been demonstrated in a mouse system (*268*).

Exogenous estrogen therapy, given for long periods to hypogonadal women, produces endometrial hyperplasia even when progestational drugs are given cyclically for 3–8 days per month (*269*). Case reports of endometrial carcinoma occurring in women with long use of exogenous estrogens have appeared in the literature for 30 years (*270*), but only since 1975 have there been serious, controlled efforts to test the hypothesis. By then, very large numbers of North American women had been receiving large doses of conjugated estrogens for very long periods of time (*271*). By 1975, only 3 controlled but inadequate studies (*272–274*) of the relationship between estrogen replacement therapy and endometrial cancer had been performed (Tables 6 and 7). In the five years following the first modern studies, which appeared in that year, the number has risen to 22 (*272–294,*

endometrial carcinoma before 1975

Association between disease risk and important characteristics				
No. of cases/controls	Nulliparity	Age at spontaneous menopause	Obesity	Diabetes
105/52	42 out of 100 cases (10% in controls)	49.6 (cases) 47.9 (controls)	No data	No data
112/200 945 patients with endometrial cancer (from records)	37% in cases (31% in controls) 38% abortion in cases (25% in controls) (not signif.)	49.5 (cases) 48.0 (controls) ($P < 0.02$)	Highly significant difference; most important risk factor	Fasting blood sugar higher (compared with a well-woman group)
56/83	25% in cases 4.8% in controls (excluded unmarried nulliparous patients)	49.9 (cases) 48.7 (controls)	Cases: 22.6 kg overweight Controls: 16.6 kg overweight (stat. signif.)	No difference

reference *281* being additional data on *276*) (Tables 8 and 9). In 17 of these, strong associations have been found between past estrogen use and the development of endometrial cancer. Such studies are referred to below as positive studies, in contrast with those in which no association between estrogen use and endometrial cancer was observed—the so-called negative studies. The magnitude of the associations found is such that the factor by which large doses (certainly as little as 1.25 mg daily for 5 years and perhaps less) increase the risk from endometrial cancer is comparable to the factor by which heavy smoking increases the risk from lung cancer.

None of the negative studies has raised real doubts about the reality or strength of the association. In some, the sample size (*285, 289*) or the level of estrogen use (*273*) was impossibly small. In others, the mean duration of use was very short (*290*), or the contrast between cases and controls was obscured by the use of controls who themselves had experienced high levels of past estrogen usage (*274, 283, 285*).

Table 7. Further details from three studies before 1975 of menopausal estrogen use and endometrial carcinoma

Investigator, year and country (reference)	Age range (years)	No. of cases/controls	Relative risk by duration of estrogen use, if stated (range)	Relative risk (range)	Percentages of cases/controls who had received estrogen
Jensen et al. (1954) Denmark (272)	31–80 (controls: not stated)	105/52	16 patients had been treated with "large doses of estrogenic hormone" continuously for 1.5 to 15 years (average 6.5 years, median 5.5)	1.9	33.2/22.1
Wynder et al. (1966) USA (273)	36–78 (interviewed) 23–90 (from records)	112/200 945 (cases from records)	Postulated only that etiological basis "appears to be increased retention of certain endogenous hormones"	0.6	2/4
Dunn & Bradbury (1967) USA (274)	Cases: 63.9 (av.) Controls: 61.3 (av.)	56/83	"No difference" between groups in relation to duration of estrogen use; no difference between groups in appearance of vaginal smear	1.0	28.6/27.5

Several of the positive studies could be criticized on equally stringent grounds. The basis for computing the expected number of cases might be questioned in the two follow-up studies (*277, 288*). The use of controls gathered from the ranks of other patients with gynaecological neoplasms is probably not optimal because of the relatively low social class and presumed low estrogen-use rates of cervical and vulvar cancer patients (*275, 284*). However, it is by no means clear that estrogen use is strongly associated with high social class.

In some of the studies, the relationship between dose and risk was not examined (*272, 275, 287*), and in others the cases could not be subdivided on the basis of degree of invasiveness (*272, 277, 282*). The most often repeated criticism which has been directed at the positive studies, however, is that of ascertainment bias, a criticism which does not stand up to scrutiny (*296*). At least eight well-designed large studies in diverse populations are in essential agreement with respect to the size of the considerable increase in risk, the presence of a dose-response and/or a duration-response relationship, and the presence of an increased risk within subgroups of cases, including those defined on the basis of age, prior risk, treatment pattern, histology, chief complaint, and especially the degree of invasiveness (*276, 278, 280, 286, 291–294*).

While it would be imprudent to question the causality of the association, there are questions to which the available answers must be considered more tentative. Most of the information pertains to daily use of conjugated estrogens; associations with synthetic estrogens were found in four of the studies (*277, 278, 286, 291*). The risk also seems to be present after cyclic therapy (*278, 286, 291*). Many clinicians believe that cyclic opposition to estrogens by progestins can be presumed to prevent any carcinogenic effects (*287, 289*) (see Section 6.5.2.3); others interpret the animal models (*268*), or the persistent plasma estrogen levels after treatment (*297*) to be somewhat against this view.

Two groups found that the risk abated rapidly after cessation of estrogen use (*288, 293*), but three others found evidence of persistent risk for at least several years (*278, 291, 294*), a finding more consistent with most other evidence of human carcinogenicity. Finally, while four studies found the increased risk to accrue particularly to those at low *a-priori* risk, i.e., to thin and multiparous women (*275, 278, 284, 292*), such an effect was not found in two others (*280, 291*).

One point on which all observers agree is the relative non-invasiveness of endometrial cancer which is observed in association with

Table 8: Summary of case-control studies of

Investigators, year, and country (reference)	Nature of study	Factors accounted for	Age range (years)
Smith et al. (1975) USA (*275*)	Retrospective case-control; hospital-based, from medical records; matched pairs analysis; controls selected from other gynaecological neoplasia (206 cervix, 88 ovary, 23 vulva)	Age and year of diagnosis, hypertension, diabetes, obesity, nulliparity, referral pattern, type of control, and institution	not stated
Ziel & Finkle (1975) USA (*276*)	Retrospective case-control; health-plan based review of clinic records; excluded hysterectomized controls	Age, duration of health-plan membership, and area of residence	not stated
Hoover et al. (1976) USA (*277*)	Retrospective review of 45 853 women with breast cancer (no controls)	Age >49 years, study limited to patients not undergoing pelvic ablation or irradiation for endocrine control	>49
Mack et al. (1976) USA (*278*)	Retrospective case-control, based on records in retirement community medical care facility	Age, marital status, hysterectomy excluded, menopause, parity, obesity, gall-bladder disease, diabetes, hypertension, benign breast disease, and invasiveness of tumour	>52
Gray et al. (1977) USA (*279*)	Retrospective case-control, comparison of end. cancer with hysterectomy for benign disease from one private practice	Age, parity, weight (where possible), diabetes, and blood pressure	Average: cases 56.5, controls 56.0
McDonald et al. (1977) USA (*280*)	Retrospective case-control study of medical records of Rochester Project, Mayo Clinic	Age, hysterectomy excluded, parity, menarche, menopause, height, weight, blood pressure, diabetes, and gall-bladder disease	no data

endometrial cancer with epidemiological details

No. of cases/ controls	Association between disease risk and important characteristics				Other comments
	Nulliparity	Age at spontaneous menopause	Obesity	Diabetes	
317/317	+	no data	+	+	Socio-economic status not included
94/188	+ (confounding effect estimated to be 4%)	+ 2%	+ 2%	not examined	Indication for estrogen: hot flushes – in 72% of 54% patients, 71% of 72% controls
5 cases (of 1660 receiving hormones during initial treatment); 14 cases (of 2551 only during a subsequent course)	not dealt with	not dealt with	not dealt with	not dealt with	Calculated expected number of tumours
63/252	Risk ratio 1.4 (N.S.)	Risk ratio 1.1 for menop. at ≥50	Risk ratio 1.5 (N.S.)	Risk ratio 0.9 (N.S.)	At least 6 months exposure required; estrogen included conjugated and others
205/205	not dealt with	not dealt with	Cases heavier than controls	Risk ratio 9.8 (1.1–369.4)	Minimum 3 months estrogen use; systolic blood pressure greater for cases
145/580	1.8 (1.2–2.6)	≤51 1.3 (0.9–2.0)	Risk ratio 3.5 (2.2–5.3)	0.7 (0.3–1.4)	Excluded in situ carcinoma, 6 months estrogen use required etiologic fraction, long-term estrogen

Table 8

Investigators, year, and country (reference)	Nature of study	Factors accounted for	Age range (years)
Wigle et al. (1978) Canada (*282*)	Retrospective case-control interview study, based on Alberta cancer clinics; controls were patients with any primary cancer other than breast, cervix, uterus, ovary or other female genital organs	Age	55–74
Horwitz & Feinstein (1978) USA (*283*)	Two retrospective case-control studies: (1) compared endom. cancer with other gynaecological cancers, (2) compared endom. cancer with other patients undergoing D & C	Age, race, nulliparity, obesity, hypertension, and diabetes	Means: (1) cases 61 ± 9 (50 SD), controls 62 ± 9; (2) cases 62 ± 9, controls 61 ± 9
Hoogerland et al. (1978) USA (*284*)	Retrospective case-control study, hospital-based, data based on record review; controls were patients with other gynaecological malignancies	Age, date of diagnosis, hypertension, diabetes, obesity, age at menopause, parity	50–60
Völker et al. (1978) Federal Republic of Germany (*285*)	Retrospective case-control study, hospital based; controls were patients either hysterectomized or irradiated for abnormal vaginal bleeding	Age at diagnosis and at menopause, parity, obesity, diabetes, hypertension, income level, education, cancer prophylaxis, intake of medications	<41 >70
Antunes et al. (1979) USA (*286*)	Retrospective case-control study, hospital based; data included personal interview, medical records, pathological specimens	Hospital, race, age (within 5 yrs); two types of control – (*a*) all females other than gynaec., obstet., psychiatric, (*b*) gynaecologic; weight, heart dis., diabetes, time to diagnosis, education, age at menopause, endom. pathology	Cases: mean 60.6 Controls: matched with cases, within 5 yrs
Hammond et al. (1979) USA (*287*)	Retrospective case-control study of hypo-	Age at menarche and menopause, height,	Mean: 42.5 (estrogen treated, no carcinoma) Mean: 53.3 (estrogen treated, with carcinoma

(continued)

No. of cases/ controls	Association between disease risk and important characteristics				Other comments
	Nulliparity	Age at spontaneous menopause	Obesity	Diabetes	
					0.09, obesity 0.25, nulliparity 0.19
202/1243	not dealt with	not dealt with	not dealt with	not dealt with	Estrogen use >5 years in 23.9% cases, 5.5% controls
(1) 119/149 (2) 119/149	(1) cases 26%, controls 27% (2) cases 18%, controls 13%	Mean ages: (1) cases 50±4, controls 50±4; (2) cases 48±7, controls 50±5	(1) cases 30%, controls 33% (2) cases 22%, controls 21%	(1) cases 10%, controls 11% (2) cases 8%, controls 8%	Estrogen exposure: at least 0.3 mg conjugated estrogens for at least 6 months
587/587	All patients: risk ratio 1.25 (N.S.); estrogen exposed: risk ratio 2.4 (1.2–2.0)	>50 All patients: risk ratio 1.2 (N.S.); estrogen exposed: risk ratio 1.8 (N.S.)	All patients: risk ratio 2.8; estrogen exposed: risk ratio 1.7 (N.S.)	All patients: risk ratio 1.9; estrogen exposed: risk ratio 1.1 (N.S.)	Relative risk values computed from odds ratio by both unpaired and matched pairs analysis
130/130	Estrogen exposed: risk ratio 0.34		Estrogen exposed: risk ratio 0.30		Risk ratio values computed from matched pairs analysis
451/888	no data	no data	no data	no data	Stratified for stage of cancer for II, III & IV, risk ratio 4.0 (1–22)
301/309	No high-risk group identified				Absolute risk of developing

Table 8

Investigators, year, and country (reference)	Nature of study	Factors accounted for	Age range (years)
	estrogenic women; 1 group on long term estrogen (>5 yrs); Third National Cancer Survey Data used for controls also	weight, B.P., marital status, gravidity, state of uterus	
Jick et al. (1979) USA (*288*)	Retrospective study of incidence of endometrial cancer in estrogen users and non-users	Age, hospitalization	50–64
Nachtigall et al. (1979) USA (*289*)	Prospective double-blind study of estrogen-progestogen therapy, hospital-based	Age, diagnosis weight, race, gravidity, parity, B.P., blood sugar	Treated 55.3; controls 54.9
Salmi (1979) Finland (*290*)	Retrospective case-control study, hospital-based, interview study	Age, weight, social class, age at menarche	Cases 31–82 (282 matched pairs formed)
Weiss et al. (1979) USA (*291*)	Retrospective case-control study, interview	Age, excluded hysterectomy, nullip., obesity, B.P., income level	Cases 51–75; controls 51–74
Jelovsek et al. (1980) USA (*292*)	Retrospective case-control, hospital-based	Age, race, parity, hypertension, diabetes, obesity, age at menopause	Cases 58.7 ± 0.6, controls 59.1 ± 0.62
Hulka et al. (1980) USA (*293*)	Retrospective case-control study with interview of patient or relatives, office records and hospital records, included only invasive endometrial cancer; used both gynaecol. and community controls, intact uteri	Age, race, obesity, hypertension, diabetes, gall-bladder disease, parity, social status, marital status	Whites: 59.7 (cases) 60.1 (gyn.) 55.2 (comm.)
Shapiro et al. (1980) USA (*294*)	Retrospective case-control study, hospital-based, nurse interviews	Race, religion, marital status, education, parity, obesity, age at menopause, diabetes	Cases: 50–69 (median 60) Controls: 50–69 (median 61)

(continued)

No. of cases/ controls	Association between disease risk and important characteristics				Other comments
	Nulliparity	Age at spontaneous menopause	Obesity	Diabetes	
					cancer on long-term estrogen therapy, about 1/20
67/122					
84/84		No difference			
318/585	Risk ratio 3.0	Cases 50.6; controls 49.7 ($P<0.05$)	Mean wt: cases 73.3 kg., tentative controls 66.4 kg.	Risk ratio 2.4 (1.0–7.0)	
322/289		Not broken down – said to be no difference			
431/431	Cases matched with controls (24.5% nulliparous); risk ratio 3.6 (1.3–10.2)	Cases 46.8 ± 0.44; controls 47.5 ± 0.43 (N.S.)	Mean weight: cases 76.2 ± 1 kg; controls 66.7 ± 0.8 kg ($P \leq 0.001$)	Cases 22.5%, controls 13.0% ($P<0.001$); risk ratio 4.3 (0.5–35.7)	See their Table VIII for useful summary
256/224 gyn. controls /321 comm. controls	Data for 186 white cases and controls (153 gyn. and 236 comm.) only				See her Table I for comment on methodological differences in recent case control studies
	26.6% (cases) 14.4% (gyn.) 15.7% (comm.)	47.2 46.6 46.8	51.6% 39.9% 31.4%	19.4% 17.0% 6.8%	
	Risk ratios – not exposed: gynaec. controls 2.3, comm. contr. 2.7 (exposed: 0.5, and 1.4 respect.)		Risk ratios – not exposed: gyn. controls 2.3 (1.4–3.9) comm. contr. 2.7 (1.6–4.6)		
149/402	No specific data	>50 in 43% of cases, 54% of controls	Ponderal index ≥40: cases 34%, controls 24%	5% cases 2% controls	

Table 9. Further aspects of case-control studies of endometrial cancer

Investigators, year and country (reference)	Age range (years)	No. of cases/ controls	Relative risk by duration of estrogen use, if stated (range)	Relative risk	Cases/controls (%) who had received estrogen	Other remarks
Smith et al. (1975) USA (*275*)	not stated	317/317	Dosage, specific estrogen, and treatment schedule not indicated	4.5 (no range provided); risk highest in patients without hypertension and obesity	48/17	Estrogen use – at least 6 months before cancer was diagnosed
Ziel & Finkle (1975) USA (*276*)	not stated	94/188	years of use 1.0–4.9: 5.6 (lower 95% limit 2.7) 5.0–6.9: 7.2 (2.8) 7+: 13.9 (6.0)	7.6 (lower 95% limit 4.7)	57/15	Caution advised – other studies, and follow-up studies required
Hoover et al. (1976) USA (*277*)	≥49	5 + 14 cases		3.1 (initially) 2.1 (for subsequent course) for primary cancer ($P \leq 0.05$)	no data	Mostly nonsteroidal estrogen
Mack et al. (1976) USA (*278*)	>52	63/252	months of use 1–11 / 12–59 / 60–95 / 96+ dose ≤0.625 mg: 6.6 / 3.4 / 6.0 / 4.8 dose >0.625 mg: 0 / 29.8 / 11.9 / 19.1 total: 2.8 / 4.5 / 9.3 / 8.8	Any estrogen 8.0 (3.5–18.1), conjugated estrogen 5.6 (2.8–11.1), other estrogens 3.3 (1.7–6.4)	89/29	Also looked at degree of invasiveness; risk ratio higher for well differentiated & noninvasive tumours. Calculated incidence: non-users $53/10^5$ users $424/10^5$
Gray et al. (1977) USA (*279*)	Average. cases 56.5, controls 56.0	205/205	years of use 0–4: 1.2 (0.4–3.5) 5–9: 4.1 (0.8–28.4) 10+: 11.6 (1.5–242.7) According to strength of tablet: 0.3 mg: 4.1 (0.8–40.5) 0.625: 1.8 (0.7–4.9) 1.25: 12.7 (1.8–552.3)	Conjugated estrogen 3.1 (1.5–6.8), all estrogens 2.1 (1.2–3.5)	Conjugated estrogen 16.6/5.9, all estrogens 26.8/15.1	No clearcut effect of tumour stage

McDonald et al. (1977) USA (*280*)	no data	146/580	years of use 0.5: 4.9 (2.3–11.5) 1: 5.3 (2.1–14.4) 2: 8.3 (2.9–29.9) 3: 7.9 (2.9–21.2)	2.3 (1.4–3.6) for 6 months (or longer) use	27/28	Controls; more common history of short-term estrogen use for pregnancy or lactation suppression (40 controls, 1 case); risk ratio highest for continuous use, and for stage I cancer
Wigle et al. (1978) Canada (*282*)	55–74	202/1243	years of use 0: 1.0 1–4: 1.8 ($P<0.05$) ≥5: 5.2 ($P<0.05$)	2.2 ($P<0.01$)	47.2/26.3	Significant trend of increasing risk with duration of use
Horwitz & Feinstein USA (*283*)	See Table 8			(1) 11.98 (4.02–47.73) (2) 2.3 (1.26–4.25)	(1) 29/3 (2) 30/15	Odds ratios included 1 when series (2) was stratified for reason of hospitalization; comment on frequency of asymptomatic uterine cancer; serious concern about validity of previous studies
Hoogerland et al. (1978) USA (*284*)	50–60		months of use: 1–6: 1.2; 7–12: 1.8 years of use: 1–3: 3.2; 3–5: 3.9; 5–10: 3.4; 10+: 6.7	2.2 (1.6–3.2)	18.4/9.2	
Völker et al. (1978) Fed. Rep. of Germany (*285*)	<41 >70		years of use 1: 0.46 1–3: 0.24 3–5: 0.34 5–10: 0.96 10+: 1.15	0.44	24/42	In presence of other risk factors (such as nulligravidae, hypertension, obesity), the risk ratios for development of cancer of the endometrium were significantly decreased when estrogen was taken

