The thalidomide episode will continue to reverberate for some time. In this paper, the author calls attention to some background aspects, discusses the current situation, and points out certain problems that still require attention.

PROBLEMS RAISED FOR THE FDA BY THE OCCURRENCE OF THALIDOMIDE EMBRYOPATHY IN GERMANY, 1960-1961

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THE first Pure Food and Drug Act passed in 1906 provided no recognition of the investigational use of drugs. The law did not require pretesting of a drug on either animals or human subjects before it was distributed in interstate commerce. The onus was on the government to prove an article unsafe before it could be removed from the market. The weakness of this law was apparent in the 1937 "elixir of sulfanilamide" tragedy. A pharmaceutical firm decided to distribute a fluid preparation of the then new drug sulfanilamide. The drug was insoluble in alcohol or water, and diethylene glycol was used as a solvent by the manufacturer without adequate toxicologic tests to establish its safety. As a result of the kidney damage produced by this compound over 100 people died and many were made seriously ill.

This tragedy influenced the passage of the Food, Drug, and Cosmetic Act in 1938 after years of legislative hearings, and the inclusion of the new drug section. The revised version required that before a new drug could be distributed in interstate commerce the sponsor of the drug must submit information to the Food and Drug Administration to establish the safety of the drug for the proposed clinical use or uses. This information, submitted as a New Drug Application or NDA, consisted of details concerning the quality control of the compound, animal studies undertaken to establish its acute and chronic toxicity and pharmacological effects, and clinical studies designed to demonstrate its safety. Under the implementing regulations, a new drug could however be distributed for investigational purposes prior to the submission of a NDA provided that the preparation was labeled clearly as an investigational drug, that the investigators signed a statement to the effect that they had facilities to test the drug and that the drug would be tested under their supervision only, and that accurate records of the distribution of the investigational drug would be kept by the firm. There was no requirement that the government be notified that the drug was under investigation or that an investigation was discontinued when this occurred.

The New Drug Application for thalidomide was presented in September, 1960. The drug had been marketed in Germany since 1957 where it was available without prescription, and in Great Britain since 1958. However, it was felt

that the evidence submitted in the application was not adequate to indicate the safety of the drug. In particular, although this drug appeared to be remarkably nontoxic in animals and human beings, little or no information was available concerning its absorption, distribution in the body, or its excretion. Since the possibility existed that the low toxicity of the drug in certain species might be related to poor absorption in those species, and that under certain conditions the absorption in other species might be increased, further work was requested relative to the metabolism of the drug. While this was being done, a report in the "British Medical Journal," December 31, 1960, drew attention to a possible side effect of prolonged use of thalidomide, namely polyneuritis.

Further information concerning this report was requested and it was learned that in reality the occurrence of this side effect was already well established in Germany and England. Indeed, the British preparation of thalidomide had carried a warning for some six months, although this information was not given to the Food and Drug Administration. Additionally, the suggestion was made that possibly a dietary defect was associated with thalidomide ingestion in these cases. Support for this hypothesis was offered by the fact that many of the victims were elderly female patients with poor dietary habits and by an apparent pattern in the geographical distribution of the cases reported.

Following the establishment of polyneuritis as a side effect of prolonged thalidomide ingestion, we felt that if the drug were taken during pregnancy the developing fetus might be exposed to the drug as long as nine months, and might be susceptible to harmful effects because of its rapid growth and imperfect enzyme systems. The information we had concerning the use of the drug during pregnancy was confined to a study of the use of the drug in treating insomnia in approximately 100 patients in the last trimester of pregnancy. In the absence of more comprehensive data, we felt the new drug application for thalidomide should not be approved unless it was made clear in the physician's brochure that the safety of the drug in pregnancy had not been established. However, by the end of November, 1961, word was received from Germany of the possible association of this drug with phocomelia and the application became inactive.

It is of interest to note that by May, 1961, when our reservations concerning the safety of thalidomide in pregnancy were first expressed, attention had already been drawn in Germany to the sudden alarming increase of congenital limb deformities and searching inquiries were under way to determine their cause. These endeavors culminated in November, 1961, when Dr. Lenz made known his suspicion that thalidomide was the cause of the deformities, and McBride in Australia independently reached this same conclusion.

