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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General Policy Topics

Guiding principles for small national drug regulatory authorities

The elaboration of guiding principles for small national drug regulatory authorities is a component of WHO's Revised Drug Strategy which was adopted by the Thirty-ninth World Health Assembly following the WHO Conference of Experts on the Rational Use of Drugs held in Nairobi in November 1985. This consultative document, which is now being circulated to Member States, is based extensively on the report of a meeting convened in Geneva in November 1987*. It was subsequently reviewed in December 1988 by the Thirty-first WHO Expert Committee on Specifications for Pharmaceutical Preparations.

Small countries which have yet to introduce comprehensive legal provisions for drug regulation can draw from a diversity of national systems in determining their own requirements. None the less, problems in establishing drug control in developing countries have too often resulted from the adaptation of provisions successful elsewhere but of a complexity that precludes their effective implementation in the country of adoption. It is of paramount importance that legislation and administrative practices are attuned to available resources and that every opportunity is taken to obtain and use information provided by regulatory authorities in other countries on pharmaceutical products and substances moving in international commerce.

Channels of communication between national regulatory authorities are improving as is evident from the information contained in WHO's monthly Pharmaceuticals Newsletter, the quarterly journal WHO Drug Information, and the UN Consolidated List of products whose consumption and/or sale have been banned, withdrawn, severely restricted or not approved by governments. Moreover, many difficulties inherent in storing, retrieving and analyzing data that subserve the many facets of the regulatory process can now be redressed by the use of microcomputers and commercial software packages.

The scope of drug control

To be effective, a small drug regulatory authority needs to operate within the context of a defined national drugs policy and to interrelate with other interested bodies, including organizations responsible for drug procurement in the public sector and the national formulary committee, where such exists.

Basic responsibilities

The responsibilities of the regulatory authority are to ensure that all products subject to its control conform to acceptable standards of quality, safety and efficacy; and that all premises and practices employed to manufacture, store and distribute these products comply with requirements to assure the continued conformity of the products to these standards until such time as they are delivered to the end-user.

Licensing functions

These objectives can be accomplished effectively only if a mandatory system of licensing products, manufacturers, importing agents and distributors is in place. A small authority has strictly limited

*Participants

capacity to undertake these tasks. For the assurances it requires in relation to imported pharmaceutical products and drug substances, it is vitally dependent on authoritative, reliable and independent information generated in the exporting country. This information is most effectively obtained through the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce.

Before a formal licensing system can become operative, it is necessary:

- to adopt a precise definition of a drug product and of the various categories of licence holders;
- to determine the content and format of licences, both for products and for licence holders;
- to detail the criteria on which licence applications will be assessed; and
- to provide guidance to interested parties on the content and format of licence applications, and on the circumstances under which an application for renewal, extension or variation of a licence will be required.

The definition of a drug product is commonly contingent upon the claims that are made for it. Ideally, controls need to be applied to any product that is offered for sale for administration to human beings for treating, preventing and diagnosing disease, for anaesthesia, for contraception and for otherwise altering normal physiological functions. In practice, exemptions may need to be granted to various specific categories of products in order to address priorities effectively. It might be decided as an interim measure, for example, to require licences only for products listed in a national formulary. Ultimately, however, control needs to be extended not only to all products moving in the major distribution channels, but to those formulated in pharmacies and hospital dispensaries, to herbal preparations, and to other traditional medicines entering into local commerce.

Analogous priorities may also need to be accorded to the registration of licence-holders, although the ultimate objective should be to embrace all manufacturers, importing agents, wholesalers involved in repackaging, pharmacies and hospital dispensaries in a system that imposes upon them relevant statutory obligations.

**Product licences**

The issuance of product licences is pivotal to any system of drug control. The licence is a legal document that establishes the detailed composition and formulation of the product, the pharmacopoeial or other officially-recognized specifications of its ingredients, its clinical interchangeability (in the case of multisource products), its packaging, shelf-life and labelling. Of itself, this goes a long way towards establishing the assurances of quality, efficacy and safety to which the system is directed. However, without a viable pharmaceutical inspectorate or access to an independent quality control laboratory operating to standards that will assure its credibility in the event of dispute, licensing provisions cannot be effectively enforced.

**Manufacturers and distributors licences**

The pharmaceutical inspectorate is responsible for ensuring that pharmaceutical products comply with conditions set out in the licence up to the time that they are delivered to the end user. Its functions are:

- to establish, through periodic formal inspections and spot checks, that all categories of licence-holder are operating in accordance with their licensed activities, prevailing standards of good manufacturing practice and other prescribed regulations;
- to maintain oversight of distribution channels, either by inspection and monitoring or by arranging for pharmacopoeial analysis of selected samples, with a view to ensuring that products are not subject to unacceptable degradation during transit and storage at the periphery.

**New drug assessments**

Within highly-evolved national drug regulatory authorities much effort is directed to establishing the efficacy and safety of new drug entities through pharmaceutical, biological and clinical assessment and through subsequent surveillance of their performance in routine use after marketing. Pre-marketing assessment is dependent upon detailed multidisciplinary technical review, and post-marketing surveillance requires a highly-developed health care infrastructure. Only in exceptional circumstances should a small regulatory authority contem-
plate allocation of scarce resources to these ends. Reliance must be vested primarily on information notified by other countries through the network of national Information Officers established by WHO.

Authorization of clinical trials

A small authority may occasionally need to consider an application to conduct a clinical trial of an unregistered drug in the treatment of a condition that has a high local prevalence. To provide for this contingency, the registration system should include provision for the importation of the necessary materials, subject to appropriate controls. Such trials should only take place after formal clearance has been obtained from the competent registration authority and after assurances have been obtained that they will be conducted in conformity with the principles contained in the World Medical Association's Declaration of Helsinki and the Proposed Guidelines for Biomedical Research Involving Human Subjects issued by the Council for International Organizations of Medical Sciences. WHO stands ready to offer independent technical advice to national authorities in these circumstances.

Terms of reference of the regulatory authority

The formal terms of reference of a national drug regulatory authority are determined by statute and regulation. Legislation relating to pharmaceutical products has developed piecemeal in many countries, and there are obvious advantages in bringing matters concerned with their regulation under one law. For example, it is important to correlate laws relating to the control of narcotic and psychotropic substances with requirements for product registration. If comprehensive overhaul of the legal system is impractical, control within the existing framework through regulations specifically related to the registration of pharmaceutical products offer advantages of economy and time-saving. Whichever option is chosen, regulatory authorities require the flexibility to respond to changing circumstances imposed by the evolution of pharmaceutical science.

In general terms, the authority should be vested with legal powers to:

- issue, vary and revoke licences for pharmaceutical products on grounds of quality, safety and efficacy and safety;
- secure the subsequent safe and effective use of each product by controlling, through the terms of the licence, the content of all labelling, including package inserts, associated prescribing information and advertising and the channels through which it may legitimately be supplied; and
- inspect and license all manufacturing premises, importing agents, wholesalers and distributors, hospital dispensaries, independent pharmacies and other retail outlets to ensure that they comply with prevailing regulations and guidelines.

Powers of enforcement

In order to implement these responsibilities the authority must command powers of enforcement backed by legal provision for penal sanction against offenders.

In establishing administrative mechanisms for decision-making, the regulatory authority should not lose necessary flexibility. In particular, it should make provision for:

- implementing decisions regarded as urgent in the interest of public safety;
- formal consultation (usually through representative bodies) with pharmaceutical companies and other interested parties, including pharmacists, doctors, nurses and patients.

Technical competence

A small licensing authority will rarely, if ever, undertake comprehensive independent assessments of the safety and efficacy of individual products. The administrative and technical responsibilities that fall within its ambit are essentially of a pharmaceutical nature and they are directed primarily to quality assurance. The professional staff must include members with a thorough understanding and practical experience of the different facets of this work.

The responsible officer is accountable for the professional validation and assessment of licence applications and for the administrative aspects of licensing and, as such, should be involved in determining priorities and developing a timetable for implementation of controls. These activities require administrative and clerical support and premises sufficient to handle the large volume of documen-
tation involved with appropriate confidentiality. Efficiency of operation is enhanced when the required information can be retrieved rapidly from a computerized data base.

Advisory bodies

The responsible officer must also have access to a standing advisory committee (or board) of independent experts — including academic and practising health care professionals — for advice on technical issues. Consideration should also be given to the need for a multidisciplinary commission to advise on matters of general policy and administration and to assure effective interrelationships with bodies responsible for drug procurement in the public sector and with the national formulary committee.

Independence of operation

To retain public confidence and respect, the authority must be seen to undertake its tasks in an independent, authoritative and impartial manner. It should be concerned exclusively with the determination of standards and the implementation of controls. Although it will need to work closely with the authority responsible for drug procurement within the public sector, it should not, itself, be responsible for procurement and it should remain independent and autonomous in its operational activities and decisions.

Administrative aspects of the licensing process

Provisional registration of existing medicinal products

Before any system of control can become effective, it is necessary to identify and catalogue all products already sold or otherwise supplied on the domestic market, both in the public and private sectors, that qualify for control. To this end, all manufacturers and importing agencies must be given reasonable notice through official gazettes, the trade press and other media of their obligation to notify the authority by a specific date of all medicinal products that they currently distribute within the jurisdiction of the authority and that they intend to continue to supply after a duly “appointed day” on which licensing requirements enter into operation. After the “appointed day” no medicinal product may lawfully be distributed or supplied unless its existence has been notified to the authority and no new product may be introduced until a request for a product licence has been granted by the authority.

Effective administration of the provisional registration procedure is dependent upon:

- prior identification of all interested manufacturers and importers;
- a precise definition of a notifiable medicinal product based primarily on the labelled claims and the indications for use;
- the issuance of guidelines on the procedure to be followed.

Each notified product must be identified by name (either brand or generic), the names and full addresses of the manufacturer and importing agent, a description of the dosage form, its composition — including active and inactive ingredients (using international nonproprietary names where appropriate) — the therapeutic class, the indications, a copy of all labelling, including any package insert, and a copy of any relevant certificates and warranties relating to the product or its components.

Screening of provisionally-registered products

A rapid screening of notified products should be undertaken at the earliest opportunity with a view to securing the withdrawal of any products which, simply on the basis of a review of their ingredients and indications, are judged not to meet admissible standards of safety. This may be achieved by the withdrawal of permission to trade in specific notified products, or the issuance of regulations imposing specified restrictions on precisely-defined groups of products.

After this preliminary review, a set of longer-term priorities needs to be set for the definitive assessment of provisionally-registered products. Consideration needs to be given to the resources required, both in manpower and information, if the review is to be adapted to a proposed time-schedule. Standards must be maintained and calls to accelerate the speed of implementation must be recognized as holding resource implications.
In planning priorities, consideration must be given to:

- the number of provisionally-registered products to be processed;
- the number of staff and/or consultants to be allocated to the task;
- the amount of relevant information available from other national authorities;
- the extent to which products can be reviewed in groups rather than individually;
- the extent to which a “laisser faire” disposition can be adopted toward such products as herbal remedies and tonics that are without potent pharmacological activity and carry imprecise claims, but which satisfy an acknowledged public demand.

Considerations of safety require that particular attention be accorded to:

- products that have either been withdrawn or are the subject of restrictive regulatory action in other countries as notified in the United Nations Consolidated List of products whose consumption and/or sale have been banned, withdrawn, severely restricted or not approved by governments, and in WHO’s Pharmaceuticals Newsletter to national drug regulatory authorities;
- products representing examples of irrational poly-pharmacy; and
- products for which exaggerated or spurious promotional claims are made in the labelling.

Subsequently, the review needs to be extended in a phased manner, giving priority to drugs that are widely used, listed in nationally-recognized formularies, or of a particularly important therapeutic class. An adequate documentation and information retrieval system is vital for this purpose.

Some traditional products and particularly herbal preparations, because of their complexity, do not lend themselves to licensing on a product-specific basis. Control is then more readily applied through consideration of individual ingredients. Several regulatory authorities have devised administrative approaches to their licensing which are based on a trivalent system of classification:

(a) all herbal ingredients, save for those items classified under (b) below, which may be dispensed for a specific, named patient by practitioners of herbal medicine who do not possess a formal medical qualification;

(b) ingredients such as digitalis leaf and atropine which, having regard either to their pharmacological potency or toxicity, need to be subjected to prescription control; and

(c) ingredients which, as a result of widespread, long-established and apparently innocuous traditional usage, are included, often within defined permissible limits, in labelled products for which limited claims are made and which are sold directly to the public from retail outlets other than pharmacies.

New product licences

No product which is first proposed for authorization after the “appointed day” should be accorded a product licence without having first been submitted to technical assessment. Such products may not necessarily contain a new active ingredient: they may constitute a new combination of two or more established substances or they may merely represent a new dosage strength, a new dosage form, or a generic version of a pre-existing nominally-equivalent licensed product. In no case should the requirement for assessment be waived. A rationale for the formulation of every new product should invariably be provided, but the extent of the required review will vary considerably according to circumstances.

The normal procedure for the authorization of a product is accomplished in three stages:

- the application is received from the manufacturer and is checked and assessed for completeness by the authority’s technical staff;
- it is submitted to the competent standing committee for advice on whether or not to authorize marketing of the product;
- the formal administrative action to grant or refuse a licence and to settle its content is then taken by the authority.

The assessment of the product must be based primarily on its safety, quality and efficacy having
regard to its intended use. In accordance with locally-determined requirements, the assessment might also impinge upon comparative efficacy and/or safety and embrace economic factors including price, cost effectiveness, and other considerations determined by national policy.

For administrative convenience, the product licence should be as simple as possible. It should always describe the product by name, manufacturer and importing agent, identify the ingredients, (preferably by their international nonproprietary names), and provide full details of the dosage form. It should also contain a serial number, the date of issuance of the licence, its date of expiry and any special conditions to be observed. It is advisable to cite certain additional items in the licence for easy reference — such as shelf-life and sales category — but, in other particulars, it should refer to the information submitted by the licence-holder in the dated product application.

Renewal and variation of licences

Licences should never be regarded as immutable. Ideally, they should be reviewed at, say, five-yearly intervals. However, many national authorities do not have the capacity to undertake this task, particularly for as long as they remain engaged in the initial review of provisionally-licensed products. In these circumstances many products fall to review on an ad hoc basis. Sometimes this is inspired by recently generated concern regarding safety. More frequently, a product attracts attention because the licence-holder has altered the formulation in some way — by changing, for instance, the source of the starting materials, the nature of the excipients, the route of synthesis of an active ingredient, or the claims made in labelling and promotional material.

The precise circumstances in which licence-holders are required to apply for variations in a product licence differ from country to country. These circumstances should be clearly defined in all product licence documents, including provisional licences.

Licence-holders should be required, in all circumstances, to inform regulatory authorities immediately of unanticipated adverse effects which could possibly be associated with a licensed product and which might call for restrictive licensing action or the withdrawal of the product licence.

Technical aspects of the licensing process

General considerations

Although countries vary in their resources and priorities, advantage accrues from harmonizing documentary requirements to the fullest possible extent since this simplifies registration procedures and reduces costs.

The most important starting-point for imported products is the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce. This gives basic information on composition, an assurance that the product is manufactured in accordance with good manufacturing practices in premises which are subject to inspection, and information on the regulatory status of the product in the country of export. A certificate, issued in compliance with the model format recommended by WHO, should be required whenever application is made to licence an imported product.

Products containing long-established chemical entities

For products indicated for standard uses and that contain established ingredients, the following elements of information usually suffice as the basis for both a product licence and for a computerized data retrieval system:

- name of the product
- active ingredient(s) [by international nonproprietary name(s)]
- type of formulation
- therapeutic category
- quantitative formula (including excipients)
- quality control specifications
- indications, dosage, method of use
- contraindications, warnings, precautions
- bioavailability data (in vitro/in vivo)
- stability data, shelf-life
- container, packaging, labelling
- intended method of distribution: controlled drug; prescription item; pharmacy sale; general sale
- manufacturer
- importer/distributor
- regulatory status in the exporting country.
If the dosage form is a novel one, such as a delayed-release tablet, or if a new route of administration is proposed, supporting data from clinical studies will be required.

**Products containing new chemical entities**

Considerably more extensive information is required to support a marketing application for a new drug substance in order to provide assurance of efficacy and safety as well as of quality. In particular, detailed accounts are required of:

- chemistry (structure, physical properties, synthesis, specification, impurities, stability characteristics)
- pharmacological properties (in animals, in man)
- toxicological data (short and long-term studies in animals, including carcinogenicity studies)
- reproductive and teratological studies in animals
- clinical studies.

Small regulatory authorities need to adopt caution in licensing newly-developed products because they do not possess the capacity:

- to undertake the multidisciplinary assessment applied to them within large, highly-evolved authorities;
- to monitor their performance in use through post-marketing surveillance.

