



**Oral History Interview with  
Bernard L. Oser, Ph.D.  
President, Director & Chairman  
Food Research Laboratories  
1926 -1976**

**FDA Oral History Program  
Final Edited Transcript  
August 2, 1988**

# Table of Contents

Table of Contents .....	2
Oral History Abstract .....	3
Keywords .....	3
Citation Instructions .....	3
Interviewer Biography .....	4
FDA Oral History Program Mission Statement.....	4
Statement on Editing Practices .....	4
Index .....	5
Interview Transcript.....	7
Deed of Gift .....	79

## **Oral History Abstract**

Bernard L. Oser is widely recognized as a pioneer and preeminent expert in food additive safety research. He earned a masters degree in science from the University of Pennsylvania in 1920 and a PhD from Fordham University in 1925. In 1926 he joined Research Food Laboratories as Assistant Director, and over the next 50 years also served as president and director (1957-1970), chairman (1970-72) and finally retired as corporate director in 1976. In the 1950s he advocated for the increased use of toxicological studies to evaluate food and food additive safety, and in the 1970s conducted influential studies on the carcinogenicity of saccharin.

## **Keywords**

toxicology; food additives; color additives; Delaney Clause; carcinogens; laboratory animals; research methodology

## **Citation Instructions**

This interview should be cited as follows:

“Bernard Oser Oral History Interview,” History Office, U.S. Food and Drug Administration, Department of Health and Human Services, August 2, 1988.

## **Interviewer Biography**

Suzanne Junod, Ph.D. is an historian in the FDA History Office at the U.S. Food and Drug Administration. Soon after beginning her career at FDA in 1984, Suzanne helped to organize the FDA History Office. She is a subject matter expert in FDA history and her scholarly writings have been published in *the Food, Drug, and Cosmetic Law Journal*, the *Journal of Federal History*, and the *Journal of the History of Medicine and Allied Sciences*, as well as edited compilations. She is an active officer in the Society for History in the Federal Government. She earned her Ph.D. at Emory University in Atlanta, where she studied under James Harvey Young.

## **FDA Oral History Program Mission Statement**

The principal goal of FDA's OHP is to supplement the textual record of the Agency's history to create a multi-dimensional record of the Agency's actions, policies, challenges, successes, and workplace culture. The OHP exists to preserve institutional memory, to facilitate scholarly and journalistic research, and to promote public awareness of the history of the FDA. Interview transcripts are made available for public research via the FDA website, and transcripts as well as audio recordings of the interviews are deposited in the archives of the National Library of Medicine. The collection includes interviews with former FDA employees, as well as members of industry, the academy and the legal and health professions with expertise in the history of food, drug and cosmetic law, policy, commerce and culture. These oral histories offer valuable first-person perspectives on the Agency's work and culture, and contribute otherwise undocumented information to the historical record.

## **Statement on Editing Practices**

It is the policy of the FDA Oral History Program to edit transcripts as little as possible, to ensure that they reflect the interviewee's comments as accurately as possible. Minimal editing is employed to clarify mis-starts, mistakenly conveyed inaccurate information, archaic language, and insufficiently explained subject matter. FDA historians edit interview transcripts for copy and content errors. The interviewee is given the opportunity to review the transcript and suggest revisions to clarify or expand on interview comment, as well as to protect their privacy, sensitive investigative techniques, confidential agency information, or trade secrets.

## Index

- A.O.A.C. International, 14, 17
- Abbott Laboratories, 46, 52, 53, 55
- advisory committees, 59
- antibiotics
  - tissue residues, 22
- arsenic poisoning, 50
- bread hearings, 39
  - emulsifiers, 40, 41
  - myrj, 40, 42
- brominated vegetable oil, 44
- carcinogenicity, 74
  - in humans, 72
- carcinogens
  - safety threshold, 71
- career
  - Philadelphia General Hospital, 10
  - textbook on detoxification, 9
- Carson, Rachel, 70
- cod liver oil, 14, 16
  - Scott's Emulsion, 16
- color additives, 18
  - coal-tar, 18, 19
  - international standards, 33
  - mauveine, 18
- Color Additives Amendment, 33, 59
- color chemistry, 19
- Coumarin, 63
- Crawford, Lester, 57, 59
- DDT
  - use as delouser during World War II, 21
- Delaney Clause, 37, 47, 52, 75
  - ambiguous language, 73
- Delaney Committee
  - testimony, 56
- detoxification, 8
- Division of Nutrition, 67
- Dow Chemical Company, 42
- experimental methodology
  - variables, 75
- Flavor & Extracts Manufacturers Association, 62
- food additives, 20
  - benefits vs. risks, 76
  - definition, 58
  - safety thresholds, 67
- Food Additives Amendment, 47, 59
  - grandfather clause proposed, 57
- Food and Agricultural Organization of the United States, 32
- Food Protection Committee, 73, 75
- Frazier, Elicitor, 67
- Generally Recognized as Safe (GRAS), 11, 22, 61, 63
- Gordon Research Conferences, 28, 30
- Hawk, Phillip, 7, 16
- Hesse, Bernard, 18
- Hoover Diet, 14
- Imperial Chemical Industries, 39
- International Union of Pure and Applied Chemistry, 14
- Joint Expert Committee on Food Additives, 32
- laboratory animals, 11, 59
  - breeder colonies, 12
  - breeder diet, 12, 13
  - rats' incompatibility with humans, 37
- LD50 toxicology test, 17
- Lehman, Arnold, 10, 22, 25, 26, 27, 44, 56, 58, 60, 61, 62, 66, 67, 68, 69
- Ley, Herbert, 52
- Miller Act, 34
- National Academy of Sciences, 54, 59
  - National Research Council, 35
  - pesticide toxicity, 38
- National Toxicology Program, 49
- naturally occurring substances in foods, 64
- nutritional bioassay, 11
- oleic acid, 68
- orange drink, 43
- Perkin, William Henry, 18
- personal history
  - education, 7, 8
- Pesticide Amendment, 59
- pesticides, 20
  - Aramite, 35, 38
  - carcinogenicity, 38
  - Dow Chemical Company, 21
  - maleic hydrazide, 42

no adverse effect level, 35  
 Vitamin D, 21  
 Poison Squad, 20  
 polyoxyethylene esters, 39  
 publications  
     What's New in Food and Drug Research?,  
         11  
 saffrole, 63  
 Smith, Robert, 10  
 Society of Toxicology, 31  
 sodium chloride, 48  
 sodium metabolism, 49  
 sweetening agents  
     Calorie Control Council study, 48  
     cyclamate, 46, 47, 53, 54, 55, 59, 60  
     Dulcin, 45  
     P4000, 45  
     saccharin, 47  
     sodium hippurate, 48  
     Sucaryl, 46, 51  
 sweetening agents  
     saccharin, 45  
     sodium hippurate, 48  
 Tox Roundtable, 27, 30  
 toxicological testing  
     FDA methods, 27  
 Toxicology  
     hazard, 75  
 Toxicology and Safety Evaluation  
     conference, 30  
 toxicology testing  
     chronic studies, 22, 23  
     FDA methods, 25  
     LD50, 22  
     safety, 31  
     veterinary pathology, 23  
 U.S. Pharmacopeia Vitamin Commission,  
     14  
 U.S. Pharmacopeia, 17  
 vitamins, 11, 14, 29  
 Vos, Bert, 56  
 Wiley, Harvey, 17, 19, 45  
 Williams, R. Tequin, 8, 10, 49  
 Wodicka, Virgil, 67, 68  
 World Health Organization, 32

## **Interview Transcript**

SW: Today we're interviewing Dr. Bernard Oser in Rockville, Maryland. It is August 2, 1988, and with us is Mr. Ron Ottens. Dr. Oser, why don't you give us a little bit of background on how you came into the field of Toxicology and then we'll talk more about your relationship with FDA.

BO: Very good. I graduated in chemistry from the University of Pennsylvania, in 1920, and between then and 1926, I went on for graduate work at Jefferson Medical College and then to Pennsylvania medical school, and I got my doctorate in '27 from Fordham University, although I had left in '26.

SW: In chemistry?

BO: In physiological chemistry. In 1926, I rejoined Dr. Hawk.

SW: Dr. Phillip Hawk.

BO: Pardon?

SW: Is this Dr. Phillip Hawk?

BO: Phillip Hawk, yes, who had left Jefferson in 1922 to establish field research laboratories, and he had a number of clients, one of whom wanted a clinical laboratory set up, and that's why

he specifically engaged me. This was a medical institute in New York, and I'd had several years' experience in clinical chemistry at Philadelphia General Hospital, particularly in setting up blood chemical methods which had never been used before; they were just coming in.

In the meantime, Dr. Hawk's book on physiological chemistry, the first edition of which came out in 1907, was then in its eighth edition, and I collaborated on it and bid on that, and a lot on the ninth and even more on the tenth, when I introduced the first chapters on vitamins, the first full chapters which were, by the way, reprinted separately and distributed to friends and clients. But then I also introduced Blood Chemical Methods in the book and so on.

My doctorate degree was obtained at Fordham University, which at that time was the center in the United States of studies in intermediary metabolism. That's what it was called, and Dr. Sherwin, who headed up the department, was very well known in this country as a pioneer in that field. Intermediary metabolism became known in the book and generally as the "detoxification and metabolism." The world pioneer, a leader in that field, was R. Tequin Williams, who wrote the first book on detoxification, and I got to know him ultimately.

SW: Now explain detoxification.

BO: Pardon?

SW: Explain detoxification; I'm not familiar with that.

BO: Detoxification is the process whereby substances are metabolized to less toxic forms and are generally either excreted or exhaled and so on. The tendency is detoxification [of?]

xenobiotics. Those are foreign substances, and that began to play a role in the book, what were succeeding editions. Now, I worked on the ninth edition and on the tenth edition and introduced a lot of new material, and I continued that until the fourteenth edition, when the book finally went out of print. So I had between 40 and 50 years with that book. Dr. Hawk gradually retired from it. He would write the index.

SW: (laughter), and left it to you to do the rest.

BO: And, by the way, we had a very voluminous index. You don't have the book here? Shame on you.

RO: Were you doing human studies on detoxification then?

BO: At that time, both human and animal studies were being done. There was not as much; there was really no opposition on the carefully controlled conditions to doing human studies.

SW: What kind of substances were you working with?

BO: Ah, mostly chemical compounds that went through relatively simple processes of oxidation, reduction, and methylation; about five or six different processes. But mostly, they were oxidational reduction.

RO: Were those chemicals that were in the human food chain?

BO: Not much. No, they were basic chemicals like amino acids.

SW: So you were doing more theoretical research at that stage?

BO: Phenolic compounds. Nothing as exotic as what we know today, as pesticides were their multivariate moieties in heterocyclic molecule. That was, that came up much later, and during a period that Teq Williams in England pioneered, and as a matter of fact, just a jump ahead of it, I became the organizer and the head for many years. Actually about 30 years of an expert panel which I organized, really originally for the flavor industry and I had the membership of that panel, was mostly from the United States, some from Canada and England, but were regarded by Arnold Lehman years later as the unchallengeable, and Teq Williams was a pioneer in the more exotic types of metabolic processes, and after he died, we replaced him by his successor at St. Mary's Hospital, which was Dr. or Professor Robert Smith, Bob Smith.

Before I rejoined Hawk – I say rejoined because I was with him at Jefferson, and when he left Jefferson to start Food Research Laboratories, he called me and asked me to come back and join him in New York. During the years that I was working at the Philadelphia General Hospital introducing new methods, blood chemical methods mostly, and taking my work for the master's degree at the medical school in Pennsylvania, I became quite “proficient” in clinical chemistry, and that was one of the reasons why Hawk wanted me back. I kept the chapters of the book up to date. I showed you a picture last night of . . .

Of the editions of the book. I think it may be in here, all 14 editions of the book at one time. We put, when I was heading Food and Drug Research Laboratories, I put out a quarterly

publication called *What's New in Food and Drug Research?*, and I scooped a lot of the press because I had so much contact down here that I knew what was coming, and I published the first GRAS list that the FDA put out before it got into the press. And so, anyhow, were not up to toxicology yet.

