since 1955, and phocomelia did not appear there until 1961. Almost all the few Swiss cases have been traced to Contergan from Germany.

Little is known about the metabolism of thalidomide, how the body excretes it or how long the deformity-producing factor persists in the body. About all that is certain is that it is insoluble in water and in fat. Obviously the usual laboratory animals metabolize it differently from human beings; it does not induce sleep in the animals. Investigators at the Grünenthal laboratories have tried unsuccessfully to produce phocomelia in rats, mice and rabbits. They have shown that the drug passes through the placenta of rabbits, but the offspring were normal in these experiments. G. F. Somers of the Distillers Ltd. laboratories has fed massive doses to pregnant rabbits. The rabbits did not sleep; they did, however, produce offspring with abnormalities remarkably similar to those in human infants. Since thalidomide makes a horse sleep, it may be that the horse will react in other ways as man does. Experiments with monkeys and apes will also be of interest. When the proper experimental animal is found, thalidomide does offer the possibility of studying the origin of malformations.

It is not yet possible to determine the exact number of infants born with phocomelia in West Germany, but the outbreak was devastating. The records of the Institute of Human Genetics in Münster show three cases of bilateral phocomelia in 1959, 26 cases in 1960 and 96 in 1961. Up to this spring 13 pairs of twins afflicted with phocomelia had been registered. Since twins occur once in every 100 births, the institute estimates that there will be 1,300 cases in the state of North Rhine-Westphalia, where it is located. It is an indication of the prevalence of phocomelia that the state's Ministry of Health has set up a registry for all children with defective hands and arms who will need orthopedic help. As of January, 800 had been registered, 80 per cent suffering from phocomelia, and reports were in from only half the state. By now the total may have reached 2,000. Applying this experience to the population of West Germany as a whole, the country anticipates a minimum of 4,000 cases. I should not be surprised by a total of 6,000. There is every reason to believe that two-thirds of the infants will live for many years; indeed, the children appear to have a normal life expectancy.

In England, alas, the incidence is also high. Reports of phocomelia associated with Distaval appear regularly in *The Lancet*, the British weekly medical journal. Clifford G. Parsons of Birmingham has advised me that almost every physician at a medical meeting in England last spring had seen at least one case. The total for the the country will probably be in the hundreds, however, not in the thousands.

Reports are still coming in from all over the world showing that phocomelia has occurred wherever thalidomide has been used. Sweden has had 25 cases, from Contergan purchased in Germany. Switzerland has had four cases. The Portuguese preparation, Softenon, has caused seven cases in Lebanon. Distaval has produced a case in Israel. In Peru, Contergan obtained by the father in Germany caused a case. Lenz has written me of an outbreak of phocomelia in Brazil. As yet I have received no figures for Portugal.

In September, 1960, when the Merrell Company applied to the Food and Drug Administration for permission to distribute the thalidomide compound, none of these untoward developments could have been anticipated. Clearance was delayed because the initial submission of papers was found to be "incomplete." Over the next few months, while the manufacturer gathered and filed additional material in support of the application, the first indications of the drug's neuropathic side effects were reported in the German medical press. Frances Oldham Kelsey, a physician and pharmacologist at the agency, took note of these reports. She also noted that the proposed label for the drug recommended its use against the nausea of pregnancy. From her work with quinine in connection with the malaria project during World War II, Mrs. Kelsey had become "particularly conscious of the fact that the fetus or newborn may be, pharmacologically, an entirely different organism from the adult." She therefore requested more data from the manufacturer to show that the drug was safe in pregnancy. Before her questions were answered the outbreak of phocomelia in Germany had brought withdrawal of the drug from the market in that country.

If thalidomide had been developed in this country, the story would have been quite different. Almost everyone agrees that with no knowledge of the delayed neuropathic effects of the drug and no appreciation of its dangers in pregnancy, the thought would not have occurred to anyone that it might injure the unborn

child. Therefore permission for sale of the drug as a sedative would have been granted; it was an excellent sedative and appeared to be safe.

In the U.S. there have been only a few cases of the syndrome—two of them the twin offspring of a German woman who had married an American and brought Contergan with her to the U.S. Even the families of U.S. personnel stationed abroad have escaped—with one exception. At the U.S. Army headquarters in Heidelberg, in March, Thomas W. Immon was able to assure me that not one of the 16,000 babies born in U.S. hospitals in Germany during 1961 had phocomelia. More recently, however, he has had to report the birth in a U.S. Army hospital of one infant with phocomelia. The mother, a German, reported that she had taken Contergan in the early weeks of her pregnancy.

