

AUTOBIOGRAPHICAL REFLECTIONS

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AUTOBIOGRAPHICAL REFLECTIONS¹**Frances O. Kelsey, Ph. D., M. D.**

In thinking about my life, I recall a letter I received in 1987 from an eighth grader in Vermillion, South Dakota, and I remember this for two reasons: first, we had lived in Vermillion, and my daughters went to the Jolley School where this girl was an eighth grader. But, second, because she asked me some questions that I did not feel I answered very well at the time she asked them, and I thought I might weave the answers into my reflections. The girl had to give a speech at her school on a woman who had a career in spite of obstacles. She had gotten a little background information on me from the library and seemed to have done a good job. She asked me for a few more facts, but what drew me up short was when she said: "But, most of all, perhaps you could describe how hard it was to be a woman studying science and medicine when most of your classmates were men. Perhaps you could also tell me how frustrating it must have been to find work when most people thought a woman should only be a housewife." So I thought in reflecting on my life and my

¹ Editorial note: This was drawn from the following: oral history interviews conducted in 1974, 1991, and 1992; presentation, Founder's Day, St. Margaret's School, Duncan, B. C., 1987; and presentation, groundbreaking, Frances Kelsey School, Mill Bay, B. C., 1993. The FDA History Office is indebted to Dr. Caroline Hannaway for her work in merging these sources in the present document.

introduction to the study of drugs I would give an overview as what she might have considered obstacles, but more important about how good fortune always seemed to come along at the right moment, just when I thought I was down on my luck. One probably should not tell people to "trust luck and you will get along in life," but it worked pretty well as far as I was concerned.

Early Life and Education

I was born in Cobble Hill on Vancouver Island, British Columbia, Canada, in 1914. My father was an officer in the British army and retired to Canada; that is why I was born in Canada. I was named Frances Oldham and was known as Frankie. Things were somewhat different in those days. The roads were narrow and we did not get a car until I was nine years old. We were dependent on a horse and buggy to get around. My mother taught my older brother how to read and write, and I just listened in and picked it up. For the next two years we traveled and I went to schools both in Victoria, British Columbia, and in England.

I think I was used to being in a class with men because the first school I started out in, Leinster Preparatory School, a small private school in Shawnigan Lake, British Columbia, was theoretically an all-boys school, and for several terms I was the only girl. Later more girls were present. So I started off in the atmosphere of boys, particularly since I had a brother who was two years older.

The school was run by two Irishmen, a father and son, and there was no grade structure. You worked to the level of your ability and the ability of the teachers. I learned a lot of Latin and some algebra and geometry, but the school was a little weak on things like history, French, and English. The school was in existence for about three years until the Depression, I think, foundered it. After a year of private coaching by Marjorie Gillette, I went off to Victoria to finish up eighth grade and high school.

I did get some very important and useful lessons in Cobble Hill while I was still at home. I had painting lessons in a class run by Connie Bonner. We largely painted flowers and birds. I took piano lessons from Mrs. Edna Baiss. She was a concert pianist in Ireland before she and her husband James came to British Columbia to run a poultry farm just outside Cobble Hill. I took dancing lessons in the old Wilton Hotel. A series of people ran it, but the person I remember best was a young instructor not much older than myself named Dorothy Bird. The Birds lived at Mill Bay and she was extremely talented. She went off to study at the Cornish School in Seattle and then to New York where she worked for many years with Martha Graham. The last time I saw her, she was organizing a class in modern dance in the Long Island Public School System. In another area, I owe part of my early education to my old friend Jerry Mudge, who taught me how to shoot and fish and, without my parents'

knowledge, gave me my first driving lessons.

I graduated from high school at the age of fifteen. This might seem young, but there were two things to explain it, one was this good beginning I had had, but the other was that we only had three years of high school in those days, so you did eleven years to get through a little earlier. I think the year after I graduated high school became four years. My family thought I was a little young to go to college, and so the school was somehow talked into putting on "Senior Matriculation." In those days you could do first-year college in high school, and it was called "Senior Matric." I do not think that is a possibility now. I knew I wanted to go on to university, but I had not much idea what it involved. My mother had two sisters, one was a doctor and one was a lawyer. In those days, of course, they did not practice very much, but they felt that their lives were greatly enriched by their extra education. My aunt who was a doctor took her training and then married a doctor, but she did do some laboratory work.

I was very surprised when I looked back at my high school scores to see that I got honors in all things: composition, Latin authors, Latin composition, French translation and French grammar--nothing about science. All I had taken was chemistry and math, and chemistry lost me when we came to the Law of Mass Action. I knew I wanted to go into science, but not in chemistry; I thought it would be biology. I had no idea what

biology was about, or where I could go for help. We did not have college counselors at the school at that time. Universities did not go around "drumming up" students, and few of the girls in those days went on to college. I do not say none did. Some of them went for a year or two, admittedly for the social life. Other popular careers at that time were nursing and business college. Some girls did go on, but not enough to give me the idea to do so.

So here I was a bit in the dark and stuck another year in school with only chemistry for science, and then I had a very lucky meeting in the summer, just before I was due to go back to school, with a young biology teacher, Dr. Anthony Kingscote. At that time he must have been in Guelph (the Ontario College of Agriculture) returning for a holiday. He was already starting his career as a parasitologist. He heard of my interest in biology and gave me a most marvelous overview of the field during a picnic. We went along the beach finding all these orders of animals and so on. Then he said there was one thing I had to do:

I had to take biology in my first year of college so I could take zoology in my second, and then in my third and fourth years I could specialize and have a really good degree when I was through.

This threw me into despondency because I was obliged to go back to school and biology certainly would not be taught there. But it was arranged that I would go to Victoria College, drop

Latin, and take biology. That was great. The wonderful teacher there, Jeff Cunningham, really stimulated me, and, if I had gone to the University of Victoria or to the University of British Columbia, I am sure that I would have been a marine biologist.

There was one little hitch; I had to wear a school uniform, and I must have looked awfully funny in my navy blue tunic, white shirt, and long black stockings amongst all the coeds at Victoria College dressed up to the nines. That was not the day of blue jeans in college--students dressed up. Here I was week after week in this same attire, but it was worth it and I enjoyed it.

The second year I took zoology at Victoria College, went on to McGill University in Montreal, and took specialized courses with professors who were more widely known than Jeff Cunningham at Victoria College, but not to my mind nearly as stimulating. Come my senior year I wondered what would I take in biology, and here another lucky chance arose. A friend of mine was engaged to a medical student, and he said, "Why don't you try a little human biology and then take some courses with the medical students." So I signed up for biochemistry, which included some endocrinology, physiology, and pharmacology. Now pharmacology was an afterthought because I already had more credits than I needed for graduating. Somebody said "It is a very interesting course. You really ought to take it." I said, "Fine," and I signed up for it, and it was very interesting. Pharmacology, I should explain, is the study of the way chemicals act on the

body. That is a general definition and more specifically one thinks of it as the way drugs act on the body--substances that are used to cure, treat, or prevent disease, and, of course, today the recreational drugs.

Come graduation with my B.Sc., I thought my biochemistry would make me the appropriate person for a laboratory to hire, but this was the depth of the Depression. There were absolutely no jobs, and the few openings that there were almost invariably filled by men. I do not think that this was due to any particular prejudice against women. The general explanation was that men would be the supporters of the family and therefore they should have jobs first. I do not think there was a particular grievance at that time that women were overlooked, and certainly there were many men graduates who had no job to go to. This situation led me to realize that my choices were either to do graduate studies or to join the bread line. Those were about the only alternatives in those days, and I decided graduate work would be more interesting.

A person might wonder why I did not decide that in the first place. Well, I was little awed. I thought one had to be really bright and brainy to be a graduate student, and, of course, that is not the case if one is interested in one's subject. Also, in those days, since there was no work to get, there was no reason to hurry to get through graduate school. Graduate students stayed on and on at a low salary, working very hard at teaching

and not getting all the research done that they might. Finally, I thought it was probably a good idea to go to graduate school and get a Master's degree.

The department I wanted to get into was biochemistry, because this was a very exciting time in the field of endocrinology. Endocrine glands pour out their secretions--or hormones--into the blood stream, and then these act at a site distant from the gland itself. The biochemistry department at McGill was working on the pituitary gland, and until about four or five years earlier, the only thing that people thought the pituitary gland did was to influence growth. Tumors would produce very tall people, absent the gland gives dwarfs. Then, in the very early 1930s, it was discovered that all sorts of exciting things were coming out of the pituitary, all sorts of hormones that stimulated other glands: the thyrotropic hormone stimulates the thyroid, the gonadotropic hormone stimulates the gonads, and so on. So the pituitary gland got the name of the master gland or, more picturesquely, the conductor of the endocrine orchestra.

I thought that was great and that I would like to work in that field, but when I went to the biochemistry department I learned there was not any space available, all the places were filled. I was obviously very disappointed and the professor, taking pity on me, said, "Why don't you go upstairs to the pharmacology department. Dr. Raymond Stehle is working on the

posterior lobe of the pituitary and he does not like graduate students very much, but he might take you." I went up to the pharmacology department, said what I would like, and I was somewhat surprised. Dr. Stehle said "Fine, then you can be my graduate student for a year. I am not very good with graduate students or I don't enjoy them very much, but I would be very happy to give you all the help I can."

I should explain that at that time the posterior lobe was a very drab sort of affair, and the posterior and anterior are so close together in humans and other animals that you cannot exactly separate them. The posterior pituitary is actually connected to the brain by a little stalk, and if one looks at it under the microscope it looks just like brain tissue. If injections of that are made, there are some very quick, short-term effects. A rise in blood pressure, for example, is one effect, as is stimulation of the uterus. Another effect is to cause a let-down in dairy cows so they give their milk more readily--important in a dairy country like Canada.

This lobe did not have the glamour in those days of the anterior pituitary, so there was no one else working with Dr. Stehle. But I had anticipated the interest, and in the last ten or twenty years the posterior pituitary has come into its own. At that time it was not thought that the brain could give rise to secretions, but now it is an accepted fact that it does. We now know the posterior lobe secretions actually control the anterior

lobe, so I do not know whether it should be called the super conductor or what. That was not so in my day; it was not a particularly prominent organ to work on.

There were two problems about it. One was whether all these different effects were caused just by one chemical or by several forms. That is what Dr. Stehle and colleagues were working on. The other problem was where these chemicals came from. Did they indeed come from the brain, or did they come from the anterior lobe and just drift into the posterior lobe? That is the research I came to later. With Dr. Stehle, I studied the effect of the posterior pituitary on the water balance of frogs and that was the topic of my thesis. For a year I sat surrounded by frogs in little cages set in water. I would lift them up, dry them, weigh them, inject them, put them back in the water, and then weigh them at 15 to 20 minute intervals for four hours. I would get the most beautiful curves on graphs, and I was able to find out which part of the extract caused this particular effect. Then I did many other things for Dr. Stehle, like learning how to do the assays for various other activities. There was so little of this substance and chemical methods were not sensitive enough in those days, so a biological test had to be used.

I got my master's degree in a year. Then what? It was the same situation, no work. Dr. Stehle had a small grant and he said "I will give you \$50 a month to be a research assistant, and you keep looking for a position. As soon as you get something

better, you be sure and take it." Believe it or not, \$50 a month was a sum that one could live on, not lavishly, but adequately. So, I lived on that and continued working with Dr. Stehle on the posterior pituitary.

In February 1936 he said to me, "I just learned that they are opening a new pharmacology department at the University of Chicago, and the professor who has been hired as chairman, Dr. Eugene Geiling from the Johns Hopkins University, has also been doing work on the posterior pituitary gland. He may want help when he goes there. Why don't you write and tell him what you have been doing. Ask him if he wants a research assistant or explain that you will be interested in getting a Ph.D., and perhaps a fellowship or scholarship." So I did. Postage was three cents in those days. Not much was lost, and my hopes were not very high, but to my great surprise I got back a letter Air Mail, Special Delivery, on February 15 (I remember the date). It said: "If you can be in Chicago by March 1st, you may have the Research Assistantship for four months and then a scholarship to see you through a Ph.D. Please wire immediate decision."

There was just one thing that bothered me a little about that letter. It started out, "Dear Mr. Oldham," and here my conscience tweaked me a bit. I knew that men were the preferred commodity in those days. Should I write and explain that Frances with an "e" is female and with an "i" is male? Dr. Stehle said, "Don't be ridiculous. Accept the job, sign your name, put Miss

in brackets afterwards, and go!" That is what I did, and, to this day, I do not know if my name had been Elizabeth or Mary Jane, whether I would have gotten that first big step up. My professor at Chicago to his dying day would never admit one way or the other.

Research, Professional Development, and Family in Chicago

Dr. Geiling was very conservative and old-fashioned. He really did not hold too much with women as scientists. But he was very fair and a number of women graduated from his department while he was professor at Chicago. I was his first Ph.D. student. I went to the University of Chicago in March of 1936. The graduate school was on the quarter system, so I had a month there and then entered in the spring quarter.

The work that Dr. Geiling was doing concerned whether these posterior pituitary hormones came from the posterior lobe or the anterior lobe. He felt, being a pharmacologist--and we all had some inkling--that nerves did have a special chemical for transmission. He did not think it unreasonable to think that nerve tissue could make hormones; other people thought otherwise.