Table 9 (continued)

Investigators, year and country (reference)	Age range (years)	No. of cases/ controls	Relative risk by duration of estrogen use, if stated (range)	Relative risk	Cases/controls (%) who had received estrogen	Other remarks
Antunes et al. (1979) USA (*286*)	See Table 8		years of use <1 / 1–5 / >5 2.2 (0.9–5.5) / 2.9 (1.3–6.7) / 15 (4.9–4.5) Also in relation to dose: <1 mg 3.5 (1.6–7.6) 1–2 7.1 (2.8–18) >2 3.7 (0.8–16)	Matched hospital controls 6.0 (3.7–9.7) Gynaecol.service 2.1 (1.5-upper limit not stated). Adjusted risk: 5.5 (2.3–12.9) for hospital controls, 2.4 (1.5–3.7) for gyn. controls	not stated	Excess risk for stilbestrol and conjugatedestrogen; cyclic use had similar risk to continuous
Hammond et al. (1979) USA (*287*)	See Table 8			Third Cancer Survey: comparison 9.3 (4.7–16.7) and 3.8 for white women in the two study groups	3.7/1.0	No increased risk for breast cancer; no cancers developed in 80 patients given added progestins
Jick et al. (1979) USA (*288*)	50–64			Annual risk for users 1–3%, non-users 0.1–0.3%	75/39 % of controls with intact uteri who were estrogen users	Risk said to fall within 6 months of discontinuing estrogen use
Nachtigall et al. (1979) USA (*289*)	See Table 8			1 cancer (in untreated) 0 (in treated)		
Salmi (1979) Finland (*290*)	See Table 8		Mean time of estrogen use: 10.2 months (cases) 14.2 months (controls)	0.8		
Weiss et al. (1979) USA (*291*)	See Table 8		years since first use 1–2 / 3–4 / 5–7 / 8–10 / 11–14 / 15–19 / 20 1.2 (0.4–3.7) / 5.4 (2.5–11.5) / 4.7 (2.6–8.4) / 11.7 (6.2–21.8) / 24.2 (11.8–49.4) / 10.2 (5.3–20) / 8.3 (2.8–24.5) Dosage mg/day: ≥0.5 2.5 (1.1–5.3); 0.6–1.2 8.8 (5.0–12.7); 1.25 7.6 (8.0–11.8)	No overall figure		Cessation of use led to decline in incidence; little influence of cyclic vs continuous use; higher risk of less advanced cancer

Jelovsek et al. (1980) USA (*292*)	See Table 8	years of use 0.5–3: 1.4 (0.6–3.5) 3–5: 1.4 (0.3–6.5) 5–10: 4.8 (1.6–14.5) >10: 2.6 (1.1–5.9)	2.4 (1.4–3.9) Whites 2.9 (1.7–5.1) Blacks 0.6 (0.–2.5).	12.3/5.6	Estrogen usage at least 6 months before index date; increased risk confined to stage I, grade I and stage IA, grade 2
Hulka et al. (1980) USA (*293*)	See Table 8	Data for white cases/controls: (<3.5 yrs) (>3.5 yrs) gyn controls: risk ratios 0.8 (0.4–1.7) 4.1 (1.8–9.6) comm. controls: risk ratios 0.7 (0.4–1.7) 3.6 (1.9–6.8) Dose: ≤0.625 vs gyn. 1.6 vs comm. 2.3 >0.625 vs gyn. 1.8 vs comm. 1.4	Gyn. controls: whites 1.8 (0.9–2.5) blacks 0.7 (0.3–2.1) Comm. controls: whites 1.4 (0.9–2.1) blacks 1.5 (0.4–5.1)	White women 32.8/22.9/27.1 Black women 10/12.7/8.2	Relative risks are for long duration of use only; no risk for <3½ yrs; minimum latency period 3–6 yrs; estrogen-free for 2 yrs changed the risk to control level
Shapiro et al. (1980) USA (*294*)	See Table 8	Divided by time of latest use of conjugated estrogen and duration of use: <1: <1yr –, ≥1yr 0.9, total 0.9 1–4: <1yr 7.9, ≥1yr 1.6, total 2.6 ≥5: <1yr 8.8, ≥1yr 3.6, total 6.0	For cases taking conjugated estrogen for at least 5 yrs and last used > 2 yrs previously: 3.3 (1.4–8.0)	45/24 (conjugated estrogen 40/17)	For non-conjugated estrogen, risk ratio 0.9

estrogen use. The excess cases of cancer appear to be less often invasive at the time of diagnosis (*278, 280, 286, 298–300*) and they can be expected to have a relatively small impact upon mortality (*301*). Whether this is because of the earlier opportunity for diagnosis or because of some difference in the natural history of disease is unknown, and it is consistent with but not explained by similar characteristics of endometrial cancer in young obese women (*302*) and of this cancer related to feminizing ovarian disease (*295*).

8.2.2 *Conclusions and recommendations*

The Scientific Group concluded that the two major areas of ignorance in regard to the risks of endometrial cancer associated with estrogen therapy are the persistence of the oncogenetic effect, and the nature of the dose-response curve at low doses and durations of use.

The Scientific Group made the following recommendations:

(1) Novel approaches should be developed, if possible, to determine the persistence of the oncogenetic effect (if any) of estrogens on the endometrium and the nature of the dose-response curve at low doses and duration of use.

(2) A thorough assessment should be made of combined estrogen-progestin therapy, to determine whether added progestins are protective against the development of endometrial cancer.

(3) The morbidity in both physical and psychological terms, which accompanies the occurrence of endometrial cancer, should be quantified since this makes a large contribution to the gross costs of estrogen use.

(4) Programmes and algorithms of regular screening for endometrial disease, by endometrial biopsy, should be evaluated and their benefits quantified.

8.3 Breast cancer

The Scientific Group considered that the epidemiology of breast cancer is even more suggestive of endocrine origins than that of endometrial cancer (*303*). The risk from this much more common and serious disease is related to a variety of endocrine phenomena, including the ages at menarche, menopause and first pregnancy. Early oophorectomy has long been recognized to be strongly protective. Several mechanisms for the relationship between endogenous hor-

mones and breast cancer risk have been proposed, but current evidence does not permit one to be specified. Both naturally occurring and synthetic estrogens, and progestins appear under some circumstances to be carcinogenic for breast cancer in animal species (*304*).

The Scientific Group considered data on the relationship between estrogens and breast cancer which were derived from studies that included both pre- and postmenopausal women. Several clinical studies (*305–311*) have reported the long-term follow-up (from existing records) of women treated with estrogens, and conclude that, if anything, the risk of breast cancer is decreased. This conclusion must be regarded with strong scepticism because of the short duration and incompleteness of follow-up and the questionable nature of the comparisons made or implied (*304*).

More recently, there have been reports of an increased frequency of breast cancer in estrogen-treated cohorts (Table 10). A small but not statistically significant excess of disease has been reported to occur in women after being treated during pregnancy with diethylstilbestrol (*312*). Women treated with conjugated estrogens in two large gynaecology practices have appeared to experience a small excess incidence of breast cancer (*313, 314*), but in one of these studies (*313*) there are serious methodological irregularities (*304*) and neither of them explicitly included a control group, relying instead upon the application of convenient population-based breast cancer rates for a source of expectation. While most studies on oral contraceptive use and breast cancer have not identified a relationship between the two, they have generally been confined to studying the premenopausal period in parous women. One of these studies (*315*) has shown an increased rate of breast cancer in women with pre-existing benign breast disease who used oral contraceptives. In the most recent report of a large study (*358*), women nearing the menopause after long use of oral contraceptives appeared to suffer an increased risk, but chance could account for this observation. A recent case-control study (*382*) of nulliparous women younger than age 32 who had used the pill for as long as six years also demonstrates an increase in risk (relative risk 2.2). The Group noted the paradoxical observation that current oral contraceptive use for more than 2 years' duration appears to reduce the risk of benign breast neoplasia (*257*).

A number of case-control studies were performed in a variety of American settings and in one Yugoslav centre in the early 1970s (*316–322*) (Table 11). None of these studies found an unequivocal association between estrogens and breast cancer, but none adequately

Table 10. Cohort studies

Investigators, year, and country (reference)	Nature of study	No. studied	No. of breast cancers (observed)	No. of breast cancers (expected)	Relative risk (overall)
Bibbo et al. (1978) USA (*312*)	Telephone survey of mothers who took diethylstilbestrol (DES) during pregnancy	693 mothers who took DES and 668 controls	32 in exposed 21 in non-exposed	Standardized incidence ratio for both groups = 1.79 compared with general population represented by Connecticut Cancer Registry	4.6 vs 3.1% (N.S.)
Burch et al. (1975) USA (*313*)	Hysterectomized women followed up in a private practice	735	21	18	–
Hoover et al. (1976) USA (*314*)	White women treated with conjugated estrogens in one private practice	1891	49	39.1	1.3 (1.0–1.7)

Table 11. Case-control studies of

Investigators, year, and country (reference)	Nature of study	Factors accounted for	Age
Boston Coll. Drug Surveillance Program (1974) USA (*316*)	Hospital-based, case-control study	Hospital, parity, marital status, smoking, history of hypertension or hysterectomy	45–69
Craig et al. (1974) USA (*317*)	Cross-sectional case-control study of patients with breast cancer and both community and neighbourhood controls	Year of birth, education, marital status, adequacy of housing, religious attendance, smoking history, age at first childbirth, lactation, parity, use of hormones, age at menarche, menopause, hysterectomy, history of thyroid disease	44–74

of breast cancer

Relative risk for periods of follow-up				Association between disease risk and important characteristics		
				Parity	Ovarian status	Benign breast disease
years						
<5	5–9	10–14	⩾15	Nulliparous: risk ratio 1.3	Ovaries intact:	Diagnosed before starting estrogen: 2.1
0.9 (0.5–1.5)	1.2 (0.6–2.0)	1.3 (0.6–2.4)	2.0 (1.1–3.4)	1–2 children: risk ratio 1.3	risk ratio 1.1 Ovariecto-mized:	Diagnosed after starting estrogen: 4.0
				3 + children: risk ratio 0.8	risk ratio 1.3	

estrogen therapy and breast cancer

No. studied	Relative risk by duration of estrogen use, if stated (range)	Relative risks
Benign breast disease = 51; breast cancer = 52; controls = 774	Estrogen use in 8% of benign breast tumours, 9% breast cancers, 8% controls	No significant difference
156/176 (population controls; 150 neigh-bourhood controls)		Estrogen used by 17.8% of cases and 21.2% of controls – no significant difference

Table 11

Investigators, year, and country (reference)	Nature of study	Factors accounted for	Age
Mack et al. (1975) USA (*318*)	Case-control study based on retirement community (white, affluent)	Date of birth, hypertension	Median 71
Casagrande et al. (1976) USA (*319*)	Case-control study involving two groups of white middle class Americans	Age, age at menopause, socioeconomic class, hysterectomy, oophorectomy, age at diagnosis of breast cancer	50–64 50–59
Sartwell et al. (1977) USA (*320*)	Hospital-based, case-control study	Age, race, marital status, parity, age at first pregnancy, hospital pay status	15–74
Brinton et al. (1979) USA (*321*)	Study of breast cancer screening programme	Marital status, religion, family income, patient's education, spouse's education, age at menarche, age at first birth, surgical or natural menopause, family history of breast cancer, height, weight, previous breast biopsy, use of hormones	<50 (33.3% patients, 36.3% controls) 50–59 (39.2% patients, 39.5% controls) ≥60 (27.4% patients, 28% controls)
Ravnihar et al. (1979) Slovenia, Yugoslavia (*322*)	Hospital-based, case-control study	Age, date of admission, residence, occupation, duration of schooling, marital status, pregnancy, parity, menstrual history, family history of breast cancer, height, weight	20–64

Table 12. Recent case-control studies

Investigators, year, and country (reference)	Nature of study	Factors accounted for	Age	Number studied
Ross et al. (1980) USA (*323*)	Case-control based on retirement community (white, affluent)	Age at menarche, height, weight, age at first pregnancy, parity, age at menopause, benign breast disease, oophorectomy, family history	Mean: 72	147/281

(continued)

No. studied	Relative risk by duration of estrogen use, if stated (range)					Relative risks
						1.6 (no confidence interval provided)
90/83	Mean duration of estrogen use was the same in combined cases as in combined controls					1.2
284/367		months of use		years of use		0.82 (0.6–1.2)
		<6	6–11	1–1.9	2–4.9	5
	relative risk:	0.87	0.61	1.40	0.70	0.62
405/1156		years of use				0.97 (0.7–1.4)
		<5	5–9	10–14		15
	relative risk:	0.89 (0.5–1.4)	1.77 (0.9–3.2)	0.59 (0.2–1.6)		0.53 (0.5–2.0)
374/748						No significant difference

of estrogen therapy and breast cancer

Relative risk by duration of estrogen use, if stated (range)				Relative risks
Total accumulated dose (mg):	0	1–1499	⩾1500	Estrogen use for ⩾7 years: 1.8
all subjects:	1.0	0.8 (0.5–1.5)	1.9 (1.0–3.3)	
ovaries intact:	1.0	0.9 (0.4–1.7)	2.5 (1.2–5.6)	
ovaries removed:	1.0	0.9 (0.2–3.2)	0.7 (0.2–2.4)	

Table 12

Investigators, year, and country (reference)	Nature of study	Factors accounted for	Age	Number studied
Jick et al. (1980) USA (*324*)	Case-control study from pre-paid health plan records and interviews of "menopausal cases of breast cancer"	Age, menstrual history, family history, history of prior breast disease, education, race, weight, height, parity, age at first pregnancy	45–64	97/139
Brinton et al. (1980) USA (*325*)	Case-control study of white breast-cancer detection clinic screenees; interviews	Age, age at menarche, menopause and first childbirth, family history of previous breast biopsy	35–74	881/863
Hoover et al. (1981) USA (*326*)	Case-control study of prepaid health plan enrollees; record review	Age, age at menarche, menopause and first childbirth, family history, weight, parity, oophorectomy	Mean 57/58	345/611
Kelsey et al. (1981) USA (*327*)	Case-control study of hospital patients; interviews	Age, race, religion, education, birthplace, age at menarche, menopause and first pregnancy, family history, previous benign breast disease, oophorectomy	45–74	332/1353

solved the methodological difficulties that are inherent in studies of breast cancer and estrogen use. These two factors are linked in several important ways (age at menopause, presence of oophorectomy), whether or not they are linked etiologically.

More recently, another round of methodologically sounder case-control studies has been performed, using healthy population controls (*323–326*) (Table 12). These have provided repeated but not invariable indications that a relationship exists. One group (*323*) found a relative risk of 2.5 after a relatively high cumulative dosage, but only in women who had experienced natural menopause. Another group (*324*) found a risk of similar magnitude, again only after natural menopause. Two other studies (*325, 326*) also found an increase in risk after high dosage but, in contrast to the other two, the higher risk appeared in those who had undergone *surgical* menopause. These

(continued)

Relative risk by duration of estrogen use, if stated (range)					Relative risks
					Women aged 45–64 with spontaneous menopause: 3.4 (2.1–5.6) 45–54: 10.2 (4.5–23) 55–64: 1.9 (1.0–3.5) hysterectomized: 1.1
Years used:	0	5	5–9	10+	Ovaries removed 1.5 (0.9–2.8); ovaries intact 1.2 (0.9–1.5); total 1.2 (1.0–1.5)
ovaries intact:	1.0	1.2	1.2	1.1	
ovaries removed:	1.0	1.4	1.6	1.7	
total:	1.0	1.2	1.3	1.2	
Years between first and last prescription:	0	4	5+		Premenopausal: 1.7 (0.7–4.0) Postmenopausal: ovaries intact 1.3 (0.8–2.1), ovaries removed 1.5 (0.3–6.6), total 1.4 (1.0–2.0)
	1.0	1.4	1.7		
Months of use:	never	1–49	50+		At least 1 ovary intact: 0.9 (0.6–1.2) Ovaries removed: 0.9 (0.6–1.5)
at least 1 ovary intact:	1.0	0.9	0.6		
ovaries removed:	1.0	0.7	1.0		

inconsistencies cannot at present be resolved, although one study in each pair found that the effect of estrogens was particularly strong in the presence of benign breast disease (*323, 325*).

A final study, done as carefully as those just described but employing hospital controls (*327*), showed no association between estrogen use and any increase in breast cancer.

8.3.1 *Conclusions and recommendations*

In summary, the Scientific Group noted that a definite link between exogenous estrogen use in peri- and postmenopausal women and breast cancer has not been established; but until the reasons for the inconsistencies become clear, the Group considered that prudence demands that such a link should be assumed to exist. The Group con-

sidered that the details of risk remain unclear except for indications that there may be a significant risk for women with pre-existing benign breast disease, and for the fact that the positive findings of an association have been limited to women who have taken relatively large doses of conjugated estrogens for relatively long periods. The effects of estrogen-progestin combinations cannot be predicted. The Group concluded that there is no evidence to suggest that a risk appears after low doses of conjugated estrogens, but that other risk factors such as benign breast disease appear to modify the risk from estrogens in an upward direction. There is no information about the minimum or maximum latent period before diagnosis.

The Scientific Group made the following recommendation:

Further epidemiological studies on the role of exogenous estrogens given to peri- and postmenopausal women must be carried out in relationship to breast cancer etiology. The studies should be large enough and the information accurate enough to permit an appraisal of the modification of risk by dose and duration, as well as by such recognized risk factors as family history, benign breast disease, and surgical menopause. Because of the fear inspired by the thought of this disease, it takes on an importance even larger than its actual frequency and high mortality and morbidity would merit.

8.4 Gallbladder disease

Because of limitations of time, the Scientific Group considered only briefly the possible associations between exogenous estrogen therapy and the occurrence of gallbladder disease. It noted two reports of an increased risk of surgically confirmed gallbladder disease or cholesterol cholelithiasis in peri- and postmenopausal women receiving estrogen replacement therapy (*316, 328*), where the relative risks of the occurrence of this disease were 2.5 to 3.7. Two other recent studies, on the other hand, found no increase in risk (*289, 329*). The Scientific Group concluded that the risk of cholelithiasis required further study in prospective investigations of estrogen replacement therapy and of estrogen-progestin combinations used for the treatment of symptoms after the menopause. Possible mechanisms for an increased risk resulting from estrogen therapy have been reviewed recently (*330*).

9. FERTILITY-REGULATING METHODS FOR WOMEN APPROACHING THE MENOPAUSE

9.1 Introduction

Major problems face the perimenopausal woman from the standpoint of family planning. Despite a substantial reduction in natural fertility at this time, pregnancy can occur. For the individual woman, it may be difficult to determine when the menopause has occurred and when there is no need for further contraception. The risks associated with pregnancy, to both mother and fetus, rise substantially for women over the age of 35, as do those for women over the age of 40 who smoke and who use oral contraceptives. Thus the assessment of the risk-benefit ratio of various forms of fertility regulation assumes a different perspective in the years just prior to the menopause. In the following sections, data on fertility in women approaching the menopause and on the factors which might influence the choice of fertility-regulating methods are considered, and recommendations for further research are made.