Unfortunately the people of Canada have had a different experience, even though the Dominion Government has a drug-regulating agency like that of the U.S. With two thalidomide preparations on the market in 1961, many pregnant women were exposed to the drug. At least 12 have delivered offspring afflicted with deformed arms and legs. The manufacturers issued a warning to physicians in December, advising them not to prescribe thalidomide for pregnant women. It was not until March, however, that governmental authorities asked the manufacturers to withdraw the drug entirely. Between now and the fall there will undoubtedly be additional casualties.

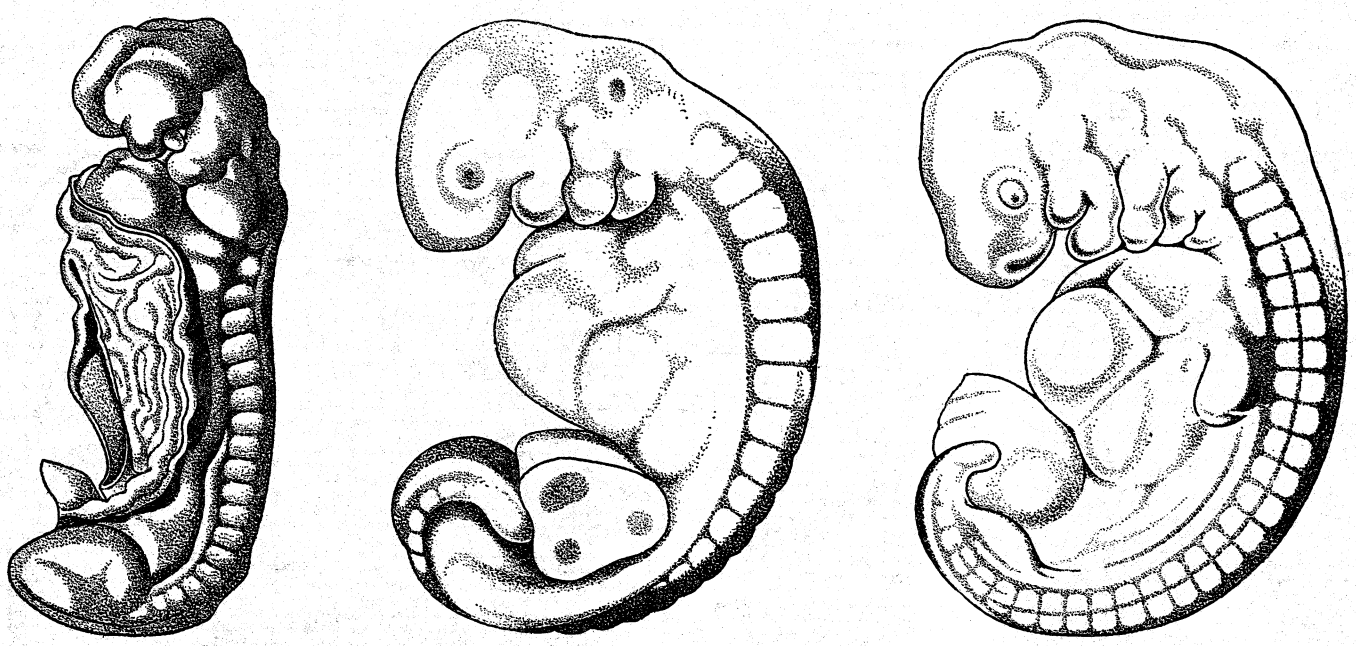
A generation ago new drugs, particularly those for relatively minor complaints such as insomnia, only gradually achieved widespread popularity. The rather small number of people using them in the first few years provided, albeit unwittingly, test cases not only for the efficacy but also for the long-term safety of the drug. Today "educational" representatives of drug houses visit each physician regularly. Pounds of lavish and expensive drug brochures assault the physician by mail. Most medical journals are crowded with handsome advertisements, many printed in full color on heavy cardboard or metallic paper, extolling the virtues of this year's model or modification of some recently invented tranquilizer, diuretic or antihypertensive compound. New drugs thus find huge markets within a few months.

