WHO Drug Information

*WHO Drug Information* provides an overview of topics relating to drug development and regulation that are of current relevance and importance, and will include the lists of proposed and recommended International Nonproprietary Names for Pharmaceutical Substances (INN). Its contents reflect, but do not present, WHO policies and activities and they embrace socio-economic as well as technical matters.

The objective is to bring issues that are of primary concern to drug regulators and pharmaceutical manufacturers to the attention of a wide audience of health professionals and policy-makers concerned with the rational use of drugs. In effect, the journal seeks to relate regulatory activity to therapeutic practice. It also aims to provide an open forum for debate. Invited contributions will portray a variety of viewpoints on matters of general policy with the aim of stimulating discussion not only in these columns but wherever relevant decisions on this subject have to be taken.

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WHO Drug Information

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General Policy Topics

When are generic drugs interchangeable?

Whether it is primarily a function of government or of professional self-discipline to constrain prescribing costs is a political issue. Many national drug regulatory authorities are required, in their licensing function, to confine their attention to matters of quality, safety and efficacy. Others are empowered also to consider, as a condition of registration, whether products meet a perceived medical need. Nonetheless, public expenditure on drugs is everywhere identified as an important and potentially negotiable element in the overall cost of public health services. Increasingly, governments reveal a determination to reduce drug costs, not only through direct price controls and selective registration but also through selective reimbursement of prescription costs, compulsory generic registration, or promotion of generic prescribing and dispensing. The dilemma that emerges for all governments is to reduce public expenditure on drugs as far as is practicable without eroding the standards of the health services they provide and yet assuring a socially productive investment in new drug development.

Generic drugs

One consequence of this quest for economy in the public sector in recent years has been a marked expansion in copyist or generic manufacturing which has sharpened competition in the provision of products no longer protected by patent. Thus, in the United States of America it has been accelerated by the 1984 Drug Price Competition and Patent Term Restoration Act, while in Bangladesh it was one of the prime targets of the 1982 Drug Act. The advent of large numbers of generic (or multisource) products presents a challenge for drug regulators, for nominally equivalent generic products cannot simply be assumed to be therapeutically equivalent. They contain the same amount of the same therapeutically active ingredients in the same dosage form and they should meet existing compendial standards. They may differ, however, in colour, shape and flavour, in the identity of other ingredients and also, because of differences in manufacturing techniques and quality controls, in more subtle respects, including stability and bioavailability. Regulatory authorities consequently need to consider not only the quality, efficacy and safety of generic products but also their interchangeability both one with another and with the original innovative product.

Regulatory controls

The rigour with which national regulatory authorities interpret and apply the test of interchangeability differs even among the most highly developed countries. As a matter of policy, the US Food and Drug Administration requires that each generic product must satisfy three sets of criteria of therapeutic equivalence. These relate to:

• manufacturing and quality controls,
• product characteristics and labelling, and
• bioequivalence.

Other highly evolved authorities share a concern to apply the first two of these criteria, which also determine the basic parameters of quality, but many adopt a relatively pragmatic approach to the need for experimental demonstration of bioequivalence and some require only comparative in vitro dissolution data.

Manufacturing and quality controls

The quality of a pharmaceutical product cannot be adequately controlled solely by pharmacopoeial analyses of samples of the finished dosage form. Rigorous standards of manufacture need to be maintained if consistent purity, stability and bioavailability are to assured. It is a basic tenet of
drug regulation that these standards should be codified by regulation and enforced by inspection, and that they should touch upon every aspect of the manufacturing process from the design and maintenance of the premises, including facilities for sanitation and hygiene, to the provisions made for in-process quality control.

Product characteristics and labelling

Product interchangeability demands comparability not only in the dosage form, but also in the instructions for its use, and even in the packaging specifications when these are critical to stability and shelf-life. By common usage the concept of interchangeability relates to therapeutic performance rather than to safety. Historically, however, serious consequences have arisen from the inclusion of inadmissibly toxic excipients in products. Although contemporary standards of manufacture and control now virtually exclude such tragedies, recalls of defective batches of products already in circulation remain commonplace wherever rigorous standards of inspection are applied, and more recently introduced products are still occasionally withdrawn from use as a result of unacceptable toxicity in innovative excipients. These substances are by no means always physiologically inert. Indeed, many patients have become sensitized to excipients that remain in widespread use. Tartrazine, sulfites, lactose, lanolin, monosodium glutamate, ethylenediamine, parabens and chlorocresol are among the compounds most commonly cited. Their continued availability has given rise to cogent appeals that the full composition of each finished pharmaceutical product should be declared on the label.

Bioequivalence

Chemical equivalence does not necessarily imply bioequivalence — or comparability of bioavailability, which is an expression of the rate and extent of absorption of a drug from a dosage form. A finished solid dosage form is thus not simply a conveniently packaged therapeutic substance, but a delivery system, sometimes of considerable sophistication. Variations in excipients or physical characteristics may lead — intentionally or unintentionally — to therapeutically significant changes in bioavailability. At present these changes can be reliably estimated, for the most part, only in human volunteers from the time curve of the drug's concentration in the systemic circulation or its excretion in the urine. But, because individuals differ in their handling of drugs rigorous assurance of the bioequivalence of comparable products has to be established on a statistical basis on comparable groups of subjects under carefully controlled conditions.

Determination of the bioavailability of a dosage form is a costly undertaking that is demanding of human resources. It is clearly not a cost-effective requirement for highly water-soluble substances when neither precise dosage nor consistency of response is a critical consideration. The US Food and Drug Administration consequently does not invariably require results of bioavailability studies as a condition of registration of a generic product and most other regulatory authorities retain a considerable measure of discretionary judgement on the circumstances in which such testing may be waived.

Imported products

In many developing countries now creating local manufacturing capacity, in vivo bioavailability testing remains an impractically costly proposition and this constraint should be considered in the choice of drugs to be produced. However, precisely the same concerns arise in connexion with imported products. Unless assurance can be provided that a product has been manufactured in accordance with internationally defined standards and that it has been subjected to the full assessment required for marketing authorization in the country of origin, uncertainty about quality and interchangeability will remain. The recourse, for authorities of importing countries, is to obtain the necessary assurances from the competent authority in the country of export. This can be done within the context of the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce, which will be the subject of a forthcoming contribution to this Journal.
Points of View

International exchange of information

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Exchange of information on the scientific properties and clinical use of drugs provides the foundation for sound delivery of health care. The new WHO Drug Information makes an important contribution to this endeavour. Through this and similar media, and also through the informal channels of communication it has fostered among governmental officials, the World Health Organization enables the United States Food and Drug Administration to learn much about the experience of other countries in regulating marketed drugs. Information on approvals, new uses, safety concerns and revision of labelling are all of interest to regulatory authorities and of direct benefit to patients. Utilizing WHO messages as an "alert", the FDA is able to obtain any further details it may require from relevant authorities.

WHO has long produced, not only in its Drug Information bulletin (the predecessor to this journal) but also in its drug information circulars and its monthly mailings to drug regulatory authorities, excellent vehicles for reliable exchange of information between Member States. The service has embraced not only regulatory decisions but a wide range of related matters including, notably, training opportunities at international level for regulatory officials. The new and expanded format of WHO Drug Information is to be welcomed as a means of providing comprehensive coverage of such issues. One of the keys to WHO's success over the years in obtaining, collating and disseminating technical information needed by regulatory authorities has been the designation of a named person — a drug information officer — within each country to serve as a contact point with WHO Headquarters in Geneva for receiving and transmitting information on pharmaceuticals and to ensure, when appropriate, that incoming information is disseminated nationally to health professionals and others with a need to know.

This network of individuals has also been of direct value to the FDA which has used it both for communicating urgent messages concerning matters of safety such as drug recalls, warnings and market withdrawals and for sending important mailings to other regulatory authorities to update them on current FDA activities. Its existence has also been used to advantage in our cooperative activities with other organizations. Thus, the American Medical Association (AMA), and the US Pharmacopeia (USP) have collaborated with the FDA in distributing the AMA's "Drug Evaluations" and the "USP Dispensing Information" to regulatory authorities worldwide. The Pharmaceutical Manufacturers' Association and the Proprietary Association have also used the facility to send complimentary copies of the "Physician's Desk Reference" and the "PDR for Non-prescription Drugs", to the same destinations. The many letters and comments we have received provide ample assurance that these standard reference materials have immediate utility in other countries.

Many non-governmental organizations, including bodies representative of health care professionals, and teaching and other academic institutions, share with regulatory authorities and pharmaceutical manufacturers a concern for drug-related issues. I would personally like to see such organizations, institutions and, indeed, their individual members taking a more active interest in the educational aspects of drug use and particularly in the dissemination of relevant information at the country level. I hope that physicians, nurses, and pharmacists can be persuaded to participate more fully in these activities and that publications like WHO Drug Information, that aim to provide a wide-ranging overview of topics and literature of contemporary relevance will help to stimulate their interest.
The Conference of Experts on the Rational Use of Drugs held in Nairobi, Kenya, in November 1985 laid the foundation for WHO's Revised Drug Strategy which was subsequently adopted by consensus at the 1986 World Health Assembly. The Strategy seeks to help countries assume their national responsibilities in drug control through effective information-sharing rather than by conferring a supranational role on WHO. In doing so, it provides a set of principles and goals for the future, and recognizes the appropriate roles in rational drug use that can be played by various sectors of society including governments, industry, health professionals and representative organizations, patient and consumer groups, universities and the media. WHO is cast in a particularly important role and, in producing *WHO Drug Information*, it has taken an important step toward assuring that the Organization is, and will continue to be, an important source of information and insight that is of substantial value to public health worldwide.
Reports on Individual Drugs

Hepatitis B vaccines

Immunological and epidemiological study of viral hepatitis has greatly extended knowledge of this group of infections over the past decade. At least four etiologically distinct forms are now recognized. Among the causative agents more recently documented, the group of hepatitis non-A, non-B viruses is now recognized not only as being widespread and responsible in some areas for many sporadic cases of acute hepatitis in adults; it is also an important cause of post-transfusion hepatitis wherever identifiable carriers of hepatitis B have been eliminated from the donor pool (1-5). Delta virus has also attracted attention, particularly in South America, since it appears to be a cause of acute fulminant hepatitis notably among individuals who are carriers of hepatitis B (6-8).

Most disquieting of all, however, is the scale of the public health problem caused by hepatitis B. Data from highly developed countries, where first infections typically occur in young adults and are often severe, suggest that the prevalence of infection is increasing year by year (9, 10).

In developing countries infection occurs earlier, during the first years of life, and in large areas of Eastern Asia, Africa (11-13) and South America (14,15) it is virtually inevitable. In these circumstances, the initial infection is characteristically subclinical, but as many as 20% of the infected children subsequently become chronic carriers of the disease.

At a conservative estimate, there are more than 200 million persistent carriers of hepatitis B in the world (16), all of whom are at greatly increased risk of developing chronic active hepatitis, cirrhosis, and ultimately hepatocellular carcinoma (17-19). Globally, this is one of the ten most common types of cancer. In some areas of Asia and sub-Saharan Africa it is the most highly prevalent malignant condition and a frequent cause of death in young adult men (20).

Plasma-derived products

The chronic carrier state, once established, is currently irreversible because viral DNA becomes integrated into the liver cells of the host (21, 22). Pre-exposure immunization thus offers the only feasible prospect of control. The first subunit vaccine (Hepatovax® or H-B Vax®; Merck, Sharp & Dohme), which is obtained from the plasma of human carriers of the hepatitis B surface antigen, was introduced commercially in 1982. More recently, in an effort to attain self-sufficiency, several developing countries have also begun to manufacture plasma-derived vaccines and in 1985 WHO issued detailed requirements as an aid to assuring the quality of such products (23). It is notable that China aims to produce 38 million doses annually by 1990 (6) but, if global requirements are to be met from such sources, potential manufacturing capacity will need to be substantially increased.

Some 4.4 million doses of the plasma-derived products have now been distributed in the United States alone for use in high risk groups. On the basis of this and other experience it is estimated that a full course of immunization induces an effective antibody response in over 90% of healthy young adults. Despite progressively declining levels of antibody, this provides substantial protection against infection for at least five years (24). Early concerns regarding the safety of the product, and particularly the risk of transmission of human immunodeficiency virus and other infectious agents potentially present in the donated plasma, have now been effectively dispelled (25). None the less, despite the proven cost-benefit of preventive immunization (16), acceptance of the vaccine remains disappointing among health professionals, one of the priority target groups for protection. Moreover, the incidence of hepatitis B in the United States continues to rise because those at greatest risk — homosexual men and parenteral drug abusers — have not been effectively reached (26).
Yeast-derived products

With a view to increasing the scale of manufacture, reducing unit costs, and eliminating unfounded concerns regarding transfer of infectious viral DNA or free viral particles, several attempts have been made in recent years to derive hepatitis vaccines from other source materials (27). These have now resulted in the marketing of two genetically engineered vaccines (Recombivax H®, Merck, Sharp & Dohme and Engerix B®, Smith, Kline & French). Both are derived from yeast cells into which a plasmid containing the gene for hepatitis B surface antigen has been inserted (28). The immunogenicity of the resultant purified vaccines has been shown to be comparable to that of the plasma-derived preparation both in intensity and duration (29-31).

Prospects for mass immunization

There are encouraging signs that the newer products will shortly become available at prices considerably less than the existing plasma-derived vaccine. If, as seems likely, several other companies seek to register competing products during 1988 prices will probably be driven down further. This will be of immediate advantage to developed countries where immunization strategy is focused on small, well-defined groups of adults at relatively high risk of infection. The hope is more distant that, by scaling up production, manufacturers will ultimately be able to reduce costs to a level that will enable developing countries to meet their objective of protecting all children from hepatitis B infection throughout the period that the chronic carrier state is most likely to develop.

In technical terms, this already seems feasible. The fetus is protected throughout pregnancy by the integrity of the placental barrier. At birth, however, the infant risks immediate infection with hepatitis B from carriers within the family. In Eastern Asia mother-child transmission is highly prevalent, the greatest risk being presented by mothers with detectable levels of both surface antigen (HBsAg) and core antigen (HBeAg) in their plasma (32). In Africa, where hepatitis B e antigen is less prevalent, infections are typically acquired in infancy or early childhood from a wider circle of carriers (9). In both circumstances immunization at birth offers a tangible prospect of protection because the immunogenic response of newborn infants to hepatitis B vaccine is singularly brisk. Over 90% of newborns develop antibodies by six months of age in response to two 5 µg doses (30) and studies of infants born to HBsAg- and HBeAg-positive mothers has raised expectation that both the plasma-derived and yeast-derived vaccines (5 µg in each of three doses administered at birth, one month and six months), given together with hepatitis B immunoglobulin (0.5 ml at birth), can protect 80-90% of infants from becoming chronic carriers (33, 34). Preliminary evidence, which requires further confirmation, also suggests that protection against clinically significant infection persists for 5 years or more in infants vaccinated between 6 months and 2 years of age (35).

An undeniable a priori case thus exists for implementing neonatal vaccination programmes at the earliest possible opportunity wherever the carrier state is common. However, a need also exists, before mass immunization campaigns are widely implemented, for large-scale studies that will address some of the residual uncertainties and explore the logistic problems involved (16). More needs to be known, in particular, about the need for boosting immunity later in childhood and beyond to protect against the risk of clinical hepatitis. Studies must also be planned that will leave no doubt about the extent to which vaccination now will be effective in reducing the incidence of hepatocellular carcinoma in years to come. Such investigations are ambitious and complex undertakings. But every effort must be made to generate this vital information as and when hepatitis B immunization is introduced into the routine neonatal care services of the countries where it is most needed.

References


General Information

Informed consent — the drug information dilemma

Canada — Ideally, all patients — and particularly those with chronic conditions — should be offered a full explanation of the purpose and potential problems of the drugs they receive. Well-written drug information leaflets, it is anticipated, would provide the answer to many communication problems between doctors and patients. However, it is conceded that undue emphasis is readily accorded to potential adverse effects with the result that the patient may become frightened and non-compliant. Doctors will need to remain aware that excessive zeal in warning of unpleasant or potentially dangerous unwanted effects can lead to rejection by patients of essential treatment and that printed handouts may complement, but cannot replace the advice of a sympathetic and understanding doctor.


West African Pharmaceutical Federation meeting

The theme of the 6th General Assembly of the West African Pharmaceutical Federation, held in Fajara, The Gambia, from 3rd to 9th May, 1987 was “Drug Management and Control”.

The President of the Federation, Mr Nicholas Palmer, pointed out that, whereas more than US$ 40 per capita is spent annually on pharmaceuticals in developed countries, some countries in the African region are spending less than one hundredth of this amount. In some cases, they will be buying less in 1987 than in 1980.

Dr. P. O. Emofo, Director of Pharmaceutical Services in the Federal Ministry of Health, Lagos, Nigeria, advised developing countries which lack the necessary manpower and infrastructure for effective quality control of imported pharmaceuticals to use the Certification Scheme and the information services developed by WHO in order to avoid importing substandard and counterfeit medicines. He claimed that WHO’s services could be more effectively utilized and that governmental agencies should have greater influence over the selection of imported drugs, even when supply of pharmaceutical products is effected through the private sector. Only in this way can trade become focused on products in the National Drug Formulary and the Essential Drugs List. For Dr. Emofo it is “a sad reflection on pharmaceutical practice that, while professional scientists carry out research in the interest of the health of mankind, the marketing of the products of research is in the hands of non-health professionals who regard drugs as mere commercial commodities”. The 6th Scientific Session of the Federation will be held in Freetown, Sierra Leone, in February 1988, while the next General Assembly will be held in Nigeria in February 1989.


Scalp lotions in baldness

Two pharmaceutical manufacturers are seeking to develop the market potential of potent, systemically active compounds by developing topical formulations for an entirely different and cosmetically oriented indication — the treatment of male pattern baldness (alopecia androgenetica).

Minoxidil scalp lotion (Regaine®, Upjohn) is already available in Canada and has recently been approved in several other countries. Because it is a potent hypotensive agent, monitoring of patients with heart conditions is recommended. An article in the Lancet reviews published data on the efficacy, safety, and cost of minoxidil in the treatment of male baldness. The authors conclude that topical
application of minoxidil can, indeed, sometimes induce hair growth in men with androgenic alopecia. However, a cosmetically satisfactory result is achieved in only some 10% of users and this persists only for as long as treatment is maintained. The authors anticipate that, despite these unimpressive results, licensing of the product will result in a great demand for it. They advocate the inclusion on the labelling of precise information on who is likely to benefit and to what extent.

The prostaglandin E$_2$ analog viprostol is being investigated for the same indication by Cyanamid International. It is a potent vasodilator and this probably accounts for its effect in restoring hair growth. The company is also investigating the efficacy of the same gel formulation in treating Raynaud’s syndrome and erectile impotence.

References

Benefits and risks of lowering high blood pressure

United Kingdom — The traditional view, based on actuarial data, is that — within physiological limits — the lower the blood pressure the better the prospect of survival. The extent to which this correlation applies when moderately raised blood pressure is lowered therapeutically is less certain. In a study published in the Lancet (1) involving 902 patients who received the 81-selective $\beta$-blocker atenolol for up to 10 years, 91 died within this period: 40 from myocardial infarction, 21 from stroke, and 30 from other causes.

After reviewing the literature and analysing their own data the authors conclude that, in all age groups, lowering diastolic blood pressure (phase V) to below 85 mm is likely to increase rather than reduce the risk of death from myocardial infarction. They do not exclude the possibility that the low diastolic blood pressure is merely a reflection of impaired left ventricular function with its poor prognosis, but they favour the possibility that the effect is due to impaired coronary perfusion of an ischaemic heart.

A leading article in a subsequent issue of the Lancet (2) contests this explanation, given that the same relationship was not evident for stroke. It suggests, instead, that the negative inotropic effect of $\beta$-blocking agents or the metabolic actions of diuretics may outweigh the beneficial effects of these drugs in mild hypertension.

Despite that possibility, however, it advises doctors that any change in the approach to treatment of hypertension would be premature for as long as these findings remain unconfirmed in large prospective studies.

References

World malaria situation

Malaria continues to confront many governments with a major public health problem. About 100 million clinical cases are estimated to occur each year, and over 400 million people live in areas where the disease remains endemic but where effective control of transmission remains impracticable.

The evolution of disease also continues to be influenced by the resistance of vectors to insecticides and of parasites to drugs. Many anopheline species are now resistant to more than one insecticide and resistance of Plasmodium falciparum to chloroquine has now been detected in more than 50 countries. However, chloroquine can still be effective even where a measure of resistance exists, particularly in communities with a high level of acquired immunity.

Stability problems in tablet and capsule manufacturing

United States of America — According to a report recently released by the Food and Drug Administration on standards of tablet and capsule formulation in the United States, smaller firms with annual sales of less than US$ 1 million experience greater difficulties in complying with required manufacturing practices than larger firms. Stability problems were most commonly cited, but the small companies were at greatest disadvantage in the control of components, containers and closures. Over half the companies studied required further regulatory follow-up.


Prescription-only medicines (POM) list amendments

United Kingdom — A new amendment allows certain topical hydrocortisone and sustained release ibuprofen preparations to be sold without prescription. The amending order also tightens control on podophyllin resin, which is now exempted from prescription control only if the concentration in the final formulation of ointments and impregnating plasters does not exceed 2 per cent. Benzodiazepines and other substances that have recently been scheduled as Controlled Drugs because of their abuse potential have been deleted from the list of prescription-only medicines since their new status automatically subjects them to prescription control.


Plasma substitutes

United Kingdom — A recent issue of the Drug and Therapeutics Bulletin carries a short review of commercially developed colloidal solutions used as plasma substitutes to support the circulation in hypovolaemic shock, either when blood is not needed or before it is available.

- **Dextran 70** with a relative molecular mass of 35,200 remains widely used. Its colloid osmotic pressure of 268 mm H₂O is lower than that of other plasma substitutes and its half-life is about 12 hours. Its main disadvantage is that infusion of large volumes inhibits platelet aggregation, renders fibrin more susceptible to fibrinolytic enzymes, and reduces the activity of factor VIII complex. It interferes with blood cross-matching and occasionally induces anaphylactoid reactions, some of which are serious.