When I rejoined Hawk in 1926, it was then that I began to introduce these new chapters, and one in particular on vitamins, regarding vitamins and nutrition. Now my contact with vitamins was this: the word vitamin was coined in 1912 by Casimir Funk, whom I got to know through one of his associates even before I left Philadelphia. In addition to writing on the subject, which I did, we began to do nutritional bioassays around that time because there were no chemical methods for vitamins in those days. The only way you could assay for vitamins was biologically, and we used guinea pigs for vitamin C and rats for the B or B complex, as we called it, and chicks for the form of vitamin D that they could utilize, and so on. So there were a number of different species of animals we had a little experience with, and that began to grow. And shortly after I joined him, I found that what we were buying, it was not my responsibility, but we were buying rats from Wistar Institute. Now, the Wistar Institute for the rat was equivalent to Jackson Laboratories in Maine for mice. Jackson Laboratories specialized in a large number of strains of mice, each of which had some particular properties that made them suitable for certain lines of research.

When we started our colony after I got in there, Dr. Hawk said, "What do we know about breeding rats?" I said, "Not much, but we're paying too much for them; we're paying \$4.00 apiece for a rat and \$7.00 for a breeder rat."

So it happened that my sister was working at Wistar Institute. She, too, was a clinical laboratory technician originally, and then she came to work for the Wistar Institute and she knew

how to handle rats and how to breed them. She he said, “Well, let’s get her up here temporarily to get us started.” So she came up for a temporary job which lasted about 60 years, and she was really in charge of our breeding colony and our biological work with rats and other animals for a long time, very experienced, but had no Ph.D., never did, but she knew a lot more than Ph.D.’s that we employed. However, we did begin to breed rats, and for the purpose of running vitamin assays.

Now, we became very conscious of several things. First of all, in order to conduct an experiment with a large number of rats, the proper thing to do is to breed rats or have access to rats and litters so that you could take all the males of a litter and distribute them statistically over the number of dosage groups or controls. So having available rats and litters was novel with us, and even FDA used to have to go out and buy rats on the open market against bids. It was the best bidder, the lower bidder, and they had a lot of trouble with rats in the old Agriculture Building.

And another thing that I thought they needed to do was to know something about the diet that they were put on, the breeder diet and the controlled diets, and that, of course, we became specialists in because for every type of vitamin assay, you needed a special type of diet deficient presumably only in one factor, and that was the factor that you were testing for, you see. So we became very much concerned in breeder diets. And, as a matter of fact, we took one of the most commonly used salt mixtures in experimental diets at that time, called the Osborne-Mendel mixture, and we devised a simple method of preparing it. Instead of using carbonates and acids to make up the mixture of the proper mineral content for the rat, which, by the way, was determined in various ways, but the one that we particularly used was based on the analysis of rat’s milk up at Yale.

So we developed that diet, which later became the USP diet. This salt mixture, which became pretty well known, possibly because we included it in the chapter on maintenance of rats in our book. That became to be known as the Hawk-Oser Mixture. Hawk had nothing to do with it, but he was the boss. At any rate, we had laboratories around the country asking to buy it. So it wasn't much more difficult to make a hundred pounds at a time than it was to make 10 pounds, so we used to make it available to a limited number of laboratories. They used it, and it became fairly popular.

But anyhow, the breeding of the rats, the use of divided litters, and they pay a great deal of attention to the basal diet; even the Wistar Institute, which bred rats mostly to study anatomical features as the animals grew older, and also to investigate the behavioral characteristics and so on.

Standard dieting the rat, and the diet, I thought, was credible for good bioassay work. We did that for many years at great expense. Eventually, other feed manufacturers, particularly Purina, began to come out with natural mixtures, but they never disclosed the composition. They were very close-mouthed about that, and I thought if you're doing this kind of work, you ought to know what you're feeding the animals. And so Herb Schaeffer, who was at that time at Ralston-Purina, was in charge of that. He said, "Never mind, take it easy, and they took that attitude for a long time. Even later on, when I wanted to know whether any of the ingredients of this diet were ever treated with pesticides, I never could get a definite answer. The answer was yes, but he didn't know what pesticides and things of that sort. I was a stickler for that kind of control in work with rats, and this partially explained to my satisfaction why there was so much difference among laboratories, a lot of disagreement about laboratories doing bioassay work.

[TAPE 1, SIDE A, 00:20:00]

Fortunately, we got into great depth, and I became a member of the U.S.P. Vitamin Commission, the A.O.A.C. Committee on developing vitamin methods, and the International Union of Pure and Applied Chemistry internationally, because we were buying cod liver oil from all over the world, not from all over the world, but from Norway, from Japan and South America, from various places. And the price, not only the price, but the duties paid on those oils were based on their potency. The potency was stated by the seller and was presumably checked by the buyer, and they always had arguments, you know, to how potent the oil was, and the duty was based on our assays because we assayed every oil that came into this country, the East Coast and West Coast as well, cod liver oil especially.

Now, vitamins A, B, and C were the first three vitamins that were identified by any kind of a number. Nobody knew what their composition was. They knew that the oil-soluble vitamin was A, B was water soluble, and C was ascorbic acid, as we later found out, and that had been known for its therapeutic value for several hundred years because it was used by Limeys on long sea voyages; and early in the twenties, 1922, it was discovered that vitamin A had two factors. One was heat labile, the other was heat stable, and the heat-stable one became known as vitamin D; that was the fourth vitamin. And then B also had a stable factor and an unstable factor. The unstable one became known as vitamin B1 and the stable one, vitamin B2, and they were among the first of the B complex that were actually identified as thiamine and riboflavin. Since then there have been at least a dozen, maybe 15 factors that had resulted from breakdown of the vitamin B complex. Some of them retained the status of vitamins; others did not because they were found not to be essential, at least in the Hoover Diet, and so they were dropped, and that's

why you have gaps between B1, B2, B3 was really skipped at the time, and then B4, B6; they kept skipping, you know, and their latest one was, I think, B15. Anyway, this is the history of vitamins from the early twenties to about the mid-forties.

The discovery of new vitamins: every time you discovered a new vitamin, you knew that that vitamin had to be included in the diet of the species, which was mostly the rat. I'm going to add to that to say why we had to use the rat.

RO: Excuse me, Dr. Oser. You mentioned that your Food Research Institute examined every entry of cod liver oil.

BO: Of cod liver oil.

RO: Was this for the industry or for what?

BO: It was mostly for the buyer and to resolve the differences, which were almost universal, between the seller who claimed higher potency than the buyer, who claimed lower, because they paid for the unit age, you see.

SW: Did all the buyers just get referred to you, or did you just become a specialist in that area, or was it a concerted effort to . . .

BO: Well, we were the, we were pioneers in developing the methods. We became known as the ones that were recognized by the Customs Department and by Food and Drug as experts in

those vitamins. You have to remember that we were not then using chemical methods for vitamins. There were none.

SW: You were using animals, right?

RO: Only bioassays.

SW: Right.

BO: Yes, later on we began to get microbiological methods with some of the vitamins, particularly of the B group. The first standard for vitamins A and D was cod liver oil, then regarded as the most potent source of those vitamins in nature. It was replaced early in the '30s by halibut liver oil, which was many times more potent, but the cod liver oil was one of our special fields, and, as a matter of fact, was responsible for my heading up the laboratory as I did in the early '30s. Why? Because Dr. Hawk went to Norway to teach them how to make cod liver oil. Instead of by the crude methods that they were using then, which even included allowing cod livers to rot and siphoning off the oil or decanting off the oil, we introduced the centrifugal process and got fresh cod liver oil out rather than oxidized or partly oxidized oil.

Our client at that time, by the way – I guess this is important from your point of view, was Gottenbon, who made Scott's Emulsion. Did you ever hear of Scott's Emulsion?

SW: Yes, I've got pictures of train cars advertising it.

BO: Well, Scott's Emulsion was the best-known cod liver oil preparation outside of the oil itself in this country. And Dr. Hawk went over there to introduce centrifugation into the production of cod liver oil, and when he went away he said, "You take charge." And I began to take charge, and I was no businessman, I want to tell you that (laughter from all three). I didn't know how to keep books and I didn't know how to dictate letters or anything of that sort, but I learned the hard way, and I never did really learn. I never was a good businessman.

Anyhow, that experience in developing vitamin methods and running bioassays, and we were then the only laboratory in the country doing bioassay work outside of the universities and the few industrial laboratories that company laboratories, you know, internally.

In the early '30s, a couple of laboratories began to appear. That was about 10 years after the founding of our laboratory by Dr. Hawk. We did a lot of work in nutrition, published many papers, and participated in the adoption of official methods for the A.O.A.C. and the U.S.P. particularly, and other feed associations, and so on. So, really, it was almost all nutrition.

Now, along about after the passage of the 1938 amendment to the 1906 Food and Drug Act, we began to get calls from industrial outfits whose idea of toxicology was LD50's.

[END OF TAPE 1, SIDE A]

BO: A toxicological test mostly in industry was an LD50, but this was for either drugs or toxic chemicals, not pesticides; that wasn't emphasized yet. And it was mostly for internal purposes.

However, it should be mentioned, the first animal work that was done at the Food and Drug was when Wiley was the head of – who was the father of the Food and Drug Act, you know, the father, not the founder; he had a long, long struggle to get that Act, and that reads like

fascinating fiction. At any rate, Food and Drug employed a man who was a consulting chemist in New York, whose name was Hesse, Bernard Hesse, no less. He was the first Bernard in toxicology.

SW: Okay. (Laughter)

BO: And he did work largely on food colors, which was a target of Wiley's attack. Let me say something about food colors. They were discovered by accident in 1856. You heard the story about mauve, m-a-u-v-e. Well, mauve was discovered from the gunk in a sink turning purple, and when Perkins, a very famous chemist in those days, analyzed it, he found it was a derivative of aniline and was brilliantly colored, and it began to produce mauve as the one and only coal-tar color, so-called "coal tar color," because it was made from that kind of gunk.

SW: In England.

BO: England. Perkins, I said. But Germany ran away with it.

BO: In Germany, you know, you could make colors out of coal tar; well, they made them. They made them by the score, but they made them for use in textile dyeing. There were never concerns about toxicity; there were just dye colors, dyes, textile dyes. And there were a lot of them. And they named them by odd names, you know, people's names and so on, because they didn't know in many cases what they really were chemically, synthetically, but if they did, it was

the fellow who identified them, like Scheele was a German, S-c-h-e-e-l-e. He had a number of colors named after him, and so on.

To digress a bit, that was in 1856 that the first color was developed. In 1956, there was a big celebration held in the dye industry in this country, and I attended some of the affairs, and at one of them we were given a big fat book on all those colors, their history and their uses and so on, and the book had a mauve cover, and everybody who attended got a mauve bowtie, which I still have and use occasionally when I go to one of these affairs where color chemists are involved.

Anyway, a great many of these colors were used, and a great many of them ultimately found their way in foods, because nobody was too concerned about safety in those days, so they began to use these coal-tar colors in foods. So that's why in the 1906 Act there is a special provision governing coal-tar colors, which had to be "harmless and suitable for use," and each batch that was produced had to be sent down to the Food and Drug to be certified, so each batch had a certification number and so on, we think. We don't know for sure, but that's the way it was supposed to be. And they began to take a definite interest in their safety along around the turn of the century, and Wiley hired this man Hesse to run tests, you see. And there came about a rather limited number; I would say originally there may have been 20 or more coal-tar colors that were certifiable.

Wiley was a little more concerned than any of his predecessors in the safety of what was being added to food either intentionally or unintentionally as what we would now call contaminants or either migrants from contact with food-processing equipment, packaging, and so on. So he decided to set up his own studies, and he had no qualms about using human subjects. He selected from his department, which was, I think, the Department of Agriculture at that time,

12 so-called “volunteers” to go on human studies, and they were put on a normal diet to stabilize their weight, and they were fed supplements (doses) of these various things like sulfites and saccharine and colors and benzoates. Sodium benzoate was one of his targets, and so on. This is all written up, finally, in Bulletin 84 of the Department of Agriculture. I hope you still have one in your library.

SW: Yes, we do, we’ve got one here in the office.

BO: Yes, well, I have one, although I can rarely find it because we have a fairly large library for an independent laboratory, and every time I take it out, it never goes back to the same place.