He thought one way to prove his point would be to find an animal in which the anterior lobe and the posterior lobe were completely separated so that it could not be said that the activities would diffuse from one to the other. By the time I worked for him, he had found this to be the case in the armadillo, the whale, the porpoise, in birds, and seals. My work was with the armadillo,

and that is what I did my Ph.D. on: the anatomy and the pharmacology of the posterior pituitary gland of the nine-banded armadillo.

The armadillo is not one of your common laboratory animals, I can assure you. I could say that nobody before or since has worked on it, but that is not quite true. It was of some interest, because for some reason or another they always had genetically identical quadruplets, so the geneticists were interested. Then, lo and behold, about 1972 it was discovered that the armadillo is the only animal that can be extensively infected with leprosy. Here was an animal that could be used in studying leprosy, the lesions and all, and the drugs that might be effective. So like the posterior pituitary, the armadillo came into its own. I might add another very strange coincidence, from about 1960. A doctor in Israel who was treating leprosy patients for sleeplessness found quite accidentally that thalidomide relieved their pain and caused regression of the lesions. Today thalidomide is one of the main drugs used in treating leprosy, which illustrates that even the worst of drugs may be used under certain circumstances where the risks are justified.

I did my Ph.D. on the adult armadillo, receiving my degree in 1938, and then a year's post-graduate study on why these two lobes were separate. That meant studying the embryos. Armadillos have a very weird cycle and there is no way they can

be bred in the laboratory. We had to get our supplies from Texas at that time. Possibly that is still done. There was an armadillo farm in Texas, very close to the Lyndon Baines Johnson ranch. They used to ship the armadillos up to us. On one occasion when I wanted to study embryo armadillos, I had to go down to the armadillo farm in Texas to hunt and catch a few to get my embryonic armadillos.

Before I leave this period of graduate work, I would like to describe two pieces of work which actually I did out on the West Coast. One was work with whales, and the other was involved the ling cod, rather different animals. As I mentioned, Dr. Geiling, my major professor at Chicago, had found that the whale pituitary had only these two lobes and even before he came to Chicago, he had located the whaling stations in the Queen Charlotte Islands, one in the northern island at Naden Harbor and one at the south at Rose Harbor. Each summer, he would take students or guests, professors or technicians, out to the whaling stations and collect pituitaries, plus other organs. Once people knew we were doing work on whales, they said "Oh, please, bring me back an adrenal or please bring me back a heart." Hearts, which weighed 200-300 lbs., could not be brought back, but still we always tried to oblige.

During two summers I got to go to the whaling station at Rose Harbor. Once was with a medical student who took good photographs. The second time, I was by myself. The visitors

would stay at the manager's house, eat in the bunkhouse with the managerial staff, and then we were free to wander around the whaling plants and get material as we wanted.

The whales were caught by 90-foot boats. I think they had a crew of about 11 or 13, and the harpoon gun was at the bow. Now the great adventure each year, for the scientists going out there, was to be able to go out in the whale boat. The first year I was there, I heard every excuse under the sun, "It was a bad day, this, that, and the other," and I could not go in the boat. The second year I was able to go and I think, in part, it was because the son of the manager was spending his summers working on that boat, and he was to keep an eye on me. It was a lovely day, early in the morning, and he very kindly took me up in the barrel with him and we spotted a sperm whale. The different kinds of whales can be distinguished by the spout. I cannot remember the differences now, but I know that is how you tell. We directed the helmsmen, the harpooner, and everything, and we got the whale. Now, I did not realize how lucky I was, because I learned the reason I had not been able to go before was that whalers are very superstitious, and one of the superstitions was that having a woman on board a whaling vessel brings bad luck. This was important to the crew because a certain amount of their pay was based on the number and type of whale that was caught. At least I think I broke that jinx. I did score another mark for women in that I was the only scientist taken out on

these whaling expeditions who was not violently seasick.

The second venture on the West Coast, involving the ling cod, was of a somewhat different nature. It had to do with the fact that it was known that the pancreas had a rather unusually high level of zinc in it compared to other parts of its body. It was not a dramatically high amount, and it was quite difficult to measure because it was so slight. But it was distinctly higher than in certain other parts of the body. The pancreas, like the pituitary, really is a two-part organ. There is the main body, the main pancreas, that secretes the digestion enzymes and pours them into the intestine, and then scattered amongst these are little islets of tissue that were long thought to be where insulin came from. But this was pretty hard to prove because, when the pancreas was ground up, the enzymes ate up the insulin so there was nothing to be measured. That was a problem.

The question of where the insulin came from was solved very neatly by Dr. Macleod, who was at the University of Toronto, and later, of course, got the Nobel Prize for his work on insulin. He was aware that in certain fish the islet tissue was an entirely separate organ (a little sort of pea-like body) quite apart from the rest of the pancreas. He extracted these little islets and sure enough he was able to get the blood sugar lowering effect of insulin. That clinched the question of whether the insulin came from these tissues.

Dr. Geiling and Dr. E. W. Schoeffel, a microchemist at the

American Medical Association were curious as to whether this was actually in the part of the pancreas excreting the enzymes or in the part that made the insulin. They thought one way to find out would be to go back to the fish that had these separate organs, and analyze them. There was a public Canadian publication that described this, and the ling cod was one species that had the separate pancreas.

I had jigged (not very successfully) for ling cod off Mill Bay. So I rather rashly volunteered to collect islet tissue during my summer vacation. I set off with these bottles, preservatives, and so on. They had to be explained to the customs, which was a little difficult, but I did, and I knew with my luck in fishing I could not possibly get enough by jigging. I went to see where the commercial ling cod fishing was done, in Mysteria. This was in 1937 or 1938, I am not quite sure. I was told it was all done by Japanese fisherman. Then I thought of my friend, Commander Guy Windeyer. I knew he spoke Japanese fluently and I knew he was friends with many of the prominent, well known Japanese in the area. Sure enough, in next to no time, he had fixed with this very fine fisherman, to pick us up at Crofton or Chemainus at dawn. Guy Windeyer, myself, and my young brother went, and Guy Windeyer's niece was also, I remember, another one on this expedition. She was a visitor from London. The fishermen would slaughter for the weekly market, tens or hundreds, I do not know how many, of these cod and the

entrails would be spread out all over the deck. There we were down like soothsayers poring over the entrails looking for these tiny little nubbins of tissue. We did get enough of them, sent them back, and sure enough the zinc was in the islet tissue and not in the acinar tissue.

Now let me describe my first introduction to problems with new drugs. That occurred not long after I had come to the University of Chicago. In fact it was in September of 1937. This is known as the "Elixir of Sulfanilamide Tragedy" and this was the equivalent of the thalidomide tragedy but at an earlier date. I should explain that the U.S. food and drug laws came in 1906, but they were primarily directed towards foods. Foods were then usually prepared in the homes, but they were beginning to be mass produced. Refrigeration was poor, the foods were filled with preservatives, and so on. They were very unhealthy and unpleasant, so the laws were to make things better in that line.

With regard to drugs, there were not many drugs available, because America had been busy with the Civil War, medicine was at a pretty low ebb, and most of the drugs were nostrums, patent medicines, and so on. There was one serious problem, many of the drugs contained (although it was not in the labeling or anything) such addicting substances as morphine, heroin, marijuana, and so on. I have read statistics that the rate of addiction in those days was as high as it is now, but, of course, people were not aware then that they were inadvertently taking these addicting

drugs. So one of the requirements of the 1906 Act was that the presence of all 13 of these substances had to be noted in the labeling and the second was that the drugs should be labeled honestly. Research in drugs picked up during World War I and afterwards. There were a lot of new and active drugs and some quite toxic ones, but the old law still held (although many people tried to change it, quite unsuccessfully), and then came this episode.

Sulfanilamide had been introduced about 1933 in Germany. It was the wonder drug; it completely changed the face of medicine.

Here was something that would actually attack some infectious germs and save many lives. People, who previously would have died of pneumonia, or streptococcus or staphylococcus infections and so on, were saved by this new drug. It caught fire, and its use spread very rapidly all over the world, so fast that no basic scientific work had really been done on this drug. But it had drawbacks, the patient had to take a large dose, the pills were pretty unpalatable and disagreeable to take, it caused gastrointestinal upsets, and so on.

One manufacturer had a great idea. It was decided to put up a liquid solution, which would be easier to take and would be particularly agreeable to children. Now the drug is not soluble in either alcohol or water, which most drug solutions are made up in, so the company officials had their chemists go along the shelf and find a solvent that would dissolve the sulfanilamide.

I guess the first thing the manufacturer found that was successful was diethylene glycol, which is antifreeze. This was never tested in animals and the liquid form of the drug was just put right on the market. A little pink coloring and a little cherry flavoring was put in it, and it sold like wildfire. It was a great boon especially in the South where they like liquid medicines and find them easier to take, and of course it is easier for children too. Then, the reports came in of fatalities. One doctor in a small town had five patients die in a short space of time. They had all taken this drug. People knew so little about sulfanilamide that they were not sure whether it was the sulfanilamide or the solvent that was causing the deaths.

The Food and Drug Administration immediately went around and seized all the stocks in bottles that it could get. But they did not have the scientific staff or expertise at that time to use in running the culprit to earth nor did they have the laboratory facilities. Dr. Geiling had worked with the Food and Drug Administration previously, when he had been in Baltimore, helping them in other cases, some of which he used to describe in his toxicology classes. So the FDA called him up and said "Help us out!" He said he certainly would, and in this instance, he worked very closely with the American Medical Association, which in those days had very good laboratories and very good people evaluating new drugs.

Dr. Geiling immediately set up animal studies for acute and

chronic toxicity--dogs, rabbits, rats, and, I think, some monkeys. He could see the importance of those cases. None of the rest of us really could, I suppose being fairly new in the area. And he was well aware of the inadequacy of the 1906 law. So he required that all the graduate students pitch in and play some role, small though it might be, in these animal experiments.

My particular task was to watch the rats. Dr. Geiling set up cages of rats and they were sitting--I can see them yet--on big glass funnels that led into glass beakers, graduated cylinders, that measured the volume of urine. The rats were variously treated. One lot, for example, got the sulfanilamide alone; one the diethylene glycol alone; one got the extract of what was sold on the market; one got the flavoring and materials; and one got a liquid with nothing wrong with it at all. Finally the last lot got the mixture we made up in the laboratory, diethylene glycol and sulfanilamide. In no time at all, it was perfectly apparent that it was the diethylene glycol that was at fault. For all the rats getting mixtures with diethylene glycol in them, one could see the urine gradually turn red, and then decrease in volume, and then finally stop, because the problem was with the kidneys. The rats soon died, just as the kids did.

This precipitated passage of the 1938 Food and Drug law, which was still in effect in 1960 when I went to work with the Food and Drug Administration. The 1938 law required that before a new drug was put on the market, the sponsor, or the

manufacturer, must give evidence of why he thought that the drug was safe for its proposed use or uses. The type of evidence that he was required to present was first the chemistry; what was this drug, how was it broken down, how was it stored, things like that. The second was the animal tests that he had done, and the third was the clinical studies. If the agency felt that those were satisfactory then the drug could be marketed.

Before leaving sulfanilamide, I would like to note one interesting matter, and that is that at about the time the American company was considering putting this drug on the market, a Canadian firm petitioned the Canadian Food and Drug directorate for permission to change the solvent in their vanilla extract from alcohol to diethylene glycol. The firm felt that the latter was a good substance for a solvent, but also that it would avoid excise tax. Astute pharmacologists in the Canadian government laboratories said "We don't know anything about the toxicity of this diethylene glycol, let us get a little more background." Then, of course, the word on the elixir came out and the Canadian manufacturer quickly withdrew his petition. I think it illustrates that by careful work with animals, something like the elixir sulfanilamide tragedy can be avoided. In that instance, problems would have shown up in just a few rats.

After getting my Ph.D. in 1938 and a year or two of postgraduate work, the job situation did not look much better. The Depression was still on. I did have one or two

opportunities. One was that I thought I might be able to go back to Canada, but it did not pan out. The professor could not get the necessary money for my salary (\$1,800), and it began to look a little bad. I really wondered if men had more opportunities than woman. Then World War II came. That changed the whole situation not only for scientists, but for everyone. No longer could a person hope to get by or get an interesting job without a good educational background.

Quite suddenly a group working under Dr. Geiling at the University of Chicago got involved in a big project to find new anti-malarial drugs. I would like to describe this, because I think it illustrates very well the way new drugs can be brought onto the market. The way this happened was that obviously malaria was a serious problem in war time, and of course World War II had broken out by that time. But then with the fall of the Dutch East Indies, 90 percent of the world's supply of quinine, at least for the Allies, disappeared. There was one other drug available, a German drug called Atabrine, but it was considered pretty toxic and people did not like to take it. So, there had to be a crash program to get some other treatment for malaria. An office was set up in Washington, D.C., the Office of Scientific Research and Development, and various universities and other laboratories around the country conducted the studies, which were directed from Washington. Various things happened more or less in sequence. First, of course, the government laid

its hands on all existing supplies of quinine. There was still a little malaria in the United States, and quinine was used for treating that. It was used a bit in obstetrics. It was also used in things like bromoquinine, tonic water, and so on. So the standing supplies were saved for real emergencies and also to be used as a drug against which to compare other possible antimalarials.

