AMERICAN ACADEMY OF PEDIATRICS

COMMITTEE ON DRUGS

DRUG TESTING IN CHILDREN: FDA REGULATIONS

THE testing of drugs for use in children is difficult to accomplish, and it is even difficult to write about. Anything that smacks of "experimentation" on a child or even the use of a placebo given to a sick child is an emotionally charged subject. To carry out procedures that cannot be considered as essential to therapy, especially when they are painful or tiresome, seems abhorrent.

However, it is recognized that the effects of many drugs on children may vary considerably from the effects on adults even when careful calculation is made to arrive at a dosage proportional to the body weight or estimated body surface area. Pharmacologically, children cannot be regarded as little adults. Intensified, or toxic effects of drugs administered to children, especially infants, may reflect immaturity in enzymatic mechanisms for drug metabolism, as well as other detoxification and excretory functions.

In view of these circumstances, there is need for special caution in prescribing medication in the treatment of childhood disorders, particularly when the medication is used for an extended period of time or when a newly marketed drug is employed. Even greater caution is needed with the use of a new drug under investigation, in advance of approval for marketing. Known serious adverse effects of drugs in children include the effects of sex hormones on growth, steroids on genital development, and antibiotics on tooth enamel.

According to the regulations of the Food and Drug Administration, a drug which has not been subjected to investigation in children may not be labeled for use in pediatric therapy. It must first be demonstrated as safe and effective for children as well as for adults. Therefore, drug manufacturers commonly label many drugs "not to be used in children since its use has not been established as safe for children under 12 years." This has given rise to the term "therapeutic orphans"[1]—children suffering from illnesses for which there may be no drugs approved for use before the age of 12.

The solution to this dilemma is not the deletion of the "not to be used in children" clause from the labeling of drugs but scientific data on which to base valid recommendations for pediatric dosage. These data by law must be based on "adequate, well controlled studies"; testimonial statements even by experts are unacceptable.

To meet the requirements of the Federal Food, Drug, and Cosmetic Act and its regulations, the evaluation of an experimental drug requires thorough investigation on animals followed by human clinical investigation in three phases. In phase 1 the drug is usually administered to normal subjects to observe its pharmacological and toxicologic effects and to secure information to indicate appropriate dosage. In this phase, when the subjects will not personally benefit from medication and when the potential hazard is unknown, the experiment must be explained to each individual and his written consent must be obtained. There is reluctance, on both moral and legal grounds, to give an experimental drug to a healthy child purely to observe its effect. Furthermore, the validity of authorization by parent or guardian is questionable. Observations made on adults will therefore be considered acceptable in phase 1. If a therapeutic effect has been confirmed in adults, with reasonable evidence of safety, the investigator may proceed with treatment of the sick child, combining phase 1 and 2 studies.

In phase 2 of clinical investigation, the experimental drug is administered to a small number of subjects for evaluation of its therapeutic effect as well as its safety. Such treatment of the sick child can be approved; in fact, it may be demanded if

equivalent alternative therapy is lacking. The parents or guardian must be informed of the experimental nature of the treatment. Written consent from parent or guardian is required, except when impossible or "not in the child's best interest"—a situation which the attending physician must determine with great care. Since the concern regarding drug effects is greatest for the infant, cautious investigation might require successive trials at different age levels beginning with school age children (6 to 12 years) and in reverse age order finally to neonates.

When favorable results have been obtained to justify the next step, phase 3, the drug is administered to large numbers of patients. Written consent is not essential here but the physician should see that a note appears in the clinical records indicating that the parent or guardian has been afforded an explanation of the experimental treatment and that the procedure has his approval.

A section of the Food and Drug Administration's New Drug Regulations makes a provision for investigational use of a drug by a physician after sending to the Food and Drug Administration a simple outline of the purpose and nature of the study. The communication should be directed to the Office of New Drugs, Bureau of Medicine, Food and Drug Administration, Washington, D.C. 20204. This modified form of "IND," or Claimed Exemption for an Investigational New Drug, has special application for the physician interested in research *per se*, rather than in conducting studies which will lead to approval of a drug for marketing by a pharmaceutical firm. As in all "IND's," the physician, after sending his study plan and credentials to the Food and Drug Administration, need not wait for "approval" or other communication from the Food and Drug Administration before beginning his study, and no time is lost by withholding a new experimental drug from a sick child.

The approval of a new drug for marketing is based on the best evidence the sponsors can submit to the Food and Drug Administration. The application must show convincing evidence that the drug is not only effective for the uses claimed but that it can also be administered with reasonable safety. There is always the possibility that hazards not apparent during the period of investigation may come to light after a new drug has been widely prescribed. The Food and Drug Administration requires that the labeling (or package insert) describe all known adverse effects and give information regarding precautions and contraindications. Advertisements must include this information in brief summary.

The sometimes unpredictable effects of drugs on children require that drug testing in this age group be conducted, but tests should be conducted with caution. While "social benefit" may not constitute justification for drug testing of healthy children (who could not, in any case, "volunteer" on an informed basis), the great need for information regarding effects of drugs, especially on very young children, can be met by carefully conducted tests of new drugs on ill children who may be expected to benefit from administration of the drug. The design, recording, and reporting of such studies is in the interest of the profession, the drug industry, and, most importantly, the children.

ADDENDUM

While the intent of the Canadian regulations under the Food and Drugs Act is essentially similar to those of the United States and the problems raised in the foregoing statement are thus applicable to children in both countries, there are some differences in the regulations themselves. Pediatricians wishing more information regarding Canadian regulations should write to: Jeffrey Bishop, M.D., Acting Director, Bureau of Drug Advisory Services, Food and Drug Directorate, Ottawa 3, Ontario.

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REFERENCE

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