At any rate, he ran these studies on these volunteers, who were known as the “poison squad.” And, incidentally, one of them I later became acquainted with and knew for some time, a nice old fellow; Weber, his name was. You probably have some more records available on what went on at the time than I do, because Wiley himself didn’t write much in the way of scientific books. He wrote diatribes, you know, criticizing labeling and drugs, also some things that were going on in those days, justifiably, and so, but I was more interested in what methods he used and so I don’t have a great deal of copies of the original work. It was eventually published in Bulletin 84, and results were meaningless, you know, because the digestive disservices, irritation, the anxiety and things of that sort, which has nothing to do with toxicology as we know it today. It might be really toxicology, but we don’t know.

Anyhow, here I was deeply involved not only in assay work for nutrients, but along came the World War II, and some things loomed up which required a much more serious approach, the toxicology safety evaluation. One was pesticides; that word was coined around about that time,

by the way; pesticides not merely known for their efficacy as bactericides and fungicides, rodenticides, and other pest killers, but for the possibility that residues might be left in human food. So we didn't have methods that went down to, you know, anything, but they were the crudest percent solids and moisture and nitrogen, sulphur. Things like that didn't tell you very much, and we had to develop specific methods for each pesticide, micro methods, to determine how much of the residues might be left in which foods. So the discovery of vitamin D was the major impetus that gave rise to developing a whole slew of pesticides. Now there are more than you can count. Some of them have very, very limited use. I'll tell you the story about that.

Dow Chemical Company used to make a pesticide, and they found that there was a very small market for it and they dropped it. But there was one company up in Canada that continued to order year after year, and they made small quantities to supply that one company. Eventually, they developed enough curiosity to wonder why that company was using this pesticide. And you know why they were using it? To kill beaver, see, because up in the Canadian woods, beavers were a pest, and they wanted to get rid of them. So they used this one compound, was very effective. I don't know what the situation is now, but that was one of the things that happened when you develop specialized products. They have limited use until something better comes along.

Well, sulfur drugs came into being in the thirties, and actually the sulfur drug sulfanilamide was the reason we got the 1938 amendment passed. But during World War II, not only were pesticides being developed, DDT was sprayed on people during World War II, because in Italy it was one of the best louse killers that could be used. So they actually sprayed pounds of it on these Italians.

But sulfur drugs came to be replaced by penicillin, the first of the antibiotics, and that led to a whole slew of antibiotics, and that became important from a toxicological standpoint to determine what the levels were when permitted levels were announced by the FDA after their own toxicological studies and those of others. So, pesticides and antibiotics gave a major boost to interest in safety evaluation of unintentional food additives, residues.

SW: Okay. Before we go on, let me ask. Now, you had started talking about what your laboratory was doing after the '38 Act was passed, that companies had come to wanting certain studies and whatever. Can you elaborate just on what you remember about the impact of the '38 Act?

BO: Well, so far as this work, toxicological work was concerned was this. I mentioned before that for industrial purposes, LD50 was a toxicological test. Now it has been abandoned. FDA doesn't recognize LD50's anymore, but an awful lot of stuff has been done. Stuff I call tests have been done on food additives and on GRAS substances which are not food additives based only on toxicological studies at the acute toxicity level, LD50's mostly. When the companies were required to do more than that subacute toxicity, and especially chronic toxicity, then they had to know how to keep rats alive during their normal lifetime. The normal lifetime of a rat was found to increase with the advances of nutrition, so you had to keep animals going for perhaps three years, in a few cases more. You had to do new reproduction studies and so on. Well, largely because of the influence of Dr. Lehman and his group down here, two years was considered to be adequate for a chronic toxicological study, provided what you did was sufficient

in the way of biochemical and other behavioral observations and anatomical observations and pathology.

Now, the demand for improved toxicological methods became a windfall for pathologists. Nobody did much pathology in those days originally. We did not employ a pathologist then. What little pathology we needed to do, we farmed out to good pathologists, who were available, and they were not human pathologists, they were veterinary pathologists. And this was a boon to veterinary pathologists who were willing to do work, not on dogs and horses and chickens and so on, but on laboratory animals. So when industry was required to do work, they said, "What do we know about it?" Well, we at Food and Drug Research Laboratories – no, then we were only called the Food Research Laboratories – we knew a little about it. We got a lot of business that way, from Dow, DuPont, and lots of major companies.

SW: Okay. We need to dig just a little deeper here. Was it the large companies primarily that paid? They knew that they needed those three types of studies.

BO: It was the large companies, because who could afford it in those days? Now, when I say who can afford it, we do a two-year study originally on rats, a two-year study on rats for the purpose of safety evaluation, finding no effect doses for less than \$100,000. Actually, we started to do that in a limited way at about \$35,000. But to do a good study with enough pathology and so on – and that became a major part of the course – we could do it for \$100,000, but you can't do that today. To do a good study today, \$500,000 is probably a good round figure, and it may be even more than that. If you ask the big companies who will do it on more than one species like rats and dogs and so on, it may run to even a million dollars before they come out with a

product that tends to have a big market. Of course, the risks are great too, you know, and the substances that we are exposed to may be at low levels or in some cases higher levels, that they're testing agricultural crops, you know, but a lot of work goes into it and many, many more animals. We used to start with groups of 10, five males and five females; then it became 10, 10 males and 10 females per group, and three dosage groups under control. So that's four times 10, right?

RO: Four times 20.

BO: Four times 20, less than a hundred animals. But then what was considered an improvement in toxicology was that increased the requirement up to 50 males and 50 females. I say what was considered to be, because I think that that was an illusion or a delusion, thinking that just adding more would give you . . .

[TAPE 1, SIDE B 00:20:22]

SW: Better results.

BO: A more accurate result.

SW: Okay. Now, all this you say is when the safety provisions of the '38 law came out. I mean, large companies began looking into these studies as a result of the '38 Act?

BO: Sure.

SW: But now those, I guess what interests me is that in the law it did not specify the kinds of tests being done, so is this something FDA recommended or was it something industry knew? I mean, how did everybody know that these are the kinds of studies that should be done?

BO: Okay, now, I can't follow a chronology, but I'll tell you how it came about that FDA recommended it. FDA was doing studies involving toxicology and rendering opinions involving safety, whether it involved toxicology or not, maybe that it was analytical, I would say beginning with the late '30 and when Lehman came in, which was in the early '40s, intensively before the 1938 Act became really effective. They were using methods which they themselves developed, and they had people doing chronic work and people doing sub chronic work and so on, and the appraisal book, you know . . .

SW: Right.

BO: I used to call the black book because we had several copies. One of them was bound in black, so the "black book" contained the methods that FDA was using. Now, they were urged to publish these methods by people in industry because they said, "Okay, you want this kind of work done, how do you do it? Who does it? Do we have to do it?" So it turned out that Lehman would only go so far as to publish the methods that they were using in the form of this book.

Later on, changes in methods began to appear against the wishes of most toxicologists in the *Federal Register*. Now, why did toxicologists object to publishing these methods? I can tell

you because I was among them. When the government publishes something, it's like a Bible. I won't say a Bible, but if it gets frozen, it's the law whether it's actually intended to be or not. The *Federal Register* is an official document, and they think being published there has the semblance of having government endorsement, you know, unless it happens to be a critical paper of what industry is doing or something like that. So we didn't like the idea of publishing these methods. Why? Because toxicological methods were only being developed at that time.

FDA set the pace, but a lot of work was done in many disciplines: microbiology, pathology, chemistry, biology, and so on. More and more data came out even involving methods that were not bioassay methods, like microbiological methods and from nutrition. You remember all that work that came out with a promise that it would displace all biological work, bioassay work? Well, it didn't really. So we weren't very encouraging about publishing work. But then, you know, if you can't lick 'em, join 'em.

SW: Okay, but Lehman's article, as I recall, came out in the '50s; it didn't come out until the '50s. But you're saying that these companies, as soon as the '38 Act was passed, were starting. Did they already know of FDA efforts in that area?

BO: They knew that FDA had its methods.

SW: Okay.

BO: But FDA was reluctant to come out and publish them partly for that reason.

SW: But they knew that there were sub chronic studies?

BO: The studies were, they were good for the time, but I wouldn't say primitive, but they were still in the process of developing the methods because new types of products were coming out, and even the products that were coming out demanded some changes, some differences in the methods of testing. For example, one thing that Lehman, that the Food and Drug did, which was a great help when it came to food additives, was demand that they be tested by feeding by oral ingestion; whereas a lot of toxicological work was being done, particularly on drugs and on pesticides, and so on, by parenteral routes, you see, intravenous, gastric intubation, which most of us didn't regard as dietary.

SW: Yes.

BO: Then you have to remember that it was very difficult to publish toxicological papers either, by those methods, where the results were negative. In other words, you were getting no adverse effects and in essence were raising a large number of animals on normal diets and not seeing any adverse effects in many cases because you didn't look. You didn't know what to look for in other cases because the tests were not properly done. They were too short for one reason or another.

So, I have to tell you about a group called the Tox Roundtable. I really shouldn't tell the whole story. Let's go off the record for a moment.

BO: I don't go to meetings anymore. I used to send somebody else after I got to be "executive," you know, but we used to have good times. We went to odd places I never heard of, and one was in Delaware and another one was up in Michigan somewhere, and every year it was a different place, but we really were secluded and we had a lot of benefit out of it because we were exchanging experiences, which were not duplicated in different laboratories so much as to contribute generally to the basic subject of toxicology and what you ought to do and what you ought not to do, and where you get your animals and how you breed them, and so on.

RO: Were the government toxicologists ever invited?

BO: No.

RO: Never.

SW: Never (laughter).

BO: That's why I'm telling you this. They were not invited, but in 1930, '30 or '31, a professor at Johns Hopkins started a conference. The first one was at Johns Hopkins and the second one was at Gibson Island, an island that is near Annapolis and the Chesapeake, where a country club in desperate financial straits rented its premises for this conference which was started at Hopkins and which became known by the name of the man who started it, who was really a nobody. He was an assistant in the Department of Biochemistry. His name was Gordon. And thus was born The Gordon Research Conferences. Do you know what they are?

[END OF TAPE 1, SIDE B]

SW: No.

BO: Well, I'll tell you what they are now. The Gordon Research Conferences continued to be held every year limited to about, I think it was, and each week brought together specialists from all over the country and guests from abroad to spend a week discussing a very limited subject, first of which was vitamins. And in the early '30s, all of the vitamins hadn't been discovered yet. I was present when a long-distance call was received describing the identification of vitamin B2 and the synthesis of riboflavin at this conference. It became a rather prestigious conference, and a few weeks were devoted to it, each week a difference subject, you know.

And then it got so that toward the end of the '30s, this country club found that it had reached the point of financial recovery, and then we were no longer welcome there. We used to sleep in dormitory rooms, in some cases holding as many as 20 army cots, 20 beds to a room. You got one towel a week. It was awful.

The best thing about it was the bourbons, and they made bourbons like I never drank them before. They were like big ice-cream-soda glasses, you know. They almost filled it with ice and then poured the bourbon on top.

Anyhow, that developed into a nutrition conference of some reputation and magnitude. It was well known. It became known as vitamins and nutrition because we began to pay more attention to proteins than we ever had before, proteins and calories and that sort of thing. And so

vitamins were and shall always remain an important part of nutrition ever since they were discovered.

The subject of these Gordon Research Conferences really broadened, so we looked – I say we because I became a member of the Board of Managers; they called it the “management committee” or something like that – we looked for a place in New England. And it turned that we found boys’ schools had closed for the summer and there were no jobs for their staffs. So one of them welcomed the idea of a group coming in and keeping the staffs and kitchen staff in serving all meals and so on. It was very pleasant. That was up in New London, and that continued and expanded until today there are 12 weeks in the summer, and there are, I think, eight or nine schools, so, say, eight times 12, 96 weeks of conferences in various schools in New Hampshire. The Gordon Research Conferences continue not only there, but they have several in Santa Barbara for the West Coast. So that’s the Gordon Research Conferences.

Well, along in the ‘40s, I kept arguing at the Tox Roundtable, I said, “Why don’t we have a Gordon Research Conference, not limited to us 20 or 25, but invite other specialists and guests, and so on, and let them get grants to cover their expenses, and so on, and their registration fees, and have them join and organize a conference on toxicology,” which I called “Toxicology and Safety Evaluation.” I’ll tell you about that in a minute.

We also continued with our nutrition conferences every year, and I being on the Board of Managers, was able to manipulate it so that the two were in successive weeks, so I stayed up there for two weeks.

That went on for a number of years until they caught on and then decided that they had so many conferences going on there that they had to give priority to some of the others, and we

managed finally to split up. By that time I was no longer active as a member of the board and, nevertheless, we used to go up every year.

