Linked to Malformed Babies

'Heroine' of FDA Keeps Bad Drug Off of Market

By Morton Mintz
Staff Reporter

This is the story of how the skepticism and stubbornness of a Government physician prevented what could have been an appalling American tragedy, the birth of hundreds or indeed thousands of armless and legless children.

The story of Dr. Frances Oldham Kelsey, a Food and Drug Administration medical officer, is not one of inspired prophesies nor of dramatic research breakthroughs.

She saw her duty in sternly simple terms, and she carried it out, living the while with insinuations that she was a bureaucratic nitpicker, unreasonable — even, she said, stupid. That such attributes could have been ascribed to her is, by her own acknowledgement, not surprising, considering all of the circumstances.

What she did was refuse to be hurried into approving an application for marketing a new drug. She regarded its safety as unproved, despite considerable data arguing that it was ultra safe.

It was not until last April, 19 months after the application was filed with the FDA, that the terrible effects of the drug abroad were widely reported in this country. What remains to be told is how and why Dr. Kelsey blocked the introduction of the drug before those effects were suspected by anyone.

The Washington Post

DR. FRANCES O. KELSEY
. . . skepticism wins

Dr. Kelsey invoked her high standards and her belief that the drug was "peculiar" against these facts:

The drug had come into widespread use in other countries. In West Germany, where it was used primarily as a sedative, huge quantities of it were sold over the counter before it was put on a prescription basis. It gave a prompt, deep, natural sleep that was not followed by a hangover. It was cheap. It failed to kill even the would-be suicides who swallowed massive doses.

And there were the reports on experiments with animals. Only a few weeks ago the American licensee told of giving the drug to rats in doses 6 to 60 times greater than the comparable human dosage. Of 1510 offspring, none was delivered with "evidence of malformation."

In a separate study, one rat did deliver a malformed offspring, but the dosage had been 1200 times the usual one. Rabbits that were injected with six times the comparable human dose also were reported to have produced no malformed births.

Recently, the FDA publicly

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Vital FDA Delay Keeps Bad Drug Off of Market

decried the "excessive contacts" made with its personnel by pharmaceutical manufacturers who are anxious to speed the agency's handling of new-drug applications.

Many Requests

So it was not at all surprising that dozens of contacts were made with Dr. Kelsey by representatives of the American licensee for thalidomide, the chemical name for the sedative. They had what they strongly believed was a clear and overwhelming case — but Dr. Kelsey delayed, and delayed, and delayed.

They visited her in her drab, furnished, bare-floor office in an eyesore Tempo on Jefferson dr. sw. They phoned. They submitted a flow of reports and studies. It was apparent that substantial investments and substantial profits were at stake. And all of this was routine.

The application had come to Dr. Kelsey—simply because it was her turn to take the next one—in September, 1960.

The European data left her "very unimpressed." In an interview, she said she had "lived through cycles before" in which a drug was acclaimed for a year or two—until harmful side effects became known.

And, she said, she could not help regarding thaladomide as "a peculiar drug." It troubled her that its effects on experimental animals were not the same as on humans—it did not make them sleepy.

Same Questions

Could there be danger in those few people whose systems might absorb it? Could there be a harmful effect on an unborn child whose mother took it? (In other countries obstetricians were innocently prescribing it as an anti-emetic for pregnant women.)

Dr. Kelsey regarded the manufacturer's evidence of thalidomide's safety as "incomplete in many respects." The drug was not, after all, intended for grave diseases, or for the relief of intolerable suffering, but primarily for sleeplessness, for which many drugs of known safety were already on the market.

All of this being so, she saw no need either to hurry or to be satisfied with the approach that, nine chances out of ten, it's safe. She was determined to be certain that thalidomide was safe ten times out of ten, and she was prepared to wait forever for proof that it was.

When the 60-day deadline for action on the application came around, Dr. Kelsey wrote the manufacturer that the proof of safety was inadequate. Perhaps with an understandable feeling of frustration the manufacturer produced new research data, new reasons for action. Each time a new 60-day deadline drew near, out went another letter: insufficient proof of safety.

Upheld by Superiors

Dr. Kelsey's tenacity—or unreasonableness, depending upon one's viewpoint—was upheld by her superiors, all the way.