Chemists were put to work synthesizing Atabrine. This was soon accomplished, but it took about a year to assure the authorities that the American Atabrine was at least no more toxic than the German Atabrine. Others tried to synthesize quinine. This was accomplished, but it is such a tedious process with a low yield, that it has never, as far as I know, become economically feasible. Then everyone was asked to comb their shelves for chemicals that might possibly serve as antimalarials or have antimalarial activity. These were all to be sent to Washington where they were given a survey number and then they were sent out to the various cooperating institutions for assaying. Other organic chemists were put to work synthesizing compounds that might be like existing compounds that were known to have at least some antimalarial activity.

At the University of Chicago, we had a toxicological setup whereby the more promising drugs were fed to animals--rats and dogs, for example, and occasionally monkeys. In addition, there was a screening procedure using chickens and ducks. Little baby

chicks and ducklings were given types of malaria. The malaria was not exactly the same as the human form, but a type that responded to the drugs in the same way. I believe that during World War II something like 5 or 10 percent of all the duck eggs and ducklings in the United States were used in these screening operations. We worked mostly with chicks, and we would infect the chickens with the malaria parasite and then mix the drugs we were testing into the food, usually at several different doses. Then, as time went by, we would take blood samples from the chickens and look to see whether malaria parasites were present or absent. Also, we would observe the health and well-being of the chicks. Some of the birds were given quinine as a control.

During the course of the war, over 14,000 drugs were screened as possible antimalarials. In addition to the people synthesizing drugs for this purpose, others were asked to send in remedies. Drug firms, chemists, and pharmacists were urged to search their shelves for anything promising, and we did get some very funny remedies that people would write in about. I remember one, a dried fish that was supposed to be soaked in milk. We solemnly did that and fed the chicks with it. Another came from a veterinarian in Texas. It looked like ink and was shipped in what looked like an ink bottle. He said he was hoping to use it to treat a plasmodium-like parasite in cattle. He also said that he had just tried it on his secretary without ill effects, and he planned next to try it on cattle. When we read this, we said it

shows the relative value placed on women and cattle in Texas.

Not all of the 14,000 drugs were tested by us, of course, but by other laboratories too, not only in the United States, but also in Great Britain and Australia. It was a big team project.

We cooperated very closely with the English and Australian groups. Now, most of the people working on this project were paid by the government. I could not be, as I was a foreigner. I was not a U.S. citizen at the time, and that was useful, because those who were paid by the government were only permitted to spend about 10 percent of their time in research, and I could put 100 percent of my time into research, if need be. If that seemed appropriate I would do it, otherwise I would help in the routine screening. With any drug the pharmacologist wants to know how it is handled by the body; how it is absorbed, where it goes in the body, how high a level is in the blood, how it is broken down, excreted, and so on. We did basic work of this type with quinine and Atabrine to begin with as a prototype for other drugs.

There were fifty or so people in the various units around the country involved in this work, both in the animal work and in a group that studied the drugs in volunteers at the Statesville Prison in Joliet, Illinois. This was one of the first really good facilities for testing drugs in prisoners. The Chicago group worked closely with the parasitologists and they were the ones who oversaw the chickens and maintained the infections. Dr. William Taliaferro and his wife, Dr. Lucy Graves Taliaferro, were

very active in this. Dr. William Taliaferro was one of the first to describe what is known as the exoerythrocytic stage of the malaria parasites. The parasites are not in the red blood cells, but in the spleen and liver, and they are the ones responsible for the repeated attacks.

Our unit worked on some of the drugs that proved useful among the hundreds of others that had to be discarded. We worked on chloroquine, which is now available. But, overall, the project did not really find the answer. The substitute drugs have their unpleasant side effects. Also, strains of malaria have developed that are resistant to drugs that previously were useful.

The project started about 1941 and went on to about 1945. We were able to do a little research on the side, particularly in studying the metabolism of the drugs--how they were handled in the body. One of the studies we did was rather interesting in that connection. Rabbits are very good at breaking down quinine.

They have an enzyme in the liver that breaks it down very rapidly. This is not something we discovered. In fact, after we thought that we had done so, we found that it had been discovered after the First World War. But we did look into it in somewhat more depth. We thought it would be interesting to find out how this enzyme, or how this ability to break down quinine, might act: (a) in pregnant rabbits; and (b) in embryo rabbits. We found that during pregnancy there was less ability in the mother

to break down the quinine and that the embryo rabbits had no ability at all to do so until after birth. This was one of the early illustrations--not the first--that the embryo or the young may handle a drug differently from the mother, because their enzyme systems develop slowly and are not all present at the time of birth. Their kidney function is not perfect at that time so they do not excrete drugs as rapidly as they do later. I co-authored an article on this work on quinine in rabbits with a colleague, F. E. Kelsey. He became my husband.

F. Ellis Kelsey was an instructor at the University of Chicago. He arrived just about the time the antimalarial work started, or perhaps a year before, and we worked together on that. He had a Ph.D. in biochemistry from the University of Rochester. We married in 1943, during the war. When the war was over, a problem arose, because two members of the same family in those days--I do not know if it is still true now--could not be employed in the same department by the University. They felt that was nepotism or despotism or something like that. So, we thought the only way out would be for one of us to go to medical school. Not that either of us intended to practice, but it seemed like a very good extra asset to have an M.D. in addition to a Ph.D. I do not know whether I won or I lost out. I think I actually won, but I was the more logical choice to get an M.D. since, in fact, I had had almost the first two years of medicine while getting my Ph.D., and, of course, as a woman, I needed the

extra credentials. Let us face it, I needed all the help I could get to obtain a job.

I entered medical school at the University of Chicago in the class of 1946, and my husband continued his teaching and research in the Department of Pharmacology at the university. Medical school was not bad, because this was the first year after the war. Students were much older. On the average, they were aged 27, instead of 21 or 20. They were much more mature, and less likely to rag the women. Then, because of the scarcity of men, there was a higher percentage of women in the class. There were seven of us for 70 places (10 percent), and earlier only one or two per year would get in. Now 35 to 50 percent of incoming medical school classes are women and they do very well and get residency training in a way that we never did. So, medical school was not bad as far as I was concerned, particularly, as we had some very fine women professors on the staff, who had the respect of their male counterparts. Furthermore, the university medical school at Chicago was oriented more for teaching and research than for private practice. Again, the atmosphere was not as competitive.

I had already done, as I noted, a good deal of the work needed for the first two years of medical school. I think that students probably find those the hardest, in a way, because they feel they are not getting to care for people. Instead they are learning a lot of science that they feel may not be applicable

later. So, perhaps those are the hardest years, and therefore for me they were not so bad. I did not have a particular specialty because I had entered medicine not so much with the thought of practicing, but rather as an additional help in pharmacology. I graduated in 1950.

One of my children was born during my first year at medical school in 1947, and the second was born two years later in 1949.

Chicago was on a quarter system so it was possible to have three quarters on and one quarter off. You could choose your quarters, more or less; it was very flexible so it was ideal timing. I was very cautious about using drugs during my own pregnancies. I do not smoke so that never came up and, in those times, I do not think we could afford to do much drinking.

I had no intention, as I said, of going on to practice medicine, and as soon as I got out of medical school, I had a job waiting for me as an editorial associate at the Journal of the American Medical Association. The new Editor there was a Canadian, Dr. Austin Smith, who had trained in Toronto, and he was a pharmacologist. I knew him because he had an appointment at the University of Chicago in the Pharmacology Department. He would give several lectures a year. Dr. Geiling was always anxious to get outside persons to have at least part-time faculty appointments so there would be intermixing to broaden the scope of the department and give us these contacts.

Dr. Smith felt that, with all the new drugs coming on the

market, there should be more articles in JAMA about them, but he also felt the caliber of writing in many of the articles submitted was not very good. He wanted me to pick out good papers and help the office polish them up a bit. Well, not all the science was very good either and I do not know if I was very successful in that line, but my main job was to try and pick good papers, and I hope we did that.

When I went to the AMA (American Medical Association), there were two other medical reviewers besides myself who had recently come aboard. There was also the associate editor, other editors and so on, but we were the lower echelon so to speak. We shared one large bull pen, a room that had half-glass partitions so we looked out over this sea of manuscript editors, who, of course, knew all the nuances of grammar and things like that with which we could not altogether cope.

We all agreed that many of the submissions were poor, and we also observed that no matter whether we turned them down or not they inevitably got published in some other journal, because the journals circulated amongst us. We would see these articles and realize that we had reviewed them and recommended they not be accepted. Certain names would keep recurring both in articles and things like letters and so forth. We kept a sort of informal list. We would jot down, "Oh, it's Dr. So-and-so again, or So-and-so and So-and-so." Then eight years later, when I came to the FDA, I saw many familiar names as contributors of clinical

studies to the NDAs (New Drug Applications). I have to be honest and admit that there were some articles I turned down then that now I would have accepted, but I think that is true of all editors. I am glad to say that those articles too got published. My list-keeping then dated from an early period.

Medical Teaching, Research, and Practice in South Dakota

I was at the AMA for two years until 1952, and then my husband got an offer to be head of the Pharmacology Department at the University of South Dakota Medical School in Vermillion, South Dakota. That was a story, too. There had been a great tragedy there. The tragedy was that two volunteer subjects died in what we would now call a Phase 1 drug study. At that time, the medical school at the University of South Dakota was a two-year medical school situated in a small town of about 5,000, which had a small hospital, but it was more for emergencies and minor things. Ten miles away there was a very excellent hospital staffed with specialists and so forth. The building that the medical school was housed in then was known as the old chemistry building, because that, in essence, is what it was. When they got a new chemistry building, the pre-clinical sciences moved in to the old chemistry building. So it was not a modern, up-to-date building of any sort.

But the dean of the medical school, Dr. Donald Slaughter, who was also chairman of the pharmacology department, was very interested in research. He had spent a number of years at the

University of Michigan where there was, and I think still is--it is supported by the Public Health Service--a unit devoted to studies on morphine and related compounds.

Interestingly enough, Dr. Ralph Smith, who recruited me to the FDA, also worked at Michigan and I think got his Ph.D. there.² I am not absolutely certain. He also was involved in research on morphine before he came to the FDA. After Dr. Smith retired from the FDA, he served for two or three years at the National Academy of Sciences as executive secretary or what have you, for a group interested in or focusing on drugs of addiction.

Anyway, morphine was the area of Dr. Donald Slaughter's interest. He was a well-known pharmacologist and coauthor of a textbook on pharmacology. He was an interesting sort of a person. This study involved a comparison of two morphine-like compounds. I have an idea what they were, but I have no real means of documenting it. But one compound was a good deal more active than the other. I think that was perhaps the essence of the study. The compounds were to be given to volunteers, either blinded or alternately--I forget which. Then the volunteers were to be tested for their perception of pain. The volunteers were not patients. They were university employees or relatives of university employees who had volunteered for some drug trials.

² Ralph G. Smith received his M. D. from the University of Toronto in 1925; his Ph. D. in pharmacology from the University of Chicago in 1928; served on the faculties of the University of Michigan (1928-1943) and Tulane University (1943-1950); and came to FDA in 1950 to head the new drug branch.

It was a pretty straightforward sort of study, except that it involved injection of the drugs either intramuscularly or subcutaneously or intravenously. I cannot remember which.

It just so happened that when the study was scheduled to take place Dr. Slaughter had to go to a hospital because of severe gout, I believe, in a knee. This was not new; he had had other episodes. He had demanded great attention additionally at this time because his wife, sadly enough, was dying of one of the autoimmune diseases, and this was in the days before there were steroids or adequate treatment of any type. He also had the usual stresses and strains of being dean of a medical school.

However, in his absence the study went on under the guidance of his young assistant who had just completed his internship, and had had some experience as an instructor in pharmacology. It is said that the subjects were to receive the drug and then testing was to begin at a suitable period thereafter. They had not finished the injection of all the subjects--maybe they had done three or four or five--when the first one lost consciousness. While they were trying to revive this person, another one had a similar experience, and then a third. I think the injection was stopped midway in the third one. At least, there was some depression of the needle or something, but it was reversible. The two subjects that could not be revived were taken off by ambulance to the hospital about ten miles away. This was also before the days when there were morphine antagonists. I think

they were being developed, and I believe Parke-Davis actually flew some out to the hospital in Yankton, but it did not prevent this tragedy. Some of these derivatives Dr. Slaughter was testing were not morphine, and whether they would react in a similar fashion I do not think was known. Anyway, they certainly did not have them on hand in the pharmacy, and I understand they had to get them from elsewhere.

Then, after this occurred, as I understand it, there was a hearing, and Dr. Slaughter assumed complete responsibility even though he had not been present. So he recognized that he was the senior investigator. I think the volunteers were somehow tested, but that is possibly a reconstruction and not a real memory. They were never supposed to lose consciousness given the dose. It should not have produced this effect. There was some thought that there might have been a mix-up in the way the solutions were prepared since one drug was known to be so much more potent than the other. As I say, we were not there at the time, and it was obviously a very traumatic event.

It was some time months after this that the professor was readmitted to another hospital because of his gout, and then it came to light that he had become addicted to morphine, as many people who worked with these drugs did. Halsted, a surgeon at Johns Hopkins, did. Many addicts, especially professional ones, can control their addiction. I think the outcome was ruled a misadventure. I do not know if they gave the survivor payments

or anything like that, but the tragedy pointed out the need for control over investigational drugs. There was no question of Dr. Slaughter being imprisoned or anything like that. I found out these details from a friend who happened to be at the university at the time who refreshed my memory. I do not think there was any suggestion that Dr. Slaughter's addiction led either to the gout or to this episode. But it illustrates several things: one, the need for great caution in Phase I studies, which we now have, of course, and two, the hazard of experimenting with an addicting drug. Dr. Slaughter went for treatment, and then shortly after that he died. That was why they were looking for another pharmacologist at the University of South Dakota.