Now, toxicology and safety evaluation. I think I mentioned to you yesterday that there is no word in the English language for the opposite of toxicology. You say a toxicological test for poisons and so on, but to test by toxicological methods, the safe levels of exposure to poisons is another field. It's the other end of the spectrum of toxicology, you see. You have to determine from toxicology what the effects of large doses are over long periods to know what to look for at the low levels of dosage, also for long periods. And that safety evaluation, the words "safety evaluation" embodying toxicological procedures, there is no single word for in our language.

When the Society of Toxicology was formed, and it was formed as an outgrowth of the Gordon Research Conferences, and journals were formed as an outgrowth of the Gordon Research Conferences, the seal of the society has the word "Salve" on it, which means "Health" or "Safety." It's not a very specific word, but that is the nearest we came to a Latin root which could be embodied in a word like Salvatology as the other extreme of Toxicology, but it never really worked and we still don't have it. And that always bothers me because, when – who headed up nutrition here after Elmer Nelson died? Who? It was Lee Kline, and then when Lee Kline retired, it was, oh my God, one of my best friends [Leo Friedman], and now the name won't come to me. He left FDA, went up to MIT to head up a department of toxicology, and he called the subject "The Toxicology of Foods," and I objected in public to that term.

As a matter of fact, there was a strange thing. We were both on a program in a hotel in New York run by women editors from throughout the country; there must have been a thousand of them, editors of newspaper columns or newspaper departments' pages for women and editors of *The Ladies Home Journal*, *Cosmopolitan*, *Redbook*, all the magazines, a great number of

women in that program and in that auditorium. And Leo was his first name; Friedman, that was his name. He gave a paper describing toxicology as he knew it. And, by the way, he was a nutritionist originally, and that's no sin; I was a nutritionist originally. And he worked with Elmer Nelson and Lee Kline, and he described the subject of food toxicity, and I thought that was a horrible joining of words because it focused attention on the hazards such as they were or were suspected to be in foods or food additives (food toxicology). I was dying for a word that would emphasize the safety evaluation of foods and food additives. Anyway, I lost. It became "The Toxicity of Foods," and that term still persists in the literature and departments also.

Now let's get off that. What was I talking about?

It was being done in this country particularly and to a lesser extent in England, and still less in Italy and so on. The work that was being done here was the pioneer work. We really took the lead internationally.

Now, when the World Health Organization became involved and the Food and Agricultural Organization of the United States, they joined forces, FAO and WHO, in having a joint conference in Geneva, and they decided to establish an outfit called JECFA (Joint Expert Committee on Food Additives). I was in at the first meeting and remained an active member of it for a number of years and on that committee for, I guess, the first three or four years.

Now, they're not only specialists in toxicology in various areas from industry, but also government people were represented too, and Fitzhugh was the chief representative of FAO and I got to know him very well.

Later, other people came on. Herb Blumenthal until recently was an active member. Dick Ronk is an active member now of JECFA.

Now, what happened there was we brought our methods into that group and they weren't obliged as individual countries to adopt them. There was nothing compulsory in that regard, and they didn't so different countries have had different laws. They try to absorb them into certain recommendations which come out every year, which may or may not be adopted by any individual country.

For example, then the Color Additives Amendment came into being, I calculated from data supplied by the World Health Organization that there were 80 different colors that were used in about, as I recall, maybe 30 different countries. No two countries had the same color laws, and in England, for example, there were about 30 colors that were permitted to be used in foods and in confections, beverages, and so on; whereas in the U.S., there were 19 at that time, and now that has been reduced to probably five or six.

So, despite the fact that there is a JECFA, there are still differences in the color laws among different countries due in part to the fact that in England they were using many more and so no reason, from a clinical standpoint, to change. In Germany, they were producing colors in the chemical industry which were satisfactory as far as they were concerned and were not quoted in our country. Nevertheless, they participated at the meetings in discussing these colors. Up to now, I don't know exactly where JECFA stands on colors, and I haven't concerned myself with them because there's been a color industry committee and I don't like to interfere with that because I've had no part in it.

SW: Well, let me go back and ask you, we were talking the World War II period and the new pesticides and the new chemicals that were coming on the market. What was your laboratory testing during that period? What were you all doing during the war?

BO: I'm glad you asked, but I didn't want this to be a session promoting our lab.

SW: What your lab was doing, though, helps us to see what the industry was doing.

BO: I'll tell you about some of the work that we were doing. The FDA over the years has been involved in a more diversified area of toxicology than perhaps any other regulatory agency in the world. It didn't all start with Food and Drug in 1940, because even before and before the 1938 Act, particular toxicological questions were rising all the time. The problem is that most of that work was handled in a kind of unilateral way. FDA would make a decision, and the only place this would find publication, not find but receive publication, was in the quarterly bulletin of the Food and Drug Officials of the United States and in the bulletins of the Food and Drug Law Institute. I have examples of this here which I can show you, but I want to answer your question now. I want to tell you just by title, and if you want me to discuss any of them a little more intensely, I'll do that.

When the Miller Act was passed – you know what the Miller Act is?

SW: Yes.

BO: Pesticides. Miller Bill was passed. It provided for referral of disputed questions between a petitioner, let's say, and Food and Drug to ad-hoc expert panels, panels chosen because of their expertise on a particular subject involved. Now, that could be done at the will of FDA or of the petitioner. The appointment, however, was according to that statute made, or maybe it was the

regulations, made by referring to The National Academy of Sciences National Research Council, which was asked to set up a panel of candidates from which the experts were chosen to presumably resolve the question. Now, FDA was not bound to accept the recommendation of that panel. It had to go on the record, however, and whether they accepted it or not, but at least it went to an advisory panel.

Now, the first such pesticide that was referred to such a panel was one that was made by a nationally recognized and so well-known rubber company whose name has changed since then, and it was on a substance known as Aramite. Did you ever hear of it?

SW: Yes.

BO: Okay. So we brought our Aramite work, which was done over a long period of time, and was based on more than one species, and so on, to this panel, which for the reason that FDA did not regard the lowest level as being a “no adverse effect level.”

By the way, that used to be called “a no effect level,” and then it became known, at my urging, as a “no adverse effect level,” and then I continued to urge that it be called a “no observed adverse effect level,” because, you know, you can’t look for everything. You only look where you find suspicion or reason to find that “adverse effect,” so that really should be called a “Noael” rather than just “Nel.” Okay.

RO: Well, now, was this done on the parent compound, Dr. Oser?

BO: What?

RO: Was your toxicology work based on the parent compound or because, as you know, a lot of pesticides will weather.

BO: That's right.

RO: What happens, then, after the weathering?

BO: That's right. Well, it varies with the pesticide. Sometimes the oxidation product or the heat production and processing pesticide food or something like that may be involved; food meaning something like something entrapped, you know, or repellent and so on. The pesticide itself isn't fed; it's put into the diet usually. You got me?

SW: Yes.

BO: The animal study is done by feeding as a supplement generally present in their animals' diet, greater doses of that stuff that you're testing, something like Aramite, for example.

RO: But the metabolism in an animal may not be the same.

BO: Ah ha! That's another story. We're coming to that.

RO: Okay.

BO: When I get finished with that, you can say I'm through. That's my latest hobby: proving, not proving, but demonstrating why the rat is not necessarily a surrogate for man. That's another story. Man is not a big rat. Do you have my paper on that?

RO: Yes, we do.

BO: Okay. So Aramite went to this advisory committee, and the advisory committee, what we found was that there was one animal at the lowest dose level; we had 20 animals per group at that time. There was one animal at the lowest dose level, which indicated a hyperplastic change in the liver – not a tumor, but theoretically possibly a forerunner of a benign tumor, which is theoretically possible as a forerunner of a malignant tumor. That how the word “cancer” came to be modified since the Delaney Clause was adopted through the next 20 or 30 years. Now, all of these precursors to true malignancy are lumped together, and that's still a controversial thing, and I don't take the side of those who would lump these things together, because hyperplasia and benign tumors are reversible, I think. If that's all they are, they're reversible at least during a two-year period. They may come up the third or fourth year. We don't know that, but under the test conditions I don't think that these precursor conditions ought to be combined on an equal basis numerically with frank malignant cancer.

SW: Okay.

BO: FDA lost that one, and the panel ruled that this one hyperplasia out of 20 animals of the lowest dose level was not really a malignancy, nor did they accept at that time the precursor doctrine, and they allowed us to go on with our one part per million of Aramite applied to apples and pears, as we had; but recommended, because we had already started another study more specifically designed to reveal the potential for carcinogenicity and we had already started it, company was doing a big business with it, wanted to hold onto it, we had started a study where we used a hundred rats per group, a hundred rats of each sex per group, I think it was, and two hundred in the control group, and we carried that on. And we also started another group of dogs (40 dogs) only at the highest level, on the recommendation that the advisory committee made, and they said come back to us when all this work is done and it will be reconsidered.

Well, we came back after, say, two and a half years or so; I don't remember the dates now. But it wasn't the same advisory committee. FDA has the option of choosing the advisory committees, by the way. They didn't use the approach of having The Academy of Sciences select a panel from which FDA would select the expert group, but they jointly, with The Academy of Sciences and FDA, selected a new five-member panel. And when we came back, what we reported was that at the lowest level in rats and mice, we got no hyperplasia or precursor of cancer, but in the dogs we got an even more severe and earlier response, probably due to the fact that we went to such a high dose. We lost dogs from nine months on, you see, and that was the end of Aramite.

RO: How many levels did you use?

BO: Three. By the way, if you want a copy of our published reports on Aramite or on anything that we publish if it's available yet, I'll be glad to send them. Another thing that we worked on in the early days, Agene, A-g-e-n-e.

SW: Oh. Expand on that one a little; that comes up with the bread hearings.

BO: Right. Bread hearings; it came up with the bread hearings (nitrogen trichloride) and . . .

SW: Bleaching flour.

BO: The bread hearings went over a long period, and a number of things that we worked on related to it, sponsored by additives manufacturers who are concerned with the bread hearings. One of the principal ones being polyoxyethylene esters, the partial esters of polyoxyethylene. Now, their common names were tweens, spans, and myrj. Myrj was the one that came up in the bread hearings. We did all the work for it; was then called Atlas Powder Co. ICI. Now it's ICI.

SW: Oh, okay.

BO: That's ICI now. They took it over.

SW: Well, tell us about your testing.

BO: The problem there was not simply toxicological, but I really don't think there was any significant hazard involved in myrj. But it became a political and consumer problem. The point was that myrj retained the freshness of bread. So there must be a thousand pages on it. What is freshness? What it really boils down to is freshness is squeezeability, because that's what a consumer goes into a store and she tests how fresh the bread is. Bread is wrapped now, which is a two-edge sword. It's nice to keep it away from insects and so on. The way the French allow the bread to be kept, you know, you carry two loaves of bread on back of a bicycle in France, and it's all right. But here, everything has to be wrapped. Well, that's for sanitary reasons, and there should be no objection to it. But the objections are that bread stales more rapidly unless it's wrapped, because staling is in part dehydration, but it's also another reaction takes place in the molecular structure of the starch in bread; and so there's good reason for using what became known as softening agents in bread.

SW: Emulsifiers?

BO: So, softening was one aspect of freshness, but what was not involved in the use of these softening agents was retention of the fresh taste of bread. See.

SW: Yes.

BO: It undergoes some changes in taste, as you well know.

SW: Oh, yes.

BO: If you don't use these agents.

SW: Well, now the spans and myrjs and tweens will be entered. Are those the same thing as emulsifiers? Is that the generic class?

BO: Yes.

SW: Okay.

BO: They're not chemically the same, but they are polyoxyethylene esters with different lengths of the polyoxyethylene chain esters, and the esters are of the fatty acids, oleic, stearic, and palmitic, and so on. So we did the major work on these emulsifiers, which, by the way, were first used in drugs before they were used in foods. They were used in drugs because you could dispense an oily drug in an emulsified form which was stable when used with these emulsifiers which are very stable.

SW: Well, now, what kind of test did you devise for the ones that you did?

BO: Well, they were really growth tests; we did some metabolism work. We showed that the caloric value, for example, of, let's say, a polyoxyethylene stearate was equivalent to its stearate acid content, and that's all because the polyoxyethylene moiety was not metabolized; see, that went through.