9.2 Fertility and the need for family planning in women approaching the menopause

Data derived from historical records concerning European populations and from reports from some developing countries in the present century, where fertility regulation was not planned or practised, show a marked decrease in fertility during the women's fourth and fifth decades, which is very similar for all the different groups studied (*331*). The data show a steep downturn in the number of births per thousand married women in the 35–39 year age group (approximately 220–450 births per thousand in the 30–34-year age group, to approximately 180–400 per thousand at 35–39 years, to 100–220 per thousand in the 40–44-year age group in different surveys (*331*)), but the annual risk of pregnancy is still around 10% for women aged 40–44 and approximately 2–3% for women aged 45–49 years. Even over the age of 50, the risk may not be zero (*331*). In industrialized countries where there is widespread contraceptive use, there are still significant numbers of births to older women although in recent years there has been a substantial fall in fertility among women over the age of 40 (*332*).

The age at which reproduction ceases, in populations not using any contraception, has been assessed from the mean age at which women

bear their last child, and from the age-specific prevalence rate of infertility. Few data are available on the former, but in European populations it is estimated to be about 40 years. In contrast, it has been estimated to be about 37 years in poorly nourished women in Papua New Guinea (*33*). The definition of age-specific infertility encompasses a number of possible factors (*333*). including sterility of the male partner, infrequent coitus, practice of contraception, and actual female sterility (or lack of fecundability due to an aggregate of factors that are specific to the female and prevent conception). It is clear from a number of studies, however, that the median age of the female member of a couple, when she fails involuntarily to become pregnant, is estimated to be about 40 years (*333*). The median age of sterility thus antedates the age of menopause by about 10 years in developed countries, and by a somewhat smaller number in developing countries that have a lower age at menopause (*331*). These data are population data, however, and it is to be noted that 50% of women over the age of 40 years are still potentially fertile.

Factors in the female that contribute to the age-related decline in fertility include a reduction in the number of ovulatory cycles, an increased frequency of luteal phase defects, and increases in the frequency of mechanical obstruction to the tubes because of infection or complications of pregnancy and delivery, in addition to a lowered frequency of coitus. In population studies, the only practicable approach to estimating the frequency of anovulatory cycles and of luteal phase defects has been the recording of basal body temperatures, which show monophasic patterns or hyperthermic phases less than 10 days in length, respectively. In two large series (*4, 5*), the frequencies of anovulatory cycles and cycles with a short luteal phase are shown in Table 13. The prevalence of abnormal cycles in the 40–45-year age group was in the range of 16% to 30% and in those over 45 years, from 30% to 51%. Studies in which urinary estrogens and pregnandiol have been measured confirm such observations (*334, 335*). Altered ovulation patterns may therefore contribute only a portion of the decline in fertility prior to the menopause (*331*). The available data refer to populations of North American, Swiss, German and New Zealand women. No comparable data are available for women in developing countries.

There is also prolongation of the duration of postpartum amenorrhoea in older breast-feeding women (*336, 337*). The frequency of intercourse is reduced among older couples in all societies that have been studied and this, of course, has a substantial effect upon the probability of conception (*331*).

Table 13. The proportion of abnormal menstrual cycles during the later years of reproductive life[a]

Döring's series				Vollman's series			
Age (years)	An-ovulatory cycles (%)	Cycles with a short luteal phase (%)	Total abnormal cycles (%)	Approx. age (years)[b]	An-ovulatory cycles (%)	Cycles with a short luteal phase (%)	Total abnormal cycles (%)
31–35	7	9	16	30–34	3	10	13
36–40	3	16	19	35–39	2	9	11
41–45	12	18	30	40–44	4	12	16
46–50	15	36	51	45+	18	12	30

[a] Based on data from R. F. Vollman (*4*) (Tables 35 and 44) and G. K. Döring (*5*) (Table 1).

[b] Age groups are approximate because the original data were tabulated by gynaecological rather than chronological age; the data were retabulated by Gray (*331*).

An additional factor, which could account for the reduction of fertility with age, is the rising incidence of spontaneous abortion among older women. Most of this increase is due to a rise in the frequency of trisomic abnormalities (*338*).

Pregnancy in the older woman entails a greater risk of morbidity and mortality for the mother and fetus and the infant. Obstetrical complications increase with age (*339–342*), as do chromosomal abnormalities and other congenital defects in the fetus (*338, 340–342*). For example, maternal mortality rates in both developed and developing countries among women 35–39 years of age are 2–4 times higher than the rates among women aged 25–29. For those aged 40 years and over, they are 3–5 times higher (Table 14). The contribution of maternal age *per se* and of luteal-phase defects to these problems is not clear. Also, the risk of infant mortality is higher among the offspring of older mothers (*344*).

Although fertility is low during the decade preceding the menopause, the risk of conception is not negligible and the hazards of pregnancy are considerable. The Scientific Group considered, therefore, that from the medical viewpoint fertility control is indicated among sexually active women prior to the menopause.

9.3 Problems of family planning in perimenopausal women

There are two major problems confronting the woman approaching the menopause in her decision with regard to contraception. First, it may be difficult to determine when the menopause has occurred

Table 14. Non-abortion maternal mortality: age-specific rates per 100 000 live births by selected countries with at least 500 000 births during specified periods[a]

Country or area and period	Age groups (years)					
	≤19	20–24	25–29	30–34	35–39	≥40
Chile						
1956–58	158.0	107.7	163.5	279.3	445.5	577.4
1961–63	144.0	102.2	140.5	237.5	556.3	497.2
1966–68	134.6	81.6	104.3	193.8	317.8	456.4
France						
1951–53	42.9	43.2	53.0	73.7	169.8	256.2
1956–58	17.7	21.0	33.5	65.6	114.4	215.5
1961–63	20.9	16.0	21.6	46.2	88.7	144.6
1966–68	13.0	12.5	14.9	31.1	67.9	124.3
1970–72	11.9	9.7	13.7	32.1	50.3	101.9
Germany, Federal Republic of						
1961–63	49.4	39.3	55.0	101.2	178.8	285.2
1966–68	40.2	22.8	33.7	61.4	125.7	235.6
1970–72	30.2	20.7	27.0	47.1	112.4	185.1
Italy						
1956–58	74.9	61.7	77.9	114.9	200.3	339.2
1961–63	54.5	49.6	64.0	100.8	183.1	306.4
1966–68	28.4	40.9	37.8	74.4	130.8	245.6
1970–72	18.8	26.1	29.0	54.0	111.2	183.1
Japan						
1951–53	186.8	111.0	113.7	174.1	315.3	594.3
1956–58	175.2	104.8	114.2	199.2	381.8	709.9
1961–63	117.7	59.7	78.4	151.8	375.6	874.2
1966–68	64.1	42.5	49.6	109.9	260.7	678.8
1970–72	50.2	23.4	31.5	65.9	182.9	487.6
Mexico						
1961–63	204.2	128.4	127.7	196.3	280.2	384.3
1966–68	152.1	90.9	110.6	146.3	239.4	254.0
1970–72	136.0	85.9	100.7	142.6	232.0	246.2
Sri Lanka						
1956–58	338.9	280.7	317.1	377.7	585.2	910.7
1961–63	221.6	209.7	222.0	265.5	397.7	595.4
1966–68	132.9	135.0	156.5	181.6	297.5	481.7
United Kingdom: England and Wales						
1951–53	33.9	35.2	45.3	73.1	132.2	289.0
1956–58	19.5	20.2	30.6	44.5	90.1	220.5
1961–63	10.6	17.0	18.0	31.3	61.8	122.9
1966–68	10.7	10.0	16.3	26.0	43.0	85.8
1970–72	7.8	9.7	9.8	17.1	41.7	64.3
USA						
1951–53	51.7	34.5	45.0	78.0	138.7	269.5
1956–58	23.7	17.0	25.3	47.3	84.8	161.2
1961–63	17.1	14.4	22.0	45.3	75.0	127.3
1966–68	14.9	13.3	17.9	34.9	63.4	117.6
1970–72	13.7	9.2	13.5	25.1	55.2	85.2
Venezuela						
1956–58	130.5	82.7	90.0	141.5	205.1	279.7
1961–63	78.6	48.5	74.3	97.7	162.0	234.2
1966–68	77.8	41.5	67.2	97.5	154.1	215.5

[a] Data taken from C. Tietze (*343*).

and when there is no further need for contraception. Secondly, it may be difficult to decide which contraceptive method is the most appropriate.

The menopause is not an abrupt event. Menstrual cycles become more irregular with age and there is a tendency towards longer intermenstrual intervals during the five years preceding the menopause (*3*, *4*). It is difficult to determine what length of amenorrhoea is indicative of the onset of the menopause, because in some women menstruation may cease abruptly, whereas in others there may be variable lengths of amenorrhea followed by a subsequent menstrual period. For example, in one study (*2*), amenorrhea of 6 months' duration was associated with the menopause in only 52% of women aged 45–49 years and in 70% of women over the age of 53 years. The remaining women (48% and 30%, respectively) had a further menstrual period. Even after amenorrhoea lasting 1 year, approximately 10% of women will have a further period. Some of these periods are associated with ovulatory cycles (*2*).

In view of this variability, it is difficult to predict whether an individual woman is menopausal and it would seem prudent for women to use some form of contraception for at least 12 months after their last menstrual period. The choice of family planning methods for the woman approaching the menopause must take account of the risks associated with pregnancy, as well as the risks in the methods used and the likelihood of these risks. The issue of reversibility in this age group is minor. Each of the major methods of fertility regulation will be considered from these standpoints. If a woman has achieved her desired family size, it may be wise for her or her spouse to adopt sterilization if this is available and acceptable. However, some women may wish to continue the use of interval contraception and the choice of method can be complex because of the need to strike a balance between the acceptability and efficacy of the method and the potential risks to health.

9.4 Considerations with regard to individual methods of family planning in women approaching the menopause

9.4.1 *Hormonal contraceptives*

The Scientific Group considered that the efficacy, acceptability and cost of orally administered steroidal contraceptives are well established; the major issue concerning their use in women approaching

the menopause is their safety. In this regard, the possible associations between oral contraceptive use, cardiovascular disease and breast cancer are of particular significance.

9.4.1.1 *The association of cardiovascular disease with oral contraceptive use.* Studies of the possible relationship between cardiovascular disease (including myocardial infarction, venous thromboembolism, subarachnoid haemorrhage and other strokes) and oral contraceptive use have reported data on women throughout the reproductive age group. In this section, those data relating particularly to women approaching the menopause (i.e., in general, women over the age of 40) have been selected for special consideration. The data on the possible relationship relate predominantly to women in the developed countries.

An association with myocardial infarction in particular was suggested initially by two retrospective case-control studies of patients discharged from hospital or dying as a result of a myocardial infarct (*244, 345, 346*) (Table 15). Neither of these studies was specifically directed at the question of contraception in women approaching the menopause but both provided data on women between 40 and 44 years of age. In the first of these reports (*244*), married women under 45 who had been treated for myocardial infarction during 1968 to 1972 were identified in the discharge records of hospitals in England and Wales. The authors calculated that the risk of hospital admission for myocardial infarction in 40–44-year-old women currently using oral contraceptives was 5.7 times greater than that in nonusers in the same age group. A second study (*345*) calculated that there was a 4.7-fold increase in the risk of death from myocardial infarction in 40–44-year-old women using oral contraceptives, as compared with nonusers. These investigators extended their observations in a subsequent report (*346*) and made a revised risk estimate of 2.8 (95% confidence limits: 1.2–7.2). The dosage of the constituents of the oral contraceptives used by the subjects in the above studies was not reported, although it can be inferred that the doses of estrogen were higher (more than 50 μg ethinyl estradiol or its equivalent daily) than those currently recommended. Reduction in estrogen dose in oral contraceptives has been reported to lower the morbidity and mortality from ischaemic heart disease (*250*), and the morbidity but not the mortality from thromboembolic disease (*347*).

The data from two of the above studies (*244, 345*) have been reanalysed to show that extrapolation of "these excess risks to other

countries or to different segments of the same country can be misleading unless the differences in other risk factors—especially the smoking habits of women—are taken into consideration" (*348*). It was estimated that the relative risk of nonfatal myocardial infarction associated with the use of oral contraceptives was 2 to 1, which is statistically not significant. The relative risk in a particular society was estimated to depend on the proportion of smokers and could vary from 0.9 to 1 up to 11.7 to 1. The effect of age was not clear in this analysis, although the author concluded that the estimated mortality risk for myocardial infarction among oral contraceptive users aged 40–44 years may have been elevated artificially because of some inaccuracy in classifying them as current users. A further analysis of the data (*349*) confirmed the view that among users of oral contraceptives who were under 50 years of age, cigarette smoking was the most important factor in increasing the likelihood of myocardial infarction. The use of oral contraceptives alone, in the absence of other risk factors, had only a small effect on increasing the risks of dying from myocardial infarction, but oral contraceptive users more than 30 years of age who had other risk factors that increased the likelihood of myocardial infarction appeared to have a substantially higher death rate. The author concluded that women who are 40 years of age or older and have any other predisposing factors should not take oral contraceptives. The author estimated that the death rate from myocardial infarction in women without predisposing conditions in the 40–44-year-old age group was 5.1 per 100 000 population, that the relative risk of death for oral contraceptive users was 2.0 (giving an estimated death rate of 10.2 per 100 000 per year), and that the estimated death rate therefore attributable to oral contraceptive use in that age group was 5.1 per 100 000 per year.

A further retrospective study in the USA (*350*) examined women under 46 years of age who had been hospitalized during the first six months of 1975 with a final diagnosis (on discharge) of myocardial infarction. From a total of 954 patients, 26 (of whom 14 were aged 41–45) otherwise apparently healthy and fertile women (i.e., capable of child-bearing) were selected for study, of whom 24 were smokers. The relative risk of myocardial infarction for all age groups among oral contraceptive users was 14 after stratification for age, but the authors stated that the risk of nonfatal myocardial infarction was estimated to be "extremely small" among the nonsmokers. The Scientific Group considered that special care was required in the interpretation of this study in view of the small numbers involved.

Table 15. Retrospective studies of the association between oral contraceptive use and cardiovascular diseases, including myocardial infarction

Investigators, year, and country (reference)	Nature of study	Factors accounted for	No. of cases/ controls	Oral contraceptive users (%) (cases/controls)	Estimated relative risk
Mann et al. (1975) England and Wales (*244*)	Case-control study of survivors of myocardial infarction based on interviews and postal questionnaires; controls selected at random from women discharged from hospital for other illnesses	Age, cigarette smoking, hypertension, diabetes, pre-eclamptic toxaemia, and obesity	63/174	Using oral contraceptives in month before admission 29.3/8.4 ($P<0.001$)	Risk ratio for hospital admission with myocardial infarction, 5.7 (40–44 age group); recalculated for non-smokers, 2.0 (not significant) (*348*)
Mann & Inman (1975) England and Wales (*345*)	Case-control study of women dying from myocardial infarction under age 50; living age-matched controls from same practices	Hypertension, diabetes, obesity, thyroid disease, renal disease, pre-eclamptic toxaemia, social class, parity	145/181	15.4/3.8 (current users)	Risk ratio 4.7 (40–44 years age group) (no smoking data available)
Mann et al. (1976) England and Wales (*346*)	Extension of previous study (*244*) (see above)				2.8 (1.2–7.2)
Jick et al. (1978) USA (*350*)	Retrospective case-control study of survivors of myocardial infarction; controls selected from women discharged with other diagnoses	Birth date, race, marital status, spouse's occupation, parity, weight, height, past medical history, smoking, tea/coffee consumption, family history, menstrual and contraceptive history, drug use	26/59 (apparently healthy pre-menopausal women)	71.4/12.9 (in age group 41–45)	Risk ratio of 14 (5.5–37) for all age groups (27–45 years) after age stratification; risk of non-fatal myocardial infarct estimated to be "extremely small" among non-smokers; 18 out of 26 myocardial infarction subjects were smokers using oral contraceptives, 2 had used oral contraceptives and did not smoke

Shapiro et al. (1979) USA (*351*)	Retrospective case-control study of women with definite myocardial infarction, based on interview; controls from women aged less than 50 from the surgical, orthopaedic and medical services of the same or a nearby hospital	Age, ethnic group, religion, marital status, parity, years of education, geographic area, cigarette smoking, obesity, diabetes, lipid abnormality, hypertension, angina pectoris, pre-eclamptic toxaemia	234/1742	8/2 (for age group 40–44) 6/2 (for age group 45–49)	3.7 (for 40–44 age group) 3.9 (for age group 45–49) Summary risk ratio estimates: no smoking, 4.5 (1.4–14.1); 1–24 cigarettes per day, 1.2 (0.3–4.4); ⩾25 cigarettes per day, 4.3 (2.2–8.2)
Krueger et al. (1980) USA (*352*)	Retrospective study of fatal acute myocardial infarction with two control groups: (1) women who died of causes other than heart disease during the same interval; (2) women hospitalized during the period and surviving hospitalization	Geographic area of index event, age, marital status, population group, medical characteristics, smoking history, parity	163/163 (deceased controls)/ 163 (living controls)	12/10	All subjects, 1.21 (0.63–2.27); 40–44 age group, 1.11 (0.45–2.60) (for this age group in white cases and controls without contraindications to oral contraceptive use, the odds ratio is 7.89 (1.66–36))

Table 16. Prospective studies of the association between oral contraceptive use and cardiovascular diseases, including myocardial infarction

Investigators, year, and country (reference)	Nature of study	Factors accounted for	No. of cases/controls	Mortality rate	Estimated relative risk
Royal College of General Practitioners (1977) United Kingdom (*243*)[a]	Prospective study of oral contraceptive users and controls, based on reports from general practices	Age at entry, parity, social class, cigarette smoking, hypertension	23 000/23 000	From cardiovascular diseases among oral contraceptive users/nonusers: 25.8/5.5	Overall, 4.7; for 1–59 mths of use, 3.4; for >60 mths of use, 9.7; for nonsmokers, risk ratio for death from circulatory disease, 4.7
Vessey et al. (1977) United Kingdom (*353*)	Prospective study of oral contraceptive users and controls, based on family planning clinics	Age, social class, cigarette smoking, obesity, hypertension, pre-eclamptic toxaemia, stroke, rheumatic fever, rheumatic heart disease, congenital heart disease, venous thromboembolism	22 937/16 205 woman-years of observation (oral contraceptive users/IUD users)	Oral contraceptive users: 13.6 Diaphragm or IUD users: 0	No calculation available (two nonsmokers among nine patients dying from cardiovascular disease)
Pettiti et al. (1979) USA (*354*)	Prospective cohort study of women seeking general health check-ups	Age, education, marital status, parity, obesity, cigarette smoking, medical history, estrogen use, oral contraceptive use	16 579 women, 26 cases myocardial infarction	Among current oral contraceptive users: 7.7% (cases), 9.4% (controls)	Risk ratio 0.8 (0.2–2.6) (smoking overwhelmingly the most important risk factor)

[a] See footnote 1 on page 87 for more recent data.