He died shortly before the pharmacology course was going to be given. The university called on surrounding universities to help them out in providing teachers or instructors for the course. Dr. Geiling in Illinois, which was not, after all, that far away from the southeastern part of South Dakota where the medical school was, volunteered to go out. A number of the faculty or instructors at the University of Chicago went out, as well as some from other surrounding universities. Dr. Geiling was very impressed by the school, by the spirit, the enthusiasm, and the type of students that were there. So when an opening came for a new chairman, he recommended to my husband that he look into the matter, and he recommended my husband to the university authorities.

During that year, my husband had left the University of Chicago and was working for a firm that was a pioneer in the development of nuclear pharmaceuticals--it was called Chicago Nuclear--and finding other uses for isotopes. The founders had worked at Oak Ridge on the atomic bomb project and started up this small company. My husband was working there, and while it was an interesting experience, he wanted to get back into teaching again. So that is how we considered going to South Dakota.

My husband received the offer to become head of the Pharmacology Department at the medical school in Vermillion. As I noted, this was in a town of 3,000-5,000 people on the Missouri River, and as may be imagined there were very few openings for a female M.D., Ph.D. in a town of that size. I certainly was not eligible to work at the university in my husband's department, due to the same problem as in Chicago. I did not have a license.

I did not particularly want to practice medicine, or I was not sure if I did. So to go to South Dakota was a big decision for us, which often happens in many families where both husband and wife have careers. It is very seldom that both can be accommodated with a good job at the same time. I had two sort of outs. One was to go to law school, and as I liked studying, that was not too bad an option, and the second was to take an internship. That would at least give me a license and, who knows, I might find that I liked to practice medicine.

We went to South Dakota in the summer of 1952 and I started my internship in January or February of 1953. The Sacred Heart Hospital, within 10 miles of Vermillion, at Yankton, where I interned, happened to be a very good hospital, and my internship was a very good experience, because it was an entirely different type of medicine than what I had been exposed to at the rather academic University of Chicago.

When I finished my internship, I applied for and was awarded a Lederle teaching fellowship for three years. It was paid for by this large drug firm, and they did not influence me, the least bit, in my attitude to drugs. These fellowships were started about the year I applied, or possibly a year or two earlier; they had not been in operation long. They were to support faculty members at universities and were unrestricted as to the type of research that could be pursued. The aim was to upgrade in general the teaching of basic sciences in medical schools. It was a very generous fellowship and it did not cause a conflict with two people in the department being paid by the university, because I was paid by an outside firm. So, it was possible for me to spend the next three years doing research and teaching by virtue of my fellowship. This was from 1954 to 1957.

I did some locum tenens work and then got into the new field of radioisotopes and radioisotope drugs. There was increasing interest in isotopes and nuclear medicine, so I "commuted" to Chicago to get training in that. It was an overnight train trip

to go to Chicago. I would go for two or three days to watch and assist and then come back to Vermillion. To get licensed a doctor was required to have assisted in the treatment or diagnosis of a certain number of patients and to have become familiar with calculating doses and things like that. I was the first person in the state of South Dakota to get licensed to use radioisotopes in medicine. I was not the last, because we organized classes for the doctors who were out in the state, and trained them also to apply for licenses.

My research at South Dakota had to do with the thyroid gland. Thus I was going back to endocrinology. Part of my work was conducted at a large mental institution not far from Vermillion. There had always been some sort of belief that thyroid disorders were tied in with certain mental disorders, and there were numerous studies on the thyroid gland in this type of population. Since there was a new diagnostic procedure for thyroid disorders, radioactive iodine, some of the patients at the mental institution would be referred to us to see if they had any thyroid problems. In the course of our work we did seem to find an abnormal number of patients who had what we call a high iodine uptake, although they certainly showed no sign of being hyperthyroid. It turned out that this institution was situated just on the edge of the goiter belt and they had never used iodized salt there for some reason; perhaps it was due to a small economy, or they just never thought of it. When they replaced

the ordinary salt with iodized salt, we went back and found these subjects to be normal in their iodine uptake.

In this instance, it turned out to be iodine deficiency--a dietary problem. If that is severe enough, it can in turn cause severe mental problems or learning disability. There were the occasional patients in the mental institution whom we did diagnose as having definite thyroid problems. But the overall population was suffering from a low-grade iodine deficiency.

While in South Dakota, too, I actually returned to my earlier studies on the pituitary because we found that the beaver was like the armadillo, whale, porpoise, and some birds in that it, too, simply had these two lobes--the anterior and the posterior--and no intermediate lobe. The beaver was available. We had a friend who was a great hunter and was always willing to get a beaver. I remember we had a live one once. We kept it overnight and it gnawed all the legs off the stools.

After my Lederle fellowship years from 1954 to 1957, I was a sort of volunteer researcher, but I also did what was known as "practice sitting." This was somewhat like babysitting. There were many rural areas where only one doctor would be available, so, when the physician wished to get away to go to a medical meeting or take a vacation, I would go and look after his practice for varying periods, say two or three days. I think the longest period I did this for was about six or eight weeks when the people in a town were looking for a replacement for a doctor

in one of these areas.

I did this rather than opening my own practice, because I somehow felt that would tie me down, and the girls were still fairly young. Plus I enjoyed the teaching--I did some of that too. I rather enjoyed the amount of practice I did. It offered variety and it was not too confining. Also, I did still have the contacts at the university.

Certainly doctors were in short supply in the late 1950s in the isolated areas where it was quite hard to attract and hold physicians. Many of these places had very nice hospitals--by virtue of the Hill-Burton Act--and the patients got excellent care, I thought. It was possible to get to a larger center either by flying or by ambulance or driving. But, for the day-to-day ailments and emergency situations, it was essential to have the doctor reasonably close.

Every medical encounter was of interest because I was on my own and there were a variety of emergencies or even just ordinary run-of-the-mill conditions that I would have to cope with or treat. It was a very good experience for me, because the medical school I had been trained in was very research oriented. We saw many patients with esoteric diseases at the University of Chicago, but very seldom a broken limb or a case of measles or appendicitis. I saw the more common ailments in South Dakota. I did while I interned too, because that was in a general hospital.

Coming to FDA and an Introduction to the Drug Approval Process

Then after my husband and I had been in Vermillion for some time it seemed as though we had an itch to get back to the big city again. This time I got the first job offer, and I will say that I got cold feet at the idea of being the sole support of the family until my husband got a job. Very fortunately, almost at the same time, he was offered one by the National Institutes of Health, so in 1960 we moved to Washington, D.C., both with jobs.

Mine came about because we ran into the Director of the Bureau of Medicine of the Food and Drug Administration at that time at a pharmacology meeting. He was Dr. Ralph Smith, also a Canadian, and also a pharmacologist. He said the agency was expanding, and how would I like to work there as a medical officer. It did not seem like a bad idea and so I mulled it over, and when my husband got the job offer in Washington too, I accepted. Just to show how the job market had changed, I also got an offer from the National Institutes of Health for another job at the same time, so things were looking up.

I went to the Food and Drug Administration in 1960. I started on August 1, and the first month I was there, the FDA was in a temporary building--Wake Hall, I believe it was called--which was out in the area where the Robert F. Kennedy Stadium now is. Then, after a month, we moved into other temporary buildings on the Mall, on 7th Street, close to the HEW (Department of Health, Education, and Welfare) building. These were World War II temporary buildings, pre-fabs, and we were lucky because some

government agencies were still in World War I pre-fabs.

My first month was spent going around and finding out what the parts of the agency did and then I came back to our little pre-fab. Only the Bureau of Medicine was in it; other parts of the agency had bigger buildings. After my short indoctrination period, I was given my first assignments as a reviewer of new drug applications. I had been hired as a medical officer and this meant that I would review the medical part rather than the pharmacology of new drug applications. Dr. Smith, who brought me in, was looking for medical officers, not pharmacologists. I had the medical training as well as my pharmacological training, and there were certain advantages to being a medical officer at that time. In those days pharmacologists were not actually in the Bureau of Medicine, but in, I believe it was called, the Bureau of Science. But they used to work with the Bureau of Medicine people. We would send our applications over there for them to review the animal work. So my review work was to be on the human studies from the start.

Before turning to thalidomide, I have to describe a New Drug Application in the setting of when I first came to the FDA. Things were somewhat different from what they are now, but in essence, at that time, when a drug firm felt it had a drug that was ready to be marketed, they would come to the Food and Drug Administration with what was known--and still is, of course--as a "New Drug Application" (NDA). This was a compilation of material

to show that the drug was safe for its proposed use or uses. It would consist of three parts. There would be a chemistry part which described the drug, how it was made, what different ingredients went into it, how the manufacturer would insure purity at all steps along the way, how they would insure that the drug would always be the same each time they made it, how stable it was--these and various other sundry aspects would come under the chemistry part. The chemists in our group reviewed that part.

Then there would be pharmacology--the animal studies that had been done to show the drug was safe. These studies would usually be to test for acute toxicity, in which a single dose of varying amounts was given to animals--usually rats, mice, or dogs--in essence, to see how little killed them rather than how much they could tolerate. What is usually done is to have a large group of animals and then determine the dose which will kill half of them. This is the LD 50. If the dose that would kill all of them had to be found, there would always be a few very resistant ones. At the other end, if it was the dose that would kill the least number, there would always be a few sensitive ones. Instead, a fairly large group of animals was selected and then the researcher would see at what cut-off point 50 percent of them survived, or to say it the other way, at what point 50 percent died. That would be the LD 50. This gives a measure of whether it is an extremely toxic drug or a relatively

non-toxic drug. Then there are also studies in which the drug is given for a long period of time at various dosage levels, always choosing one which will give some adverse effects. This gives some idea of the toxicity. With a very high dose there might be liver problems, for example. This would not necessarily mean that the drug could not be used in man because it might be effective at a much lower dose, but at least it would alert people to look out for that. That would be the pharmacology part, and it usually was reviewed by the pharmacologists. Sometimes, in those days, the medical officers would feel they could do that as well. Nowadays it is always done by the pharmacologists.

Finally there would be the clinical studies. These would be the clinical trials in which the drug had been given to physicians who were supposed to be adequately trained, and the physicians were supposed to make careful observations and honestly record their findings of the trials. The case reports would be submitted in the application.

We knew that many clinical trials were poorly performed, particularly at that time. As a newcomer I must say I was quite shocked sometimes at the caliber of the work that had gone into the applications in support of safety. That has definitely improved over the years. Our requirements are now much more stringent, and the whole science of clinical pharmacology and the testing of drugs has developed greatly in the last fifteen or

twenty years. We now have better methods of trying out drugs. We have better-trained people, who, if they are not doing these studies, are at least designing them and seeing that they are done properly. The Kefauver legislation had something to do with that. It strengthened the requirements for one thing. And, as a consequence of the tightened investigational drug regulations, by which the drug companies now have to send in the studies right from the start, the legislation has done a great deal to insure better studies.

At the time I arrived at the FDA I think there were about twelve or thirteen medical officers in the group reviewing new drug applications--and a number of those people were half-time. It was very difficult in those days to get people to work as medical officers in the government. The pay was very low compared to what a physician could earn elsewhere, and many physicians did not like that type of desk work. The FDA depended a lot, for example, on people who had just completed their residencies and were starting out in practice in town and would give half a day to reviewing applications. There would be a pretty big turnover of physicians going to, say, drug firms, which of course happens now. This is to be expected because the same type of skills are utilized at the FDA as at the drug firms. There is no question that we have lost a number of people to industry.

There were a few other medical officers. For example, at

that time there were three or four medical officers stationed throughout the country. One was in San Francisco, Dr. Ralph Weilerstein. One was in Chicago. I cannot remember the man's name, but he was quite active. I think there was one in the New York area. For a while these positions all died out, and then they started reviving them again. As I recall, the Division of Antibiotics was really a different section under its own rules at that time, because they had petitions, not new drug applications. So they were not included in the number of medical officers I gave.

My immediate supervisor was Dr. Ralph Smith, but there was also Dr. Irwin Siegel, who was deputy to Dr. Smith and had a lot to do with indoctrinating new people. I would often go to him with problems, and then to Dr. Smith.

I was not swamped with too much work at first. I cannot remember the application load at that time, but it was nothing like it is now with the investigational drug exemptions and the much larger new drug applications that the medical officers have to evaluate. The volume of the NDAs has increased. For example, I think the thalidomide NDA was four volumes; now the NDAs come in 150 to 200 volumes or more. I would describe a volume as a metropolitan phone book in size. That gives an idea of thickness. The increase in size of NDAs is certainly, in part, due to the more detail required to establish both safety and now, of course, efficacy as well.

Thalidomide

I came on the first of August 1960 and I think I got the thalidomide application in early September 1960. I believe it was the second one that was given to me. I was the newest person there and pretty green, so my supervisors decided, "Well, this is a very easy one. There will be no problems with sleeping pills."

So that is how I happened to get the application. I never got another one quite like that one. I know the other drug given to me at the same time was a rectal enema, which I think had the name of Lavema. It did get marketed, so I must have approved it.

