

# Drugs for infants and children

Report on the Tenth  
European Symposium on  
Clinical Pharmacological  
Evaluation in Drug Control

Schlangenbad  
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# CONTENTS

	<i>Page</i>
Introduction .....	1
Drugs and children .....	2
Legal and ethical aspects of drug trials .....	3
Role of regulatory agencies .....	4
Technical problems of drug evaluation .....	6
Drug kinetics .....	7
Adverse reactions and interactions .....	8
Intensive monitoring .....	9
Drug utilization studies .....	10
Compliance .....	11
Problems of particular therapeutic classes of drug .....	14
Drugs for the long-term treatment of asthma .....	14
Anticonvulsants .....	16
Antibiotics .....	17
Cytostatics .....	18
Analgesic/antipyretic drugs .....	19
Recommendations .....	20
Annex 1 Selected bibliography .....	24
Annex 2 List of participants .....	29



## INTRODUCTION

The Tenth European Symposium on Clinical Pharmacological Evaluation in Drug Control was held in Schlangenbad, Federal Republic of Germany, from 27 to 30 October 1981. It was attended by 29 participants from 25 countries, 14 temporary advisers, 6 representatives of other organizations and 7 observers.

Dr Echterhagen, Kurdirektor of the Schlangenbad Spa, welcomed the meeting once more to Schlangenbad, one of the smaller spas in Hesse where particular attention is paid to the general and supportive treatment and rehabilitation of the patient with chronic rheumatic disorders.

Professor L. von Manger-König, Special Consultant on Health Affairs to the Federal Ministry of Youth, Family Affairs and Health, addressed the meeting on behalf of the Ministry. The decision taken by the Ministry eleven years before to initiate meetings of this type had proved to be a fruitful one. The nine symposia already held had been constructive and influential and their recommendations had in some fields provided the starting point and impetus for further activities, especially as regards the development of clinical pharmacology and the design of health policies in that area. As those and related fields developed further they would play a major role in the attainment of WHO's goal of health for all by the year 2000. The European Region could make a particularly substantial contribution to that programme in the field of drugs in view of its research capacity and its vast and diverse experience. The initiatives required could be taken both at the national and the regional level.

Dr Leo A. Kaprio, WHO Regional Director for Europe, stressed the generosity of the Federal Republic of Germany in sponsoring the meetings: the conclusions of the symposia had been widely quoted and there could be no doubt that they had influenced and would continue to influence the development of policies. He recalled that the tenth symposium in the series marked an anniversary, and expressed the wish that the meetings should continue to be held annually as long as they produced results of practical value. The series also served as an illuminating example of the way in which a Member State could catalyse action on health matters in the

international community. It was the policy of WHO to consult with organizations that were active in a given programme area, and Dr Kaprio therefore welcomed the participation of representatives of both inter-governmental and nongovernmental organizations in the symposia. Finally, the present meeting involved both the family health and the pharmaceutical sectors within the World Health Organization, reflecting the recommendation of the eighth symposium that the meetings should be organized around drug-related problems bearing on other major programme areas of WHO.

Professor H.J. Dengler was elected Chairman of the Symposium and Dr I. Eichler and Dr G.R. Venning Vice-Chairmen. The Rapporteurs were Dr M.N.G. Dukes and Dr I. Lunde.

## DRUGS AND CHILDREN

Awareness of the relevance of age and of the developmental as well as the nutritional status of the young patient as major determinants of drug action and disposition has been the result largely of therapeutic accidents in which adverse effects on the foetus, infant or child have prompted detailed pharmacological studies. These adverse effects could have been prevented or at least minimized if appropriate drug evaluation, including kinetic studies at various ages, had been carried out before the drugs in question were prescribed to sick infants and children. It is now widely recognized that the effects of many drugs upon the paediatric patient may differ considerably from those observed in adults, even when dosage has been adapted either to body weight or body surface area. Where a drug exerts an unexpectedly powerful effect in a child, this may reflect either differences in the drug's kinetics in the young as compared with the adult, or a greater receptor response either because of more marked binding or because a greater number of binding sites are available.

There is therefore every reason for caution in the use of medicines in children, particularly if a drug is to be given for a long period and might therefore interfere with growth and development. Such effects may be delayed and may not become evident until many years after the drug has been administered. Particular caution is required when a newly marketed drug is prescribed for children, since in most instances only small numbers of young patients will have been studied during the premarketing period.

The only means of ensuring the safe and effective use of drugs in children is to base their prescription upon scientific data obtained for the particular age group and disease under consideration. This is applicable, not only to the newborn infant, on whom most attention has been focused,

but also to the older child and adolescent in whom there are continuing and significant physiological changes as the developmental process proceeds.

Even where well-conducted studies have been carried out, individualization of therapy is vital since, whilst the sequence of steps in the developmental process progresses in a predictable fashion in any given individual, it may show wide variation between individuals. Since the physician is not able to determine the precise status of organ and cellular development in any given patient, he must anticipate a variation in drug response from patient to patient. He must also anticipate pronounced variation from time to time in the response of the individual child, which may or may not parallel fluctuations in symptoms. These inter- and intra-individual differences render the task of using even well-established drugs in the paediatric population considerably more difficult than in adults.

In considering the problem of drugs in children, the question of administration during pregnancy and lactation of drugs that may reach the foetus or infant cannot be ignored; the emerging possibility of direct administration of drugs to the foetus must also be borne in mind. Recent and current investigations are throwing light, both on the manner in which drugs administered to the pregnant woman reach the infant and on the effects and kinetics of drugs in the foetus at various stages of development. Certain relevant aspects, such as the circulation of drugs between the foetus and the amniotic fluid via ingestion and urinary excretion, however, are still very incompletely understood. A complicating factor is that different receptors develop at different rates during foetal life, whilst some physiological processes, such as hepatic activity, are relatively well developed. The entire field of developmental pharmacology requires substantial expansion.

### **Legal and ethical aspects of drug trials**

Freedom of research is a basic principle in society, and if it is proposed to limit it in any way there must be good justification for doing so. In fact, this freedom is inherently limited by the right of the research subject himself to physical integrity and self-determination. Both the need for informed consent and the evaluation of the risk-benefit ratio are therefore of essential importance. With regard to the latter, however, the difficulty is that it is usually exclusively the trial subject who is at risk, while it is other persons, i.e. subsequent users of the drug, who will benefit. The investigator must himself consider the risk-benefit issue in the first instance and not seek informed consent unless he himself considers the risk acceptable.

Where children are concerned it is usually the *parent* or *guardian* who will be asked to give informed consent: the information that they need for the purpose will include an explanation of both risk and benefit. Children themselves are not, in most legal systems, competent to give legal consent

in matters such as this and, since it has been doubted by some whether parents are competent to consent to a trial which might be of no individual benefit to their child, this has on occasion led to the view that no experiments at all on children are acceptable. This interpretation was in the past placed on the 1947 Nuremberg Codex, whilst the International Pact of 1966 failed to deal with the specific issue of children at all. The Declaration of Helsinki of 1964 (later modified in Tokyo in 1975) does allow for informed consent to be given on behalf of trial subjects who are not legally competent. Current national codes and laws tend to follow this principle, which is clearly essential if drugs likely to be of value in children are to be studied in them.