Two other studies in the USA have been reported (*351, 352*). In the first (*351*), the overall risk ratio estimate of acute myocardial infarction for women who had used oral contraceptives in the preceding month was 4.0, with figures of 3.7 for women aged 40–44 years and 3.9 for women aged 45–49 years. In the second (*352*), the excess risk of myocardial infarction (odds ratio 2.1 for subjects under 40 years old and 7.9 for subjects aged 40–44 years) was confined to white women who had no contraindications to the use of oral contraceptives.

Three prospective studies of the association of oral contraceptive use and general disorders of the circulatory system, including myocardial infarction, have also been published (*243, 353, 354*) (Table 16). In the first of these (*243*), the mortality rate in women who had at some time used the pill was increased by 40% as compared with controls, and the overall relative risk was calculated to be 4.7, rising to 9.7 for 60 or more months of oral contraceptive use. In this study smoking appeared to have no influence on the risk associated with oral contraceptives.[1] The excess annual death rate attributable to oral contraceptives, among women who had used them at some time or other, was about 5 per 100 000 for those aged 15–34 years old, but increased to 33 per 100 000 for those aged 35–44 years, and to 143 per 100 000 for those aged 45–49 years. The second study (*353*) reported on 9 deaths (3 of them in women aged 40 years or over) from a variety of cardiovascular causes including mitral valve disease with hypertension, cardiomyopathy, and congenital heart disease among the oral contraceptive entry group which comprised 49 681 woman-years of observation. No calculation of relative risk was available but only 2 of the 9 patients dying from cardiovascular disease were nonsmokers. The third prospective study (*354*) was a cohort study of 16 759 predominantly white, suburban middle-class women in the USA, in whom there was no excess risk of myocardial infarction, regardless of whether the subjects smoked or not. Overwhelm-

[1] Since the meeting of the Scientific Group, the Royal College of General Practitioners has published a more complete analysis on 249 deaths, supplementing the 101 previously reported. In the more recent publication (*355*), the duration of the oral contraceptive used had no effect on mortality risk; the excess annual death rate among women under 35 years old was 1 per 77 000 for nonsmokers and 1 per 10 000 for smokers; among women aged 35–44 years, it was 1 per 6700 women for nonsmokers and 1 per 2000 for smokers; and among women aged 45 years and over, the excess risks were 1 per 2500 and 1 per 500 for nonsmokers and smokers respectively. The authors concluded that it was clear that smoking was the major risk factor.

ingly the most important risk factor (and the only one in women over the age of 45 years, although the numbers were small) for the occurrence of myocardial infarction, subarachnoid haemmorhage, other strokes, and venous thromboembolism was cigarette smoking.

The Scientific Group considered that all these studies are noteworthy for the very small numbers of women approaching the menopause on whom data on the risks of cardiovascular disease, including myocardial infarction, are available. The studies suggest that the major risk factor for myocardial infarction is smoking and that oral contraceptive use *per se* in women with no other risk factors has a relatively small effect on the likelihood of fatal or nonfatal myocardial infarction. These data relate to subjects studied only in the developed countries. In some developing countries, total cardiovascular mortality rates are also relatively high—e.g., for Thailand, in women aged 35–44 years, the rate was 34.9 per 100 000 population, compared with a maternal mortality rate of 16.9 (*207*); any increase attributable to oral contraceptives could thus be of considerable significance in such populations, despite the benefits in terms of reduced maternal mortality. The Group considered that further data are clearly needed to establish whether it is safe for oral contraceptives to be used by this age group, although it recognized clearly that to obtain this information would pose substantial ethical problems, because it is widely believed that oral contraceptives should not generally be used in older women (*356*).

9.4.1.2 *The association of breast cancer with oral contraceptive use.* Another controversial potential risk of oral contraceptive therapy is breast cancer. A WHO Scientific Group (*257*) studied the literature published up to 1977 and concluded that there was no clear evidence from the aggregated data to suggest either an adverse or a beneficial effect of oral contraceptive use on breast cancer risk. They concluded that there was some evidence to suggest that oral contraceptives might increase the risk of breast cancer among certain subgroups of women, and the evidence currently available applied only to relatively short periods of oral contraceptive exposure and a very limited duration of follow-up. They stated that no inference could therefore be drawn about the long-term effects of oral contraceptives on the subsequent risk of breast cancer. The Scientific Group considered three recent reports (*357–359*) (Table 17), all of which suggested an association between oral contraceptive use and breast cancer in women approaching the menopause, in the 40–56-year-old age

Table 17. Recent studies of the association between oral contraceptive use and breast cancer in women approaching the menopause

Investigators, year, and country (reference)	Nature of study	Factors accounted for	Age group and No. of cases and controls	Percentage of those currently using oral contraceptives	Risk ratio estimates
Fasal & Paffenbarger (1975) USA (*357*)	Retrospective case-control, hospital-based study-controls from medical and surgical services	Age, race, religion, education, menopausal status, prior benign breast disease	40–49 years: 348 cases, 336 medical controls, 340 surgical controls	13.8 (cases) 7.4 (medical controls) 10.9 (surgical controls)	2.0 (medical controls) 1.3 (surgical controls)
Vessey et al. (1979) United Kingdom (*358*)	Retrospective hospital based case-control study (controls from medical and surgical services)	Age, parity, social class, age at menarche, age at first birth, menopausal status, smoking habits, history of breast biopsy, family history, breast cancer, gallbladder disease	46–50 years: 115 case-and-control pairs (whole study included age group 16–50 years, with 621 case-and-control pairs)	Whole study: 11.6 (cases), 11.3 (controls)	46–50 years: 2.4 41–45 years: 0.70 All ages: 0.96 (0.7–1.3)
Jick et al. (1980) USA (*359*)	Retrospective case-control study in a consumer-owned cooperative (controls selected from women hospitalized for acute illness or elective surgery)	Age, estrogen use, menstrual history, family history, prior breast disease, education, race, weight, height, parity, age at first pregnancy	46–50 years: 18 cases among nonusers (8247 woman-years), 6 cases among users (688 woman-years) 51–55 years: 6 cases among nonusers (3647 woman-years), 5 cases among users (196 woman-years)	46–55 years: 31 (cases), 5 (controls)	46–50 years: 4.0 (1.8–9.0) 51–55 years: 15.5 (5.2–46)

group. In the first of these studies (*357*), the overall risk ratio estimate for breast cancer (comparing oral contraceptive users and non-users) was 1.1, but in the 40–49-year-old age group a relative risk ratio of 2.0 compared with medical controls and 1.3 compared with surgical controls could be derived from the data in the report. In the second study (*358*), the risk ratio estimate was again somewhat less than 1.0 for current oral contraceptive users, as compared with non-users at all ages below 46 years, but there was an estimate of 2.4 for 115 women aged 46–50 years with breast cancer, although there was an opposite trend in 205 such women aged 41–55 years. In the third study (*359*), the risk ratio estimate for oral contraceptive use was 4.0 (range 1.8–9.0) at ages 46–50 years and 15.5 (range 5.2–46) at ages 51–55 years, but the number of cases in this study was small. The Scientific Group concluded that the data suggested that there may be a relation between oral contraceptive use and breast cancer which is age-dependent. Further studies of larger numbers of subjects are required to establish whether there is indeed an increased risk of breast cancer for oral contraceptive users in the perimenopausal age group in order to allow a more precise evaluation of the risks. In view of the known endocrine factors in the pathogenesis of breast cancer, the possible increased risk for oral contraceptive users may represent the introduction of an additional period of risk for estrogen-related disease (*360*).

9.4.1.3 *Overall morbidity and mortality with oral contraceptive use.* Overall morbidity and particularly mortality figures for oral contraceptive use, as compared with the risks associated with pregnancy and childbirth and legal abortion, are difficult to find in the perimenopausal age group. One recent survey of mortality associated with reversible methods of fertility regulation (*361*) used a computer model which simulated sets of reproductive events occurring during the childbearing years of a hypothetical birth cohort of women under various regimens of fertility control. "The cohort is moved through the reproductive ages in steps of one month, each step representing sequential physiological states of fecundability, pregnancy, and post-gestational non-fecundability under specified assumptions as to contraceptive use and effectiveness until permanent sterility intervenes." Data adapted from this survey for the 40–44-year-old age group are shown in Table 18. The Scientific Group concurred with the authors' conclusions that over the age of 30 years the risk to life, which is almost entirely method-related, increases rapidly for pill-users who

smoke. The mortality risk among oral contraceptive users was higher after the age of 40 than the maternal mortality risk for women not using contraception. With regard to all other methods, the risk remained virtually constant or (in the case of those using barrier methods without abortion) increased moderately but remained far below the level of mortality associated with complications of pregnancy and childbirth without fertility control. At all ages, the lowest level of mortality by far was achieved by a combined regimen of barrier contraception with recourse to early abortion in case of failure. A similar computer model has been used in the developing countries but was noted by the Scientific Group to be totally inappropriate (*362*).

9.4.1.4 *Conclusions.* The Scientific Group concluded that there is adequate evidence that, for women in developed countries approaching the menopause, the currently available hormonal steroid contraceptives present increased risks of morbidity and mortality from cardiovascular, cerebrovascular and thromboembolic disease. The possibility that combined contraceptives containing natural estrogens may not increase such risks to the same degree is worthy of further study (see section 7.2.4). In most developing countries, where the degree of risk from such diseases has not been established, and where the availability of safe therapeutic abortion services is considerably restricted, the place of oral contraception remains to be established and further studies should be done to evaluate the relationship between risks and possible benefits. The Group concluded that further work should also be undertaken to establish the place of progestogens only (as oral, injectable and implantable contraceptives) for women in this age group in different regional and sociocultural settings, particularly as most studies, for example those of pure oral progestins, report no effect on carbohydrate metabolism, and little or no effect on lipid and protein metabolisms (*363*). In fact, they have been shown to produce falls in lipoprotein triglyceride and cholesterol levels (*364*). As noted earlier in the report, the influence of hormonal steroid contraceptives on age at menopause and their effects on the postmenopausal phase of life must be evaluated, as must the optimal time when women in the perimenopausal age group may be advised to discontinue their use of hormonal steroidal contraception.

9.4.2 *Intrauterine devices*

The Scientific Group noted that there is a paucity of data regarding the risks associated with the use of the intrauterine device (IUD) in

women approaching the menopause. The available data are presented in Table 18. The uterine bleeding or spotting, which sometimes occurs with the use of IUDs, may create special problems in the perimenopausal period since it may mask pelvic pathology, particularly uterine

Table 18. Mortality associated with pregnancy and childbirth, induced abortion, oral contraceptives (by smoking status), IUDs and barrier methods in women aged 40–44 years[a]

Pregnancy and childbirth (no controls)	Induced abortion	Oral contraceptives		IUD	Barrier methods only	Barrier methods plus abortion
		Non-smokers	Smokers			
68.2[b]	2.7[d]	17.7[e]	60.9[e]	1.4[e]		
21.6[c]	1.7[c]	Birth-related 0.4[c]	0.4[c]	Birth-related 0.4[c]	Birth-related 4.0[c]	
		Method-related 17.7[c]	60.9[c]	Method-related 1.4[c]		Method-related 0.2[c]

[a] Based on data from Tietze, C. & Lewit, S. (*361*).
[b] Per 100 000 live births.
[c] Per 100 000 women per year.
[d] Per 100 000 first trimester abortions.
[e] Per 100 000 users per year.

malignancy. There has been a single report of difficulty in removing an IUD associated with perimenopausal uterine atrophy (*365*). The use of the IUD in women approaching the menopause has the advantage that it does not interfere with natural cyclical bleeding and therefore enables the woman to know when she has reached her menopause. The Scientific Group again recommended that further data be obtained on the risks associated with IUDs in the perimenopausal age group.

9.4.3 *Barrier methods*

The Scientific Group considered that in the light of reduced fertility in the perimenopausal age group the use of diaphragms with contraceptive creams or condoms may provide a sufficient level of protection against pregnancy for couples to whom abortion in the event of failure of the method is acceptable. The Group noted again that age-specific data on these methods, as used by women approaching the menopause, are lacking.

9.4.4 *Sterilization*

The Scientific Group considered that the technical aspects of sterilization were the same in women approaching the menopause as for younger women. Reversibility is, however, a much smaller problem. The mortality associated with the procedure in a developed country is estimated to increase with age but documentation of precise rates for developed and developing countries is lacking. In developed countries, mortality rates of 10 to 20 per 100 000 sterilizations are sometimes quoted (*362*). In contrast, the mortality associated with male sterilization is practically nil and may offer a couple (where the woman is approaching the menopause) a safer form of family planning. The Scientific Group considered that, although conclusive data are lacking relating to the risk of occurrence of pregnancy, the risks of sterilization in women approaching the menopause may be greater (in relation to the possible benefits) than they are in younger women, although the high mortality associated with pregnancy in women approaching the menopause must also be considered in the risk-benefit analysis. However, the performance of sterilization during a laparotomy (for other indications) does not significantly increase the risk or the cost. The Scientific Group noted that there has been controversy regarding the adverse effects of tubal sterilization on menstrual bleeding and pain (*366*), and that the alternative of hysterectomy (instead of tubal sterilization) might be considered for women in this age group.

9.4.5 *Periodic abstinence*

The Scientific Group considered that fertility-regulating methods that depend on the identification of the fertile period and on sexual abstinence during that time may be utilized by women approaching the menopause in view of their declining fertility. However, there are no currently available reliable data to assess the feasibility or efficacy of such methods in this age group. It is not known whether the symptoms of the fertile period can be identified as readily by perimenopausal women as by those in younger age groups (*367*).

9.4.6 *Summary*

The Scientific Group summarized the situation by noting that the problem of choosing a fertility-regulating method for women

approaching the menopause is complex and must be solved by taking into account the needs of the individual woman together with any risk factors that might be present. The Group considered that further research is clearly needed on the morbidity and mortality associated with various methods of fertility regulation for women approaching the menopause both in developed and in developing countries.

9.4.7 *Recommendations*

The Scientific Group made the following recommendations:

(1) Providing the design can be made ethically acceptable, studies should be performed on women in the age group 45–54 years to monitor the safety, efficacy, complication rates, and acceptability of hormonal contraceptives, including progestogen-only preparations, intrauterine devices, barrier methods, and natural methods of family planning.

(2) Studies should be undertaken to evolve new formulations or schedules of administration of steroidal contraceptives, including the use of natural estrogens, that are acceptable to this age group.

(3) Studies should be undertaken on attitudes towards the needs for family planning, as well as different methods of contraception, in women and couples in the 45–54-year age group in different parts of the world.

10. ESTROGENS AND THE HEALTH CARE MANAGEMENT OF PERIMENOPAUSAL AND POSTMENOPAUSAL WOMEN

In the light of the considerations summarized in sections 1 to 9 of this report, the Scientific Group drew the following overall conclusions regarding estrogen therapy as part of the health care management of peri- and postmenopausal women.

10.1 Identification of health care objectives

The Scientific Group concluded that the peri- and postmenopausal periods of life are part of the normal ageing process which in itself does not require therapeutic intervention, unless associated with a specific disease or disability that can be treated or prevented. The

majority of women, in the world as a whole, should not necessarily anticipate a need for treatment of the spontaneously occurring endocrine changes associated with the decline and loss of reproductive function.

It follows that the Scientific Group did not recognize the health status of women during the peri- or postmenopausal periods as being a simple endocrine-deficiency state which could or should be corrected by attempting to recreate for each woman a premenopausal hormonal environment. Rather, the Group recognized the need for research to determine whether *specific endocrine levels* within the range found during nonreproductive life are predictive of the presence (or likely development) of a disease or disability that can and should be corrected when proper cost-benefit and risk analyses are made.

10.2 Benefits of estrogen therapy

10.2.1 *Short-term symptomatic therapy with estrogens*

The occurrence and recognition of hot flushes as a symptom needing correction or medical attention vary widely, being more common in some sociocultural settings than in others. The Scientific Group accepted the evidence that hot flushes of peri- and postmenopausal women can be ameliorated or abolished by estrogen administration, although the efficacy of short-term estrogen use to improve the sense of wellbeing and sexual function has not yet been established.

The Scientific Group considered that, when symptoms are troublesome to the individual, it is appropriate to use estrogens (provided that the lowest dose required to control symptoms is employed) with or without progestins. Under such circumstances, the patients should be supervised medically and specific contraindications to estrogen therapy should be observed. Since in most cases hot flushes decline in frequency and intensity with time, therapy can usually be of relatively short duration, thus avoiding or reducing the possible risks of cancer, particularly endometrial cancer. If estrogens are given continuously, periodic progestin administration may reduce the incidence of endometrial hyperplasia which is reported to follow unopposed estrogen therapy. The Group recommended that further research is necessary to establish the need for the addition of cyclic progestins to increase the safety or efficacy of such treatment.

10.2.2 *Estrogens, with or without progestins, for preventing or treating disease or disability associated with tissue changes*

Prevention and treatment of osteoporosis are the major indications when considering the long-term use of estrogens. Others include atrophy of the genital or urinary tract (vagina, vulva, portions of the urethra and bladder), for which topical estrogens have been used; because the drug, used even in this way, can be absorbed systemically, this route of administration will not prevent the estrogen from having effects on other tissues. Other deficiency states affecting tissues or organs, e.g., in the development of atherosclerosis and changes in the skin, have not been established as being amenable to treatment or prevention by hormonal use and require further study.

The Scientific Group recognized the ability of estrogens to retard bone loss, as shown by prospective studies, and to decrease the risk of fractures, as indicated by case-control studies. However, the Group did not at present recommend the universal or widespread use of estrogen for the prevention of osteoporosis or fractures for at least two reasons: the fact that loss of bone sufficient to cause fracture affects only 25% or less of the population, and the fact that factors other than estrogens, such as activity, calcium, diet and vitamin D (sunlight), may also be important. The Group considered that treatment may be warranted for individuals at high risk such as women who have been castrated at an early age. The Group recognized that there may be a place for estrogen therapy in established osteoporosis, but this needs additional study to define appropriate age limits and duration of therapy. The Group recommended research into methods for the identification of subjects at risk of fracture, and into the identification of other useful preventive measures which may reduce the need for estrogen therapy. There is also a need for a method of identification of women at highest risk of genital tract atrophy, who can benefit from estrogens.

The use of estrogen for preventive purposes may need to be prolonged. When the benefits are judged to warrant such long-term treatment, as in women with high risks of fracture or some other serious outcome, the magnitude of the risk (e.g., of cancer of the endometrium or breast) in the individual subject must be assessed before a decision regarding treatment is reached. Relevant overall considerations would include the presence or absence of the uterus and the presence or absence of benign breast disease. When the effects of long-term estrogen therapy in coronary artery disease can be quanti-

tated accurately, it is possible that it will become the overriding consideration if the beneficial effect turns out to be important. Such evidence as is available suggests that preventive treatment does not require large estrogen doses. The utility of adding progestins cyclically to protect against cancer is subject to the same considerations as described in section 10.2.1, and no evidence is currently available on the possible benefits of added progestins with regard to the risk of developing breast cancer or atherosclerosis.