I came to review thalidomide, then, as a new drug application. At that time, we had sixty days after receipt of the NDA in which either to reject it, or if we had no objection or if we forgot that the 60 days had elapsed, the drug automatically became approved and the company could put it on the market. It was possible to say that the application was incomplete and then detail the deficiencies. There would, of course, be a prod on the fifty-ninth day after the arrival of every application to make sure that at least some letter had been issued to the firm if there was a matter for concern. There was always the fear, that through somebody being asleep at the switch the sixty days might go by and then the approval would be automatic. I understand it had happened once.

We had to be pretty specific in saying that an application was incomplete. Reviewers had to be fair about this, and all

three disciplines would marshal their objections. It really was not sporting to hold one application aside and then when the sixty days had elapsed just to sneak that incomplete in. We were supposed to try and pass on or describe why when the application was being turned down. In general, we were supposed to do an honest and thorough review. This could be done on a small application.

The thalidomide application was reviewed by three people: a chemist, a pharmacologist for the animal work, and a medical officer, which, of course, was myself. The chemist was Lee Geismar, who is still with the Food and Drug Administration, and the pharmacologist was Jiro Oyama, who I believe is not with the agency any more. Now, in those days, as I mentioned, the pharmacologist was in another building and another bureau entirely. The chemists were in a separate division or branch--I cannot remember what they were designated as in those days--and the medical officers were in still a third. Nowadays, the arrangement has the chemist, the pharmacologist, and the medical officer working virtually side-by-side within the same division in the same building and on the same floor. This means that they can frequently get together and exchange problems.

Unfortunately, in those days, we were separated. We were not much of a team, although Lee Geismar and I were in the same building, and I am sure we would go to meetings together. In those days the medical officers actually got great support from

the chemists, who were the ones, in a way, who instructed us more than anyone else did in the art of drawing up these letters to drug companies--using the right sections of the law. Lee would have had a great deal of work and responsibility in this area.

There was no reason why a drug should have to fail in all three areas to be rejected, but if it failed in even one aspect it would still be held for that sixty days. If the chemistry, for example, was incomplete, the chemist alone could hold it. In those days the letters went out under the medical officer's signature; now they go out from the division director.

All three of us found problems reviewing thalidomide the first time around. The chemist's review showed that there were some matters that had to be cleared up. I thought the chemistry problem was interesting because Lee Geismar had been trained in Germany, and could read German. Since the drug was originally made by a German firm, a lot of the submissions were in German. Of course, the company was supposed to translate the material, and Lee found that they had made mistakes in translation. It was rather interesting that we could pick that up. I do not know if the mistakes were of any great significance, but it was very handy having someone who could read foreign languages, because many of these early chemical studies were done in Germany. Dr. Joseph Murray of Merrell called on Lee Geismar, the chemist who reviewed the application. She had some information on the chemistry, but even at that date--6 January 1961--the chemistry

was not settled completely; there were some problems.

From the pharmacological standpoint, thalidomide looked good, but the pharmacologist did point out that there was a question about absorption. In his review, I think he indicated that how safe it was might be a matter of the absorption of the drug. Thalidomide is relatively non-toxic in animals but it is very poorly absorbed. In animals it could be taken in large doses orally without ill effects.

As regards the clinical area--which was my own area--it was expected that an ideal sleeping pill would meet certain criteria, such as the fact that it would not produce a hangover the next day and so on. The claims made in the NDA for thalidomide were too glowing for the support in the way of clinical back-up. That was the initial thing that perhaps led us to require more substantiation. The claims were just not supported by the type of clinical studies that had been submitted in the application. I cannot remember what the exact number of doctors' reports in the initial submission was, I think about thirty, and many of them were more testimonials than scientific studies. That was the good bulk of them.

The application may have satisfied the pharmacologist's criteria or the FDA's criteria for pharmacological work, but if the clinical part was still poor then this would be a non-approval. But it would also be a concern if the pharmacology were incomplete. If the medical reviewer was uneasy about the

clinical work, then he or she would certainly want more pharmacology studies. As I noted, we all three found deficiencies in the thalidomide application, and told Merrell so. Then they brought together more information, but we still found deficiencies so they resubmitted.

In those days, when a drug was under review there would be a great curiosity on the part of the drug companies. It was understandable that the firms would want to know how the review was progressing and, of course, that they would have considerable disappointment when those sixty-day letters came. I do not know if that is still the case. I am out of touch with that aspect of it now, as I am not on the reviewing end. There are more formal meetings set up now, and the firms are discouraged from making continual contacts with FDA reviewers.

I have been asked whether the drug companies had too great an access to me. That is a rather hard question to answer because one has to be fair and see their interests. Many of the drug companies genuinely feel that they have a really good drug (and occasionally they do), and they have spent a lot of time getting these applications ready--lining up the people to do the work, getting the animal studies, etc.--so their hopes are riding high. With thalidomide, because it had been successfully marketed in Europe, I think one of the possible reasons why Merrell's application was so poor was that it seemed like a sort of pushover, that it would have no problem at all being approved.

Perhaps they had not given the application the attention it deserved, such as getting the best people as investigators, which is a standard approach in the case of an unknown drug. It is necessary in the case of thalidomide to take the European experience with the drug into consideration.

Dr. Joseph Murray was the contact man from Merrell. His background was in bacteriology; he was a bacteriologist, not an M.D. I think he was quite frustrated, to put it mildly, by the problems raised in the review. I suppose he had been given the responsibility of getting the NDA approved as quickly as possible, and to have these roadblocks thrown up must have been quite annoying.

My first dissatisfaction with the thalidomide application, as I mentioned, centered on the quality of the clinical reports, because they were more in the nature of testimonials rather than well-designed, well-executed studies. I requested Merrell, I believe, to get better clinical studies and to provide us with a little better evidence of these various and sundry claims that they had made.

Thalidomide had been marketed and very widely distributed in Europe since about 1957. The next step in the story was probably in late January or early February of 1961 when my attention was drawn to a letter to the editor by Dr. Leslie Florence in the British Medical Journal of 31 December 1960 in which he reported peripheral neuritis, a very painful tingling of the arms and

feet, in patients receiving the drug thalidomide for a fair period of time. This effect was very severe in some cases, and possibly not reversible. I was browsing the journal when I read this in late January or early February 1961. The BMJ was one of the journals we browsed through. Its format is very amenable to that. Although this issue had been published on 31 December 1960, there was a problem with delivery of our journals--I think it was a mail strike--and the journal did not reach us until late January or early February. But the peripheral neuritis did not seem the sort of side effect that should come from a simple sleeping pill. We immediately drafted a letter to the company asking for more information and more proof of safety. It was apparent that this effect might be associated with the use of the drug.

We later learned that this effect had been recognized not only at this time, but earlier in Europe, and it was the main reason why the drug had been removed from over-the-counter status in Germany and made a prescription item. (I do not think it was ever sold over-the-counter in England.) The labeling of the drug by the European companies had carried a warning of the possible side effect of peripheral neuritis, and I believe it was on the labels at the time that the application was submitted to us because these side effects are often realized before they are reported in print in journals. Despite this side effect being known in Europe at the time we received the application,

communications were poor in those days, and we were simply not aware of this till we had had the drug for about six to eight months. So there was an awareness of this adverse effect before this publication appeared, but not by us.

We have no way of knowing whether Merrell in general was aware of this problem. They did have representatives overseas, but sometimes the foreign operations of a domestic drug firm are completely separate from those in the United States. Dr. Murray claimed that he had noted the letter in the BMJ at about the same time we did. It seemed to be a surprise to him. But he did not bring it up with us, although we had several phone calls in this period. I asked him about it, I think, on about the third phone call. He had evidently been aware of the report, but had not volunteered the information that thalidomide could cause peripheral neuritis.

As a follow-up to this letter in the BMJ, there was a meeting involving Dr. Murray, Dr. Smith, and me. Dr. Murray claimed that at this meeting he was able to convince me that Merrell had first learned of the toxic side effects of thalidomide from the December issue of the British Medical Journal. If that was the case I think their intelligence was very poor because the problem was well recognized. They should have known it if they had done their homework, or if contacts had been good between the two continents. I do not think we had any way of knowing whether European business associates had notified

the Cincinnati company that this was an apparently established side effect. The Food and Drug Administration explored very thoroughly whether Merrell had been negligent in this matter. As I recall they could not establish anything.

I cannot recall if I was taken aback by all this, but when I came to the Food and Drug Administration I was unaware of certain things that I learned after I arrived here! For instance, the fact that many of these clinical studies were poorly conducted and poorly reported, and that there was some laxness in attention to details such as this.

It appeared then as though Dr. Murray had not promptly drawn this side effect to our attention. He did go rather promptly overseas to Europe to look into the matter and certainly gave the impression on his return when he reported to us that this side effect was not particularly serious and possibly was tied in with an inadequate diet--perhaps some vitamin deficiencies--because he stated there were regional differences in where it was noted. I never did see this claim written up anywhere in the literature.

It was not until sometime later that we learned that this was apparently a severe side effect, and quite widely distributed; quite a number of people suffered from it. We were not impressed by Dr. Murray's report. We requested documentation and we asked him to contact all the investigators in the United States who had used the drug in patients for a prolonged period of time to find out if they had any cases of peripheral neuritis

in their patient population. I believe several were located by this means. Also, of course, we were not aware of the widespread distribution that thalidomide had had in the United States.

I had asked Merrell earlier for a list of investigators who had been given thalidomide, and the list had some thirty or forty investigators on it. We asked that each of these be specifically questioned as regards the peripheral neuritis. Now, the wording in the letter to Merrell was such that it gave an excuse for them to provide the FDA only with a list of those investigators who had had thalidomide long enough to have had patients on it for a period of time; I think we asked for the names of those patients who had been using it for four months or so. We did not get the list of the persons that had received thalidomide in the drive to publicize the drug, that is, the other thousand or so patients. We did not become aware of this widespread distribution of thalidomide until after the drug had been withdrawn. There were the genuine investigators who had worked with it for a long period and whose findings had been submitted to us, and then there were those physicians who were told that the drug was about to come to market and that they need not bother much about keeping records.

The next development was that in April 1961 the company tried a new approach to move its application forward by trying to prove the value of the drug through making comparisons of its safety to the lack of safety of barbiturates. It was continually

being said that you could not commit suicide with thalidomide. I did not think that was a sufficient reason unto itself. Marilyn Monroe's death coincided with the time the publicity on thalidomide appeared, and this was, and still is, a favorite quote: "If Marilyn Monroe had taken thalidomide she would still be alive." I should point out that I think there is a grain of truth in the argument that many people make a suicide gesture and will take pills hoping and assuming that somebody will find them in time and pump them out. One could admittedly take many thalidomide tablets in most cases and survive. But this did not outweigh the potential danger, and it did not outweigh what was unknown about thalidomide at that time.

On 25 May 1961, I wrote a letter to Dr. Murray expressing concern that evidence of neurological toxicity apparently was known to Merrell without being forthrightly disclosed in the application. I think Dr. Murray was rather upset at receiving this letter. He thought it was slightly libelous. Obviously, in that telephone conversation I had at the time I wrote to him, he was aware of the problem of peripheral neuritis. So I think I was on perfectly safe ground in saying that he had not forthrightly disclosed it. It was very different if a problem was disclosed the day after an application had been approved because withdrawing an application was quite a tedious procedure.

It was as well to make sure every problem that was seen had been ironed out before an application was approved.

I suspect that Merrell knew about these problems even before Dr. Murray had seen the letter. I think this because when he phoned me it was the day the letter went out from here, so he had not received my letter. It looks as though the letter was dated the same day he phoned, so that I might not phone him and say, "We have learned this." I might just put in the letter, "provided that it was in the sixty-day framework."

It was the side effect of peripheral neuritis that led us to ask about the use of thalidomide in pregnancy because, at just about that time, there was an interest in the effects of drugs in the fetus. The agency was alerted to a problem about embryos and newborns being unable to handle drugs in the same way that an adult can. They do not have the mature enzyme systems, the mature kidney systems, and so on. An article had appeared in 1960 that assembled the information known up to that time. There were other occurrences with certain drugs. One of the vitamin K preparations was shown to have a severe effect on the new born. The drug chloramphenicol (Chloromycetin), was shown to be particularly toxic for very small babies because their livers were not able to metabolize the drug as an adult's liver could. The pediatricians in the FDA were working very closely to develop guidelines about the safety of drugs in infants. These would include, of course, the safety of drugs for fetuses that might be used in pregnancy. Also just about that time steroid hormones were used in threatened miscarriages, and it turned out that a

number of the female babies born to mothers who had this treatment had some degree of masculinization because of these progestin type drugs. All of these things were making us think, "When you give a drug to a pregnant woman you are exposing, in fact, two people to the drug, the mother and the child."

Other people besides us in the Food and Drug Administration were interested in these questions. There was, for example, Dr. Irvin Kerlan who was in the adverse reaction area; he was very interested and very concerned about the effects of drugs. Kerlan was also a pediatrician and he worked closely with pediatricians. He had worked with the pediatric group in drawing up the warning about, "bear in mind the child is not a small adult." Another was Dr. John Nestor, who was a medical officer and a pediatrician; he too was particularly interested in this area. Dr. Irwin Siegel was interested in this too, because he was a clinical pharmacologist who was very knowledgeable about drugs and had a good clinical background. Thus, the Food and Drug Administration was becoming increasingly aware of this area. I was interested in it because of my own practical experience with the quinine and embryo study earlier. So when the thalidomide-peripheral neuritis question came up, then we wanted to know what had been the experience with thalidomide in pregnancy.