Where a trial is nontherapeutic (e.g. kinetic studies in healthy children) and therefore cannot be of any benefit to the trial subject, parents and guardians should be regarded as competent to give informed consent for altruistic reasons, but clearly will sometimes not be prepared to do so.

It is not clear whether the child himself should have a right of veto or even a right of codetermination, but he should certainly be informed, in a manner appropriate to his age and understanding, and older children should clearly be regarded as capable of refusing participation if they wish, irrespective of their legal competence.

It would be valuable if ethical committees could publish the results of their deliberations on individual cases involving minors, since this might be of use to others faced with analogous problems.

### **Role of regulatory agencies**

At a time when the performance of drug regulatory agencies is being reassessed and reviewed, there is particular reason to examine their activities with respect to studies of drugs in children and the sale of drugs for paediatric use. As in other fields, an agency can be given authority to interfere with the career of a drug at various stages:

1. If a *new compound in course of development* is to be studied in children, the drug regulatory agency should ensure that the trials are ethically acceptable and scientifically valid.

2. When setting requirements for the issuing of *marketing licences*, an agency can specify that, for any new drug that is likely to be used in neonates, infants or older children, appropriate studies must be conducted in these groups at an early stage so that information on the paediatric use of the product can be incorporated into the data sheet. For drugs not intended for use in children, the agency can ensure that clear and motivated statements on this matter are prepared at the time of registration and incorporated into the product information (e.g. "safety and efficacy in

children have not been established"). Data sheets may require revision if the situation with respect to use in children changes and an agency can ensure that such revisions are made.

3. During the career of a drug on the market, the drug regulatory agency can help to ensure *appropriate and efficacious use* in children, for example, by making sure that doctors are kept up to date on new developments relevant to its paediatric use and are warned when problems emerge.

4. The drug regulatory agency can pay particular attention to *adverse reactions* reported in the young, study and define them, and if necessary modify the licensing conditions accordingly. Since adverse reactions involving growth and development are not readily detected by spontaneous or intensive monitoring, agencies should seek to develop appropriate study techniques for this purpose, including epidemiological approaches.

5. In view of their awareness of the total therapeutic situation, drug regulatory agencies are well placed to develop an active policy with respect to the availability of special *paediatric dosage forms* of drugs likely to be needed in children. Such dosage forms can improve compliance and render more accurate dosage possible. Agencies can take the initiative in encouraging manufacturers to develop such forms when appropriate. On the other hand, restrictions may be called for; in particular, it is undesirable to license paediatric dosage forms of drugs that are contraindicated throughout a large part of childhood (e.g. the tetracyclines), since the mere existence of such a dosage form may lead to misunderstanding and misuse in unsuitable age groups.

Comparative studies of existing regulations and the activities of drug regulatory agencies to date suggest that a consistent approach has not been adopted. Drug legislation and regulations tend to be drawn up with the average adult population in mind; rules applicable to children, like those relating to the elderly, are sometimes still completely lacking even after many years of regulation, and differ considerably from country to country. More striking is the failure to take consistent decisions in this field, even where regulations exist.

In addition, both regulators and manufacturers seem to hesitate to accept responsibility in this sensitive field. So-called guidelines for investigators offer so many options and qualifications that they sometimes give no guidance at all. For too many registered drugs, the physician finds himself faced with the statement that data on use in children are not available, and this statement is commonly retained in package inserts over many years, long after use in children has become common; such use is

therefore not covered by dosage recommendations and appropriate warnings.

As far as ethical guidelines for investigators are concerned it might be advisable for their development, in so far as studies in children are concerned, to be entrusted to bodies other than drug regulatory agencies, since many of the relevant questions are ethical rather than technical in character. Professional bodies, perhaps in conjunction with international organizations such as WHO, may be more appropriate sponsors for such guidelines. As in other fields, however, drug regulatory agencies should not hesitate to take the initiative where other bodies fail to do so.

### **Technical problems of drug evaluation**

It is clear that, when dealing with experiments in minors, ethical and technical considerations cannot be viewed entirely separately. Ethical considerations may rule out the use of certain techniques in children, and it is for ethical reasons that it will generally be impossible to seek "healthy volunteers" among minors. Both factors result in a situation in which studies have to be performed under conditions that are technically less than optimal.

Since it will generally not be possible to work with healthy volunteers, most studies must be undertaken in sick children needing therapy ("*therapeutic research*"); to a limited extent, however, kinetic measurements may also be performed in sick children who will derive no immediate benefit from the procedure ("*nontherapeutic research*"). Such studies, if carefully interpreted in the light of what is known from studies in adults, can provide a reasonably satisfactory basis for the introduction of a drug into paediatric therapy; they will in due course be supplemented by data obtained in practice.

Clinically useful, *noninvasive* techniques have so far been largely lacking in paediatric pharmacology. Recently, however, echo- and impedance cardiography, laser Doppler blood-flow meters, transcutaneous pO<sub>2</sub> electrodes, ear-lobe photocells, electroencephalography with telemetric transmission, time-lapse filming of newborn behaviour, use of stable isotopes, studies of respiratory function, and many other techniques have been introduced into paediatrics and are now being tested for their applicability to drug studies in children. Such new techniques may make it possible to obtain data without employing methods that, in children, are either ethically unacceptable or involve subjecting a child to an unreasonable degree of discomfort.

Pharmokinetic studies often require repeated *blood sampling* or *quantitative collection of urine*, which are not always feasible or ethically acceptable. However, improvements in the selectivity and sensitivity of chemical

assays have at least reduced the sample volumes needed, rendering capillary rather than venous sampling possible. Saliva sampling is more acceptable than blood sampling and has been shown to be useful in certain clinical situations, though saliva levels do not always correlate with blood levels, and interindividual variations in salivary penetration and salivary samples cannot always be conveniently controlled.

In some situations, too, it is possible to avoid taking numerous blood samples from a few patients by taking single samples from a larger number of patients.

*Pharmacokinetic data* obtained in children must be interpreted with caution, and conclusions emerging from kinetic studies may have to be rejected in the light of therapeutic investigations. Pharmacokinetic data are of limited value unless at least a crude relationship has been established between the concentration of the drug in the body and the degree of effect.

*Compliance* (see also p. 11) is a particular problem in paediatric therapeutic studies since failure may occur either at the parental or patient level or both. It is not uncommon to find that drugs have not been regularly taken unless intake is supervised and checked.

## Drug kinetics

Drug absorption, distribution and elimination are often radically different in adults and in children of various ages, because of both quantitative differences in the composition and structure of the body and the progressive development of physiological function. In young children, for example, the relatively large size of the gastrointestinal system, the ready absorption of drugs through the skin and the high volume of body water all alter drug absorption or distribution. Protein binding can be quite different for some drugs in children, though for others it follows the adult pattern; such situations underline the need for the individual study of each new drug or type of drug in children. The studies performed with drugs at one particular stage of childhood may be entirely invalid at another; there is, for example, a limited capacity to metabolize some drugs via "adult" mechanisms in the very young, but this limitation may be compensated for by the existence of other mechanisms, and as childhood proceeds the capacity to metabolize may increase to above the adult level.

Such factors as these have consequences of vital importance to the assessment of drug kinetics, action and safety in children. In particular:

1. The *relative activity* of a drug can be substantially greater or less in the infant than might be expected on the basis of any theoretical calculation: specific studies, both kinetic and dynamic, may therefore be needed to determine the *efficacy and dosage* of a drug in children of various ages.