10.3 Risks of and contraindications to estrogen use

The Scientific Group accepted that the studies associating estrogen use with the development of endometrial cancer indicate that this must be considered a risk factor, especially when estrogens are used for periods longer than 2–3 years. An increased risk of development of breast cancer with estrogen use has not been established and requires further study as well as special attention because of the high incidence and mortality of this disease.

Estrogens have also been implicated in the growth of existing endometrial and breast cancers, in the precipitation of myocardial infarction, and in causing hypertension, changes in liver function, and thromboembolic problems. These effects have been reported to be variably influenced by estrogen dose, duration of therapy, smoking, genetic susceptibility, concomitant disease and age. In the light of this, a number of contraindications to estrogen therapy have been widely accepted, including the presence of liver disease, existing or recent breast or endometrial cancer, prior thromboembolic episodes or existing cardiovascular disease. Some gynaecological conditions may be confused or exacerbated by exogenous therapy, including fibromyomata, undiagnosed uterine bleeding and breast disease.

The Scientific Group concluded that the existence of risks and contraindications should be widely taught to the public and to health-care providers and that this knowledge should be used in formulating future policies on estrogen use.

10.4 Selection of modalities for therapy

10.4.1 *Type and route of estrogen administration*

A variety of therapeutic estrogen preparations is available; they are frequently described as belonging to the following classes:

(*a*) *Natural estrogens:* these are substances found in various biological fluids; they may be administered in the form found naturally, or in the form of synthetic esters. Examples of natural estrogens include:

estradiol-17β
estrone and its sulfate
estriol

Their synthetic esters include:

estradiol benzoate
estradiol valerate
estradiol undecylate

The term "conjugated estrogens" is applied frequently to a mixture of estrogen conjugates extracted from pregnant mares' urine (principally sodium estrone sulfate, sodium equilin sulfate, sodium equilenin sulfate and sodium 17α-estradiol sulfate). The term is also applied to estrogen conjugates such as piperazine estrone sulfate.

(*b*) *Synthetic estrogens:* these include steroidal estrogens such as ethinylestradiol, mestranol, and quinestrol.

A second class of synthetic estrogens is nonsteroidal, and includes diethylstilbestrol and dienestrol. They differ qualitatively from the steroids only in that they will not permit blastocyst implantation in the ovariectomized progesterone-maintained rat (*368*). A complete list of the estrogen preparations may be found in reference *368*. They may be administered by a variety of routes: oral, intramuscular, percutaneous, by pellet or silastic implant, intravaginal.

From the standpoint of oral therapy, the approximately equivalent dosages of the most commonly used preparations have been estimated (*368*) to be as follows: estradiol valerate 2 mg = conjugated equine estrogens 1.25 mg = piperazine estrone sulfate 1.5 mg = ethinyl estradiol 50 μg. However, the relative potencies of administered estrogens vary somewhat depending on the assay end-point used for comparison. Various end-points have been used, e.g., effects on the human endometrium (*369*), corticosteroid-binding globulin (*370*), gonadotrophin levels (*228, 371*). It has been shown that even for the same estrogen preparation, an individual dose may exert subphysiological, physiological and pharmacological responses at different sites of action (*372*). Such considerations render difficult the comparison of different estrogens, given in different dosages and by different routes of administration, from the point of view of both risk and benefit.

Most but certainly not all studies of estrogen therapy in peri- and postmenopausal women, particularly in the USA, have employed con-

jugated estrogens of which the major component is sodium estrone sulfate. Oral administration of this steroid, and also of estradiol esters, is followed by circulating levels of estrone which are higher than those of estradiol (*373, 374*), as opposed to the situation in normal ovulating women where estradiol levels exceed those of estrone. Various disorders associated with an increased frequency of endometrial cancer, such as obesity, polycystic ovary disease, and ovarian tumours, are associated with greater-than-normal levels of estrone production (*375*). Whether alternative methods of estrogen administration (e.g., vaginal, percutaneous or intramuscular), which can result in circulating hormone levels similar to those seen in the normal cycle (*376*), would result in observations different from those made with other estrogen preparations requires further study.

There is also some evidence that natural conjugated estrogens or natural estrogen esters may differ from synthetic estrogens in their effects on blood clotting factors (*236, 237*) and on serum cholesterol and triglycerides (see section 7.2.4). It has been reported that synthetic estrogens may produce more severe derangements of liver function than natural estrogens (*377*). Such considerations are clearly of importance in the assessment of possible risk factors associated with estrogen use.

The Scientific Group recognized no superiority of benefit or excess risk which can be attributed to a specific estrogen formulation. The Group urged continued research to determine whether specific formulations or routes of administration are preferable for specified objectives. Estrogens taken orally are subject to a greater degree of hepatic and intestinal metabolism than steroids absorbed via the vaginal route, transdermally, by injection or by implantation. Estradiol itself can be preferentially conveyed to the tissues in its original state by these latter routes.

10.4.2 *Use of progestogens*

The use of progestogens to modify estrogen action on target tissues has been mentioned with respect to reduction of the risks of estrogen overstimulation and carcinogenesis in the endometrium. Progestogens have been shown to be effective in amelioration of hot flushes as a substitute for estrogens. More research is needed to discover whether there are progestogen risk factors (e.g., thromboembolic and metabolic problems) similar to those described for the estrogens.

10.4.3 *Use of contraceptive formulations*

The Scientific Group recognized that combined oral contraceptives instead of estrogens alone are used to treat peri- and postmenopausal women, particularly in developing countries, because of their convenience and low cost. There have also been suggestions that combined estrogen-progestin formulations can be used to obtain estrogen effects which may be modified by the protective effects of progestin against endometrial cancer. The Group recognized that when such preparations were used instead of conventional estrogen therapy, unnecessarily high doses of estrogen could be administered, particularly if used for prolonged periods, and could lead to excess risks as described for oral contraceptives. The Group noted reports that the progestins do not reduce the beneficial effects of the estrogens against bone loss (*378*), and may in fact prevent such a loss in their own right (*379, 380*). They may, however, negate the beneficial effects of the estrogens on serum lipids and lipoproteins (*225*). The Group recommended that further study is required on these aspects.

10.5 Screening for high-risk individuals

The Scientific Group noted that the symptoms and tissue changes that occur as a consequence of a decline of ovarian function starting in the perimenopause can be attributed to the reduction in estrogen and perhaps progesterone secretion. If genital atrophy, osteoporosis and other tissue changes are due to estrogen deficiency, then direct or indirect measurement of hormonal levels might identify the subjects at risk. Studies on the inverse relationship of the fasting urinary calcium level (an indirect measure) with serum estrogens (direct measure) as a possible predictor of osteoporosis provide hope that research on such an approach to risk identification may be useful. It is possible that the measurement of estrogen activity by vaginal or urinary cytology or by urinary or serum hormone levels could be used to predict which peri- or postmenopausal women are at increased risk for disease or disability associated with estrogen lack. These procedures might also help to identify subjects with high endogenous estrogen levels who may be at risk of developing breast or endometrial cancer and thus identify those who might benefit from progestins, as has been suggested with regard to exogenously administered estrogen. While the loss of ovarian function is partially offset by peripheral tissue production of estrogens, no such compensating factor has been identified for the loss of progesterone.

11. GENERAL RECOMMENDATIONS

The Scientific Group has made specific recommendations at the end of each section of this report in relation to the topics covered. In addition, the Group made the following general recommendations:

(1) *Health service needs:* at the request of Member Governments, WHO-sponsored research should be undertaken to determine the impact on health service needs of the rapidly increasing numbers of postmenopausal women in developing countries.

(2) *Definition of terms:* uniform terminology should be adopted by health care workers with regard to the menopause.

(3) *Endocrinology:* uniform endocrine standards should be developed which can be applied to the description of peri- and postmenopausal conditions and diseases.

(4) *Age at menopause:* descriptive epidemiological studies of the age at menopause should be performed in a variety of settings, including the developing countries, and the results assessed in terms of the implications for health and family planning services.

(5) *Sociocultural significance of the menopause:* the reasons for the apparent differences between different cultures in their perceptions of the menopause and in the significance of menopausal symptoms should be established.

(6) *Symptoms of the menopause:* appropriate methods of identifying perimenopausal symptoms should be developed for use in different cultural settings.

(7) *Osteoporosis:* a uniform terminology should be applied by health care workers to the description of osteoporosis and methods should be developed for the screening of individuals at risk of development of this disease with a view to its prevention.

(8) *Coronary heart disease in relationship to the menopause:* the possible effects of estrogen deficiency and long-term estrogen therapy on the natural history of atherosclerotic heart disease should be established.

(9) *Breast cancer:* further studies should be done on the possible relationship of long-term oral contraceptive use and estrogen therapy in peri- and postmenopausal women to the development of breast cancer.

(10) *Endometrial cancer:* the place of progestin therapy should be evaluated in relationship to the risks of developing endometrial cancer in peri- and postmenopausal women treated with estrogens.

(11) *Family planning methods:* the safety, efficacy, complication rates and acceptability of different methods of fertility regulation in women approaching the menopause should be established.

(12) *Methods of estrogen and progestin administration:* the optimal regimens, preparations and routes of administration of estrogens and progestins should be established for use in peri- and postmenopausal women.

(13) *WHO's role:* WHO should be requested to promote research to develop widely applicable guidelines for the treatment of perimenopausal symptoms and for the prevention of diseases such as osteoporosis, urogenital atrophy, and possibly atherosclerotic cardiovascular disease (if a link with the menopause is established) in postmenopausal women.

REFERENCES

1. WORLD HEALTH ORGANIZATION. *Sixth report on the world health situation. Part I. Global analysis.* Geneva, 1980.
2. VAN KEEP, P. A. ET AL. ed., *Consensus on menopause research.* Lancaster, MTP Press, 1976.
3. TRELOAR, A.E. ET AL. Variation of the human menstrual cycle through reproductive life. *International journal of fertility,* **12**: 77–126 (1967).
4. VOLLMAN, R. F. *The menstrual cycle.* Philadelphia/London/Toronto, W. B. Saunders & Co., 1977.
5. DÖRING, G. K. The incidence of anovular cycles in women. *Journal of reproduction and fertility,* Supplement **6**, 77–81 (1969).
6. SHERMAN, B. M. ET AL. The menopausal transition: analysis of LH, FSH, estradiol, and progesterone concentrations during menstrual cycles of older women. *Journal of clinical endocrinology and metabolism,* **42**: 629–636 (1976).
7. REYES, F. I. ET AL. Pituitary-ovarian relationships preceding the menopause. I. A cross-sectional study of serum follicle-stimulating hormone, luteinizing hormone, prolactin, estradiol and progesterone levels. *American journal of obstetrics and gynecology,* **129**: 557–564 (1977).
8. VAN LOOK, P. F. A. ET AL. Hypothalamic-pituitary-ovarian function in perimenopausal women. *Clinical endocrinology,* **7**: 13–31 (1977).
9. BAKER, H.W.G. ET AL. Testicular control of follicle-stimulating hormone secretion. *Recent progress in hormone research,* **32**: 429–476 (1976).
10. DE JONG, F.H. & SHARPE, R.M. Evidence for inhibin-like activity in bovine follicular fluid. *Nature,* **263**: 71–72 (1976).
11. YEN, S. S. C. ET AL. Pulsatile patterns of gonadotropin release in subjects with and without ovarian function. *Journal of clinical endocrinology and metabolism,* **34**: 671–675 (1972).
12. WIDE, L. ET AL. Radioimmunosorbent assay of follicle-stimulating hormone and luteinizing hormone in serum and urine from men and women. *Acta endocrinologica, Suppl.* **174** (1973).

13. CHAKRAVARTI, S. ET AL. Hormonal profiles after the menopause. *British medical journal,* **2**: 784–786 (1976).
14. GOLDENBERG, R. L. ET AL. Gonadotropins in women with amenorrhea: use of plasma follicle-stimulating hormone to differentiate women with and without ovarian follicles. *American journal of obstetrics and gynecology,* **116**: 1003–1012 (1973).
15. KORENMAN, S. G. ET AL. Reproductive hormone function: the perimenopausal period and beyond. *Clinics in endocrinology and metabolism,* **7**: 625–643 (1978).
16. SIITERI, P. K. & MACDONALD, P. C. Role of extraglandular estrogen in human endocrinology. In: R. O. Greep & E. B. Astwood, ed., *Handbook of Physiology,* Vol. 2, Part I. Baltimore, Williams & Wilkins, 1973, pp. 615–629.
17. MARSHALL, D. H. ET AL. The relation between plasma androstenedione and estrone levels in untreated and corticosteroid-treated postmenopausal women. *Clinical endocrinology,* **9**: 407–412 (1978).
18. MACDONALD, P. C. Determinants of the rate of estrogen formation in postmenopausal women. *European journal of obstetrics, gynaecology and reproductive biology,* **9**: 187–189 (1979).
19. HEMSELL, D. L. ET AL. Correlation of the extent of conversion of plasma androstenedione to estrone with age. *Journal of clinical endocrinology and metabolism,* **38**: 476–479 (1974).
20. ABRAHAM, G. E. ET AL. Metabolism of testosterone and androstenedione in normal and ovariectomised women. *Journal of clinical investigation,* **48**: 696–703 (1969).
21. LONGCOPE, C. ET AL. Steroid secretion by the postmenopausal ovary. *American journal of obstetrics and gynecology,* **138**: 564–568 (1980).
22. JUDD, H. L. ET AL. Effect of oophorectomy on circulating testosterone and androstenedione levels in patients with endometrial cancer. *American journal of obstetrics and gynecology,* **118**: 793–798 (1974).
23. JUDD, H. L. Hormonal dynamics associated with the menopause. *Clinics in obstetrics and gynecology,* **19**: 775–788 (1976).
24. CRILLY, R. G. ET AL. Effect of age on plasma androstenedione concentration in oophorectomized women. *Clinical endocrinology,* **10**: 199–201 (1979).
25. JUDD, H. L. ET AL. Endocrine function of the postmenopausal ovary: concentration of androgens and estrogens in ovarian and peripheral vein blood. *Journal of clinical endocrinology and metabolism,* **39**: 1020–1024 (1974).
26. ROSENFELD, R. S. ET AL. Twentyfour-hour secretory pattern of dehydroisoandrostrone and dehydroisoandrostrone sulphate. *Journal of clinical endocrinology and metabolism,* **40**: 850–855 (1975).
27. ABRAHAM, G. Ovarian and adrenal contribution to peripheral androgens during the menstrual cycle. *Journal of clinical endocrinology and metabolism,* **39**: 340–346 (1974).
28. JUDD, H. L. & YEN, S. S. C. Serum androstenedione and testosterone levels during the menstrual cycle. *Journal of clinical endocrinology and metabolism,* **36**: 475–481 (1973).
29. GRAY, R. H. The menopause – epidemiological and demographic considerations. In: R. J. Beard, ed., *The menopause.* Lancaster, MTP Press, 1976, pp. 25–40.
30. MCKINLAY, S. ET AL. An investigation of the age at menopause. *Journal of biosocial sciences,* **4**: 161–173 (1972).
31. THOMPSON, B. ET AL. Menopausal age and symptomatology in a general practice. *Journal of biosocial sciences,* **5**: 71–82 (1973).

32. MACMAHON, B. & WORCESTER, J. Age at menopause: United States 1960–62. *US Vital and Health Statistics,* Series II, No. 19 (1966).
33. SCRAGG, R. F. R. Menopause and reproductive span in rural Niugini. In: *Proceedings of the Annual Symposium of the Papua New Guinea Medical Society, Port Moresby,* 1973, pp. 126–144. (The median estimates were calculated on augmented data by Dr J. C. Barrett).
34. HOFMANN, D. & SOERGEL, T. Studies on the age of menarche and the age of menopause. *Geburtshilfe und Frauenheilkunde,* **32**: 969–977 (1972).
35. HAUSER, G. A. ET AL. Der Einfluss des Menarchealters auf das Menopausealter. *Gynaecologia,* **152**: 279–286 (1961).
36. HAUSER, G. A. ET AL. Menarche and menopause in Israel. *Gynaecologia,* **155**: 38–47 (1963).
37. TRELOAR, A. E. Menarche, menopause and intervening fecundability. *Human biology,* **46**: 89–107 (1974).
38. WYON, J. B. ET AL. Differential age at menopause in the rural Punjab, India. *Population index,* **32:** 328 (1966).
39. FINNEY, D. J. *Probit analysis.* 2nd ed. London, Cambridge University Press, 1952.
40. FROMMER, D. J. Changing age of menopause. *British medical journal,* **2**: 349–351 (1964).
41. JASZMANN, L. ET AL. The age at menopause in the Netherlands. *International journal of fertility,* **14**: 106–117 (1969).
42. BURCH, P. R. J. & GUNZ, F. W. The distribution of menopausal age in New Zealand. An exploratory study. *New Zealand medical journal,* **66**: 6–10 (1967).
43. FRERE, G. Mean age at menopause and menarche in South Africa. *South African journal of medical sciences,* **36**: 21–24 (1971).
44. ABRAMSON, J. H. ET AL. Age at menopause of urban Zulu women. *Science,* **132**: 356–357 (1960).
45. BENJAMIN, F. The age of the menarche and of the menopause in white South African women and certain factors influencing these times. *South African medical journal,* **34**: 316–320 (1960).
46. WALSH, J. The age of the menopause of Australian women. *Medical journal of Australia,* **2**: 181–215 (1978).
47. BENGTSSON, C. ET AL. Is the menopausal age rapidly changing? *Maturitas,* **1**: 159–164 (1979).
48. BRAND, P. C. & LEHERT, PH. A new way of looking at environmental variables that may affect the age at menopause. *Maturitas,* **1**: 121–132 (1978).
49. FLINT, M. Cross-cultural factors that affect age at menopause. In: P. A. Van Keep et al., ed., *Consensus on menopause research.* Lancaster, MTP Press, 1976, pp. 73–83.
50. SOBERON, J. ET AL. Relation of parity to age at menopause. *American journal of obstetrics and gynecology,* **96**: 96–100 (1966).
51 LINDQUIST, O. & BENGTSSON, C. The effect of smoking on menopausal age. *Maturitas,* **1**: 191–199 (1979).
52. KAUFMAN, D. W. ET AL. *American journal of public health,* **70**: 420–422 (1980).
53. JACOBS, S. H. & MURRAY, M. A. F. The premature menopause. In: S. Campbell, ed., *The management of the menopause and postmenopausal years.* Lancaster, MTP Press, 1976, pp. 359–368.
54. SELE, V. & STARUP, J. Premature ovarian failure. *Acta obstetrica gynecologica scandinavica,* **50**: 24 (1971).