- **Gelatin**-based solutions which include:
  - Succinylated gelatin, Gelofusine® (Consolidated Chemicals).
  - Polygeline, Haemaccel® (Hoechst).

Both preparations have higher colloid osmotic pressures and shorter half-lives. Neither preparation affects bleeding time or coagulation factors, except through dilution, but, like dextran 70, both occasionally induce anaphylactoid reactions.

- **Hetastarch**, a 6% solution of hydroxyethyl starch in 0.9% saline (Hespan®, Du Pont) has a particle size and colloid osmotic pressure similar to that of 5% albumin solution. The smaller molecules are rapidly eliminated by glomerular filtration within 24 hours but larger polymers can only be eliminated by glomerular filtration once they have been hydrolysed by plasma α-amylase. As a result, the effective half-life of the product is considerably longer than that of other plasma substitutes, and has been estimated to be about 17 days. Moreover, 30% of the infused dose is taken up by the reticuloendothelial system, mostly in the liver and spleen, and the possible clinical implications of this remain uncertain. As far as is known, hetastarch has no effect on clotting mechanisms, but it shares with other plasma substitutes the slight risk of inducing anaphylactoid reactions.

It is concluded that dextran 70 is not suitable as a plasma substitute when a large volume is needed.
Gelatin preparations are recommended in these circumstances since they do not affect haemostasis and their short half-life allows blood or plasma to be given subsequently without risk of fluid overload. It is acknowledged that in other situations the exceptionally long half-life of hetastarch can be advantageous, but it is emphasized that it is expensive and infusions over 1500 ml are best avoided until their safety has been further assessed.


Yellow fever epidemic

Nigeria — A second serious epidemic of yellow fever, which is thought to have been transmitted by urban Aedes aegypti has been notified from Northern Nigeria and is reported to have caused more than 200 deaths. The National Yellow Fever Task Force has responded by formulating a plan of immunization which, in the first phase, will involve vaccinating 1.4 million people in the affected and high-risk areas and some 3.5 million people living in neighbouring areas. As a result of these outbreaks, plans are now in hand to include yellow fever vaccination within WHO's Expanded Programme on Immunization.


Time to drop cyanocobalamin?

Australia — Since April 1987, cyanocobalamin has no longer qualified for reimbursement under the Pharmaceutical Benefits Scheme. A large proportion of injected cyanocobalamin is excreted in the urine within 24 hours and this proportion increases as a function of the dose. Hydroxocobalamin is better retained and regular three-monthly injections have maintained normal haematopoiesis and normal serum vitamin B_{12} levels in patients with deficiency states for many years.

Treatment is effective in all types of deficiency which can result from pernicious anaemia, gastric or ileal resection, or inadequate intake, as in Asian lactovegetarians and food faddists. It is also effective in some types of neuro-ophthalmological disorder, particularly tobacco amblyopia. It is emphasized, however, that there is no justification for its use as a tonic or in the treatment of multiple sclerosis, for which it is sometimes recommended.


More over-the-counter drugs expected in Japan

Japan — During the Eighth General Assembly of the World Federation of Proprietary Medicines Manufacturers, held in September 1986, Mr Shinji Nitta, President of the Proprietary Association of Japan, predicted that the OTC drug market in Japan, after being stagnant for decades, is now poised to expand dramatically. The government, he claimed, perceives promotion of self-medication as a means of assuring better use of existing resources. Mr Nitta emphasized that, as a corollary to the introduction of more effective OTC drugs, manufacturers and suppliers must be prepared to expend greater efforts in providing consumers with the information that contemporary society demands. Discussions are already in hand with the authorities concerned with a view to drawing up guidelines both for manufacturers and suppliers in anticipation of the "switch" to OTC drug development.


Assessment of barbiturates

The WHO Expert Committee on Drug Dependence met in Geneva in April 1986 to review 31 barbiturates at the request of the United Nations Commission on Narcotic Drugs. Its recommendations regarding the control of these substances under the Convention on Psychotropic Substances adopted in 1971 have now been published.
It is proposed that five additional substances be brought within the ambit of the Convention: allobarbital (Schedule IV), butalbital (Schedule III), butobarbital (Schedule IV), secbutabarbital (Schedule IV), vinylbital (Schedule IV).

The Committee recommended against scheduling the remaining 26 short-acting substances: aprobarbital, benzobarbital, butallylonal, buthalital sodium, cyclopentobarbital, difebarbamate, febarbamate, heptabarb, hexethal, hexobarbital, mephebarbital, metharbital, methyllumal, methohexitol sodium, nealbarbital, phenallymal, prazitone, probarbital sodium, propallylonal, proxibarbal, talbutal, thialbarbital, thiamylal sodium, thiobutabarbital, thiopental sodium, vinbarbital.

The Committee was informed that, as result of inclusion of phenobarbital in Schedule IV, problems had arisen in a number of developing countries over its use in the treatment of epilepsy. Phenobarbital is of particular importance to many developing countries because it is an effective, cheap and long-established anticonvulsant and it is included in the WHO model list of essential drugs. The Committee recommended further investigation of the implications that scheduling may have for its availability.


Drug-induced cutaneous reactions

United States of America — A survey has been undertaken by the Boston Collaborative Drug Surveillance Program of suspected drug-induced cutaneous reactions in hospitalized patients. Among 15,438 inpatients admitted consecutively to a hospital service between 1975 and 1982 2.2%, or 347, developed an allergic cutaneous reaction before discharge. Three quarters of these reactions were attributed to antibiotics, blood products and inhaled mucolytics. The highest reaction rates were reported with amoxicillin (51.4 reactions per 1000 patients), sulfamethoxazole/trimethoprim (33.8/1000), and ampicillin (33.2/1000).


Cholinergic drug in Alzheimer's disease

United States of America — Encouraging results have been reported in 14 patients with Alzheimer's disease after treatment for three weeks with tacrine (tetrahydroaminoacridine), a centrally active anticholinesterase. Following treatment, all patients showed significant improvement in tests of orientation and memory and twelve patients are continuing to take the drug in a long-term study.

Tacrine has formerly been used intravenously as a respiratory and central nervous system stimulant, and as an antagonist to tubocurarine and other nondepolarizing muscle relaxants.

ASEAN Reference Substances

In 1980 a collaborative project was launched among the six ASEAN countries to establish reference substances for use in pharmaceutical analysis. The aim was to make them available to the national drug control laboratories within the group at the lowest possible cost. Twenty-six substances have now been established and at the 5th Meeting on the project, which was held in Bangkok in October 1986 to review progress in establishing other substances assigned to each country, a proposal to set up a regional training centre was tabled by Thailand.


Stability of medicines at room temperature

A recent article in the Pharmaceutical Journal proposes a simple aid for assessing whether or not products which should have been refrigerated, but which have been stored for a significant period of time at room temperature, are still suitable for use. It suggests that the labelling of all such products should provide information on their stability within a defined range of storage temperatures and it offers recommendations on how this information could be clearly presented in a standardized format.


Drugs for the elderly: underestimated costs?

United States of America — The burgeoning costs of health care, including those of pharmaceutical products, are arousing debate in the United States, as in other countries. During Congressional hearings on a proposed government-financed drug plan for the elderly, Mr Robert Allnutt, Executive Vice-President of the Pharmaceutical Manufacturers Association, expressed concerns that the eventual cost of the scheme could readily be underestimated. This would lead inevitably, in the industry’s view, to proposals for cost-containment measures that would restrict therapeutic choice, diminish quality of care and discourage the investment needed for innovative research. This, in turn, would deny those in need of the benefits intended for them. He questioned whether reliable data existed to define the number of elderly people in the United States who are deprived on financial grounds from obtaining the medicines they need.


Influenza vaccine composition for 1987-88

United States of America — In consonance with the prevailing WHO recommendations, the Public Health Service recommends that influenza vaccines for use in the 1987-1988 season be trivalent and contain the following antigens:

- A/Taiwan/1/86(H1N1)-like antigen
- B/Ann Arbor/1/86-like antigen
- A/Leningrad/360/86(H3N2)-like antigen.


Chloroquine-resistant Plasmodium falciparum now present in West Africa

Single cases of chloroquine-resistant Plasmodium falciparum malaria have recently been reported for the first time from Benin and Nigeria. In the latter instance the parasite was assayed by the 48-hour in vitro test of Nguyen-Dinh & Trager and found to be sensitive to chloroquine only at a concentration
The patient responded promptly to treatment with quinine (650 mg three times daily for 3 days) and tetracycline (250 mg four times daily for 7 days).

The first case of chloroquine-resistant *Plasmodium falciparum* in Africa was reported from Tanzania in 1979. Subsequently, resistance spread through the East and Central regions of the continent and, in 1985, it was reported as far west as Cameroon. These reports have serious public health implications since malaria transmission is intense in West Africa. Any reduction in the efficacy of chloroquine, the most widely used antimalarial drug, would affect 80-100 million people living in Nigeria alone. Previous experience leaves no doubt that chloroquine-resistance can extend rapidly after its first appearance in a geographic region. An urgent need has arisen for the efficacy of chloroquine to be systematically monitored by all health care personnel in West Africa.


**Computerized drug information accessible to consumers**

**United States of America** — The United States Pharmacopeia Drug Information (USP DI®) is now available on-line from a computerized database. Free standing kiosks designated as Pharmacy Information Centers (PIC™) enable consumers to interrogate the data-base directly. These will be installed wherever they are likely to be used intensively, particularly within or near the prescription counter of pharmacies and in doctors' offices. A touch screen terminal allows the consumer to call up information on approximately 300 different USP DI leaflet abstracts that cover more than 95% of the products prescribed in ambulatory care. Drugs are cross-referenced by brand and generic names. Although the text is brief enough to be read a printed copy can also be generated. The system has been developed by Medical Strategies, Inc. and enquiries should be addressed to the United States Pharmacopeial Convention, Inc.


Predicting biological activity of molecules by computer models

**United States of America** — The "Computer Automated Structure Evaluator" or CASE has been developed to explore and to predict possible structure/function correlations among biologically active compounds and it is presented as a potential alternative to using animals for toxicity testing. The computer is first primed with the structures and known biological properties of an extensive set of reference molecules. From these, structural features can be identified that seem to contribute to a specific biological characteristic such as carcinogenicity. To evaluate a molecule of unknown activity, the computer breaks it into overlapping linear fragments of up to 12 atoms in length. It then searches for those compounds within its data base that contain each of these fragments, noting whether the molecule is active or not. Although the system does not have regard to the broader spatial and electrical configurations of the compound, it is claimed that it can, for instance, rate the carcinogenicity of an unknown drug and that it has already been used to determine the structural basis for the biological activity of known mutagens, carcinogens, pesticides and antibiotics.


Potential teratogenicity of megadoses of vitamin A

**United States of America** — Basing their argument on five case reports T. H. Shepard and others suggest in a letter to *Teratology* that a public statement should be issued warning that megadoses of vitamin A — which is the reduced
form of retinoic acid — may be teratogenic in man. These case reports describe defects that have been demonstrated in monkeys and human fetuses exposed to retinoic acid. The smallest dose of vitamin A suspected of generating these defects is 25,000 units per day (equivalent to about 7.5 mg of retinoic acid).


Information to the public on the correct use of drugs

Italy — A small illustrated folder entitled ABC of Drugs has been published in Italian by the National Health Service in collaboration with the Federation of Pharmacists with a view to educating the public on the safe and effective use of medicines. The brochure is available free of charge from all pharmacies in Italy and the same material has been prepared in the form of a video cassette which will be shown on the national television network.


Nedocromil: not enough evidence

United Kingdom — Nedocromil (Tilade®, Fisons), which has recently been registered in the UK, is described as a new “mast cell stabilizing agent”. Like sodium cromoglicate (Intal®), it offers protection against provoked bronchial constriction in asthmatics, and single doses are claimed to be more effective and longer-lasting than cromoglicate.

However, the Drugs Newsletter of the Northern Regional Health Authority questions the strength of this claim by pointing out that there are no published comparisons of nedocromil and sodium cromoglicate in the prophylaxis of asthma and bronchospasm in clinical practice, and that contradictory statements have been made about their relative efficacy. It has still to be shown, it concludes, whether nedocromil offers any advantage over sodium cromoglicate in practice, or, indeed, whether it is effective in patients who do not respond to cromoglicate.

Reference: Nedocromil — not enough evidence. Drug Newsletter, Northern Regional Health Authority, Newcastle upon Tyne, United Kingdom, No. 41, January 1987.

Cefalosporins: what’s changed?

United Kingdom — The clinical value of three cefalosporins first marketed after 1982 is discussed in a recent issue of the Drug and Therapeutics Bulletin:

• Cefadroxil carries the claim of being effective in urinary tract infections when administered only twice daily, but it seems that it has not been directly compared with other oral cefalosporins, such as cefradine and cefalexin, given in this dosage regimen. Cefaclor, the Bulletin reminds its readers, remains the only oral cefalosporin active against Haemophilus infections.

• Ceftizoxime, it is argued, so closely resembles cefotaxime that price alone determines the choice between them.

• Ceftazidime, which is acknowledged to be the first parenteral broad-spectrum cefalosporin with reliable activity against Pseudomonas, is identified as too expensive for general use as a first-line broad-spectrum drug.


Chinese publications on helminthiases

In order to assure their accessibility to a wider readership, the World Health Organization issues from time to time abstracts or translations of papers on helminthiases published in the Chinese medical and scientific press. This material may be obtained, on request, from the Division of Parasitic Diseases, World Health Organization, 1211 Geneva 27, Switzerland.
Post-marketing surveillance: the way forward

Pharmaco-epidemiology is a fragile science. Its best safeguard is close and open collaboration among its exponents in the pharmaceutical industry, government, academia and the healthcare system. This is the message of Dr Hugh Tilson, Director of Epidemiology, Information and Surveillance, Burroughs Wellcome Company, USA, delivered in a lecture recently published in the United Kingdom by the Centre for Medicines Research.

Dr Tilson recognizes that through the application of record-linkage techniques to large multipurpose computerized data bases containing prescribing information and individual health records it is now possible to undertake studies of drug performance that were not previously feasible either in scope or in cost.

For the first time a ready means exists for resolving problems raised by spontaneous reporting systems. He warns, however, that, in the wrong hands, these data bases could provide the raw material for confusion, contention and misrepresentation. His concern is that everyone involved, the professions, the manufacturers, the regulators and the public, must appreciate the inherent limitations of experimental science.

Problems cannot be solved when there are not enough patients to study; complete assurances cannot be provided if nothing is found; the future cannot be predicted with certainty on the basis of what is found today. Nor, of course, can the field of pharmaco-epidemiology ever be immune from conflicts of interest.

Pharmaco-epidemiologists working in the industry must not be involved in promotional gambits. It is vital that they earn the respect of their colleagues in academia, not least because the greatest expertise regarding drug-related problems resides within the industry itself.

Reference: Tilson, H. Post-marketing surveillance, the way forward. Centre for Medicines Research, Wodmansterne Road, Carshalton, Surrey SM5 4DS, United Kingdom.

Protection of animals used for experimental purposes: EEC Directive approved

European Economic Community — A Council Directive on animal experimentation introduces strict controls on the use of animals in scientific research and lays down requirements for the prior notification and authorization of all experiments in which they are involved. The broad objective is to ensure that animals are not subjected to undue pain and suffering and that unnecessary duplication of tests is avoided. Alternative test methods are advocated whenever they are feasible, and experiments on endangered species are prohibited.


Biotechnology: cell-line donor ownership

United States of America — The Office of Technology Assessment (OTA) has recently issued a report intended to help Congress to clarify the issues involved in the ownership of human tissues and cells utilized in recombinant DNA technology and for the synthesis of monoclonal antibodies. At present, the benefits of commercial products developed from human cell cultures are never shared with the donor who is rarely aware that his tissues have been put to commercial use. The question of the ownership of these tissues and cells first arose in 1980 when the Supreme Court ruled that federal patent law applies to new life forms. The OTA report identifies three broad policy issues that Congress might address:

• regulating commerce in human tissues and cells, and in the derivative products, including cell lines and gene probes;

• directing the Secretary of Health and Human Services to modify and extend existing guidelines for protection of human subjects; and

Reference: Tilson, H. Post-marketing surveillance, the way forward. Centre for Medicines Research, Wodmansterne Road, Carshalton, Surrey SM5 4DS, United Kingdom.
• ensuring that doctors and others involved in health care disclose their potential research and commercial interests to patients.


Counterfeit medicines in West Africa

At the Commonwealth Pharmaceutical Conference in Nairobi in March 1987 a disquieting account was presented of the extent of trading in fake, adulterated and counterfeit products in West Africa. Mr Agboifo, Nigeria, ascribed much of the problem to an inadequacy of drug legislation in developing countries. In some of the countries basic statutes had not been revised for over 20 years; doctors were allowed to run a shop attached to their clinics; private hospitals were run without pharmacists; and drug inspectors were not necessarily registered pharmacists.

These inadequacies, together with lack of law enforcement and lack of resources for adequate control, had led, in some instances, to the sale of potent drugs in open markets side-by-side with fake, adulterated and counterfeit drugs. Mr Agboifo, who showed examples of counterfeit drugs available in West Africa, was strong in his condemnation of this trade, and urged all governments to provide the administrative and financial resources for an effective system of control.


Low toxicity of ibuprofen in acute overdose

United Kingdom — Since ibuprofen became available for over-the-counter sale 203 cases of overdosage have been reported to the National Poison Information Service at New Cross Hospital, London. Although the incidence of such cases has greatly increased, their outcome is largely reassuring. In one case, however, ibuprofen may have caused death, although symptoms were typical of overdosage of other drugs taken by the patient. Few patients required treatment, other than gastric lavage or emesis, and, overall, ibuprofen gives the impression of being much less toxic in acute overdosage than either aspirin or paracetamol.


The future of pharmaceutical sciences

An informed view of the major objectives and challenges in pharmaceutical research today is offered by the Secretary of the Board of Pharmaceutical Sciences of the International Pharmaceutical Federation (FIP), Prof. D. D. Breimer, in an editorial prepared for the International Pharmacy Journal. His prediction is that the next decade is destined to see major advances in many fields, including:

• design of new therapeutic substances, based on techniques of receptor mapping and molecular graphics, that are more precisely related than was previously possible to the mechanisms and causes of disease;

• design of drug delivery systems, based on physico-chemical principles, with rate specifications derived directly from pharmacodynamic and pharmacokinetic considerations;

• drug targeting, based on physiological, biochemical and immunological determinants;

• optimization of drug dosage through characterization of the patient’s metabolizing enzyme activities

• administration of bioengineered proteins and other macromolecules by non-parenteral routes, based on principles of membrane biochemistry and biopharmaceutics;

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and new methodologies in quantifying and monitoring pharmacological effects; and

• assessment and prediction of drug toxicity and adverse reaction profiles, based on improved understanding of mechanisms of drug metabolism.

The common thread within each of these activities is that they focus on human physiology at the molecular and organizational levels as providing the means for a more precise, scientifically-based approach to therapeutic management.


Prospects for vaccination against dental caries

United Kingdom — Despite the encouraging decline in dental caries reported in recent years in most industrialized countries, millions of children around the world remain at risk of extensive tooth decay. In a recent issue of the British Dental Journal R. R. B. Russell & N. W. Johnson review the possibility of developing a satisfactory preventive vaccine against caries.

A sound understanding of the disease process and of the role of the etiological agent, Streptococcus mutans, has provided the basis for the development of safe and potentially highly effective vaccines which will shortly be submitted to clinical trial in man.

Some years will elapse, however, before the value of these preparations can be confirmed. In the meantime, basic research on the mode of action of caries vaccines and the search for new, more effective, polyvalent vaccines must continue if the struggle against dental caries is to be fully engaged.


Monoclonal antibodies (MAbs) for cancer diagnosis


• An antibody, MAb COL-4, reactive against carcinoembryonic antigen, has also been shown to react preferentially with adenocarcinomas of the colon. Results of clinical trials have confirmed that it is of value in identifying metastatic as well as primary lesions and that it may be particularly useful in differentiating primary ovarian carcinoma from colonic adenocarcinoma metastatic to the ovary.

• Another antibody, MAb B72.3, generated against a membrane-enriched fraction of human metastatic breast carcinoma, has been used successfully to distinguish malignant mesothelioma of the pleura from adenocarcinoma of the lung. Nineteen of 22 lung adenocarcinomas were highly reactive with the antibody, whereas malignant mesothelial lesions and small-cell carcinomas of the lung were largely non-reactive.


Costs to develop a new drug reach US$ 125 million

United States of America — The Pharmaceutical Manufacturers Association reports that the average costs of new drug development have increased nearly two and one-half times since 1976. According to a study funded by the Association, the most important factor underlying the escalation of costs is an increasing involvement with drugs for chronic and degenerative diseases which inevitably require more extensive development and testing. The direct cost of developing a new chemical entity is now estimated to be approximately US$ 65 million. However, if allowance is made for loss of
return on invested capital of approximately 8% per annum, the real cost approaches US$ 125 million.


Abuse of over-the-counter sympathomimetics

A strong case is presented in an article published in the British Medical Journal for making sympathomimetic drugs available only on prescription. Concern is focused on the explosive rate at which abuse of these substances has developed in the United States of America, partly as a result of their ready availability over-the-counter and partly because of a large illicit traffic in counterfeit products.

The abuse potential of amphetamine and its potential to induce paranoid psychoses have long been recognized, and related sympathomimetics such as methylphenidate, amfepramone and phenmetrazine are now internationally scheduled as controlled drugs. However, other sympathomimetics, including ephedrine, pseudoephedrine and phenylpropanolamine, remain available over-the-counter as constituents of proprietary medicines for coughs and colds. In the United States their abuse has created a public health problem with its own vernacular including terms such as "pseudospeed" (various combinations of ephedrine, phenylpropanolamine, caffeine), "look alikes" (the same stimulants formulated and packaged closely to resemble amphetamine tablets) and "poor man's cocaine". Many of these drugs, which are manufactured in "garage laboratories", were sold widely by mail order until the US Postal Service refused to deliver them. None the less, "pseudospeed" is reported to remain the most commonly abused drug after alcohol and cannabis among adolescents in central New York. Its production continues to generate vast profits, and those engaged in its distribution continue to operate one step ahead of the law.