In most countries, with the exception of Canada, governmental regulation of the pharmaceutical trade is less stringent than it is in the U.S. The Food and Drug Administration, however, is limited to considering only the safety and not the efficacy of a drug, and it exercises no control until the drug is ready for sale. During testing, conducted by and for the drug houses, a new compound may be distributed for clinical trial to many physicians. They are supposed to warn patients that the drug is experimental and to obtain a release signed by the patient. Not all physicians keep careful records of the cases in which they have distributed such test drugs. Clearance by the Food and Drug Administration, which rests on evidence of safety submitted by drug companies, must often be based in part on reports from observations made under clinical conditions that are, to say the least, not ideal. Certainly the procedure needs strengthening here.

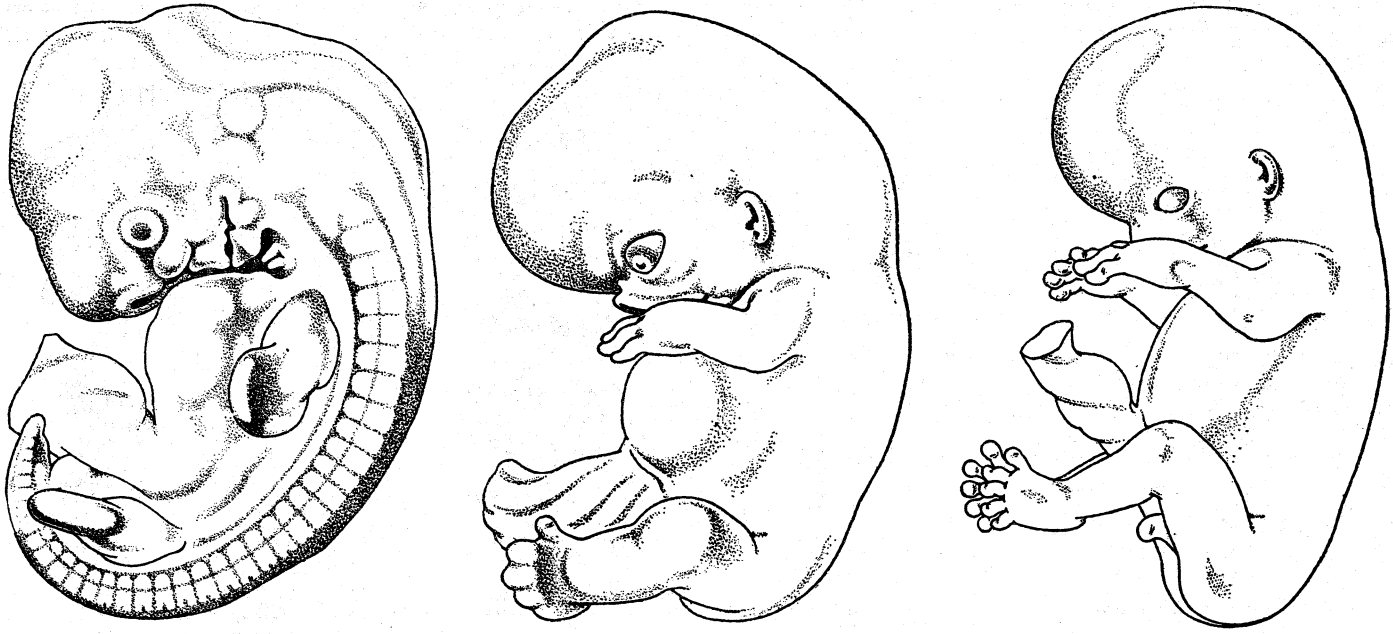
Until recently no thought had been given to the need for the testing of drugs for potential harmfulness to the human embryo. In my laboratory at the Johns Hopkins School of Medicine I have not been able to obtain abnormalities in baby rabbits with thalidomide primarily because the massive doses I have used bring on so many abortions. This illustrates one of the problems of testing new drugs: what size dose in animal makes for a fair test? As thalidomide shows, animals may not react at all like humans.

Of course, no drug can ever be certified as completely safe. But all the hazards of a given drug should be established before it is marketed. In dealing with cancer and other serious diseases there is some justification for taking chances with new drugs. The less serious the illness is, the more certain it should be that the drug is harmless as well as effective. In the case of thalidomide, I wonder how long it would have taken to determine the cause of the malformations if the drug had produced some more common but less spectacular congenital defect. Any drug labeled safe should be relatively harmless for all people of all ages, including the unborn. Married women of childbearing age should avoid drugs as much as possible, particularly new ones.