55. FLINT, M. P. Transcultural influences in perimenopause. In: A. A. Haspels & H. Musaph, ed., *Psychosomatics in perimenopause.* Lancaster, MTP Press, 1979, pp. 41–56.
56. FLINT, M.P. & GARCIA, M. Culture and the climacteric. *Journal of biosocial sciences,* Supplement No. **6**: 197–215 (1979).
57. MAOZ, B. ET AL. The perception of menopause in five ethnic groups in Israel. *Acta obstetrica et gynecologica scandinavica,* Suppl. **65**: 69–76 (1977).
58. VAN KEEP, P. A. & KELLERHALS, J. M. The impact of sociocultural factors on symptom formation. *Psychotherapie Psychosomatik,* **23**: 251–263 (1974).
59. HALLSTRÖM, T. *Mental disorder and sexuality in the climacteric.* Stockholm, Scandinavian University Books, Esselte Studium, 1973.
60. UTIAN, W. H. The true clinical features of postmenopause and oophorectomy, and their response to estrogen therapy. *South African medical journal,* **46**: 732–737 (1972).
61. MOORE, B. ET AL. Experience of a national health service menopause clinic. *Current medical research and opinion,* **3**: 42–56 (1975).
62. JONES, M.M. ET AL. Quantitation of menopausal symptomatology and its response to ethinyl estradiol and piperazine estrone sulphate. *Current medical research and opinion,* **4**: 12–20 (1977).
63. WOOD, C. Menopausal myths. *Medical journal of Australia,* **1**: 496–499 (1979).
64. PRILL, H.-J. Menopause und klimakterische symptome. *Münchner medizinischer Wochenschrift,* **106**: 2246–2251 (1964).
65. JASZMANN, L. ET AL. The perimenopausal symptoms. *Medical gynaecology and sociology,* **4**: 268–277 (1969).
66. MCKINLAY, S. M. & JEFFERYS, M. The menopausal syndrome. *British journal of preventive and social medicine,* **28**: 108–115 (1974).
67. BALLINGER, C.B. Psychiatric morbidity and the menopause; screening of a general population sample. *British medical journal,* **3**: 344–346 (1975).
68. BUNGAY, G. T. ET AL. Study of symptoms in middle life with special reference to the menopause. *British medical journal,* **281**: 181–183 (1980).
69. NEUGARTEN, B.L. & KRAINES, R.J. "Menopausal symptoms" in women of various ages. *Psychosomatic medicine,* **27**: 266–273 (1965).
70. WINOKUR, G. Depression in the menopause. *American journal of psychiatry,* **130**: 92–93 (1973).
71. WEISSMAN, M. M. & KLERMANN, G. L. Sex differences and the epidemiology of depression. *Archives of general psychiatry,* **34**: 98–111 (1977).
72. SHEPHERD, M. ET AL. *Psychiatric illness in general practice.* London, Oxford University Press, 1966.
73. SKEGG, D. C. ET AL. Use of medicine in general practice. *British medical journal,* **1**: 1561–1563 (1977).
74. PFEIFFER, E. ET AL. Sexual behaviour in middle life. *American journal of psychiatry,* **128**: 1262–1267 (1972).
75. HALLSTRÖM, M.T. Sexuality of women in middle age: the Göteborg study. *Journal of biosocial science,* Suppl. No. **6**: 165–175 (1979).
76. JASZMANN, L. J. B. Epidemiology of the climacteric syndrome. In: S. Campbell, ed., *The management of the menopause and postmenopausal years.* Lancaster, MTP Press, 1976, pp. 11–23.
77. BAKKE, J. C. A double-blind study of a progestin-estrogen combination in the management of the menopause. *Pacific medicine and surgery,* **73**: 200–205 (1965).

78. MARTIN, P. L. ET AL. Graded sequential therapy in the menopause: a double-blind study. *American journal of obstetrics and gynecology,* **111**: 178–186 (1971).
79. UTIAN, W. H. The mental tonic effect of estrogens administered to oophorectomized females. *South African medical journal,* **46**: 1079–1082 (1972).
80. GEORGE, G. C. W. ET AL. Effect of exogenous estrogens on minor psychiatric symptoms in postmenopausal women. *South African medical journal,* **47**: 2387–2388 (1973).
81. DAVIDSEN, P. C. B. ET AL. Cyclical therapy with estradiol valerate/norgestrel at the menopause. Report of a double-blind investigation. *Ugeskrift for Laeger,* **136**: 1805–1808 (1974).
82. BULLOCK, J. L. ET AL. Use of medroxy-progesterone acetate to prevent menopausal symptoms. *Obstetrics and gynecology,* **46**: 165–168 (1975).
83. COOPE, J. ET AL. Effects of "natural estrogen" replacement therapy on menopausal symptoms and blood clotting. *British medical journal,* **4**: 139–143 (1975).
84. THOMSON, J. & OSWALD I. Effect of estrogen on the sleep, mood and anxiety of menopausal women. *British medical journal,* **2**: 1317–1319 (1977).
85. CAMPBELL, S. & WHITEHEAD, M. Estrogen therapy and the menopausal syndrome. *Clinics in obstetrics and gynecology,* **4**: 31–47 (1977).
86. DENNERSTEIN, L. ET AL. Hormone replacement therapy and the menopause. *Australia/New Zealand journal of obstetrics and gynaecology,* **18**: 139–143 (1978).
87. DENNERSTEIN, L. ET AL. Menopausal hot flushes: a double-blind comparison of placebo, ethinyl estradiol and norgestrel. *British journal of obstetrics and gynaecology,* **85**: 852–856 (1978).
88. DENNERSTEIN, L. ET AL. Hormone therapy and affect. *Maturitas,* **1**: 247–259 (1979).
89. DENNERSTEIN, L. ET AL. Some clinical effects of estrogen-progestogen therapy in surgically castrated women. *Maturitas,* **2**: 19–28 (1979).
90. DENNERSTEIN, L. ET AL. Hormones and sexuality: the effects of estrogen and progestogen. *Obstetrics and gynecology,* **56**: 316–322 (1981).
91. POLLER, L. ET AL. A double-blind cross-over study of piperazine estrone sulphate and placebo with coagulation studies. *British journal of obstetrics and gynaecology,* **87**: 718–725 (1980).
92. MOLNAR, G. W. Body temperatures during menopausal hot flushes. *Journal of applied physiology,* **38**: 499–503 (1975).
93. STURDEE, D. W. ET AL. Physiological aspects of menopausal hot flush. *British medical journal,* **2**: 79–80 (1979).
94. MELDRUM, D. R. Elevations in skin temperature of the finger as an objective index of postmenopausal hot flushes: standardization of the technique. *American journal of obstetrics and gynecology,* **135**: 713–717 (1979).
95. TATARYN, I. V. ET AL. Postmenopausal hot flushes: a disorder of thermoregulation. *Maturitas,* **2**: 101–107 (1980).
96. TATARYN, I. V. ET AL. LH, FSH and skin temperature during the menopausal hot flush. *Journal of clinical endocrinology and metabolism,* **49**: 152–154 (1979).
97. CASPER, R. F. ET AL. Menopausal flushes: a neuroendocrine link with pulsatile luteinizing hormone secretion. *Science,* **205**: 823–825 (1979).
98. MULLEY, G. ET AL. Hot flushes after hypophysectomy. *British medical journal,* **2**: 1062 (1977).

99. SPOONER, J. B. Classification of side effects to Danazol therapy. *Journal of international medical research,* **5**: 14–17 (1977).
100. DONOSO, A. O. ET AL. Effects of castration on hypothalamic catecholamines. *American journal of physiology,* **212**: 737–739 (1967).
101. FUXE, K. ET AL. Castration, sex hormones and tuberoinfundibular dopamine neurones. *Neuroendocrinology,* **5**: 107–120 (1969).
102. ANTON-TAY, F. & WORTMAN, R. J. Norepinephrine turnover in rat brains after gonadectomy. *Science,* **159**: 1245–1246 (1968).
103. BAPNA, J. ET AL. A method for studying norepinephrine and serotonin metabolism in small regions of the rat brain: effect of ovariectomy on amine metabolism in the anterior and posterior hypothalamus. *Endocrinology,* **89**: 1345–1349 (1971).
104. BEATTIE, C. W. ET AL. Influence of ovariectomy and ovarian steroids on hypothalamic tyrosine hydroxylase activity in the rat. *Endocrinology,* **91**: 276–279 (1972).
105. BRODY, M. J. & KADOWITZ, P. J. Prostaglandins as modulators of the autonomic nervous system. *Federation proceedings,* **33**: 48–60 (1974).
106. CLAYDEN, J. R. ET AL. Menopausal flushing: double-blind trial of a non-hormonal medication. *British medical journal,* **1**: 409–412 (1974).
107. HUTTON, J. D. ET AL. Relation between plasma estrone and estradiol and climacteric symptoms. *Lancet,* **1**: 678–681 (1978).
108. KATO, J. The role of hypothalamic estradiol receptor in the action of clomiphene. *Acta obstetrica gynecologica japonica,* **18**: 29–35 (1971).
109. MOLNAR, G. W. Investigation of hot flushes by ambulatory monitoring. *American journal of physiology,* **237**: R306–310 (1979).
110. CHRISTIE-BROWN, J. R. W. & CHRISTIE-BROWN, M. E. Psychiatric disorders associated with the menopause. In: R. J. Beard, ed., *The menopause.* Lancaster, MTP Press, 1976, pp. 57–80.
111. ROUSE, P. Premenstrual tension: a study using the Moos menstrual questionnaire. *Journal of psychosomatic research,* **22**: 215–225 (1978).
112. COPPEN, A. ET AL. Total and free plasma tryptophan concentration in the plasma of depressive patients. *Lancet,* **2**: 1415–1416 (1972).
113. AYLWARD, M. Estrogens, plasma tryptophan levels in perimenopausal patients. In: S. Campbell, ed., *The management of the menopause and postmenopausal years,* Lancaster, MTP Press, 1976, pp. 135–148.
114. ASHCROFT, G. W. ET AL. 5-Hydroxytryptamine metabolism in affective illnesses: the effect of tryptophan administration. *Psychological medicine,* **3**: 326–332 (1973).
115. PEET, M. ET AL. Plasma tryptophane concentrations in depressive illness and mania. *British journal of psychiatry,* **128**: 255–258 (1976).
116. NISKANEN, P. ET AL. The daily rhythm of plasma tryptophane and tyrosine in depression. *British journal of psychiatry,* **128**: 67–73 (1976).
117. KAPLAN, H. S. *The new sex therapy: active treatment of sexual dysfunctions.* New York, Brunner-Mazel, 1974.
118. KINSEY, A. C. ET AL. *Sexual behaviour in the human female.* Philadelphia, Saunders, 1953.
119. UDRY, A. ET AL. Effect of contraceptive pills on sexual activity in the luteal phase of the human menstrual cycle. *Archives of sexual behaviour,* **2**: 205–214 (1973).

120. BANCROFT, J. Hormones and sexual behaviour. *Psychological medicine,* **7**: 553–556 (1977).
121. STUDD, J. ET AL. The climacteric. *Clinics in obstetrics & gynecology,* **4**: 3–29 (1977).
122. GARDNER, H.L. & KAUFMAN, R.H., ed., Atrophic vulvovaginitis. In: *Benign diseases of the vulva and vagina.* St. Louis, C.V. Mosley, 1969, p. 216.
123. PARMLEY, T.H. & WOODRUFF, J.D. Complete vaginal occlusion in postmenopausal women. *Obstetrics and gynecology,* **46**: 235–238 (1975).
124. CHAKRAVATI, S. ET AL. Relation between plasma hormone profiles, symptoms and response to estrogen treatment in women approaching the menopause. *British medical journal,* **2**: 983–985 (1979).
125. PERSKY, H. ET AL. The relationship of plasma estradiol to sexual behaviour in young women. *Psychosomatic medicine,* **40**: 523–535 (1978).
126. BAUM, M.J. ET AL. Effects of progesterone and estradiol on sexual attractivity of female rhesus monkeys. *Physiology and behaviour,* **18**: 659–670 (1977).
127. PERSKY, H. ET AL. Plasma testosterone level and sexual behaviour of couples. *Archives of sexual behaviour,* **7**: 157–173 (1978).
128. CARNEY, A. ET AL. Combination of hormonal and psychological treatment for female sexual unresponsiveness: a comparative study. *British journal of psychiatry,* **133**: 339–346 (1978).
129. SCHIFF, I. ET AL. Effects of estrogens on sleep and psychological state of hypogonadal women. *Journal of the American Medical Association,* **242**: 2406–2407 (1979).
130. LENCIONI, L.J. Comparative and statistical study of vaginal and urinary sediment smears. *Journal of clinical endocrinology & metabolism,* **13**: 263–270 (1953).
131. SMITH, P. Age changes in female urethra. *British journal of urology,* **44**: 667–676 (1972).
132. BROWN, A.D.G. Postmenopausal urinary problems. *Clinics in obstetrics and gynecology,* **4**: 181–206 (1977).
133. SHAHRAD, P. & MARKS, R. The effects of estrogens on the skin. In: S. Campbell, ed., *The management of the menopause and postmenopausal years,* Lancaster, MTP Press, 1976, pp. 243–251.
134. WEINSTEIN, G.D. ET AL. *In vitro* interconversion of estrone and 17β-estradiol in human skin and vaginal mucosa. *Journal of investigative dermatology,* **51**: 4–10 (1968).
135. RAURAMO, L. Effect of castration and oral estradiol valerate and estriol succinate therapy on the epidermis. In: S. Campbell, ed., *The management of the menopause and postmenopausal years,* Lancaster, MTP Press, 1976, pp. 253–262.
136. KEIRSE, M.J.N.C. Etiology of postmenopausal bleeding. *Postgraduate medical journal,* **49**: 344–348 (1973).
137. BROWN, J.B. ET AL. Preliminary observations on urinary oestrogen excretion in certain gynaecological disorders. *Journal of obstetrics and gynaecology of the British Commonwealth,* **66**: 177–211 (1959).
138. VAN LOOK, P.F.A. Failure of positive feedback. *Clinics in obstetrics and gynecology,* **3**: 555–576 (1976).
139. GAMBRELL, R.D., JR. Postmenopausal bleeding. *Journal of the American Geriatrics Society,* **22**: 337–343 (1974).
140. PROCOPÉ, B.J. Etiology of postmenopausal bleeding. *Acta obstetrica et gynecologica scandinavica,* **50**: 311–313 (1971).

141. GAMBRELL, R. D., JR. Postmenopausal bleeding. *Clinics in obstetrics and gynecology*, **4**: 129–143 (1977).
142. LIN, T.-J. ET AL. Clinical and cytological responses of postmenopausal women to estrogen. *Obstetrics and gynecology*, **41**: 97–107 (1973).
143. WHITEHEAD, M. I. ET AL. The effects of cyclical estrogen therapy and sequential estrogen/progestogen therapy on the endometrium of postmenopausal women. *Acta obstetrica gynaecologica scandinavica*, Suppl. **65**: 91–101 (1977).
144. KISTNER, R. W. The menopause. In: R. M. Caplan & W. J. Sweeney, ed., *Advances in obstetrics and gynaecology*. 1978, pp. 551–566.
145. GAMBRELL, R. D., JR. ET AL. Management of postmenopausal bleeding to prevent endometrial cancer. *Maturitas*, **1**: 99–106 (1978).
146. CAMPBELL, S. ET AL. The modifying effect of progestogen on the response of the postmenopausal endometrium to exogenous estrogens. *Postgraduate medical journal*, **54** (Suppl. 2): 59–64 (1978).
147. STURDEE, D. W. ET AL. Relations between bleeding pattern, endometrial histology and estrogen treatment in menopausal women. *British medical journal*, **1**: 1575–1577 (1978).
148. THOM, M. H. ET AL. Prevention and treatment of endometrial disease in climacteric women receiving estrogen therapy. *Lancet*, **2**: 455–457 (1979).
149. TSENG, L. & GURPIDE, E. Estradiol and 20α-dihydroprogesterone hydrogenase activities in human endometrium during the menstrual cycle. *Endocrinology*, **94**: 419–423 (1974).
150. ALBRIGHT, F. ET AL. Postmenopausal osteoporosis. *Journal of the American Medical Association*, **116**: 2465–2474 (1941).
151. NEWTON-JOHN, H. F. & MORGAN, D. B. Osteoporosis: disease or senescence? *Lancet*, **1**: 232–233 (1968).
152. HORSMAN, A. ET AL. Cortical and trabecular osteoporosis and their relation to fractures in the elderly. In: DeLuca, H. F. et al. ed., *Osteoporosis: recent advances in pathogenesis and treatment*. Baltimore, University Park Press, 1981, pp. 175–184.
153. NORDIN, B. E. C. Osteoporosis and osteopenia. *Clinics in endocrinology & metabolism*, **2**: 155 (1973).
154. HORSMAN, A. Bone mass. In: B. E. C. Nordin, ed., *Calcium, phosphate and magnesium metabolism*. Edinburgh, Churchill Livingstone, 1976.
155. CAMERON, J. R. & SORENSON, J. Measurement of bone mineral *in vivo*. *Science*, **142**: 230–232 (1963).
156. EXNER, G. U. ET AL. Bone densitometry using computer tomography. *British journal of radiology*, **52**: 14–23 (1979).
157. DOYLE, F. Radiologic assessment of endocrine effects on bone. *Radiological clinics in North America*, **5**: 289–302 (1967).
158. ANDERSON, J. B. ET AL. A new technique for the measurement of metacarpal density. *British journal of radiology*, **39**: 443–450 (1966).
159. NELP, W. B. ET AL. Absolute measurement of total body calcium (bone mass) *in vivo*. *Journal of laboratory and clinical medicine*, **79**: 430–438 (1972).
160. SMITH, M. A. & TOTHILL, P. Development of apparatus to measure calcium changes in the forearm and spine by neutron activation analysis using calciformium-252. *Physics in medicine and biology*, **24**: 319 (1979).
161. LINDQUIST, O. ET AL. Age at menopause and its relation to osteoporosis. *Maturitas*, **1**: 175–181 (1979).