Controversy on safety of anabolic hormones in animal production

United States of America — The plan to ban the use of anabolic hormones for growth promotion in food-producing animals by the European Economic Community (EEC), on the grounds of protection of public health, has raised concern within the United States of America where this action is seen as a barrier to trade. The decision is at variance with the view of the Food and Drug Administration which has concluded that estradiol, progesterone, testosterone, and zeranol are safe when used according to labelled directions. Trenbolone acetate is alone among candidate steroidal compounds in not having been approved for this use by the FDA.

A paper recently published in the FDA Veterinarian reviews the methods used to calculate a safe threshold concentration in meat for these compounds and the Agency is looking to the Codex Committee on Residues of Veterinary Drugs in Foods, jointly sponsored by WHO and FAO, to provide an influential, technically-competent international forum for a discussion of the underlying safety issues.


WHO Diarrhoeal Disease Control Programme

The Interim 1986 Report of the WHO Diarrhoeal Disease Control Programme covers its activities in planning, training, health education and communications as well as its research involvement. Emphasis continues to be accorded to the need for increased availability of oral rehydration therapy, which is defined as the administration of a physiologically appropriate fluid by mouth to prevent or correct the dehydration resulting from diarrhoea.

During 1986 the Programme provided technical support to 11 countries seeking to develop a capability for local production of oral rehydration salts (ORS). By the end of the year 47 developing
countries were already manufacturing supplies. The research activities of the Programme include the development of improved ORS formulations, an evaluation of antidiarrhoeal drugs including chlorpromazine and colestyramine, the clinical assessment of live oral typhoid vaccines, a survey of the epidemiology of rotavirus infections and field trials of candidate rotavirus vaccines and diagnostic tests.


Planned Pan American Conference on Pharmaceutical Education

A Pan American Conference on Pharmaceutical Education, jointly sponsored by the American Association of Colleges of Pharmacy and the Pan American Health Organization, will be held in April 1989 in Miami, United States of America. The objective is to identify and define the role of the pharmacist in the provision of health care with particular focus on rational drug use.


Informatics in batch control

Italy — Prof. F. Pocchiari, Director of the Istituto Superiore di Sanità and a member of the WHO Executive Board, makes a plea for the development of efficient computerized record-keeping systems that would allow rapid and complete localization of production batches of drugs released into the distribution chain. Too often, the complexities of the current system prevent a company from localizing its products rapidly and completely in the event of a batch recall. This difficulty has apparently been aggravated by the recent development of "parallel import channels" between Member States of the European Economic Community as a result of wholesalers and pharmacists taking advantage of national price differentials. An effective computerized system, Prof. Pocchiari contends, would hold the added advantage of identifying illicit sales of prescription drugs, initially bought using public funds, outside the authorized channels.


Antibiotic treatment of bacterial endocarditis

United Kingdom — The Drug and Therapeutics Bulletin, basing its views on a 1985 report of a working party of the British Society of Antimicrobial Therapy, emphasizes that successful management of bacterial endocarditis depends on early diagnosis, prompt treatment, and secure identification of the causative agent which, in 80% of cases, is a streptococcus or a staphylococcus, most frequently Str. viridans. Even when the necessary antibiotics and microbiological facilities are immediately available, 15%-30% of patients still die from the condition.

Antibiotic therapy should never be started before blood cultures have been taken. While the results are awaited, treatment with benzylpenicillin + gentamicin is essential. Flucloxacillin should be added if the patient is a drug addict, has skin sepsis or other signs suggesting Staph. aureus infection, or has a prosthetic valve. For elderly patients, and those with impaired renal or vestibular function, netilmicin may be preferable to gentamicin. Similarly, Intravenous vancomycin + gentamicin or rifampicin + erythromycin offer alternatives to patients severely allergic to penicillin.

The sensitivity of streptococci (including Str. viridans) to penicillin is variable. Ideally, the dose should be adjusted in accordance with the minimum bactericidal concentration or the more readily measured minimum inhibitory concentration. Treatment should be continued for four weeks and gentamicin should be added for the first two weeks because it is claimed to exert a synergistic effect even when the organism is fully sensitive to penicillin.
Staph. aureus can rapidly destroy previously healthy heart valves and patients with staphylococcal bacteraemia of unknown origin should be regarded as having endocarditis even if no heart murmur is detected. Treatment with flucloxacillin is usually supplemented initially with gentamicin or fusidic acid, depending on sensitivity, but their value remains debatable.

Staph. epidermidis is an important cause of prosthetic valve endocarditis. Flucloxacillin and gentamicin (or fusidic acid) may be used if the strain is fully sensitive to these drugs. If it is resistant to flucloxacillin, rifampicin + vancomycin or gentamicin may be successful, but antibiotics alone may not eradicate the infection and early valve replacement is often needed.

Treatment should be monitored by assessment of serum bactericidal activity. When an aminoglycoside is used, drug levels should be measured twice weekly and renal function should be monitored.

Urgent valve replacement may be needed if rapid haemodynamic deterioration occurs or if the response to treatment is inadequate. After recovery, all patients should be given a medical card suggesting prophylaxis for future bacteraemic procedures.


Can fish oil prevent heart disease?

United Kingdom — A standardized concentrate of oil extracted from fish flesh (Maxepa®, Duncan Flockhart) will shortly become available on prescription for the treatment of certain hyperlipidaemias. The product, which has been found to produce a sustained fall in plasma triglycerides, contains the polyunsaturated fatty acids eicosapentaenoic acid and docosahexaenoic acid. These are structurally different from polyunsaturated fatty acids based on linoleic acid which are more commonly found in the Western diet (1).

Work on the product was inspired by an observation made in the 1970s that Greenland Eskimos and Japanese fishermen have low levels of coronary artery disease, despite eating a high cholesterol, high fat diet and being heavy smokers. It has recently been confirmed that total cholesterol plasma concentrations are reduced by fish consumption and that very high intakes of fish oil (90-120 g/day) lower the concentration of low-density lipoprotein (LDL) cholesterol by decreasing the rate of LDL synthesis (2). It has already been shown that fish oil supplements can reverse hypertriglyceridaemia, but their value in hypercholesterolaemia remains uncertain. Their possible potential in the treatment of thrombogenic disorders will need to be confirmed in clinical trials. Similar benefits might reasonably be expected to derive from preexisting formulations of fish liver oil (3). Meanwhile, it is widely agreed that it makes good sense to eat more fish, provided it is not fried or salted, in place of foods with a high content of saturated fat such as cheese, fatty meats, and meat products.

References

Four reasons for local post-marketing drug surveillance

United States of America — In reviewing the need for post-marketing drug surveillance Dr J. S. Gardner, Director, Drug Epidemiology Unit, Upjohn Company, USA, cites four circumstances in which localized population studies can be of value:

- To establish the safety and effectiveness under local conditions of a product already marketed in other countries, having regard to regional differences in disease patterns, nutritional status and climate that may affect drug performance.
- To establish the benefit of the product under local conditions. Oral contraceptives, for example, offer
a supplementary advantage to many Asian women by ameliorating highly prevalent iron deficiency anaemia.

• To establish local confidence in the product, particularly in a political environment in which some multinational companies have been accused of "dumping" unacceptable or low-quality products on the markets of developing countries.

• To create a system for postmarketing surveillance as an element in quality assurance, particularly when a new product is first manufactured locally.


Oral contraceptives reduce ovarian cancer risk

United States of America — Since 1977, at least 11 published studies have suggested that the use of oral contraceptives decreases the risk of epithelial ovarian cancer. However, it has not been certain whether the effect varies with the oral-contraceptive formulation or the histology of the cancer. Sufficient case material has now been reviewed within the Cancer and Steroid Hormone Study (CASH) of the Centers for Disease Control and the National Institute of Child Health and Human Development both to confirm the protective effect and to suggest that it is not influenced by either of these two factors. It is notable that the effect was seen in women who had used oral contraceptives for as little as three to six months, and it persisted for at least 15 years after discontinuation of use.


Drugs and sport

United Kingdom — Drug abuse or "doping" is defined by the International Olympic Committee (IOC) as the use of a substance which could artificially improve an athlete's physical and/or mental condition in order to augment performance. A competitor may be penalized if a banned drug or its metabolite is detected in the urine. Some of these substances, which are tabulated below, are contained in widely-available medicines and the Drug and Therapeutics Bulletin has published a commentary intended to help doctors and pharmacists advise patients involved in competitive sports.

• Out of competition testing — Many athletes have used anabolic steroids in the belief that they enhance muscle bulk—though there is little evidence that they improve athletic performance. Random tests for these substances are now made during the training period as well as during competition. Other drugs forbidden in the training period include cocaine and amphetamines. Offenders taking any of these are liable to be banned from competition.

• Accidental rule-breaking — Some of the listed substances can be taken unintentionally in medicines that are prescribed or even bought over-the-counter. Codeine and related compounds are often contained in products taken for cough or diarrhoea; ephedrine and other sympathomimetics are contained in decongestants for hay fever and colds. Athletes are well advised never to take a medicine until they have checked with a doctor or a pharmacist that it does not contain a banned substance. Anyone taking a banned drug, even for a legitimate purpose, is liable to be disqualified from competition.

• Prescribing for the athlete — Problems arise mainly in the symptomatic relief of pains, colds and gastrointestinal upsets. An antihistamine and/or sodium cromoglicate may be given for hay fever, but not an oral or parenteral corticosteroid. Topical corticosteroids are permitted. Analgesics such as acetylsalicylic acid and paracetamol are allowed but not in combination with codeine or dextropropoxyphene. Diarrhoea may be treated with diphenoxylate or loperamide, if necessary. Anticonvulsants, antidepressants, antiemetics and benzodiazepines may generally be used, but in some sports, e. g., modern pentathlon, neither anxiolytics nor β-blockers are permitted. In case of
### Drugs prohibited by the International Olympic Committee

<table>
<thead>
<tr>
<th>CLASSES (including &quot;related compounds&quot;)</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Stimulants (e. g., amfetamines, caffeine, cocaine, ephedrine)</td>
<td>Caffeine permissible up to 12 µg/ml in urine.</td>
</tr>
<tr>
<td>B. Narcotics (e. g., morphine, codeine, buprenorphine, phenazocine)</td>
<td>Includes codeine and dextropropoxyphene (avoid use of analgesic mixtures).</td>
</tr>
<tr>
<td>C. Anabolic steroids (e. g., testosterone, stanozolol)</td>
<td>Testosterone doping is defined as “increasing the testosterone/epitestosterone ratio in urine beyond 6:1”.</td>
</tr>
<tr>
<td>D. β-Adrenoreceptor blockers (e. g., propranolol)</td>
<td>Medical commission of the IOC may test for this in sports not requiring high physical activity.</td>
</tr>
<tr>
<td>E. Diuretics (e. g., acetazolamide, furosemide)</td>
<td>Use of these drugs to achieve weight loss is potentially dangerous.</td>
</tr>
</tbody>
</table>


In doubt, an athlete should approach the medical adviser to the governing body of the sport.


### Patient information leaflets

A consultation document on patient information leaflets prepared by a working party of the Association of the British Pharmaceutical Industry (ABPI) has been circulated for comment to all member companies and interested bodies. Some preliminary ideas on the content and distribution of the information required were exchanged in a seminar sponsored by the British Pharmaceutical Society in May 1987. Professor Charles George of Southampton University, commenting on a study undertaken by his group, expressed concern that few patients currently taking drugs seem to be aware of any potential side-effects of their treatment. Patients clearly need more information, but to present it in a way which everyone can understand is a great deal harder than it sounds.

He favoured a double-sided layout with essential information on dosage and storage on the front and more detailed information on the back. Regardless of the difficulties, however, he was convinced of the benefits of providing the additional information.

More than 40% of the patients had used the leaflets as their main source of information about their medicines, and among patients taking nonsteroidal anti-inflammatory drugs, in particular, there was a striking improvement in the level of knowledge about adverse effects.

Mr D. Sharpe, Chairman of the Pharmaceutical Services Negotiating Committee, warned that generic preparations could present a problem since the annual cost of supplying leaflets for about 75 million prescriptions for these products would need to be met. Dr F. Wells, Medical Director, ABPI, considered that the answer to this lies in original pack prescribing: the simplest way to ensure that patients receive the information they need is to include a leaflet—approved by the Department of Health when a product licence is issued or renewed—in the sealed retail packs.
Approved patient package inserts are already required by law in some other countries within the European Economic Community where original pack prescribing has long been the norm. Guidelines for manufacturers developed independently within the Federal Republic of Germany (2) and the Netherlands (3) require that the information:

- be provided whenever the product is dispensed;
- be written in a concise manner that is readily intelligible to lay people and that avoids unnecessary concern;
- indicate precisely how the product should be used, what may be expected of it and how it should be stored;
- describe adverse effects recognizable to the patient; and
- include no reference to other products except when this is necessary for an understanding of the use of the product.

References

Projected study on drug labelling in developing countries

United States of America — The Office of Technology Assessment is planning to undertake a study on drug labelling in developing countries at the request of the Senate Committee on Labor and Human Resources and the House Committee on Energy and Commerce. Congress is interested in the issue for reasons of international health and safety, industrial competitiveness, and the international reputation of the US pharmaceutical industry which is a major supplier of pharmaceuticals to developing countries. The industry has been heavily criticized in the past for “mislabelling” certain products destined for these countries and this assessment will explore whether this still remains a problem. Despite the contention the issue has aroused both within Congress and between the pharmaceutical industry and public interest or consumer groups, there has been no objective, broadly-based evaluation of the facts. The central issue is not simply whether differences in labelling exist between products sold on the domestic markets and those intended for export, but whether any such differences have implications for the way that products are used and, particularly, for their safety. A “pilot” stage of the study will be completed early in 1988 and the final report should be available before the end of that year.


Prescription-Event Monitoring (PEM) News

United Kingdom — The Drug Safety Research Unit located within Southampton University has created, in the development of its Prescription-Event Monitoring (PEM) scheme, what its Director, Prof. W. H. W. Inman describes as “probably the largest record-linkage scheme in the world”. The success of the concept has attracted unconditional grants from many sources and the Unit is now managed by a Trust on the understanding that decisions on which drugs are to be monitored will not be influenced by consideration of whether or not their manufacturers are sponsors of the Unit. PEM provides information on new drug use within the entire English population of more than 50 million people. However, it is a selective system insofar that it is applied only to new chemical entities as they appear on the market, or to drugs that have caused specific problems. Each study involves large cohorts of patients who are identified by prescriptions written by general practitioners. Linkage is effected between general practice and hospital records, and information from death certificates provided by the Office of Population Censuses and Surveys. The system can be applied
prospectively or retrospectively and can both generate and test hypotheses. The initial target for a new drug is to identify the first 20,000 patients to receive it after its release for general use. On occasion, however, PEM has “banked” as many as 200,000 or more prescriptions as an insurance against the possible need to mount a retrospective investigation (perhaps many years after the drug’s first introduction), should a long-term hazard such as carcinogenicity ever be suspected. This “prescription bank” is partly on microfilm and partly on computer.

Prof. Inman considers it useful, conceptually, to classify post-marketing surveillance activities in terms of who conducts them:

- Regulatory postmarketing surveillance conducted by governmental departments of health. This is usually restricted to the collection of voluntary reports of suspected drug adverse reactions and to the assembly of published and unpublished individual case reports.

- Independent postmarketing surveillance conducted by universities or independent research institutions.

- Promotional postmarketing surveillance conducted by individual drug companies in order to introduce doctors to new products and sometimes also to satisfy demands of regulatory authorities.

He cites four reasons why promotional post-marketing surveillance is unsatisfactory:

- Companies often have to pay doctors to use their product rather than the long-established alternatives they customarily prescribe.

- A rival company is unlikely to agree to its product being prescribed under identical conditions in order to provide a comparison.

- Companies are anxious to avoid adverse experiences during the early stages of marketing a new product and will apply special precautions and contraindications which will make the drug appear safer than it is likely to be under normal conditions of use.

- Since companies often experience difficulty in recruiting sufficient numbers of patients, their studies may take five or more years to complete.


Adverse effects of biomedical devices

United Kingdom — Dr G. E. Diggle, Senior Medical Officer, Department of Health and Social Security is compiling an overview of adverse effects associated with biomedical devices in the Adverse Drug Reaction Bulletin. He classifies these devices according to the intimacy of their contact with tissues. The first category comprises true implants, such as vascular grafts, replacement joints, and neurosurgical shunts which are positioned surgically and remain indefinitely in direct contact with the surrounding tissues. Catheters for long-term central venous access occupy an intermediate group, while devices such as urinary catheters and oxygen-permeable contact lenses, which do not breach epithelial barriers, constitute a third category.

Adverse effects associated with devices in each category are termed either as class specific (such as thrombogenicity which is common to a range of devices), or product specific (such as cardiovascular collapse following mechanical failure in a cardiac valve prosthesis). When complete, the review will cover both types of events and also discuss the risks and management of implant-induced infections, tumours, thromboses and thromboembolism.


Canada — The Health Protection Branch of the Ministry of Health and Welfare has introduced a toll-free bilingual (English and French) 24-hour telephone service to enable health care professionals and members of the general public to report failures and malfunctioning of medical devices.
The Branch has defined medical devices as any article, instrument or apparatus which is sold or presented for use in the diagnosis, treatment or prevention of disease or abnormal physical states, for correcting functional abnormalities, or for contraception. This embraces articles as diverse as pacemakers, syringes, contact lenses, vaporizers and heating pads.


Stability of yellow fever vaccines

Based on the results of a thermostability study undertaken on one random batch of commercially produced yellow fever vaccine, it is provisionally proposed that, in order to qualify for use in WHO programmes, such vaccines should meet the following two criteria after two weeks of storage at 37\degree C:

- The vaccine should still contain a number of plaque-forming units (PFU) equivalent to not less than $10^3$ mouse LD$_{50}$ per human dose.
- The loss of virus titre should be not more than $1.0 \log_{10}$.

These criteria will be proposed for adoption by the Expert Committee on Biological Standardization during its meeting in December 1987.


Animals can be patented

United States of America — The Patent and Trademark Office is considering patent applications for "non-naturally occurring non-human multi-cellular living organisms" or genetically altered higher animals. A Supreme Court ruling in 1980 cleared the way for patenting microbes, but expressly excluded human beings from patent eligibility. A more recent judgement, in supporting a patent application for a genetically manipulated pacific oyster, greatly increased the scope for establishing proprietary rights to living animals. The basic condition to be satisfied before a patent can be issued is that the animal constitutes a "manufacture" or composition of matter not found in nature.


Low-dose or high-dose acetylsalicylic acid for preventing major vascular events?

Preliminary results have been released from the largest multicentre study yet undertaken to evaluate the relative efficacy of low- and high-dose acetylsalicylic acid in preventing myocardial infarction and stroke in patients with cerebrovascular disease. They are claimed to indicate that a daily dose of 300 mg is as effective as 1200 mg and that the lower dose is associated with fewer adverse effects. Dr Charles Warlow, one of the principal investigators of the United Kingdom Transient Ischaemic Attack/Aスピリン Trial (UKTIA), considers that the findings provide the first firm clinical evidence of the therapeutic equivalence of the two dosages in inhibiting thrombogenesis.


Dot-ELISA test for visceral leishmaniasis

Honduras — The dot enzyme-linked immuno-sorbent assay (Dot-ELISA), a rapid visually-read microtechnique for serodiagnosis of human visceral leishmaniasis, has been field-tested in a known endemic area in Honduras. Of 305 individuals screened using a serum dilution of 1 : 32, positive reactions were obtained in 8 out of 9 patients with parasitologically confirmed visceral leishmaniasis.
Cross reactions occurred in 1 of 3 children with cutaneous leishmaniasis. The equipment required for the test is readily portable and its operation is not dependent upon a source of electrical power. The method is inexpensive, rapid, yet sensitive, simple to perform and relatively specific under field conditions.


Increased incidence of antibiotic-resistant gonorrhoea in the USA

**United States of America** — The incidence of antibiotic-resistant gonorrhoea caused by penicillinase-producing *Neisseria gonorrhoeae* continues to increase and is spreading to previously unaffected areas. In 1986, 16,608 such cases were reported to the Centers for Disease Control. This represents 1.8% of the total number of reported cases of gonorrhoea and a 90% increase over the 8,724 cases reported in 1985. Since 1984 the incidence has risen fourfold. In earlier outbreaks, travel to known areas of endemic antibiotic-resistant gonorrhoea and prostitute contact were evident risk factors for infection. However, this is no longer the case now that antibiotic-resistant gonorrhoea has become epidemic. Control of the disease has thus become extremely difficult and expensive. In areas where resistance is known to be prevalent, doctors are advised that all patients with a presumptive diagnosis of gonorrhoea should be treated with either ceftriaxone or spectinomycin.


Acellular and whole-cell pertussis vaccines

**United States of America** — A report on experience with acellular pertussis vaccines in Japan produced by a US Public Health Service Interagency Group to Monitor Vaccine Development has been reviewed by J. D. Cherry & E. A. Mortimer in the *Journal of the American Medical Association*. Since febrile and other common systemic reactions are clearly less frequent with acellular than with whole-cell vaccines, it is confidently expected that febrile convulsions will be encountered less commonly with the new vaccines. However, it is uncertain whether use of the acellular vaccines will also reduce the encephalopathy and other alleged adverse reactions to existing DPT vaccines, including sudden infant death. These reactions, it is suggested, may have been drastically reduced in Japan not by the change to acellular pertussis vaccines but by raising the immunization age from 3 months to 2 years. The authors conclude that the clinical and serological data compiled in Japan leave no doubt that the acellular vaccines are as immunogenic as the whole-cell products, but they suggest that further data are required on the safety and efficacy of the Japanese vaccines in infants.