2. *Safety data* valid for adults may not hold good for children because of differences in drug absorption, distribution and elimination.

3. Again, *interactions* (including interactions induced by self-medication products) can be qualitatively and quantitatively different in children.

In addition, illness in children can have a drastic effect on drug kinetics and on the child's reaction to drugs.

### **Adverse reactions and interactions**

For the reasons set out earlier in this report, a wide variety of adverse drug reactions occur in children, and in some cases these are different in nature or degree from those observed in adults. Interactions may also be different in children.

Adverse reactions in children can be minimized by:

- (a) more complete studies of new drugs at an early stage as regards paediatric use;
- (b) more restricted prescribing to children as well as to pregnant women and nursing mothers;
- (c) optimization of dosage.

The study of adverse reactions in children deserves a higher priority than it has hitherto been given. Approaches to this problem are discussed below.

### *Spontaneous reporting*

Spontaneous reporting is in many countries still the mainstay of adverse reaction investigations and is likely to remain so. It has the great merit of covering the entire population, but is likely to need to be supplemented by a range of other techniques, particularly in fields presenting special problems, which clearly include the use of drugs in children. Such supplementary techniques will include intensive monitoring (see below), prospective studies of adverse reactions, and various specialized epidemiological techniques.

Spontaneous reporting can be intensified in particular fields, and such an intensive approach is likely to be needed to cover the child population, since spontaneous reports of adverse reactions in children do not appear to be readily submitted and data in this field are consequently scanty. It may be useful, in defining the limits of intensified study, to distinguish between the treatment of potentially fatal disorders, the treatment of disorders with

a more favourable prognosis, and treatment merely intended to alleviate symptoms, since adverse reactions sufficiently important to modify therapy in one situation will be of secondary importance in another.

### **Intensive monitoring**

In general, it is difficult to obtain a clear picture of the adverse reactions to drugs used in hospitalized children. Intensive monitoring, in the hospital centres where it has so far been employed in paediatric wards, has sometimes proved more effective than spontaneous reporting in detecting and quantifying the adverse reactions that occur under these conditions, and in developing hypotheses on the nature of drug effects in children. Such monitoring, though unavoidably expensive and complex, can if properly conducted provide data of wide relevance that are also of value outside the hospital environment.

The techniques used are not appreciably different from those employed in intensive monitoring in adults. It is essential to use specially trained staff, who are then assigned to the wards to collect detailed information systematically on all cases. This involves, *inter alia*, reviewing the medical record, doctors' orders, and other written data, attendance at ward rounds and interviews with nurses and physicians. The ability of the staff in question to make their own observations is of special importance in view of the fact that children, and especially young children, may fail to complain specifically about unpleasant sensations that they experience. Detailed records of drug exposure must be kept. As in other forms of intensive monitoring, the monitor records not only suspected adverse reactions, but also a wide range of specified adverse events, such as fever, coma, convulsions, renal failure, hypoglycaemia, leucopenia and rash, as well as background data on the patient, all of which may lead to the recognition of correlations between a drug and an adverse event. Once data have been obtained on a large number of patients, it will commonly be possible to identify previously unsuspected adverse reactions by comparing the rates of adverse events in various groups of patients exposed to different drugs.

Because the pattern of paediatric drug exposure differs from country to country it is essential that a number of different intensive monitoring centres in different parts of the world become involved in such work. This may throw light, not only on differences in adverse reaction incidence and on the reasons determining this incidence, but also on the correctness of certain prescribing patterns.

### *Effects on growth and development*

As pointed out earlier, long-term effects of drugs on growth or development in children can be extraordinarily difficult to identify. The classic

dispute as to whether corticosteroids and ACTH present different degrees of risk when used in asthmatic children is a case in point. The methods for studying this type of risk are not well developed, but it is clear that prospective studies are needed in all groups of children subjected to very long-term drug therapy, e.g. asthmatics and epileptics, and that such studies should involve not only new drugs, but also those already in use for a long period of time.

### *Adverse reactions involving the foetus and breastfed infant*

Interference of drugs with intrauterine development may cause adverse reactions that affect the foetus directly and in an obvious manner (e.g. foetal tachycardia, foetal death, developmental effects evident at birth) or in a more subtle fashion, producing defects that only become evident in later life. The detection of the former type of defect involves more complete notification than hitherto of suspected links between drug administration and problems detected at or around the time of birth; the fact that in some countries notification of congenital defects is either very incomplete or is handled in such a manner that the data are not available for etiological study is a serious problem in developing an epidemiological approach. The study of defects that become evident in later life and of their possible association with drugs administered to the mother is again largely impeded by the incompleteness of data; full records of drugs given in pregnancy need to be retained for long periods, e.g. until the offspring have attained full adulthood.

The transfer of drugs in maternal milk and adverse reactions to them is a related problem in which the approaches to a scientific solution are again similar. For any new drug it is at least important to know whether significant amounts enter the milk, so that the possibility of adverse reactions in the infant can at least be assessed hypothetically. Here, too, the possibility of long-term effects on growth and development cannot be excluded, and unless a drug is not excreted at all in the milk it should in principle be avoided during breastfeeding, or the latter should be stopped so that the mother can be treated.

### **Drug utilization studies**

Drug utilization patterns in children are generally different from those in adults and require separate study. As with intensive monitoring, this work needs to be undertaken in a number of centres in countries with differing therapeutic traditions but using standardized methodology (such as that developed by the WHO Drug Utilization Research Group). In some respects special methods are needed, e.g. because the defined daily dose

based on adult usage will not be applicable without considerable adaptation.<sup>a</sup>

Particular matters requiring study include:

- (a) parental and patient compliance;
- (b) exposure to drugs via the mother, i.e. during pregnancy and lactation, as previously discussed;
- (c) parent-selected medication with over-the-counter remedies;
- (d) the appropriateness of drugs and doses used at various ages;
- (e) the sometimes considerable differences in prescribing between hospitalized patients and outpatients;
- (f) evaluation of existing prescribing practice in order to identify the groups of drugs not used to their full therapeutic potential or otherwise not used optimally.

Drug utilization studies in children may be performed in different ways according to the drugs being investigated:

(a) Those types of therapy that are handled by the general practitioner (or in some countries the general paediatric practitioner) can be studied in general population samples. A prescription sample study running over a sufficient period of time, and employing a reliable sampling technique, will provide sufficient information; this approach is relatively economical.

(b) When the utilization of drugs in chronic diseases (which are relatively rare in children) is investigated, utilization studies will normally have to be performed in defined populations where individual drug use can be followed and where record linkage can be used for gathering other types of relevant information. These studies are necessarily more costly and require careful advance planning.

## Compliance

In recent years, various attempts have been made to determine the extent to which medication prescribed for children is, in fact, properly taken. The nature and extent of this compliance problem depends on the definitions employed. In theory it could be argued that compliance is only adequate if it attains 100% in all respects; more usually, a minimum acceptable level of compliance is considered to exist, but the level regarded as acceptable varies in different studies, as do the methods for determining compliance

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<sup>a</sup> The adapted defined daily doses for children of various ages can be taken from various standard works of reference. e.g. von Harnack, G.A. & Jansson, F. *Pädiatrische Dosistabellen*, Stuttgart, Thieme, 1980.

