Vos, Fitzhugh, Laug, Woodard

ORAL HISTORY OF THE
U.S. FOOD AND DRUG ADMINISTRATION

PHARMACOLOGY

Transcription of Recording of

Meeting to discuss the History of

Pharmacology in the Food and Drug

Administration

Rockville, Maryland, June 20, 1980

Present: Dr. Bert J. Vos
Dr. O. Garth Fitzhugh
Dr. Edwin P. Laug
Dr. Geoffrey Woodard,
Retired FDA Pharmacologists

Dr. James Harvey Young
Emory University

Fred L. Lofsvold
Wallace F. Janssen
Robert G. Porter
U. S. Food & Drug Administration

INTRODUCTION

This is a transcription of a taped interview, one of a series conducted by Robert G. Porter and Fred L. Lofsvold, retired employees of the U. S. Food and Drug Administration. The interviews were held with retired F.D.A. employees whose recollections may serve to enrich the written record. It is hoped that these narratives of things past will serve as source material for present and future researchers; that the stories of important accomplishments, interesting events, and distinguished leaders will find a place in training and orientation of new employees, and may be useful to enhance the morale of the organization; and finally, that they will be of value to Dr. James Harvey Young in the writing of the history of the Food and Drug Administration.

The tapes and transcriptions will become a part of the collection of the National Library of Medicine and copies of the transcriptions will be placed in the Library of Emory University.

Vos, Fitzhugh, Laug, Woodard

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Public Health Service

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TAPE INDEX SHEET

CASSETTE NUMBERS: 1,2,3,4,5

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DATE: June 20, 1980 PLACE: Rockville, Maryland LENGTH: 279 Min.

INTERVIEWEES	INTERVIEWERS
Dr. Bert J. Vos	James Harvey Young
Dr. O. Garth Fitzhugh	Emory University
Dr. Edwin P. Laug	Fred L. Lofsvold
Dr. Geoffrey Woodard	Wallace F. Janssen
Retired members of The Division of Pharmacology, FDA	Robert G. Porter
	U. S. Food & Drug Administration

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		9	4	" " Dr. Laug
		14	7	" " Dr. Vos
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	B	0	16	History of Division of Pharmacology Continued
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		3	17	John Draize
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Attachments:

I List of Publications and Curriculum Vitae
Edwin P. Laug

II List of Publications, O. Garth Fitzhugh

PHARMACOLOGY MEETING

Mr. Porter: This is a recording being made at Rockville, Maryland on June 20, 1980. Those present are Dr. James Harvey Young, Dr. Bert J. Vos, Dr. O. Garth Fitzhugh, Dr. Edwin P. Laug, Dr. Geoffrey Woodard, Fred L. Lofsvold and Robert G. Porter. All except Dr. Young are retired employees of the Food and Drug Administration. Drs. Vos, Laug, Fitzhugh and Woodard all had many years of service in the Division of Pharmacology. The purpose of the meeting is to discuss events which took place during their service in FDA. We would like to begin by asking each of our guests to make a brief statement as to his educational background and his years of service in FDA. And, with that, I would like to start with, Dr. Woodard, would you volunteer to start?

Dr. Woodard: I'm closest I guess. I came to work for the Division of Pharmacology in 1936 as a minor laboratory apprentice, which is, I think, about as low as you could get with the GS Service. And after I came here I continued my schooling at George Washington University and after a number of years ultimately got a PhD in Pharmacology.

Dr. Young: When was that?

Dr. Woodward: In 1951. And during the years that I was here - I left in '57 - during the years that I was here, which were about 21 years, I was largely involved with toxicology, I mean with acute toxicity, and with pharmacal dynamics. At the end of that period I was primarily involved with bioassay in the pharmacal dynamics branch of the division. Since '57 I had my own laboratory up until the time that I have suspended work, which was a couple of years ago.

Mr. Porter: How about you, Dr. Fitzhugh?