For most people the story of thalidomide has ended. The tragedy will go on, however, for the infant victims of the "harmless" sedative and their families for the rest of their lives.



DEVELOPMENT OF HUMAN EMBRYO from third week after conception (*far left*) through eighth week (*far right*) is crucial. The embryo grows from about a quarter of an inch in length at end of third week to one and a quarter inches at end of eighth. Thalid-



omide seems to cause almost all its deformities when the mother takes the drug during the fourth, fifth or sixth week of pregnancy, as limb buds, ears, intestinal tract, heart and blood vessels are forming and going through first growth. These embryos are normal.

[From the American Journal of Diseases of Children, August 1962, vol. 104, pp. 111–113]

THALIDOMIDE—A LESSON IN REMOTE EFFECTS OF DRUGS

In late January, 1962, my attention was attracted to reports of an outbreak of congenital malformations in children being born in Germany and its possible relation to a specific drug. Because of my interest in congenital malformations of the heart I decided to examine the situation myself. My trip was supported by grants from the International Society of Cardiology Foundation, the Heart Association of Maryland, and the National Institutes of Health. I traveled throughout West Germany with the exception of West Berlin. The results of this investigation seem to me so important and so pressing that I feel it my duty to report them to the medical profession without further delay.

The malformation with which I was concerned was phocomelia; the name comes from the Greek words *Phokos*, meaning seal, and *Melos*, meaning extremities. According to definition the development of the limb buds is so affected that the hands and feet arise from the trunk in a way suggestive of the flippers of a seal. Actually the injury affects the long bones of arms and legs; the hands and feet arise beyond the affected bone. In some instances the arms are rudimentary—4 such children are shown in Figure 1. The malformation involves both sides, but usually one side is more seriously affected than the other. The legs, too, may be affected. In 50% of the cases the arms only were affected, and in another 25% both the arms and legs are affected. At birth, a central hemangioma extending from the forehead over the nose to form a moustache on the upper lip is considered by Pfeiffer as characteristic of the syndrome. In some babies the external ear was absent. In the most severe cases malformation of the gut occurred accompanied by duodenal stenosis and anal atreasia, asplenia, and occasionally by a malformation of the heart. Mental retardation was found in only approximately 1%.

Phocomelia had long been known as a rare malformation. In 1959 a few cases were seen; these increased in 1960. By 1961 there was a veritable "epidemic" of phocomelia in Germany. Last November, Lenz suggested the possibility that the occurrence of the sudden outbreak of this malformation was connected with the use of a new sleeping tablet. The drug is known as thalidomide. It is a synthetic preparation whose chemical structure is shown in Figure 2. The drug was made by Grünenthal and marketed as Contergan in Germany, Distaval in the British Commonwealth, Softenon in Portugal, Kevadon (on trial in the U.S.A., but not released by the Food and Drug Administration), and Talimol in Canada. Thalidomide was also added to other medicines. The German drugs known as Algosediv, Peracon Expectorans, Grippex, and Polygripan all contain thalidomide, and so do the English drugs, Valgis, Tensival, Valgraine, and Asmaval.

The drug was invented by a German firm and first marketed during 1958; by 1960 it became Germany's most popular sleeping tablet and tranquilizer. The drug was sold without prescription until its long-continued use was found to cause polyneuritis; thereafter it was sold freely on prescription.

In November, 1961, W. Lenz in Hamburg (Germany) and W. G. McBride in Australia independently and almost simultaneously realized there was a close association between the new sleeping tablet and the outbreak of phocomelia. Both doctors reported their findings to their respective manufacturers in Germany and in Australia, and they also reported them to their Medical Societies. As soon as A. Spiers in Scotland heard these reports he checked his 10 recent cases of phocomelia with great care and obtained positive proof that 8 of the 10 mothers had taken Distaval. Thus, in three widely separated parts of the world, phocomelia occurred in the offspring of women who had taken thalidomide in early pregnancy.

The drug was withdrawn from the market at the end of November, 1961. Since then much circumstantial evidence of the relation between thalidomide and phocomelia has been collected. Lenz told me in March, 1962, that he had collected 50 cases of women with infants who have phocomelia in whom he knows the date of the last menstrual period (in about one-half of the instances the date of conception) as well as the date at which Contergan was taken, either as recorded on a hospital chart or a photostatic copy of the prescription. He found the sensitive period was between the 30th and 60th day after the last menstrual period; in most cases the drug had been taken between the 30th and 50th day. In the cases in which the date of conception was known the sensitive period was from the 28th to 42d day inclusive.