Although she takes her work seriously indeed, her contacts with applicants are, in her words, "usually amiable. We see their point, and they see ours. But the responsibility for releasing a drug is ours, not theirs." And that is the responsibility she would not forget.

In February, 1961, she chanced to read, in a British medical journal, a letter from a British doctor questioning whether certain instances of peripheral neuritis—a tingling and numbness in the feet and the fingers that is sometimes irreversible—might not be due to intake of thalidomide. To her this was a danger signal.

She called the letter to the attention of the applicant. His investigators reported that the incidence was apparently negligible, one case among 300,000 adult users. Six months later, Dr. Kelsey said, the incidence among adults who took thalidomide regularly for months at a time was found to be 1 in 250.

But neither she nor the applicant yet had the slightest inkling that the drug could be responsible for the birth of malformed babies. That awful circumstantial evidence became known to the applicant—in a cablegram from Europe—on Nov. 29, 1961.

Application Withdrawn

He reported it to Dr. Kelsey early the next day. Although this was followed by a formal withdrawal of the application, as late as last month the applicant described the birth abnormalities as "alleged effects" of thalidomide.

The story begins in 1954, six years before Dr. Kelsey, a pharmacologist as well as a physician, went to work in the FDA's Bureau of Medicine. She and her husband, F. Ellis Kelsey, a pharmacologist who is now a special assistant to the Surgeon General of the Public Health Service, came here from the faculty of the University of South Dakota School of Medicine.

For the account that follows, the primary sources were Dr. Kelsey and reports by Dr. Helen B. Taussig to a medical meeting in April and in the June 30 issue of the Journal of the American Medical Association.

pediatrics at the Johns Hopkins School of Medicine in Baltimore, went to West Germany in January to investigate the relationship between thalidomide and an enormous increase in the birthrate of malformed infants.

Eight years ago a West German manufacturer conceived of the drug, synthesized it—and discarded it after discerning no effect on test animals. In 1958 another West German firm also developed thalidomide and found it to be, by all indications, the best sleeping compound ever devised.

Large Sale

The sale was tremendous. It even came to be used for grip, neuralgia, asthma, in cough medicines and to calm children before they were given electroencephalograms.

In Germany it was marketed as Contergan, in the British Commonwealth as Distaval, in Portugal as Softenon. Dr. Kelsey's native Canada accepted it on April. 1, 1961, for manufacture by one firm under the name Talimol and by another firm, the William S. Merrell Co. of Cincinnati, under the name Kevadon. It was the 134-year-old Merrell firm that was seeking to market Kevadon as a prescription drug in the United States.

At this time—April, 1961—West German investigators were desperately groping for an explanation of an unprecedented outbreak of phocomelia, the malformation hitherto so rare that it isn't even listed in some medical dictionaries. An 86-year-old Gottingen specialist in human deformities told Dr. Taussig that he had in in his whole lifetime "seen as many individuals with two heads as he had with phocomelia."

Usually, phocomelia deprives its victim of one arm. Rudimentary fingers that look, said Dr. Taussig, "like the flippers of a seal" arise from the stub below the shoulder.

Clinic Cases

In eight West German pediatric clinics there were no cases at all between 1954 and 1959. In 1959 there were 12, in 1960 there were 83, in 1961 there were 302.

These were not the ordinary textbook cases. Not just one arm was affected. These children were without both arms, or without both legs, or without three limbs, or they were without any limbs at all.

In some, the external ear was missing and hearing was grossly impaired. There were deformities of the eyes, esophagus and intestinal tract; and even this is not a complete list.

Once the suspected link with Contergan was established, Contergan was taken off the West German market. The expectation is that the last mothers who could have taken it during early pregnancy, the danger period, will be delivered in August. The estimates are that by the end of next month the total of deformed children born in West Germany will be between 3500 and 6000. Two out of three are expected to live. Most are apparently of normal mentality.

The drug was withdrawn from the British market five days after the withdrawal in West Germany. The Guardian, Manchester, has predicted that August will see the birth of 800 deformed English children. The Ministry of Health has begun to fit 50 victims with artificial limbs.

Eight in Canada

An article prepared for the May 19 issue of Maclean's Magazine said that at the time of writing eight victims of phocomelia had been born in Canada, two of them to physicians' wives who had used "samples of thalidomide donated to their husbands."

Because the Department of Health did not order thalidomide withdrawn from sale until March 2, Maclean's said the last Canadian casualties are not expected until November.