In general, a small authority is best advised to wait until this information has been generated and assessed elsewhere before authorizing such a product for use.

In the case of products intended exclusively for tropical parasitic disease, much of this evidence may need to be built up in countries with limited resources. The expertise of the World Health Organization is at hand to offer advice in these circumstances. Once a decision is taken to authorize such a product for general use, the regulatory authority and the manufacturer share a responsibility to ensure that a monitoring mechanism is put in place to detect unanticipated reactions. A mutually-acceptable plan for post-marketing surveillance should be settled in advance and included in the product licence as a condition of approval.

**Herbal products**

The use of herbal and other naturally-occurring substances is part of the fabric of traditional medicine. Because of the complex, and sometimes imprecise nature of the ingredients they contain and the paucity of scientific information on their properties, products containing these substances, often in combination, can rarely be reviewed on a rigorously scientific basis. Where time-honoured practices do no apparent harm, there is no urgency for regulatory intervention other than to set up a system for provisional registration.

However, prolonged and apparently uneventful use of a substance offers insecure testimony of its safety. In a few instances, recently commissioned investigations of the potential toxicity of naturally-occurring substances widely used as ingredients in these preparations have revealed previously unsuspected potential for systemic toxicity, carcinogenicity and teratogenicity. Small regulatory authorities need to be quickly and reliably informed of these findings. They should also have the authority to respond promptly to such alerts, either by withdrawing or varying the licences of registered products containing the suspect substance, or by rescheduling the substance in order, for instance, to disallow its use by non-medically-qualified practitioners.

All regulatory authorities should also be alert to the practice of incorporating potent pharmacologically-active compounds, such as steroids, into herbal preparations. When this is done clandestinely it is a manifestly dangerous practice which demands immediate withdrawal of the products and a review of the manufacturer’s licence.

**Combinations of potent, therapeutically-active substances**

The justifications for formulating fixed combinations of potent, therapeutic substances are few. All biologically-active substances have a potential to induce harm as well as therapeutic benefit. The administration of two or more such substances, rather than one, increases the potential for adverse
Fixed-ratio combination products are consequently acceptable only when the dosage of each ingredient meets the requirements of a defined population group and when use of the combination provides a clear advantage over separate administration of the individual active compounds, either in therapeutic effect or compliance, or when it enhances safety — as in the case of multiple chemotherapy intended to reduce the emergence of resistant pathogens.

**Generic products**

In many countries, for reasons of economy, drugs destined for use in the public sector are purchased on open tender. This favours the use of generic products, and the practice in some countries is for tenders to be issued, bids examined, and contracts offered by the procurement authority without reference to the drug regulatory authority.

The licensing of generic products poses a challenge to all regulatory authorities, particularly when the product to be supplied is not registered in the country of origin. The need for expert assessment is accentuated because not all drug-exporting countries submit drugs intended exclusively for export to the same rigorous controls as drugs intended for the domestic market. Nominally equivalent generic products should contain the same amount of the same therapeutically-active ingredients in the same dosage form and they should meet required compendial standards. However, they are not necessarily identical and in some instances their clinical interchangeability may be in question. Differences in colour, shape and flavour, while obvious and sometimes disconcerting to the patient, are often inconsequential to the performance of the product, but differences in sensitizing potential due to use of different excipients and differences in stability and bioavailability have obvious clinical implications. Regulatory authorities consequently need to consider not only the quality, efficacy and safety of such products, but also their interchangeability one with another and with the original innovative product. This concept of interchangeability applies not only to the dosage form but also to the instructions for use and even to the packaging specifications when these are critical to stability and shelf-life.

Some highly-evolved authorities require that every generic product must satisfy three sets of criteria of therapeutic equivalence. These relate to:

- manufacturing and quality control;
- product characteristics and labelling; and
- bioequivalence.

Others adopt a more pragmatic approach to the need for experimental demonstration of bioequivalence. Study 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. In developing countries the *in vivo* bioavailability testing of all domestically-manufactured products would be impractically costly. The regulatory authority should be in a position to help local manufacturers by advising them on drugs which pose potential bioavailability problems.

In the case of imported products, assurance should be obtained through WHO’s Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce that the product has been produced in accordance with WHO’s standards of Good Manufacturing Practices and that, in the light of a full assessment, it has been authorized to be placed on the market in the country of origin.
Personal Perspectives

Address to Ninth General Assembly of the World Federation of Proprietary Medicines Manufacturers*

Dr Hiroshi Nakajima
Director-General
World Health Organization

I greatly appreciate the invitation to address your Annual General Assembly today. The industry represented by this Federation holds the unique prerogative of supplying medicinal products directly to consumers. Each one of us here today — with greater or lesser frequency — buys your products. Wherever there are families, there are household medicines. Whenever temporary illness strikes, there is need for symptomatic relief.

Forty years ago, when the World Health Organization was founded and at a time of intensive development of public health services in many of the more highly-developed countries, health and health counselling were widely regarded — even within the public mind — as being the preserve of the health professional. Health education was on no political agenda. Healthy lifestyle, as a concept, had yet to be invented. The art of medicine maintained its mystique and was intended to do so. The labels of medicines, made to individual order within pharmacies, identified the name of the patient rather than the nature of the product. The patient was given dosage instructions, but rarely any other information or explanation. The transaction was undertaken exclusively on a basis of trust.

We now live in a very different world. Life has become more complex, more problematic in many ways, both for individuals and institutions. Better educational opportunities have created societies that are more open and that demand to be better informed. As people become more affluent, their expectations are heightened. They begin to view health in a positive context, not merely in terms of survival against adversity. They gain confidence from the unprecedented technical progress that has been made in every field of medicine within the experience of a single generation — progress for which the industry, time and again, has provided the motive force for change. They recognize that they are living longer and their quality of life has been transformed beyond all reasonable expectation. Suddenly, however, they are faced with the realization that there is a price to pay: that health, like any other commodity, must be costed.

Regardless of the benefit that accrues, every medical intervention represents an inevitable charge, either on the individual or the community. The more that is done to extend and ameliorate the quality of life, the more we must each expect to contribute financially to society's collective commitment. Increasing sophistication in health technology continues to extend the horizons of medicine, and this is enabling countless disadvantaged people to live fuller and more productive lives, but it does nothing to relieve the immediate burden of expense upon the health care services. Inevitably, doctors are suddenly finding themselves under pressure to count the cost of treatment.

This need for cost-consciousness has been dramatically exacerbated, of course, by the advent of AIDS and society's desperation to prolong the lives of increasing numbers of young people with greatly lowered resistance to infection. But the dilemma was already disconcertingly broadly-based and is now casting a sombre shadow over many potentially exciting developments in preventive medicine and the care of the chronically sick. What is the cost that society is prepared to countenance for extending a life? Where does the doctor's professional duty begin and end? How can considerations of cost-containment be reconciled with the Hippocratic Oath and the legal liabilities that devolve from it?

The hapless clinician cannot be left to search his conscience in isolation. A crisis is in the making that everyone with a responsibility for the provision of medical services will be forced, sooner or later, to heed. What can be done? Every option must obviously be explored to increase the efficiency of health care without jeopardizing standards. Doctors

* Held in Rome from 4 to 7 June 1989
must be seen to be disciplining themselves to become cost conscious and they must be prepared to reconsider, in the light of changing circumstances, the extent to which their extensive training and skills remain essential to the delivery of primary health care. Better informed people have more competence to help themselves. Pharmacists and community nurses are equipping themselves to provide more comprehensive counselling services. Drug regulatory bodies are becoming more indulgent in the range of products they are prepared to countenance as non-prescription items. Your companies are at hand to support these trends.

Much depends on the way you respond to the challenge. I have no doubt that your long-term interest lies, not simply in being on the marketplace as vendors of proprietary medicines, but in being ready and waiting to assume a key role in the delivery of primary health care. You will be judged by the extent to which you are prepared to think beyond product promotion to possible ways in which you might use your privileged access to the public to educational purpose. Your prerogative to address the consumer directly is not accorded lightly within the field of health. It embodies a trust conferred by society never to exploit privilege to commercial advantage in a way that runs counter to the public interest. We depend upon you to use your resources imaginatively, constructively and dispassionately to facilitate the development of the health care infrastructure wherever you establish your markets.

Those markets are far from homogeneous. The “affluence gap” between rich and poor yawns ever wider. The World Health Assembly, in 1978, called upon WHO to develop further the dialogue with pharmaceutical industries in order to assure their collaboration in meeting the health needs of the large underserved segments of the world’s population. It has been estimated that today, in some countries, the annual per capita sum spent on medicines is higher than US$ 100; in others it remains less than US$ 2. More than one-third of the human race is still denied adequate access to essential drugs and vaccines. Where there is deprivation of this degree, proprietary medicines are likely to be bought, not to safeguard health, but in a desperate attempt to restore it. Our call to you is to respond to need where it so obviously exists, never to exploit it.

A bottle of vitamins offers little to those in search of food. Research your markets. Maintain a presence wherever your products are sold. Learn about the practices and infrastructure of traditional medicine where they are widely practicable in order to explore how you can best complement them, and seek to exorcise — through the influence of this Federation — unacceptable marketing practices wherever they may occur.

Last year, the World Health Assembly adopted a further resolution that dispels any excuse for complacency. It makes a plaintive call for the initiation of programmes for the prevention and detection of the export, import and smuggling of falsely-labelled, spurious, counterfeit or substandard pharmaceutical preparations. This is a brutal reminder of man’s potential for inhumanity to man; of an unflinching capability within the criminal subculture to exploit even the sick and disadvantaged; of the duty of each one of us to serve the common cause; and of the need to assure universal implementation of the standards and practices embodied within this Federation.

We have a long road to travel to assure the universal availability of necessary drugs of good quality at prices that countries can afford. Our dialogue must continue. We need your collaboration and support to root out the cancer that has developed within the system; to promote exemplary standards of manufacture and trading; to positively support the health infrastructures and the regulatory processes of the countries in which you operate; to further the objectives of WHO’s Certification Scheme for the Quality of Pharmaceutical Products moving in International Commerce; and to respect and serve with every sensitivity the vital needs and priorities of the collectivity of communities in this world that it is our destiny to share.

I recognize the pivotal role of your Federation in this challenge. I welcome your commitment to become more broadly representative of industry in developing countries. The issues are clearly defined and WHO relies upon you to act in a spirit of partnership to address them. Together, we will not only stand, we will roll back many of the constraints that, for far too long, have impeded the effective delivery of primary health care.
Oral contraceptives and breast cancer

Apprehension that prolonged use of combined oral contraceptives might initiate or promote the development of breast cancer has existed for more than twenty years. Notwithstanding intensive epidemiological investigation and the arrival of early users of these products into their fourth and fifth decades, definitive conclusions are still not at hand. Because of the considerable scale on which oral contraceptive products have been used in many developed countries, any significant excess of the disease should ultimately be reflected in national or regional cancer registries. Thus far no such trends have been reported. But, even if they were to appear, they could well prove difficult to interpret because the basis upon which many registry records are compiled has changed appreciably throughout this period.

The urgency to resolve the existing uncertainty at the earliest opportunity has provided impetus to explore the problems not only prospectively but also retrospectively through case-control studies. Taken together, the latter have failed to provide a consistent message. Instead, indecisive claims and counterclaims have generated a pendulum of concern that has provided little help to prescribers, users or drug regulators. Until a few months ago, the balance of evidence was largely reassuring. Indeed, negative studies continue to be published (1, 2). Now, however, two new case-control studies undertaken respectively in the United Kingdom (3) and the United States of America (4), and a re-analysis of data derived from one of the largest studies previously conducted in the USA (5, 6), have reawakened controversy.

The British study (3), which is based on data derived from 755 women who developed breast cancer, together with matched controls, is interpreted by the investigators as indicating that oral contraceptives are implicated in about one-fifth of such cancers presenting in women under 36 years of age. The risk was estimated to be increased by about 40 per cent among women who had used oral contraceptives for 4 to 8 years and by about 70 per cent in women who had used them for more than 8 years. The analogously-designed Boston study (4) — involving two groups of approximately 400 women — suggests that, by the age of 45, women who have used oral contraceptives for up to 10 years face twice the risk of developing breast cancer than women who have never used them. The association was demonstrated in virtually all subgroups examined and it was even more pronounced among women with more than 10 years of exposure. Similarly, a reworking of the results of a large study conducted by the Cancer and Steroid Hormone Group in the USA (5, 6) suggests a positive association may exist that was previously not identified. In this instance, however, it applies only to women who used oral contraceptives for more than four years before their first full-term pregnancy.

As yet, neither the United States Food and Drug Administration nor the British Committee on the Safety of Medicines considers that the new evidence warrants warning labelling or other regulatory action.

An FDA expert panel is sceptical that the studies will ultimately overturn the more reassuring conclusions drawn in earlier publications, and it points to the possibility that — should the postulated associations reflect reality — the results may demonstrate a potential of oral contraceptives to promote the development of breast cancer, rather than to induce it (7). If this is so, a compensatory fall in the incidence of the disease should occur among long-term oral contraceptive users who survive into the later decades of life. The UK Committee on the Safety of Medicines has adopted a similar stance in advising that “there is no need for a change in oral contraceptive prescribing practice on the evidence presently available” (8). It emphasizes, in particular, that the marked excess of cases described in the British study is not reflected in national cancer statistics and that findings attributable to the effects of older contraceptive products containing relatively high doses of estrogen may not be applicable to currently-available preparations.

The Lancet, in commenting that “the pendulum now seems to be hovering some way from total reassurance about breast cancer in younger women” strikes a less defensive note, but with wry pragmatism it adds: “If cancer registration data continue to yield no support for an association of any sort, some day
the call may soon have to go out not for more research into oral contraceptives and breast cancer but for an inquiry into the basic tenets of the case-control technique, if only in this controversial and difficult area" (9).

References

Efficacy of hepatitis B vaccine

Hepatitis B vaccines have been shown to be immunogenic in several controlled studies, but the duration of the period of protection has remained uncertain. The need for this information is particularly important since concentrations of antibody to hepatitis B surface antigen have been reported to decline rapidly with time and infection has occasionally been recorded within a few years of vaccination.

These initial concerns have now been largely redressed by the first population-based study to be reported (1). The data were derived from Eskimo communities living in remote villages in western Alaska in whom hepatitis B virus infection was previously hyperendemic. Between November 1981 and May 1982, 1630 inhabitants of these villages who were considered to be at high risk of infection, including both infants and young adults, received plasma-derived hepatitis B vaccine in three intramuscular 20 µg doses — or 10 µg in children aged 10 years or less. Each individual subsequently remained in the survey for five years, during which time both the concentrations of hepatitis B surface antigen and markers for active infection were monitored annually.

Overall, 95 per cent of those vaccinated reacted with an immediate immune response of 10 or more sample ratio units and were classified as having responded positively. After five years the antibody concentration fell below this threshold in approximately 20 per cent of the sample. However, no one developed either clinical hepatitis or hepatitis B surface antigen during this period, although evidence of abortive infection — a spontaneous boost in the surface antigen, together with the appearance of hepatitis B core antigen — was recorded in four persons, including one "non-responder".

The results of the study are of prime importance because they provide direct confirmation that hepatitis B vaccine can provide long-lasting protection against infection during the periods of greatest risk, both in infancy and in early adulthood. In a commentary carried in the same issue of the journal in which the survey is published (2), it is emphasized that, globally, hepatitis B virus is a leading cause of morbidity and mortality, not only from fulminant hepatitis but also from the long-term sequelae of cirrhosis and hepatocellular carcinoma. These diseases are most highly prevalent in Asia and Africa, but even within the United States of America it is estimated that 300 000 persons are infected annually, and that the direct medical costs exceed US$1 million daily (3).

The outcome of the study in Alaska will certainly lend momentum to efforts to incorporate hepatitis B vaccination in national immunization programmes in Asia and Africa where, in some regions, more than 90 per cent of the population have been infected by the age of 15 years. Experience in The Gambia, where 60 000 infants have already received the vaccine, indicates that a four-dose schedule, started within the first month of life, can be conveniently integrated into the country's expanded programme of immunization (4). Here, too, the number of non-responders has been estimated to be low — probably less than 2 per cent — and it is anticipated
that the antibody concentrations achieved will be adequate to provide effective protection throughout the period that they remain at high risk of developing persistent infection. This will be evaluated in the years ahead using information obtained from a cohort of at least 1000 vaccinated children who may also, eventually, provide an indication of the measure of protection afforded against chronic hepatic disease.

References


2. Francis, D.P., Margolis, H.S. Worldwide elimination of hepatitis B transmission: we have the way, we need the will. *Journal of the American Medical Association*, 261: 2400 (1989).