The sensitive period may be found to vary, and some women may prove to be immune, but the circumstantial evidence is overwhelming that the drug, if

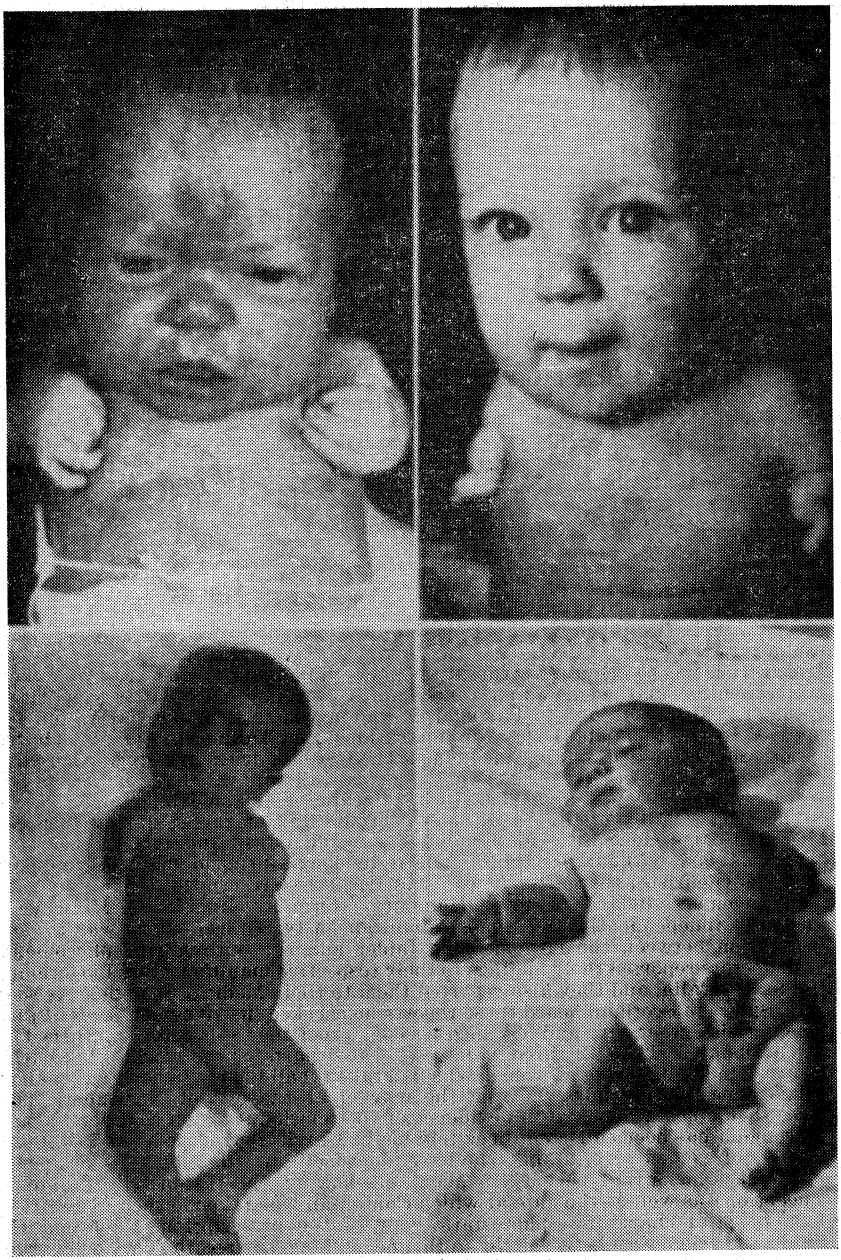
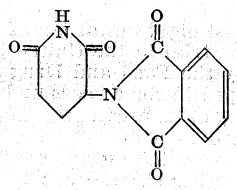


FIGURE 1



Thalidomide.

FIGURE 2.

taken during a sensitive period, can cause phocomelia. A single dose of thalidomide at the sensitive time is thought sufficient to damage the embryo.