References


Measles and vitamin A deficiency

Evidence mounts in Africa, as well as in some of the most densely populated countries of Asia, that measles is an important predisposing factor for the development of blindness in children with severe vitamin A deficiency. In Thailand, some 30% of children with measles were found to have serum vitamin A concentrations below 0.35 µmol/l (100 µg/l), a level at which there is high risk of corneal ulceration. In Indonesia, children who had measles during the preceding 4 weeks were 11 times more likely to show signs of corneal xerophthalmia. Half the children in schools for the blind in Malawi and Tanzania have a history of measles immediately preceding the blinding episode. In Africa as a whole, where the incidence of corneal damage following measles can reach 4%, corneal scarring
accounts for the majority of cases of childhood blindness. High-dose vitamin A supplementation should thus be provided to all children with measles in communities in which vitamin A deficiency is a recognized problem. The recommended oral dose is 100,000 IU for children below 12 months of age, and 200,000 IU for older children. If any of the eye signs of vitamin A deficiency are present, two full doses should be given on successive days, and a third 4 weeks later.


**Suprofen: worldwide withdrawal**

The manufacturer of suprofen (Suprol®, Cilag), a nonsteroidal anti-inflammatory agent, has informed WHO that sales of preparations containing this substance have been suspended worldwide. The decision has been prompted by the foreclosure of the European market as a result of a recommendation by the Committee for Proprietary Medicinal Products (CPMP) of the European Economic Community (EEC) that current authorizations should be suspended. The company has maintained its claim that the product’s overall safety profile is consistent with other products of this class but that controversy over the “loin pain syndrome” has diminished sales to the point where the product is no longer economically viable.

References: Communication to WHO from Cilag Ltd, May 1987, and notifications from the United Kingdom, the United States of America, the Federal Republic of Germany and Italy each dated 1986.

**Skin reactions with transdermal clonidine**

United Kingdom — Severe localized skin reactions, consisting of pruritus, erythema and vesication are reported to have occurred in four of five patients who were receiving clonidine via a skin patch delivery system (Catapres-775®, Boehringer-Ingelheim) after an average of 20 weeks therapy. Because transdermal drug delivery systems are increasing in popularity and in view of previous reports of localized reactions, the authors stress the importance of carrying out long-term studies involving periods of exposure of at least 6-12 months if the apparent risk is to be adequately assessed.

The intensity of the research effort now unleashed upon AIDS reflects the urgency of the situation: worldwide, 5 to 10 million people are probably already infected, and at least one third of these are expected to develop the disease within the next few years. Since the causative virus is able to integrate into the human genome where it can remain latent for years, curative treatment remains a distant prospect. Hope still remains focused primarily on the possibility of developing a preventive vaccine. However, the task is daunting, not least because of variability in the antigenic target. The initially-described human immuno­deficiency virus (HIV) is the dominant causative organism, but newly identified antigenically-related human retroviruses have been isolated from individuals in West African countries, some of which are also claimed to be capable of inducing immune deficiency (1). It has even been claimed that extensive genetic variation of the virus can occur in vivo to the extent that many different viral forms may co-exist in individuals with long-established infections (2).

New vaccines

The United States Food and Drug Administration is currently considering several applications for testing candidate vaccines (3) and it has already sanctioned investigation in high-risk volunteers of a product based upon a purified viral antigen derived from a recombinant envelope glycoprotein of HIV that has induced high levels of neutralizing antibodies in chimpanzees (4). The external portion of the envelope glycoprotein (gp120) is a major target for both antibody-mediated neutralization and cyto­toxic immunity, and several similar products, some of which contain non-glycosated envelope subunits to expose epitopes that may be important for neutralization, are under development. In some of these the glycoprotein is contained in recombinant adeno- or vaccinia virus in order to obtain a live vaccine with greater immunogenic potential.

Unfortunately, a disadvantage inherent in each of these vaccines is that the resultant antibodies may well be strain specific (5). Nor can there be any certainty that immunodominant determinants on the envelope glycoprotein have important protective and neutralizing value in vivo (6, 7). Much interest has consequently centred of late upon the possibility of developing vaccines that are not strictly preventive, but that block the single common pathway by which these viruses enter the target cells. Cells are apparently vulnerable only if their surface membranes contain specific T4 receptors (sometimes called CD4 receptors) which are molecular configurations found characteristically in “helper” or “inducer” T4+ lymphocytes (8, 9).

Evidence that these serve as binding sites for the virus is extensive (10) and derives both from immunoprecipitation studies (11, 12) and from direct experimental confirmation that monoclonal antibodies directed against specific components of the receptor competitively block the entry of HIV and related viruses into T lymphocytes (13-15). These antibodies, when injected into baboons, induce a second generation of “anti-idiotype” antibodies that simulate T4 receptors in that they bind—and thereby partially neutralize—HIV (16). The hope is that, when they are administered to HIV-positive individuals, T4 antibodies will effectively prevent the virus from penetrating host cells through both these mechanisms. Confirmation of this expectation, however, must await evidence from animal models that prolonged T4 receptor blockade does not, in itself, induce clinically-evident immunosuppression.

Immuno-modulating agents

Investigation of the influence of physiological and synthetic immuno-modulating agents on the pathogenesis of HIV infection has already yielded several promising leads. Applications to investigate some twelve such candidate substances have already been lodged with the United States Food and Drug Administration and preliminary studies already undertaken in AIDS patients of an isolate from normal human leucocytes confirm that it may have useful palliative action (17). A reliable standardized means of screening such substances
in vitro would have obvious value, and this may now have been provided by the development, within the United States National Institute of Allergy and Infectious Diseases, of a cloned cell line derived from a monocyte precursor that is chronically infected with HIV in a latent form (18). Preliminary examination of a variety of recombinant lymphokines (substances normally produced by activated lymphocytes) has shown that some promote, while others—notably gamma interferon—strongly inhibit the expression of the virus. These findings leave no doubt that immunologically active components of normal cells are involved in triggering and regulating HIV production and that, in some cases, their administration in pharmacological dosage may have a potential to ameliorate the clinical progression of the disease.

Antiviral agents

Activity thus far remains centered largely upon reverse transcriptase inhibitors since this enzyme is directly associated with the intracellular replication of retroviruses. Other possible targets for antiviral therapy, including the T4 receptors that determine intracellular penetration and some of the later stages of the replicative cycle that control the assembly of the virus, still generate interest but some previously promising leads remain unconfirmed. Verification is still awaited, in particular, of a claim emanating from the United States National Institute of Mental Health that the T4 receptor-binding site in the HIV envelope protein has been identified and isolated as an octapeptide that is effective in inhibiting HIV penetration into cells by competitive receptor blockade (19).

Definitive reports have recently been published of the double-blind placebo-controlled study that established the efficacy of the reverse transcriptase inhibitor, zidovudine (azidothymidine, AZT) as a specific antiviral agent (20, 21). These confirm the potential of the drug to extend the life span of patients with AIDS and AIDS-related complex, but a high incidence of severe neutropenia and anaemia underscores the need for close medical supervision throughout treatment. Zidovudine, none the less, represents an impressive achievement and these results have stimulated interest in other inhibitors of reverse transcriptase in the hope that less toxic alternatives will emerge. At least twenty such compounds have already been subjected to preliminary screening in vitro and some appear to inhibit viral cytopathogenicity or infectivity at doses substantially lower than those toxic to the host cells (22). However, the predictive value of the available screening tests has been challenged (23) and substances such as foscarnet (phosphonoformate) which demonstrate only moderate selectivity in vivo have performed with promise in preliminary clinical studies (24).

Aside from zidovudine, some ten other inhibitors of reverse transcriptase are already being tested in patients with AIDS. For the most part the results have been described as "either controversial or uncertain" (22) but proposals are already being formulated to examine the effect of various drug combinations on grounds of synergy, attenuation of toxicity and diminution of risk of emergence of hypothetical resistance. As experimental investigation of these many varied agents and regimens advances from the laboratory to the clinic some pressing logistic and ethical questions are bound to emerge. What considerations should determine research priorities? What criteria should be observed to define response to treatment? How might these criteria be best defined to facilitate comparative assessments? Under what circumstances can placebo-controlled studies reasonably continue to be sanctioned? This is not to suggest that any anomalous constraint or direction be imposed upon clinical research in this field, but merely that particular consideration be given, in planning work, on how the results will contribute to and influence the existing body of knowledge. The research community clearly faces an obligation to define appropriate strategies and objectives and to assure that they are monitored through a rigorous process of self-audit and self-criticism.

References


Inactivation of HIV by pasteurization

Many countries hold significant quantities of plasma collected from donors before the introduction of routine screening for HIV antibody and its suitability for the manufacture of albumin products has been questioned. In a recent letter to the Lancet, Dr B. Cuthbertson and others provide reassuring information based on experience obtained in two major plasma fractionation units in the United
Kingdom. Albumin products are prepared by cold-ethanol fractionation and are then pasteurized in the final container by heating at 60°C for 10 hours, a procedure that is already known to inactivate hepatitis B virus.

Using various albumin products heavily spiked with RF strain of HIV-1, no virus could be retrieved on subsequent culture after it had been exposed to a temperature of 60 ± 1°C for 30 minutes.

The authors conclude that, when properly pasteurized, human albumin preparations present no hazard of viral transmission, even when they have been derived from HIV-contaminated plasma pools.


Monitoring zidovudine-induced bone marrow toxicity

Writing to the Lancet from the Hvidovre Hospital, Copenhagen, Dr C. Pedersen and Dr S. Ingeberg suggest that measurement of serum levels of thymidine kinase using a radio-enzyme assay (Profligen TK-REA®, Sangtec) may provide a convenient method of monitoring the bone marrow toxicity of zidovudine and related drugs.

Serum thymidine kinase has been found to increase at least threefold during zidovudine treatment, and the authors attribute this to inhibition of the enzyme thymidylate kinase. The resultant pyrimidine "starvation" has been associated with an increase in mean red cell volume and other defects in haemopoiesis.

Similar increases in serum thymidine kinase have been observed in patients with vitamin B12 deficiency and during methotrexate therapy.


Management of Pneumocystis carinii pneumonia in AIDS

Aerosol pentamidine

An open trial of aerosolized pentamidine in AIDS patients with first episodes of Pneumocystis carinii pneumonia has been reported from San Francisco in a recent issue of the Lancet. Each of 15 patients received 300 mg pentamidine from a nebulizer which they inhaled daily for 20 minutes over a three-week period. Thirteen of these patients improved both symptomatically and radiologically during this time and without receiving any other specific therapy. Serum concentrations of pentamidine remained low and, aside from an irritant cough which occurred in 12 patients, no adverse reactions were recorded. The authors conclude that this treatment regimen represents a significant advance over the standard intravenous courses of pentamidine or trimethoprim-sulfamethoxazole, which are reported to cause severe adverse effects in about half the treated patients.


A role for steroids?

Two groups of doctors writing independently to the Lancet claim to have obtained a beneficial response in AIDS patients with severe Pneumocystis carinii pneumonia by administering steroids in association with trimethoprim-sulfamethoxazole. Both groups claim that this reduced the death rate and shortened the hypoxic and febrile period. In one of the centres post-mortem examinations were performed to confirm that the use of steroids inhibits the formation of severe non-specific pulmonary fibrotic lesions typical of this type of pneumonia. However, opportunistic viral infections contributed to each of the three deaths that occurred among these patients. The authors question whether by reducing steroid dosage or
adding an antiviral drug the apparent risk of suprainfection could be reduced.

References

An autoimmune component in AIDS?

In a letter to the *Lancet*, Dr A. Hausen and colleagues from the Ludwig Boltzmann Institute for AIDS Research in Innsbruck, Austria, develop a case for increased investigation of the potential of immunosuppressant substances in the treatment of AIDS. They cite, in support of their argument, the above clinical studies in which the addition of steroid therapy to an antibiotic regimen strikingly reduced the mortality within a group of AIDS patients with *Pneumocystis carinii* pneumonia. These results, in the authors' view, could be explained by postulating that the development of systemic immunity against CD4 T-cells is an important component in the pathogenesis of AIDS which could be interrupted by administration of immunosuppressive agents that inhibit activation and proliferation of T-cells, possibly by reducing secretion of interleukin-2.


Diagnosis of early HIV infection in seronegative individuals

Doctors from Abbott Laboratories and from the Rush-Presbyterian St Lukes Medical Center, Chicago have reported that a recently developed enzyme immunoassay specific for HIV antigen may be of value in the diagnosis of the acute viral syndrome caused by HIV infection. Early diagnosis currently poses difficulty because, at this stage, some patients are still seronegative for HIV.

Initial serum samples obtained from four homosexual men with a transient clinical syndrome characterized by fever, rash, myalgia-arthralgia and pharyngitis were all positive for HIV antigen but consistently negative for serum HIV antibody as measured by commercially available ELISA and Western-blot analysis.

On subsequent testing, which in one instance was undertaken only eleven days later, sera from three of the four patients became negative for the antigen and positive for the antibody.


Factor VIII: HIV-contamination

Federal Republic of Germany — The Federal Health Office has informed manufacturers of Factor VIII concentrates that heat treatment has not always prevented transmission of HIV. To further assess the situation, the Office has requested all manufacturers to submit the following information for review:

- a copy of the data sheet;
- a description of the methods by which donors are selected and the steps taken to detect and exclude HIV-positive donors;
- a step-by-step description of the inactivation procedure;
- an evaluation of whether HIV transmission has resulted from blood products derived from donors that have reacted negatively to the HIV-ELISA test;
- a declaration as to whether the company has instituted or is envisaging any monitoring measures on its own initiative.

Pharmaceutical Products Approved

Clofazimine

United States of America — The Food and Drug Administration has approved the antileprosy agent clofazimine (Lamprene®, Ciba-Geigy), a designated orphan drug for the treatment of lepromatous leprosy, which has long featured in WHO’s Model List of Essential Drugs. Cross-resistance has not been demonstrated with dapsone or rifampicin. It is thus of particular value in dapsone-resistant cases and in erythema nodosum leprosum, but it has not been demonstrated to be effective in the treatment of other inflammatory reactions associated with leprosy. Studies are also being conducted on its use in infections caused by Mycobacterium avium intracellulare, one of the opportunistic infections in patients with acquired immunodeficiency syndrome (AIDS).


Intradermal human diploid cell rabies vaccine

United States of America — An intradermal human diploid cell rabies vaccine (Imovax Rabies I.D.®, Merieux Institute) has become available within the past year, both in the USA and several other countries, for pre-exposure prophylaxis. It is not, however, recommended for post-exposure use.

Details of a dose-ranging study involving 124 volunteers, who had not previously been exposed to rabies, have recently been published. Comparisons were made of the efficacy of the intradermal, intramuscular and subcutaneous routes of administration for primary immunization. At various points of time during the two years subsequent to immunization comparable titres of rabies neutralizing antibody were detectable in individuals who had received either three doses of 0.1 ml intradermally or three doses of 1.0 ml intramuscularly. Adverse reactions, which were not severe, were not apparently influenced by the route of administration.

The authors predict that virtually all immunocompetent persons who receive the recommended schedule of three 0.1 ml intradermal doses of vaccine will develop adequate rabies neutralizing antibody titres of 0.5 IU/ml of serum or greater. They thus recommend this regimen for pre-exposure prophylaxis both for persons at occupational risk and those living in or visiting countries where rabies is a constant threat. They emphasize, however, that it is the response to post-exposure booster immunization — not the magnitude of antibody titre following primary immunization — that determines protection from clinical rabies.

The development of the low dose intradermal vaccine has reduced the cost of the vaccine by a factor of ten. The authors caution, however, that this should not result in excessive use of booster doses and a needlessly increased risk of systemic allergic reactions.


Tranexamic acid

United States of America — The Food and Drug Administration has designated tranexamic acid (Cyklokapron®, KabiVitrum) an orphan drug and approved its use in haemophiliacs to reduce bleeding during tooth extractions. In mild haemophilia tranexamic acid may eliminate the need for transfusion of blood clotting factors and, in more severe cases, the need for these factors will be reduced. Treatment is usually started one day before surgery and continued for 4 to 10 days. Retinal degeneration has been observed in animals given tranexamic acid intravenously or orally at prolonged high dosage. Although no such changes
were reported during the clinical trials, even after chronic administration, an ophthalmological examination is recommended before and during treatment that is continued for longer than a few days.


**Synthetic human calcitonin**

United States of America — The Food and Drug Administration has approved synthetic human calcitonin (Cibacalcin®, Ciba), a polypeptide hormone comprising 32 amino acids in the naturally occurring sequence. The product is indicated exclusively for the treatment of symptomatic Paget’s disease of bone (osteitis deformans). The risk of diminishing effectiveness as a result of antibody formation is less with human calcitonin than with non-human forms of the hormone.


**Flunisolide**

United States of America — The Food and Drug Administration has approved flunisolide delivered in a metered-dose aerosol inhalant at a concentration of approximately 0.25 mg per puff (Bronalide® Inhaler System, Syntex) for the symptomatic control of steroid responsive bronchial asthma. The recommended adult dosage is two puffs twice daily, or 1 mg/day, and patients are advised not to exceed four puffs twice daily (2 mg/day). Safe use in children under 6 years has not been established. For older children the dosage should not exceed 1 mg/day.

Reference: New Drug Application 18-340, Food and Drug Administration, USA.

**Methacholine chloride**

United States of America — The Food and Drug Administration has approved methacholine chloride (Provocholine®, Hoffmann- La Roche) for administration by inhalation as a challenge agent in the diagnosis of bronchial airway hyperreactivity in patients who do not have clinically apparent asthma. The drug is a parasympathomimetic (cholinergic) bronchoconstrictor. Patients with severe hyperreactivity of the airways experience severe bronchoconstriction and respiratory distress at a dose as low as 0.25 mg/ml. Methacholine challenge must therefore be performed only under the supervision of a physician familiar with all the contraindications, warnings and precautions, and all aspects of the technique, including the management of respiratory distress. Challenge is contraindicated in patients with clinically apparent asthma, wheezing or very low baseline pulmonary function tests. If severe bronchoconstriction occurs, it should be reversed by the administration of a rapid-acting inhaled bronchodilator agent (β-agonist).


**Paracetamol/methionine combination**

United Kingdom — The licensing authority has approved a paracetamol/methionine combination product (Pameton®, Sterling-Winthrop). Methionine is a paracetamol antidote. Thus, although the product has the same analgesic efficacy as monocomponent formulations of paracetamol, it offers some protection against overdose and is primarily intended for use in situations where an intentional or accidental overdose might occur. Each tablet contains paracetamol 500 mg and methionine 250 mg.


**HIV Western-blot kit**

United States of America — The Food and Drug Administration has licensed a Western-blot kit for performing a qualitative in vitro assay for antibodies to human immunodeficiency virus (HIV)
infection in human serum or plasma. The kit, which is based upon an enzyme-linked immunoelectro-transfer technique, is manufactured by Biotech Research Laboratories and is intended primarily for use when a blood donor reacts positively to a screening assay, such as the enzyme-linked immunosorbent assay (ELISA). The high sensitivity of the ELISA test has resulted in some nonspecific or false-positive results and the greater specificity of the Western blot test will enable these individuals to be distinguished from those that are potentially infective. A negative Western-blot test cannot totally exclude the possibility of infection with HIV but, if two different blood samples drawn at least six months apart are negative, individuals excluded from donating blood on the basis of a positive ELISA test may be readmitted as donors.

Persons with positive Western blot tests for antibodies to HIV should be referred for medical evaluation, which may include additional testing. A clinical diagnosis of AIDS can only be made if the case definition established by the Centers for Disease Control is met.


Other products approved

**Adamexine** (expectorant)
Adamucol®, Ferrer, Spain
oral solution 5 mg/ml
*Indication:* bronchitis.
*Caution:* in patients with gastric ulcer.

**Amisulpride** (neuroleptic)
Solian®, Delagrange, France
tablet 50 mg.
*Indications:* schizophrenia and acute psychoses.
*Caution:* concomitant use of alcohol should be avoided. Renal insufficiency may necessitate reduction of dosage. Special care required in the elderly and in patients with phaeochromocytoma or parkinsonism. Not to be combined with levodopa.

**Amrinone** (inotropic vasodilator)
Inocor®, Winthrop, Belgium.
injection fluid 5 mg/ml.
*Indication:* short-term treatment of congestive heart failure resistant to other therapies.
*Contraindications:* thrombocytopenia, severe renal insufficiency, pregnancy and lactation.
*Caution:* platelet count and serum electrolytes should be monitored.
*Adverse effects:* thrombocytopenia, gastrointestinal disorders, cardiac dysrhythmias and hypotension.

**Astromicin** (aminoglycoside antibiotic)
Fortimycin®, Kyowa Hakkokogyo, Japan.
powder for injection 200 mg/ampoule.
*Indications:* infections caused by susceptible microorganisms.
*Contraindications, precautions and adverse effects:* as for other drugs of this class.

**Bisoprolol** (β-adrenoreceptor blocking agent)
Detensid®, Merck-Clevenot, France.
tablet 10 mg.
*Indication:* arterial hypertension.
*Contraindications:* atrioventricular block, severe bradycardia, congestive heart failure.
*Caution:* in asthma and patients receiving amiodarone.

**Bunazosin** (antihypertensive)
Detantol®, Eisai, Japan.
tablets 0.5, 1 and 3 mg.
*Indications:* essential hypertension, renal hypertension, hypertension secondary to phaeochromocytoma.
*Contraindication:* hypersensitivity.
*Caution:* in patients with impaired liver function.
Safety during pregnancy and lactation and in children not established.
*Adverse effects:* neurological, cardiovascular and gastrointestinal symptoms.

**Buspirone** (anxiolytic)
Buspar®, Mead Johnson, Belgium.
tablet 5 and 10 mg.
*Indications:* anxiety and nervous tension, sleep disturbances, irritability.
Contraindications: hypersensitivity, severe hepatic insufficiency.
Caution: in epileptic patients.