Aerosolized pentamidine in *Pneumocystis carinii* pneumonia

It is estimated that in more than 60 per cent of cases an opportunistic protozoal infection, *Pneumocystis carinii* pneumonia, is the first clinical manifestation of acquired immunodeficiency disease (AIDS). It also supervenes in an additional 15 to 20 per cent of patients in whom AIDS presents in some other way (1, 2). Approximately 15 to 20 per cent of these episodes are fatal and there is a high frequency of relapse.

Earlier efforts to suppress the infection have been either marginally successful or unacceptably toxic. Zidovudine has been claimed to reduce the frequency of relapse, but its effect is rarely sustained for more than a few months (3, 4). Trimethoprim-sulfamethoxazole has been claimed to successfully suppress infection in patients with AIDS first presenting with Kaposi's sarcoma, but adverse effects are often troublesome (5, 6). Many patients are unable to tolerate this treatment, and zidovudine cannot be used concomitantly since it potentiates the risk of bone marrow depression. Pyrimethamine-sulfadoxine has also been studied but, again, severe toxicity and treatment failures have been reported (7, 8). Pentamidine has been used intravenously for the past five years to treat clinically-evident infections but it is too toxic when administered by this route for preventive therapy (9).

Tangible progress has now been achieved through the development of an aerosol formulation of pentamidine which, it is hoped, might inhibit infection at dosages that do not give rise to serious dose-related systemic toxicity. Experience already gained in the United States of America and France in administering pentamidine by this route at doses of up to 300 mg every 4 weeks has resulted in the approval by the US Food and Drug Administration of a preparation of the isoethionate salt manufactured by Lyphomed Inc (10). It is indicated for individuals who have experienced at least one previous episode of pneumonia, or who have a T4 lymphocyte count of 200/mm$^3$ or less. These groups were defined on the basis of a large, long-term epidemiological study undertaken by the US National Institute of Allergy and Infectious Diseases which has demonstrated that patients with a severely depressed T4 lymphocyte count are at risk of developing this form of pneumonia even if they have no symptoms of HIV infection. The selected dosage, which is higher than has often been used in the past and which induces coughing or wheezing in some patients, is recommended on the basis of a clinical trial sponsored jointly by the manufacturer and a community group in San Francisco that represents the interests of AIDS patients.

Thus far, the results of this study have not been reported in detail, but an encouraging account has recently been published of an analogous study undertaken in France (11). A randomized controlled comparison between zidovudine alone and pentamidine taken concurrently with daily zidovudine in patients who had recovered from an initial attack was terminated prematurely on ethical grounds after 41 patients had been treated for 6 months or longer. Of these, infection recurred in 15 of 21 patients who had received zidovudine alone, but only in one of 19 patients who had additionally received the aerosol in the form of particles with a medium diameter of 4.6 µm at a dose of 4 mg/kg pentamidine base at intervals of two weeks for the first month, and then monthly.

Further trials are now planned to investigate the effect and acceptability of these products at even
higher doses and to assess their longer-term effects on pulmonary function.

References


Antihaemophilic factor and AIDS

It is estimated that 60 to 80 per cent of patients with haemophilia who were exposed to factor VIII concentrates before 1984, when heat-treated preparations were introduced, are seropositive to HIV by Western blot assay (1-3). By mid-1988, within the USA, almost 700 of these patients had developed clinical evidence of AIDS (4). Cases of seroconversion are now being described following the use of heat-treated lyophilized preparations (5-7), and the question has been raised as to whether these patients are also necessarily infected or whether they might possibly have been immunized by preserved viral proteins (8). It is pointed out that, in general, microorganisms are killed by heat at temperatures lower than are required to denature their protein components. HIV-1 cultures and polymerase chain reaction analysis can now rapidly demonstrate whether these patients are infected or not, and the University of Minnesota, USA is calling for serum samples on which to undertake these investigations (9). Confirmation of active infection would provide a compelling stimulus to develop recombinant antihaemophilic factor which is now undergoing phase II trials (10) and, should it prove to be safe and effective, to make it available for daily prophylaxis at a cost comparable to that of the currently-available blood-derived products.

References


Fenoterol and fatal asthma

A case-control study, undertaken in New Zealand and recently published in the Lancet (1), is interpreted by the investigators as indicating that unsupervised inhalation of the beta-agonist compound, fenoterol, by patients with severe asthma considerably increases the risk of a fatal attack. Their suggestion that use of fenoterol may induce serious cardiac dysrhythmias or inappropriately delay the admission of patients with severe acute asthma to hospital as a result of its potent bronchodilating action, has resurrected controversies that developed in the 1960s over the use of isoprenaline forte inhalers in the same circumstances (2-5).

The study is founded upon information on 125 patients aged between 5 and 45 years who died in hospital between 1981 and 1983 during a severe exacerbation of asthma. Controls — four for each case — were identified from hospital records as asthmatics admitted and subsequently discharged from hospital close to the time that the matching case died. Fenoterol inhalers had been prescribed before admission with significantly greater frequency in those who died than those who survived — odds ratio 1.55 — and this association became more apparent when control patients with less severe grades of asthma were excluded from analysis. No association was demonstrated with any other anti-asthma drug widely used in New Zealand.

During the period at issue, mortality from asthma within this age group was estimated approximately to have doubled from the time that fenoterol was first introduced to New Zealand in 1976. On the basis of their data, the authors estimate that fenoterol might have been implicated in approximately 40 per cent of the "excess" deaths. At first sight this conclusion is persuasive. It becomes more problematic, however, in the light of information that use of fenoterol — in comparison with that of other anti-asthma drugs — remained steady in New Zealand in subsequent years, whereas mortality from asthma is estimated to have decreased from 4.1 per 100 000 in 1979 to less than 1.8 per 100 000 in 1987 (6).

In the light of this inconsistency, the design of the study was bound to become a focus for debate. Claims have been made that potentially important sources of bias and artefact were either unappreciated or underemphasized (6-8). Whereas the diagnosis in each of the fatal cases had been verified by the New Zealand Medical Research Council's Asthma Task Force, the control patients were selected solely on the basis of hospital records. Some, it has been claimed, may not have been asthmatic, others were admitted to hospital for other reasons, and it is disputed whether the severity of the disease was as great among the controls as among the patients who died. Moreover, it is questioned whether the available evidence is sufficient to support the crucial assumption that all patients prescribed fenoterol inhalers actually used them during their terminal attack.

In essence, the critics claim, the study confuses the question of whether fenoterol has an acute toxic effect when used during an attack with the separate question of whether chronic long-term dosage increases the risk of death. In this study, they argue, the severity of the illness was classified, not with respect to the acute episode that occasioned the admission, but with respect to imprecise and arguably inappropriate markers for chronic asthma. This defect, they conclude, is fundamental because it leaves open the possibility that fenoterol was preferentially prescribed for patients who were experiencing the most severe attacks of asthma and was then falsely linked with the deaths that subsequently occurred.

The last word in this dispute has doubtless still to be printed. But, regardless of the ultimate outcome, it points to a central dilemma in the conduct of
epidemiological research. To escape criticism studies need to be meticulously designed and implemented. Unfortunately, the pursuit of perfection in this field is immensely costly. Moreover, when drug-related hazards are at issue, pressures inevitably emerge to communicate suspicions at the earliest opportunity. Short cuts may sometimes be taken in generating data and presenting the results. With publication, however, these pressures are immediately transferred to drug manufacturers, to individual prescribers and, not least, to drug regulatory authorities. For the latter, the dilemma is particularly acute when expert opinion is divided. The time is, perhaps, fast approaching when a forum needs to be provided to enable regulators, epidemiologists and interested manufacturers to discuss these issues as they arise in an international context.

References


4. Wilson, J.D., Sutherland, D.C., Thomas, A.C. Has the change to beta-agonists combined with oral theophyllines increased cases of fatal asthma? Lancet, 1: 1235-1237 (1981).


Ciclosporin enemas in refractory chronic proctitis

Preliminary data presented in the Lancet suggest that ciclosporin (250 mg in 5 ml) administered as a retention enema can induce sustained improvement in patients with chronic distal ulcerative colitis refractory to corticosteroids and mesalazine (5-aminosalicylic acid). Six of eight such patients were improved both clinically and sigmoidoscopically after a single enema and, in three of them, improvement was sustained for at least two weeks. In one instance, a scheduled colostomy was cancelled. There was no indication of drug-induced mucosal toxicity, and only on one occasion was ciclosporin detected in venous blood samples. Two patients complained of nausea, but no other adverse effect attributable to the drug was encountered, and no deterioration was noted either in renal or hepatic function.

The enema contained about half the daily oral dosage recommended in inflammatory bowel disease, which is limited by the risk of nephrotoxicity. Whereas oral ciclosporin is usually administered in lipophilic solution, the injectable form used for the enema was hydrophilic. This, the authors suggest, may explain why the drug was not significantly absorbed.

General Information

Proposed revision of Australian therapeutic goods legislation

Australia is planning to revise its legislation dealing with therapeutic goods to provide more uniform controls over imported and locally-manufactured products. It is hoped to introduce the changes in early 1990.

One of the proposals is to require certification for each imported pharmaceutical product as to its marketing status in the country of manufacture and the standard of the manufacturer. Certification in compliance with the WHO Certification Scheme will generally be required. Other forms of certification will generally not be accepted. Certification will be required for final dosage forms including those for medicinal drugs, herbs, vitamins and minerals.

Countries which may experience difficulties with this proposal are asked to contact Mr P. Pflaum, First Assistant Secretary, Therapeutics Division, Department of Community Services and Health, GPO Box 9848, Canberra ACT 2061, Australia.

Epidemiologists at odds

Large pharmacoepidemiological studies are difficult to conduct, costly to organize and often fallible in the results they provide. Too often, in the opinion of Professor Alvin Feinstein of the University of Yale, this fallibility derives from neglect of basic scientific principles.

In reviewing the axioms of epidemiological investigation in a recent issue of Science (1) he complains of the uncertainty that arises when investigators are tempted to use convenient collections of data for testing hypotheses that were not entertained at the time the information was compiled. More pointedly, he takes issue with those who adjust control groups after the results have been analysed; with the large number of studies beset with unresolved and unreconciled contradictions; with the infrequency with which precautions are taken to exclude ascertainment bias; with questionable statistical manoeuvres that are sometimes adopted in lieu of demonstrating true dose-responses; and with the credulous acceptance of erroneous death-certificate diagnoses.

Few of his peers are likely to share his scepticism to the extent of continuing to question the existence of a causal relationship between long-term administration of exogenous estrogens and endometrial cancer and between diethylstilbestrol and vaginal carcinoma. None the less, a sharp reminder is timely that there is no place for uncritical application of epidemiological techniques in the investigation of adverse drug effects. The field is fraught with difficulties. Feinstein and his colleagues have themselves identified 56 different situations in which evidence interpreted as supporting a cause-effect relationship in at least one epidemiological study has been refuted by the results of another (2). Nor is clinical medicine usefully served when, as so often happens, remote risks of treatment are considered in dissociation from the perceived benefits. At a time when utility data bases, originally constructed for other purposes, are perceived as providing a major resource for identifying and quantifying drug-related risks, there is greater need than ever for contemplative reconsideration of how bias and artefact can best be prevented from distorting comparative data and confounding their interpretation.

References


Analgesics and renal disease

Habitual use of analgesics has been recognized as a significant cause of chronic renal disease since 1953 (1). In Australia, where much of the early research was conducted in the 1970s, it was estimated that as many as a quarter of the patients needing chronic dialysis or transplantation were suffering from analgesic nephropathy (2). Elsewhere, the disease...
has seemed to be less prevalent and more unevenly distributed, but it may none the less account for 15 to 20 per cent of terminal renal disease in both the Federal Republic of Germany (3) and Belgium (4).

On the basis of both epidemiological and toxicological data, habitual use of phenacetin was long regarded as the prime factor predisposing to the characteristic pathological lesion, renal papillary necrosis, and the risk of cumulative exposure seemed to be exacerbated when it was taken in together with acetylsalicylic acid and caffeine in analgesic mixtures (5). Persuasive biochemical explanations have been advanced to explain the mechanisms involved but these have implicated, not phenacetin itself, but its major metabolite, paracetamol. Unless it is efficiently detoxified through an oxidative mechanism catalysed by prostaglandin hydroperoxidase, the latter accumulates in the renal medulla. Acetylsalicylic acid, by inhibiting prostaglandins and also by decreasing the supply of reduced glutathione, tends to impede this oxidative process (6). This, in turn, may promote medullary necrosis by causing an accumulation of reactive intermediary products capable of binding to cellular macromolecules. Caffeine, which inhibits adenosine, might further exacerbate cellular damage by increasing the demand for oxygen in the renal medulla (7).

Because of the coherence of this array of facts and hypotheses, and in the absence of reports of habituation to paracetamol, it was confidently anticipated that the problem of analgesic nephropathy could be overcome by withdrawing phenacetin from use and by subjecting all analgesic mixtures to prescription control. However, fourteen years after these measures were taken in Australia, the results are less decisive than had been expected. During the 12-month period ending in October 1987, analgesic nephropathy remained the primary diagnosis in 13 per cent of all patients within the country newly requiring dialysis (8). Elsewhere, there are few indications of any amelioration of the situation. In Belgium, for example, the proportion of dialysis patients diagnosed as having analgesic nephropathy has failed to decline with time, even though the volume share of phenacetin in the national analgesic market is estimated to have fallen from 30 per cent in 1970 to less than 1 per cent in 1988 (4). In these circumstances, the outcome of a case-control study recently published in the New England Journal of Medicine (9) is of particular interest. It was conducted in the United States of America in an area of North Carolina where the regular use of analgesics — in the form of "headache powders" containing phenacetin or paracetamol — is estimated to be particularly high. The data were obtained from 554 adults with newly diagnosed chronic renal disease and 516 matched controls. Renal disease was found to be significantly more prevalent among daily users of analgesics than those who used them infrequently. Whereas the risk was most marked among users of phenacetin (odds ratio 5.11; 95% confidence interval 1.76-14.9), it was similarly and independently increased among users of paracetamol (odds ratio 3.21; confidence interval 1.05-9.80). In contrast, daily use of acetylsalicylic acid was without demonstrable risk. The plausibility of the results was heightened by evidence of a dose-response effect and by showing that the relative risks remained essentially unchanged when adjustments were made for other diseases, including diabetes and hypertension, and for the various indications for which the analgesics were taken.

An accompanying commentary on the trial (10) emphasizes that "case-control studies cannot determine cause and effect but can only suggest associations that need to be confirmed by prospective observations". At the same time, however, it cites a comparable, but as yet unpublished, study recently completed in the Federal Republic of Germany (11) which provides strong corroboration of the results obtained in the American study. In this instance, a review of 517 patients with end-stage renal disease indicated that cumulative lifetime consumption of analgesic mixtures in excess of 1 kg is associated with a dose-related risk of renal disease. Again, whereas the risk was most strongly associated with phenacetin, an association was also demonstrated with paracetamol/acetylsalicylic acid combinations, and particularly those additionally containing caffeine.

The commentary concludes by raising several inevitable questions. It asks whether sales of analgesics over-the-counter should be limited to preparations containing a single ingredient. It suggests that substances more recently marketed for such use, including paracetamol and ibuprofen — which, as nonsteroidal anti-inflammatory drugs, cannot be assumed to be devoid of nephrotoxic potential (12,13) — should be subjected to particularly careful monitoring. It proposes that more consideration should be given to the importance of other possible risk factors, including smoking and the use of alcohol and caffeine. Not least, it makes a
plea for investment in preventative and educational measures commensurate with the scale on which over-the-counter analgesics are advertised and used, and with the “billion-dollar cost” of the federally-subsidized end-stage renal disease programme within the United States.

References


Resistance to antivirals

Until recently, reports of resistance to antiviral agents were rare and sporadic. This has now changed dramatically. Herpes simplex and cytomegalovirus resistant to aciclovir and ganciclovir, respectively, are now well established as causes of progressive opportunistic infection in patients with AIDS (1-4).

Aciclovir is activated only when it is phosphorylated by viral thymidine kinase, and mutants of herpes simplex deficient in this enzyme have been demonstrated in unresponsive patients and generated in vitro. Resistant strains of cytomegalovirus also develop by mutation and possibly as a result of pressure of selection when patients carrying multiple strains are treated. In view of this, it has been questioned in a recent editorial in the New England Journal of Medicine (5) whether it is prudent to use aciclovir and ganciclovir to suppress these diseases in severely immunocompromised patients or whether reliance should be placed in other antivirals, such as foscarnet and vidarabine.