SW: Yes.

BO: So you've got the caloric – we developed a method for measuring caloric value biologically, not in a calorimeter that gives you an overestimate. But biologically, you could estimate it in animals, or rats are very good for that; they give you beautiful dose-response curve and so on. Anyway, we did that; we did a number of other things on these emulsifiers, and many other laboratories, I should say, also did.

SW: But you found no problems, toxicologically speaking, with them?

BO: Our concern was the toxicology of several of them. I think there have been three or four of them, but myrj was the thing that inspired the work originally because of the bread hearings. Okay, so that was another thing we did.

Another product of the same type for another client we had also investigated made by a different method. That was called Stay Soft, but it was the same type of polyoxyethylene fatty acid ester, but made by a different procedure, and they had to go through this on their own because Dow wouldn't let anybody know what they were doing. Dow came into this field of sequestering agents and emulsifiers later than any other companies, but they moved faster and in greater depth.

Now, another thing that we worked on which was of interest and concern to Food and Drug was maleic hydrazide. That was also done for the rubber company, and it was a pesticide, and we found that it could be used at safe levels. And when it went on the market, it became a

very big seller, maleic hydrazide. Years later it came out under a different name, Alir, and FDA found on further testing that it was not as innocuous as our work indicated.

By the way, this is not unusual. You'll hear me mention later on that toxicological studies are one of the most non-reproducible types of assays, non-reproducible conducted for regulatory purposes. I have yet to see two good laboratories do the same toxicological study following what are presumably the same guidelines come out for exactly the same result.

RO: What was maleic hydrazide used for?

BO: Maleic hydrazide. It was a pesticide. What specific use, now here you're reaching into the depths of my memory and I can't tell you exactly, but I could tell you maybe if I looked in among these papers deeply. But the point is that there was a long gap. When I heard about what happened to Alir – this is not for the record.

Orange drink became very popular when oranges were too expensive and they used to make the orange drink out of terpene less orange oil and citric acid and a few other things together with no orange juice itself, but it was a drink. They didn't call it orange juice. And it was very popular. All told I would say not approaching Coca Cola, but striving in that direction.

One of the troubles with that drink was it was sold in glass bottles, and the oil tended to separate and leave a ring on top. There wasn't that much oil in it, but it left a definitely perceptible ring anywhere from about an eighth to a quarter of an inch thick, so you really should shake well before using. But brominated vegetable oil was found to be of sufficient density to increase the specific gravity of the little bit of oil that remained there so that it stayed in

suspension and didn't form an objectionable ring, and they began to make ring less orange drink, and it was very popular.

We did toxicological work on it and really not very much because when we went down and talked to Arnold about it, Arnold Lehman, he had already published a small item in one of these bulletins saying that brominated vegetable oil was safe. The reason he said it was safe was because he reasoned that it would be metabolized to the bromide ion if anything, and then the oil. And the bromide was far less than was contained in a dose of Bromo-Seltzer. He really was a very, he had his feet on the ground, you know. He used what knowledge was available at that time to permit certain things to be done which would not be permitted today. They made mistakes in the old days on what we used to call AMF; what I used to call AMF, "Assumed Metabolic Fate," because there are a lot of things that are in our diets today whose "Metabolic Fate" we assume from analogy from other or similarly related compounds.

So, anyway, the situation reached a head when in Canada they also tested brominated vegetable oil and found that at some level it was toxic – not necessarily at the level it was present in the orange drink, but they called an industry group together and said, "Look, how much are you using?"

"Well, we're using 150 parts per million brominated vegetable oil."

"Do you need that much?"

They began to look at each other, the industry people, not toxicologists.

"Well, how little can you get along with?"

Somebody must have raised his hand; I wasn't there but I heard about this.

"Well," he said, "well, we don't really need that much but we get along with 15 parts per million," so 15 parts per million it became. And it is to this day 15 parts per million.

But that was another thing where FDA, by the way, was on the wrong side, and so were we, by the way, because we thought that either 150 parts per million wasn't a toxicological problem.

Well, let's jump over a number of smaller items: Polyguard, ethyleneoxide, carbarazone, monosodium glutamate, we were deeply involved in. I'll get into the sweetening agents.

The most important sweetening agent that was permitted to be used for a long time was saccharin; before that, there were several others which FDA banned. Dulcin was one, and something called P4000 was another. FDA found Dulcin to be potentially carcinogenic, and P4000 a hepatic toxicant liver injury. So they were dropped, and I don't think it was any great opposition because there was not that much use of either of them.

But saccharin had come into use even before the turn of the century and, incidentally, was one of the targets of Wiley's attack. See? Now, Wiley's attack on saccharin was based on the fact there was nothing which required foods or beverages which used it to label its presence, and he said – and I think I quote him in this; I've done it years before too – “The real problem with saccharin was not the question of safety but question of fraud. Misleading the consumer to think that saccharin is an equivalent substitute for sugar.” Now, they still call it a substitute for sugar, and I disapprove of that too. I talked to the Cumberland Packing people time and again about it. That's misbranding, in my opinion. I don't mind saying this; it's misbranded because it's called a “sugar substitute,” and none of these artificial sweetening agents are substitutes for sugar. They're sweeteners. They're substitutes for the sweetness of sugar, but they don't provide the bulk, they don't provide the calories, and they don't provide the texture that sugar imparts to foods in which it's used, and baked goods, for example, and so on. So I don't believe the word “substitute” is properly used there, and I don't believe “imitation” is properly used

there. Imitation is a word that's no longer urged so forcefully by FDA or the industry.

Analogous is good, but nobody knows what analogous is.

Okay, so sweeteners. So when cyclamate came out, it immediately became very popular because it did not have the bitter taste that saccharin has for a reasonable proportion of the population. I wouldn't say a majority, but I've heard other people estimate that about 10 percent of the population cannot use saccharin because of its bitter taste. I am among the great majority, 90 percent in that case, because I've been using saccharin since the early '40s. Why? Because it doesn't bother me and it's easier to use. I steal it from restaurants. I don't buy it. And I told the president of the company that. He said, "I don't care where you get, as long as you use it." I pull it out in his presence; I've had lunch with him.

So the trouble with cyclamate was that it was too expensive. But it was found by Abbott that if they combined saccharin with 10 times its weight of cyclamate, that would equal the amount of sweetness you would get because saccharin is 10 times as sweet as cyclamate. So if you used 10 times as much, you'd get an equal amount in a 10-to-1 mixture of sweetness from both. And cyclamate is a very efficient mask for the beet bitterness of saccharin.

Now, there are other anti-bitter agents that are used with saccharin; it isn't all saccharin. It has to be diluted because you can't use such small amount as well; a quarter-grain tablet maybe, yes, you could get a reasonable amount of sweetness, or half grain, perhaps too much in my case. But that mixture worked out very well in a product called Sucaryl, which they came out with. So we were asked to investigate the toxicity of the mixture of 10-to-1.

When that came to us, I tried to talk them into doing cyclamate also and saccharin also at the same time, because in that case you'd have the opportunity to compare the three in the same

strain of animals, the same basal diet, the same environment, the same laboratory control conditions, and so on.

Well, they got to look at the price of the work and decided that the way we planned to do this cyclamate using these large groups of animals now, not 10 groups, 10 males and 10 females, but using sizable groups, 50 of each sex, which was what FDA was recommending at that time. And so we ran the toxicological study for the mixture. By that time, by the way, the Food Additive Amendment had been passed and we had the Delaney Clause to contend with. And it didn't matter what dose you fed to one animal for how long; if you did your work properly, you examined all the organs and all the tissues, you were bound to find, at a high enough dosage level, that a substance was carcinogenic.

And I should say there are many hundreds more substances which have not been tested that way than have been tested. So we had to report what we found, and what we found were liver tumors at the highest dose level. And, of course, that began to spell the end of cyclamate, only because FDA chose to pick cyclamate as the culprit in that mixture, and I began to criticize FDA for it. We had public arguments about it.

A number of other details and procedures I objected to, one being the high dose that was fed, another being, of course, the long term, and another being the arbitrariness of picking one substance rather than the other, which, by the way, has come under more scrutiny than cyclamate since then. Saccharin, you know, and saccharin is still, you might say, teetering on the fence. As a matter of fact, how I'm surviving after 50 years of its use. And most of all, for one other reason, most of all because, in going over the data of the studies that have been conducted on both saccharin and cyclamate, they both have about the same molecular weight and the same percentage of sodium. That percentage of sodium is so high that if you start a weanling rat on it,

it may be gaining as much as 10 or 20 times of sodium as it requires, and we don't know what the effect of so much sodium is. If you were to feed that much sodium in the form of sodium chloride, you'd kill your animals. But sodium chloride is not metabolized in the body; it's excreted or stored, but it does not metabolize. We don't have free sodium or free chlorine. It's not even an intermediate in the sodium compounds that are excreted or the chlorine that is excreted as sodium chloride, and it's toxic, there's no doubt about that. I'm not talking about cardiac patients; I'm talking about good old ordinary homespun toxicity. If you give a hundred times the equivalent of the so-called "safety factor" of sodium chloride to the three or five grams that we normally are supposed to ingest, you'd kill animals quickly.

So, acknowledging their sodium content is that high, what do you do about it? Well, you have to do a different type of study. You have to compare sodium cyclamate and sodium saccharin with some other presumably innocuous sodium salt. Now, when that came up prior to the study that the Calorie Control Council sponsored – a big study – they actually spent more on that study than had ever been spent in industry before for a sweetening agent. It was done up in Michigan by a good laboratory. They accepted a suggestion I made to use sodium hippurate as the control. Now, I talked to a lot of people about that, what would be a good control, and my suggestion that hippurate would be good because the hippurate is the end product of benzoic acid metabolism, an end product of metabolism, this would be through a metabolic process. Hippurate acid is metabolized from benzoic acid. I thought it would be a good thing to use because the anion is not metabolized just like saccharin is not metabolized.

Well, they listened to it. I even had a man lined up who was a specialist in potassium and sodium metabolism. He has since died, but he was the man I recommended to do it. No, they set it up. Well, as it turned out, after a period of months, the controls on sodium hippurate began to

die; they died off. But those that were on sodium cyclamate survived. In other words; this end product of metabolism, given a high enough dose, was more toxic; even though it was metabolized in the body, it was more toxic than cyclamate. So nothing was done about that except to continue the study with just a lower dose of the sodium hippurate, and a lower dose, which I felt would not be toxic at all, of the sodium cyclamate. You get me?

SW: Yes.

BO: Good. I'm glad I'm talking to people who understand what I'm talking about. A lot of people don't.

I thought that that was the wrong term to take. They should have scuttled that sodium part of the study completely and looked for another sodium salt. There was one which Teq Williams recommended to me, but it was a sodium compound whereas the anion was not metabolized. It had no relation to food or food additives. It was an exotic compound. I didn't want to use it for that reason; that would be the first argument against it if the work came out the way we expected.

Well, now the industry has realized that all else had failed and they're beginning to look into and NTP (National Toxicology Program) is looking into the question of relation of sodium, but it's going to fail because they're not considering the fact that the anion must be unmetabolized. And if they ever find such a compound, I'd like to know about it. But I'm getting kind of sick of it now because of this saccharin business. I've been in a majority among the toxicologists who were designing protocols. I've been in a minority, I mean. There is just so much you can take.

[END OF TAPE 2, SIDE B]

BO: . . . metals, which in high doses are definitely toxic. Some of them are necessary as nutrients, but in high doses they can produce entirely unfavorable, in fact, even lethal effects. What are they? Well, every protein contains or every food contains proteins which contain carbon, hydrogen, oxygen, nitrogen. Some contain sulfur, some contain phosphorous, some even contain iodine, some contain chlorine, and that's my list.

Do they? None of them does, not a one. Why? Because carbon, hydrogen, oxygen, nitrogen, sulfur in the form of proteins or other compounds like phosphorous, other compounds nobody eats, phosphorous and chlorine and iodine, all of them. We don't eat any of them in the form of the element, but we talk about them as if they're the same regardless of the chemical form in which they're present; ignoring the fact that, for example, mercuric mercury is far more toxic than mercurous mercury and is far less toxic than methyl mercury. You see? So you can't speak of mercury without talking about the compound arsenic compared to arseneous or arsenate and arsenate are entirely different, and arsenic as a cation is different from arsenic as an anion. Right?

SW: Yes.