The cause of the West German outbreak was hard to trace. Hereditary factors, blood incompatibility between parents, abnormal chromosomes, radioactive fallout, X-rays, detergents, food preservatives — all of these things, and more, were suspected, checked and discarded as possibilities.

A Hamburg pediatrician, Dr. Widukind Lenz, made preliminary studies showing that about 20 per cent of the mothers who brought deformed infants to his clinic had taken Contergan. Dr. Taussig wrote:

"On Nov. 8, 1961, it occurred to him that Contergan was the cause. He requestioned his patients and the incidence promptly rose to about 50 per cent. Many of the patients said they had considered the drug too innocent to mention it on the questionnaire . . .

Maker Warned

"On Nov. 15 he warned Grunethal (the manufacturer) that he suspected Contergan was the cause and that the drug should be withdrawn."

Five days later, at a pediatric meeting in Dusseldorf he reported his suspicions and his actions but did not name the drug. That night Dr. Taussig related, "a physician came up to him and said, 'Will it the drug Contergan? I ask because we have such a child and my wife took Contergan.'

"A couple of days later it was generally known that Contergan was the drug under suspicion. On Nov. 26 Grunenthal withdrew the drug from the market. On Nov. 28 the Ministry of Health issued a firm but cautious and widely publicized statement that Contergan was suspected to be a major factor in the production of phocomelia."

Dr. Taussig reported that an Australian physician, Dr. W. G. McBride, saw three severe cases in April, 1961, and three more in October and November. "He found that all six mothers had taken Distaval in early pregnancy," the Journal article said.

In Stirlingshire, Scotland, Dr. A. L. Spiers saw 10 severe phocomelia victims during 1961 and ultimately "obtained positive proof that 8 out of 10 of these patients had taken Distaval."

Difficult Connection

Making the connection — which some physicians say is not conclusively established—was extraordinarily difficult.

Dr. Lenz, for example, had to contend with the lack of records during the time when Contergan was sold without prescription, and with his patients' natural difficulty in recalling if and precisely when they had taken a sleeping pill months earlier.

"In one instance," Dr. Taussig wrote, a doctor "swore the mother had not received Contergan. He had prescribed an entirely different sedative. On investigation at the pharmacy . . . Dr. Lenz found the prescription was stamped 'drug not in stock, Contergan given instead'."

Dr. Taussig said the investigations of Dr. Lenz in particular indicate that the embryo is endangered if a mother takes thalidomide within about 20 to 40 days after conception, a time when she may not even know that she is pregnant.

He believes that during that sensitive period the chances that a mother who has taken the drug will deliver a deformed baby are at least two in five.

Company View

The Merrell firm says that conclusive proof is lacking for such assumptions and cites a clinic in Kiel at which, Merrell reported, half of the deformed children were delivered to mothers who probably had not taken thalidomide.

"Everyone admits," Dr. Taussig wrote, "that no information is available concerning how many women may have taken the drug in the sensitive period and have had a normal child."

Dr. Kelsey said the molecular complex of thalidomide is being broken down and studied in an effort to determine the causative agent in thalidomide.

In all of this Dr. Taussig sees compelling reason for caution in the use of new drugs by women of child-bearing age. A Canadian physician interviewed by Maclean's said, "There is too much demand on the part of the public for relief of mild or even moderately severe symptoms. People won't put up with even the slightest discomfort or headache; they demand medication from their doctor. If they can't get it from one, they'll go to another."

Dr. Taussig also wants the 1938 Food and Drug Act strengthened to provide greater assurance that new drugs will not harm unborn children. But to Assistant FDA Commissioner Winton B. Rankin, the significant thing about the law is that it gave Dr. Kelsey the weapon she needed to block the marketing of thalidomide in the United States.

"The American public," he said, "owes her a vote of thanks."

The 47-year-old Dr. Kelsey lives at 5811 Brookside dr., Chevy Chase, with her husband and daughters, Susan, 15, and Christine, 12.

She is grateful for the praise—but recognizes that, had thalidomide proved to be as safe as the applicant believed, "I would have been considered unreasonable."

She intends to go on "playing for that10th chance in 10" to assure safety in new drugs "to the best of my ability." For 20 years she taught pharmacology. She knows the dangers, and she has not the slightest intention of forgetting them.