Here was a drug that given for three or four months could cause severe neuropathy. With thalidomide, a growing infant might, perhaps, be exposed to it for five or six or up to nine

months. This was the sort of drug that was taken as a mild sedative/hypnotic, and the mother might take it a lot during pregnancy. I do not know exactly what the genesis of this concern was. But I think it was the fact that this was something we were thinking about in terms of all drugs, due to other recent examples. It was in the setting; it was really a new thing--this concern about safety of drugs and childhood.

Merrell, the drug company, did not know of any problems with thalidomide in pregnancy, but they had not conducted a study, except for one using it in late pregnancy in order that the mother might be more comfortable, which we did not feel was sufficient. We pointed out that this was a relatively short period of use compared to what might be the effects of nine months of use. Of course we were not thinking in terms of absent arms or legs necessarily. We just thought that if it did something to the adult in this period of time, it might well have an adverse effect on the child. The drug company was unwilling to undertake a study, but they did agree to put a big warning on the labeling, that this drug should not be taken during pregnancy since it was not known what its effects would be. We were really more concerned about the peripheral neuritis, which they were also willing to put on the labeling, but, for one reason or another, they never quite satisfied our demands. Then, quite suddenly, the news came from Europe about the deformities.

In the meantime, Dr. Murray was growing more frustrated. He

was particularly disappointed because Christmas is apparently the season for sedatives and hypnotics, and the company had hoped that with the submission in September 1960 the drug would be out in time for that Christmas season. Then it looked like a second Christmas season was coming around with no drug. He indicated in a memo that they wished to get it out because it was a seasonal drug.

Merrell continued to try and convince me and the FDA. In early September 1961, Merrell held a conference in which they called in their clinical investigators. This sort of event is difficult, because the drug company brings in people from the outside, sometimes people associated with universities and so on, who have worked for the firm and are interested in pharmacology and drugs. They think the Food and Drug Administration is obstructionist and so on. Of course, the drug company has selected the people whom they know are going to back them. So such a conference is quite an ordeal, there is no question about it. But when the question "Is thalidomide safe in pregnancy?" arose at Merrell's conference, that ended the criticism of the FDA as people realized that the data were not there. The drug really could not be said to be safe. I think it was at that time the suggestion was advanced that if thalidomide were to be released they would have to put on a disclaimer that its safe use in pregnancy was not known. This type of disclaimer was the sort of thing we had done before, and I think we said, "If you can

just give us some case histories of where it has been used throughout pregnancy..." The ironic thing was that Dr. Murray said, "Had there been any problems with this they would have been observed since the drug has been so widely used." Thus there was a realization of the increase in this type of birth defect, but it had not been connected to the drug. But we were not aware that the Europeans had already noticed an increase in phocomelia.

In fact, FDA records show that one of Merrell's clinical investigators had delivered deformed babies. This was very interesting because H. Weicker was very close to it. He had a hunch and he wrote around to various centers in the United States to see if they had experienced any increase in these deformities, which he knew had occurred in Germany. There was only one center in the United States that did show some cases and that was in Cincinnati. But Weicker was thrown off because he was given to understand that the drug was marketed in this country. So he thought, "It can't be thalidomide." He discounted, I think, the Cincinnati results as not being anything like what was happening in Germany. If thalidomide was the cause, then surely the deformities would be in the States as well as in Germany. But he did not realize that the drug had never been marketed. We have copies of the letter the German firm sent out and it would give one to understand that the drug was being marketed in this country. I hardly think the company would have been confused about this, but it certainly gave out the information.

Now the extraordinary thing was that it was quite a long time before a positive connection between thalidomide and the deformities was made. The company claimed it was a false association and that it could not possibly be the drug. It had been so widely used, and it was not possible that this was just coming to public attention. Even the specialists, the teratologists who specialized in birth defects, had difficulty, because this was not a typical drug that caused a typical defect.

The defects occurred in doses that had absolutely no effect in the mother. Even if one looked only at the mother, the drug did not have many adverse effects (perhaps a little drowsiness), so it was unusual in this respect. This, I think, was another reason why it took so long for general acceptance that the drug was at fault.

On 30 November 1961, Dr. Murray of Merrell informed the FDA that the German firm was withdrawing the drug from the market. I remember very well when he called and told us about the information they had received from Germany possibly linking the drug with birth defects. I was--I admit it--very surprised. This was what we had been wanting to make sure would not happen with the drug and it appeared it had. Our objections, as I have pointed out, were really on theoretical grounds, largely based on the fact that there was no evidence that it was safe. Until we had such evidence we had to question the safety. We received further information from two FDA officials who were in Germany at

approximately the time the news came out. They wrote a report on what they had found. Merrell notified us that they were discontinuing clinical trials with the drug in the United States until they got further information concerning these preliminary reports from Germany on birth defects. So, in essence, we waited for further information and we did get some in the form of literature reports. I believe we got a long memo from the U.S. Scientific Attaché. The scientific attaché in Europe sent a report, for example, to the National Institutes of Health--possibly early in January 1962--explaining or describing the circumstances of the problem with the drug in Europe.

Today we would just fly over to Europe and investigate this matter ourselves. This is one of the great benefits of the improvements in the law and the greater stress on safety and so on: we have become much more active in pursuing these clues and settling matters ourselves, not necessarily depending on second- or third-hand information. We have become much more closely allied, as it were, with food and drug establishments in other countries, with exchange of information. There are other countries which have adopted regulatory systems, and we do have a fair exchange of information with those countries.

So, in November 1961 Merrell indicated to us that they would not do any further testing on the drug until they got more precise information. Merrell then sent out warning letters to doctors in the United States on 5 December 1961. This first

letter only went to a rather limited number of investigators-- those whose names had been submitted in the NDA, for example. So the thirty or forty investigators that were named in the New Drug Application were contacted, and we assumed that these were all the people that had the drug.

On 8 March 1962 the formal withdrawal of the application was submitted. There is nothing that would lead me to think we had requested the withdrawal. I think Merrell withdrew it of their own accord when they were finally convinced that there really was a problem related to the drug. Until that time they were hopeful that it was not so. As I recall, they did request permission to continue three types of studies (one was cancer) where there would be no hazard involved.

It may seem that there was a rather long period between November and March. But, for any adverse reaction report like this, there is always a period of doubt where one is not sure that there is a real correlation. Except for rather small notes, there were no published articles on the problem of deformities, for example, until about February 1962. We were aware that this drug was in the investigational stage, and we felt that it was well under control by the sponsors. In other words, we believed that they had informed their investigators and had warned them.

At a certain point the FDA began to suspect that all was not right. My recollection is that when we got the letter in March 1962 indicating the company wished to withdraw the application,

it indicated that in December 1961 all active investigators had been notified of the problem and told to discontinue studies until the matter was cleared up. The company then stated that a letter had now been issued on 21 February 1962 to all investigators--all who had received the drug--telling them of this. This led us to think at the FDA that there might have been some people who had not received the earlier letter. My recollection is that this is what led us to request the list of all the physicians who had been supplied with the drug.

This was the letter the FDA sent to Merrell on 11 April 1962. Now, in any drug trial, one expects a certain number of the physicians never to bother to test the drug or just to indicate they are disinterested in it, so one knows that often fewer persons have used the drug than those who have been sent it. Certainly the latter is the bigger number.

We got reinforcement of our belief that it was the drug that caused the deformities from Dr. Helen Taussig, a renowned woman pediatric cardiologist, at the Johns Hopkins University. Dr. Taussig was famous for developing the Blalock-Taussig surgery for blue babies. She had had many residents train under her including one, Dr. John Nestor, whom I have already mentioned and who worked for the Food and Drug Administration. She learned of this problem of deformities from a German physician who had trained with her in Baltimore. Her specialty was pediatric heart defects, and the German physician wrote to her that many of these

children had cardiac defects and that she should come to Germany and look them over. She came back with striking photographs after having talked to everyone over there. She talked to drug manufacturers, to parents of deformed children, to scientists, and to epidemiologists. She received support for this trip from the American Heart Association, the Maryland Heart Association, and the NIH, and she spent about six weeks in Germany visiting various centers where they had had experience with these deformities. We always link thalidomide with limb defects, but actually a number of the children had congenital heart disease, too. This, of course, was her primary interest.

Dr. Taussig called Dr. Nestor about the end of March or early April 1962 and told him she was just back from Europe where she had seen some very shocking effects, apparently due to a drug; she wished to discuss them with representatives of the Food and Drug Administration. On 6 April 1962 he and I drove over to her home in Baltimore and she told us what she had learned. She was the first-hand contact who was able to show us the evidence--the pictures, the case histories, and the various bits and pieces of evidence that led to the conclusion that this was definitely drug-related. I remember she was particularly struck by the fact that some of these affected children were children of employees of the drug firms in question. She was not aware at the time that this drug was on clinical trial in this country. So, I think she had called Dr. Nestor more as a matter of interest and

concern, not knowing that there was some experience with the drug in this country. She was gathering her information just after Merrell had formally withdrawn its application.

She was named president of the American Heart Association, so she was much esteemed. She talked about the drug at that society's meeting, and got people much more concerned than they had been in the past. She informed a meeting of the American College of Physicians on 11 April 1962 about the outbreak of phocomelia. She even talked before the House Committee that was considering, at that very time, strengthening the United States drug laws. She presented her findings there, and I was in the audience.

Our request for the complete list from Merrell followed our visit with Dr. Taussig and our realization that this was a very definite association and that therefore we would have to take all the measures we could to make sure that none of the drug was remaining in this country where it might be used. The letter was sent on 11 April 1962. In supplying this list, the company also gave us the copies of the form letters they had sent out dated December 1961 and March 1962. In their wording the company stated that all active investigators as well as others who had received the drug were contacted by letter on 20 March 1962. This was what made us realize that not all the investigators had received the letter of December 1961. There might be persons who were unaware of the problem and had supplies of the drug in their

possession. So this was the beginning of the inspection of every individual investigator who had gotten the drug and there were over 1,000. Following the receipt from Merrell of the complete list of more than 1,000 physicians who had received the drug, we broke down the list into specialty areas in various states. This was the prelude to going around to each one of the doctors individually, pick up the supplies of the drug they had on hand, find out if they had used the drug, and if it was being used in any pregnant women, and if they had any birth defects as a result. Out of that we got two or three reports. By this questioning and by looking at birth statistics, we could associate ten cases of phocomelia with the thalidomide that was released for clinical trials in this country, and seven or more cases in those who had gotten the drug overseas.

As I recall, Mr. Winton Rankin took leadership on this problem in the FDA in many respects, over and above Dr. Smith and Dr. Siegel, who were in the Bureau of Medicine. We received Merrell's reply on 25 April 1962. That was the reply that gave the complete list of over a thousand physicians and the copies of these form letters that went out to the physicians both in December and March.

The next significant date in the chronology of events is 20 July 1962, when E. R. Beckwith met with Larrick and told the FDA Commissioner that a recall had been undertaken and completed. This was almost two months after we had received the list with

the larger number of investigators on it. But I was not too much involved in this aspect; I was back on other INDs and NDAs. Another group was taking over in this. But I think one thing to note is that an inspection and recall like this is a fairly ponderous thing. It takes a little time to get out the directions, questionnaires, and other things that the physicians have to be asked, so an overnight recall cannot be made.

I do not know what the Merrell recall consisted of--whether they simply sent letters of notification or whether detail men went from office to office with notifications. It was around that time, though, that we did come into possession of directions to detail men that made us realize that this drug was being handled very casually by the firm when it was being distributed to the investigators. They were told that the drug was virtually ready to be approved and, in essence, it was a detailing procedure to get them familiar with this drug. But we were not aware of this earlier.

I did meet with the representatives from Merrell probably about that time, and I think there is a report of that--I have a memo of that in the file. Merrell officials were anxious to learn if I had been treated perhaps a little harshly by their representative. We discussed some of the aspects and problems of this in the handling of the drug.

In the memo that I wrote on this meeting I addressed myself to officials in the FDA, noting the pressure that had been put on

me. It has been said that I was told by them, "If you can't stand the heat, get out of the kitchen!" I cannot say I remember that. The meaning that was conveyed to me was that this went with the job. I do not believe this was addressed so much at the pressure I had received--although this entered into it. Rather, there was a fair amount of pressure, in general. I think I always accepted the fact that one was going to get bullied and pressured by industry. As I explained earlier, it was understandable that the companies were very anxious to get their drugs approved; the manufacturer's goal was to get drugs on the market. They may have been a little over-eager, and therefore brought some pressure to bear. There was, for example, the time they kept calling me, and they just came right out and said, "We want to get this drug on the market before Christmas, because that is when our best sales are."

I might note that before I came to the FDA, it was very common for reviewers and people there to go out to lunch at fancy restaurants with the drug firm representatives. There was an end to that by the time I came, but I still used to hear tales of eating at the Rive Gauche and things like that. The drug company men were in quite a bit to the FDA, and I do not know if this has stopped now.

I think the Agency in general tends to be under pressure, not only from manufacturers, but also from the public and Congressional committees and so on. It is a way of life in the

Food and Drug Administration, and it was common to accept this pressure and realize it was inevitable.

I wrote in a memo, "I tried to put across the concept that in some cases expediency might dictate that another alternative to quitting might be to yield to the pressure, therefore I felt some attention should be given to the fact that certain companies did seem to be exerting too much pressure." Now there is probably a good deal less of this. There are more orderly arranged meetings and so on. I was quite new to the job when I wrote the memo. An experienced bureaucrat would not write that kind of memo.