Camostat mesilate (enzyme inhibitor)
Foipan®, Ono Pharmaceuticals, Japan.
tablet 100 mg.
Indication: symptomatic treatment of acute pancreatitis.
Contraindications: severely ill patients unable to take fluids by mouth. Pregnancy. Safety in children not established.
Adverse effects: thrombocytopenia, hypersensitivity, gastrointestinal symptoms.

Carteolol (β-adrenergic receptor blocking agent)
Mikelan®, Oberval, France.
tablet 20 mg.
Indication: arterial hypertension.
Contraindications and precautions: as for other compounds of this class.

Cefbuperazone (cefalosporin antibiotic)
Keiperazon®, Kaken, Japan.
Tomiproant®, Toyama, Japan.
powder for injection 0.5 and 1 g/ampoule.
Indications: infections with susceptible microorganisms.
Contraindications, warnings, adverse effects: as for other cefalosporins.

Celiprolol (β-adrenergic receptor blocking agent)
Selectol®, Hormon-Chemie; Celiprolol Woelm, Federal Republic of Germany.
tablets 100 and 200 mg.
Indications: hypertension, angina pectoris.
Contraindications and precautions: as for other compounds of this class.

Cetirizine (H₁ histamine antagonist)
Zyrtec®, UCB, Belgium.
film coated tablet 10 mg.
Indications: seasonal rhinitis and conjunctivitis, allergic rhinitis, pruritus, urticaria.
Adverse effects: slight transient sedation.

Clebopride (antiemetic)
Amitos®, Banyu, Japan.
Clast®, Meiji Saika Kaisha, Japan.
tablet 0.68 mg.

Indication: gastric ulceration.
Contraindications: not to be used by women who are, or who may become pregnant or during lactation. Safety in children not established.

Diclofenamide (carbonic anhydrase inhibitor)
Glaucol®, Oy Star, Austria.
tablet 50 mg.
Indications: chronic wide-angle glaucoma, acute secondary glaucoma, pre-surgical lowering of intraocular pressure.
Contraindications: hypersensitivity, hepatic or renal insufficiency, hyponatraemia or hypokalaemia, respiratory or hyperchloremic acidosis, adrenal insufficiency. Not to be used during pregnancy.

Etodolac (nonsteroidal antiinflammatory agent)
Lodine®, Ayerst, France.
coated tablets 100 and 200 mg.
Indications: symptomatic long- or short-term treatment of chronic rheumatoid disease including polyarthritis and ankylosing spondylitis, painful and incapacitating arthroses, exacerbations of acute arthritis.
Contraindications: hypersensitivity, gastro-duodenal ulcer, renal or hepatic insufficiency.
Cautions: not to be used during the first or last trimesters of pregnancy. Use in late pregnancy may result in premature closure of the ductus arteriosus and haemorrhagic manifestations in the neonate.

Fluoxetine (antidepressant)
Prozac®, Lilly, Belgium.
capsules 20, 30, 40 and 60 mg.
Indication: depression with concomitant anxiety.
Contraindications: hypersensitivity; not suitable for children.
Caution: in patients with impaired hepatic or renal function.
Adverse effects: anticholinergic symptoms, reversible leukopenia, elevated transaminase concentration.

Flutamide (anti-androgen)
Eulexine®, Unilabo, France.
tablet 250 mg.
Indication: metastatic prostatic carcinoma.
**Caution:** patients should be monitored to detect methaemoglobinaemia or hepatic dysfunction.

**Gliclazide** (hypoglycaemic agent)
Glimicron®, Dainippon, Japan.
tablet 40 mg.
*Indication:* non-insulin dependent diabetes mellitus inadequately controlled by diet and exercise.
*Contraindications:* severe ketosis, diabetic coma or precoma, juvenile diabetes, hepatic or renal impairment, severe infection, gastrointestinal disorders.

**Ifosfamide** (cytostatic agent)
Ifomid®, Shionogi, Japan.
powder for injection 1 g/ampoule.
*Indications:* small-cell pulmonary carcinoma, prostatic, cervical and uterine carcinoma, osteosarcoma.
*Contraindications and precautions:* as for other cytostatic agents.

**Interferon alfa-2a** (recombinant DNA interferon)
Roferon-A®, Roche, The Netherlands.
powder for injection 3 x 10^6 IU/ampoule.
*Indication:* hairy cell leukaemia.
*Contraindications:* pregnancy, lactation, hypersensitivity.
*Cautions:* contraceptive measures are necessary during treatment and for 3 months thereafter; caution is also needed in patients with central nervous system dysfunction or renal, hepatic or bone marrow insufficiency.

**Interferon alfa-2b** (recombinant DNA interferon)
Intron®, Schering, The Netherlands.
powder for injection 5 and 10 x 10^6 IU/ampoule.
*Indication:* hairy cell leukaemia.
*Contraindications:* pregnancy, lactation, hypersensitivity.
**Caution:** patients with recent myocardial infarction; contraceptive measures are necessary during treatment and for 3 months thereafter.

**Metaclazepam** (minor tranquillizer)
Talis®, Kali-Chemie, Federal Republic of Germany.
coated tablets 5 and 10 mg.

**Indications:** acute and chronic anxiety and nervous tension.
*Contraindications:* children under 18 years of age; further contraindications as for other drugs of this class.
*Caution:* special care required in elderly patients.

**Misoprostol** (synthetic prostaglandin)
Cytotec®, Christiaensen, Belgium.
tablet 0.2 mg.
*Indication:* gastric and duodenal ulcer.
*Contraindications:* hypersensitivity, inflammatory intestinal disease, pregnancy.
*Caution:* contraceptive measures are necessary throughout treatment.

**Mupirocin** (broad spectrum antibiotic)
Bactroban®, Beecham, Belgium.
cream 20 mg/g
*Indications:* treatment of skin infections due to susceptible organisms; local prophylaxis of post-surgical or post-traumatic infections.
*Contraindications:* hypersensitivity, renal insufficiency with extensive dermal lesions or ulcers.
*Caution:* not to be applied to the eye or intranasally.

**Nabumetone** (nonsteroidal antiinflammatory agent)
Mebutan®, Bencard, Belgium.
tablet 500 mg.
*Indication:* rheumatic pain and inflammation.
*Contraindications, precautions:* as for other drugs of this class.

**Silibinin** (antidote)
Legalon®, Madaus, Belgium.
powder for injection 75.5 mg/ampoule.
*Indication:* severe intoxication with *Amanita phalloides*.
*Caution:* blood electrolytes should be monitored.

**Somatostatin** (somatotropic hormone release inhibitor)
Somatostatic Linz®, Curamed Austria.
Somatostatin, Serono, Austria.
Modustatine®, Labaz, Belgium.
Somatostatine, UCB, Belgium.
powder for injection 250 µg/ampoule.
*Indications:* severe acute gastrointestinal bleeding, after pancreatic surgery, adjunctive treatment
of intestinal ileus, pancreatic or biliary fistula. Caution: blood glucose levels should be monitored throughout treatment at intervals of 3-4 hours.

Somatrem (N-methionyl growth hormone)
Somatonorm®, Kabi Vitrum, The Netherlands.
Indication: short stature in children with complete or partial pituitary growth hormone deficiency.
Contraindication: diabetes mellitus.
Cautions: diagnosis must be confirmed before treatment is started; treatment is only effective while cartilaginous discs remain open; monitoring of thyroid function is necessary.

Terolidine (anticholinergic agent)
Mictrol®, Kabivitrum, Sweden.
Indication: incontinence, neurogenic bladder dysfunction.
Contraindications: urinary retention.

Tertatolol (β-adrenoreceptor blocking agent)
Artex®, Servier, France.
Indication: arterial hypertension.
Contraindications: asthma, congestive heart failure, atrioventricular block, Raynaud’s syndrome, severe bradycardia, severe renal insufficiency, pregnancy. Not to be combined with amiodarone.
Precautions: as for other drugs of this class.

Trifluridine (antiviral agent)
Bephen®, Bournonville, Luxembourg.
Indication: herpetic keratitis.
Contraindications: concurrent bacterial infection.

Trimazosin (alpha-adrenoreceptor blocking agent)
Cardovar®, Pfizer, Austria.
Indications: hypertension, chronic left ventricular insufficiency.
Contraindication: obstructive heart disease.
Caution: during pregnancy and lactation and in children. Ability to drive or operate machinery may be impaired. Blood and hepatic function should be monitored.

Triptorelin (synthetic analogue of luteotropic hormone releasing factor)
Decapeptyl®, Ipsen, France.
Indication: metastatic prostatic cancer.
Adverse effects: hot flushes, pain at injection site, impotence, transient hypertension.

Tulobuterol (β-adrenoreceptor stimulating agent)
Respacal®, UCB, Luxembourg.
Indications: treatment and prophylaxis of bronchial asthma and chronic obstructive bronchitis.
Contraindications, precautions: as for other drugs of this class.

Ulinastatin (proteolytic enzyme inhibitor)
Miracrid®, Mochida, Japan.
Indications: acute pancreatitis, acute exacerbation of chronic pancreatitis, acute circulatory insufficiency.
Contraindications: hypersensitivity. Safety not established during pregnancy and lactation or in children.
Adverse effects: granulocytopenia, raised serum transaminases, diarrhoea, local irritation at the injection site.
Reports from Regulatory Agencies

Aspartame

United States of America — The Food and Drug Administration has issued a final rule declaring aspartame safe for use as an inactive ingredient in human drug products. The labelling of such products obtainable over-the-counter must carry a warning directed to patients with phenylketonuria indicating that the product contains phenylalanine and disclosing the amount contained in each dosage unit.


Bromisoval

Netherlands — Having regard to the dependence potential of the weak sedative bromisoval and the risk of subsequent chronic intoxication, The Board for the Evaluation of Medicines has requested that all preparations containing bromisoval be withdrawn from the market or, in the case of combination products, reformulated to exclude bromisoval.


Buprenorphine

Finland — In the light of apparent abuse of buprenorphine (Temgesic®) discovered from prescription surveillance in the Helsinki area, the National Board of Health subjected the product to a nationwide intensive prescription monitoring programme for three months from 1 November 1986. In addition, a warning letter was issued to physicians and the product information was revised to indicate that renewable prescriptions are not to be issued.


Ceftriaxone

Australia — The Drug Evaluation Committee has revised the approved product information for products containing ceftriaxone (Rocephin®, Roche) as follows:

The indications now additionally include:

- initial treatment of meningitis in children and immunocompetent adults presumed or proven to be caused by Haemophilus influenzae type B, Neisseria meningitidis, Streptococcus pneumoniae or Enterobacteriaceae, pending culture and sensitivity results;
- as a single 1 g dose intravenously or intramuscularly immediately prior to vaginal or abdominal hysterectomy and prior to biliary tract surgery in high risk patients;
- treatment of uncomplicated gonorrhoea in men and women as a single parenteral dose of 125-250 mg.

The labelled warnings must include the following text:

“The usual daily dosage should not exceed 2 g except in certain conditions such as endocarditis, osteomyelitis, etc. due to susceptible organisms where higher doses may be necessary. The dose, however, should not exceed 4 g/day. The duration of therapy should usually not exceed 14 days except in special conditions such as endocarditis, osteomyelitis, infected joints, etc. Prolonged therapy results in a high incidence of adverse effects particularly diarrhoea, rash, eosinophilia, elevated liver enzymes and, to a lesser extent, neutropenia.”

A proposed indication relating to prophylactic use in prosthetic joint surgery was rejected on the grounds of inadequate data.

Dantron

Federal Republic of Germany — The Federal Health Office has informed the World Health Organization that the laxative substance dantron is no longer permitted as an ingredient in pharmaceutical products. These products have either to be withdrawn or reformulated to exclude dantron. The decision is based upon Japanese toxicological studies that show that dantron has a carcinogenic and genotoxic potential in rodents. Similar action has been subsequently taken in Japan, United Kingdom and the United States of America, and one of the major manufacturers (Riker Laboratories) has withdrawn these products worldwide.

References
Notifications from:
Department of Health and Social Security, United Kingdom (January 1987).
Riker Laboratories, United Kingdom (January 1987).
Ministry of Health and Welfare, Japan (February 1987).
Food and Drug Administration, United States of America (March 1987).

Dipyridamole

Israel — The Pharmaceutical Branch of the Ministry of Health has amended the approved indications for preparations containing the vasodilator agent dipyridamole as follows:

• prevention of thrombogenic disorders;
• as an adjunct to oral anticoagulants in patients with artificial heart valves;
• for use in association with acetylsalicylic acid (aspirin) in patients with recurrent chronic deep vein thrombosis resistant to oral anticoagulant therapy; and
• for patients undergoing coronary artery surgery.

Chronic coronary deficiency is disallowed as an indication, having regard to the lack of definitive evidence that it is of value in this condition.


Flunarizine

Federal Republic of Germany — The Federal Health Office has informed the World Health Organization that the product information for preparations containing flunarizine (Sibelium®, Janssen) has been modified to indicate that:

• lassitude and weight increase are liable to occur at the beginning of treatment;
• involuntary movements, rigidity, tremor and depression may occur, particularly in elderly patients and at high dosages (over 10 mg/day);
• orofacial dyskinesia may develop during prolonged treatment.

It is stressed that these disorders of movement necessitate immediate discontinuation of treatment or reduction of the dose.


Glafenine

Oman — The Central Drugs Committee has prohibited the importation of pharmaceutical products containing glafenine, having regard to reported adverse reactions.

Reference: Letter to WHO from the Directorate General of Pharmacy and Medical Supplies, Muscat, Oman, 17 December 1986.

Mefloquine

Australia — The Drug Evaluation Committee has extended the approved indications for mefloquine (Lariam®, Roche) to include short-term prophylaxis of Plasmodium falciparum malaria. Its use should be restricted to travellers spending less than one month in countries with P. falciparum malaria resistant to chloroquine-pyrimethamine combinations.

Mianserin

Netherlands — The Board for the Evaluation of Medicines has informed WHO that the approved product information on pharmaceuticals containing mianserin (Tolvon®, Organon) has been revised to include the following boxed warning:

"Tolvon® may cause bone marrow depression. This usually presents as granulocytopenia or agranulocytosis, which typically becomes evident after four to six weeks of treatment and is usually reversible after discontinuation. Should a patient develop symptoms indicative of an infection (e.g. fever, sore throat or stomatitis), a blood cell count must be performed. This adverse effect has been seen in patients of all ages, but predominantly in the elderly."

The Board has insufficient information to estimate the incidence of the effect but it considers that the number of reports it has received justifies an explicit warning.


Oman — The Central Drug Committee has prohibited the import of pharmaceutical products containing mianserin, having regard to reported adverse reactions.

Reference: Letter to WHO from the Directorate General of Pharmacy and Medical Supplies, Muscat, Oman, 17 December 1986.

Midazolam

United States of America — The Food and Drug Administration has revised the labelling of midazolam hydrochloride injection (Versed®, Roche) to emphasize the importance of observing the approved instructions for dosage and administration. Seventeen instances of respiratory or cardiac arrest have been reported in patients who received the drug. Midazolam hydrochloride is related to the benzodiazepines. It was approved in December 1985 and first marketed in March 1986 for sedation prior to surgery and diagnostic or endoscopic procedures, and for induction of general anaesthesia before administration of other anaesthetic agents.


Ornipressin

Federal Republic of Germany — The Federal Health Office has revised the approved product information for the vasopressin analogue, ornipressin (POR-8®, Sandoz), which is used to induce local ischaemia during surgery. The maximum indicated dose has been reduced to 2.5 IU and cardiac arrest is now mentioned as a rare complication.

The action resulted from reports of cardiac arrest in two patients who received ornipressin prior to surgery.


Paracetamol

Belgium — The General Pharmaceuticals Inspectorate of the Ministry of Public Health and the Environment has decided that the product information on pharmaceuticals containing paracetamol should now contain the following warning:

"This product contains paracetamol. Do not exceed the prescribed or recommended dose or duration of treatment. If the symptoms persist, consult your doctor."

If no package insert is provided, the text must appear either on the container of the drug or on the outer package.

Ritodrine

United States of America — The Food and Drug Administration has informed WHO that the product information on pharmaceutical preparations containing the β-sympathomimetic agent ritodrine (Yutopar®, Astra) has been revised to include a warning regarding the effect of this class of compounds on myocardial activity. The section on adverse effects now also includes reference to the possibility of impaired liver function.


Sodium valproate

Sweden — The National Board of Health and Welfare has additionally approved the use of sodium valproate (Ergenyl®, Erco Läkemedel AB) for the treatment of generalized epileptic attacks associated with petit mal, myoclonic or atonic attacks, and for tonic-clonic attacks (grand mal) that are inadequately responsive to other drugs. Treatment of focal epilepsy is also approved when other therapy has failed.


Sulfasalazine (salazosulfapyridine)

Australia — The Drug Evaluation Committee has additionally approved the use of sulfasalazine (Salazopyrin®, Pharmacia) for the treatment of rheumatoid arthritis which has failed to respond to nonsteroidal anti-inflammatory drugs.


Sweden — The National Board of Health and Welfare has approved an extension of the indications for sulfasalazine to include the treatment of active rheumatoid arthritis not responding to anti-inflammatory agents or antimalarials.


Triazolam

France — The National Pharmacovigilance Commission has carried out an assessment of benzodiazepines used as hypnotics or anxiolytics. In particular, triazolam (Haicion®, Upjohn) has been shown to be associated with relatively high numbers of severe adverse effects including behavioural disturbances, such as aggressivity or incoherence, amnesia, rebound insomnia and withdrawal symptoms.

Between October 1984 and December 1985, the Commission received reports of more than 100 such reactions, some of which resulted from criminal abuse of the product. The Ministry of Health has consequently decided to:

- withdraw tablets containing 0.50 mg;
- reduce to ten the number of 0.25 mg tablets per pack; and
- encourage the prescription of a lower dose tablet (0.125 mg) which will shortly be placed on the market.

Regulatory Matters

Biotechnology drugs in the EEC

The Directorate-General for Internal Market and Industrial Affairs of the Commission of the European Communities in Brussels has drafted a document entitled On Requirements for the Production and Quality Control of Medicinal Products Derived by Recombinant DNA Technology. This document, which has been submitted to the Committee for Proprietary Medicinal Products (CPMP), is intended to facilitate the collection and submission of data to support applications for marketing authorizations within the EEC for medicinal products derived by rDNA technology and intended for use in man.


Investigational new drugs available to desperately ill patients

United States of America — In the Federal Register of 22 May 1987 the Food and Drug Administration issued final procedures under which promising investigational new drugs may be made available to desperately ill patients before general marketing is authorized (1). The procedure is intended to facilitate the availability of such drugs to patients on a compassionate basis as early in the drug development process as possible, and to obtain additional data on their safety and efficacy.

The FDA may deny a request for such use if the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that a drug may be effective, or would expose the patient to an unreasonable and significant additional risk of illness or injury.

These new proposals would offer more patients access to new drugs in the preregistration period and companies would be permitted to charge for supplies provided under these arrangements. The view of the FDA is that this will provide for greater competition in drug development. Paradoxically, however, the Pharmaceutical Manufacturers Association, while praising the intent of the proposal, has warned of the possibility that, if manufacturers sell their products before they are approved, pressure to work for full approval could be reduced (2).

References

Adverse reaction reporting by companies

United Kingdom — The Medicines Act Information Letter of March 1987 provides new guidelines to licence holders on their responsibility for reporting adverse reactions to their products that are either marketed or under clinical trial in the United Kingdom. Companies are expected to validate fully and follow-up all serious reactions that they report to the Licensing Authority, wherever they may have occurred.

Reactions occurring in the United Kingdom:

- All spontaneous reports relating to new drugs must be notified immediately as well as serious reactions or effects attributed to longer established products. For this purpose, “serious reactions or effects” are those that are fatal, life-threatening, disabling, incapacitating, or which result in, or prolong, hospitalization.
• Similarly, all serious reactions or effects associated with drugs under clinical trial, or subject to post-marketing surveillance, should be reported immediately. Minor reactions should be reported in summary at the conclusion of each study.

• In addition, details of reports in published literature should be provided and followed up by the company as for any other type of report.

Reactions occurring abroad:

Reports of suspected adverse reactions to licensed products which occur in other countries must also now be submitted to the Licensing Authority when they are both serious and unpredictable. The Medical Department of the company is additionally required to advise the Licensing Authority if a specific reaction is reported to it from abroad in such numbers as to warrant a change in the approved data sheet.


Purity standards for bulk drug supplies

United States of America — The Division of Generic Drugs of the Food and Drug Administration has informed applicants seeking marketing approval for generic products that bulk drugs must meet both the United States Pharmacopeia (USP) and British Pharmacopoeia (BP) formulary standards as a de facto prerequisite to agency approval. The BP standards are being additionally required because they are considered to be more rigorous in their requirements relating to impurities.


Amendment to the EEC Cosmetics Directive

On 27 February 1987 the Commission of the European Communities amended its rules relating to cosmetic products by:

• prohibiting the sale or dispensing of such products containing captan, hexachlorophene and minoxidil (including its salts and derivatives) as from 1 December 1990;

• extending the period during which the following preservatives may be included in products: phenoxypropan-2-ol and benzalkonium chloride, bromide and saccharinate (31 December 1987), benzethonium chloride (31 December 1988);

• definitively permitting the use of green colouring agents (Colour Index Nos. 77288 and 77289) that are free of chromate ions.

Member States of the EEC are required to implement these directives not later than 31 December 1987.


Controlled drugs: renewal of prescriptions

United States of America — The Drug Enforcement Agency of the Department of Justice has issued a final ruling that reduces the required paperwork for dispensing drugs listed as controlled substances in Schedule III or IV of the national narcotic regulations.

This allows up to five renewals of an original prescription for products containing these substances within six months of the day it was issued.

The pharmacist is allowed discretion to accept verbal authorization to renew a prescription within these limits, provided details of the renewal are entered on the back of the original form.

Advisory Notices

Allopurinol

**Australia** — The Adverse Drug Reactions Advisory Committee is concerned that allopurinol may frequently be prescribed for patients who do not need it and that its potential toxicity may not be well enough appreciated by those who prescribe it for marginal indications.