More clinical information is needed, it seems, before these questions can be answered with assurance. At present, ganciclovir is the only drug of proven benefit when life or sight are threatened by cytomegalovirus infection, but the therapeutic options may widen with the completion of a planned prospective trial of foscarnet and vidarabine in patients with resistant disease. Moreover, it remains unproven that long-term suppressive therapy with antivirals favours the emergence of drug-resistant mutants. Nor is there, as yet, any indication that drug-resistant mutants will tend to establish themselves in immunocompetent patients. Whereas aciclovir-resistant herpes viruses have been isolated occasionally from otherwise healthy individuals, they have not been reported to be implicated in progressive disease, and isolates obtained from patients in relapse have thus far been sensitive to aciclovir.

There can be no doubt, however, that surveillance for virulent, drug-resistant viruses must be sustained, particularly in immunologically incompetent patients, and that the search for yet more novel antiviral agents must continue.

References


### High blood pressure in the elderly

Several large studies of hypertension recently conducted in elderly patients have demonstrated that, whereas the highest cardiovascular mortality is associated with the highest systolic and diastolic pressures, mortality also tends to rise in patients whose clinical blood pressures are reduced to readings appreciably below 150 mmHg systolic and 90 mmHg diastolic (1-3). This has led to the suggestion that a reduction of pressure induced by drugs may sometimes cause rather than prevent myocardial ischaemia (4-6). Confirmation of the existence of such J- or U-shaped mortality curves among elderly treated hypertensive patients has recently been obtained in some 700 patients over 60 years of age (mean 71.5 years) organized by the European Working Party on High Blood Pressure in the Elderly (7). Indeed, for diastolic pressure, the paradoxical effect of treatment — hydrochlorothiazide and triamterene for a period of nine months, with methyldopa added in resistant cases — was even more marked than in other published studies in that mortality was inversely associated with treated diastolic pressure throughout the observed range.

The study was particularly notable in that a similar, but U-shaped, relationship was demonstrated between diastolic blood pressure and mortality in patients randomly allocated to placebo instead of an active hypotensive regimen. Indeed, in both treated patients and controls, comparable relationships between mortality and blood pressure were established for both cardiovascular and non-cardiovascular events. For any given achieved systolic or diastolic blood pressure, mortality was lower in those taking active treatment than those taking placebo. Overall, however, these differences were not marked: 56 deaths were recorded in the treated group and 65 in the placebo group and, of these, one-third were attributed to non-cardiovascular events.

The authors do not question that an exaggerated reduction of blood pressure in response to antihypertensive therapy is harmful if it compromises the coronary or cerebral circulation. However, in the light of the information obtained from the control group, they conclude that other factors must have contributed to the excess mortality among the patients within the lower third of the blood pressure range. They note, in particular, that these patients tended to be less heavy and and to have lower blood haemoglobin levels than the average of the cohort as a whole, and they suggest that their increased death rate might simply be an expression of a deterioration in their general state of health.

### References


Volatile anaesthetics and the ozone layer

Correspondents to the Lancet have expressed concern that, because the halogenated anaesthetic gases — halothane, enflurane and isoflurane — are possibly contributing to the destruction of the ozone layer, there may be a case for reducing this possible source of pollution through encouraging, on environmental grounds, the use of alternative techniques such as regional and total intravenous anaesthesia (1). However, it has since been explained that only chlorofluorocarbons (CFCs) that are fully halogenated are regulated under the Montreal Convention (2). Whereas the latter have atmospheric lifetimes of 75 to 100 years, the halogenated anaesthetics, which contain C-H groups, should be much more susceptible to attack by naturally-occurring hydroxyl radicals in the lower atmosphere. Indeed, most new CFCs currently under development contain at least one hydrogen atom in the expectation that this will render them environmentally acceptable.

It has been assumed from indirect evidence that the mean atmospheric lifetime of halothane ranges from one to five years, but it is conceded that these reactions are highly unpredictable and they are now subject to further study (3). Confirmation that they are relatively innocuous in environmental terms will be reassuring, but there are no grounds for complacency regarding the problem at large. The total amount of halothane used worldwide per annum is less than 1000 tonnes; the annual manufactured tonnage of the "regulated" CFCs is of the order of 1 million tonnes. An editorial published in the Lancet tersely places the situation into perspective (4). Nobody, it contends, really knows how much more chlorine-loading the atmosphere can withstand.

“...the only certainty among atmospheric physicists is that global warming and stratospheric ozone depletion will interact to destabilize the atmosphere in unpredictable ways, and that a total phase-out of CFCs is not merely desirable but an absolute and urgent requirement for any strategy to combat climatic change”.

References


Disclosure of inactive ingredients

In recent years it has become appreciated that excipients in pharmaceutical products, as well as active ingredients, can have sensitizing properties. On occasion, the reported reactions have been severe and, in very rare instances, fatal. Several of the substances implicated have already been withdrawn from use by national regulatory authorities and in several countries the inclusion of some others must now be declared in labelling.

No one contests that a more complete declaration of additives and excipients in foods, cosmetics and medicines would protect individuals with known hypersensitivities and assist in the detection and investigation of chemical allergens, but concerns about confidentiality of intellectual property have tended to impede progress. The initiative of G.D. Searle & Co of Canada to voluntarily take a lead in the matter by disclosing all inactive ingredients in its full line of prescription and over-the-counter medications is consequently not only welcome, but a challenge to manufacturers at large. Complete lists of the ingredients of Searle’s products will be included on the outer labels of over-the-counter products and on packaging and/or patient inserts for prescription drugs. This information will also be included in independent drug compendia widely used within Canada, and the company has set up a permanent telephone service to deal with enquiries for supplementary information.


Registration of drug products in Malaysia

The Drug Control Authority has decided in future not to register any imported product which does not demonstrate therapeutic or pharmaceutical advantage over similar products already on the market, particularly when five or more such products are already manufactured locally.
A total of 4144 prescription drug products has been registered in Malaysia and it is considered that the addition of yet more products offering no clear advantages will accentuate difficulties in monitoring and ensuring the safety, efficacy and quality of those currently registered. The resulting liberation of the regulatory services from licensing functions will enable them to concentrate on inspection and quality control.


Is multiple sclerosis an immune disease?

Multiple sclerosis, which is most prevalent at temperate latitudes, strikes about 1 in 800 Northern Europeans. Often the disease remains mild but many foci of demyelination are always demonstrable on imaging by magnetic resonance. The widespread distribution of these lesions has long raised speculation that they are caused by an immune mechanism. Interest in immunosuppressive therapy has been sustained for almost 20 years but most formal trials have been inconclusive because they have lacked adequate statistical power.

An exception is a recently published British/Dutch multicentre study involving over 350 patients, each of whom was treated for at least three years with either a fixed dose of azathioprine or placebo (1). As in other studies in which azathioprine was used in conjunction with corticosteroids (2) the treatment had a marginal effect. Despite this setback, a recent leading article in the Lancet (3) continues to sound a note of optimism by proposing that an undefined subpopulation of patients may be more responsive or that a higher dose might have been more effective.

At first sight, optimism is difficult to countenance since similarly disappointing results have been obtained with ciclosporin (4,5). This, however, may simply reflect poor penetration of the drug across the blood-brain barrier (6). More promising is the claim, based on a study of more than 150 patients over six years, that a high-dose pulse of intravenous cyclophosphamide can sometimes slow the rate of progression of the disease for a prolonged period (7,8). Other investigators remain more equivocal in their assessment of such therapy and objective assessment is compromised, in this instance, because many of the treated patients also underwent plasmapheresis and received adrenocorticotropic hormone. None the less, possibility that immunosuppression continues to hold unexplored potential is confirmed by evidence that total lymphoid irradiation can arrest the progress of the disease for eighteen months or longer (9, 10). The Lancet commentator concludes that "although cyclophosphamide is unpleasant to take, the few late complications represent an acceptable risk when the prognosis for remaining independent is otherwise poor", and he looks forward to the time when molecular immunobiology will provide a more precisely focused means of inactivating the immune mediators of myelin injury.

References


**Measles virus vaccines: defective interfering particles**

Defective interfering particles are virus mutants that are deficient in genetic information and that interfere with the growth of the normal virus. Work being undertaken on the measles virus within the University of Geneva has led to the discovery of such particles in yields derived from the Edmonston-Zagreb strain, but not from two other strains of live attenuated vaccines. Further studies are in hand to determine whether these particles play a role in the mechanism of attenuation or in any other way modify the biological properties.


**Measles/mumps/rubella vaccine: cost benefit**

France — Immunization has long been recognized as an outstandingly effective means of controlling communicable diseases, but few precise cost-benefit analyses of its impact have been published. Such a study recently undertaken in France provides an instructive insight into the immediate and longer-term consequences of introducing a national measles/mumps/rubella vaccine programme. It is estimated that after defraying the costs of delivering the programme, a net saving to the community in contingent medical care becomes evident only after 17 years. After 25 years, however, it is projected that cumulative savings in the public health sector will exceed FFr 1245 million at current value. This is based on an expectation that, by then, the programme will have prevented 9 million cases of measles, 8 million cases of mumps, 3000 cases of congenital rubella, 25 000 cases of meningitis, over 3500 cases of encephalitis and some 1500 deaths.


**Salt-induced enhancement of measles virus yield in cultured cells**

Union of Soviet Socialist Republics — Millimolar supplementation of culture media with magnesium sulfate is claimed to result in enhanced yield of measles virus. The effect, which is being studied within the Institute for Viral Preparations in Moscow, appears to be due to stimulation of intracellular events. It is already being used to improve yields in the cell culture system routinely used for measles vaccine production in the USSR.

Regulatory Matters

Drugs for Human Use

Erratum: pyrrolizidine alkaloids

In Volume 2, Number 4 of WHO Drug Information it was reported that the Federal Health Office of the Federal Republic of Germany had suspended marketing authorizations for herbal products containing pyrrolizidine alkaloids as from 1 October 1988.

This is incorrect: the Federal Health Office gave manufacturers 4 weeks as from 10 August 1988 to provide comments and additional information on which to base possible future action with a view to the risks of hepato-toxicity and mutagenic and carcinogenic effects associated with these products. To date, the Federal Health Office has not taken any decision on changes in approval status.

Encainide and flecainide for life-threatening dysrhythmias only

United States of America — The Food and Drug Administration together with the manufacturers of encainide (Bristol Myers) and flecainide (Riker) have issued a joint statement urging doctors to reserve these drugs for the treatment of life-endangering dysrhythmias, particularly sustained ventricular tachycardia. The warning results from interim data obtained in a multicentre trial intended to determine whether these antidysrhythmic agents could improve survival in patients with acute cardiac infarction by preventing or suppressing premature ventricular beats. It was found, after the patients had been treated for an average of 10 months, that, of 730 given encainide or flecainide 56 had died, whereas death had occurred in only 22 of 725 given placebo. The trial was immediately terminated.

Patients currently taking these drugs are advised to consult their doctor since unsupervised adjustment or interruption of treatment may precipitate a fatal dysrhythmia.


Federal Republic of Germany — On the basis of the same data, the Federal Health Office is considering, together with the manufacturer, the need to restrict the approved uses of flecainide to life-threatening supraventricular tachycardia, including AV re-entry tachycardia and Wolff-Parkinson-White syndrome, and to contraindicate its administration to patients who have sustained a recent or earlier cardiac infarction.


Fenbufen

United Kingdom — The data sheet for fenbufen, a nonsteroidal anti-inflammatory agent, has recently been amended to accentuate warnings of adverse mucocutaneous effects (1). Since the product was first marketed in the United Kingdom in 1980, more than 6000 notifications have been received. Of these, 80 per cent relate to mucocutaneous reactions, characterized by a generalized and florid erythematosus rash of sudden onset, often associated with pruritus. A small proportion of the reports cite more serious conditions, including 178 cases of erythema multiforme and 30 of Stevens-Johnson syndrome, of which two were fatal.

In at least seven such cases, the initial reaction was followed by lung disorders, including allergic alveolitis and pulmonary eosinophilia (2). These were characterized by cough, fever, malaise and breathlessness and required admission to hospital. A diagnosis of pulmonary eosinophilia was made in 5 patients, all of whom had osteoarthritis. The two remaining patients — one of whom was seropositive for rheumatoid arthritis — were diagnosed as having an allergic alveolitis. All seven patients recovered within 4 to 6 weeks of stopping fenbufen.

References

Imipenem/cilastatin

Japan — Following reports of convulsions and disturbances of consciousness in patients taking the broad-spectrum antibiotic, imipenem in combination with the penicillinase inhibitor cilastatin, the Subcommittee on Adverse Drug Reactions has decided that the approved product information should be amended to include a relevant warning. This emphasizes that patients with renal impairment or pre-existing disease of the central nervous system must be treated with particular caution and that the preparations should be withdrawn immediately, should reactions occur.


Potassium chloride voluntary withdrawal

France — Following eight reports of perforation ascribed to rapid intestinal release of potassium, the last two brands of rapid-release potassium chloride tablets available in France have been withdrawn from the market with the agreement of the manufacturers.

References
1. La Revue Prescrire, 8: 492 (1988).

Slimming aids

Netherlands — The Ministry of Welfare, Public Health and Cultural Affairs has issued revised guidelines for licensing slimming aids which provide dietary bulk with little calorific value. Existing authorizations will remain valid until 1 January 1990, but from this date all products sold as meal replacements must comply with the new labelling regulations which require:

- the full composition of the product to be displayed together with an accompanying assurance that it fulfils all vital nutritional requirements;
- precise directions to be provided on the proper use of the product emphasizing that it should not be used for more than six weeks at any one time; and
- a warning that patients with metabolic disorders should consult a doctor before using the product.


Tamoxifen

Federal Republic of Germany — The Federal Health Office is proposing to amend the approved product information for the anti-estrogenic compound, tamoxifen, to indicate that even at low dosage and following short periods of treatment occasional cases of visual disturbance, cataract, corneal changes and/or retinopathy have been associated with its use. Statements previously made to the effect that such changes occur predominantly in patients with existing eye disease, in elderly patients, and those taking high dosages for long periods are now regarded as invalid and will be deleted.


Veterinary Drugs

Amoxicillin

United States of America — The Food and Drug Administration has approved an extension of the indications for amoxicillin trihydrate suspension to include treatment of respiratory infections (shipping fever, pneumonia) in lactating cattle with amoxicillin-susceptible microorganisms (including Pasteurella multocida, P. haemolytica, Haemophilus spp., Staphylococci spp. and Streptococci spp.) at a dose of 3 to 5 milligrams per pound body weight. Milk from treated cows must not be used for human consumption during treatment or for 96 hours (8 milkings) after the last dose. Previously, this antibiotic was registered for use only in non-lactating animals. The product has also been additionally approved to treat acute necrotic pododermatitis (foot rot) due to Fusobacterium necrophorum.

Carcinogenicity and veterinary drugs

**United States of America** — The Food and Drug Administration has emphasized, on the basis of guidance prepared by the Center for Veterinary Medicine, that care is mandatory in the handling of veterinary drugs that have been demonstrated in animal studies to possess carcinogenic potential, even when they present no tangible hazard to man when used in accordance with the labelled recommendations. A warning of carcinogenic potential, indicating the drug name and species implicated, should be included in the labelling.


Chloramphenicol

**Hungary** — The Ministry of Agriculture and Food has banned the use of chloramphenicol for therapeutic purposes in milk and egg-producing animals, having regard to its potential to induce aplastic anaemia in man, and the prolonged period during which residues remain demonstrable after discontinuation.

Reference: Letter from the National Institute of Occupational Health to IRPTC/UNEP.
Advisory Notices

Allergenic extracts:

risk of anaphylaxis

United States of America — The Food and Drug Administration has requested doctors to ensure that it is notified of all fatalities associated with exposure to an allergenic extract. Information currently available from reports submitted to the Agency and from a retrospective survey among members of the American Academy of Allergy and Immunology indicate that at least 14 deaths have resulted from such exposure since 1980, and that a further 4 deaths have been attributed to skin tests for allergies. On this basis the Agency estimates that the overall risk of death from such exposure is of the order of 0.2 per million.

Whereas it accepts this risk as extremely small, it is concerned that such incidents may be substantially under-reported and that they might be reduced further if essential precautions were always followed. It notes that many of the patients known to have died were asthmatic and it emphasizes that patients with an allergic diathesis are at increased risk of anaphylaxis. It also reminds doctors that different types of extract cannot be regarded as allergenically interchangeable; that initial dosage should always be based on the results of skin tests; that patients should always remain under observation for at least 20 minutes after each injection; that individuals receiving &beta; adrenoreceptor blocking agents may not be responsive to epinephrine or inhaled bronchodilators; and that the administration of these substances should be undertaken exclusively by physicians experienced in their use and in the emergency management of anaphylaxis.


Dapsone:

severe cutaneous reactions

Denmark — The Adverse Drug Reaction Committee of the National Board of Health has advised doctors that it has received 27 reports of adverse effects associated with the use of dapsone in the treatment of patients with severe acne, lupus erythematosus, pustulous psoriasis and dermatitis herpetiformis. Anaemia, often haemolytic, was most frequently reported (12 cases) followed by liver dysfunction (6 cases), fever, skin reactions and agranulocytosis. Some of the haematological reactions became evident only after several months' treatment. In all but two cases the reaction resulted in a decision to discontinue treatment.