(e.g. tablet count, analysis of metabolites in body fluids, self-reporting) and the pattern of deviation (no medication taken at all, missed doses, incorrect doses, variable dosage intervals, incorrect indication for use, etc.).

Of the objective methods of studying compliance that have been developed (e.g. involving the use of markers that can be detected in the urine), all those that are harmless can be considered ethically acceptable, although the parent and/or the patient should at least be informed subsequently that compliance has been monitored in this way.

In fact, the level of compliance found in investigations performed in children appears to be rather less unsatisfactory than in adults, but it nevertheless varies from 10% to 90% (with an average of only some 50%) in patients taking short-term medication, the rate of compliance becoming progressively less satisfactory as treatment proceeds. Compliance in long-term treatment, even for relatively serious disorders, has been estimated to vary from 20% to 80% with a poor average. As in adults, it is to be expected that, in the long run, up to 50% of chronic cases will cease to take their medication at all, that 70% of those continuing to take a drug will repeatedly miss out doses (half of them doing so knowingly) and that very many long-term cases will modify the treatment intervals considerably. The figures are clearly only rough estimates, and there is some reason to believe that in children, as in adults, the rate of compliance is in fact even less satisfactory across the board than that emerging from published studies.

Steps to improve compliance must be based on a recognition that the problem exists, an identification of causal factors (which may lie with the parent/guardian, the child or both) and understanding of those factors that can induce a patient to take medication properly and a parent or guardian to ensure that a drug is administered as prescribed.

#### *Factors conducive to compliance in paediatric therapy*

Factors conducive to compliance with prescribed drug regimens in children may be summarized as follows:

<i>Factor</i>	<i>Remarks</i>
Demographic	Fewer children, older children Parents married Higher level of parental education and income
Social	Well-organized families with well-established routines Few general family problems

<i>Factor</i>	<i>Remarks</i>
Psychological	Perception of disease sufficient Constructive attitude to treatment Knowledge of drug regimen
Disease	Shorter duration of disease Symptoms and signs requiring alleviation Previous experience of same disease
Prescriber	Small number of drugs prescribed Low frequency of dosage Short course of treatment
Medication	Drug immediately available Explanation given by physician Packaging unit and concentration adapted to child's needs Labelling clear Dosage unit unambiguous (avoid "teaspoonful", etc.) Form of drug acceptable to child (taste, etc.)
Pharmacist	Drug prescribed by usual physician known to pharmacist Explanation given by pharmacist
Link between prescriber and family	Good relation between physician and patient/parent Friendly approach Explanation of condition and total therapeutic approach

### *Methods of increasing compliance*

The methods of increasing compliance in individual cases are evident from a study of the factors conducive to compliance, as listed above. Where one irremediable defect is present (e.g. lack of parental cooperation) other means may have to be adopted to ensure that compliance is adequate (e.g. admission to hospital). Research on means of improving compliance in paediatric treatment as a whole is clearly needed, and pharmacists, physicians and the public will require education in this entire field, since the extent of undercompliance is not sufficiently realized.

## PROBLEMS OF PARTICULAR THERAPEUTIC CLASSES OF DRUG

### Drugs for the long-term treatment of asthma

#### *The physician*

In the treatment of asthma, as in that of acute respiratory disease, a tendency to overprescribe is observed among many doctors. One important element in avoiding unnecessary long-term therapy is a careful diagnosis, distinguishing between asthmatic and nonasthmatic forms of obstructive respiratory disorder, since the latter, though they may be recurrent, generally do not need continuous treatment at all. In the asthmatic, the physician should realize the importance of selecting carefully the smallest number of drugs needed to provide adequate relief, and the need to reassess the efficacy of long-term treatment at intervals, since tolerance may develop or the condition change to such an extent that modification of the therapy is required. The use of fixed combination drugs should be very critically reviewed, since most such combinations are illogical or at least unsuited to any identifiable type of case. Where local treatment can be used, it should be preferred to systemic therapy. The physician should resist the temptation to undertreat the acute attack whilst overtreating the underlying chronic condition. In choosing a drug for the asthmatic patient, the physician should give greater weight to safety than to convenience of administration, other things being equal.

#### *The patient and his/her parent*

The intensity of drug treatment for asthma is to a large extent a product of the psychological state of the patient and his/her family. Whilst the physician, as pointed out above, may tend to undertreat the acute attack, the patient or his/her parent may well overtreat it by making excessive use of the remedies that have been prescribed. The physician should provide adequate therapy, but make it clear how dangerous it is to exceed the dosage prescribed, and how important it is to call in medical help if the normal therapy fails to provide sufficient relief.

Asthmatics frequently take large numbers of symptomatic remedies available over the counter; these are often of doubtful efficacy.

#### *Research*

In defining research goals in this field, one aim must certainly be to find agents active systemically that are capable of preventing mass cell

degranulation. In more general terms, the aim should be to reduce the level of adverse reactions as compared with those associated with existing products.

### *Regulation*

Various types of drug used in this field require re-evaluation according to current clinical pharmacological standards, since some are of value only in particular types of case and others only in doses that produce unacceptable adverse reactions. The long-term effects of some existing drugs on growth and development in children are still not sufficiently clear.

In reviewing the claims of new drugs submitted for licensing in this area, products that appear to be of value only in a small proportion of cases should be viewed critically, since in view of the frequency and rapidity of spontaneous recovery they may in fact be totally inefficacious.

The possible development of tolerance to drugs intended for long-term use should have been examined before they were accepted for marketing.

The situation of over-the-counter asthma remedies and the type of labelling permitted for these products in many countries need to be reconsidered since, as pointed out above, many asthmatics tend to employ these products together with their prescribed medication.

### *Specific drugs*

1. *Bronchodilators.* Long-term treatment with bronchodilators, even where they are used to excess, does not appear to have harmed children, but the question continues to require study. If a bronchodilator is considered to be the drug of choice in a given child, careful reassessment of the response at regular intervals is needed, using simple pulmonary function measurements, particularly since the degree of asthma in children can change considerably as time proceeds.

2. *Methylxanthine derivatives.* It is important to study not only the kinetic properties in different age groups but also the range of variation, which appears to be considerable. In the individual patient, the physician should regularly check blood levels.

3. *Corticosteroids.* Despite their great value in the acute condition and when given locally, prolonged systemic use of these drugs in the asthmatic child should wherever possible be avoided in view of their gross adverse effects, including those on growth.

4. *Anticholinergic drugs.* These are of value only in selected cases. Side effects may cause problems unless these drugs are given topically.

5. *Antihistamines.* The use of these drugs in the asthmatic child is traditional in some countries but their usefulness is limited, perhaps to a particular type of case, and this therapeutic approach requires re-assessment.

6. *Expectorants.* These appear to be of little or no value in the asthmatic.

7. *Combinations of bronchodilator beta-agonists and methylxanthines.* When these two types of drug are used together, no more than an additive effect can be anticipated, and it will sometimes be found that a single drug, given in an adequate dose, will suffice. The combination is justifiable where it enables side effects to be reduced, but the dose of each drug must in that case be selected individually, i.e. fixed combinations should not be used. The correctness of using either type of drug during the first year of life is questionable and requires further study.