While some adverse reactions associated with the drug are due to hypersensitivity or idiosyncrasy, others may reflect the consequences of inappropriately high doses, particularly when renal function is impaired.


Pivmecillinam and oesophageal injury

**United Kingdom** — The Committee on Safety of Medicines has received reports of dysphagia or oesophagitis in patients who had taken Selexid® (pivmecillinam) or Miraxid® ( pivampicillin + pivmecillinam). It also cites a report from the Swedish Adverse Drug Reaction Advisory Committee which describes 20 patients who developed retrosternal pain, with or without dysphagia, during the first few days of treatment with pivmecillinam.

Endoscopy showed oesophageal ulceration in 15 patients. In most cases the patients had swallowed their tablets with very little fluid or just before lying down, though a few had apparently taken them with water or food.

Pivmecillinam has a local irritant effect on the oesophageal mucosa that can be largely avoided by taking the tablets with at least half a glass of water.


Cardiotoxicity of astemizole

**United Kingdom** — The Committee on Safety of Medicines has received reports of three cases of ventricular tachycardia following overdose with astemizole (Hismanal®, Janssen Pharmaceuticals). Two patients respectively took a single overdose of 200 mg and 400 mg; the third had taken 20 mg daily intermittently over 2-3 years and had a plasma concentration of astemizole in excess of the therapeutic range. All three patients recovered, but the manufacturer has written to all doctors pointing out that:

- the electrocardiogram should be monitored in cases of suspected astemizole overdose so that appropriate antidysrhythmic treatment can be given, if necessary.
- the dose of astemizole is 10 mg ONCE DAILY. Up to 30 mg daily can be given for a few days when treatment is started, but thereafter the 10 mg daily dose MUST NOT BE EXCEEDED.


Amphetamine congeners

**Canada** — The Expert Advisory Committee on Psychotropic Drugs of the Health Protection Branch of the Ministry of Health and Welfare has recently reviewed the use of amphetamine congeners contained in anorectic agents including amfepramone, chlorphentermine, fenfluramine, mazindol and phentermine.

- It has recommended that the routine use of anorectic drugs for obesity should be discouraged and that more reliance be placed on alternative methods of treatment including self-monitoring of
weight, nutritional education and increased physical activity.

- It reminds doctors of the abuse potential of anorectics containing amphetamines and underscores the need for continued control of these products and monitoring of their use.

The Committee also makes a plea for further clinical studies to be carried out to confirm and more precisely define the value of amphetamines in other conditions, and particularly:

- the use of fenfluramine in the treatment of childhood autism and as an adjunct in the treatment of type II diabetes and bulimia.
- the use of mazindol in the treatment of mild parkinsonism and narcolepsy and in the control of micturition.


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**Aminoglycoside antibiotics**

**Singapore** — The Department of Pharmacology of the National University has reminded doctors of the need to restrict the use of the aminoglycoside antibiotics including amikacin, gentamicin, kanamycin, neomycin, netilmicin, sisomicin and tobramycin, having regard to the risk of nephrotoxicity, ototoxicity, neuro-muscular blockade and hypersensitivity.

It is proposed that these drugs should be used only in severe infections caused by pathogens resistant to other less toxic antibiotics and in severe infections, such as bacterial endocarditis, when immediate broad-spectrum combination antibiotic therapy must be instituted before blood cultures are available. Serum drug concentrations must always be measured in order to ensure adequate drug levels, while renal function should be closely monitored.

Reference: *Drug Information Newsletter*, University of Singapore, 5, No. 4, October 1986.
Essential Drugs

Schistosomiasis affects 200 million people

Schistosomiasis is a water-borne parasitic infection caused by several species of trematode worms (blood flukes). It affects about 200 million people in tropical and subtropical regions where it is a hazard particularly to individuals who enter fresh water emanating from irrigation and water resource development schemes. Its socioeconomic impact is outstripped only by malaria.

Microscopic miracidia released from eggs excreted by infected individuals penetrate various species of freshwater snails where they develop into free-swimming cercariae that can penetrate human skin and thus complete the transmission cycle. The adult worms which develop from the different species of cercariae mature in the blood vessels of different organs and produce distinctive clinical forms of the disease.

Intestinal schistosomiasis

This disease, which is most commonly caused by Schistosoma mansoni, is widely endemic in tropical regions of Africa, South America and the Eastern Mediterranean. The adult worms, which do not multiply in the body, develop in the mesenteric and portal vessels and the clinical sequelae of the disease are caused predominantly by eggs shed by female worms. Many are excreted in the faeces but others become embedded in the liver and the large intestine where they induce granulomatous and fibrotic reactions.

Light infections cause few clinical symptoms but severe chronic infections, associated with high faecal egg counts, can result in portal hypertension characterized by hepatosplenomegaly, oesophageal varices and ascites. Polyp formation within the large intestine occurs less frequently in most areas but is common in Egypt where it is associated with chronic bloody diarrhoea.

Similar patterns of infection are caused by:

- S. mekongi, which is endemic in South-East Asia.
- S. intercalatum, which occurs in Central Africa.
- S. japonicum, which occurs predominantly in China, Indonesia and the Philippines and is responsible for Oriental or Asiatic intestinal schistosomiasis. Granulomatous lesions in the brain sometimes result in epilepsy and focal neurological signs.

Urinary schistosomiasis

This disease, caused by S. haematobium, is endemic in the Eastern Mediterranean region and Africa. The adult worms lodge in the vesical plexus and the females produce eggs that are either excreted in the urine or remain embedded in the bladder wall. Haematuria, which increases with the intensity of the infection, results from ulcerative and papillomatous lesions in the bladder, while involvement of the lower ureters can lead to chronic obstructive uropathy and subsequent renal failure. In some areas S. haematobium is an important cause of bladder cancer.

Prevention

Attempts have been made to eliminate the snail vector using environmental, chemical and biological methods, but these approaches are costly and can be implemented effectively only on a very localized scale. However, niclosamide is still used effectively as a molluscicide where transmission sites are small and seasonal.

Efforts are now directed to reducing the number of schistosome eggs in contaminated water through:

- community health education;
- efficient sewage disposal and provision of potable piped water supplies; and
- chemotherapy.
Chemotherapy

Various operational approaches are used with the dual objectives of reducing:

• the incidence of severe disease, and
• the intensity of transmission.

The best results have been obtained where specialized mobile teams work in close collaboration with primary health care workers in an effort to treat a high proportion of the infected individuals in a locality within a short period of time.

Selective treatment

Either all infected individuals within an exposed population, or all individuals exposed to particular risk are treated. The selection process may be based upon:

• identification and treatment of groups of individuals at particular risk, particularly of children (selective group treatment), or

• screening of urine and/or stool specimens obtained from every individual in an entire group or community (selective population chemotherapy), or

• a combination of risk assessment and screening.

Screening is generally done either by microscopic examination of urine or fluid extracts of faeces, or by detecting blood in urine with chemical reagent strips. Serodiagnostic tests are used mainly for the diagnosis of individual patients in non-endemic areas.

Mass treatment

The treatment of the entire population without diagnosis is not considered to be cost-effective unless reliable epidemiological data indicate that at least some 75% of the population is infected.

Drug selection

Praziquantel has transformed the treatment of schistosomiasis. It is effective, often in a single dose against all strains of the parasite. It is thus of particular value in patients with mixed infections and those who do not respond adequately to other drugs. It is also extremely well tolerated and is well suited for mass community treatment.

Extensive use over several years has provided no evidence of serious adverse effects or long-term toxicity nor has it been shown to have mutagenic or carcinogenic activity in experimental animals.

However, older drugs are still widely used. These include metrifonate, which is active against *S. haematobium*, and oxamniquine, which is effective against *S. mansoni*.

Antimony salts, stibocaptate, hycanthone and niridazole have now been largely superseded because of their greater toxicity.

Praziquantel

tablet 600 mg

Praziquantel is chemically unrelated to other anthelmintics and is highly active against a wide range of trematodes and cestodes, including all species of schistosomes pathogenic to man.

It is rapidly absorbed when taken orally and 80% of the dose is excreted as metabolites in the urine within 24 hours. Schistosomes, however, do not metabolize praziquantel. Immediately after exposure the worms contract, lose their anchorage on blood vessels, and gradually disintegrate.

Uses

*Schistosomiasis*

Praziquantel is effective in all forms of schistosomiasis, both in the acute stage and in patients with extensive hepatosplenic involvement.

Even when a radical cure is not obtained, egg counts in faeces or urine are often considerably reduced for more than one year.
Dosage of praziquantel in schistosomiasis

<table>
<thead>
<tr>
<th></th>
<th>Dose (mg/kg)</th>
<th>Initial cure rate (%)</th>
<th>Reduction in egg count after 1 year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. haematobium</em></td>
<td>40</td>
<td>80-95</td>
<td>90-95</td>
</tr>
<tr>
<td><em>S. mansoni</em></td>
<td>40-60</td>
<td>60-90</td>
<td>95</td>
</tr>
<tr>
<td>Mixed <em>S. haematobium</em>/<em>S. mansoni</em></td>
<td>40-60</td>
<td>60-75</td>
<td><em>S. haematobium &gt; S. mansoni</em></td>
</tr>
<tr>
<td><em>S. intercalatum</em></td>
<td>40</td>
<td>60-80</td>
<td>95</td>
</tr>
<tr>
<td><em>S. japonicum</em></td>
<td>60</td>
<td>60-80</td>
<td>95</td>
</tr>
<tr>
<td><em>S. mekongi</em></td>
<td>60</td>
<td>60-80</td>
<td>95</td>
</tr>
</tbody>
</table>

Praziquantel is of particular value in:
- intestinal schistosomiasis due to *S. japonicum*, *S. intercalatum* or *S. mekongi* since these are not responsive to oxamniquine;
- *S. mansoni* infections unresponsive to oxamniquine;
- double infections with *S. haematobium* and *S. mansoni* which otherwise require treatment with both metrifonate and oxamniquine.

*Other trematode (intestinal, liver and lung fluke) infections:*

Praziquantel is highly effective in infections due to the following trematodes: *Fasciolopsis buski*, *Metagonimus yokogawi*, *Heterophyes heterophyes*, *Clonorchis sinensis*, *Opisthorchis viverrini*, *Opisthorchis felineus* and various species of *Paragonimus*.

**Dosage in other trematode infections**

Virtually 100% cure rates have been obtained in the majority of fluke infections with a dose of 25 mg/kg three times daily for two consecutive days. Larger doses are required for eradication of *Fasciola hepatica*, but no firm recommendation can be offered on the basis of currently available information.

**Contraindications and precautions**

The possibility should be borne in mind, when praziquantel is used in areas endemic for cysticercosis, that its parasiticidal effect on cysts in the cerebrum is likely to provoke a brisk localized oedematous reaction. No evidence is on record that this has ever resulted in serious sequelae.

**Use during pregnancy and lactation**

Praziquantel has not been shown to be teratogenic or embryotoxic. However, it is preferable to delay treatment until after delivery unless immediate intervention is essential.

Because praziquantel is excreted into breast milk, breast-feeding should be interrupted for 72 hours after dosage.
Adverse effects

Praziquantel is exceptionally well tolerated. However, in patients with heavy worm loads treatment may induce abdominal discomfort, nausea, headache, dizziness and, rarely, pyrexia, urticaria and rectal bleeding.

Storage

Praziquantel tablets should be kept in a well-closed container, protected from light.

Metrifonate

tablet 100 mg

Metrifonate is an organophosphorus compound originally used as an insecticide. It has selective and variable schistosomicidal activity against *S. haematobium* that results from its partial metabolism to a highly active anticholinesterase, dichlorvos. Schistosomal cholinesterase is more susceptible to this metabolite than that of the human host, but transient reductions in both plasma and erythrocyte cholinesterase activity are demonstrable at therapeutic dosage. However, despite early concerns about its potential toxicity, metrifonate is well tolerated and has been used effectively and extensively in mass control programmes.

Uses

Urinary schistosomiasis (mainly *S. haematobium*).

Dosage

*Adults and children:* 7.5 mg/kg on three occasions at intervals of 2 weeks cures 40%-80% of cases. Even when viable worms remain, egg counts after one year are reduced to less than 20% of pre-treatment levels.

The responses to doses of 10 mg/kg at intervals of 3, 6 or 12 months are similar.

Contraindications and precautions

Mass chemotherapy should not be undertaken in communities recently exposed to insecticides or other agricultural chemicals with an anticholinesterase action.

Treated patients should not receive depolarizing neuromuscular blocking agents until at least 48 hours have elapsed from the time of administration.

Use during pregnancy and lactation

Metrifonate has not been shown to be teratogenic or embryotoxic. However, it is preferable to delay treatment until after delivery unless immediate intervention is essential.

In the absence of information on whether metrifonate is excreted in breast milk, it should preferably not be administered to nursing mothers.

Adverse effects

Cholinergic symptoms rarely occur with currently recommended dosages. Transient nausea, vomiting and a feeling of weakness were encountered during early trials at higher dosages.

The depressed blood cholinesterase activity has not been reported to give rise to clinically-evident signs or symptoms.

Overdosage

Atropine sulfate (1 mg every 6 hours) may be used as a specific antidote to relieve symptoms of cholinergic activity. This does not impair the antiparasitic action.

Pralidoxime iodide has potential value as an enzyme reactivator in the unlikely event of life-threatening enzyme inhibition, but there are no reports of its use in these circumstances.

Storage

Metrifonate tablets should be kept in a tightly closed container and stored at a temperature not exceeding 25°C but preferably in a refrigerator.
Oxamniquine
capsule 250 mg - syrup 50 mg/ml

A tetrahydroquinoline derivative with selective and variable schistosomicidal activity against *S. mansoni*. Male schistosomes are more susceptible than females but residual female worms cease to lay eggs after exposure and lose pathological significance.

Resistant strains, which have been reported particularly in South America, have subsequently been effectively treated with praziquantel.

Oxamniquine is reliably absorbed when administered orally and is extensively metabolized to inactive acid metabolites that are excreted in the urine. It is well tolerated and has been used effectively and extensively in mass control programmes.

Uses

Intestinal schistosomiasis (*S. mansoni*) both in the acute stage and in patients with hepatosplenic involvement.

Dosage

The effective dose varies. The following regimens provide general guidance but definitive recommendations should be based on local experience.

**South America, the Caribbean Islands and West Africa:**
Adults: a single dose of 15 mg/kg.
Children (less than 30 kg): 20 mg/kg in 2 divided doses.

**East and Central Africa and the Arabian peninsula:**
Adults and children: 30 mg/kg daily in 2 divided doses.

**Egypt, South Africa and Zimbabwe:**
Adults and children: 60 mg/kg administered over 2-3 days. The maximum single dose should not exceed 20 mg/kg.

Cure rates of 60% to 90% have been reported. Even when viable worms remain, egg counts after one year are reduced to less than 20% of pre-treatment levels.

Contraindications and precautions

Since seizures have been precipitated, epileptic patients should remain under observation for several hours following treatment.

Use during pregnancy and lactation

Oxamniquine has not been shown to be teratogenic or embryotoxic. However, it is preferable to delay treatment until after delivery unless immediate intervention is considered essential.

In the absence of information on whether oxamniquine is excreted in breast milk, it should preferably not be administered to nursing mothers.

Adverse effects

Mild and transient dizziness and drowsiness occur in about one third of patients. Headache, vomiting and diarrhoea may also be troublesome, but they may be due to the action of the drug on the worms.

Hallucinations, excitation and epileptiform convulsions have rarely been reported.

Serum transaminases are transiently raised in some patients, but the drug may be safely used in patients with severe hepatosplenic involvement.

In Egypt and some other countries within the Eastern Mediterranean Region some patients develop transient fever, peripheral blood eosinophilia and scattered pulmonary infiltrates (Loeffler's syndrome) after a three day course of treatment has been completed.

Storage

Oxamniquine tablets should be kept in a well-closed container, protected from light.
A prospective schistosome vaccine

Scientists from the Institut Pasteur and Transgène in France have successfully cloned and expressed an antigen from extracts of adult worms of *Schistosoma mansoni* which, in the laboratory, promises to protect animals against schistosome challenge.

RNA from adult worms was used to synthesize complementary DNA which, in *Escherichia coli*, produces a protein identical to an antigen present in adult worms. In rats and hamsters a fragment of this protein stimulates production of specific IgG and IgE antibodies that recognize the naturally occurring protein.

References


Hospital drug formularies

*United Kingdom* — The objectives and the value of drug formularies continue to attract discussion and the topic has recently been the subject of editorial comments in both the *Lancet* and the *British Medical Journal*.

The *Lancet* claims uncompromisingly that the debate on local hospital formularies is over: formularies are here to stay and their influence on prescribing will undoubtedly grow. It defends the strength of this assertion by pointing out that the initiative for this development has come from within the profession and that local therapeutics committees throughout Britain now sponsor some sort of recommended drug list. The advantages, it contends, are plain to see. At the very least, unnecessary drug expenditure is identified and restricted, while at best, more intangible benefits can be anticipated through continuing education of young (and older) doctors.

The commentary acknowledges warnings within the pharmaceutical industry that acceptance of such an approach countrywide will compromise future drug innovation, and it concedes that local formularies may discourage the development of "me-too" agents. If so, they may succeed in directing research towards therapeutic needs rather than commercial innovation. There are no grounds for believing that a good new drug supported by well-conducted clinical trials will not quickly be recognized and incorporated in recommended drug lists. Some doctors, it recognizes, will complain that their freedom to prescribe will be jeopardized. While no one would question a doctor's right to prescribe appropriately for his patient, surely no one would defend inexpedient or unnecessarily expensive drug administration.

The *British Medical Journal* takes up the latter point by emphasizing that individual clinical freedom carries with it the responsibility to define a personal formulary and to relate it to the agreed recommendations of fellow prescribers. Most hospital doctors, it believes, would appreciate regular information about their prescribing patterns and the relative costs of the drugs they use. It looks forward to the day when hospital formularies become operational, accepted, and successful in every district hospital and it stresses that, whereas the British National Formulary lists over 4000 drugs, some successful hospital formularies contain as few as 400, a number that has obvious potential for rationalizing purchasing as well as prescribing practices.

The article cites the example of a provincial hospital where the annual forecast drugs bill was significantly underspent when a formulary policy was supported by ward pharmacy services. It also cites the estimate of the American Society of Hospital Pharmacists that operating a formulary system—not merely producing a list—can save 17% or more on overall drug costs and up to 40% on multisource products.

References

Another endorsement of primary health care

Nigeria — The correspondent of The Lancet in Nigeria comments that Nigeria's decision to adopt a National Drug Formulary and to compile a list of 205 "essential" drugs comes as no surprise to those familiar with the commitment of Prof. Olikaye Ransome-Kuti, the Federal Minister of Health, to primary health care. Henceforth, the Minister has decided that import licences will only be awarded for products that are on the essential drugs list.

The list, which will be reviewed every year, will not include traditional medicines which will continue to be available, as before, to rural populations. Many health professionals in Nigeria, it seems, are not yet aware of the adoption of the list, and others have already expressed concern that it will restrict the freedom of choice of prescribers in the government health services.

The government itself, however, perceives rationalization of procurement and distribution as the only way to eliminate some of the existing shortages and inefficiencies and to increase the availability of essential drugs without raising their prices. It recognizes the need to persuade doctors of these advantages and to encourage them to adopt a more scientifically based approach to their prescribing practices. Some, it is claimed, are still in the habit of prescribing antibiotics, injectable antimalarials, antipyretics and analgesics for every case of fever. Such polypharmacy may impress the occasional patient, but it is beyond the reach of most and disregards the risks of unnecessary drug-induced toxicity.

The correspondent notes with satisfaction that since the WHO Model List of Essential Drugs was first drawn up in 1977, more than 80 countries have adopted similar lists adjusted to their specific needs. The Nigerian decision is regarded as particularly important, however, not only because of the size of the population that will benefit but because of the influence the decision will have in other countries throughout Africa.


Joint Therapeutic Commissions in Africa: commercial sponsorship

Warner-Lambert — which for several years has sponsored "Tropicare", a million-dollar health care education programme for Africa — has recently announced that senior executives of the company will participate in Joint Therapeutic Commissions in Senegal, Ivory Coast, Cameroon, Zaire, Kenya and Nigeria. The objective of these Commissions is to foster cooperation between industry and developing countries as a way of achieving WHO's target of "Health for all by the year 2000". Thus far, the Commissions have operated independently of corporate interests and have included among their members key health officials, the Deans of the Schools of Medicine and Pharmacy, heads of university departments and local representatives of WHO, UNICEF and USAID.

Reference: Tropicare, Warner-Lambert International, P. O. Box 377, Morris Plains, NJ 07950, USA.

Living with limited drug lists

United Kingdom — Since April 1985 the prescribing of drugs in certain categories within the National Health Service has been restricted to a "limited list". One year after the introduction of the list, the Drug and Therapeutics Bulletin sent a questionnaire to 1500 general practitioners of whom 717 replied. Most doctors found few, if any, difficulties in adapting to the list, but an important minority reported that they and their patients had experienced problems. In particular, many patients were resistant to changing from an unlisted to a listed benzodiazepine. Perhaps significantly, the two categories that created the greatest difficulties for prescribers — cough medicines and multivitamin preparations — are also those for which evidence of efficacy is scanty and convincing indications are few. Given the concern that the list aroused when it was first introduced, the outcome of the questionnaire is interpreted as a resounding vindication of the government's policy. Even fewer problems would have emerged, it is suggested, if doctors had
been more closely consulted, and if the public had been better informed about the advantages of rationalization.


**Effects of national drug policy in Bangladesh**

A Bangladesh Government Committee has recently formulated proposals aimed at reducing drug prices, providing incentives for local production and improving process quality control. A proposal to "grade" companies according to their quality-control capabilities has attracted particular attention and given rise to lengthy discussion on how appropriate criteria might be set.