Dr. Fitzhugh: I have a doctor's degree in Pharmacology and Physiology from the University of Virginia in 1936. I taught Pharmacology and Physiology at the University of Vermont for 3 years and then went to Vanderbilt University, stayed as a Research Associcate for 2 years. I came to the Division of Pharmacology, I suppose as a Junior Pharmacologist, as a P2, and started very low in the scale of salaries as they are now. I was in charge of the chronic toxicity from that time on. I'm trying to think of the years - 1938 I think I came - Fall of 1938, and stayed with the Food and Drug Administration until 1970. And then I worked for the EPA for slightly over a year. Going through that with many various positions from a Junior Pharmacologist to Chief of the Branch of Chronic Toxicity; and I was Associate Director of the Division, that Bert was heading. I almost forget the name of it now, Bert.

Dr. Vos: Division of Toxicological Evaluation.

Dr. Fitzhugh: Toxicological Evaluation. And then after that was dissolved, we came into the various offices or bureaus. I don't know what positions I held now, until I go back and looked at the various positions. Anyway, all that time I was in charge of the chronic toxicity. I was in charge of the pesticide and food additive petitions until the time I retired. Much of that was administrative work in the latter years rather than the first part of it, because then I was directly working in charge of the laboratory. In later years it was more administrative. Briefly, that's it.

Mr. Porter: Okay. That's fine. This just sets the scene for anybody that listens to the tape, and it also helps the typist identify voices later as we all talk. Dr. Laug?

Dr. Laug: I sent something that's in the records of an earlier meeting in December 1979 and it's even more concise than what I'm going to say now. Do you want me to repeat it then, essentially?

Dr. Young: Yes.

Dr. Laug: Well, then, briefly, I came to the Food and Drug Admnistration as a P2 Pharmacologist in 1935. I am by training a PhD in Biochemistry from the University of Pennsylvania.

In 1935 the Division of Pharmacology was being reorganized. The idea, among other things, was once and for all to settle the problem of the lead and arsenic pesticides that were in those days being used on apples. At the organization of the new Division of Pharmacology in 1935, I was appointed Assistant Pharmacologist to do research on the toxicology of lead. Such studies to give scientific support for setting tolerances for lead (and also arsenic) in fruits sprayed with lead arsenate.

At time of retirement in 1965, I was Chief Special Investigations Branch, Division of Pharmacology. I published 64 papers in technical Journals on methodology and basic research to give support for the setting of tolerances for toxic substances in foods and drugs. Broadly, these studies concentrated on three general areas of toxicology.

(1) The heavy metals, such as lead, mercury, arsenic, etc.

(2) The organic insecticides, such as DDT, Lindane, Aldrine, Dieldrin, etc.

(3) Impact of radioactive contamination on foods, following the atmospheric release of radioactive substances in connection with the testing of atomic bombs.

Mr. Porter: Thank you. Dr. Vos?

Dr. Vos: I had a PhD in Physiological Chemistry and Pharmacology from the University of Chicago in 1934, an M.D. in 1937. I was interested in the Food and Drug Administration as a result of a recruiting tour that Dr. Calvery made around the various universities. He spoke at Chicago and induced several of us to apply for Civil Service ratings. Subsequently I got a telegram saying, "would you accept a GS3 position?" So I wired back, "I accept" and resigned my position in Chicago. Dr. Calvery promptly wired me back and said, "Don't resign yet". This was a standard procedure. They had 3 people at the top of the list and they sent each one of them a telegram "Will you accept?"; they weren't offering the position, they were just trying to see who was available. So for a period of a few weeks there, I was a little uncertain as to what my future was. But I then started on October 15, 1939, as a P-3 Pharmacologist at $3,200 a year. I qualified for a P-4 with my training, but they didn't offer me that. Times then were a little rough and you took what you could get. As an interesting picture of what personnel practices were then, I got my first increase in salary after I'd worked for 23 months. I didn't get a promotion, but I got a $100 a year increase. After 23 months my salary was raised from $3,200 to $3,300. I think that gives an interesting look back as to what things were like. Not only were salaries low, but promotion was slow. You had to wait until somebody resigned or died;