The most conservative estimate is that by August 1962, 3,500 babies will have been born in Germany with phocomelia; two-thirds of whom will live. England will probably have several hundred. The drug was not passed by the U.S. Food and Drugs Administration; therefore, its use was not permitted to the U.S. Army of Occupation in Germany, and consequently the wives of men in our Armed Forces have been spared. There were 16,000 births in 1961 among the wives of the Army of Occupation, and no cases had been reported up to March 10. 1962. The U.S. Army Headquarters had no knowledge of cases of phocomelia which might have occurred among German wives of American soldiers who were cared for by German doctors.

Although our law requiring careful tests on animals before a drug is released by the Food and Drug Administration has been a tremendous protection to our country, nevertheless, the routine testing of the effects of drugs on the offspring of pregnant animals is not regularly required. Needless to say, this experience in Germany and the British Commonwealth illustrates the need for stricter laws and for routine testing of the effect of all drugs on pregnant animals.

Definite proof that thalidomide does cause phocomelia must await further confirmatory animal experimentation or the cessation of the outbreak in August, 1962, which will be eight months after the withdrawal of the drug. Nevertheless, the circumstantial evidence is so strong that this drug does cause congenital malformations, and the effects on the children are so terrible that I feel that the situation should be brought to the immediate attention of the medical profession in this country. It is also important to remember that in many instances the damage is done before the mother knows she is pregnant. Therefore, young women must learn to be cautions about new drugs. Until research concerning the proper tests has been completed, doctors must bear in mind that sleeping tablets, tranquillizers, and other apparently innocent drugs may do terrible harm to the rapidly growing embryo and the unborn child.

HELEN B. TAUSSIG, M.D.,
Professor of Pediatrics, Johns Hopkins Hospital, Baltimore.

[From Science, May 25, 1962, vol. 136, No. 3517]

DANGEROUS TRANQUILITY

In late January 1962 my attention was attracted to an outbreak of congenital malformations in children in Germany and its possible relation to a specific drug. Because of my interest in congenital malformations of the heart I decided to examine the situation myself.

The malformation was phocomelia, which is characterized by reduction in the length of the long bones of the arms or legs, or both. In extreme cases the appendages are reduced to completely functionless nubbins. Occasionally the external ear is absent, and in the most severe cases the visceral organs are badly malformed.

Phocomelia has long been known as a rare malformation. In Germany, a few cases were seen in 1959, more were seen in 1960, and cases in "epidemic" numbers were seen in 1961. By November 1961, W. Lenz of Hamburg and W. G. McBride in Australia suggested that the outbreak was connected with the use of a new sleeping pill and tranquilizer containing thalidomide [alpha-(N-phthalimido)glutarimide]. A. Spiers in Scotland confirmed the relation by show-

ing that the mothers of at least eight out of ten of the affected babies had taken the drug. Thalidomide was on trial in the United States, but fortunately it had not been approved for use by the Food and Drug Administration, owing to the fact that polyneuritis developed in some users and owing also to Dr. Frances O. Kelsey's doubt about the safety of its use in pregnancy.

The drug was first marketed in Germany in 1958, and by 1960 it had become Germany's most popular sleeping tablet and tranquilizer. It was sold without prescription until the polyneuritis showed up; thereafter it was sold freely on prescription.

Thalidomide was withdrawn from the market in Germany by November 1961 and slightly later in England, Australia, and Canada. Much additional circumstantial evidence of the relation between thalidomide and phocomelia has now been collected. Lenz (personal communication) has studied 50 cases of women whose offspring have phocomelia and who had also taken the drug during pregnancy. He finds that the period of sensitivity is between days 30 and 60 after the last menstrual period, and that in most cases the drug had been taken between days 30 and 50. In those cases in which the date of conception was known, the period of sensitivity was from the 28th to the 42nd day.

The most conservative estimate is that by August 1962 some 3500 babies with phocomelia will have been born in Germany and several hundred will have been born in England and elsewhere.

Definite proof that thalidomide does cause phocomelia must await further confirmatory animal experimentation or cessation of the outbreak in August 1962, 8 months after withdrawal of the drug. Nevertheless, the circumstantial evidence that this drug does cause congenital malformations is so strong, and the effects on the children are so terrible, that I feel the situation should be brought to the immediate attention of the public in this country. It is also important to remember that in many instances the damage is done before the mother knows she is pregnant. Therefore, young women must learn to be cautious about new drugs. Until new laws have become effective, and indeed until research for the proper tests on pregnant animals has been completed, physicians must bear in mind that sleeping tablets, tranquilizers, and other apparently innocent drugs may do terrible harm to the rapidly growing embryo and the unborn child.—HELEN B. TAUSSIG, M.D., *Johns Hopkins Hospital, Baltimore, Md.*

(*This editorial is based on a longer editorial to be published soon in the* New England Medical Journal.)