BO: So you can't talk about arsenic poisoning. You really talk about the compounds that are involved. The same is true of copper, the same is true of zinc and so on. You go all the way down the line. Cobalt. Cobalt is essential to B12, right? That's where we get them mostly from,

and it isn't cobalt that we're consuming B12. But it persists among, I won't say chemists, it persists among doctors, toxicologists, Ph.D.'s and nutritionists to refer to the copper requirement in the diet.

The iron requirement. Oh, yeah, I should have mentioned iron; I left out iron. Selenium. You know? And that is a bad habit because in the minds of the public who hear all of these things, any form of these elements should be avoided, and if we avoided all forms of these elements, we'd die.

So that's a mere trifle, but I insist on proper nomenclature. I'm a "semantic nut." I'll tell you more about that, too, later on.

SW: Well, you said that the designs for the experiment from the beginning were, you thought were flawed for testing it so that we still don't really know whether it was the cyclamate portion.

BO: No, I don't think the experiment was flawed. I think the interpretation, the conclusion that was reached by Food and Drug, was wrong. It was flawed in this sense maybe, that I recommended at the same time we were testing the Sucaryl-saccharin mixture, I mean the cyclamate-saccharin mixture; we should also have tested cyclamate alone and saccharin alone. And that way we should know, first of all, which of the two elements was responsible for the observation of liver tumors that we got and we'd be able to understand it better.

So it was Herb Ley at that time who, what happened was – I've got the dates and the publication, by the way, in *Human Pathology*.

But when we were examining the first few animals that died in that study, we found what we thought were some tumors. Now, when you find tumors in a study, whoever it is who

sponsors that study should know right away. So we telephoned Abbott and told them what we were finding. I think that was on a Wednesday. Thursday, they had their own pathologist come down to our laboratory, which at that time was in (blank), and they looked at the slides and then decided that maybe we were right; we were finding tumors and the experiment wasn't nearly over yet. But, still, I thought that they ought to know what was in the works.

They took the slides, 10 of them, down to Food and Drug the very next day. Food and Drug (I'm not using names now because I don't know exactly who was responsible) called together a group. The Surgeon General at that time was one of the parties who examined the slides – I can't remember his name right off – and they called together, I think it must have been seven people from the National Cancer Institute, their own pathologist, and the Surgeon General, and I've forgotten who else. There must have been about seven people, I think, there. We were not there.

The Abbott people took the slides down to Washington and they examined them immediately on a "hurry call," and I think that was on a Friday, and they came to the conclusion that, yes, this was it, that there were tumors. And the Delaney Clause was, of course, in effect, and the next day Herb Ley called a press conference (that was Saturday) and announced that cyclamate was going to be banned. The exact dates I don't think were established that day, but there was going to be a sequence of dates. The first was going to involve its addition to foods and beverages, I think. The next was going to be table sweeteners, you know, things that were harder to recall. And the last was going to be drugs, and that was going to be months later. That is the next day, and I say we had no part in it at all, none.

SW: All that was in a space of like four days?

BO: Altogether, it was from the middle of the week to the end of the week, something like that. It was that abrupt. As a matter of fact, when that got out in the press, there were two English publications which criticized FDA for its abrupt action. I forgot the words they used, something like discourteous, but it didn't go much further than that. And it all depended on four rats, four slides, because whereas they went down with 10 slides, every pathologist didn't agree with every other. But there were four that they all agreed on, and on that basis he ruled that cyclamate had to go.

Well, of course, I won't go into the legal part of it. The right of appeal Abbott handled because we had no part in that, and I didn't want to have any part in it. All I wanted to say was, "This is what we found, here it is, that's what you get," and so cyclamate did go off the market.

There were a couple of interesting consequences of that. One was, as far as I was concerned, I had to defend our reputation because our name was drawn into it, and I disapproved of the abruptness of that action. I disapproved of the conclusion that it was saccharin that was the culprit.

RO: Cyclamate.

BO: Cyclamate was the culprit. And I also disapproved of the conclusion because at that time we were still talking about the question of the dose, the high dose affecting the sodium intake of these weanling rats. And I showed from the food intake of these weanling rats that they were actually getting, the first few weeks on tests, about three or more times the sodium intake that rats required. In other words, they started off very high when the very young animals on a dose

of human body waste, they eat more. So they were getting higher than the adult dose of cyclamate. And then it comes down about three or four weeks, it begins to approximate the adult level. So it was a wrong conclusion to draw from that experiment, and it was a very hasty conclusion.

RO: Do you think there was any political influence?

BO: The political?

RO: Do you think there was any political influence that caused that conclusion?

BO: That caused them to make that decision? Well . . .

RO: I realize you're on the scientific side of the question.

BO: I don't know and I can't say, and I don't say there was, but it certainly wasn't a deliberate conclusion and it wasn't made by a toxicologist; it was made by unknown people who are mostly interested in carcinogenesis, mostly just interested in cancer. So eventually I had to defend our position before the National Academy of Sciences and I had to defend it in an answer to a letter which somebody from FDA wrote to *Human Pathology*, and I had to correct that letter and cite the dates and the times and the observations that were made and so on. So I got the impression that from the industry point of view, our studies were defective, and they weren't; they weren't as complete as I would have liked them to be, but it was because the client didn't want to pay for

it. So, altogether, it left a bad taste in the minds of many people in the industry, and, of course, it adversely affected the saccharin business too. But that's another story; I had nothing to do with that. That came later, as a matter of fact.

RO: Was this 10 animals out of a hundred that you found tumors in?

BO: I think it was 10 animals out of some 70, because there were some animals that were sacrificed during the study, and maybe some deaths or whatever.

All of this has been published, and if you want it, write it down, ask me for it, and I'll send it to you.

So that was the cyclamate story. And then everybody else got into the act: some of the lawyers for the cyclamate people; Abbott got involved; they tried to find flaws in the experiment because other studies were done, other laboratories, and didn't find what we found. I had reasons for the differences, one being that there's a wide range of variation of toxicological results due to not unexplainable but unknown causes, because all of the details of environment, methods of feeding, controlling dosage, and so on were not readily available. Papers were not being published yet to refute what we had found, you see. But I stood by our guns. This is what we found, and we were obliged to report it. We had no other recourse but to report it. We wanted to do further studies on it, but, no, they assigned it to another laboratory. They did a much bigger study and came out with similar results. As a matter of fact, worse results than ours. We felt that the 5 percent level came through clear. They said, "Maybe 3 percent, that's all we're going to shoot for." People in industry said that. They got this super expert committee together and they conducted this huge experiment, much larger than the one that we had run, and

they came out – there’s no question that they found in effect a 3 percent, but maybe also at 1 percent. If you read their report, you’ll see that it’s equivocal about 1 percent, but 5 percent was definitely a tumorigenic response. So, so much for the cyclamate thing. I’ve had to defend our work ever since on it, but that’s the way it is.

SW: Well, let’s go back, then, and I guess I’m interested in getting your impressions of the kinds of scientific work that was done by FDA, looking at it from the outside by Bert Vos, and you’ve already talked a little bit about Arnold Lehman.

BO: Yeah, well . . .

SW: I get the feeling that you came, I mean, that industry freely consulted with the agency even though they didn’t give exact, they sort of approved the methodologies that were being used.

BO: Let me give you a quotation from the chief counsel of FDA on a different subject, the subject of general recognition of safety. What is general recognition? He said that “I don’t care how many toxicologists subscribe to this notion that certain substances generally recognized as safe are the conditions of impending use.” If any one of our toxicologists disagree with it, then it isn’t generally recognized as safe, you see. That seems to be kind of an arrogant position to take. It’s not typical of FDA. What FDA will do is say, “Suspend action,” and ask for more advice from other experts, or ask for an advisory committee, or so and so. On that advisory committee alone, in 1952, I wanted to testify before the hearing committee, the Delaney Committee, on the

question of referring disputes to experts. I wrote a letter to the acting commissioner at that time – his name was Crawford – suggesting the approach to ad hoc expert committees in the event that there is such a dispute. I have that letter here, and I have his answer. And his answer was – this was 1952, before the Miller Act was passed, before the Food Additive Act was passed, the Color Additives, the New Drug, and so on – his answer was: “You’ve made some very good points.” I’ll read it to you; I’ll find it but I won’t stop talking.

[TAPE 3, SIDE A, 00:20:00]

He said, “You made some very good points, but in our opinion, that procedure would be too cumbersome,” I think is the word, “too costly, and really not accomplish anything.” And Crawford signed the letter and dismissed that concept altogether. When the Food Additive Bill was passed in 1958, the effort was made to include a “grandfather clause.” It was unsuccessful. FDA would not agree to a grandfather clause that would mean exempting everything that was approved prior to the effective date of the act. Right? No, they didn’t, but they defined food additives as, you know, as involving any substance . . . Gee, I want to be able to read that too. It’s a little long and I used to be able to recite it by heart with my eyes closed.

RO: Your paper?

BO: My paper. Well, I don’t think I have the whole definition here.

RO: Oh, I didn’t know how much you wanted.

BO: Well, wait a minute; I have the law here. Where's the Food and Drug Law I have here?

I haven't talked much about Lehman, and I should, because Lehman was one guy I take my hat off to in FDA. I don't mean there aren't others, but he, I think, was a prince of a guy who acted as though he had both feet on the ground. Here it is, the definition in Section 201(s). "The term 'Food Additive' means any substance the intended use of which results or may reasonably be expected to result (jot down the word "reasonably") directly or indirectly in its becoming a component or otherwise affecting the characteristics of any food including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food . . ." That's everything you can do to food except eat it. Including any sort of radiation intended for such use. If some substance is not generally recognized, in other words any substance that does any of these things used for any of these purposes – if such substances not generally recognized.

By the way, there are a lot of negative statements in Food and Drug definitions. In other words, in order not to be a food additive, it must be generally recognized as positive. Among experts qualified by scientific training experience to evaluate its safety as having been adequately shown through scientific procedures or, in the case of a substance used in food prior to 1958, through either scientific procedures or experience based on common use in food. By the way, it doesn't say whose. Except the experts. To be safe under the condition of its intended use and other certain exceptions above which are prior sanctioned pesticide chemicals, residues, and so on.

So that is what a food additive is supposed to be. Why did I pick that out now? We're talking . . .

SW: You were talking about the experts.

BO: This was back in 1958. Oh, yes, we were talking about expert panels. I wrote to Crawford then that something like this and I wrote that in 1952 ought to be included to resolve disputes, and he turned it down. Then it was brought up again by others and discussed in the hearings and so on, and it never was passed when the Food Additive Bill was enacted. However, when the Pesticide Amendment was enacted, there was a provision for referring to advisory committees, which was exactly what I was talking about. When I wrote to Crawford, I even suggested the organizations that ought to be asked to make suggestions of candidates for the expert committee. But when the Food Additive Bill and the Color Additive Bill was passed, neither of them had complete option to call in advisory committees or expert committees, except in the case of color additives only if there was a question of carcinogenicity. So there were three different provisions for referrals to advisory committees, you see, and that was another thing that I objected to the law as it was being discussed and so on. But that's the way the chips fell.

Now, FDA did consult investigators, or NCI did, rather. The National Academy of Sciences held a symposium on the subject. I testified there about the cyclamate episode and so on. But, as it turned out, other laboratories who investigated either cyclamate alone or in a few cases with a mixture a German laboratory particular, they could not confirm what we found. But that's what we found, and I wasn't going to be moved from that position.

I think that in terms of the animals used, our species, our strain of rats, which was an inbred strain in our laboratory and by that time had been inbred for a period of at least 30 years, we used our diets and so on. I felt that this is what we had to report. That's what we found, and

I still don't believe cyclamate is any more toxic than saccharin, and I think that to the extent that you find tumors in large doses, you have to rule out the sodium content, because at that period in a rat's life, say the period of three to six to seven weeks of age when it's on a test diet, it is getting an enormous dose above the dose that you think is the adult dose of both sodium and cyclamic acid.

There were other things that came up in this study. For example, it was discovered first in man in England, and then later in the rat, that some animals and some men (people) are able to convert cyclamate to cyclohexylamine. Now, cyclohexylamine as such had never been tested up to then, and some studies were initiated and we did one on cyclohexylamine. The trouble with those studies was that they were designed not the way an ordinary carcinogenicity study is designed where you want to give a dose high enough to induce a tumor, but they were designed to give cyclohexylamine...