With regard to the number of thalidomide-affected births determined by the FDA, as I recollect, we obtained information of some seventeen deformed children born in this country; in about half of these the drug had been obtained overseas--either brought back or the mother had been overseas at the time that she was pregnant and returned home to deliver in this country. There is a list of eight or nine cases in this country in the hearing report. I do not believe we have uncovered additional cases since then. I do not claim that these were all the cases there were. The records make it difficult to get information. This type of drug may be handed out rather casually to a patient who may never be seen again. The patients may not even have been aware that this was a drug that later caused a problem. There are even various reasons why parents do not wish to publicize the

fact that they have had such a problem. In addition, of course, we would only find the cases of the children that had been born deformed. To this day I do not think we know how many stillbirths or abortions were related to the drug. In fact, it may not have been recognized that the mother was pregnant if the baby was so badly damaged early in its development that the pregnancy terminated, perhaps even before the mother knew she was pregnant.

There were probably not many more cases in the United States. We do know that this type of deformity has been recognized for centuries, and we do get reports today of similar types of deformities. But, obviously, there are other external or internal forces that may lead to this deformity. Thalidomide is only one of them.

This recall, of course, caught the eye of the persons who were pressing for drug reform, and there was a very striking newspaper article in the Washington Post by a reporter, Morton Mintz, that also got a lot of attention. In next to no time, the fighting over the new drug laws that had been going on for five or six years suddenly melted away, and the 1962 amendments were passed almost immediately, and unanimously.

The 1962 Kefauver-Harris Amendments and the 1963 investigational drug regulations introduced a number of new procedures which led to the strengthening of the control of drugs entering the market in the United States. The greatest change

was that before a company could even start testing a drug in man it had to submit to the FDA the information that led it to believe it was safe to do so. This would consist of certain chemistry background material and not necessarily be as complete as would be required for a New Drug Application. Then there would be animal studies, the extent of which, in initial submission, would depend on the type of clinical trials it was proposed to undertake. Third, the company would describe the proposed clinical trials: who they would be done by; the qualifications and facilities of the investigators; and the type of population that would be involved--whether it was volunteers, women, children, sick patients, and so on. Then, as additional investigators were added to the trials, their names would be submitted to the FDA so they were aware of the extent of the investigation. And at least once a year the company was required to send in a report bringing information up-to-date. In the interim, if any severe or alarming side effects developed, the company was required to tell the Food and Drug Administration immediately. When the drug company selected investigators to do their studies, these investigators in turn were required to make certain commitments to the company: that they were qualified; that they would keep good records; that they would advise the company of any adverse effects; that they would get patient consent; that they would supply complete case histories; and so on.

One very dramatic last minute addition to the 1962 amendments was by Senator Jacob Javits of New York. He had raised the question, "Do people know they are getting investigational drugs?" It was very clear from our survey of these 1,000 doctors in the thalidomide case that many of the mothers and patients had not been told this, and the doctors themselves did not quite understand the status of the drug. So a very important amendment to the law, not a regulation, was that patient consent must be obtained before a new drug, an unapproved drug, was given in a clinical trial.

Nowadays we know exactly what is being tested and who is testing it and we get results back as soon as possible. Then if we get reported adverse reactions, we may stop the studies and so on. We have much better exchange of information with other countries. Other countries adopted these particular types of regulations that are the same as ours, and I hope that this will do something at least to prevent another thalidomide or elixir of sulfanilamide tragedy. The trouble is that with these great new developments that come along at intervals--we are now in a very dramatic period where we are getting all these exciting new drugs--the entry of new drugs can outrun, or go faster, than our regulations control. We hope this will not be the case and we keep a very sharp eye on it.

I believe the news about the widespread distribution of thalidomide was the entree to getting the Kefauver-Harris

Amendments approved. My endeavors in investigating the safety of thalidomide also led to my receiving the President's Award for Distinguished Federal Civilian Service in August 1962. It is actually documented somewhere that it was Kefauver's group that sent my name forward to the president, because the list of selectees that year had already been announced, and I was very much a last minute addition, just two or three weeks before the event.

It was an interesting ceremony in the Rose Garden, and the astronauts were in the background. Maybe it was just John Glenn. I am not sure. I have pictures somewhere that they provided. My husband and daughters were present. My brothers Stuart and John and my niece Nancy came from the West coast. I was allowed to bring twelve people, amongst whom I think three were to be from the FDA and the rest could be personal ones. I keep my medal in the bank now. After I got robbed once or twice I thought that I had better put it away. I guess the robbers did not see it in my house or did not think it was worth anything! So I just popped it in the bank.

The event itself was interesting. I thought that I was accepting the medal on behalf of a lot of different federal workers. This was really a team effort. I guess one person had to be singled out. But, anyway, there is no doubt that thalidomide did ensure that there would be some improvements in the law on drug regulation. But, it has to be remembered that I

was very new to the agency and pretty naive about how things were done and brought about when I was involved with thalidomide.

**Post-Drug Amendments Reorganizations of New and Investigational
Drugs in the Bureau of Medicine**

After the Kefauver-Harris amendments, the Bureau of Medicine of the FDA was reorganized in such a way that it included two branches. One branch handled the INDs, that is, the notice of claim for investigational exemption for a new drug--the material that the company submitted prior to starting human trials. We coined the acronym IND for this. People think it means Investigational New Drug, and, in a way, perhaps they are correct. We already had the designation NDA, New Drug Application. We realized we had to get a second set of initials that would be in keeping with NDA and not in line. So we hit upon IND, and what it stands for is the notice of claim of investigational exemption for a new drug. That was one branch, the IND Branch. The second branch considered the New Drug Applications. As soon as the manufacturer felt he had obtained enough information--the clinical trials and background material that the drug was then safe and effective for the various proposed uses--he would, as before, submit a New Drug Application. A second group of medical reviewers were in that branch.

I became chief of the Investigational Drug Branch. At that time, some of the pharmacologists were still separate. The

medical officers were still in our old building--the temporary quarters on 7th Street--and the chemists, indeed, were still separate. In essence, I had about twelve or thirteen physicians who looked over IND applications to see whether it would be safe to start studies. We started with a big group of INDs because the law went into effect around 1 June, and for any drug that was under test at that time, or somewhat before, the companies had to provide these new INDs. Then, as new drugs came to clinical trial, they would be added. I think there were about two or three hundred INDs to begin with, and by the mid-seventies they were coming in at a rate of about six or nine hundred a year. Perhaps a third of them were for drugs that had a marketing potential. Many of them were for studies by individual physicians or small groups of physicians who, perhaps, were using the drug to study its metabolism in a person. Other INDs were from physicians who wished to use a marketed drug for unapproved use; frequently a company would be willing to give them some background information but would not want to sponsor a trial, so the physician did it himself.

Then about 1965 or 1966 we had a reorganization of the branches, because there were some problems, and there was another inquiry. First, the load of INDs was very large for the small group available to review them, and, second, there were some problems of overlap as to who was responsible when an NDA was in for a drug but clinical trials were continuing. Examples were

brought to light that again there was this tendency of widespread distribution of a drug with inadequate control. A well-known example of this was DMSO (dimethyl sulfoxide), which happened after thalidomide. Again we were notified afterwards of the investigators who had received the drug. There was a tendency for this sudden blossoming out and a fear that the companies might not be able to monitor these great numbers of investigators sufficiently well, either for safety or to get good information on whether a drug might be useful or safe.

Instead of having a separation between the IND drug branch and the NDA drug branch, the new rearrangement was that the medical reviewing staff was broken down into six divisions based on the type of drug or condition for which it would be used-- endocrines, radiopharmaceuticals, and so on. Now, both the INDs and the NDAs were reviewed within the appropriate division. I believe it was at that time the pharmacologists became part of the division and the chemists, instead of being a separate branch or whatever, joined them in a branch of pharmacology-chemistry. It was a team concept where the medical officer, chemist, and pharmacologist worked right within the same division. This is essentially still the arrangement.

Creation and Work of the Scientific Investigations Function

For about six months I was director of the division that dealt with anticancer drugs and radioisotopes. Then the problem of the scientific value of some of the clinical reports came into

question again. Earlier in the IND days, when it was a separate branch, we had actually gone out and reviewed some of the studies conducted by clinical investigators and compared them, for example, to those submitted to the company and to us. We found some rather serious discrepancies, and a procedure was developed whereby investigators found to be doing this type of study poorly could be disqualified from receiving investigational drugs in the future. Some were keeping very poor records, sometimes they were falsifying the information, and there were a variety of problems.

This really started before the Kefauver-Harris Amendments. I think some of the first work was done around 1960-1961, when one investigator was found to be falsifying records and was actually prosecuted by the Justice Department; he pleaded nolo contendere. There were one or two others while the Investigational Drug Branch was operating because this was a particular area about which we had to be concerned. Then when the reorganization occurred and the divisions took over and handled both the INDs and NDAs, this type of work rather fell by the wayside. It was realized that there was no group that could ensure that the investigational drug regulations pertaining to clinical investigators were being enforced or followed. Nobody was responsible for looking out for the poor performers or crooks or what have you as we had done in the Investigational Drug Branch. Dr. James Goddard, FDA Commissioner, decided that the issue was sufficiently important that there should be a separate

unit formed that would concentrate in this area and report directly to the Bureau of Medicine director.

So, in early 1967 the forerunner of my group, the Scientific Investigations Staff, was set up in the Bureau of Medicine director's office; it became known after a series of reorganizations as the Office of Scientific Evaluation. It consisted of five programs. Some of these were surveillance, to make sure that the investigator was being told of his obligations: that he was aware of patient consent and the type of consent he got; that he was aware of the need to keep good records; that he reported adverse reactions; and so on. While doing this we actually verified some of his work. One program, for example, involved a more or less random selection of New Drug Applications--those just about to be accepted, say, or under review. We visited the sponsor to find out what monitoring facilities he had and, just on a random basis, visited maybe eight or ten investigators.

When we finished our visits we notified both the company and the individual investigator of any discrepancies that we found.

There was a feeling that the responsibility for informing the investigator and keeping surveillance over him rested with the sponsor, and this was a message we were trying to get across.

I think there was acceptance of it. We had another program after 1967 in which we visited the institutional review committees--the committees that were supposed to review, approve,

and almost monitor, as it were, any ongoing study involving investigational drugs in institutionalized persons. These would be hospitalized patients, patients in mental institutions, prisoners, and so on. We had still another program to see that the animal studies were being carried out professionally, honestly, appropriately, and completed in a reasonable time.

There were originally four in the division--myself and Dr. Alan Lisook who is an M.D., and Dr. Elwood Harkins and a secretary. Then we got two of what we used to call Food and Drug Officers in the old days. Later they became Consumer Safety Officers. Both were people who had actually worked as inspectors in the field, and they helped us here.

It was a fairly small division to carry out five operations. We did have assistance. In the field there were a number of offices throughout the United States, and certain inspectors in these offices got special training in conducting this type of inspection. They were called the 200-C Inspectors. They completed some of these assignments themselves. As for others in the division, Dr. Lisook, for example, would go out or prepare a talk that I would present on the type of problems that we encountered.

Our modus operandi at the beginning was to look where the money was, particularly in prison studies, which we knew tended to be poorly performed. We had visited some prisons previously and seen that the circumstances, their equipment, their

personnel, and so on, were not up to scratch. So those were groups we looked at particularly. A little later we particularly looked at studies in nursing homes. We definitely started with the prisons. Then the exposé of prison studies came, and, it came in a curious way, because a couple of men named Austin R. Stough and Cranfill K. Wisdom had a franchise as it were to do drug studies in a number of prisons including, I think, one in Alabama and one in Oklahoma. Actually Alan Lisook had been down there to Alabama, and although the drug study was not the greatest, we could not really pin any scientific fault on them with regard to accuracy. The subjects were actually there, after all. Interestingly enough, the agency had a contract with Stough and Wisdom when they were in Oklahoma to study something about the toxicity of hair dyes or excretion of hair dyes in the urine, I think it was. In Alabama they just did drug studies. Anyway, they were a well-known group. Then they got a contract to supply plasma for processing. In some way the NIH was involved, but Cutter Laboratories actually did the work of getting the various fractions of antibodies or whatever one gets out of plasma, globulin. So they would draw the blood from the prisoners, spin down the red cells, reinject them back in the prisoners, and then sell the plasma. But they were pretty careless in the apparatus, and an epidemic of hepatitis broke out in the prisons. There were a number of deaths, as I recall. This led to an inquiry by the state of Alabama, which appointed a board headed by the

chairman of medicine at the university.

One of the recommendations of this board was that studies done in prisons--maybe just Alabama prisons, but anyway prisons--should be reviewed by an impartial review board. The NIH had just set up such a requirement for grants and contracts, and their suggestion was that this should also be applied to these prison studies, because the people that reviewed some of the work they did found flaws, or problems, or hazards. I think they were shocked at the equipment and so on, much as we were.

That led the agency in some way to consider the Institutional Review Board (IRB) as a requirement for drug studies, regardless of whether the studies were funded by the NIH or not. I think it had been considered earlier but dismissed as impractical, because the number of sites doing drug studies greatly outnumbered those to which grants or contracts were awarded. Under the system developed by the NIH, the institution got assurance from or made an assurance to the NIH that it would have such a committee, that it would consist of certain people, that there would be a reasonable balance between science and non-science people, and so on. But we realized that we did not have the manpower to set up and approve all these assurances. Instead we developed the regulations which are added as a long paragraph to the clinical investigator statements, describing the committees and saying they should follow the directions set up by the agency. So that was the tie-in between the prisons and

review committees. Dr. Lisook was the man who went to all of the prisons and knew what they were like and some of the sins of omission that were committed.