Floctafenine

Belgium — The Adverse Drug Reaction Monitoring Centre has received six reports of severe anaphylactic reactions associated with the use of the analgesic, floctafenine. One patient had experienced a similar reaction previously after taking the closely-related analgesic, glafenine. The Centre stresses that floctafenine is contraindicated in patients who have reacted adversely to glafenine and that treatment must be discontinued immediately should pruritus, urticaria or any other sign suggestive of a risk of anaphylaxis occur.


Injectable vitamin preparations:

serious allergic reactions

United Kingdom — The Committee on Safety of Medicines has informed doctors that between 1970 and 1988 it received 90 reports of adverse reactions that had occurred in patients during or immediately after injection of a preparation containing high doses of B-group vitamins, vitamin C and metabisulfite. Many of these — including 41 cases of anaphylaxis, 13 cases of dyspnoea or bronchospasm and 22 cases of rash or flushing — were allergic in character.

Lofepramine: severe hepatic reactions

**United Kingdom** — Between 1983 and 1987 the Committee on Safety of Medicines received 57 reports of abnormal liver function associated with the use of the tricyclic antidepressant, lofepramine. These include one case of hepatic failure, 9 cases of jaundice and 5 of hepatitis. Other reports are suggestive of cellular damage and cholestasis. All reactions occurred within 8 weeks of starting treatment and all were reversible upon discontinuation. The Committee has asked doctors to report in detail all suspected hepatic reactions due to antidepressant drugs and to indicate any possible predisposing factors, including use of alcohol.


Low osmolar radiocontrast media and shock

**Japan** — Having reviewed reports of shock associated with the use of low osmolar radiocontrast agents, the Subcommittee on Adverse Drug Reactions has suggested that physicians and medical personnel be advised by circular letter to exercise the same precautions during the administration of these preparations as are required for other contrast media.


Lysine acetylsalicylate injectables and shock

**Japan** — The Pharmaceuticals and Chemical Safety Division has written to all doctors to remind them that cases of shock have been reported in patients following the administration of an injectable preparation containing lysine acetylsalicylate. This preparation, which was first introduced in 1982, is indicated as an analgesic in severe neuralgia and post-operative pain, and in the emergency management of severe fever.


Mianserin: blood dyscrasias

**United Kingdom** — Reports of blood dyscrasias received by the Committee on Safety of Medicines over the last few years have confirmed concern about the potential of the antidepressant, mianserin, to provoke these effects, particularly in the elderly. From the time the product was introduced in the United Kingdom in 1976 until 1988, 239 reports of haematological disturbances were received. These include 68 cases of agranulocytosis and 84 cases of granulocytopenia or leukopenia. Clinicians are reminded that a full blood count should be requested routinely every four weeks during the first three months of treatment. Whenever a patient develops fever, sore throat or other signs of infection, treatment should be immediately suspended and a further count obtained.

The Committee has also indicated that it wishes to receive reports of all haematological adverse reactions associated with the use of other antidepressant drugs.


Nefopam: risk of urinary retention

**United Kingdom** — The Committee on Safety of Medicines has received 53 reports in which the analgesic, nefopam, was associated with urinary retention, hesitancy, poor stream or dribbling. In only one case was a previous history of prostatism elicited and all cases recovered when nefopam was withdrawn. A further 12 reports cite confusion and 22 cite hallucinations. The Committee advises that nefopam be used with caution, particularly in the elderly, in patients with symptoms of urinary retention and in those taking other medicines with anti-cholinergic properties.

Parenteral nutrition: need for thiamine-containing vitamin supplements

United States of America — The Food and Drug Administration has advised physicians that patients being fed intravenously require a preparation that contains thiamine. Deficiencies that are potentially fatal can develop rapidly because thiamine is consumed at a high rate in patients receiving intravenous glucose. The American Society for Parenteral and Enteral Nutrition (ASPEN) has alerted its members to three deaths attributed to thiamine deficiency which occurred during a transient period of shortage of intravenous multi-vitamin supplements.


Propofol: convulsions, anaphylaxis and delayed recovery from anaesthesia

United Kingdom — The Committee on Safety of Medicines has advised anaesthetists that it has received reports of serious reactions attributed to the short-acting intravenous anaesthetic, propofol. It emphasizes that particular care be taken in administering it to epileptic patients. It is estimated that the product has now been used on some two million occasions from the time it was introduced in the United Kingdom in June 1986. Since then, the Committee has received 37 reports of seizures in which the drug is thought to have been implicated, 13 of which were in known epileptics. Sixteen reports of involuntary movements and 10 reports of opisthotonos are also on record.

Among the remaining reports are 32 anaphylactic reactions — which in most cases resulted in severe bronchospasm and profound hypotension as well as in flushing and/or oedema — and 13 cases of cardiac arrest necessitating emergency resuscitation.

The need for an adequate period of recovery after minor interventions is also stressed. In some cases an hour or more had elapsed before consciousness had been fully reestablished and some of these patients lapsed back into unconsciousness after a short period of wakefulness.

Sulfonylureas and hypoglycaemia

The Adverse Reaction Monitoring Centre in Belgium has drawn the attention of doctors to an article in the British Medical Journal which points out that the use of chlorpropamide, glibenclamide and other sulfonylureas in the management of diabetes frequently results in episodes of hypoglycaemia. Fatal reactions are particularly likely to occur in the elderly and in patients with cardiac, renal or hepatic insufficiency, and the Centre stresses that these drugs should only be prescribed when dietary measures have failed.

It notes, additionally, that the hypoglycaemic effect may be potentiated by concomitant use of salicylates, beta adrenoreceptor blocking agents and antibacterial sulfonamides and that similar incidents have recently been reported in AIDS patients receiving high dosages of sulfamethoxazole + trimethoprim for treatment of Pneumocystis carinii pneumonia.

References

Suxamethonium chloride: severe bradycardia

Denmark — The Adverse Drug Reaction Committee of the National Board of Health has received 29 reports of patients who developed severe bradycardia or asystole after a single injection of the depolarizing neuromuscular blocking agent, suxamethonium chloride. No predisposing factors were evident but it is suggested that, even though suxamethonium chloride does not normally reduce heart rate, its weak parasympathomimetic effect may, in some cases, have potentiated bradycardia induced by fentanyl or other concomitantly administered drugs. Anaesthesiologists are requested to provide details of all other drugs administered to the patient when reporting such effects.

Federal Republic of Germany — The Federal Health Office has amended the approved product information for products containing suxamethonium chloride to indicate that it has been associated with cases of cardiac dysrhythmia in children.


Tetracyclines: benign intracranial hypertension

United Kingdom — The Committee on Safety of Medicines has received reports of benign intracranial hypertension in patients taking prolonged courses of oral tetracycline antibiotics for acne. Nine of these cases were associated with minocycline, 5 with tetracycline, 2 with demeclocycline and 1 with oxytetracycline.

Dosage was within the normal range in most cases and none of the patients was taking any other drug known to be associated with this condition. Most cases presented with headache and visual disturbances typical of the condition. Papilloedema occurred in almost every case and, in some, it was unilateral. The visual disturbances included persistent blurring of vision, scotomata and diplopia due to VIth nerve palsy. The onset occurred in some cases within a few weeks of starting treatment, but in others it was delayed for several months.

In comparison with the scale on which tetracyclines are used, benign intracranial hypertension is obviously a rare event. However, since half the reported cases may be expected to suffer permanent loss of vision, doctors have been urged to consider the possibility of raised intracranial pressure in any young person complaining of headache or visual disturbances while receiving tetracyclines.

Essential Drugs

Intestinal infections due to nematodes

Many hundreds of millions of people throughout the world harbour nematodes in the intestine. In their social and economic implications these parasitic infections constitute a major public health problem, particularly in developing countries. Infection is transmitted by eggs or larvae which begin their cycle of development within the human host when, depending on the species, they either actively penetrate intact skin or become ingested or, very rarely, inhaled. The larvae of the most widely prevalent species remain dormant but potentially infective for long periods in contaminated soil; the larvae or cysts of other species are ingested when the flesh of reservoir hosts is eaten raw or undercooked.

Control

Interruption of transmission is the key to effective long-term control. In some instances this is dependent simply upon ensuring that meat and fish are adequately cooked. For the soil-borne infections, however, major public health initiatives are required, including:

- education in personal, family and community hygiene and the use of shoes or sandals;
- construction of latrines and efficient sewage disposal systems; and
- pre-treatment of human faeces destined for use as fertilizer to destroy all parasites.

Effective and regular community-based chemotherapy will also reduce transmission but, in the absence of other measures, this does not provide a practicable basis for long-term control.

ASCARIASIS

Over 1000 million people worldwide are estimated to be infected with *Ascaris lumbricoides* (roundworm) and, of these, at least 20 000 die annually. A risk of infection exists wherever faecal disposal is inadequate and the disease remains endemic in many regions of south-east Asia, Africa and Central and South America.

Children are particularly vulnerable since they are at risk of ingesting ascaris eggs while playing in soil contaminated with human faeces. Dust and contaminated fruit and vegetables pose a hazard to all members of the community.

Once ingested, the eggs hatch in the small intestine and motile larvae penetrate the mucosal blood vessels. They are carried first to the liver and then to the lungs where they ascend the bronchial tree before being re-swallowed. Eventually they re-enter the small intestine where they mature, over a period of two months, into adult worms.

This larval migration sometimes induces transient hypersensitivity and inflammatory reactions resulting in pneumonitis, bronchial asthma and urticaria. Subsequently, colonization of the gastrointestinal tract by adult worms, which survive for about one year, may cause anorexia, abdominal pain and discomfort and other gastrointestinal symptoms. From time to time, all or part of a worm may be vomited or passed in the stools.

Obstruction of the small intestine by worms or, less frequently, their migration — often subsequent to inadequate treatment — into the appendix, the biliary tract, the pancreatic ducts, or even the upper respiratory tract, can create a life-threatening emergency requiring surgery.

Chemotherapy

Ideally, all infections should be treated, since even a single worm can induce serious allergic reactions or cause life-threatening complications.

In highly endemic areas mass treatment of entire communities is justified when over half the population is estimated to be infected. Selective treatment of infected individuals — particularly children — also reduces mortality and morbidity, but a demonstrable effect on transmission, as indicated by a reduction in the rate of reinfection, can only be expected after at least two interventions 4 to 6 months apart.
Individual infections are eradicated by a single dose of pyrantel or levamisole. Piperazine is also effective, but it is less well-tolerated. Broad spectrum anthelmintics hold obvious advantage where other nematode infections are known to be endemic: the benzimidazoles (mebendazole, albendazole and flubendazole) are each effective in a single dose.

**HOOKWORM**

Over 900 million people in tropical and subtropical countries are estimated to be infected with either *Ancylostoma duodenale* or *Necator americanus*, and associated anaemia causes at least 50,000 deaths annually.

Eggs shed in large numbers in infected human faeces develop rapidly in warm, moist soil into filariform larvae which are capable of penetrating intact human skin. They pose a hazard to anyone walking barefoot over contaminated ground. Additionally, *A. duodenale* may be transmitted by ingestion of larvae.

The invasive larvae are first carried in the blood stream to the lungs. They subsequently ascend the bronchial tree before being carried in the gastrointestinal contents to the small intestine where they become attached. As they mature into adult worms, they digest considerable quantities of blood and cause further losses by lacerating the mucosa. Clinically evident infection is characterized by abdominal discomfort, peptic ulcer-like pains and eventually by hypochromic, microcytic anaemia which becomes severe in the absence of treatment, particularly when iron intake is inadequate or marginal.

**Chemotherapy**

Ideally, all cases should be treated. However, where the risk of reinfection is high, this may be impracticable. In these circumstances high priority should be given to women in the second and third trimesters of pregnancy, children, and patients debilitated by such conditions as malnutrition, tuberculosis or anaemia.

Broad-spectrum anthelmintics should be preferred wherever other nematode infections are endemic and mebendazole, albendazole and flubendazole are each effective. Levamisole is also promising in the treatment of mixed ascariasis and hookworm infections. Although pyrantel has been highly effective in some community-based control programmes but several doses are often needed to eliminate *N. americanus* infection.

Anaemic patients require supplementary iron salts. They should continue to receive 200 mg ferrous sulfate daily for at least three months after the haemoglobin concentration has regained the threshold of 12 g/100 ml.

**STRONGYLOIDIASIS**

Some 50 to 100 million people are estimated to be infected with *Strongyloides stercoralis*. It is widespread, not only in moist rainy areas of the tropics and subtropics, but also in some areas of southern and eastern Europe and of the United States of America.

Infective larvae in contaminated soil penetrate intact skin and cause an itchy erythematous rash at the point of entry. They are carried in the bloodstream to the lungs where they ascend the bronchial tree before being swallowed. They then enter the small intestine where they penetrate the mucosa and mature into adult worms. Eggs shed by female worms are transformed into larvae that are excreted into the intestinal lumen. Most larvae are excreted in the stool, but some may penetrate the mucous membrane of the lower bowel or the perianal skin. This results in autoinfection which intensifies and perpetuates intestinal colonization.

Infection may remain asymptomatic, but recurrent cutaneous and gastrointestinal symptoms and signs are common. In patients whose immune mechanisms are depressed either by disease, cytotoxic drugs or irradiation, the larvae may become widely disseminated. This gives rise to severe haemorrhagic enteritis and pulmonitis, diarrhoea, malabsorption, oedema, liver enlargement and paralytic ileus. Encephalopathy, pyogenic meningitis and Gram-negative septicaemia are particularly serious complications. In endemic areas, vulnerable patients should be screened regularly and treated promptly as need arises. It is particularly important to exclude infection before immunosuppressive therapy is started.

**Chemotherapy**

All infected patients should be treated. Albendazole administered for three consecutive days is well
tolerated and initial reports suggest it may eradicate up to 80 per cent of infections. It is both more effective and better tolerated than tiabendazole which induces disabling nausea and malaise in a high proportion of patients. Mebendazole has also been used but, to be effective, it must be administered for longer periods.

ENTEROBIASIS

*Enterobius vermicularis* (pinworm or threadworm) occurs worldwide. Unlike other pathogenic helminths, it is highly prevalent in temperate zones and developed countries.

Enterobiasis is almost exclusively an infection of man and it occurs most commonly in children. The condition is self-limiting within a few weeks if reinfection does not occur. Most female worms migrate to the anal region where their eggs, which contaminate perianal skin, night clothes and bed linen, are a source of reinfection to the patient and to room-mates.

Once ingested, the eggs hatch in the jejunum to liberate larvae. Within a few weeks these develop into mature worms in the colon, particularly in the caecal area. Most infections are asymptomatic, but intense anal pruritus can occur. Scratching may then lead to eczematous dermatitis and secondary bacterial infection. The pruritus can result in children becoming hyperactive and emotionally labile. Sustained reinfection is an occasional cause of vulvovaginitis and appendicitis.

**Control**

Prevention of reinfection is dependent upon scrupulous hygiene, including daily washing of the perianal area, regular changes of clothes and nightwear and strategies to prevent infected children from scratching.

**Chemotherapy**

Worms are readily eradicated by a single dose of mebendazole, albendazole, flubendazole, or pyrantel. However, since reinfection readily occurs, at least one further dose is required two to four weeks later. Piperazine is also effective if it is taken regularly for at least 7 consecutive days.

TRICHURIASIS

Trichuriasis, or whipworm infection, which is caused by the nematode worm *Trichuris trichiura*, is estimated to affect some 500 million people. Children aged 5 to 14 years are particularly vulnerable. Most cases occur in the moist, warm, tropical regions of Asia, Africa, Central and South America and the Caribbean islands.

Eggs, excreted in faeces, can survive for several years in soil. If these are ingested they hatch in the jejunum to liberate larvae which mature into adult worms that lodge mainly in the caecum.

Light infections are symptomless and without clinical significance. Since the worms cause focal necrosis at their points of attachment in the large intestine, anaemia results if the infection is heavy. Concomitant bacterial or protozoal infections are also common and may require additional specific treatment. Protracted diarrhoea occasionally results in rectal prolapse.

**Chemotherapy**

Chemotherapy is required whenever symptoms supervene or when faecal samples are found to be heavily contaminated (up to 10 000 eggs per gram). A single dose of albendazole can be effective in mild to moderate infections but heavier infections require a 3-day course of either mebendazole, albendazole or flubendazole.

TRICHOSTRONGYLIASIS

Trichostrongyliasis, which results from infection by *Trichostrongylus orientalis* or other closely-related species of nematode worms, affects several million people living mainly in rural communities in Asia.