These proposals and the effects of the Drug Control Ordinance enacted in Bangladesh in 1982 to encourage the production of good quality essential drugs have recently been reviewed in the *Lancet*. The most controversial measure resulting from the Ordinance was the removal of some 1700 drugs described as "useless, non-essential and/or harmful", which led to a wave of protest not only from multinational and local companies but also from the Bangladesh Medical Association. It is anticipated that simmering controversy may flare again as a result of the current proposals to reduce prices further. However, most companies have learned to live with the drug policy and, for some local manufacturers, it has brought substantial benefits. Four local companies now figure in the top ten producers and, although sales by multinational companies have not dropped in absolute terms, their share of the market has declined by about one third from 65% to 43% in 1985.

Underlying these changes, it is claimed, is a vast increase in the local production of the 45 drugs designated as essential for primary health care. These are now said to account for more than half the production capacity of seven of the top ten companies. Moreover, by requiring companies to obtain prior approval for the import of raw materials for these products, not only have the prices been reduced, but considerable savings have been made in foreign exchange.

The Minister of Health and Family Affairs, Mr Salauddin Quader Chowdhury, has described the Bangladesh drug policy as "a dynamic step that could be beneficial to the Third World at large. If there is anything for which this particular administration will be remembered nationally and internationally, it will be in bringing forward a revolutionary policy in drug administration which is suited to the limited financial resources of our country and the priorities of our people".

Recent Publications

French Pharmacopoeia
10th edition, 4th supplement

France — The 4th supplement of the 10th edition of the French Pharmacopoeia has recently been published. Several chapters have been revised or modified and a new chapter is included on drug interactions. Among the 272 monographs contained in the volume, 96 are new. An interesting insight is provided into the pace at which international collaboration is now developing in this field: almost three quarters of the monographs presented conform to the European Pharmacopoeial specifications.


Pharmaceuticals classified as narcotic substances on sale in Europe

The Council of Europe has published the 25th edition of Proprietary and other pharmaceuticals classified as narcotic substances and on sale in the 21 Member States of the Council of Europe (position as 1 April 1986). The document has been prepared by the Committee of Experts on Pharmaceutical Questions (Partial Agreement) and contains two lists:

- List 1 adopts a common official nomenclature for narcotic substances which are classified in alphabetical order under the Latin version of the agreed international nonproprietary names.
- List 2 is an updated inventory of proprietary pharmaceutical products on sale in Member States which are controlled under the international narcotics conventions.


USAN and USP Dictionary of drug names - 1988 edition

United States of America — The 1988 edition of this volume provides a comprehensive list of more than 20,000 nationally "established names" of pharmaceutical substances that is derived from the list of US Adopted Names complemented by names drawn from the US Pharmacopeia and the US National Formulary. 4948 international nonproprietary names (INN) selected by WHO are also included as well as approximately 2500 graphic formulas. Additionally, more than 5600 brand names of products produced by research-oriented firms are listed. These names are cross-indexed in the main list by pharmacological-therapeutic categories.


Manual on drug supply for developing countries

The Fédération Internationale Pharmaceutique (FIP) and the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) have sponsored the publication of the second edition of a manual for developing countries entitled "Management of drug purchasing, storage and distribution".

The distinction between "vital drugs", which include analgesics, and "essential drugs", which embrace preparations for less severe diseases, creates a distinction which is confusing rather than illuminating, and some statements like "quality defects are rare since the manufacturer is, in his own interest, keen to sell perfect goods" have an idealistic ring. However, the manual provides useful information on drug storage and distribution, transport and training of personnel. Of particular
interest are the chapters on the cold chain for vaccines and sera, and on improving distribution and communication at primary health care level.


Self-medication in Benin

Benin — An urgent need to promote better standards of self-medication is called for in a doctoral thesis recently submitted by Aubert-Stéphane Akangah to the National University of Benin. Almost three quarters of the individuals interviewed in a survey of 275 urban households in Cotonou tried to solve their health problems by self-medication. Many others visited a health centre, a traditional healer or a religious sect. Over half the households kept a box containing pharmaceutical products of which over a third were remnants of previous prescriptions. The main “stand-bys” were analgesics, antimalarials, laxatives, anti-diarrhoeal agents, anthelmintics, antibiotics and “tonics”. Out of the total of 291 pharmaceutical products catalogued in the survey only 25 were on the national list of essential drugs.


Guidelines for the review of dependence-producing drugs

Guidelines for the WHO review of dependence-producing psychoactive substances for international control are available on request from the World Health Organization.


An index to GMP regulations

The WHO Collaborating Centre for Drug Information and Quality Assurance (Budapest, Hungary) has compiled, in Drug Regulation Index No.4, a bibliography of documents, guidelines and regulations relating to Good Manufacturing Practices (GMP) as published by international organizations and national regulatory authorities.

Reference: Drug Regulation Index No.4, 1987, WHO Regional Office for Europe, Scherfigsvej 8, 2100 Copenhagen, Denmark.

Drug registration in Singapore

Singapore — The Ministry of Health has issued a guide that provides an overview on how the registration system required under the 1975 Medicines Act will be implemented. The booklet describes in detail the different types of licences that will be required for manufacturing and marketing pharmaceutical products, the certification procedures required for importing and exporting supplies, and general requirements to be observed in record-keeping when products are recalled or their licences are varied, suspended or revoked.

Initially, the following groups of items will be exempted from registration:

- Traditional medicines,
- Homoeopathic medicines,
- Raw materials,
- Locally manufactured products solely for export,
- Products imported for specific treatment of individual persons only (prior approval must be obtained from the Ministry of Health before import).

Once all currently marketed products have been registered a General Sales List will be compiled to indicate which may be sold over-the-counter from outlets other than pharmacies. All other products, including those subjected to prescription control, will be available only from registered pharmacies.

Informatics and telematics in health

The pace of development in computer and telecommunications technology is rapidly opening up new possibilities. The impact of this technology, thus far, has been much greater in clinical medicine than in public health, and it is for this reason that WHO has recently issued a manual to apprise national health authorities of the potential uses of informatics in the management of health services, including pharmacy and drug logistics control systems. It includes advice on training personnel in the use of available systems, describes hardware and software packages and offers information on the costs and maintenance of equipment.


AIDS - The safety of blood and blood products

The need to ensure that donor blood and products derived from it carry no risk of transmitting the viruses responsible for serious diseases has intensified considerably with the advent of AIDS. The various issues that fall to consideration were identified and discussed at a meeting convened by WHO in April 1986, and the proceedings have now been published. Knowledge in this field is fast expanding, but the book retains relevance and brings together in a convenient and interrelated way the various technical and ethical challenges posed by this new disease, many of which remain to be resolved.


Pharmacists as health counsellors

Pharmacists are in a position to provide much valuable counsel to patients not only on the treatment of acute self-limiting illnesses, but in broader aspects of health education. It is encouraging to see that more material is being published to assist them in developing this role.

In collaboration with the Fédération Internationale Pharmaceutique (FIP), and with the committed support of Prof. P. F. D'Arcy of the Department of Pharmacy, Queens University of Belfast, Northern Ireland, United Kingdom, WHO has recently published a booklet for pharmacists on the management of acute diarrhoea in children (1). The focus, inevitably, is upon the need for early and adequate oral rehydration.

A similar initiative has been taken within the United Kingdom where the Pharmaceutical Society has published a guide on drug abuse (2). In parallel with this it has also published a report of a study undertaken in the United Kingdom on the pharmacist's role in preventing drug abuse (3). Experience gained in a series of seminars has left no doubt that pharmacists have the ability and will to evaluate and provide information on drugs of abuse and that there is an evident demand for their advice.

References

Health Horizons: a new publication of the IFPMA

Switzerland — The International Federation of Pharmaceutical Manufacturers Associations (IFPMA) has changed the format and extended the scope of its newsletter which will be produced three times a year and mailed free of charge on request. The first issue contains an update on the prospects for developing new drugs and vaccines for malaria; profiles of the independent experts who will oversee the IFPMA code of advertising practice; an interview with Dr Machado, Brazil's former Minister of Health; an account of the assistance offered by the Association of British Pharmaceutical Industries in
the Maldives; an update on AIDS research, and a personal view on the strategy of health care by Dr R. Braumann, President of Médecins sans Frontières.


Medical Horizons: a new publication of the British Healthcare Export Council

United Kingdom — The British Healthcare Export Council, which promotes UK exports of healthcare products and services, has announced the publication of a new magazine that will provide commentaries on technological breakthroughs and clinical innovations as well as articles on all aspects of health management, including developments in the British National Health Service, the manufacture and design of equipment, the architecture and maintenance of buildings and information technology as it relates to healthcare.

Details available from: British Healthcare Export Council, 2 Harewood Place, London W1R 9HB, United Kingdom.

Progress: a newsletter of the WHO Special Programme on Human Reproduction

The Special Programme of Research, Development and Research Training in Human Reproduction (HRP) of the World Health Organization has issued the first issue of a quarterly newsletter entitled “Progress”. The aim is to review new information on contraceptives and on social and behavioural issues related to their use. The first issue deals with the safety of IUDs, the performance of the WHO vaginal ring in Phase III trials and projected clinical trials of an antifertility vaccine. Opportunity is also taken to invite funding applications for relevant research proposals from independent investigators, particularly in developing countries.

Reference: Progress, c/o HRP, World Health Organization, 1211 Geneva 27, Switzerland.

Drug Bulletins Review

The WHO Regional Office for Europe issues occasional reviews containing selected contents from independent drug bulletins, summaries and conclusions of some of the listed articles, technical information released by national regulatory authorities within the Region, and recent WHO publications concerning drugs and drug policies.


Essential Drugs Monitor

The fourth issue of the Essential Drugs Monitor, a newsletter published by the WHO Action Programme on Essential Drugs and Vaccines, contains information on the steps to success in essential drugs supply, and commentaries on the progress of the Action Programme in Burundi, the philosophy of the Food and Drug Administration of the United States of America towards generic products, and national drug policies in Nicaragua, the Yemen Arab Republic and the Eastern Caribbean States. It also highlights an interview with Dr Z. Chowdhury of the People’s Health Centre at Savar, Bangladesh.

Smallpox and its Eradication

The definitive history of the world's most triumphant achievement in public health

In 31 chapters, Smallpox and its Eradication recounts the history of one of humanity's worst diseases, moving from ancient times, through the discovery of vaccination, to the spectacular WHO-led programme that finally vanquished the disease. Authored by experts personally involved in the eradication campaign, the book gives posterity a minutely detailed account of both how the disease once reigned and what was necessary, step by step and country by country, to eliminate the "ancient scourge" once and for all. Virtually everything ever known or believed about the disease, and everything that happened during the global eradication campaign, has been collected and preserved in this richly illustrated account.

For scientists and clinicians, Smallpox and its Eradication will serve as a complete and final review of knowledge on the clinical features, virology, pathology, immunology, and epidemiology of smallpox and other orthopoxviruses. For students of public health and medical historians, the book offers access to a wealth of previously unpublished data and personal experiences that make up the saga of a public health event unprecedented in scope and unparalleled in the magnitude of its achievement. For posterity, Smallpox and its Eradication will serve, above all, as an inspiring reminder of the time when the world united, behind a humanitarian goal, and destroyed a disease forever.

Published by the World Health Organization

Address orders to: World Health Organization, Distribution and Sales, 1211 Geneva 27, Switzerland, or to any of the sales agents listed on inside back cover.
International Nonproprietary Names for Pharmaceutical Substances

In accordance with article 3 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances, notice is hereby given that the following names are under consideration by the World Health Organization as Proposed International Nonproprietary Names.

Comments on, or formal objections to, the proposed names may be forwarded by any person to the Pharmaceuticals unit of the World Health Organization within four months of the date of their publication in WHO Drug Information, e.g., for List 58 Prop. INN not later than 28 February 1988.

The inclusion of a name in the lists of proposed international nonproprietary names does not imply any recommendation for the use of the substance in medicine or pharmacy.

Proposed International Nonproprietary Names (Prop. INN): List 58

<table>
<thead>
<tr>
<th>Proposed International Nonproprietary Name (Latin, English)</th>
<th>Chemical Name or Description, Molecular and Graphic Formulae</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
</tr>
</thead>
<tbody>
<tr>
<td>alaninum</td>
<td>L-alanine C₃H₇NO₂</td>
<td>56-41-7</td>
</tr>
</tbody>
</table>

Comprehensive information on the INN programme can be found in: WHO Technical Report Series, No. 581, 1975 (Nonproprietary Names for Pharmaceutical Substances. Twentieth Report of the WHO Expert Committee), ISBN 92 4 1205591 4 (price: Sw. fr. 8.--); an account of this publication will be found in Annex 2 of the present List. All names from Lists 1–47 of Proposed International Nonproprietary Names, together with a molecular formula index, will be found in: International Nonproprietary Names (INN) for Pharmaceutical Substances. Cumulative List No. 6, 1982, World Health Organization, Geneva (ISBN 92 4 056013 0) (price: Sw. fr. 55.--). This publication consists, in the main, of a computer printout which groups together all the proposed and recommended international nonproprietary names (INN)—in Latin, English, French, Russian, and Spanish—published up to April 1982. The printout also indicates in which of the 47 individual lists of proposed names and 21 lists of recommended names each INN was originally published, and gives references to national nonproprietary names, pharmacopoeia monographs, and other sources. In addition, the list contains molecular formulae and Chemical Abstracts Service registry numbers. For easy reference, national nonproprietary names that differ from INN, molecular formulae, and Chemical Abstracts Service registry numbers are indexed in a series of annexes. A final annex describes the procedure for selecting recommended INN and outlines the general principles to be followed in devising these names. All the textual material published in this volume appears in both English and French.

These publications may be obtained, direct or through booksellers, from the sales agents listed on the back cover of WHO Drug Information. Orders from countries where sales agents have not yet been appointed may be addressed to: World Health Organization, Distribution and Sales Service, 1211 Geneva 27, Switzerland.


2 Other lists of proposed and recommended international nonproprietary names can be found in Cumulative List No. 6, 1982.
alocicium
alocic

Nonproprietary Name (Latin, English)

Chemical Name or Description, Molecular and Graphic Formulae

Chemical Abstracts Service (CAS) registry number

N-[(2RS,4R)-2-methyl-4-thiazolidinyl]carbonyl]-β-alanine, methyl ester

C₉H₁₆N₂O₃S 105292-70-4

anoxetinum
anoxetine

(±)-6-[(α-[2-(dimethylamino)ethyl]benzyl]oxy]flavone

C₂₆H₂₅N₃ 79130-64-6

atipamezolum
atipamezole

4-(2-ethyl-2-indanyl)imidazole

C₁₄H₁₆N₂ 104054-27-5

azithromycinum
azithromycin

(2R,3S,4R,5R,8R,10R,11S,12S,13S,14R)-13-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl]oxy]-2-ethyl-3,4,10-trihydroxy-3,5,8,10,12,14-heptamethyl-11-[(3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]-oxy]-1-oxa-6-azacyclopentadecan-15-one

C₃₈H₇₂N₂O₁₂ 83905-01-5
<table>
<thead>
<tr>
<th>Proposed International Chemical Name or Description, Molecular and Graphic Formulae</th>
<th>Chemical Name or Description, Molecular and Graphic Formulae</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
</tr>
</thead>
<tbody>
<tr>
<td>bamaluzolum</td>
<td>4-[(o-chlorobenzyl)oxy]-1-methyl-1H-imidazo[4,5-c]pyridine</td>
<td>C_{14}H_{12}ClN_{3}O 87034-87-5</td>
</tr>
<tr>
<td>bamaluzole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>benazeprilatum</td>
<td>(3S)-3-[[1S]-1-carboxy-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid</td>
<td>C_{22}H_{24}N_{2}O_{5} 86541-78-8</td>
</tr>
<tr>
<td>benazeprilat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>benazeprilum</td>
<td>(3S)-3-[[1S]-1-carboxy-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid, 3-ethyl ester</td>
<td>C_{24}H_{28}N_{2}O_{5} 86541-75-5</td>
</tr>
<tr>
<td>benazepril</td>
<td></td>
<td></td>
</tr>
<tr>
<td>bendacololum</td>
<td>(αR,α'S,2S,2'R)-α,α'-(iminodimethylene)bis[1,4-benzodioxan-2-methanol]</td>
<td>C_{20}H_{23}NO_{6} 81703-42-6</td>
</tr>
<tr>
<td>bendacolol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>benidipinum</td>
<td>(±)-(R*)-3-[(R*)-1-benzyl-3-piperidyl] methyl 1,4-dihydro-2,6-dimethyl-4-(m-nitrophenyl)-3,5-pyridinedicarboxylate</td>
<td>C_{28}H_{33}N_{3}O_{6} 105979-17-7</td>
</tr>
</tbody>
</table>
**Proposed International Chemical Name or Description, Molecular and Graphic Formulae**

**Nonproprietary Name (Latin, English)**

**Chemical Abstracts Service (CAS) registry number**

<table>
<thead>
<tr>
<th>Nonproprietary Name (Latin, English)</th>
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<th>Molecular and Graphic Formulae</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
</tr>
</thead>
<tbody>
<tr>
<td>betiatidum</td>
<td>N-[N-[N-(mercaptoacetyl)glycyl]glycyl]glycine benzoate (ester)</td>
<td>C_{15}H_{17}N_{3}O_{6}S</td>
<td>103725-47-9</td>
</tr>
<tr>
<td>betiatide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>brequinarum</td>
<td>6-fluoro-2-(2'-fluoro-4-biphenylyl)-3-methyl-4-quinolinecarboxylic acid</td>
<td>C_{23}H_{15}F_{2}NO_{2}</td>
<td>96187-53-0</td>
</tr>
<tr>
<td>brequinaar</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>broloconazolum</td>
<td>(+)-1-(p-bromo-β-phenylphenethyl)imidazole</td>
<td>C_{19}H_{15}BrN_{2}</td>
<td>108894-40-2</td>
</tr>
<tr>
<td>broloconazole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>clanfenurum</td>
<td>1-(p-chlorophenyl)-3-(6-fluoro-N,N-dimethylanilinoyl)urea</td>
<td>C_{16}H_{15}ClFN_{3}O_{2}</td>
<td>51213-99-1</td>
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<tr>
<td>clanfenur</td>
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<td></td>
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</tr>
<tr>
<td>clipoxaminum</td>
<td>(+)-(αR*)-3-hydroxy-4-methyl-α-[(1S*)-1-[(3-phenylpropyl)amino]ethyl]benzyl alcohol</td>
<td>C_{19}H_{23}NO_{2}</td>
<td>109525-44-2</td>
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<tr>
<td>clipoxamine</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>crisnatolum</td>
<td>2-[(6-chrysenylmethyl)amino]-2-methyl-1,3-propanediol</td>
<td>C_{22}H_{23}NO_{2}</td>
<td>96389-68-3</td>
</tr>
<tr>
<td>crisnatol</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Proposed International Chemical Name or Description, Molecular and Graphic Formulae
Nonproprietary Name (Latin, English)  Chemical Abstracts Service (CAS) registry number

**cromakalimum**  
cromakalim  

\((\pm)-\text{trans-3-hydroxy-2,2-dimethyl-4-(2-oxo-1-pyrrolidinyl)-6-chromancarbonitrile}\)

\(\text{C}_{16}\text{H}_{18}\text{N}_{2}\text{O}_{3}\)  
94470-67-4

[Diagram of cromakalim]

**cysteinum**  
cysteine  

\(\text{L-cysteine}\)

\(\text{C}_{3}\text{H}_{7}\text{NO}_{2}\text{S}\)  
52-90-4

[Diagram of cysteine]

**dalbraminolum**  
dalbraminol  

\((\pm)-1\text{-phenoxy-3-[[2-[[1,3,5\text{-trimethylpyrazol-4-yl]amino}ethyl]amino]-2-propanol}\)

\(\text{C}_{17}\text{H}_{26}\text{N}_{4}\text{O}_{2}\)  
81528-80-5

[Diagram of dalbraminol]

**daptomycinum**  
daptomycin  

\(\text{N-decanoyl-L-tryptophyl-L-asparaginyl-L-aspartyl-L-threonyl-L-ornithyl-L-aspartyl-L-alanyl-L-aspartylglycyl-o-seryl-threo-3-methyl-L-glutamyl-3-anthraniloyl-L-alanine, \(\varepsilon\),-lactone}\)