[END OF TAPE 3, SIDE A]

BO: ... but as to whether findings can be legitimately be called facts is questionable in every case, and they ought to be recognized, especially when disputes arise over methodology.

SW: Okay. Well, let's go back. Well, why don't you talk about Arthur Lehman for a little while.

BO: Why don't I what?

SW: Talk about Lehman for a little while.

BO: Lehman, he's my boy. Lehman came in Food and Drug Administration after his predecessor Calvery suddenly, I think, suddenly and unexpectedly died. I didn't know Calvery; I knew who he was and where he came from. He had a good background, the University of Michigan and so on. But this was about 1940 I think that he died, and Lehman came in shortly thereafter.

Now, Lehman's background up to that time was in drugs. He is an M.D., and his work...

First of all, I'm going to give you a present. I've had a photograph of Lehman and I don't have a duplicate of the photograph, except a Xerox, and that's a very nice Xerox of Lehman.

He is a very nice person. He had both feet on the ground, and when there was a doubt, he said there was a doubt. When it needed more work to come to a decision, he said it needed more work. When he said there was no doubt, he said there was no doubt, like in brominated vegetable, for example, that I mentioned before.

When I approached him with the idea of setting up our own expert panel to evaluate flavors – now, flavors are the largest single category of food substances; they're not food additives because they're GRAS, you see, and we had the right under the law to do that – Lehman said when I told him about it and told him about who I was putting on this panel – and I put every member of the expert panel on flavors, was my personal appointee – the organization formally approved it, but it was just pro forma, you know; the president welcomed them to the panel. The panel was and is an independent agency, autonomous. Nobody has ever told us who should go on and who should go off, except one case, one particular case who is now a member

of that expert panel, and I don't want to mention his name. But, of all the members of the panel, which there were, I think, eight of them originally, one by one they're either passed away or retired or resigned or whatever, and each one has been replaced by another person that I appointed or recommended and the FEMA (Flavor & Extracts Manufacturers Association) group approved. That's going on all the time, so the panel that existed at the time and was formed over 25 years ago is not the same as the panel that exists today. As a matter of fact, it kept changing over the years as we lost members and replaced others; and today there is only one member of the panel who was an original member. I'm not including myself because I represented FEMA as a consultant and I was being paid by FEMA to organize and to conduct and chair this panel over the years. So, outside of myself who is an original member, there's only one surviving member, and he's a retired professor from the University of Virginia Medical School, and he was the head of the Federation for FASEB (Federated Association of the Society for Experimental Biology). Well, you know those guys.

Who asked me if I know Ken Fisher?

SW: Me.

BO: Well, he's been associated with that recently, and I think still is. However, when I appointed that group, first of all, I told Lehman that I was going to approach the question of flavors in such a way that the industry paid for the determination as to whether they were generally recognized as safe, because it would cost FDA millions of dollars to do it. We ultimately started with about 200 substances. FDA started with 37 synthetic substances. Over the years we gradually built it up to the point where today there are 1800 different substances on

the flavor of GRAS list recognized by FDA. A large number of them, about 1500 of them, were put in the form of regulations, so that FDA didn't have to say these are generally recognized as safe by the industry-supported panel, you know. Instead they could say that we have put them on the regulations because they are safe for use. So, that was a legal maneuver to get away from the GRAS exemption. But they're known as "GRAS flavors," you see.

What FDA did was, by the way, wrong, in my opinion. They took the list that we had developed and were publishing. And we had published 14 papers on the GRAS lists over the years, each time coming up with new data or new substances, new uses, and so on. Only about a handful have had to be withdrawn, partly on the basis of new evidence. Like saffrole, for example, was dropped, which was the main constituent of root beer or sassafras, 85 percent saffrole. Well, that was withdrawn, so it's no longer on the GRAS list. Coumarin was withdrawn, and a few others like that, but not many. So the list remains intact.

But what Food and Drug did, which I always regarded as a mistake, was to take that list and separate it into natural substances and synthetic substances. Two mistakes, the false assumption that because of natural occurrence in foods, they could be regarded as safe. Not true, and I could give you the evidence for the thousands of substances that have been found in foods that are chemicals. I'm not saying they're unsafe; I'm not saying they're safe. But there are a thousand in coffee, which alone has about a thousand identified substances, identified by different investigators, different laboratories, and so on. This has all been published by a Dutch publication, and I have picked out and I have here, if I find it again. I picked out the 17 spices that are included in about a hundred categories of foods. I have tabulated the number of naturally occurring identified chemicals that are present in those spices, and those spices have been assumed to be safe by FDA, who asked us to include them in our GRAS list originally.

So when FDA came out with its first white list, which later became known as “GRAS list,” here they are; well, there are several slides here which illustrated in naturally occurring substances and foods. I have one table here which shows some classes of naturally occurring substances that are present in foods which are either good gothregens, cyanogens, lathrogens, alkaloids, estrogens, citrates, oxalates, carcinogens, and several other categories which occur naturally in foods.

But the Dutch publication covers volatile compounds. I talked with one of them just recently and asked, “Why do you call them volatile compounds? You don’t mean that, you mean chemical compounds which have been identified in natural sources,” and here is my condensation of a big, thick book which – and I have the details for two categories. One is citrus flavors naturally occurring, and the other is coffee, just to illustrate how many substances there are, but here, I made this table.

In these classes of foods, coffee, tea, cocoa, milk, cheese, beef, chicken and turkey, citrus fruits, apples, raspberries, strawberries, potatoes, carrots, tomatoes, and onions. This is a kind of a spectrum of foods or food categories, and this shows chemical compounds by organic classification: hydrocarbons, alcohols, carbonyls, acids, esters, bases. I think this is sulfur compounds; I can’t see it very well. I should have looked at the type version of it, which is here somewhere, and so on. So here, you see, take cheese; there are 32 identified hydrocarbons, 11 of these carbonyls, 27, 25, 14, 6, and altogether is a bad . . . I have this typed here somewhere.

RO: It’s in here.

BO: Oh, is it in here? Well, that's just meant to cover some of the highlights in these tabulations. Well, here, it's done this way. The foods are up here and the chemicals are here, and the totals are down here. At this time I had 751 compounds listed in this publication. In coffee, I have since added to that, and there are about 850, I would think, but I have been told by people who know coffee, like the General Foods people, they say there are over a thousand than we have in our records, and so on, so that these chemicals being a chemical doesn't mean it's a poison.

SW: Right.

BO: It's a natural constituent. Here is citrus fruits. Here are the names of the hydrocarbons and the names of the alcohols and the names of the carbonyls, and these are more carbonyls and acids and estrogens, and so on, a huge number of. And this publication gives the references from which all this information is derived. The latest version of it is 1950, and I think this one I've got is only 1975. Of course, it's hard work to do all this calculation, but I think that there is very strong evidence that being natural doesn't mean it isn't chemical or it is safe, you see. So those are the two errors involved in dividing them that way.

FDA, I think, gave some force to that division simply because neither they nor anybody else had all the information that was needed, particularly with a regard to spices. I think that spices, if they were tested the way single components are tested, most of them would turn out to be toxic in one way or another. If you go to the highest dose that's tolerated, in other words, it permits the animals to live. In the highest dose that's tolerated, you can find significant amounts of toxic substances and spices. It is very commonly known that some of them, like pepper, for

example, it's easy to kill with pepper if you can put it in a capsule and give toxic doses of it, you know. It's also easy to kill with salt, the same way. It's how much you can tolerate, how much you can voluntarily eat in foods or can you make foods with such levels of xenobiotic substances (foreign substances). You might not be able to make the food at all. For example, if you put too much emulsifier in bread to keep it soft, you'll make soup.

SW: Well, I think we are about done unless you have something else you want to talk about. You were going to say something about Lehman.

BO: Here's something which I'm going to give you, and that's a list of Lehman's publications from 1926 to '62. Did I ever give you this? Okay. A number of these publications numbers from 1 to . . . Well, altogether 149 papers. I have to tell you about those papers too. These were done before he came to FDA, and they had to do with drugs mostly, and quinine, and so on. But since he came to Food and Drug, so the time this ended, and that was from about 1948 to 1962. There were about 100 publications that he had. Now, the point about Lehman's publications was that many of them were very brief statements of rulings that were made by him and his associates, not on the basis of long toxicological studies or even short toxicological studies in some cases, but on the basis of alleged metabolic faith like I pointed out to you. They were short, and many of them were published in those two journals that I mentioned. I'll show you examples of them. Altogether there are about a hundred that appeared from FDA authored by Lehman and his associates – relatively few, by the way, from Lehman alone, and relatively few based on any lengthy toxicological studies. So I think that I'll give these to you if you want to ask any specific questions about any of them, and I have copies of them. I don't have copies of

all of them, but here's what they look like. Well, here's a Lehman publication, *Lehman Alone*. Here are a group of publications by Lehman, and here's a copy of the procedures, the appraisal book. You say you have that here? They called it *The Rogue's Gallery Paper*.

SW: Oh, I've heard that term. I just haven't heard the original.

BO: That's because it had their pictures. Almost all of the authors here appear on this. My first contact with FDA was with the Division of Nutrition, as I indicated to you, with Nelson and Kline later, and Frawley and Laug, and a few other people from the Division of Nutrition. The Division of Nutrition now hasn't played much of a role in this situation. These are Lehman's.

Now, in another file I have quite a few more of Lehman's, and he did a few papers which clarified the basis for some of their reasoning, what the dosage range ought to be, or why a hundredfold safety factor came into being, how it came into being, and what the limitations of that are. And Virgil Wodicka, you know, was very much against the hundredfold safety factor, because if you had anything that was used in the human diet, say, to the extent of 1 percent and you had to use experimental diet of 100 percent, that's ridiculous. Nobody will live on an additive alone. But, say it's only 0.1 of a percent. That means feeding 10 percent in the diet. Now, that is the highest level that legitimate toxicologists have ever thought it reasonable to test an additive at. Elicitor Frazier in England, who was their top man in food toxicity, specified that anything that is innocuous in an animal at 10 percent, just forget it, see. I think he was right, because nobody eats anything approximating 10 percent, and if you do, you're bound to get an imbalanced diet in some way.

For example, if you wanted to feed, let's say, oleic acid, oleic acid is one of the three major constituents of normal fats, stearic, oleic, and palmitic are the three fatty acids that are most prevalent in vegetable oils and things like that. In addition to that, you now have partially hydrogenated oil, completely hydrogenated oils, and you have oils like arachidonic acid and now a form of oleic acid called omega eight, and so on. It's very complex now whereas it used to be very simple. But if you were to feed stearic acid at 10 times the level that you normally consume fat in the diet, an animal couldn't survive; it would be, we ordinarily eat about 5 percent. We eat more, but 35 percent had been recommended as a limit of the percentage of fat calories that ought to be eaten in the form of fat. But you can't eat 10 times that, so that that ratio, that safety factor ratio of 100, is only for those substances that are used at levels of a fraction of a percent, or parts per million or parts per billion. So Virgil, and I have always argued on that point. He's not been in favor of the uncritical adoption of the hundredfold safety factor, and neither am I, but it is better, in my opinion, going through a lot of mathematical ramifications to come out with what's considered a safe level at an acceptable risk of one in a million for cancer, you know. We haven't talked at all about that yet, but that's another long, current controversial story.

I mentioned something about Lehman and his group in this recent paper because I feel that with the passage of time, he hasn't been recognized sufficiently, and his group and awards have been created in his honor. You know, a Lehman award in the study of toxicology is a very important award to receive. But that's the way he's been honored by the award, but not by the work he's done. People don't know about the work he's done before and during his tenure at FDA.

Anyway, I wrote this five-page thing, and if you want that, I'll be glad to send it to you, this kind of a personal thing. I'll read you about 10 lines if I may. Do you mind?

SW: No.

RO: No, not at all. I'll tell you one thing we can do, Dr. Oser, if there any of these papers you'd like to attach, we can attach these to the transcript.

BO: Okay, but some of them will involve a lot of copying because I don't have too many of them. I gave you some, and I'm going to give you a few copies of the more recent thing, which I call *Toxicology Then and Now*, some of which I've been covering in this talk. But I said here, and this was published in a . . . You know what a [blank] is?