Dormant eggs can survive for long periods in soil. Once ingested, they release larvae which mature into adult worms within 25 to 30 days. Most cases are asymptomatic, but heavy infections can cause mild anaemia and enteritis.

**Chemotherapy**

A single dose of pyrantel or albendazole is highly effective.
CAPILLARIASIS

Capillaria philippinensis is endemic in the Philippines and southern Thailand where fish provide a reservoir of infection. Intestinal colonization occurs as a result of eating raw or undercooked fish. Only sporadic cases of intestinal capillariasis are notified each year, although larger epidemics are on record.

The adult worm matures and reproduces in the jejunum. The resulting heavy infection causes an enteritis characterized by malabsorption and a protein-losing enteropathy. The condition usually presents with abdominal pain, diarrhoea, and sometimes steatorrhoea. In the absence of effective treatment, it can become fulminant and result in death within four weeks.

Control

Adequate cooking of fresh-water fish would totally prevent infection.

Chemotherapy

Prolonged treatment with mebendazole or albendazole offers the only prospect of cure.

ALBENDAZOLE

chewable tablet 200 mg, 400 mg
suspension 100 mg/5 ml in bottles of 20 ml,
200 mg/ml in bottles of 10 ml

A benzimidazole derivative which blocks glucose uptake in many intestinal and tissue nematodes and some cestodes. It is poorly absorbed from the gastrointestinal tract and rapidly undergoes extensive metabolism in the liver. The absorbed fraction, which has a plasma half-life of some 8 hours, is largely eliminated in the urine as the sulfoxide.

Uses

Treatment of ascariasis, hookworm infections, strongyloidiatis, enterobiasis, trichuriasis, trichostongyliaisis and capillariasis. It is widely used in community-based control programmes.

Dosage

Adults and children over two years:

Ascariasis, hookworm infections, enterobiasis and trichuriasis

400 mg as a single dose. Single infections of ascariasis or enterobiasis may respond to a single dose of 200 mg. Heavy trichuris infections generally require treatment for three consecutive days. In enterobiasis, it is necessary to treat all members of the household concurrently.

Strongyloidiatis

400 mg daily for 3 consecutive days. If, after three weeks, eggs or larvae are demonstrable in the stools, a second course of treatment should be administered.

Capillariasis

400 mg in 2 divided doses daily for 10 - 20 days.

Contraindications

Known hypersensitivity.

Use in pregnancy

Albendazole has been shown experimentally to have teratogenic potential. Although high priority should be accorded to the treatment of pregnant women, albendazole should not be administered during the first trimester.

Adverse reactions

Transient gastrointestinal discomfort and headache have occasionally been reported.

Overdosage

Emesis or gastric lavage may be of value if undertaken within a few hours of ingestion. Otherwise treatment is symptomatic and supportive. No specific antidote exists.
Albendazole preparations should be stored in well-closed containers.

**LEVAMISOLE**
- tablet 40 mg, 50 mg (as hydrochloride)
- syrup 40 mg/5 ml

Levamisole, the laevoisomer of tetramisole, acts by paralyzing the musculature of susceptible nematodes. Unable to maintain their anchorage, the worms are ejected by normal peristaltic action, usually within 24 hours.

Levamisole is rapidly and almost completely absorbed from the gastrointestinal tract. Peak plasma concentrations occur within 2 hours and levamisole has a plasma half-life of about 4 hours. It is extensively metabolized in the liver and is excreted mainly in the urine as metabolites and unchanged drug.

**Uses**
Treatment of ascariasis and ascariasis/hookworm mixed infections.

**Dosage**
- Adults and children
  A single dose of 2.5 mg/kg is used widely both for individual treatment and community-based campaigns. In cases of severe hookworm infection a second standard dose may be given 7 days after the first.

**Contraindications**
In the doses used for treatment of helminthic infections there are no absolute contraindications.

**Use in Pregnancy**
Safe use in pregnancy has not been established. Whenever possible, treatment should be deferred until after delivery.

**Adverse effects**
Abdominal pain, nausea, vomiting, dizziness and headache are occasionally reported.

**Overdosage**
Emesis or gastric lavage may be of value if undertaken within a few hours of ingestion. Treatment is otherwise symptomatic and supportive.

**Storage**
Levamisole tablets should be stored in well-closed containers.

**MEBENDAZOLE**
- chewable tablet 100 mg
- suspension 100 mg in 5 ml

A benzimidazole derivative which blocks glucose uptake in many intestinal and tissue nematodes. The small amounts absorbed after oral dosage undergo extensive metabolism within the liver to inactive substances. The plasma half-life is usually 2 to 9 hours, but it is considerably lengthened when hepatic function is impaired. Mebendazole is excreted in the faeces as unchanged drug and metabolites.

**Uses**
Treatment of ascariasis, hookworm infections, enterobiasis, trichuriasis and capillariasis. It is widely used in community-based eradication programmes.

**Dosage**
- Adults and children over two years
  Mebendazole should preferably be taken between meals.

<table>
<thead>
<tr>
<th>Infections</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ascariasis</strong></td>
<td>A single dose of 500 mg is effective.</td>
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<tr>
<td><strong>Hookworm infections and trichuriasis</strong></td>
<td>100 mg twice daily for 3 consecutive days.</td>
</tr>
</tbody>
</table>

77
course may be given after 3 to 4 weeks if eggs persist in the faeces. Recently, a single dose of 600 mg has been shown to be effective in hookworm infections.

**Enterobiasis**

100 mg as a single dose, repeated at least once after an interval of 2 to 4 weeks. It is advisable to treat all members of the household concurrently.

**Capillariasis**

200 mg twice daily for 20 to 30 days.

**Contraindications**

Known hypersensitivity.

**Use in pregnancy**

Mebendazole has been shown experimentally to have teratogenic potential. Although high priority should be accorded to the treatment of pregnant women, mebendazole should not be administered during the first trimester.

**Adverse effects**

Transient gastrointestinal discomfort and headache have occasionally been reported.

**Overdosage**

Emesis or gastric lavage may be of value if undertaken within a few hours of ingestion. Otherwise treatment is symptomatic and supportive. No specific antidote exists.

**Storage**

Mebendazole preparations should be stored in well-closed containers.

**Piperazine**

tablet 500 mg hydate (as citrate or adipate)
elixir (as citrate) equivalent to 500 mg hydate/5 ml

Piperazine may selectively block neuromuscular cholinergic receptors in *Ascaris lumbricoides* and *Enterobius vermicularis*, but this has not been demonstrated conclusively.

Piperazine is readily absorbed but the plasma half-life is highly variable. It is partially metabolized in the liver and the remainder is excreted unchanged in the urine.

**Uses**

Treatment of ascariasis and enterobiasis.

**Dosage**

**Ascariasis**

The following schedule is commonly used both in treating individuals and in community-based campaigns:

- **Adults and children over 12 years:**
  75 mg/kg to a maximum of 3.5 g

- **Children between 2 and 12 years:**
  75 mg/kg to a maximum of 2.5 g

- **Children under 2 years:**
  50 mg/kg to be administered under medical supervision.

This amount may be taken in a single dose on an empty stomach, but it has been claimed that better results are obtained when the total dose is divided and taken over two consecutive days.

**Enterobiasis**

50 mg/kg on each of 7 successive days. This course is repeated after an interval of 2 to 4 weeks. It is advisable to treat all members of the household concurrently.

**Contraindications**

Known hypersensitivity.

Patients with epilepsy or impairment of renal or hepatic function.

**Precautions**

Treatment should be discontinued if hypersensitivity or severe intolerance develops, or if neurological signs occur.
Drug interactions

Piperazine and pyrantel are antagonistic in their mechanisms of action. They should **never** be administered together.

Concurrent administration of chlorpromazine has been reported to potentiate the risk of seizures.

Use in pregnancy

Safe use in pregnancy has not been established. Although high priority should be accorded to the treatment of pregnant women, piperazine should not be administered during the first trimester.

Adverse effects

Gastrointestinal irritation occasionally occurs. Hypersensitivity reactions, including skin rashes, fever and joint pains are not uncommon. When they occur, treatment should be withdrawn immediately and the patient warned against taking piperazine again.

Transient neurological symptoms may also occur, particularly dizziness, paraesthesia and slight incoordination. Epilepsy and neuropsychiatric conditions may be exacerbated.

Overdosage

Overdosage can result in convulsions, respiratory depression and transient paresis of the limbs. Emesis or gastric lavage may be of value if undertaken within a few hours of ingestion. Treatment is otherwise supportive and symptomatic.

Storage

Piperazine preparations should be stored, protected from light, in tightly closed containers.

PYRANTEL

chewable tablet 250 mg (as embonate)
oral suspension 50 mg (as embonate)/ml

A pyrimidine derivative which depolarizes neuromuscular junctions of susceptible nematodes. The paralysed worms are subsequently expelled in the faeces. It is poorly absorbed from the gastrointestinal tract. Most is excreted unchanged in the faeces. The absorbed fraction is partially metabolized in the liver and the residuum is excreted in the urine as unchanged drug and metabolites.

Uses

Treatment of ascariasis, hookworm infections, enterobiasis and trichostrongyliasis.

Dosage

**Adults and children**

A single dose of 10 mg/kg is sufficient to eliminate many infections due to ascariasis, hookworm, enterobiasis and trichostrongyliasis.

When treating enterobiasis, however, a second dose should be given routinely after 2 to 4 weeks. All members of the household should be treated concurrently.

Heavy hookworm infections are relatively resistant and three further doses should be given on consecutive days.

A single oral dose of 2.5 mg/kg administered regularly 3 or 4 times a year in mass treatment control programmes has been reported to reduce substantially the prevalence of ascariasis.

Contraindications

Known hypersensitivity

Precautions

Lower doses should be administered when liver function is impaired.

Drug interactions

Pyrantel and piperazine have an antagonistic effect. They should **never** be given concurrently.

Use in pregnancy

Safe use in pregnancy has not been established. Although high priority should be accorded to the treatment of pregnant women, pyrantel should not be administered during the first trimester.
**Adverse effects**

Mild gastrointestinal disturbance, headache, dizziness, drowsiness, insomnia and rash are occasionally reported.

**Overdosage**

Emesis or gastric lavage may be of value if undertaken within a few hours of ingestion.

**Storage**

Pyrantel preparations should be stored in tight, light-resistant containers.

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**TIABENDAZOLE**

chewable tablet 500 mg

A benzimidazole derivative which inhibits cellular enzyme systems specific to various helminths. It is associated with a high incidence of acute incapacitating reactions and its systemic use remains justified only in strongyloidiasis when albendazole is not available. It is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1 hour after ingestion. Approximately 90 per cent is excreted in the urine, principally as conjugates formed in the liver.

**Uses**

Treatment of strongyloidiasis, as an alternative to albendazole.

**Dosage**

25 mg/kg in three divided doses daily taken for 3 consecutive days preferably after meals. Higher doses for longer periods may often be required.

**Contraindications**

Known hypersensitivity. Treatment should be suspended immediately should suspicion of allergy arise.

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**Use in pregnancy**

Tiabendazole has been shown experimentally to possess teratogenic potential. Although high priority should be accorded to the treatment of pregnant women, tiabendazole should not be administered during the first trimester.

**Precautions**

Whenever possible, anaemia, dehydration and malnutrition should be corrected before treatment. Patients should be advised not to drive or operate machinery.

**Adverse effects**

Dizziness, gastrointestinal irritation, drowsiness, pruritus and headache are common, and many patients are incapacitated for several hours. Less commonly, tinnitus, visual disturbances, hyperirritability, numbness, hyperglycaemia, hypotension, collapse, hepatic dysfunction and transient leukopenia have been reported. Hypersensitivity may present as fever, flushing, chills, conjunctival inflammation, angioedema, anaphylaxis, lymphadenopathy or rashes. Erythema multiforme and Stevens-Johnson syndrome may subsequently occur, particularly if treatment is continued. Crystalluria, sometimes with haematuria, can occur, and the urine may develop an asparagus-like odour.

**Drug interactions**

Serum levels of theophylline and other xanthine derivatives may rise above the toxic threshold when tiabendazole is administered concomitantly.

**Overdosage**

Emesis or gastric lavage may be of value if undertaken within a few hours of ingestion. Otherwise, treatment is symptomatic and supportive. No specific antidote exists.

**Storage**

Tiabendazole tablets should be kept in tightly closed containers.
Newly Registered Products

Antithrombin III
anticoagulation factor
Kybernin®: Behring, Italy
injection fluid 50IU/ampoule
*Indications*: prophylaxis and therapy of thromboembolic episodes due to acquired antithrombin-III deficiency.

**butyl methoxydibenzoylmethane + padimate O**
ultraviolet screen
Photoplex®: Herbert Labs, United States of America
lotion 3% + 7%
*Indications*: protection against sunburn.

Cethexonium bromide
antiseptic
Inhaxol®: Laboratoires Sauba, France
nasal drops 0.5 mg
*Indications*: infections of the nasal mucosa, rhinopharyngitis.
*Contraindications*: infants under 30 months of age.
*Precautions*: not to be used for more than 10 days.

Gamolenic acid
(in evening primrose oil)
prostaglandin precursor
Epogam®: Scotia Pharmaceuticals, United Kingdom
capsule 40 mg
*Indications*: symptomatic relief of atopic eczema.
*Caution*: epileptic patients.
*Adverse effects*: nausea, indigestion, headache

iopromide
non-ionic radiocontrast agent
Ultravist 150, 240, 300, 370®: Schering, Netherlands
solution for injection containing iopromide/iodine
*Indications*: various radiographic diagnostic procedures, including myelography and ventriculography. Increases contrast in digital subtraction angiography, and computerized tomography.
*Contraindications*: clinically evident hyperthyroidism. Hypersensitivity.
*Warning*: not for subarachnoidal application.

Ipriflavone
metabolic agent
Osten®: Takeda, Japan
tablet 200 mg
*Indications*: loss of bone mass due to osteoporosis.
*Precautions*: safety during pregnancy, lactation not established.
*Warning*: not to be used concomitantly with estrogens.
*Adverse effects*: hypersensitivity, gastrointestinal symptoms, dizziness.

Irsogladine maleate
anti-ulcer agent
Gaslon®: Nippon Shinyaku, Japan
tablet 2, 4 mg; granules 8 mg/g
*Indications*: gastric ulcer
*Precautions*: safety in children and during pregnancy not established.
*Adverse effects*: gastrointestinal symptoms, mild changes in hepatic function. Occasional skin eruptions necessitating discontinuation of therapy.
isradipine
calcium channel blocking-agent
Prescal®: Ciba Laboratories, United Kingdom
tablet 2.5 mg
*Indications*: essential hypertension.
*Precaution*: safety in pregnancy, lactation and in children not established.
*Caution*: patients with heart disease, particularly aortic stenosis, uncontrolled sick sinus syndrome, and patients with low systolic blood pressure.
*Adverse effects*: headache, flushing, dizziness, tachycardia and palpitations.

nipradilol
beta-adrenoceptor blocking agent with vaso-dilating properties
Hypadil®: Kowa, Japan
tablet 3 mg
*Indications*: essential hypertension, angina pectoris.
*Contraindications*: severe bradycardia, atrioventricular block, sinoauricular block; diabetic ketoacidosis and metabolic acidosis; cardiogenic shock; bronchial asthma, bronchial spasm; heart failure; pregnant and lactating women and other women of childbearing potential.
*Caution*: in the elderly, diabetics, patients with severe hepatic/renal dysfunction. Safety in infants and children has not been established.
*Warning*: pregnancy should be excluded. Withdrawal should be gradual.
*Adverse effects*: bradycardia, circulatory disturbances, shortness of breath, dizziness, headache, drowsiness, insomnia, gastrointestinal symptoms, hypersensitivity, weakness, sweating, tinnitus.

oxidronate disodium + stannous chloride
radiodiagnostic agent, carrier for technetium-99
Osteoscan®: Mallinckrodt Diagnostics, United Kingdom
powder for injection 3.0 mg + 0.24 mg
*Indications*: bone and myocardial scintigraphy.
*Caution*: patients should be encouraged to drink fluids liberally before and after examination. Radiopharmaceuticals should not be administered to patients under 18 years of age or during pregnancy or lactation unless the information to be gained outweighs the potential hazard.

sermorelin
synthetic growth hormone releasing factor (GHRF)
Groliberin®: KabiVitrum, Sweden
powder for injection 100 µg/ml
*Indications*: diagnosis of pituitary secretion of growth hormone.
*Adverse effects*: transient flush.
Recent Publications

American Hospital Formulary Service Drug Information: 89

The American Hospital Formulary Service Drug Information, which is published by the American Society of Hospital Pharmacists, prides itself as "the most comprehensive authoritative source of evaluative drug information". It is certainly one of the most frequently updated. Every year, for the past thirty years, a new annual edition has been published to assure the claim that it covers virtually every single drug entity available in the United States. The task, which involves over 250 independent clinicians and pharmacists in the review process, is formidable and, since the unwieldy loose-leaf format was replaced by a single bound volume in 1984, it has become a prime source of reference far beyond North America.