[From American Journal of Obstetrics and Gynecology, St. Louis, vol. 84, No. 7, p. 979, Oct. 1, 1962]

PHOCOMELIA AND THALIDOMIDE

To the Editors:

This is a comment with reference to the article, "Phocomelia," by P. M. Dunn, A. M. Fisher, and H. G. Kohler of Birmingham, England, as well as your editorial in the same issue (August 1). As part of a government mission to Europe to inspect these babies, I think the magnitude of the tragedy can scarcely be overstated.

At the end of November, 1961, when the possible relation between thalidomide and phocomelia was reported, the drug was withdrawn from the West German and British markets. Nevertheless, the incidence in West Germany is terrific. The most conservative estimate is that a minimum of 3,500 infants will be born with phocomelia by August, 1962, 8 months after the withdrawal of the drug.

Phocomelia has appeared where the drug has been available. Thus, the British Commonwealth has several hundred cases of phocomelia. Sweden has reported 25 cases with 100 per cent history of Contergan. Belgium has a number of such cases; Softonon is sold there. Italy has recently reported 5 cases in 5 weeks. Brazil has an epidemic of phocomelia related to thalidomide. Canada had both Talimol and Kevadon and, unfortunately, these drugs were not withdrawn until April 1, 1962; therefore, it will be November before the last of these unfortunate babies have been born. The United States Army of Occupation in West Germany has been spared because the United States Food and Drug Administration refused the application of the Merrill Company to market Kevadon and no drugs are permitted in the United States military services which have not been approved by the Food and Drug Administration. A few cases, however, will undoubtedly occur in the United States as travelers from other countries have bought the drug abroad and brought it to this country.

The Food and Drug Administration would probably have permitted the sale of thalidomide had the drug been invented in this country because it was the finding that the long-continued use of the drug had caused polyneuritis in adults, combined with the advertisement by the Merrill Company that in addition to being a sedative the drug was an antiemetic in pregnancy, which led to the refusal of the Food and Drug Administration to permit the sale of the drug in this country, as Dr. Kelsey did not think it had been proved safe for pregnancy. The routine testing for the teratogenic action of drugs has not been required in this country. Indeed, it still remains to be seen how easily the teratogenic action of the drug can be produced in animals. The injury occurs as the embryo is developing; thus, the damage is done early in pregnancy—often before the woman knows that she is pregnant. Therefore, women of the childbearing age must be taught to stay away from drugs.

Physicians in Germany, England, and Canada are urging that careful records be kept of *all* drugs taken by women during pregnancy, and that this information together with a report of the infant's condition be sent to a central computing office in an effort to detect any untoward effects of drugs.

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Department of Pediatrics,
The Johns Hopkins University School of Medicine.

[From Circulation, March 1963, Vol. XXVII, No. 3]

EDITORIAL [1]—THALIDOMIDE

The effects of the thalidomide upon the unborn child are now well known. Even though the precise mechanism by which thalidomide impairs growth remains to be explained, it is clear that thalidomide has totally different effects upon the adult and the embryo.

For man, it is an excellent sleeping tablet but its long-continued use injures the nervous tissue and causes polyneuritis. In the growing human embryo it injures the mesenchymal tissue and causes phocomelia and abnormalities of the internal organs. In most laboratory animals the drug is ineffective. It has, however, now been shown that the absorption of thalidomide varies greatly in different animals. Rabbits fed 75 times the dose given to humans have a blood level three times that normally found in man after a therapeutic dose of 100 mg. These high doses have caused phocomelia in the offspring of rabbits when fed to a pregnant rabbit at the critical time.

It is important to appreciate that injury to the embryo occurs during a relatively brief specific time, i.e., the time when the limb buds are forming. Thus the drug can be taken at other times during pregnancy without injury to the child. The number of women who may be immune and may be able to take the drug during the "sensitive" period and have a normal child is not known. Nevertheless, a single dose of 100 mg. of thalidomide during the "sensitive" period, which for woman appears to be between 28 and 42 days after conception or the thirtieth to sixtieth day after last menstrual period, may cause severe injury to the fetus. A single dose of 50 mg. is suspected of causing injury; even as little as nine daily doses of 30 mg. of thalidomide have been known to cause severe deformity of the offspring.