While the teratogenic effect of thalidomide has attracted a great deal of attention, the neuropathy caused by the drug has been comparatively neglected. Not all patients who received thalidomide for prolonged periods developed neuropathy, the usual figure cited being one in 250. However, it has not been established whether there are differences in the metabolism of the drug that might explain the individual differences nor has it been determined that polyneuritis and the phocomelia are related phenomena. Vitamin B preparations have been recommended for the treatment of the neuropathy but the value of such therapy has not been conclusively established. The similarity of the teratogenic effects produced by thalidomide and those produced in animals by diets deficient in the vitamin B-complex has led to the suggestion that the drug may act as an antimetabolite. Even before the

teratogenic effect of thalidomide was recognized, Duraiswami had reported that isoniazid, another drug known to cause neuropathy in human subjects, causes fetal anomalies in the chick embryo and an abnormally high incidence of stillbirths among the offspring of albino rats and mice treated with the drug during gestation.

While the thalidomide episode has undoubtedly stimulated research in the field of teratology, it should be pointed out that when the thalidomide application was under study there was developing an increasing interest in the effects of the drugs and other environmental hazards on the human fetus and newborn, all of which contributed to our caution in evaluating the application. This subject had previously been somewhat neglected despite the rather extensive animal studies undertaken in this field by such investigators as Warkany, Ingalls, and Fraser. However, in 1940, Gregg recognized the adverse effect of the virus of German measles on the human fetus and the teratogenic effect of aminopterin was described by Thiersch in 1952, while in 1958 Wilkins described the occurrence of nonadrenal pseudohermaphroditism in female infants born of mothers who received synthetic progestins during gestation.

Additionally, evidence was accumulating to indicate that the fetus and the newborn infant often behave so differently toward certain drugs as to warrant consideration as separate categories of the human species. Again these findings gained support from animal studies. Thus, while I was working with the antimalarial drugs research program at the University of Chicago in 1943, we found that while the liver of the adult rabbit metabolized quinine rapidly due to the presence of an enzyme, quinine oxidase, the fetal rabbit liver had little or no quinine oxidase activity. Later, both Fouts and Brodie showed that the newborn of guinea pigs, mice, and rabbits lack oxidative drug enzymes, and suggested that these findings might explain some of the difficulties encountered in administering drugs to newborn infants. The susceptibility of newborn infants, particularly premature infants, to chloramphenicol, first reported by Sutherland in 1959, has been recognized as being due to the fact that certain liver functions including the ability to form glucuronides are immature in newborn infants. The resultant high blood level of chloramphenicol leads to circulatory collapse. Again, some drugs compete with bilirubin for the inadequate hepatic enzymes so that their administration may result in higher levels of indirect bilirubin leading to jaundice and increased risk of kernicterus, while yet others displace bilirubin bound to plasma proteins thus increasing the blood level of the more freely diffusible form.

In the face of mounting evidence that the pharmacologic response of the immature human may differ, both quantitatively and qualitatively, from that of the adult, the Committee on Fetus and Newborn of the American Academy of Pediatrics issued a statement in October, 1961, before the thalidomide-phocomelia relationship was published, pointing out that tests on mature animals and human adults or older children are unsatisfactory criteria for recommendations concerning the fetus and infant. The committee recommended that "existing drugs and agents as well as agents that are developed in the future for use in the fetus and infants must be subjected to much more extensive preclinical investigations than is being carried out at the present time." It was suggested that the pharmacological properties of drugs should be studied in vitro and in vivo in the fetus and newborn animal and compared with those in the adult of the same animal species. It was further recommended

that where no pharmacological studies of the drug in immature subjects had been performed, a statement of this fact should be included in the labeling. This statement is in accord with our approach at the Food and Drug Administration. The present policy is to require that before a drug is tested in women of the childbearing age a screening test in pregnant animals be done. Furthermore, if the drug is to be used in infants, acute toxicity studies must be run on newborn rats. Recommendations for the pediatric use of the drug must be substantiated by adequate clinical studies to establish the safety and effectiveness of the drug in the appropriate age group or groups.