So we published the regulations, and there were to be no more prison studies except for the good of the prisoners or something like that. They were going to require an independent committee at the FDA, to look over them, which I thought was a lousy idea. Anyway, whatever the proposal was, one of the drug firms and a union of prisoners or a group of prisoners challenged us, and we stayed those regulations. We disagreed with the idea that some proposed of outlawing the use of prisoners altogether because we really found no major problems with the drug testing.

I was on the committee at the time when they were reconsidering the various IRB and consent requirements. I think mine had to do with the prisoner requirements. I am not so sure that I was not roped in as secretary or something. Every now and then I see minutes of what we discussed. But at that time--I do not know where the figure came from--90 percent of all Phase I studies were done in prisons in this country. Now, in Europe, they shuddered at the very thought of studies in prisons, because of the German wartime experience.

The FDA did not anticipate that the prison population that was the primary population for Phase I tests would disappear and there was some concern. I think the companies did not want to get involved in any way, and there was a great outcry at the time

when this threat of loss of drug trial candidates came up. The concern was: Where will we get the subjects for Phase I studies if we cannot go to prisons? One drug firm representative even said with a perfectly straight face, "I think we will have to think of something like national conscription where you give your time to be in the drug tests." I suppose that was the rhetoric of the time.

We now see particular groups that populate the Phase I tests, like students or street people. We visit these sites, if they are doing certain types of studies, a bioequivalency, for example. Actually, we do not look at too many Phase I studies now. Our focus has changed. Unless we happen to get a complaint, and occasionally one will come through and we will look into it--somebody did not get paid when they thought they should or something like that. But the bioequivalence studies and the Phase I studies seem basically to be done either in students or in street people which can be a bit of a problem. There have been, for example, advertisements in the Washington papers about participating in drug studies, helping people out, and getting paid. A bus will pick you up at Union Station or something, transport you to Baltimore, say. So they are reaching out and getting people.

I think maybe there are difficulties in finding recruits for studies, because the problem is often in the dropouts. People will drop out of the study, and this, of course, is expensive for

the firms, because they may have to scrap the study and so on. If there was a great demand to get into these studies, probably there would be less likelihood of people dropping out. I do not know if that is true or not. We do not have any hard information on that. It is just my speculation. But there is an increasing demand for them through the generic testing, and it is a little bit of a problem where people come from and so on.

Now quite a bit of drug testing is done overseas, because many overseas countries, England, for example, do not require an IND for doing Phase I type studies. We will accept the data unless we have reason to throw it out.

I think the amendments and IND regulations helped the FDA get much better clinical investigations, and this was not the only improvement. We had a much bigger organization, we attracted many experienced physicians, and we drew up guidelines to specify how we thought certain drugs should be tested. Also, we had better liaison--better contact--I think, with the sponsors, and in a more orderly fashion, because the IND requirements indicated that the study should proceed with what we called Phase I trials first, meaning, that these were in normal volunteers. Phase II might be an extremely limited clinical study under experts, involving five or ten centers. Finally, Phase III might be a more general test, not extending in the way thalidomide did, but proceeding in an orderly fashion that might involve, say, a hundred investigators. Throughout these stages

the company is supposed to keep in touch with the FDA by way of reports at yearly intervals, medical officers' reviews, incoming reports, reports of the new protocols or new persons added, and the FDA may--at any time--challenge the qualifications or what-have-you of the investigator, for example, whether he has the facilities to do it.

I think this kind of scrutiny has increased the quality of the investigational work being done. Also, clinical pharmacology developed tremendously from the sixties into the mid-seventies. There were more well-qualified people in the field. Now, admittedly, those were not the people who were going to work on a rather mundane what might be called "me-too" type of drug. It was harder to attract good investigators for those. So, some of our problems lay with the less glamorous drugs.

I am now in what we call bioresearch monitoring. Every time a regulation is made insisting people do something some way, there has to be an inspectional program, to make sure they are doing it that way. So we go out on regular visits to doctors. We make sure they are conducting the studies as they said they would; that the patients have given consent, that for all the trials, before they are begun, they have gotten the approval of the local committee of both scientists and non-scientists. We go out to the animal laboratories and make sure that they are following our Good Laboratory Practices, whether their records are accurate, with no fudging--and believe me we find fudging in

all areas, clinical and animal. We go to these Institutional Review Boards that review the studies from the point of view of the patient consent. We do accept foreign studies under the understanding that we may go out and inspect those too. So we frequently go to Canada or England, or elsewhere, and look at important studies to make sure that they are done properly. Other countries have adopted, for example, our Good Laboratory Practices, and we work with them in that respect. The Canadian laws are virtually the same as ours and we work very closely, with Canada particularly, but also with England in a tripartite committee. We are able to discuss common problems, so that is a great step forward.

We also examine more closely the clinical investigators who are working on drug trials. When I first came to the FDA it was word of mouth that there was a small group of investigators who were working on a lot of different studies. A bunch of us would jot down a name when we saw it and compare notes. It was the same thing I had done when I worked at the AMA. Then once we got the IND system in, we had a data retrieval system. One of the things that went into that--first, it was IBM cards--was the physician's name and the drug he was studying, and so we could then match them up. Of course we have that now in a glorified fashion. We were starting to do that a bit manually as I recall, even developing informal lists, and then we were thinking of doing it more formally. It was so much easier once we had the

IND. With the NDA there were only the few people the company had chosen who sent in studies. In the thalidomide study, as I have noted, we believed we had something like forty investigators, but yet we found out later that over a thousand people had gotten the drug. But now we can keep a good tab on this.

I have recorded a list of ineligible investigators in a paper on the bioresearch monitoring program. It is clear how it shot up. It was quite modest at the beginning because we did not have much of a system. From the first one in 1964 up to December of 1990, there are seventy-one listed. Earlier on, these investigators tended to be more favorable to the drugs. We had one program which was to look at people who were participating in over a certain number of studies but it was not very fruitful. We have also had some very good people who have worked on a number of studies.

Theoretically, we do not know how these investigators are compensated and are not privy to that information, but obviously they do get some compensation. I guess in the early days it was the honor of having your name in the published paper, which the company usually wrote. But I am sure that there would be always some financial reward, including in some cases stock interests and so on. For some drugs we did run some figures. The investigators are paid, and they have always been paid fairly well. The patients, except in Phase I tests, are rarely paid. An investigator might receive a thousand dollars a patient for a

one-week study and might have twenty, thirty, or forty patients.

Certainly when disqualified, for many of these investigators this is a concern--their livelihood is taken away or something. Or they claim that if we make them have an agreement or something, it will cut down the number of studies. There are no bones about it, some people obviously are making drug trials their business.

In fact, we had one who said, "This is a very competitive business." He was referring to the business of being a clinical investigator. We have him on record in one of our informal hearings. I was a little shook up to think of drug trials in terms of being a business, but I guess they are.

The suspicious investigators were pretty obvious when there was too great a success reported. Their results can be compared with a lot of different results from other people. These are all written out and you can really go over them pretty well. John Nestor was one of the early investigators in this area. He is sort of a legend around here. For example, there was a general practitioner on the outskirts of Washington who did a lot of studies, and one of them involved the use of a ballistocardiograph, which is a very sophisticated instrument for measuring the output of the heart by seeing how much the patient jerks when his heart beats. Anyway, John just could not believe, because he was a pediatric cardiologist, that a general practitioner on the outskirts of Washington would have access to

a ballistocardiograph. It is a hospital instrument. He found not only that the man did not have access, but the man was out of the country for much of the time when all these case reports were filled in, and he did not have the competency to conduct the tests. He was testing a wide variety of substances, too--did not stick to just one. It really got John's goat that someone could claim to be using a ballistocardiograph, without having the skills and knowledge that it would take to run one, or the finances to buy one. Of course, all these events are available in narratives at the records. I do not think everything is destroyed of these early investigations. We have the records, the reports, on most of them at the FDA. Some fraudulent investigators were prosecuted.

One funny story was in Vet Medicine. They disqualified a vet. I guess they prosecuted him, and they had to call the pets' owners as witnesses, and the reports would be Fido with a broken leg and all this sort of thing, what he did, and how wonderful this medicine was. Well, Fido just had a little scratch or something. It was almost as though it were a parody on one of our investigations, but these were real patients.

To turn to informed consent, the statements in the 1962 law and the Food and Drug regulations about this are exactly the same. They used the same words, because frankly this was a new concept for the Food and Drug Administration. We never imagined we could have gotten away with anything, however much we thought

the doctor should do, because at that time the doctors felt they were the Lord Almighty. That the patient should take what the doctor gives them because doctor knows best. And if the doctor thinks it is important that this drug be studied in a fashion that the patient does not know he is getting an unproven drug--not to worry. Big Daddy will take care of you.

We had to draw up a report titled "Consent for Use of Investigational New Drugs On Humans: Statement of Policy."³ We sent it around. I think I still have some of the background things we sent out to a number of people around the country. I do not know what the reason was why it was not put into the law at that time. I guess there has always been a difference of opinion as to whether a policy statement has the force of law. At least we were able to use it as a guide and quote it, but I do not know if we had had a court case whether it would have been challenged. This is a technical problem. I have heard some of the lawyers say it was just as good as a regulation.

Obviously people conducting trials gave the least possible thought they could to consent. We ran across things. I have files full of statements such as "I hereby agree to take this drug. It is doing very well in Europe, and I absolve Dr. So-and-so, the hospital, the janitor, and everyone else from any harm that I may suffer in the course of taking the drug." Literally that type of consent was extremely common, and some hospitals'

³ Cf. 32 Fed. Reg. 3994-3995 (11 March 1967).

legal departments required it for protection even though it would not stand up in a court of law. We almost never see it any more.

Some people really were not very happy with the thought of informed consent. Louis Lasagna's view was something along the lines of even well-informed responsible clinicians had rejected the idea of getting informed consent from patients. In other words, there probably were times in which it was okay to withhold the patients' consent. My reply to that was not really cast as a rebuttal. It was just a statement of plain fact. I was pleased with the way my article on it came out, because it laid the ground work for the handout, I think in a way, of that policy statement to some extent.⁴

There was an informed consent policy in the agency at the time, even though it was not in writing. The only thing in writing was this little bit in the 1572s and 73s the investigator signed that he would get informed consent unless it was impossible and so on. In the same way the sponsor signed that he would see that his investigators were aware they had to get informed consent. There was absolutely nothing to indicate what informed consent was. I am sure a part of my paper on informed consent was based on what the NIH had in their little handbook. I think they gave some guidelines or guidance in that little

⁴ F. O. Kelsey, "Patient Consent Provisions of the Federal Food, Drug, and Cosmetic Act," in I. Ladimer and R. W. Newman, eds., Clinical Investigation in Medicine: Legal, Ethical, and Moral Aspects (Boston: Boston University Law-Medicine Research Institute, 1963), pp. 336-344.

yellow Bible thing. The NIH preceded us, I think. They had some guidance; I cannot remember what it was. Any thoughts I would get originally would come from the few inspections we had made where we found these terrible examples of either lack of consent or poor consent. My statements there were ones that many people at one time or other had echoed and which we thought were reasonable ones.

Then, of course, there was the loophole that in Phase III informed consent need not be in writing, because Phase III in those days was the late stages where they were just distributing a drug rather widely to get different experiences for toxicity and so forth, and a lot was known about the drug. You could get informed consent, but it was to tell the people that this marvelous drug actually was not technically approved. But you had to make a notation in the patient's record that you had so gotten consent.

Well, we would go out; Dr. Lisook would go out. The doctor would say, "Oh, yes, I got the informed consent." "Where is it in your patient records?" Of course, it would not be there. I guess the doctor did not have quite the nerve to write in that he had got it, but he did not mind telling us, verbally assuring us.

So it was honored in the breach more than the observance even after those guidelines. But when we had a survey in which we looked at clinical investigators--it was from nine sponsors and large small, and middle-sized companies, and a whole pile of

investigators--I think we tabulated what we saw in the way of consents, and the results were not the greatest.

I hope this later discussion gives an indication of my post-thalidomide career. Essentially, to sum up my work at the FDA since 1962, I have been in three review divisions. I was head of the new IND branch responsible for setting up the whole IND system for the first time this material had to be submitted. We had a very interesting operation going, and then, of course, that was dissolved. I went briefly into a review division--that was the anti-cancer and oncology division--in the next rearrangement and then I moved into this new unit in 1967 that I have been in ever since. It has kept changing names; it has kept changing centers; it has kept changing this, that, and the other. At one time we were united with Biologics, for example. But still it does essentially the same thing, monitoring the conduct of studies, at first it was the clinical studies, then we soon got into the animal studies, and then the IRBs. Finally came the agency-wide bioresearch monitoring program. That is where we are today, and it was a long time before we got into compliance. I must say we came in with my kicking and screaming, because I did not think we really belonged there. But actually it has not been too bad. I always felt we should be very close with the reviewers and the reviewing medical officers, and get lots of feedback between them and us. But we have managed to preserve our professional outlook and continue to have a good rapport, I

hope, with the field investigators. It has been an interesting career.