### **Anticonvulsants**

Anticonvulsant drug therapy should only be instituted after the prescribing physician has duly considered the risk-benefit ratio. An appropriate decision requires an assessment of the severity of the problem, the probability that drugs may help, the likelihood of adverse effects, and the possibility that an alternative therapy might be safer and more effective. However, because seizures are dramatic events causing marked emotional reactions, such consideration is frequently limited, and a drug that has suppressed the initial episodes may be continued for a long period without the alternatives having been considered.

The decision, even as to initial therapy, is not helped by the questionable validity of animal studies, the lack of human studies in which treatments have been compared, and the inadequate and nonspecific classification of patients in studies that have been reported. Initial therapy is therefore frequently empirically based, although there is now some agreement as to the first and second choice drugs for most seizure types.

Relative choices for given seizure types would be expected to change with time as a result both of new drug introductions, and the increasing availability of reports on comparative studies, efficacy and adverse effects; to some extent, this seems to have been the case in the past. The evaluation of anticonvulsant drugs is, however, particularly difficult as the effect on the frequency of convulsions is only one aspect of the risk-benefit equation — more subtle effects on cognitive function and personality may not even have been considered in formulating the conclusions in published reports.

Short-term controlled studies can be used to evaluate the effectiveness of such drugs in general terms, and to assess the commoner adverse effects.

There is, however, a pressing need for more long-term stratified evaluation in which both old and new anti-epileptic drugs are compared with each other. Such comparisons are essential in order to determine continuing effectiveness, long-term adverse effects or rare complications, and the particular suitability or unsuitability of individual drugs for various patient subgroups.

Animal models for the study and comparison of anti-epileptic drugs are currently of uncertain and unproven value and need to be further developed.

### *Adverse reaction monitoring*

Voluntary systems for the reporting of adverse effects have met with limited success. It may be difficult to distinguish certain adverse effects from symptoms of the disease, since untreated control groups are hard to find. Adverse effects of drugs that have been on the market for years (e.g. sodium valproate) have only recently been reported.

Theoretical improvements in intensive surveillance, recorded release, record linkage and prescription perusal systems may help in monitoring anticonvulsant drugs for continuing efficacy and adverse effects, and a reasonable comparison between drugs may then be made. The selection of methods will depend particularly upon their cost-effectiveness and the speed with which they can provide early warnings.

### *Modified products and new compounds*

Modifications to anti-epileptic drugs will require careful re-evaluation, since apparent improvements (e.g. in bioavailability) may substantially affect efficiency and safety and are not necessarily to the benefit of the patient.

Where new anti-epileptic drugs are assessed it is important to obtain data on their excretion in breast milk so that the acceptability of breast-feeding where these compounds are in use can be assessed. As a general rule, levels of these drugs appear to be too low to affect the infant, but there may be exceptions.

## **Antibiotics**

The use of antibiotics in children is characterized particularly by:

1. The *susceptibility* of the young to certain adverse reactions that do not occur in adults. Sometimes this has led to large-scale problems, e.g. damage to the teeth by tetracyclines. In all these instances alternative antibiotics are available, yet massive use of contraindicated antibiotics has been difficult to eradicate.

2. The changing *pattern of bacterial infection* as a child grows older, which makes careful individualization of treatment necessary. Problems encountered in the treatment of sepsis and meningitis of the neonate illustrate clearly the differences from the corresponding adult conditions as regards the organisms responsible and the proper approach to treatment.

3. The *particular kinetics* of some antibiotics in the young. The aminoglycosides appear to be relatively less nephrotoxic in the very young and recent experimental work suggests that this may be due to pharmacokinetic factors, though clinical evidence is still limited. In other instances, clearly, kinetic factors may render an antibiotic more toxic in the young or affect the optimal dosage. Currently available techniques render such studies possible without undue risk.

Since the reputation of the antibiotics as safe drugs appears to be in part responsible for their widespread and indiscriminate use in the young, which has in some instances proved catastrophic, medical training should place much greater emphasis on the problems of antibiotics in children. A critical approach to prescribing is essential, with individualization of treatment, use of intermittent rather than continuous therapy where possible, and virtual avoidance of certain agents hitherto widely used, except where they are acutely needed.

Since paediatric infectious disease is now a specific subspecialty, an interdisciplinary approach will often be desirable in the treatment of diseases in this field.

The pattern of sensitivity of pathogenic bacteria to antibiotics is likely to differ considerably between institutions, and local epidemiological surveillance is therefore needed in order to establish appropriate local antibiotic policies.

### **Cytostatics**

The use of cytostatic therapy in children has in the past tended to be empirical, the risk-benefit ratio of individual cytostatics in the young often being unclear. However, very considerable progress has been made in the treatment of cancer in children, and efforts are currently being made to conduct systematic comparative studies. This trend should be encouraged.

Difficulties in the proper assessment of cytostatic drugs in children result largely from the fact that individual types of cancer in the young are rare, so that it is difficult to constitute large and homogenous series for study. Response to therapy can be sudden and highly unpredictable. Ethical considerations sometimes render systematic comparative study impossible, and the need for secondary and supportive therapy complicates

the interpretation of results. Nevertheless, an attempt has to be made to carry out, subject to these constraints, the appropriate stages of clinical investigation with any new cytostatic drug if the oncologist is to obtain the information needed to treat his young patients within the limits imposed by a narrow therapeutic index. European and other forms of international collaboration are increasingly rendering it possible to perform well-planned studies on an adequate scale.

Because new cytostatic agents are continually being introduced and the fact that certain risks of cytostatics used in children only become evident after a very long period of use, careful reassessment of the acceptability of existing drugs and drug combinations in this field is needed. Long-term follow-up of patients recovering from the curable malignant conditions of childhood is essential in this connection.

### **Analgesic/antipyretic drugs**

Fever is the commonest condition that the physician is called upon to examine and treat in a child. It is often possible to avoid more than occasional antipyretic drug treatment by detecting and eliminating the cause of the pyrexia. It should be borne in mind that pyrexia in children can be beneficial as a defence mechanism, whereas drugs are always toxic to a certain extent. In young infants, pyrexia can often better be treated by general measures (sponging) than by administering drugs.

Many drugs, old and new, are used for their analgesic/antipyretic effect in children, and the pattern of drug use differs in different countries. Of the compounds most commonly used and traditionally regarded as "simple analgesics", only two, namely aspirin and paracetamol (acetaminophen), have been rigorously evaluated in children. Both lower temperature in a similar manner and appear to be equally effective. There are, however, marked differences between them as regards their pattern of toxicity and the pathways of elimination during the various phases of childhood. In normal doses, paracetamol has an extremely low toxic potential and, whilst moderate overdosage in adults can prove rapidly lethal (hepatotoxicity), there is evidence that children are relatively less susceptible to this complication, though with large enough doses it will occur. In most countries, aspirin remains the leading cause of childhood poisoning, frequently caused by accumulation through saturation of the major metabolic pathways of elimination. Aspirin has a number of other undesirable effects that can cause problems in children, including its influence on haemostasis and its considerable potential for damage to the gastrointestinal mucosa and bleeding. Unless the anti-inflammatory effect of aspirin is required, paracetamol may therefore be considered the more rational agent for use in infants and children.

Aspirin and paracetamol have been used in combination and also alternately; neither of these dosage regimens has been critically examined. Of particular importance is the question of the complex picture of intoxication that arises where both drugs have been taken, and the most effective means of dealing with it. Similar considerations apply to any other fixed or *ad hoc* combinations of analgesic agents that are employed.