In 1968, which was near the end of his presence in FDA – I don't know whether you know that he resigned very abruptly on a Friday and said, "I won't be in on Monday," and he never put in an appearance after that. Nobody really has had a satisfactory explanation of what the reason was. You may know, and I'm not going to ask you. Nobody has been willing to say that they know.

"Seated on the aisle in the last row of any important toxicological meeting, on the last row, one could usually find Dr. Arnold J. Lehman. He always sat in the back (to make it easy to escape), which he did often. He may be under a cloud of smoke from his tar-stained meerschaum pipe or from a Corona presented by one of his many admirers, but he'll be there listening intently. Perhaps even taking a few notes. But if the speakers should be unintelligible or boring, or if the slides should be illegible from that distance, Dr. Lehman will avail himself of the prepared escape route. On the wall of his office at the Food and Drug Administration, one

can read the pronouncement that ‘You too can become a Pharmacologist in Two Easy Lessons, Each Ten Years Long.’”

You know that? That’s been quoted a thousand times, and so on.

So I discussed a number of personal things about him and then discussed something of his family and his educational background, and what he did before he came to FDA and some of the peculiar things he worked on before FDA and since. These contributions cover a wide gamut of subject matter, such as pesticides and propionates, burnt toast and brominated oil, methyl alcohol and metal fragments, containers and cooking ware and so on. That’s what they did. You may remember some of them. You may have read about them.

I should mention, and I haven’t yet, but we can just touch upon it. During all this period that the laws were being developed and germinated, the public press was having a great time with the new information it was learning about how ubiquitous toxic substance are in foods.

I have a four-foot bookshelf of all the “crackpot books,” not all of them, but a collection of “crackpot books,” beginning with Rachel Carson’s *Silent Spring*, which wasn’t really a “crackpot book,” but very, very highly exaggerated, as the name implies, you know, there would be no birds singing in 10 years or something like that. Well, she was wrong. But the point is that she focused attention on the need for proving that she was wrong. But there was also a “yellow journal” press throughout the country and people who were taking up the cudgels against FDA against the government’s effort to protect itself, and using misleading data.

Now, here’s one of the cute ones that I have just recently Xeroxed, because the newspaper from which it came is falling apart. See? Now, this illustrates something that I’ve always contended, and I used to have a wonderful side for it with a Congressman sitting down and one of his aides coming in, having shown him a report, and the congressman says,

“Excellent, excellent. It’s a perfect mixture of truth, half-truths, and blatant lies.” Did you ever see that?

SW: [laughter] I’ve seen it.

BO: You did? Well, I was the one who introduced that. Where did you see it?

SW: Oh [laughter], it was in a cartoon. It is around here somewhere. We both have seen it here.

BO: I have a lot of cartoons on this subject. As a matter of fact, there was a chap from the University of Massachusetts who has given a number of times a talk based only on showing cartoons, you know, and was really good at it. It caused a lot of laughter among his audience, but they were a more sophisticated audience than among the people who read the *Enquirer*, you know. Anyway, this is half-truth.

Here’s a charcoal-broiled steak. Now, Schubek, when he had his laboratory out at the University of Nebraska, actually analyzed the charcoal-broiled steak, with emphasis on the crust. And there are any number of substances in smoke and smoke condensate and pyrolysates that are carcinogens, and he analyzed this and said, “Look, we’re eating this stuff all the time.” That was his conclusion. But these guys took the conclusion and calculated how many of these potential carcinogens there are here, and how many that come from cigarette smoke. Cigarette smoke kills what, fifty thousand people a year? So that’s what the hazard is. Oka, well, this is by way of, to us, amusement, but of course it’s kept the pot boiling all the time, and the proof of safety as

is commonly used even by FDA people. It's impossible. There is no such thing as proof of safety, just like there is no such thing as zero.

I once wrote what I thought was going to be a funny paper, called *The Mathematical, Legal, and Chemical Concepts of Zero*. Did you ever see that?

SW: No.

BO: Oh, you've gotta see that. That's a fun paper. But zero means . . . First of all, zero was an invention. Zero wasn't a concept that people do and recognize all the time. You know who is responsible for it? The Arabs. So, zero is a theoretical concept, and an indispensable one at that. There would be no mathematics today if we didn't know what zero meant. And what we have been approaching through our analytical and toxicological procedures is approaching zero, because the people who have been working on carcinogenesis have adopted various theories of cancer, one of which is that given one molecule of a carcinogen, so-called, and one cell, and they should be talking about one substance in one molecule of a substance in a cell, because one molecule of a substance and, if you get a reaction between them and if it multiples sufficiently, will become carcinogenic to rats at least.

And, incidentally, we don't distinguish and FDA doesn't distinguish and Delaney doesn't distinguish between cancer and, by the way, the word carcinogen doesn't appear in the law, but they don't distinguish between a carcinogen for rats and a carcinogen for man. But if you read all the junk I've done, you'll find I have a letter to an editor at one point saying, "Let's be more specific. We ought to speak of a rodenticarcinogen if you talk about rats, and anthropocarcinogen if you talk about man, and there is a definite difference, and it shouldn't be

assumed that the rat is a perfect surrogate for man; it's not. But in the interest of prudence – that's the word, the FDA word – in the interest of prudence, in the present state of our knowledge, we have to assume that anything that induces cancer in rats or, more specifically, when fed to rats, must be assumed to be a potential carcinogen for man.

There is also a second part to the Delaney Clause which doesn't say when fed to rats by any route deemed appropriate; that's part of the Delaney Clause. So the question is, deemed by whom? Now we talk about the Delaney Clause "found to induce cancer"; those are the key words. What do you mean by found? What constitutes finding? Is it a pathology, is it tumors, is it mortality, or what? What is your criterion for finding that something? They don't say causes cancer. Why don't they? They never said causes cancer. They talked about causing cancer, but the law is written "it's found to induce," you see. So those are vague terms. And found to induce what? Cancer? Well, cancer was defined one way in the '50s and another way today. Who defined it in the '50s? The Food Protection Committee took a stab at it and defined it in such a way as to distinguish between a malignant tumor and a benign tumor. They decided what the difference had to be both in the pathology and in one case resembling the tissue in which it was present, in the other case not, and also determining whether it's metastatic or determining whether it's lethal, another one of such criteria which the Food Protection Committee, incidentally, of which I confess to being a member at the time, defined to distinguish between benign and malignant tumors. I think I mentioned something about that in this recent paper; if I didn't, I should have.

But there is no difference under the law because now even hyperplasia is certainly suspect, and if you find hyperplasia at your lowest dosage, you better go on and do more work, or at least keep away from FDA, because if you define it that way, then using more rats or longer

time or higher doses or something like that, you'll find that it is carcinogenic, and carcinogenesis is not so unique that there are only a half-dozen things we need to worry about. I don't mean to say we have to worry about the others, but we can't say that the other thousands of substances are found in fruit naturally or that we add to food are potentially hazardous and have to be studied by the best known, best available product toxicity data we have in the most appropriate species, or in two or more species, the way it was originally expected to be, and so on. So we only take a stab at toxicology, and there are a host of uncertainties in the toxicological approach and . . .

I've written more than I have published on this subject; if I live long enough, I'm going to finish a paper, and I would say it is halfway through. But it is a very tough one, and that is to enumerate what's in the literature already, but enumerate in one paper all of the uncertainties in toxicology in both the selection of species and the selection dosage range and the selection of biochemical tests, pathological examinations, and so on that ought to be considered for assessing the validity of a toxicological test.

Now, you may find if you collect all of the literature that is available on a substance or substances, a lot more than is in any one paper is available, but it's scattered; and taken as a whole, the uncertainties in toxicological studies . . . And I've written about them in many different ways.

Here is one way called *Oxigens in Animal Feeding Studies*, and these all come under the general heading of approved guidelines, approved. But just to show you how much variation there can be in following the Red Book, the approved guidelines, and why you get differences in toxicological responses in different laboratories, here are test conditions which may vary: species, strains, sex, the age, the grouping; I should put here the housing, the pre-test diets and

test diets, and the route of administration, the dose levels, the frequency, the duration, and whether you go on to more than one generation. So much for the test conditions.

Maintenance, caging, bedding, feed cups, watering, observations, gross appearance, behavior, body weight, food consumption, water intake, biochemical examinations, metabolic, and functional tests. And the environment, the temperature, the humidity, the air flow, the lighting is important. Noise control. These are things that are controllable but which differ from laboratory to laboratory or from test to test, or from time to time.

Well, here's some more detailed discussion of these items, but this one – I've forgotten who got this up, but this one is called the decalog, the ten commandments for assessing the safety of food additives. Toxicity versus hazard. There's no question that those two are different. The Food Protection Committee went into that in great detail, and toxicology and hazard are different. Toxicology is the adverse effect on animals, and hazard is the probability that effect will carry on into man, and on to the conditions of use; and that ought to be separated, but toxicology and hazard are all jumbled up nowadays. In other words, anything that's toxic is hazardous, and in the case of the Delaney Clause, it doesn't matter what the dose is or how long you have to feed the animal or whether you have to feed the animal or can test by intravenous or other parenteral beings, you know. The normal presence in body fluids or tissues.

Well, that gives you a little something to hang on if you know that a substance is normally present in the body, like the hormones, estrogens, and so on. A certain amount of estrogenicity should be able to tolerate, we hope.

Oxigens, as we now call them, cancer-inducing substances that are produced in the body. The normal presence in foods as eaten. The history and the patterns and the levels of use. Now, for example, natural substances, we don't eat the whole plant. We eat parts of the plant,

sometimes only the seed, sometimes only the roots or an extract or leaves or what have you. The chemical structure, whether it's known or assumed, and what the analogues and homologues are normally in the diet. The metabolism, species dose, pharmacokinetics, species dose, conditions of use, the dose, meaning not only the level, but the frequency and how long that's repeated during the lifetime of the animal. Categories of assumed safe substances, categories of potential toxic substances, and the toxicological test conditions and their extrapolations from the animal to man. So this is just a two-minute listing of the uncertainties of toxicology.

Now, what happens now? We don't say we have a no-effect level and from there we can estimate what our safe levels for man are. We extrapolate – that's a bad word – by means of mathematical formulas for risk assessment; mathematical formulas for risk assessment.

Considered in its narrowest sense, you have the safety factor of a hundred, which is not written into the law. It's not a must; you're entitled to deviate from, it up or down depending on a number of conditions, which are listed in one of the slides I have here. The conditions justify deviation from the one hundred factor [margin of safety], and the justifications for going up or down.

You could also, which FDA contends it is not legally authorized to do, take into account the benefits of using additives. Why do we use them? Can we get along without them? Well, in modern society we can't get along without them, because we have managed to get along without grocery clerks by buying everything in packages, and assuming that the label tells us the truth and that we read the level, and if we read it, that we understand it. I have my doubts about a lot of that, and besides, the consumer who buys foods and should read the label before buying it doesn't provide the food for herself or himself, provides the food for his family, children, infants, elderly, and so on. So you can't expect a scientifically untrained consumer to interpret labels

accurately. Even the nutritional information that we put on labels is what I call misleading information. Nobody adds up how much thiamine they get with each portion, and so on. And do we get all of our thiamine? And do we get it all if we use “All” or “Total,” the cereals? Well, that’s not all nutrition; that’s the recommended daily allowance of vitamins. But for some people it should be less, and for some people it should be more, and so on. The consumer’s purchasing habits and the consumer’s needs and wants. So the consumer is entitled in some degree in buying what she wants because it tastes good or because it saves her making dessert, whatever the reason may be. So you have to consider the benefits in terms, in the broad terms, as well as the risks in broad terms.

The word “risk.” I classify risk as speculative, it’s hypothetical, it’s unverified, it’s heuristic, and it’s indeterminate. Individual intolerance, hypersensitivity, metabolic anomalies. These determine risks for individuals. The general toxicity, which means the occupational exposure, acute exposure, accidental exposure, or homicidal use. If you want to know something about toxicity for homicidal purposes, the best way is to be a good toxicologist. And then chronic tests involving functional effects, behavioral, organic, reproductive, carcinogenic, mutagenic, and teratogenic. Each of these is events that enter into risks. But some risks are tolerable, and people are willing to accept them more than they are willing to accept, let’s say, swimming or riding a motorbike or any kind of physical activity. So risks are considered as though they’re all in the same bag or nest.

SW: It is after three, Dr. Oser. Should we stop?

RO: Thank you very much, Dr. Oser.

[END OF INTERVIEW]

## **Deed of Gift**