Its organization, which is determined by a practical, and not overly elaborate, pharmacologic-therapeutic classification, is admirable for the busy clinicians for whom it is primarily intended. If the trend to include introductory commentaries at the beginning of each set of individual drug monographs is sustained, it will compete strongly with many of the established textbooks on clinical pharmacology.


Medicines: regulation, research and risk

No drug regulator and no executive working in an internationally-based pharmaceutical company can operate effectively without a sound working knowledge of the processes by which medicinal products are controlled within the major national markets. There is no shortage of information of a more or less ephemeral nature in the weekly trade press, but it is not so easy to find comprehensive and readable accounts of how the statutory and regulatory provisions that determine these processes have evolved. This book provides a valuable introduction to the complexities of relevant law in the industrialized English-speaking countries and in Japan, together with a brief guide to the European Directives concerning medicines as they stood at the end of 1987.

As an important bonus it also includes a series of informed essays and commentaries on matters of the moment ranging from the costs of pharmaceutical research, product patent life, product liability, and orphan drugs, to mechanisms for monitoring marketed products. The topics are wide-ranging and the reader will be hard-pressed to find them presented in a more readily-assimilable form.


Pyrrolizidine alkaloids

This book dispenses of the dogma that herbal and other traditional medicines may be assumed to be safe on the basis of long and apparently uneventful usage. Many of these preparations contain alkaloids that are known to be toxic and, among these, the pyrrolizidines have long been associated with the development in man of veno-occlusive hepatic disease and the development of cirrhosis. However, it is accidental poisoning with these substances that poses the greatest danger. In many regions plants containing them in high concentrations contaminate staple crops and constitute a threat to farm animals, particularly during the dry season. A large outbreak of human poisoning was recently reported from Afghanistan following a prolonged period of drought.

In experimental studies in animals they have produced acute and chronic toxic changes in the liver, lungs and central nervous system and they possess a dose-related potential to induce teratogenic, fetotoxic and mutagenic changes. This book draws together information cited in over 500 published studies and it provides the most comprehensive overview of the biological properties of these substances that has yet been compiled.

Guidelines for improving children’s prescription medicine use

Ten independent studies of the attitudes of children in the United States of America towards their medicines have shown that, even in the case of those on anticancer therapy, almost half of them fail to comply with instructions. A report entitled “Children and America’s Other Drug Problem”, which discusses these findings, has been issued by the National Council on Patient Information and Education, a body that represents consumers, health-care professionals, government and industry, and which receives active support from the Food and Drug Administration and the American Medical Association. Its message, issued in the form of guidelines on how to inculcate a more responsible attitude in children towards their medicines, is directed primarily to clinicians and it draws on much expert advice from professionals with extensive practical experience of the many facets of the problem.


Predicting carcinogenicity

One of the most challenging and complex tasks in toxicology today is to determine which of the daunting array of established laboratory models are most reliably predictive of the consequences to man of exposure to biologically active substances. In 1981, the International Programme on Chemical Safety, in collaboration with the National Institute of Environmental Health Sciences of the USA, initiated a large inter-laboratory collaborative study of short-term assays proposed as alternatives or supple-

ments to the classical long-term cancer bioassays performed in rodents. The first phase of the study, completed in 1985, which was directed to the identification of one or more in vitro eukaryotic tests suitable to complement the Salmonella mutation assays, has resulted in a proposal that a standardized chromosomal aberration assay should be developed for this purpose (1).

The second phase of the study appraises the results obtained when two structurally-related carcinogen/non-carcinogen pairs of compounds were subjected to a wide range of in vivo assays. The results, now published in two volumes (2), indicate that short-term in vivo tests are of value, less as primary screens, but rather to identify genotoxins most likely to present a carcinogenic hazard to man.

Much still remains to be explored regarding the relative advantages and disadvantages of short-term in vivo and in vitro models as indicators of genotoxicity. Particularly for those toxicologists concerned primarily with new drug development, the strategies for investigating non-genotoxic mechanisms of chemical carcinogenesis remain largely open to debate. The work accomplished thus far in this project indicates that, if answers are to be supplied, they are most likely to emerge through organized international collaborative efforts.

References


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 61 Prop. INN not later than 30 November 1989.

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.

Action and Use
The statements in italics indicating the action and use are based largely on information supplied by the manufacturer. The information is meant to provide an indication of the potential use of new substances at the time they are accorded proposed INNs. WHO is not in a position either to uphold these statements or to comment on the efficacy of the action claimed. Because of their provisional nature these descriptors will not be included in the Cumulative Lists of INNs.

Proposed International Nonproprietary Names (Prop. INN): List 61

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 120581 4 (price: Sw. fr. 6.-); 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. 7, 1988, World Health Organization, Geneva (ISBN 92 4 056014 9) (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 March 1988. The printout also indicates in which of the 58 individual lists of proposed names and 27 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.


Other lists of proposed and recommended international nonproprietary names can be found in Cumulative List No. 7, 1988.
<table>
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<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>
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<td>(±)-6-acetyl-7-[5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentyl]oxy]-2-chromancarboxylic acid</td>
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<td>cilutazolinum</td>
<td>cilutazoline 2-[[6-cyclopropyl-m-tolyl]oxy]methyl]-2-imidazoline</td>
<td>C(<em>{14})H(</em>{18})N(_2)O 104902-08-1</td>
<td>nasal vasoconstrictor</td>
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<td><img src="image2.png" alt="Image" /></td>
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<td>clentiazemum</td>
<td>clentiazem ((+))-cis-8-chloro-5-[2-(dimethylamino)ethyl]-2,3-dihydro-3-hydroxy-2-((p)-methoxyphenyl)-1,5-benzothiazepin-4(5(^\alpha))-one acetate (ester)</td>
<td>C(<em>{22})H(</em>{25})ClN(_2)O(_4)S 96125-53-0</td>
<td>Calcium antagonist</td>
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<tr>
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<td><img src="image3.png" alt="Image" /></td>
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<tr>
<td>cronidipinum</td>
<td>cronidipine [8-((p)-chlorophenyl)-1,4-dioxo-8-azaspiro[4,5]dec-2-yl]methyl methyl 1,4-dihydro-2,6-dimethyl-4-((m)-nitrophenyl)-3,5-pyridinedicarboxylate</td>
<td>C(<em>{35})H(</em>{32})ClN(_5)O(_8) 113759-50-5</td>
<td>Calcium antagonist</td>
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<tr>
<td>danofloxacinum</td>
<td>1-cyclopropyl-6-fluoro-1,4-dihydro-7-[(1S,4S)-5-methyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-4-oxo-3-quinolinecarboxylic acid</td>
<td>antibacterial (vet.)</td>
<td></td>
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<td>danofloxacin</td>
<td>C_{19}H_{20}FN_{3}O_{3} 112398-08-0</td>
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<tr>
<td>decitabinum</td>
<td>4-amino-1-(2-deoxy-β-D-erythro-pentofuranosyl)-s-triazin-2(1H)-one</td>
<td>antineoplastic</td>
<td></td>
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<tr>
<td>decitabine</td>
<td>C_{8}H_{12}N_{4}O_{4} 2353-33-5</td>
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<tr>
<td>deslorelinum</td>
<td>5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-o-tryptophyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide</td>
<td>LHRH analogue</td>
<td></td>
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<td>deslorelin</td>
<td>C_{64}H_{83}N_{17}O_{12} 57773-65-6</td>
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<td>dexibuprofenum</td>
<td>(S)-( + )-p-isobutyrlhydratropic acid</td>
<td>analgesic, nonsteroidal anti-inflammatory</td>
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<td>dexibuprofen</td>
<td>C_{13}H_{18}O_{2} 51146-56-6</td>
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<td>divaplonum</td>
<td>6-ethyl-7-methoxy-5-methylimidazo[1,2-a]pyrimidin-2-yl phenyl ketone</td>
<td>anxiolytic</td>
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<td>divaplon</td>
<td>C_{17}H_{19}N_{2}O_{2} 90806-12-1</td>
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<td>docebenonum docebenone</td>
<td>2-(12-hydroxy-5,10-dodecadiynyl)-3,5,6-trimethyl-p-benzoquinone</td>
<td>80809-81-0</td>
<td>antiallergic, antiasthmatic</td>
</tr>
<tr>
<td>doconexentum doconexent</td>
<td>(all-Z)-4,7,10,13,16,19-docosahexaenoic acid</td>
<td>6217-54-5</td>
<td>platelet aggregation inhibitor</td>
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<tr>
<td>ecomustinum ecomustine</td>
<td>methyl 3-[3-(2-chloroethyl)-3-nitrosoureido]-2,3-dideoxy-α-D-arabinohexopyranoside</td>
<td>98368-18-7</td>
<td>antineoplastic</td>
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<tr>
<td>edatrexatum edatrexate</td>
<td>N-[p-[1-[[2,4-diamino-6-pteridinyl)methyl]propyl]benzoyl]-L-glutamic acid</td>
<td>80576-83-6</td>
<td>antineoplastic</td>
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<tr>
<td>eflumastum eflumast</td>
<td>3'-acetyl-5'-fluoro-2'-hydroxy-1H-tetrazole-5-carboxanilide</td>
<td>70877-46-7</td>
<td>antiallergic, antiasthmatic</td>
</tr>
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<td>Chemical Name or Description, Molecular and Graphic Formulæ</td>
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<tr>
<td>elgodipinum</td>
<td>2-[(p-fluorobenzyl)methylamino]ethyl isopropyl ((\pm))-1,4-dihydro-2,6-dimethyl-4-[2,3-(methylenedioxy)phenyl]-3,5-pyridinedicarboxylate</td>
<td>119413-55-7</td>
<td>Calcium antagonist</td>
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<td>elgodipine</td>
<td>C_{29}H_{33}FN_{2}O_{6}</td>
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<td>enalirenum</td>
<td>((\pm)-cis-N-(1-benzyl-2-methyl-3-pyrrolidinyl)-5-chloro-4-(methylamino)-(\sigma)-anisamide</td>
<td>93664-94-9</td>
<td>D_{1}-dopamine receptor antagonist</td>
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<td>enaliren</td>
<td>C_{21}H_{26}ClN_{3}O_{2}</td>
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<td>epervudinum</td>
<td>2'-deoxy-5-isopropyluridine</td>
<td>60136-25-6</td>
<td>antiviral</td>
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<tr>
<td>epervudine</td>
<td>C_{12}H_{18}N_{2}O_{5}</td>
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<td>Nonproprietary Name (Latin, English)</td>
<td>Chemical Abstracts Service (CAS) registry number</td>
<td></td>
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</tr>
</tbody>
</table>
| **famiclovirum**
**famiclovir** | 2-[[2-[[2-amino-9H-purin-9-yl]ethyl]-1,3-propanediol diacetate (ester)
C_{14}H_{19}N_{5}O_{4} 104227-87-4  antiviral |
| **fasiplonum**
**fasiplon** | 6-ethyl-7-methoxy-5-methyl-2-[[5-methyl-1,2,4-oxadiazol-3-yl]imidazo-
[1,2-a]pyrimidine
C_{13}H_{15}N_{5}O_{2} 106100-65-6  anxiolytic |
| **fibrinum**
**fibrin** | an insoluble plasma protein obtained by the action of thrombin on fibrinogen. The source of the product should be indicated, e.g. fibrin (bovine).
local haemostatic agent |
| **fludeoxyglucosum** (18F)
**fludeoxyglucose** (18F) | 2-deoxy-2-fluoro-18F-α-α-glucopyranose
C_{6}H_{11}^{18}FO_{5} 105851-17-0  radioactive diagnostic agent |
| **flutomidatum**
**flutomidate** | ethyl (±)-1-(p-fluoro-α-methylbenzyl)imidazole-5-carboxylate
C_{14}H_{17}FN_{2}O_{2} 84962-75-4  anaesthetic (vet.) |
| **flutrimazolum**
**flutrimazole** | 1-[α-fluoro-α-(p-fluorophenyl)-α-phenylbenzyl]imidazole
C_{22}H_{16}F_{3}N_{2} 119006-77-8  antifungal |
<table>
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<tr>
<th>Name</th>
<th>Chemical Name or Description</th>
<th>Molecular and Graphic Formulae</th>
<th>CAS registry number</th>
<th>Action and use</th>
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<tr>
<td>galamustinum</td>
<td>6-[(bis(2-chloroethyl)amino]-6-deoxy-D-galactopyranose</td>
<td>C₁₀H₁₉Cl₂NO₅</td>
<td>105618-02-8</td>
<td>antineoplastic</td>
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<td>gedocarnilum</td>
<td>isopropyl 5-[(p-chlorophenoxy)-4-(methoxymethyl]-9H-pyrind-3-carboxylate</td>
<td>C₂₃H₂₁ClN₂O₄</td>
<td>109623-97-4</td>
<td>partial benzodiazepine receptor agonist</td>
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<td>gevotrolinum</td>
<td>8-fluoro-2,3,4,5-tetrahydro-2-[3-(3-pyridyl)propyl]-1H-pyrind[4,3-b]indole</td>
<td>C₁₉H₂₀FN₃</td>
<td>107266-06-8</td>
<td>antipsychotic</td>
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<td>icosapentum</td>
<td>(all-Z)-5,8,11,14,17-icosapentaenoic acid or (all-Z)-5,8,11,14,17-icosapentaenoic acid</td>
<td>C₂₅H₃₆O₃</td>
<td>10417-94-4</td>
<td>platelet aggregation inhibitor</td>
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<tr>
<td>isaglidolum</td>
<td>4-fluoro-2-(2-imidazolin-2-ylamino)isoindoline</td>
<td>C₄₃H₃₅FN₄</td>
<td>110605-64-6</td>
<td>antidiabetic</td>
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</tbody>
</table>
Proposed International Chemical Name or Description, Molecular and Graphic Formulae
Nonproprietary Name (Latin, English)
Chemical Abstracts Service (CAS) registry number
Action and use

**isosorbidum**
isosorbide
1,4:3,6-dianhydro-α-glucitol
C₆H₁₀O₄

**lactitolum**
lactitol
4-O-β-D-galactopyranosyl-α-glucitol
C₁₂H₂₄O₁₁

**laidiomyccinum**
laidimycin
C₃₇H₆₂O₁₂

**letrazurilum**
letrazuril
(±)-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1H-s-triazin-2(3H)-yl)phenyl](p-fluorophenyl)acetonitrile
C₁₇H₉Cl₂FN₄O₂

**levobetaxololum**
levobetaxolol
(-)-(S)-1-[p-[2-cyclopropylmethoxy)ethyl]phenoxy]-3-(isopropylamino)-2-propanol
C₁₆H₂₆NO₅