\(\text{C}_{72}\text{H}_{101}\text{N}_{17}\text{O}_{26}\)  
103060-53-3

[Diagram of daptomycin]
<table>
<thead>
<tr>
<th>Proposed International Name or Description, Molecular and Graphic Formulae</th>
<th>Chemical Name or Description, Molecular and Graphic Formulae</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>denipridum</strong>&lt;br&gt;denipride</td>
<td>(±)-4-amino-5-nitro-N-[1-(tetrahydrofurfuryl)-4-piperidyl]-o-anisamide&lt;br&gt;( \text{C}<em>{18}\text{H}</em>{26}\text{N}<em>{4}\text{O}</em>{5} ) 106972-33-2</td>
<td></td>
</tr>
<tr>
<td><strong>derpanicatum</strong>&lt;br&gt;derpanicate</td>
<td>nicotinic acid, tetraester with ( N,N')-[dithiobis(ethyleneiminocarbonyl-ethylene)]bis[(( R))-2,4-dihydroxy-3,3-dimethylbutyramide]&lt;br&gt;( \text{C}<em>{46}\text{H}</em>{54}\text{N}<em>{8}\text{O}</em>{12}\text{S}_{2} ) 99516-29-3</td>
<td></td>
</tr>
<tr>
<td><strong>doreptidum</strong>&lt;br&gt;doreptide</td>
<td>(2S)-( N)-[(( \alpha)( R))-( \alpha)-[(carbamoylmethyl)carbamoyl]-( \alpha)-ethylbenzyl]-2-pyrrolidinecarboxamide&lt;br&gt;( \text{C}<em>{17}\text{H}</em>{24}\text{N}<em>{4}\text{O}</em>{3} ) 90104-48-6</td>
<td></td>
</tr>
<tr>
<td><strong>doxacurii chloridum</strong>&lt;br&gt;doxacurium chloride</td>
<td>(1( R),2( S);1( S),2( R))-1,2,3,4-tetrahydro-2-(3-hydroxypropyl)-6,7,8-trimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium chloride, succinate (2:1)&lt;br&gt;( \text{C}<em>{56}\text{H}</em>{78}\text{Cl}<em>{2}\text{N}</em>{2}\text{O}_{16} ) 106819-53-8</td>
<td></td>
</tr>
<tr>
<td><strong>efetozolum</strong>&lt;br&gt;efetozole</td>
<td>(±)-2-methyl-1-(( \alpha)-methylbenzyl)imidazole&lt;br&gt;( \text{C}<em>{12}\text{H}</em>{11}\text{N}_{2} ) 99500-54-6</td>
<td></td>
</tr>
<tr>
<td>Nonproprietary Name (Latin, English)</td>
<td>Proposed International Chemical Name or Description, Molecular and Graphic Formulae</td>
<td>Chemical Abstracts Service (CAS) registry number</td>
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<tr>
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<td>---------------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>epicriptinum epicriptine</td>
<td>9,10α-dihydro-13'-epi-β-ergocryptine or (13'R)-9,10α-dihydro-β-ergocryptine</td>
<td>88660-47-3</td>
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<tr>
<td>fluparoxanum fluparoxan</td>
<td>(3αS,9αS)-5-fluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole</td>
<td>105182-45-4</td>
</tr>
<tr>
<td>flutemazepamum flutemazepam</td>
<td>7-chloro-5-(o-fluorophenyl)-1,3-dihydro-3-hydroxy-1-methyl-2H-1,4-benzodiazepin-2-one</td>
<td>52391-89-6</td>
</tr>
<tr>
<td>histidinum histidine</td>
<td>L-histidine</td>
<td>71-00-1</td>
</tr>
<tr>
<td>ibudilastum ibudilast</td>
<td>1-(2-isopropylpyrazolo[1,5-a]pyridin-3-yl)-2-methyl-1-propanone</td>
<td>50847-11-5</td>
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<tr>
<td>Proposed International</td>
<td>Chemical Name or Description, Molecular and Graphic Formulae</td>
<td>Molecular and Graphic Formulae</td>
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<td>Chemical Abstracts Service (CAS) registry number</td>
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<table>
<thead>
<tr>
<th>idenastum</th>
<th>2-[4-{4-(p-fluorophenyl)-1-piperazinyl}butyl]-1-(p-methoxyphenyl)-3-indazolinone</th>
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<tbody>
<tr>
<td>idenast</td>
<td>C_{28}H_{31}FN_{4}O_{2} 108674-88-0</td>
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<td><img src="image" alt="Structure of idenastum" /></td>
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<thead>
<tr>
<th>insulin arginum</th>
<th>30^a\text{-l-arginine}-30^b\text{-l-arginine}insulin (human)</th>
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</thead>
<tbody>
<tr>
<td>insulin argine</td>
<td>C_{269}H_{407}N_{73}O_{79}S_{6} 68859-20-1</td>
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<table>
<thead>
<tr>
<th>irsogladinum</th>
<th>2,4-diamino-6-(2,5-dichlorophenyl)-s-triazine</th>
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<tr>
<td>irsogladine</td>
<td>C_{9}H_{7}Cl_{2}N_{5} 57381-26-7</td>
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<tr>
<th>isamoltanum</th>
<th>(\pm)\text{-1-(isopropylamino)-3-}(\alpha\text{-pyrrol-1-ylphenoxy})-2-propanol</th>
</tr>
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<tbody>
<tr>
<td>isamoltan</td>
<td>C_{16}H_{22}N_{2}O_{2} 55050-95-8</td>
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<tr>
<th>isoleucinum</th>
<th>\text{l-isoleucine}</th>
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<tbody>
<tr>
<td>isoleucine</td>
<td>C_{6}H_{13}NO_{2} 73-32-5</td>
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<td></td>
<td><img src="image" alt="Structure of isoleucine" /></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>leucinum</th>
<th>\text{l-leucine}</th>
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<tbody>
<tr>
<td>leucine</td>
<td>C_{6}H_{13}NO_{2} 61-90-5</td>
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<td><img src="image" alt="Structure of leucine" /></td>
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<table>
<thead>
<tr>
<th>levdropropizinum</th>
<th>\text{(-)-(\text{S})\text{-3-(4-phenyl-1-piperazinyl)-1,2-propanediol}}</th>
</tr>
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<tbody>
<tr>
<td>levdropropizine</td>
<td>C_{13}H_{20}N_{2}O_{2} 99291-24-4</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="Structure of levdropropizinum" /></td>
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</tbody>
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levomoprololum
levomoprolol
(-)-(S)-1-(isopropylamino)-3-(o-methoxyphenoxy)-2-propanol
C<sub>13</sub>H<sub>21</sub>NO<sub>3</sub> 77164-20-6

libenzaprilum
libenzapril
N<sup>2</sup>-[3S]-1-(carboxymethyl)-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-L-lysine
C<sub>18</sub>H<sub>22</sub>N<sub>3</sub>O<sub>5</sub> 97878-35-8

linsidominum
linsidomine
3-morpholinosydnone imine
C<sub>6</sub>H<sub>10</sub>N<sub>4</sub>O<sub>2</sub> 33876-97-0

lomefloxacinum
lomefloxacin
(±)-1-ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolincarboxylic acid
C<sub>17</sub>H<sub>19</sub>F<sub>2</sub>N<sub>3</sub>O<sub>3</sub> 98079-51-7

lysinum
lysine
l-lysine
C<sub>6</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub> 56-87-1
mirosamicin

mirosaminum

14-hydroxymycinamic I or (-)-(1R,2S,3R,6E,8S,9S,10S,12R,14E,16S)-2-[(6-deoxy-2,3-di-O-methyl-β-D-allopyranosyl)oxy]methyl]-3-ethyl-2-hydroxy-8,10,12-trimethyl-9-[(3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl)oxy]-4,17-dioxabicyclo[14.1.0]heptadeca-6,14-diene-5,13-dione

C_{37}H_{61}NO_{13} \quad 73684-69-2

mivacurii chloridum

mivacurium chloride

(R)-1,2,3,4-tetrahydro-2-(3-hydroxypropyl)-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium chloride, (E)-4-octenedioate (2:1)

C_{58}H_{80}Cl_{2}N_{2}O_{14} \quad 106861-44-3

montirelinum

montirelin

N-[(3R,6R)-6-methyl-5-oxo-3-thiomorpholinyl]carbonyl]-L-histidyl-L-prolinamide

C_{17}H_{24}N_{6}O_{4}S \quad 90243-66-6

moveltiprilum

moveltipril

(-)-1-[(2S)-3-mercaptop-2-methylpropionyl]-L-proline, ester with N-(cyclohexylcarbonyl)thio-α-alanine

C_{19}H_{30}N_{2}O_{5}S \quad 85656-54-8
<table>
<thead>
<tr>
<th>Chemical Name or Description, Molecular and Graphic Formulae</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Proposed International Nonproprietary Name (Latin, English)</td>
<td></td>
</tr>
<tr>
<td>naxaprostenum naxaprostene</td>
<td>$\alpha$-[{2E,3aS,4R,5R,6aS}-4-{{1E,3S}-3-cyclohexyl-3-hydroxypropenyl}hexahydro-5-hydroxy-2(1H)-pentenylidene]-m-toluic acid C$<em>{25}$H$</em>{32}$O$_4$ 87269-59-8</td>
</tr>
<tr>
<td>neraminolum neraminol</td>
<td>(±)-1-(1H-indazol-4-yloxy)-3-[[2-(2,6-xylidino)ethyl]amino]-2-propanol C$<em>{20}$H$</em>{26}$N$_4$O$_2$ 86140-10-5</td>
</tr>
<tr>
<td>norfloxacinum succinilum norfloxacin succinil</td>
<td>7-[4-(3-carboxypropionyl)-1-piperazinyl]-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid C$<em>{20}$H$</em>{22}$FN$_3$O$_6$ 100587-52-8</td>
</tr>
<tr>
<td>onapristonum onapristone</td>
<td>11β-[{p-(dimethylamino)phenyl}-17α-hydroxy-17-(3-hydroxypropyl)-13α-estra-4,9-dien-3-one C$<em>{29}$H$</em>{39}$NO$_3$ 96346-61-1</td>
</tr>
<tr>
<td>ornithinum ornithine</td>
<td>$\nu$-ornithine C$<em>{2}$H$</em>{13}$N$_2$O$_2$ 70-26-8</td>
</tr>
<tr>
<td>Chemical Name or Description</td>
<td>Molecular and Graphic Formulae</td>
</tr>
<tr>
<td>----------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td><strong>orotirelinum</strong></td>
<td><em>N</em>-[1,2,3,6-tetrahydro-2,6-dioxo-4-pyrimidinyl]carbonyl-L-histidyl-L-prolinamide</td>
</tr>
<tr>
<td>orotirelin</td>
<td>C_{16}H_{19}N_{7}O_{5} 62305-86-6</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td><strong>palatrinum</strong></td>
<td>5-amino-6-(2,3-dichlorophenyl)-2,3-dihydro-3-imino-2-isopropyl-as-triazine</td>
</tr>
<tr>
<td>palatrine</td>
<td>C_{12}H_{13}Cl_{2}N_{5} 98410-36-7</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td><strong>panomifenum</strong></td>
<td>(E)-2-[2-[p-(3,3,3-trifluoro-1,2-diphenylpropenyl)phenoxy]ethyl]amino]ethanol</td>
</tr>
<tr>
<td>panomifene</td>
<td>C_{25}H_{24}F_{3}N_{2}O_{2} 77599-17-8</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td><strong>pemedolacum</strong></td>
<td>(±)-4-benzyl-1-ethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid</td>
</tr>
<tr>
<td>pemedolac</td>
<td>C_{22}H_{23}NO_{3} 103024-44-8</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td><strong>perbufyllinum</strong></td>
<td>7-[4-[4-(p-fluorobenzoyl)piperidino]butyl]theophylline</td>
</tr>
<tr>
<td>perbufyline</td>
<td>C_{23}H_{22}FN_{2}O_{3} 110390-84-6</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Chemical Name or Description</td>
<td>Molecular and Graphic Formulae</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>phenylalaninum</td>
<td>l-phenylalanine</td>
</tr>
<tr>
<td>phenylalanine</td>
<td>C₉H₁₁NO₂</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="Phenylalanine Structure" /></td>
</tr>
<tr>
<td>pirazmonamum</td>
<td>2-[[2-amino-4-thiazolyl][1-[[3-(1,4-dihydro-5-hydroxy-4-oxopicolinamido)-2-oxo-1-imidazolidinyl][sulfonyl][carbamoyl][2-oxo-3-azetidinyl][carbamoyl]-methylene]amino]oxy][2-methylpropionic acid</td>
</tr>
<tr>
<td>pirazmonam</td>
<td>C₂₂H₂₄N₁₀O₁₂S₂</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="Pirazmonam Structure" /></td>
</tr>
<tr>
<td>ponalrestatum</td>
<td>3-(4-bromo-2-fluorobenzyl)-3,4-dihydro-4-oxo-1-phthalazineacetic acid</td>
</tr>
<tr>
<td>ponalrestat</td>
<td>C₁₇H₁₂BrFN₂O₃</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="Ponalrestat Structure" /></td>
</tr>
<tr>
<td>pramipexolum</td>
<td>(S)-2-amino-4,5,6,7-tetrahydro-6-(propylamino)benzothiazole</td>
</tr>
<tr>
<td>pramipexole</td>
<td>C₁₉H₁₇N₃S</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="Pramipexole Structure" /></td>
</tr>
<tr>
<td>prolinum</td>
<td>l-proline</td>
</tr>
<tr>
<td>proline</td>
<td>C₅H₉NO₂</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="Proline Structure" /></td>
</tr>
<tr>
<td>Chemical Name or Description, Molecular and Graphic Formulae</td>
<td>Proposed International Nonproprietary Name (Latin, English)</td>
</tr>
<tr>
<td>-------------------------------------------------------------</td>
<td>---------------------------------------------------------</td>
</tr>
<tr>
<td>rilozaronum rilozarone</td>
<td>1-bromo-2-phenyl-3-indolizinyl 3-chloro-4-[3-(dibutylamino)propoxy]phenyl ketone</td>
</tr>
<tr>
<td>romifidinum romifidine</td>
<td>2-(2-bromo-6-fluoroanilino)-2-imidazoline</td>
</tr>
<tr>
<td>salmisteinum salmisteine</td>
<td>N-acetyl-L-cysteine salicylate (ester), acetate (ester)</td>
</tr>
<tr>
<td>saruplasum saruplase</td>
<td>prourokinase (enzyme activating) (human clone pUK 4/pUK 18 protein moiety reduced)</td>
</tr>
<tr>
<td>sematilidum sematilde</td>
<td>N-[2-(diethylamino)ethyl]-p-methanesulfonamidobenzamide</td>
</tr>
<tr>
<td>serinum serine</td>
<td>L-serine</td>
</tr>
<tr>
<td>Nonproprietary Name (Latin, English)</td>
<td>Chemical Name or Description, Molecular and Graphic Formulae</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>sevopramidum</strong></td>
<td>(+)-α-benzamido-( p )-[3-(diethylamino)propoxy]-N,N-dipropylhydro-cinnamamide</td>
</tr>
<tr>
<td><strong>sevopramide</strong></td>
<td>C_{29}H_{43}N_{3}O_{3}</td>
</tr>
<tr>
<td><strong>simvastatinum</strong></td>
<td>2,2-dimethylbutyric acid, 8-ester with (4R,6R)-6-[2-[(1S,2S,6R,8S,8aR)-1,2,6,7,8,8a-hexahydro-8-hydroxy-2,6-dimethyl-1-naphthyl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one</td>
</tr>
<tr>
<td><strong>simvastatin</strong></td>
<td>C_{25}H_{38}O_{5}</td>
</tr>
<tr>
<td>Proposed International Name</td>
<td>Chemical Name or Description, Molecular and Graphic Formulæ</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------------------------------------------------------</td>
</tr>
<tr>
<td>sudismasum, sudismase</td>
<td>N-acetylsuperoxide dismutase (human clone pS 61-10 copper-zinc subunit protein moiety reduced)</td>
</tr>
<tr>
<td>taprostenum, taprostene</td>
<td>α-[2Z,3aR,4R,5R,6aS]-4-[1(E,3S)-3-cyclohexyl-3-hydroxypropenyl]hexahydro-5-hydroxy-2H-cyclopenta[b]furan-2-ylidene]-m-toluic acid</td>
</tr>
<tr>
<td>taurinum, taurine</td>
<td>taurine</td>
</tr>
<tr>
<td>temafloxacinum, temafloxacin</td>
<td>(±)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-o xo-3-quinolincarboxylic acid</td>
</tr>
<tr>
<td>tepoxalinum, tepoxalin</td>
<td>5-(ρ-chlorophenyl)-1-(ρ-methoxyphenyl)-N-methylpyrazole-3-proponohydroxamic acid</td>
</tr>
<tr>
<td>texacromilum, texacromil</td>
<td>(±)-5-[2-hydroxy-3-(methylthio)propoxy]-4-oxo-4H-1-benzopyran-2-carboxylic acid</td>
</tr>
</tbody>
</table>
Proposed International Chemical Name or Description, Molecular and Graphic Formulae
Nonproprietary Name (Latin, English) Chemical Abstracts Service (CAS) registry number

threoninum | threonine | L-threonine | C₄H₉NO₃ | 72-19-5

\[
\begin{align*}
&\text{H}_2\text{C} - \text{C} - \text{C} - \text{C} - \text{CO}^+ \\
&\text{H} \quad \text{N} \quad \text{H}_2
\end{align*}
\]

tibenelastum | tibenelast | 5,6-diethoxybenzo[β]thiophene-2-carboxylic acid | C₁₃H₁₄O₄S | 97852-72-7

\[
\begin{array}{c}
\text{H}_2\text{C} - \text{CH}_2 - \text{O} - \\
\text{H}_2\text{C} - \text{CH}_2 - \text{O} -
\end{array}
\]

traboxopinum | traboxopine | (±)-2-chloro-12-[3-(dimethylamino)-2-methylpropyl]-12H-dibenzo[d,g][1,3,6]-dioxazocine | C₁₉H₂₃ClN₂O₂ | 103624-59-5

\[
\begin{array}{c}
\text{H}_2\text{C} - \text{CH}_2 - \text{N} - \text{CH}_2\text{CH}_3 \quad \text{N} - \text{CH}_2\text{CH}_3 \\
\text{H}_2\text{C} - \text{CH}_2 - \text{N} - \text{CH}_2\text{CH}_3 \\
\end{array}
\]

tryptophanum | tryptophan | L-tryptophan | C₁₁H₁₂N₂O₂ | 73-22-3

\[
\begin{array}{c}
\text{H} \quad \text{N} \quad \text{H}_2 \quad \text{CH} - \text{C} - \text{COOH} \\
\text{H} \quad \text{N} \quad \text{H}_2 \quad \text{CH} - \text{C} - \text{COOH} \\
\end{array}
\]

tyrosinum | tyrosine | L-tyrosine | C₉H₉NO₃ | 60-18-4

\[
\begin{array}{c}
\text{H} \quad \text{N} \quad \text{H}_2 \quad \text{CH} - \text{C} - \text{COOH} \\
\text{H} \quad \text{N} \quad \text{H}_2 \quad \text{CH} - \text{C} - \text{COOH} \\
\end{array}
\]

ufiprazolum | ufiprazole | 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridyl)methyl]thio]benzimidazole | C₁₅H₁₄N₂O₃S | 73590-85-9

\[
\begin{array}{c}
\text{H}_3\text{C} - \text{S} - \text{N} - \text{CH}_2 - \text{N} - \text{CH}_2 - \text{C} - \text{COOH} \\
\text{H}_3\text{C} - \text{S} - \text{N} - \text{CH}_2 - \text{N} - \text{CH}_2 - \text{C} - \text{COOH} \\
\end{array}
\]

191
Proposed International Nonproprietary Name (Latin, English)  Chemical Name or Description, Molecular and Graphic Formulae  Chemical Abstracts Service (CAS) registry number

valinum  l-valine  C₅H₁₁NO₂  72-18-4

vapiprostum  (+)-(Z)-7-[(1R,2R,3S,5S)-3-hydroxy-5-{(p-phenylbenzyl)oxy}-2-piperidinocyclopentyl]-4-heptenoic acid  C₃₀H₃₉NO₄  85505-64-2

zabiciprilum  (3S)-2-{(2S)-N-{(1S)-1-carboxy-3-phenylpropyl}alanyl}-2-azabicyclo[2.2.2]-octane-3-carboxylic acid, 1-ethyl ester  C₂₃H₃₂N₂O₅  83059-56-7

Names for Radicals and Groups

Some substances for which a proposed international nonproprietary name has been established may be used in the form of salts or esters. The radicals or groups involved may be of complex composition and it is then inconvenient to refer to them in systematic chemical nomenclature. Consequently, shorter nonproprietary names for some radicals and groups have been devised or selected, and they are suggested for use with the proposed international nonproprietary names.

proxetilum  1-{(isopropoxycarbonyl)oxy}ethyl
AMENDMENTS
TO PREVIOUS LISTS

Cumulative List No. 6, 1982

International Nonproprietary Names (INN) for Pharmaceutical Substances

\[ \text{delete} \quad \text{insert} \]

\begin{align*}
p. 4 & \quad \text{acidum aminoaceticum} & \quad \text{glycinum} \\
& \quad \text{aminoacetic acid} & \quad \text{glycine}
\end{align*}

WHO Chronicle, Vol. 26, No. 4

Proposed International Nonproprietary Names (Prop. INN): List 27

\begin{align*}
p. 131 & \quad \text{delete} \quad \text{insert} \\
& \quad \text{glipentidum} & \quad \text{glisentidum} \\
& \quad \text{glipentide} & \quad \text{glisentide}
\end{align*}

Supplement to Vol. 38, No. 4, 1984

Proposed International Nonproprietary Names (Prop. INN): List 52

\begin{align*}
p. 7 & \quad \text{delete} \quad \text{insert} \\
& \quad \text{decapinolum} & \quad \text{delmopinolum} \\
& \quad \text{decapinol} & \quad \text{delmopinol}
\end{align*}

Supplement to Vol. 40, No. 5, 1986

Proposed International Nonproprietary Names (Prop. INN): List 56

\begin{align*}
p. 1 & \quad \text{acidum piridronicum} \quad \text{replace graphic formula by:} \\
& \quad \text{piridronic acid}
\end{align*}

\begin{align*}
p. 4 & \quad \text{cefempidonum} \quad \text{in the graphic formula complete the pyridinio ring with a double bond} \\
& \quad \text{cefempidone}
\end{align*}

\begin{align*}
p. 7 & \quad \text{erythromycin stinopras} \quad \text{replace the comma between the two graphic formulas by a dot} \\
& \quad \text{erythromycin stinoprate} \\
& \quad \text{famiraprinum} \quad \text{delete the whole entry} \\
& \quad \text{famiraprine}
\end{align*}

193
famiraprinii chloridum 6-amino-1-(3-carboxypropyl)-5-methyl-3-phenylpyridazinium chloride
C_{15}H_{18}ClN_{3}O_{2}  108894-41-3

in the graphic formula complete the benzene ring with a double bond


Proposed International Nonproprietary Names (Prop. INN): List 57

p. 93 cefpodoximum cefpodoxime replace chemical name, CAS reg. no., molecular formula and graphic formula by:
(+)-(6R,7R)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7\(^{-}\)(Z)-(O-methylxime)
C_{15}H_{17}N_{5}O_{6}S_{2}  80210-62-4

p. 100 lacidipinum lacidipine replace CAS reg. no. by: 103890-78-4

p. 110 ademetioninum ademetionine at the beginning of the chemical name replace (+) by: (\(\pm\))

p. 111 Before the entries for tetronasinum and omoconazolum insert reference to:
Supplement to Vol. 40, No. 5, 1986, Proposed International Names (Prop. INN): List 56

p. 111 omoconazolum omoconazole reinstate CAS reg. no. 74512-12-2 given in List 45 Prop. INN

Procedure and Guiding Principles

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