162. BARNETT, E. & NORDIN, B. E. C. Radiological assessment of osteoporosis. *Clinical radiology,* **9**: 166–174 (1960).
163. GARN, S. M. *The earlier gain and later loss of cortical bone.* Springfield, Thomas, 1970.
164. SINGH, M. ET AL. Changes in trabecular patterns of the upper end of the femur as an index of osteoporosis. *Journal of bone and joint surgery,* **52A**: 457–467 (1970).
165. AARON, J. Histology and microanatomy of bone. In: B. E. C. Nordin. ed., *Calcium, phosphate and magnesium metabolism,* Edinburgh, Churchill Livingstone, 1980.
166. MEUNIER, P. ET AL. Physiological senile involution and pathological rarefication of bone. Quantitative and comparative histological data. *Clinics in endocrinology and metabolism,* **2**: 239–256 (1973).
167. CRILLY, R. G. ET AL. Rise in plasma alkaline phosphatase at the menopause. *Clinical science,* **58**: 341–342 (1980).
168. CRILLY, R. G. ET AL. Ageing, steroid hormones and bone. *Clinics in endocrinology and metabolism,* **10**: 115–139 (1981).
169. HEANEY, R. P. A unified concept of osteoporosis. *American journal of medicine,* **39**: 877–880 (1965).
170. JASANI, C. ET AL. Spinal osteoporosis and the menopause. *Proceedings of the Royal Society of Medicine,* **58**: 441–444 (1965).
171. HILLYARD, C. J. ET AL. Relative deficiency of plasma calcitonin in normal women. *Lancet,* **1**: 961–962 (1978).
172. HEANEY, R. P. ET AL. Calcium balance and calcium requirements in middle-aged women. *American journal of clinical nutrition,* **30**: 1603–1611 (1977).
173. KNOWELDEN, J. ET AL. Incidence of fractures in persons over 35 years of age. *British journal of preventive and social medicine,* **18**: 130–141 (1964).
174. GARRAWAY, W. M. ET AL. Limb fractures in a defined population 1. Frequency and distribution. *Mayo Clinic proceedings,* **54**: 701–707 (1979).
175. NILSSON, B. O. & WESTLIN, N. E. The bone mineral content in the forearm of women with Colles' fracture. *Acta orthopaedica scandinavica,* **45**: 836–844 (1974).
176. GALLAGHER, J. C. ET AL. The crush fracture syndrome in postmenopausal women. *Clinics in endocrinology and metabolism,* **2**: 293–315 (1973).
177. SAVILLE, P. D. The syndrome of spinal osteoporosis. *Clinics in endocrinology and metabolism,* **2**: 177–185 (1973).
178. GALLAGHER, J. C. ET AL. Intestinal calcium absorption and serum Vitamin D metabolites in normal subjects and osteoporotic patients. *Journal of clinical investigation,* **64**: 729–736 (1979).
179. NORDIN, B. E. C. ET AL. Summation of risk factors in osteoporosis. In: DeLuca, H. F. et al ed., *Osteoporosis: recent advances in pathogenesis and treatment.* Baltimore, University Park Press, 1981, pp. 359–367.
180. NORDIN, B. E. C. ET AL. Calcium requirement and osteoporosis. *Proceedings of Symposium on Nutrition and Ageing, Talloires, France, 26–30 May 1980* (in press).
181. BAKER, M. R. ET AL. Plasma 25-hydroxyvitamin D concentrations in patients with fractures of the femoral neck. *British medical journal,* **1**: 589 (1979).
182. BOLET, A. J. ET AL. Epidemiology of osteoporosis. Sex, race and incidence of hip fractures. *Archives of internal medicine,* **116**: 191–194 (1965).
183. SOLOMON, L. Osteoporosis and fractures of the femoral neck in the South African Bantu. *Journal of bone and joint surgery,* **50B**: 2–13 (1968).

184. EDDY, T. P. Deaths from falls and fractures. *British journal of preventive and social medicine,* **26**: 173 (1972).
185. EDDY, T. P. Deaths from falls and fractures. Comparison of mortality in Scotland and the United States with that in England and Wales. *British journal of preventive and social medicine,* **27**: 247 (1973).
186. PAGANINI-HILL, A. ET AL. Menopausal oestrogen therapy and hip fractures. *Annals of internal medicine,* **95**: 28–31 (1981).
187. FRUMAR, A. M. ET AL. Relationship of fasting urinary calcium to circulating oestrogen and body weight in postmenopausal women. *Journal of clinical endocrinology and metabolism,* **50**: 70–75 (1980).
188. RIGGS, B. L. Hormonal factors in the pathogenesis of postmenopausal osteoporosis. In: U. Barzel, ed., *Osteoporosis II.* New York, Grune & Stratton, 1979, pp. 111–121.
189. HORSMAN, A. ET AL. Prospective trial of oestrogen and calcium in postmenopausal women. *British medical journal,* **2**: 789–792 (1977).
190. LINDSAY, R. ET AL. Prevention of spinal osteoporosis in oophorectomized women. *Lancet,* **2**: 1151–1154 (1980).
191. NACHTIGALL, L. E. ET AL. Estrogen replacement therapy: a 10-year prospective study in the relationship to osteoporosis. *Obstetrics and gynecology,* **53**: 277–281 (1979).
192. RECKER, R. R. ET AL. Effect of estrogens and calcium carbonate on bone loss in postmenopausal women. *Annals of internal medicine,* **87**: 649–655 (1977).
193. CHRISTIANSEN, C. ET AL. Prevention of early postmenopausal bone loss: controlled 2-year study in 315 normal females. *European journal of clinical investigation,* **10**: 273–279 (1980).
194. LINDSAY, R. ET AL. Bone response to termination of oestrogen treatment. *Lancet* **1**: 1325–1327 (1978).
195. HUTCHINSON, T. A. ET AL. Postmenopausal oestrogens protect against fractures of hip and distal radius. *Lancet,* **2**: 705–709 (1979).
196. WEISS, N. S. ET AL. Decreased risk of fractures of the hip and lower forearm with postmenopausal use of oestrogen. *New England journal of medicine,* **303**: 1195–1198 (1980).
197. GORDAN, G. S. ET AL. Antifracture efficiency of long-term estrogens for osteoporosis. *Transactions of the Association of American Physicians,* **86**: 326–331 (1973).
198. MARSHALL, D. H. & NORDIN, B. E. C. The effect of 1α-hydroxyvitamin D_3 with and without oestrogens on calcium balance in postmenopausal women. *Clinical endocrinology,* **7**: 159s–168s (1977).
199. NORDIN, B. E. C. ET AL. Treatment of spinal osteoporosis in postmenopausal women. *British medical journal,* **280**: 451–454 (1980).
200. MILHAUD, G. ET AL. Effet de la thyrocalcitonine de porc sur l'osteoporose humaine. *Comptes rendus de l'Académie des Sciences (Paris),* **268**: 3100 (1969).
201. MEUNIER, P. J. ET AL. Radiological and histological evolution of postmenopausal osteoporosis treated with sodium fluoride-vitamin D-calcium. Preliminary results. In: B. Courvoisier et al., ed., *Fluoride and bone,* Bern, Huber, 1978, pp. 263–276.
202. CHESNUT, C. H. ET AL. Assessment of anabolic steroids and calcitonin in the treatment of osteoporosis. In: U. Barzel, ed., *Osteoporosis,* New York, Grune & Stratton, 1979, pp. 135–150.

203. RINGE, J. D. ET AL. Long-term treatment of primary osteoporosis by sodium fluoride. In: B. Courvoisier et al., ed., *Fluoride and Bone,* Bern, Huber, 1978, pp. 228–232.
204. RIGGS, L. B. ET AL. The fluoride-calcium regimen for primary osteoporosis. In: DeLuca, H. F. et al., ed., *Osteoporosis: recent advances in pathogenesis and treatment.* Baltimore, University Park Press, 1981, pp. 433–439.
205. REEVE, J. ET AL. Anabolic effect of human parathyroid hormone fragment on trabecular bone in involutional osteoporosis: a multicentre trial. *British medical journal,* **280**: 1340–1344 (1980).
206. CRILLY, R. G. ET AL. Postmenopausal and corticosteroid induced osteoporosis. In: *Estrogens in the postmenopause. Frontiers in hormone research,* **5**: 53–75 (1978).
207. WORLD HEALTH ORGANIZATION. *World health statistics annual: Vital statistics and causes of death 1980.* Geneva, 1980.
208. BENGTSSON, C. & LINDQUIST, O. Menopausal effects on risk factors for ischaemic heart disease. *Maturitas,* **1**: 165–170 (1979).
209. HJORTLAND, M. C. ET AL. Some atherogenic concomitants of menopause: the Framingham study. *American journal of epidemiology,* **103**: 304–311 (1976).
210. SHIBATA, H. ET AL. Relationship of relevant factors of atherosclerosis to menopause in Japanese women. *American journal of epidemiology,* **109**: 420–424 (1979).
211. ROBINSON, R. W. ET AL. Increased incidence of coronary heart disease in women castrated prior to the menopause. *Archives of internal medicine,* **104**: 908–913 (1959).
212. OLIVER, M. F. & BOYD, G. S. Effect of bilateral ovariectomy on coronary artery disease and serum lipid levels. *Lancet,* **2**: 690–694 (1959).
213. FURMAN, R. H. Coronary heart disease and the menopause. In: K. J. Ryan & D. C. Gibson, ed., *Menopause and ageing,* (DHEW Publication, No. NIH73–319), 1973 pp. 39–55.
214. PARRISH, H. M., CARR, C. A., HALL, D. G. & KING, T. M. Time interval from castration in premenopausal women to development of excessive coronary atherosclerosis. *American journal of obstetrics and gynecology,* **99**: 155–162 (1967).
215. NOVAK, E. R. & WILLIAMS, T. J. Autopsy comparison of cardiovascular changes in castrated and normal women. *American journal of obstetrics and gynecology,* **80**: 863–872 (1960).
216. RITTERBAND, A.B., JAFFE, I.A., DENSEN, P.M., MAGAGNA, J.F. & REED, E. Gonadal function and the development of coronary heart disease. *Circulation,* **27**: 237–251 (1963).
217. BENGTSSON, C. Ischemic heart disease in women. *Acta medica scandinavica,* Suppl. **549**: 75–81 (1973).
218. GORDON, T. ET AL. Menopause and coronary heart disease. The Framingham Study. *Annals of internal medicine,* **89**: 157–161 (1978).
219. RANDALL, C. L. ET AL. Causes of death in cases of preclimacteric menorrhagia. *American journal of obstetrics and gynecology,* **88**: 880–897 (1964).
220. NOTELOVITZ, M. The effect of long-term estrogen replacement therapy on glucose and lipid metabolism in postmenopausal women. *South African medical journal,* **50**: 2001–2003 (1976).
221. WALLACE, R.B. ET AL. Altered plasma lipid and lipoprotein levels associated with oral contraception and estrogen use. *Lancet,* **2**: 112–115 (1979).

222. BARRETT-CONNOR, E. ET AL. Heart disease risk factors and hormone use in postmenopausal women. *Journal of the American Medical Association,* **241**: 2167–2169 (1979).
223. PATERSON, M. E. L. ET AL. The effect of various regimens of hormone therapy on serum cholesterol and triglyceride concentrations in postmenopausal women. *British journal of obstetrics and gynaecology,* **87**: 552–560 (1980).
224. VARMA, T. R. Effect of estrogens on fasting serum cholesterol and triglyceride levels in postmenopausal women. *International journal of gynaecology and obstetrics,* **17**: 551–555 (1980).
225. BRADLEY, D. D. ET AL. Serum high density lipoprotein cholesterol in women using oral contraceptives, estrogens and progestins. *New England journal of medicine,* **299**: 17–20 (1978).
226. STERN, M.P. ET AL. Cardiovascular risk and use of estrogens or estrogen-progestogen combinations. *Journal of the American Medical Association,* **235**: 811–815 (1976).
227. AITKEN, J.M. ET AL. The effects of oophorectomy and long-term mestranol therapy on the serum lipids of middle-aged women. *Clinical science,* **41**: 597–603 (1971).
228. BOLTON, C. H. ET AL. Comparison of the effects of ethinyl estradiol and conjugated equine estrogens in oophorectomized women. *Clinical endocrinology,* **4**: 131–138 (1975).
229. WALLENTIN, L. & LARSSON-COHN, V. Metabolic and hormonal effects of postmenopausal estrogen replacement. II. Plasma lipids. *Acta endocrinologica,* **86**: 579–607 (1977).
230. GOLDZIEHER, J. W. ET AL. Comparative studies of the ethinyl estrogens used in oral contraceptives. VII. Effects with and without progestational agents on ultracentrifugally fractionated plasma lipoproteins in humans, baboons and beagles. *Fertility and sterility,* **30**: 522–533 (1978).
231. SILFVERSTOLPE, G. ET AL. Lipid metabolic studies in oophorectomized women: effects induced by two different estrogens on serum lipids and lipoproteins. *Gynaecological and obstetric investigation,* **11**: 161–169 (1980).
232. LOEPER, J. ET AL. Influence de l'estrogènothérapie sur les triglicérides. Importance du choix de la molécule et du savoir d'administration. *Nouvelle presse médicale,* **6**: 2747–2750 (1977).
233. TIKKANEN, M. J. ET AL. Treatment of postmenopausal hypercholesterolemia with estradiol. *Acta obstetrica gynaecologica scandinavica,* Suppl. **88**: 83–88 (1979).
234. WALTER, S. & JENSEN, H. K. The effect of treatment with estradiol and estriol on fasting serum cholesterol and triglyceride levels in postmenopausal women. *British journal of obstetrics and gynaecology,* **84**: 869–872 (1977).
235. ISAACS, A. J. & HAVARD, C. W. H. Effect of piperazine estrone sulphate on serum lipids and lipoproteins in menopausal women. *Acta endocrinologica,* **85**: 143–150 (1977).
236. GOW, S. & MACGILLIVRAY, I. Metabolic, hormonal and vascular changes after synthetic estrogen therapy in oophorectomized women. *British medical journal,* **2**: 73–77 (1971).
237. NOTELOVITZ, M. & GREIG, H. B. W. The effect of natural estrogens on coagulation. *South African medical journal,* **49**: 101–104 (1975).
238. VON KAULLA, E. ET AL. Conjugated estrogens in hypercoagulability. *American journal of obstetrics and gynecology,* **122**: 688–692 (1975).

239. STANGEL, J. J. ET AL. The effect of conjugated estrogens on coagulability in menopausal women. *Obstetrics and gynecology,* **49**: 314–316 (1977).
240. GITEL, S. N. & WESSLER, S. Do natural estrogens pose an increased risk of thrombosis in postmenopausal women? *Thrombosis research,* **13**: 279–283 (1978).
241. THE CORONARY DRUG PROJECT RESEARCH GROUP. The coronary drug project: initial findings leading to modifications of its research protocol. *Journal of the American Medical Association,* **214**: 1303–1313 (1970).
242. THE CORONARY DRUG PROJECT RESEARCH GROUP. The coronary drug project: findings leading to discontinuation of the 2.5 mg/day estrogen group. *Journal of the American Medical Association,* **226**: 652–657 (1973).
243. ROYAL COLLEGE OF GENERAL PRACTITIONERS' ORAL CONTRACEPTION STUDY. Mortality among oral contraceptive users. *Lancet,* **2**: 727–731 (1977).
244. MANN, J. I. ET AL. Myocardial infarction in young women with special reference to oral contraceptive practice. *British medical journal,* **2**: 241–245 (1975).
245. JICK, H. ET AL. Myocardial infarction and other vascular diseases in young women. *Journal of the American Medical Association,* **240**: 2548–2552 (1978).
246. ROSENBERG, L. ET AL. Myocardial infarction and estrogen therapy in postmenopausal women. *New England journal of medicine,* **294**: 1256–1259 (1976).
247. PFEFFER, R. J. ET AL. Coronary risk and estrogen use in postmenopausal women. *American journal of epidemiology,* **107**: 479–487 (1978).
248. ROSS, R. K. ET AL. Menopausal estrogen therapy and protection from ischaemic heart disease death. *Lancet,* **1**: 858–862 (1981).
249. ROYAL COLLEGE OF GENERAL PRACTITIONERS' ORAL CONTRACEPTION STUDY. Effect on hypertension and benign breast disease of progestogen component in combined oral contraceptives, *Lancet,* **1**: 624 (1977).
250. MEADE, T. W. ET AL. Progestogens and cardiovascular reactions associated with oral contraceptives and a comparison of the safety of 50 and 30 μg estrogen preparations. *British medical journal,* **1**: 1157–1161 (1980).
251. COPE, E. Physical changes associated with the postmenopausal years. In: S. Campbell, ed., *The management of the menopause and postmenopausal years.* Lancaster, MTP Press, 1976, pp. 29–42.
252. PRILL, H. J. Die Beziehung von Erkrankungen und sozialpsychologischen Fakten zum Klimakterium. *Medizinische Klinik,* **34**: 1325–1328 (1966).
253. DEQUEKER, J. ET AL. Ageing of bone: its relation to osteoporosis and osteoarthrosis in postmenopausal women. In: *Estrogens in the postmenopause. Frontiers in hormone research, Vol. 3,* Basle, Karger, 1975, pp. 116–130.
254. WOOD, P. H. N. Age and the rheumatic diseases. In: P. H. Bennett & P. H. N. Wood, ed., *Population studies of the rheumatic diseases (International Congress Series No. 148).* New York, Excerpta Medica Foundation, 1968, pp. 26–37.
255. LINOS, A. ET AL. The epidemiology of rheumatoid arthritis in Rochester, Minnesota: a study of incidence, prevalence and mortality. *American journal of epidemiology,* **111**: 87–98 (1980).
256. ROYAL COLLEGE OF GENERAL PRACTITIONERS' ORAL CONTRACEPTION STUDY. Reduction in incidence of rheumatoid arthritis associated with oral contraceptives. *Lancet,* **1**: 569–571 (1978).
257. WHO Technical Report Series, No. 619, 1978 *(Steroid contraception and the risk of neoplasia:* report of a WHO Scientific Group).
258. LUCAS, W.E. Causal relationships between endocrine-metabolic variables in patients with endometrial carcinoma. *Obstetrics and gynecology survey,* **29**: 507–528 (1974).

259. SOMMERS, S.C. & MEISSNER, W.A. Endocrinal abnormalities accompanying human endometrial cancer. *Cancer,* **10**: 516–521 (1957).
260. ROSENBLUM, J. M. & HENDRICKS, C. H. Estrogenated vaginal epithelium: relationship to development of carcinoma of endometrium. *Obstetrics and gynecology,* **3**: 535–545 (1954).
261. CUTLER, B. S. ET AL. Endometrial carcinoma after stilbestrol therapy in gonadal dysgenesis. *New England journal of medicine,* **287**: 628–631 (1972).
262. KRISHNAMURTHY, S. ET AL. Endometrial carcinoma following estrogen-progestogen therapy in Turner's syndome: a case report and review of the literature. *Gynecological oncology,* **5**: 291–298 (1977).
263. ELWOOD, J.M. ET AL. Epidemiology of endometrial cancer. *Journal of the National Cancer Institute,* **59**: 1055–1060 (1977).
264. GRODIN, J. M. ET AL. Source of estrogen production in postmenopausal women. *Journal of clinical endocrinology and metabolism,* **36**: 207–214 (1973).
265. GAL, D. ET AL. Endometrial carcinoma in previously ovariectomized patients. *Gynecological oncology,* **8**: 44–48 (1979).
266. LYON, J. L. & GARDNER, J. W. The rising frequency of hysterectomy: its effect on uterine cancer rates. *American journal of epidemiology,* **105**: 439–443 (1977).
267. MEISSNER, W. A. ET AL. Endometrial hyperplasia, endometrial carcinoma and endometriosis produced experimentally by estrogen. *Cancer,* **10**: 500–509 (1957).
268. PAPADAKI, L. ET AL. Hormone replacement therapy in the menopause: a suitable animal model. *Journal of endocrinology,* **83**: 67–77 (1979).
269. ROSENWAKS, Z. ET AL. Endometrial pathology and estrogens. *Obstetrics and gynecology,* **53**: 403–410 (1979).
270. GUSBERG, S. B. & HALL, R. E. Precursors of corpus uteri cancer. III. The appearance of cancer of the endometrium in estrogenically conditioned patients. *Obstetrics and gynecology,* **17**: 397–412 (1961).
271. WEISS, N. S. ET AL. Increasing incidence of endometrial cancer in the United States. *New England journal of medicine,* **294**: 1259–1262 (1976).
272. JENSEN, E. I. ET AL. Clinical studies concerning the relationship of estrogens to the development of cancer of the corpus uteri. *American journal of obstetrics and gynecology,* **67**: 1094–1102 (1954).
273. WYNDER, E. L. ET AL. An epidemiological investigation of cancer of the endometrium. *Cancer,* **19**: 489–520 (1966).
274. DUNN, L. J. & BRADBURY, J. T. Endocrine factors in endometrial carcinoma – a preliminary report. *American journal of obstetrics and gynecology,* **97**: 465–471 (1967).
275. SMITH, D. C. ET AL. Association of exogenous estrogen and endometrial carcinoma. *New England journal of medicine,* **293**: 1164–1167 (1975).
276. ZIEL, H. K. & FINKLE, W. D. Increased risk of endometrial carcinoma among users of conjugated estrogens. *New England journal of medicine,* **293**: 1167–1170 (1975).
277. HOOVER, R. ET AL. Cancer of the uterine corpus after hormonal treatment for breast cancer. *Lancet,* **1**: 885–887 (1976).
278. MACK, T. M. ET AL. Estrogens and endometrial cancer in a retirement community. *New England journal of medicine,* **294**: 1262–1267 (1976).
279. GRAY, L. A. ET AL. Estrogens and endometrial carcinoma. *Obstetrics and gynecology,* **49**: 385–389 (1977).