**sweetener**

**coccidiostatic (vet.)**
<table>
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<th>Action and use</th>
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<tbody>
<tr>
<td>losigamonum</td>
<td>(5R*)-5-{[(αS*)-o-chloro-α-hydroxybenzyl]-4-methoxy-2(5H)-furanone</td>
<td>112856-44-7</td>
<td>antiepileptic</td>
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<td>losigamone</td>
<td>C₁₂H₁₁ClO₄</td>
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<td><img src="image" alt="Losigamone" /></td>
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<td>losmiprofenum</td>
<td>(±)-2-{[3-(p-chlorobenzoyl)-o-tolyl]oxy]propionic acid</td>
<td>74168-08-4</td>
<td>nonsteroidal anti-inflammatory</td>
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<td>losmiprofen</td>
<td>C₁₇H₁₅ClO₄</td>
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<td><img src="image" alt="Losmiprofen" /></td>
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<td>miltefosinum</td>
<td>choline hydroxide, hexadecyl hydrogen phosphate, inner salt</td>
<td>58066-85-6</td>
<td>antineoplastic</td>
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<td>miltefosine</td>
<td>C₂₁H₄₆NO₄P</td>
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<td><img src="image" alt="Miltefosine" /></td>
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<td>mirtazapinum</td>
<td>1,2,3,4,10b-hexahydro-2-methylpyrazino[2,1-a]pyrido[2,3-c][2]benzazepine</td>
<td>61337-67-5</td>
<td>antidepressant</td>
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<tr>
<td>mirtazapine</td>
<td>C₁₇H₁₉N₃</td>
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<td><img src="image" alt="Mirtazapine" /></td>
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<td>moguisteinum</td>
<td>ethyl (±)-2-{(o-methoxyphenoxy)methyl}-β-oxo-3-thiazolidinepropionate</td>
<td>119637-67-1</td>
<td>antitussive</td>
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<tr>
<td>moguisteine</td>
<td>C₁₈H₂₃NO₄S</td>
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<td><img src="image" alt="Moguisteine" /></td>
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<tr>
<td>moxidectinum</td>
<td>(6R,25S)-5-O-demethyl-28-deoxy-25-[(E)-1,3-dimethyl-1-buteny]-6,28-epoxy-23-oxomilbemycin B 23-[(O-methyloxime)</td>
<td>C_{37}H_{53}NO_{18}</td>
<td>antiparasitic (vet.)</td>
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<td>moxidecitn</td>
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<tr>
<td>natrii borocaptas (^{6}B)</td>
<td>disodium undeca-hydromercaptododecaborate(2-)-^{10}B_{12}</td>
<td>Na_{2}^{10}B_{12}H_{12}S</td>
<td>neutron capture agent</td>
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<td>sodium borocaptate (^{10}B)</td>
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<td>octenaniilum</td>
<td>2'-fluoro-2-methoxy-N(1-phenethyl-4-piperidyl)acetanilide</td>
<td>C_{22}H_{27}FNO_{2}</td>
<td>narcotic analgesic</td>
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<td>octenaniil</td>
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<td>pemirolastum</td>
<td>9-methyl-3-(1H-tetrazol-5-yl)-4H-pyrido[1,2-a]pyrimidin-4-one</td>
<td>C_{18}H_{19}N_{6}O</td>
<td>antiallergic</td>
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<td>pemirolast</td>
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<td>penciclovirum</td>
<td>9-[4-hydroxy-3-(hydroxymethyl)butyl]guanine</td>
<td>39809-25-1</td>
<td>antiviral</td>
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<td>penciclovir</td>
<td><img src="image1" alt="Penciclovir Structure" /></td>
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<td>pidolacetamolut</td>
<td>5-oxo-L-proline, ester with 4'-hydroxyacetanilide</td>
<td>114485-92-6</td>
<td>analgesic, antipyretic</td>
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<td>pidolacetamol</td>
<td><img src="image2" alt="Pidolacetamol Structure" /></td>
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<td>rebamipidum</td>
<td>(±)-α-(p-chlorobenzamido)-1,2-dihydro-2-oxo-4-quinolinepropionic acid</td>
<td>111911-87-6</td>
<td>antiulcer</td>
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<td>rebamipide</td>
<td><img src="image3" alt="Rebamipide Structure" /></td>
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<td>revospironum</td>
<td>2-[3-[4-(2-pyrimidinyl)-1-piperazinyl]propyl]-1,2-benzisothiazolin-3-one 1,1-dioxide</td>
<td>95847-87-3</td>
<td>tranquilizer (vet.)</td>
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<td>revospirone</td>
<td><img src="image4" alt="Revospirone Structure" /></td>
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Nonproprietary Name (Latin, English) | Chemical Name or Description, Molecular and Graphic Formulae | Chemical Abstracts Service (CAS) registry number | Action and use
--- | --- | --- | ---
ropinirolum | 4-[2-(dipropylamino)ethyl]-2-indolinone | C₁₆H₂₄N₂O | D₂-dopamine receptor agonist
sertindolum | 1-[2-[4-[[5-chloro-1-(p-fluorophenyl)indol-3-yl]piperidino]ethyl]-2-imidazolidinone | C₂₄H₂₆ClFN₄O | antipsychotic
Proposed International Chemical Name or Description, Molecular and Graphic Formulae
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Action and use

suronacrinum
suronacrine

(±)-9-(benzylamino)-1,2,3,4-tetrahydro-1-acridinol
C$_{20}$H$_{20}$N$_2$O
104675-35-6 cholinesterase inhibitor

\[
\begin{align*}
\text{CH}_2 & \\
\text{NH} & \\
\text{H} & \\
\text{OH} & \\
\text{C}_9 & \\
\text{H}_5 & \\
\end{align*}
\]


taludipinum
taludipine

(±)-4-[o-{(E)-2-carboxyvinyl}phenyl]-2-[(dimethylamino)methyl]-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylic acid, 4-tert-butyl diethyl ester
C$_{28}$H$_{38}$N$_2$O$_6$
108687-08-7 Calcium antagonist

\[
\begin{align*}
\text{H}_3C & \\
\text{N} & \\
\text{H}_2C\text{O} & \\
\text{C} & \\
\text{O} & \\
\text{C} & \\
\text{O} & \\
\text{CH}_3 & \\
\text{CH}_3 & \\
\end{align*}
\]


taniplonum
taniplon

6,7,8,9-tetrahydro-5-methoxy-2-(5-methyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]quinazoline
C$_{14}$H$_{15}$N$_5$O$_2$
106073-01-2 anxiolytic

\[
\begin{align*}
\text{CH}_3 & \\
\text{N} & \\
\text{N} & \\
\text{OCH}_3 & \\
\text{OCH}_3 & \\
\end{align*}
\]

technetium ($^{99m}$Tc) teboroximum

[\text{bis}[[1,2-cyclohexanedione dioximato}(1-)-O][[1,2-cyclohexanedione dioximato}(2-)-O]methylborato(2-)-N,N',N''',N''''',N''''""]chloro[$^{99m}$Tc]technetium(III)
C$_{19}$H$_{25}$BCIN$_6$O$_6$$^{99m}$Tc
104716-22-5 radioactive diagnostic agent

\[
\begin{align*}
\text{O} & \\
\text{N} & \\
\text{N} & \\
\text{N} & \\
\text{B} & \\
\text{CH}_3 & \\
\text{Cl} & \\
\text{O} & \\
\text{O} & \\
\end{align*}
\]
### Proposed International Chemical Name or Description, Molecular and Graphic Formulae

**Nonproprietary Name**

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<th>Molecular and Graphic Formulae</th>
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<tbody>
<tr>
<td>tenidapum</td>
<td>((\pm)-5\text{-chloro}-2\text{-oxo}-3\text{-}(2\text{-thenoyl})-1\text{-indolinecarboxamide})</td>
</tr>
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<td>tenidap</td>
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$$C_{14}H_{9}ClN_{2}O_{3}S$$

100599-27-7 nonsteroidal anti-inflammatory

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<th>terflavoxatum</th>
<th>1,1-dimethyl-2-piperidinoethyl 3-methyl-4-oxo-2-phenyl-4H-1-benzopyran-8-carboxylate</th>
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<td>terflavoxate</td>
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$$C_{26}H_{29}NO_{4}$$

86433-40-1 antispasmodic

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<th>thymotrinanum</th>
<th>N-((N^2\text{-L-arginyl-L-lysyl}))-L-aspartic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>thymotrinan</td>
<td></td>
</tr>
</tbody>
</table>

$$C_{16}H_{31}N_{7}O_{6}$$

85465-82-3 immunomodulator

---

<table>
<thead>
<tr>
<th>toripristonum</th>
<th>17(\beta)-hydroxy-11(\beta)-([p\text{-isopropylmethylamino phenyl}])-17-(1-propynyl)estra-4,9-dien-3-one</th>
</tr>
</thead>
<tbody>
<tr>
<td>toripristone</td>
<td></td>
</tr>
</tbody>
</table>

$$C_{31}H_{39}NO_{2}$$

91935-26-1 antiglucocorticoid
<table>
<thead>
<tr>
<th>Nonproprietary Name (Latin, English)</th>
<th>Chemical Name or Description</th>
<th>Molecular and Graphic Formulae</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
<th>Action and use</th>
</tr>
</thead>
<tbody>
<tr>
<td>troquidazolum</td>
<td>( N'-(3\text{-nitro-4\text{-quinolyl}})-4\text{-morpholinecarboxamidine} )</td>
<td>( C_{14}H_{15}N_{5}O_{3} )</td>
<td>108001-60-1</td>
<td>radiosensitizing agent</td>
</tr>
<tr>
<td>troquidazole</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>velnacrinum</td>
<td>((\pm)\text{-9\text{-amino-1,2,3,4-tetrahydro-1\text{-acridinol}}})</td>
<td>( C_{13}H_{14}N_{2}O )</td>
<td>112964-98-4</td>
<td>cholinesterase inhibitor</td>
</tr>
<tr>
<td>velnacrine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vintoperolum</td>
<td>((-\text{-}(1S,12bS)-1\text{-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo}[2,3-a\text{-quinolizine-1\text{-methanol}}})</td>
<td>( C_{18}H_{24}N_{2}O )</td>
<td>106498-99-1</td>
<td>peripheral vasodilator</td>
</tr>
<tr>
<td>vintoperol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>voxergolidum</td>
<td>((\pm)\text{-}(6aR,9R,10aR)-4,6a,7,8,9,10a\text{-hexahydro-7-methyl-9\text{-[(methylthio)methyl]-6H\text{-indolo}[3,4-gh][1,4\text{-benzoxazine}}])</td>
<td>( C_{18}H_{20}N_{2}O_{5} )</td>
<td>89651-00-3</td>
<td>dopamine receptor agonist</td>
</tr>
<tr>
<td>voxergolide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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.

- butepras
- buteprate
  butyrate propionate

- crobefas
- crobefate
  $(\pm)-(E)$-6-hydroxy-4′-methoxy-3-$(p$-methoxybenzylidene)flavanone, phosphate, ion(2-)
  $C_{24}H_{19}O_8P$

- farnesilum
- farnesil
  $(2E,6E)$-3,7,11-trimethyl-2,6,10-dodecatrienyl
  $C_{15}H_{25}$
AMENDMENTS TO PREVIOUS LISTS

WHO Chronicle, Vol. 36, No. 5, 1982

Proposed International Nonproprietary Names (Prop. INN): List 48

p. 13 delete insert
loxtidinum lavoldtidinum
loxtidine lavoldtidine

WHO Chronicle Vol. 37, No. 5, 1983

Proposed International Nonproprietary Names (Prop. INN): List 50

p. 17 levocabastinum levocabastine replace the chemical name and the graphical formula by:
(−)-(3S,4R)-1-[cis-4-cyano-4-(p-fluorophenyl)cyclohexyl]-3-methyl-4-phenylisonipecotic acid

WHO Drug Information Vol. 1, No. 3, 1987

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

p. 186 pemedolacum pemedolac replace the chemical name, the CAS registry number and the graphic formula by the following:
(±)-cis-4-benzyl-1-ethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid 114716-16-4

WHO Drug Information Vol. 2, No. 4, 1988

Proposed International Nonproprietary Names (Prop. INN): List 60

p. 4 delete insert
mequitazii iodidum mequitamii iodidum
mequitazium iodide mequitamium iodide

p. 6 cefprozil cefprozil replace the chemical name and the graphical formula by the following:
The following procedure shall be followed by the World Health Organization in the selection of recommended international nonproprietary names for pharmaceutical substances, in accordance with the World Health Assembly resolution WHA3.11:

1. Proposals for recommended international nonproprietary names shall be submitted to the World Health Organization on the form provided therefor.

2. Such proposals shall be submitted by the Director-General of the World Health Organization to the members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations designated for this purpose, for consideration in accordance with the “General principles for guidance in devising International Nonproprietary Names”, appended to this procedure. The name used by the person discovering or first developing and marketing a pharmaceutical substance shall be accepted, unless there are compelling reasons to the contrary.

3. Subsequent to the examination provided for in article 2, the Director-General of the World Health Organization shall give notice that a proposed international nonproprietary name is being considered.

A. Such notice shall be given by publication in the Chronicle of the World Health Organization¹ and by letter to Member States and to national pharmacopoeia commissions or other bodies designated by Member States.

(i) Notice may also be sent to specific persons known to be concerned with a name under consideration.

B. Such notice shall:
(i) set forth the name under consideration;
(ii) identify the person who submitted a proposal for naming the substance, if so requested by such person;
(iii) identify the substance for which a name is being considered;
(iv) set forth the time within which comments and objections will be received and the person and place to whom they should be directed;
(v) state the authority under which the World Health Organization is acting and refer to these rules of procedure.

C. In forwarding the notice, the Director-General of the World Health Organization shall request that Member States take such steps as are necessary to prevent the acquisition of proprietary rights in the proposed name during the period it is under consideration by the World Health Organization.

4. Comments on the proposed name may be forwarded by any person to the World Health Organization within four months of the date of publication, under article 3, of the name in the Chronicle of the World Health Organization.

5. A formal objection to a proposed name may be filed by any interested person within four months of the date of publication, under article 3, of the name in the Chronicle of the World Health Organization.

A. Such objection shall:
(i) identify the person objecting;
(ii) state his interest in the name;
(iii) set forth the reasons for his objection to the name proposed.

6. Where there is a formal objection under article 5, the World Health Organization may either reconsider the proposed name or use its good offices to attempt to obtain withdrawal of the objection. Without prejudice to the consideration by the World Health Organization of a substitute name or names, a name shall not be selected by the World Health Organization as a recommended international nonproprietary name while there exists a formal objection thereto filed under article 5 which has not been withdrawn.

7. Where no objection has been filed under article 5, or all objections previously filed have been withdrawn, the Director-General of the World Health Organization shall give notice in accordance with subsection A of article 3 that the name has been selected by the World Health Organization as a recommended international nonproprietary name.

8. In forwarding a recommended international nonproprietary name to Member States under article 7, the Director-General of the World Health Organization shall:
A. request that it be recognized as the nonproprietary name for the substance; and
B. request that Member States take such steps as are necessary to prevent the acquisition of proprietary rights in the name, including prohibiting registration of the name as a trade-mark or trade-name.


The title of this publication was changed WHO Chronicle in January 1959. From 1967wards lists of INNs are published in WHO Drug Information.

GENERAL PRINCIPLES FOR GUIDANCE IN DEVISING INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES

1. International Nonproprietary Names (INN) should be distinctive in sound and spelling. They should not be inconveniently long and should not be liable to confusion with names in common use.

2. The INN for a substance belonging to a group of pharmacologically related substances should, where appropriate, show this relationship. Names that are likely to convey to a patient an anatomical, physiological, pathological or therapeutic suggestion should be avoided.

These primary principles are to be implemented by using the following secondary principles

3. In devising the INN of the first substance in a new pharmacological group, consideration should be given to the possibility of devising suitable INN for related substances, belonging to the new group.

4. In devising INN for acids, one-word names are preferred; their salts should be named without modifying the acid name, e.g. "oxacillin" and "oxacillin sodium", "ibufenac" and "ibufenac sodium".

5. INN for substances which are used as salts should in general apply to the active base or the active acid. Names for different salts or esters of the same active substance should differ.
only in respect of the name of the inactive acid or the inactive base.

For quaternary ammonium substances, the cation and anion should be named appropriately as separate components of a quaternary substance and not in the amine-salt style.

6. The use of an isolated letter or number should be avoided; hyphenated construction is also undesirable.

7. To facilitate the translation and pronunciation of INN, ‘f’ should be used instead of ‘ph’, ‘t’ instead of ‘th’, ‘e’ instead of ‘ae’ or ‘oe’, and ‘i’ instead of ‘y’; the use of the letters ‘h’ and ‘k’ should be avoided.

8. Provided that the names suggested are in accordance with these principles, names proposed by the person discovering or first developing and marketing a pharmaceutical preparation, or names already officially in use in any country, should receive preferential consideration.

9. Group relationship in INN (see Guiding Principle 2) should if possible be shown by using a common stem. The following list contains examples of stems for groups of substances, particularly for new groups. There are many other stems in active use.

A more extensive listing of stems is contained in the working document Pharm S/Nom 15 which is regularly updated and can be requested from Pharmaceuticals, WHO, Geneva.
Annex 2
NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES:
TWENTIETH REPORT OF THE WHO EXPERT COMMITTEE

In its twentieth report the WHO Expert Committee on Nonproprietary Names for Pharmaceutical Substances reviewed the general principles for devising, and the procedures for selecting, international nonproprietary names (INN) in the light of developments in pharmaceutical compounds in recent years. The most significant recent change has been the extension to the naming of synthetic chemical substances of the practice previously used for substances originating in or derived from natural products. This practice involves employing a characteristic "stem" indicative of a common property of the members of a group. The reasons for, and the implications of, the change are fully discussed. Also reported is the intention to change the practice with regard to the nomenclature of individual members of polymeric series.

Other sections of the report concern instructions to be followed by bodies making application for international nonproprietary names, the availability of computer-printed cumulative lists of international nonproprietary names, information supplied by WHO Member States concerning their official use of national or international names for pharmaceutical products, and proposals relative to the withdrawal of international nonproprietary names allocated to substances that are no longer in use.

The official texts relating to the procedures for selecting, and general guidance for devising, international nonproprietary names are reproduced in two annexes to the report. Other annexes give examples of international nonproprietary names that incorporate selected stems, the most frequently used initial groups of letters in international nonproprietary names, a historical review of the programme of selecting international nonproprietary names, some useful literature references, and a model of the form to be used in all applications for international nonproprietary names.