The problem concerning the safety of drugs will require much difficult research and much careful testing. In the final analysis one cannot be certain of man's reaction to a drug until it is given to man. Nevertheless, a number of excellent suggestions have been made.

It has been suggested in Germany and England that a record be kept of all drugs taken by women during pregnancy and that the report, together with the infant's condition at birth, be sent to a central computing office. Such a system would permit the detection of gross malformations that were readily apparent at birth. The cards should be set up in such a manner that subsequent information concerning mother and child could be added thereto, so that the late effects of drugs and more subtle abnormality might be detected.

The above suggestion is excellent. It would seem wise, eventually, to have some similar arrangement for testing *all* new drugs that have a systemic

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[1] From the Department of Pediatrics, The Johns Hopkins University School of Medicine, Baltimore, Maryland.

reaction. Such an undertaking is difficult; the difficulty, however, should be considered as a challenge. A central regulatory agency is necessary. A central office need not necessarily be a government office but it must be a disinterested central regulatory office with no financial interest in any drugs or substances coming within its province to evaluate.

Another excellent plea has been made in England, namely, that the law be changed in regard to prescriptions. The present law in England and the custom in our country is *never* to put the name of the drug on a prescription unless requested by the physician. The reverse is recommended. In England one woman, after she had had one infant born with phocomelia, unknowingly because no name was on the bottle, took Distaval in a subsequent pregnancy and has two children with phocomelia. To prevent such catastrophies, it would be wise always to have the name of a drug on a prescription, unless requested by the physician that the name be withheld.

Our concern should not be limited to our own country. Communications between nations is important. The fact that thalidomide was withdrawn from the German and English markets at the end of November and early December 1961 and was not withdrawn in Canada until the end of March 1962, and in Italy or Japan until the end of May 1962, shows a basic difficulty in communications. Thalidomide was marketed under at least 52 different names. To my certain knowledge phocomelia has occurred in 19 countries following the use of thalidomide. A number of countries have no food and drug regulations. The only way the doctors hear of untoward effects is through articles appearing in medical journals. Consequently warning reaches them 6 to 18 months late. It takes time for the investigator to amass the information. Frequently it takes 6 months or more for publication and another month or two for perusal of the journal in a distant land. It is fundamentally wrong that a drug suspected of a serious untoward reaction should be permitted to circulate in foreign lands after it has been withdrawn in other lands, especially when withdrawn by the firm that originated it. Communication of unfavorable and untoward reactions is quite as much the responsibility of the medical profession as is the spread of beneficial results of therapy. Furthermore, the great number of trade names under which a drug may be marketed presents a problem. Indeed, it is difficult for the physician in one land to know that a drug discussed under an entirely different name from any in their country is the same or similar to some preparation in their country. To avoid such difficulty, some central office of information appears necessary.

As we learn the dangers that drugs can cause in early pregnancy, the assumption should *never* be made that only during embryonic growth is it possible to injure the unborn child. Gross malformations occur as the embryo is developing. Serious abnormalities in function *may* occur later in pregnancy as a result of injury to the various organs of the rapidly growing fetus. Injury to liver function may not necessarily be evident at birth. Injury to the gonads might pass unnoticed until puberty; injury to the brain might be even more difficult to detect. Injury to the chromosome is yet more obscure.

Therefore, women must learn to abstain from all unnecessary drugs throughout pregnancy. Indeed, women of the childbearing period should learn to abstain from drugs because the injury to the fetus may occur before the woman knows she is pregnant.

It should also be remembered that just as x-ray and radioactive fallout may injure both sexes, drugs may yet be developed that may injure the sperm. Therefore, men, too, should be cautious about drugs. We must all learn not to clamor for new and more potent drugs. Furthermore, people must learn not to prescribe glibly to one another and not to take drugs over the back fence. What is good for one is not necessarily good for another. Caution concerning drugs may strengthen our future generations.

HELEN B. TAUSSIG.

Senator NELSON. That concludes the hearing for today. We will adjourn until 10 o'clock tomorrow morning.

(Whereupon, at 11:45 a.m., the committee adjourned, to reconvene at 10 a.m., Wednesday, November 29, 1967.)

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