280. McDONALD, T. W. ET AL. Exogenous estrogen and endometrial carcinoma: case-control and incidence study. *American journal of obstetrics and gynecology,* **127**: 572–580 (1977).
281. GORDON, J. ET AL. Estrogen and endometrial carcinoma. An independent pathology review supporting original risk estimate. *New England journal of medicine,* **297**: 570–571 (1977).
282. WIGLE, D. T. ET AL. Estrogen use and cancer of the uterine corpus in Alberta. *Canadian Medical Association Journal,* **118**: 1276–1278 (1978).
283. HORWITZ, R. I. & FEINSTEIN, A. R. Alternative analytic methods for case control studies of estrogens and endometrial cancer. *New England journal of medicine,* **299**: 1089–1094 (1978).
284. HOOGERLAND, D. L. ET AL. Estrogen use—risk of endometrial carcinoma. *Gynecological oncology,* **6**: 451–458 (1978).
285. VÖLKER, W. ET AL. Östrogentherapie und Endometriumkarzinom. *Geburtshilfe Frauenheilkunde,* **38**: 735–743 (1978).
286. ANTUNES, C. M. F. ET AL. Endometrial cancer and estrogen use. Report of a large case-control study. *New England journal of medicine,* **300**: 9–13 (1979).
287. HAMMOND, C. B. ET AL. Effects of long-term estrogen replacement therapy. II. Neoplasia. *American journal of obstetrics and gynecology,* **133**: 537–547 (1979).
288. JICK, H. ET AL. Replacement estrogens and endometrial cancer. *New England journal of medicine,* **300**: 218—222 (1979).
289. NACHTIGALL, L. E. ET AL. Estrogen replacement therapy. II. A prospective study in the relationship to carcinoma and to cardiovascular and metabolic problems. *Obstetrics and gynecology,* **54**: 74–79 (1979).
290. SALMI, T. Risk factors in endometrial carcinoma with special reference to the use of estrogens. *Acta obstetrica et gynaecologica scandinavica,* Suppl. **86**: (1979).
291. WEISS, N. S. ET AL. Endometrial cancer in relation to patterns of menopausal estrogen use. *Journal of the American Medical Association,* **242**: 261–264 (1979).
292. JELOVSEK, F. R. ET AL. Risk of exogenous estrogen therapy and endometrial cancer. *American journal of obstetrics & gynecology,* **137**: 85–91 (1980).
293. HULKA, B. S. ET AL. Estrogen and endometrial cancer: cases in 2 control groups from North Carolina. *American journal of obstetrics & gynecology,* **137**: 92–101 (1980).
294. SHAPIRO, S. ET AL. Recent and past use of conjugated estrogens in relation to adenocarcinoma of the endometrium. *New England journal of medicine,* **303**: 485–489 (1980).
295. McDONALD, T. W. ET AL. Endometrial cancer associated with feminizing ovarian tumour and polycystic ovarian disease. *Obstetrics and gynecology,* **49**: 654–658 (1977).
296. HUTCHISON, G. B. & ROTHMAN, K. J. Correcting a bias? *New England journal of medicine,* **299**: 1129–1130 (1978).
297. WHITTAKER, P. G. ET AL. Serum equilin, estrone and estradiol levels in postmenopausal women receiving conjugated equine estrogens ('premarin'). *Lancet,* **1**: 14–16 (1980).
298. MARRETT, L. D. ET AL. Recent trends in the incidence and mortality of cancer of the uterine corpus in Connecticut. *Gynecological oncology,* **6**: 183–195 (1978).
299. UNDERWOOD, P. B. ET AL. Endometrial carcinoma: the effect of estrogens. *Gynecological oncology,* **8**: 60–73 (1979).
300. WEISS, N. S. Noncontraceptive estrogens and abnormalities of endometrial proliferation. *Annals of internal medicine,* **88**: 410–412 (1978).

301. COLLINS, J. ET AL. Estrogen use and survival in endometrial cancer. *Lancet,* **2**: 961–964 (1980).
302. KEMPSON, R. L. & POKORNY, G. E. Adenocarcinoma of the endometrium in women aged forty and younger. *Cancer,* **21**: 650–662 (1968).
303. MACMAHON, B. ET AL. Etiology of human breast cancer: a review. *Journal of the National Cancer Institute,* **50**: 21–42 (1973).
304. INTERNATIONAL AGENCY FOR RESEARCH ON CANCER. *Sex hormones (II).* Lyon, 1979 (IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, Vol. 21).
305. GEIST, S. H. ET AL. Are estrogens carcinogenic in the human female? II. Atypical endometrial proliferation in a patient treated with estrogens. *American journal of obstetrics and gynecology,* **42**: 242–248 (1941).
306. GORDAN, G. S. Osteoporosis: diagnosis and treatment. *Texas State journal of medicine,* **57**: 740–747 (1961).
307. LEIS, H. P., JR. Endocrine prophylaxis of breast cancer with cyclic estrogen and progesterone. *International surgery,* **45**: 496–503 (1966).
308. SCHLEYER-SAUNDERS, E. The management of the menopause: a new approach. *Medical press,* **244**: 337–346 (1960).
309. WALLACH, S. & HENNEMAN, P. G. Prolonged estrogen therapy in postmenopausal women. *Journal of the American Medical Association,* **171**: 1637–1642 (1959).
310. WILSON, R. A. The roles of estrogen and progesterone in breast and genital cancer. *Journal of the American Medical Association,* **182**: 327–331 (1962).
311. POTOCKI, J. ET AL. [Reduction of incidence of carcinoma of breast and endometrial carcinoma in menopausal women treated with estrogens] (in Polish), *Ginekologia Polska,* **48**: 901–904 (1977).
312. BIBBO, M. ET AL. A twenty-year year follow-up study of women exposed to diethylstilbestrol during pregnancy. *New England journal of medicine,* **298**: 763–767 (1978).
313. BURCH, J. C. ET AL. The effects of long-term estrogen administration in women following hysterectomy. In: C. P. A. Van Keep & C. Lauritsen, ed., *Estrogens in the postmenopause. Frontiers in hormone research.* Basel, Karger, 1975, pp. 208–214.
314. HOOVER, R. ET AL. Menopausal estrogens and breast cancer. *New England journal of medicine,* **295**: 401–405 (1976).
315. PAFFENBARGER, R. S., JR. ET AL. Cancer risk as related to use of oral contraceptives during fertile years. *Cancer,* **39**: 1887–1891 (1977).
316. BOSTON COLLABORATIVE DRUG SURVEILLANCE POGRAM. Surgically confirmed gallbladder disease, venous thromboembolism disease, and breast tumours in relation to postmenopausal estrogen therapy. *New England journal of medicine,* **290**: 15–18 (1974).
317. CRAIG, T. J. ET AL. Epidemiologic comparison of breast cancer patients with early and late onset of malignancy and general population controls. *Journal of the National Cancer Institute,* **53**: 1577–1581 (1974).
318. MACK, T. M. ET AL. Reserpine and breast cancer in a retirement community. *New England journal of medicine,* **292**: 1366–1371 (1975).
319. CASAGRANDE, J. ET AL. Exogenous estrogens and breast cancer in women with natural menopause. *Journal of the National Cancer Institute,* **56**: 839–841 (1976).
320. SARTWELL, P. E. ET AL. Exogenous hormones, reproductive history, and breast cancer. *Journal of the National Cancer Institute,* **59**: 1589–1592 (1977).

321. BRINTON, L. A. ET AL. Breast cancer risk factors among screening-programme participants. *Journal of the National Cancer Institute,* **62**: 37–43 (1979).
322. RAVNIHAR, B. ET AL. An epidemiologic study of breast cancer and benign breast neoplasias in relation to the oral contraceptive and estrogen use. *European journal of cancer,* **15**: 395–405 (1979).
323. ROSS, R. K. ET AL. A case-control study of menopausal estrogen therapy and breast cancer. *Journal of the American Medical Association,* **243**: 1635–1639 (1980).
324. JICK, H. ET AL. Replacement estrogens and breast cancer. *American journal of epidemiology,* **112**: 586–594 (1981).
325. BRINTON, L. A. ET AL. Menopausal estrogen use and risk of breast cancer. *Cancer,* **47**: 2517–2522 (1981).
326. HOOVER, R. ET AL. Conjugated estrogens and breast cancer risk in women. *Journal of the National Cancer Institute,* **67**: 815–820 (1981).
327. KELSEY, J. L. ET AL. Exogenous estrogens and other factors in the epidemiology of breast cancer. *Journal of the National Cancer Institute* (in press).
328. HONORÉ, L. H. Increased incidence of symptomatic cholesterol cholelithiasis in perimenopausal women receiving estrogen replacement therapy. A retrospective study. *Journal of reproductive medicine,* **25**: 187–190 (1980).
329. HAMMOND, C. B. ET AL. Effects of long-term estrogen replacement therapy. I. Metabolic effects. *American journal of obstetrics and gynecology,* **133**: 525–536 (1979).
330. BENNION, L. J. & GRUNDY, S. M. Risk factors for the development of cholelithiasis in man. *New England journal of medicine,* **299**: 1221–1227 (1978).
331. GRAY, R. H. Biological and social interactions in the determination of late fertility. *Journal of biosocial science, Supplement* **6**: 97–115 (1979).
332. LERIDON, H. Patterns of fertility at later ages of reproduction. *Journal of biosocial science,* Supplement **6**: 59–70 (1979).
333. PITTENGER, D. B. An exponential model of female sterility. *Demography,* **10**: 113–121 (1973).
334. METCALF, M. G. Incidence of ovulatory cycles in women approaching the menopause. *Journal of biosocial science,* **11**: 39–48 (1979).
335. METCALF, M. G. ET AL. Pituitary-ovarian function in normal women during the menopausal transition. *Journal of endocrinology,* **87**: 19p–20p (1980).
336. JAIN, A. K. ET AL. Demographic aspects of lactation and postpartum amenorrhea. *Demography,* **7**: 255–271 (1970).
337. CHEN, L. C. ET AL. A prospective study of birth interval dynamics in rural Bangladesh. *Population studies,* **28**: 277–298 (1974).
338. ROBERTS, D. F. Genetics and ageing in man. *Journal of biosocial science,* Supplement **6**: 177–188 (1979).
339. NORMAN, D. Parental age as a factor in pregnancy outcome and child development. *Reports on population/family planning,* **16**: 1–51 (1974).
340. MINOGUE, M. Childbearing at 45 and over. *Journal of the Irish Medical Association,* **69**: 625–628 (1976).
341. KAJANOJA, P. & WIDHOLM, O. Pregnancy and delivery in women aged 40 and over. *Obstetrics and gynecology,* **51**: 47–51 (1978).
342. KUSHNER, D. H. Fertility in women after age 45. *International journal of fertility,* **24**: 289–290 (1979).
343. TIETZE, C. Maternal mortality excluding abortion mortality. *World health statistics report,* **30**: 312–339 (1977).

344. OMRAN, A. R. ET AL. *Family formation patterns and health.* Geneva, World Health Organization, 1977.
345. MANN, J. I. & INMAN, W. H. W. Oral contraception—death from myocardial infarct. *British medical journal,* **2**: 245–248 (1975).
346. MANN, J. I. ET AL. Oral contraceptive use in older women and fatal myocardial infarction. *British medical journal,* **2**: 445–447 (1976).
347. BÖTTIGER, L. E. ET AL. Oral contraceptives and thrombo-embolic disease: effects of lowering estrogen content. *Lancet,* **1**: 1097–1101 (1980).
348. JAIN, A. K. Cigarette smoking, the use of oral contraceptives, and myocardial infarction. *American journal of obstetrics and gynecology,* **126**: 301–307 (1976).
349. ORY, H. W. Association between oral contraceptives and myocardial infarction. A review. *Journal of the American Medical Association,* **237**: 2619–2622 (1977).
350. JICK, H. ET AL. Oral contraceptives and non-fatal myocardial infarction. *Journal of the American Medical Association,* **239**: 1403–1406 (1978).
351. SHAPIRO, S. ET AL. Oral contraceptive use in relation to myocardial infarction. *Lancet,* **1**: 743–747 (1979).
352. KRUEGER, D. E. ET AL. Fatal myocardial infarction and the role of oral contraceptives. *American journal of epidemiology,* **111**: 655–674 (1980).
353. VESSEY, M. P. ET AL. Mortality among women participating in the Oxford/Family Planning Association contraceptive study. *Lancet,* **2**: 731–733 (1977).
354. PETITTI, D. B. ET AL. Risk of vascular disease in women. Smoking, oral contraceptives, noncontraceptive estrogens and other factors. *Journal of the American Medical Association,* **242**: 1150–1154 (1979).
355. ROYAL COLLEGE OF GENERAL PRACTITIONERS' ORAL CONTRACEPTION STUDY. Further analyses of mortality in oral contraceptive users. *Lancet,* **1**: 541–546 (1981).
356. HENNEKENS, C. H. & MACMAHON, B. Oral contraceptives and myocardial infarction. *New England journal of medicine,* **296**: 1166–1167 (1977).
357. FASAL, E. & PAFFENBARGER, R. S., JR. Oral contraceptives as related to cancer and benign lesions of the breast. *Journal of the National Cancer Institute,* **55**: 767–773 (1975).
358. VESSEY, M. P. ET AL. An epidemiological study of oral contraceptives and breast cancer. *British medical journal,* **1**: 1757–1760 (1979).
359. JICK, H. ET AL. Oral contraceptives and breast cancer. *American journal of epidemiology,* **112**: 577–585 (1981).
360. MOOLGAVKAR, S. H. ET AL. Two-stage model for carcinogenesis: epidemiology of breast cancer in females. *Journal of the National Cancer Institute,* **65**: 559–569 (1980).
361. TIETZE, C. & LEWIT, S. Mortality associated with reversible methods of fertility regulation. In: L. G. Keith, ed., *The safety of fertility control.* New York, Springer Publishing Co. Inc., 1980, pp. 42–48.
362. SCIARRA, J. J. ET AL. *Risks, benefits and controversies in fertility control.* New York, Harper and Rowe, 1977, pp. 28–54.
363. JOHNS HOPKINS UNIVERSITY, POPULATION INFORMATION POGRAM. *Population Reports. Oral Contraceptives.* Series A, No. 3. Baltimore, 1975, pp. A 61–62.
364. GOWLAND, E. & JONES, R. A. The effect of oral norethisterone on serum lipid levels in premenopausal women. *Journal of obstetrics and gynaecology of the British Commonwealth,* **80**: 357–359 (1973).
365. GOLDBERG, M. F. & ALBEE, R. B. Difficult removal of an IUD associated with perimenopausal uterine atrophy. *Fertility and sterility,* **30**: 478–479 (1978).

366. Editorial. Late complications of female sterilization. *Lancet,* **1**: 573–574 (1976).
367. WHO TASK FORCE ON THE DETERMINATION OF THE FERTILE PERIOD. A prospective multicentre trial of the ovulation method of natural family planning. I. The teaching phase. *Fertility and sterility* **36**: 152–158 (1981).
368. BROTHERTON, J. *Sex hormone pharmacology.* London, Academic Press, 1976.
369. BROSENS, I. A. & PIJNENBORG, R. Comparative study of the estrogenic effect of ethinyl estradiol and mestranol on the endometrium. *Contraception,* **14**: 679–685 (1976).
370. MOORE, D. E. ET AL. An *in vivo* system in man for quantitation of estrogenicity. *American journal of obstetrics and gynecology,* **130**: 482–486 (1978).
371. GOLDZIEHER, J. W. ET AL. Comparative studies of the ethinyl estrogens used in oral contraceptives. The effects on plasma gonadotropins. *American journal of obstetrics and gynecology,* **122**: 625–636 (1975).
372. GEOLA, F. L. ET AL. Biological effects of various doses of conjugated equine estrogens in postmenopausal women. *Journal of clinical endocrinology and metabolism,* **51**: 620–625 (1980).
373. YEN, S. S. C. ET AL. Circulating estradiol, estrone and the gonadotropin levels following the administration of orally active 17-beta-estradiol in postmenopausal women. *Journal of clinical endocrinology and metabolism,* **40**: 518–521 (1975).
374. ENGLUND D.E. & JOHANSSON, E.D.B. Pharmacokinetic and pharmacodynamic studies on estradiol valerianate administered orally to postmenopausal women. *Acta obstetrica gynaecologica scandinavica,* Suppl. **65**: 27–31 (1977).
375. SIITERI, P. K. Steroid hormones and endometrial cancer. *Cancer research,* **38**: 4360–4366 (1978).
376. RIGG, L. A., HERMANN, H. & YEN, S. S. C. Absorption of estrogens from vaginal creams. *New England journal of medicine,* **298**: 195–197 (1978).
377. JEPPSON, S. & RANNEVIK, G. Effect of 17β-estradiol on the liver in women with intrahepatic cholestasis (hepatosis) during previous pregnancy. *British journal of obstetrics and gynaecology,* **83**: 567–571 (1976).
378. CRILLY, R. G. ET AL. The effect of oestradiol valerate and cyclic oestradiol valerate/DL-norgestrel on calcium metabolism. *Postgraduate medical journal,* **54**: 47–49 (1978).
379. NORDIN, B. E. C. ET AL. A placebo-controlled trial of ethinyl oestradiol and norethisterone in climacteric women. *Maturitas,* **2**: 247–251 (1980).
380. GALLAGHER, J. C. & NORDIN, B. E. C. Effects of oestrogen and progestogen therapy on calcium metabolism in postmenopausal women. In: *Estrogens in the postmenopause. Frontiers in hormone research,* Vol. 3. Basle, Karger, 1975, pp. 150–176.
381. ROSENBERG, L. ET AL. Early menopause and the risk of myocardial infarction. *American journal of obstetrics and gynecology,* **139**: 47–51 (1981).
382. PIKE, M. C. ET AL. Oral contraceptive use and early abortion as risk factors for breast cancer in young women. *British journal of cancer,* **43**: 72–76 (1981).
383. HASSELQUIST, M.B. ET AL. Isolation and characterization of the estrogen receptors in human skin. *Journal of clinical endocrinology and metabolism,* **50**: 76–82 (1980).