Editorial Comment: Therapeutic Orphans

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By an odd and unfortunate twist of fate, infants and children are becoming “therapeutic or pharmaceutical orphans.” Since 1962 they have been denied the use of many new drugs. The Drug Laws of 1962 had their inception following a pediatric tragedy—the thalidomide catastrophe. The laws of 1938 followed another which resulted from the use of a pediatric dosage form, “elixir” of sulfanilamide. By “legal” definition, drugs introduced since 1962 must be safe and efficacious, but only a small number of these have been studied in the pediatric age group. Certainly, there are some drugs which have an anticipated use only in adults; it would be unreasonable to ask for certification of these for use in infants and children. There are a small number of new drugs, released since 1962, which had an anticipated use for infants and children as well as for adults, and their applications for approval have been passed after the required studies in pediatric and adult patients. However, many of the drugs released since 1962 carry an “orphaning” clause, eg, “Not to be used in children... is not recommended for use in infants and young children since few studies have been conducted in this age group... clinical studies have been insufficient to establish any recommendations for use in infants and children... should not be given to children.”

Despite such clear cautions, many physicians have ignored the warnings and have prescribed the restricted drugs. It requires little imagination to wonder what a jury of laymen would decide after a defending physician admitted in court to the use of a drug despite such a clear warning.

Although the laws were designed to ensure the efficacy and safety of drugs, the age group responsible for their passage is now often deprived of the use of the medications. Testing of these drugs can not always be in controlled situations but is sometimes in the situation of use—by ordeal and often against advice. Inevitably this “unlawful” procedure will be associated with some adverse reactions, including toxic reactions, side effects, and idiosyncrasy. These reactions are common to all drugs. History has also taught that drugs previously considered harmless may be associated with temporary and permanent reactions unique to the newly born infant; even oxygen falls into this category.

It seems unfair that the use of some drugs will be denied based on relatively infrequent use and small sales potential. For example, should a child with peptic ulcer be denied the advantages of a drug which is proved to be of value to adults because that drug has not been tested in the pediatric age group? Other examples could be mentioned relative to diseases of greater frequency, but in which the needs for drugs fall below the anticipated sales volume required to warrant study in children. After cursory consideration, one might place the blame for this growing problem on the drug industry alone. However, many groups are responsible, including the government (especially the Food and Drug Administration), academic pediatric centers, and practicing physicians.

The pharmaceutical industry in the past has supplied many “service items” and will continue to supply these at a financial loss, although it would prefer to supply drugs for a large and profitable market. However, pharmaceutical firms have difficulty finding a sufficient number of clinical investigators with interest, experience, and patients for the study of new drugs. These difficulties are inversely proportional to the frequency of the disease and to the age and size of the patient. Yet it is quite clear that those who desire better drugs must inevitably include clinical investigation of drugs among their responsibilities. The Food and Drug Administration has statutory responsibility for ensuring that drugs are safe and effective. It cannot have different criteria for depth of study of drugs intended for adults as compared with those for infants and children. It recognizes, as does industry, an increasing reluctance on the part of pediatricians and others treating children to investigate the effect of drugs in the pediatric age group. At the same time, the Food and Drug Administration discouraged such studies by their interpretation of the law into guidelines which clearly indicated that written consent of patients (or their representatives) had to be given “except in unusual circumstances.” The guidelines lacked clearly defined limitations, or provisions specifically outlining requirements for studies in infants and children. This interpretation has been changed, easing the difficulties somewhat and demonstrating that reasonable cooperation can be effected. However, the climate created by present regulation of human experimentation makes drug testing difficult, and especially so unless a warm and close relationship exists between the...
doctor who gains the permission and the parent or guardian who grants it. The continuing close patient-parent-doctor relationship existing in the private practice of medicine may permit a greater ease of meeting these legal requirements.

The Food and Drug Administration recognizes the responsibility of industry to provide adequate directions and accurate dosage for use of drugs in children; likewise, it recognizes the difficulties encountered in gaining this information. It also recognizes a pressing public issue developing in the face of the above difficulties. It is trying to face the problem and to develop positive attitudes; for instance, it has recently sponsored a Conference on Pediatric Pharmacology.

Every practicing physician, especially pediatricians and pediatric surgeons, departments of pediatrics, and departments of pharmacology should closely examine their own capacities and performance in this area of greatly needed activity. If we are to have drugs of better efficacy and safety for children, those responsible for child care will have to assume this responsibility for developing active programs of clinical pharmacology and drug testing in infants and children. The alternative is to accept the status of “Therapeutic Orphans” for their patients.

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