The thalidomide incident was a major factor leading to the enactment of the Kefauver-Harris Amendments of 1962. This has led to the conclusion by some that the law, and our investigational drug regulations, were hastily drawn and thus must have been poorly drawn. This is not correct. The department's proposed legislation, which served as the basis for most of the provisions in the law as enacted, which relate to drug testing, was very carefully drafted by experts and widely studied within the Executive Branch of the government before it was sent to the Congress by our secretary. Similarly, the proposed investigational drug regulations were carefully prepared on the basis of many years of experience with the new drug law before the thalidomide situation came to public attention. Rapid developments in drug research and in promotional methods for drugs necessitated evaluation of the effectiveness of new drugs as well as their safety. Furthermore, the need for greater control and surveillance over the distribution and clinical testing of investigational drugs became apparent as abuses began to appear. The intent of the new procedures is to protect the public and the clinical investigator by ensuring that adequate preclinical studies are done on the drug before the investigator is asked to do human studies.

It has been said that there is currently absolutely nothing which would prevent repetition of the thalidomide tragedy. This is simply not true. While teratogenic effects cannot be produced in all species or strains of animals with thalidomide, a number of investigators have produced anomalies using rabbits, a species frequently used in studies of this type. Furthermore, with the rat reproduction test recommended by the Food and Drug Administration, there is a significant reduction in litter size due to fetal reabsorption, and skeletal deformities commonly occur in the survivors. This procedure involves feeding subtoxic doses of the drug under test to male and female rats for a preliminary period of six weeks and through two pregnancies. It is designed to detect not only teratogenic effects, but also adverse effects on spermatogenesis, fertilization or implantation, or on the welfare of the fetus or newborn.

Additionally, objectively designed clinical studies should have detected both the neuropathy and the embryopathy long before these side effects caused such widespread damage. The clinical studies submitted in support of the application for thalidomide in this country did not record either side effect. Retrospective inquiries, however, disclosed several cases of both neuropathy and phocomelia that had not been reported, the investigators having considered the effects to be unrelated to the drug under test. While it is not known exactly what per cent of mothers taking the drug during the critical period of pregnancy did give birth to deformed babies, the figure generally cited is 20 per cent. Such a high incidence would have been readily determined by properly designed clinical studies. Assuming the "normal" incidence of recognizable birth defects to be 5 per cent,

an increase to 20 per cent could be detected with a reasonable degree of significance by exposing less than 100 pregnant women to the drug.

In conclusion, not all toxic reactions can be anticipated by animal experiments or are manifested in clinical tests of a drug before it is released for general distribution. However, the Food and Drug Administration has an adverse reaction reporting program with approximately 450 cooperating reporting sources, and recently the American Medical Association has expanded its drug reaction reporting system to include all drugs rather than those associated with blood dyscrasias as in the past. Additionally, the 1963 Kefauver-Harris Amendments require that pharmaceutical firms report at regular intervals to the Food and Drug Administration all adverse effects associated with their new drugs. These measures will help detect the rare reactions not revealed even by well-planned clinical studies.

The success of programs currently in use for reporting drug reactions, however, depends for the most part on the ability of the individual physician to recognize drug reactions and his willingness to report these to a coordinating agency where they can be evaluated in a fair and impartial manner and appropriate measures taken. An additional safeguard would be the establishment of a national or international adverse reaction program based on a register of medical case histories which would permit an independent observer to detect correlations between drug intake and toxicity that might elude the individual clinical investigator or attending physician. Certainly it should not take many thousands of deformed children to establish the degree of hazard that is associated with thalidomide. It would indeed add inestimably to the tragedy of the thalidomide episode if we shut our eyes to the fact that it could have been largely averted.

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This paper was presented before a Joint Session of the Food and Nutrition, Laboratory, and Maternal and Child Health Sections of the American Public Health Association at the Ninety-First Annual Meeting in Kansas City, Mo., November 14, 1963.

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