A number of older drugs of this type has not been assessed at all, either in adults or children. Since the prohibition of phenacetin in many countries could result in wider use of these agents, it is essential that their efficacy and safety should be reviewed. Until this has been done, these older drugs cannot be recommended for use in children at all.

In this and future work the problem likely to be encountered is that the means available for evaluating analgesic activity in children are still very inadequate and that methodological work on this problem is required.

## RECOMMENDATIONS<sup>a</sup>

### *A. Need for investigations*

1. It is of vital importance that current knowledge of the effects of drugs in children, including the foetus, should be substantially improved and expanded. This will involve, on the one hand, much additional study of the science of developmental and paediatric pharmacology as a whole and, on the other, practical studies on individual drugs and drug groups.
2. The study of adverse reactions in children requires greater emphasis. This will involve both large-scale and intensive monitoring, post-marketing surveillance and spontaneous reporting to a greater extent than hitherto. There is a particular need for a chain of intensive monitoring centres to be established in countries where conditions of medical practice and therapeutic traditions differ. There is an equally pressing need for methods to be worked out for very long-term studies to detect any adverse effect of drugs on growth and development in children.
3. Studies of drug utilization in children are currently lacking in many countries; since patterns of use differ substantially from those in adults, such studies are urgently needed.

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<sup>a</sup> These recommendations are applicable to the entire field of paediatric drug therapy. A number of specific conclusions and recommendations bearing on particular therapeutic classes of drug will be found where these drugs are discussed.

## *B. Investigational ethics*

4. The ethical problems that arise in the study of drugs in children are not so difficult as to render such research impossible, but they do impose constraints upon it in relation to the matters to be studied, the process of decision-making in connection with proposed investigations, and the technical means to be employed. It is highly desirable that internationally agreed ethical standards applicable to drug studies in children should be established. The introduction of these standards at the national level can be entrusted to professional or official bodies, as appropriate. It will be the responsibility of national legislation to ensure that drug trials in minors are carried out with due regard to their importance but also with due respect for the rights and interests of the trial subjects.

5. No investigation should be undertaken in a child until:

(a) the investigator has satisfied himself that the risk-benefit ratio (even in cases where no benefit will accrue to the trial subject himself) is acceptable;

(b) this conclusion has been confirmed by impartial bodies (e.g. ethical committees);

(c) informed consent has been obtained from the parent or guardian;

(d) the child himself/herself has been informed in a manner appropriate to his/her age and understanding; the fact that a child may not be legally competent to give consent, either alone or together with the parent or guardian, should not prevent the investigator from respecting any refusal or protest from a child sufficiently old to express his/her view.

## *C. Techniques*

6. In studying individual drugs in children, the age groups to be examined should be carefully selected in the light of known changes in physiological function and drug sensitivity during childhood and the age groups and purposes for which the drug in question is intended.

7. A great deal can be done to minimize drug exposure, risk and discomfort during drug studies in children by making use of current techniques of optimizing study design and by employing noninvasive investigational methods already available. The further development of such approaches should be strongly encouraged.

## *D. Responsibilities*

8. The responsibility for promoting developmental pharmacology as a basic science clearly lies with the scientific and medical community. Health

authorities can, however, play a role within the framework of their responsibility for the development of clinical pharmacology. Drug control agencies can also play a part by indicating where gaps in current knowledge create practical problems.

9. The initiative in the performance of studies to define the usefulness of entirely new drugs and products in children of various ages will normally be taken by the manufacturer who has undertaken the development of the compound in other respects, though it is reasonable to anticipate that the burden of work and expense should be shared with those medical institutions most capable of undertaking it. Drug regulatory agencies should insist that this work is performed at an appropriate stage with a new drug that is likely to be of value in children, and that adequate and up-to-date information, based on the conclusions of this work, is provided to physicians, e.g. in the data sheet. Where drugs are not intended for use in children, the reasons should be specifically stated.

In this connection, studies that can provide at least a theoretical basis for administering or avoiding drugs during pregnancy and lactation should also be undertaken; they will include studies of placental transfer and of excretion in milk. Much work relevant to these issues will necessarily be undertaken in animals.

10. For the many already existing drugs that are used in children yet have never been adequately studied in this age group to determine kinetic patterns, efficacy and safety, drug regulatory agencies should collaborate internationally so as to ensure that such studies are undertaken in appropriate centres without unnecessary duplication.

#### *E. The prescriber*

11. Despite the pressure on the medical curriculum, there is a need for the medical student to gain a greater insight than hitherto into the principles applicable to the drug treatment of children, if the efficacy and safety of paediatric treatment are to be improved. This emphasis on general principles is more important than a more extensive training in the paediatric use of individual drugs, since knowledge in the latter field is constantly changing and it is of primary importance that the practising physician learns to deal critically but constructively with new drugs as they become available, interpreting the information available on them in the light of what he knows of a child's reactions to drugs.

12. Essential information on the use of individual drugs in children should be communicated to physicians through data sheets and, where appropriate, in other ways. Data sheets currently fail in many cases to provide

any information whatsoever in this respect. Whenever a drug is to be used in various paediatric age groups, a clear indication of the dosage should be given, e.g. based on body weight, but with restrictions or modifications as needed. Other sections of the data sheet may also require to be supplemented so as to cover the particular situation of children, e.g. as regards dosage intervals, adverse reactions and interactions.

13. Many prescribers clearly do not realize to what extent the actual use of drugs deviates from the pattern prescribed (“noncompliance”). Both physicians and pharmacists can improve compliance to some extent and should be shown how to do so. Whilst this problem is not unique to paediatric therapy, the particular need to adhere to prescribed therapy in this age group, in the interests of effective and safe treatment, is evident.

14. Paediatric therapy can be simplified and compliance considerably improved if paediatric dosage forms of drugs intended for use in children are made available.

#### *F. The public*

15. Package inserts and similar documents directed to the public and relating to prescription drugs should include clear statements with respect to the use of these drugs in children, though it should be made clear that this information is intended to supplement and not to supplant that provided by the prescriber and pharmacist. The need for compliance with the physician’s instructions should be stressed.

SELECTED BIBLIOGRAPHY

**General**

**Anderson, P.O.** Drugs and breast feeding. *Drug intelligence and clinical pharmacology*, 11: 208-223 (1977).

**Chrymko, M. et al.** Therapeutics bibliography for clinical pharmacists: pediatrics. *American journal of hospital pharmacy*, 37: 713-716 (1980).

**Gladtko, E. & Heimann, G.** Besonderheiten der klinischen Pharmakologie im Kindersalter. In: Kuemmerle, H.-P. *Methoden der klinischen Pharmakologie Hrsg.* Munich, Urban & Schwarzenberg, 1978.

**von Harnack, G.A.** *Arzneimitteldosierung im Kindesalter.* Stuttgart, Thieme, 1965.

**Harte, V.J. et al.** Drug prescribing in paediatric medicine. *Irish medical journal*, 73: 157-161 (1980).

**Rylance, G.** Clinical pharmacology: drugs in children. *British medical journal*, 282: 50-51 (1981).

**Shirkey, H.** Drug excretion in breast milk. In: Avery, ed. *Drug treatment*, 2nd ed. Edinburgh, Churchill Livingstone, 1980, pp. 113-116.

**Wilson, J.T. et al.** Drug excretion in human breast milk. Principles, pharmacokinetics and projected consequences. *Clinical pharmacokinetics*, 5: 1-66 (1980).

**Yaffe, S.J.** *Paediatric pharmacology: therapeutic principles in practice.* New York, Grune & Stratton, 1980.

**Legal and ethical aspects of drug trials in minors**

**von Bar, L.** Medizinische Forschung und Strafrecht. In: *Festgabe für Regelsberger.* Göttingen, 1901, pp. 229-251.

**Böth, F.** Das wissenschaftlich-medizinische Humanexperiment. *Neue juristische Wochenschrift*, 1967, pp. 1493-1496.

**Capron, A.M.** Legal considerations affecting clinical pharmacological studies in children. *Clinical research*, 1973, pp. 141–150.

*Research involving children: report and recommendations.* Washington, DC, National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1977 (DHEW Publication No. (05) 77-0004).

**Schimikowski, P.** *Experiment am Menschen.* Zur strafrechtlichen Problematik des Humanexperiments. Stuttgart, 1980.

### ***Technical problems of evaluating drugs in children***

*General considerations for the clinical evaluation of drugs in infants and children.* Rockville, MD, FDA Bureau of Drugs, 1977 (No. FDA 77-3041).

Medical, ethical and legal aspects of clinical trials in pediatrics: summary of a forum discussion held at the International Workshop on Perinatal and Pediatric Aspects of Clinical Pharmacology, Heidelberg. *European journal of clinical pharmacology*, **18**: 121–127 (1980).

### ***Role of regulatory agencies***

*Clinical pharmacological evaluation in drug control: report on the Second Symposium.* Copenhagen, WHO Regional Office for Europe, 1974 (document EURO 7407).

### ***Drug kinetics in children***

**Ehrnebo, M. et al.** Age differences in drug binding by plasma proteins: studies on human foetuses, neonates and adults. *European journal of clinical pharmacology*, **3**: 189–193 (1971).

**Friis-Hansen, B.** The extracellular fluid volume in infants and children. *Acta paediatrica*, **43**: 444 (1954).

**Friis-Hansen, B.** Changes in body water compartments during growth. *Acta paediatrica*, **1** (Suppl.): 110 (1956).

**Gladtko, E. & Heimann, G.** The rate of development of elimination functions in kidney and liver of young infants. In: Morselli, P. et al., ed. *Basic and therapeutic aspects of perinatal pharmacology.* New York, Raven Press, 1975.

**Heimann, G.** Enteral absorption and bioavailability in children in relation to age. *European journal of clinical pharmacology*, **18**: 43–50 (1980).

**Krasner, J. & Yaffe, S.J.** Drug-protein binding in the neonate. In: Morselli, P. et al., ed. *Basic and therapeutic aspects of perinatal pharmacology*. New York, Raven Press, 1975, pp. 357-366.

**Nitowsky, H.M. et al.** Studies on oxidative drug metabolism in the full-term newborn infant. *Pediatric pharmacology and therapeutics*, **69**: 1139-1149 (1966).

**Wilkinson, G.R. & Shand, D.G.** A physiological approach to hepatic drug clearance. *Clinical pharmacology and therapeutics*, **18**: 377-390 (1975).

### *Adverse reactions and interactions*

**Aranda, J.V. et al.** Adverse drug reactions (ADR) in the newborn intensive care unit. *Proceedings of the Seventh International Congress of Pharmacology* (Abstracts, No. 2880), 1978.

**Boréus, L.O.** Biverkningsmekanismer, pediatrika synpunkter: symposium om läkemedelsbiverkningar. *Socialstyrelsens kommitté för läkemedelsinformation*, **2**: 53-62 (1976).

**Collins, G.E. et al.** A prospective study of the epidemiology of adverse drug reactions in pediatric hematology and oncology patients. *American journal of hospital pharmacy*, **31**: 968-975 (1974).

**McKenzie, M.W. et al.** A pharmacist-based study of the epidemiology of adverse drug reactions in pediatric medicine patients. *American journal of hospital pharmacy*, **30**: 898-903 (1973).

**Mitchell, A.A. et al.** Drug utilization and reported adverse reactions in hospitalized children. *American journal of epidemiology*, **110**: 196-204 (1979).

**Whyte, J. & Greenan, E.** Drug usage and adverse drug reactions in paediatric patients. *Acta paediatrica scandinavica*, **66**: 767-775 (1977).

### *Drug utilization studies in children*

**Boëthius, G.** *Prescription of drugs 1970-75 in the county of Jämtland, Sweden — epidemiological and clinical pharmacological aspects*. Akademisk Avhandling, 1977.

**Boëthius, G.** Läkemedelskonsumtion under barna åren. In: *Barn och läkemedel: report on a Symposium*. Uppsala, Socialstyrelsen, 1980, Vol. 3.

### ***Problems of compliance in children***

**Mattar, M.E. & Yaffe, S.J.** Compliance of pediatric patients with therapeutic regimens. *Postgraduate medicine*, **56**: 181-188 (1974).

### ***Respiratory disease***

**Dawes, G.S. & Henderson-Smart, D.J.** Breathing before and after birth. In: Widdicombe, J., ed. *MTP international review of physiology* (in press).

*Prescribers' journal* (April 1980). Special issue on respiratory disorders in children.

**Svedmyr, N. & Simonsson, B.** Läkemedel vid astma och hosta. *Socialstyrelsens kommitté för läkemedelsinformation*, **4**: 1 (1979).

### ***Anti-epileptic drugs***

*Guidelines for the clinical evaluation of anticonvulsant drugs (adults and children)*. Rockville, MD, FDA Bureau of Drugs, 1977 (No. FDA 77-3045).

### ***Antibiotic therapy***

**Echeverria, P. et al.** Age-dependent dose response to gentamicin. *Journal of pediatrics*, **87**: 805-808 (1975).

**Klein, J.O.** Current usage of antimicrobial combinations in pediatrics. *Pediatric clinics of North America*, **21**: 443-455 (1974).

**Lipman, A.G.** Antimicrobial agents in breast milk. *Modern medicine*, March 15: 89-90 (1977).

**McCracken, G.H. & Nelson, J.D.** *Antimicrobial therapy for newborns: practical application of pharmacology to clinical usage*. New York, Grune & Stratton, 1977.

Urinary tract infections in infants and children. In: Forfar & Arneil, ed. *Textbook of paediatrics*, 2nd ed. 1978, pp. 877-891.

### ***Cancer chemotherapy***

**Mauer, A.M.** Neoplasms and neoplasm-like lesions: principles of treatment. In: Vaughan, V.C. et al., ed. *Nelson's textbook of pediatrics*. Philadelphia, 1978, pp. 1428-1430.

***Analgesic/antipyretic drugs***

**Gyllenswärd, Å.** Skall feber behandlas? *In: Barn och läkemedel: report on a Symposium.* Uppsala, Socialstyrelsen, 1980, Vol. 3.

**Yaffe, S.J.** Comparative efficacy of aspirin and acetaminophen in the reduction of fever in children. *Archives of internal medicine*, **141**: 286-292 (1981).

*Annex 2*

LIST OF PARTICIPANTS

*Austria*

Dr I. Eichler, Federal Institute of Experimental Pharmacology and Balneology, Vienna (*Vice-Chairman*)

*Belgium*

Dr J.E. Namèche, Chief, Department of Communicable Diseases, St Pierre University Hospital, Brussels

*Czechoslovakia*

Professor M. Kriska, Department of Pharmacology, Faculty of Medicine, Comenius University, Bratislava

*Denmark*

Dr L. Helleberg, Department of Rheumatology and Rehabilitation, Bispebjerg Hospital, Copenhagen

*Finland*

Professor K. Kouvalainen, Department of Paediatrics, University of Oulu

*France*

Dr J.M. Alexandre, Professor of Pharmacology, Laboratory of Pharmacology, Broussais Hospital, Paris

*German Democratic Republic*

Dr I. Amon, Department of Clinical Pharmacology, Ernst-Moritz-Arndt University, Greifswald

*Germany, Federal Republic of*

Professor Christen,<sup>a</sup> Bundesgesundheitsamt, Berlin (West)

Professor G.A. von Harnack, Director, University Paediatric Clinic,  
Düsseldorf

Dr G. Kuschinsky,<sup>a</sup> Bundesgesundheitsamt, Berlin (West)

Professor F. Scheler,<sup>a</sup> Vorsitzender der Arzneimittelkommission der  
deutschen Ärzteschaft, Göttingen

Professor H.W. Seyberth,<sup>a</sup> Universitäts Kinderklinik, Heidelberg

*Greece*

Professor D. Deligiorgis, Vice-Director, Paediatric Department,  
Aghia Sophia Children's Hospital, Athens

*Hungary*

Dr P. Cholnoki, Chief Paediatrician for the Ministry of Health,  
Budapest

*Iceland*

Dr A. Dagbjartsson, Paediatrician (Neonatologist), Landspítalinn,  
Reykjavik

*Ireland*

Dr T.V. O'Dwyer, Senior Medical Officer, Department of Health,  
Dublin

*Italy*

Professor A. Battistini, Clinica Pediatrica Ospedale, Parma

---

<sup>a</sup> Participation expenses not paid by WHO.

*Malta*

Dr H. Lenicker, Paediatrician, Department of Health, Valletta

*Netherlands*

Dr K.F. Kerrebijn, Department of Pulmonary Diseases, Sophia Children's Hospital, University of Rotterdam

*Norway*

Dr I. Lunde, Head, Pharmacotherapeutic Department, National Centre for Medical Products Control, Oslo (*Rapporteur*)

*Portugal*

Dr J.A. Mateus Marques, Directorate-General of Health, Lisbon

*Spain*

Dr R. Ramirez, Head, Department of Clinical Research and Drug Monitoring, Pharmacobiological Centre, Ministry of Labour, Public Health and Social Security, Madrid

*Sweden*

Professor K. Strandberg, Department of Drugs, National Board of Health and Welfare, Uppsala

*Switzerland*

Dr H. Seiler, Federal Public Health Services, Berne

*Turkey*

Professor I.H. Ayhan, Department of Pharmacology, Faculty of Medicine, University of Ankara

*USSR*

Dr U.V. Burov, Senior Scientific Worker, Institute of Pharmacology,  
Ministry of Health of the USSR, Moscow

*United Kingdom*

Dr G.R. Venning, Senior Medical Officer, Medicines Division,  
Department of Health and Social Security, London (*Vice-  
Chairman*)

*Yugoslavia*

Professor V. Varagic, Department of Pharmacology, Medical Faculty,  
University of Belgrade

*Representatives of other organizations*

*Commission of the European Communities*

Mr N. Bel, Head of Division, Directorate General, Internal Market  
and Industrial Affairs, Brussels, Belgium

*International Federation of Pharmaceutical Manufacturers Associations  
(IFPMA)*

Dr H. Bredehorst,<sup>a</sup> Medical Director, Hoechst AG, Frankfurt am  
Main, Federal Republic of Germany

Professor I. Borda,<sup>a</sup> Medical Department, Ciba-Geigy Ltd, Basle,  
Switzerland

*International Paediatric Association*

Professor E. Gladtko, Director, Children's Hospital of the University  
of Cologne, Federal Republic of Germany

---

<sup>a</sup> Participation expenses not paid by WHO.

*World Federation of Proprietary Medicine Manufacturers (WFPMM)*

Dr K. Reese,<sup>a</sup> Director, World Federation of Proprietary Medicine Manufacturers, Cologne, Federal Republic of Germany

*Observers*

Professor G. Olive,<sup>a</sup> National Institute of Health and Medical Research (INSERM), Paris, France

Dr L. Soyka,<sup>a</sup> Director, Clinical Pharmacology, Mead Johnson Pharmaceutical Division, Evansville, USA

Dr M. Stanulovic,<sup>a</sup> Department of Pharmacology and Toxicology, University of Novi Sad, Yugoslavia

Mr V. Venho,<sup>a</sup> Chief, Department of Pharmacology and Microbiology, National Medicines Control Laboratory, Helsinki, Finland

*Nordic Council on Medicines*

Dr L.H. Eklund,<sup>a</sup> Apoteket Örnén, Stockholm, Sweden

*Temporary advisers*

Mrs I. Agenäs, National Corporation of Pharmacies, Stockholm, Sweden

Dr B.M. Assael, II Department of Paediatrics, Faculty of Medicine, University of Milan, Italy

Dr Benz-Lemoine, Service de Pédiatrie, Centre hospitalier régional de Nancy, France

Professor L.O. Boréus, Head, Department of Clinical Pharmacology and Paediatrics, Karolinska Hospital, Stockholm, Sweden

---

<sup>a</sup> Participation expenses not paid by WHO.

Professor H. Dengler, University Medical Clinic, Bonn-Venusberg,  
Federal Republic of Germany (*Chairman*)

Dr M.N.G. Dukes, Vice-Chairman, Netherlands Committee on the  
Evaluation of Medicines, Rijswijk, Netherlands (*Rapporteur*)

Professor J. Elis, Head, Division of Clinical Pharmacology, Institute of  
Pharmacology, Czechoslovak Academy of Sciences, Prague,  
Czechoslovakia

Professor A. Eser, Faculty of Law, University of Tübingen, Federal  
Republic of Germany

Dr C. Gaudich,<sup>a</sup> Federal Ministry for Youth, Family Affairs and  
Health, Bonn, Federal Republic of Germany

Professor E. Glatke, Director, Children's Hospital of the University  
of Cologne, Federal Republic of Germany

Professor L. von Manger-König,<sup>a</sup> Special Consultant on Medical  
Affairs for the Federal Ministry of Youth, Family Affairs and  
Health, Bad Honnef-Rhondorf, Federal Republic of Germany

Dr G. Rylance, Consultant in Paediatrics and Paediatric Clinical  
Pharmacology, Children's Hospital, Birmingham, United  
Kingdom

Dr V. Tatochenko, Senior Scientific Worker, Institute of Paediatrics,  
Academy of Medical Sciences of the USSR, Moscow, USSR

Dr S.J. Yaffe, Director, Centre for Research for Mothers and Children,  
National Institute of Child Health and Human Development,  
National Institute of Health, Bethesda, MD, USA

#### *WHO Regional Office for Europe*

Dr L.A. Kaprio, Regional Director

Mr A. Grimsson, Regional Officer for Prophylactic, Diagnostic and  
Therapeutic Substances

Dr A.H.W. Wahba, Director, Development of Comprehensive Health  
Services

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<sup>a</sup> Participation expenses not paid by WHO.