you could then move up to an advanced position. I came in to work on the bio assay of ergot, which is a drug that was used in post partum hemorrhage, that is to prevent bleeding of women after childbirth. And, prior to when I came there there had been a tremendous investigation at the Food and Drug Administration in their handling of ergot. This was before my time, but as I recall, or heard it, some people had cornered the ergot market and were trying to prevent the import of ergot, which would then drive prices down. And they were accusing the Food and Drug Administration of letting in sub-standard, moldy ergot. And there was then a Congressional investigation to see if that were true. The biggest part of it was the moldy ergot. Well, of course, ergot is a fungus that grows on rye and so for it to be moldy is a little tricky. There is such a thing as moldy ergot, but ergot itself is a fungus, isn't it? The Food and Drug Administration was finally cleared of any malfeasance, I guess, whatever you want to call it. But they still felt a little sensitive on their assay of ergot. At that time ergot was assayed by injecting it into roosters and seeing how much their combs turned blue. It caused a contraction of the blood vessels in the comb and the comb turned blue. So you injected it and looked at the rooster's comb and decided that the front part was normal and the middle part was about a 1+ and the rear half, rear third, was 3+, so that was an 013 grade for that rooster.

Mr. Porter: It was a colorometric method?

Dr. Vos: Yes, and this was a rather unsatisfactory, subjective thing. That is, there were no precise criteria someone else might read the combs differently. And my job was to come up with a new bio assay for ergot. Well, I hadn't the remotest idea how to start that and I spent the first month stalling. I said I was doing library literature review, which I did. I shared an office with Dr. Fitzhugh and I guess I impressed him as the person who had been around the longest without doing anything in his brief experience at Food and Drug. Eventually we did come up with a bio assay on it, for the principal alkaloid, ergonovine. And at the same time a chemical method was developed which supplanted the bio assay ultimately. I worked in bio assay for many years. Later I worked more in administrative work. I was at one time Director of the Division of Toxicological Evaluation and for a brief time was the Acting Director of the Division of Pathology, when it was organized. I had very little experience in pathology, but this was a stop-gap appointment just before my retirement in 1970. Since then I've been doing consulting work at various places. I worked briefly for Dr. Woodard in his organization, I started there immediately after I retired. That's about all.

Mr. Porter: Thank you.

Dr. Young: Let's begin with the institutional side before we get to some of the key problems that were encountered. The size of things, the environmental feel of it, how close you felt to the Commissioner. And how homey a place was it in comparison with how it later seemed to become? The key figures and other things of that nature. Dr. Woodard?

Dr. Woodard: Well, I would like to trace a little bit of what I know of the history of the Division, how it was set up and why it was set up, because I think that actually it's not appreciated generally, but the Division of Pharmacology probably was the pioneer group that worked in toxicology and actually brought toxicology from one animal, one dose, to somewhere near the stage that the field of toxicology is today. The original Division of Pharmacology was a branch of the Division of Medicine, I believe. I do not recall who was the head of that division. The Commissioner, who was the first Commissioner of FDA, was a very astute individual and he apparently realized that there needed to be an organized attack on toxicology generally, and specifically on lead and arsenic.

Dr. Young: This was Walter Campbell?

Dr. Woodard: Walter Campbell, yes. They first got Erwin Nelson on sabbatical leave from the University of Michigan. You have to realize that the University of Michigan is the

grandfather of pharmacology. I think the first chair of pharmacology was at the University of Michigan and John Jacob Ahwell was the first pharmacologist in this country and was located at Michign before he went to Hopkins. Erwin Nelson came to the Division for two years, I believe.

Dr. Young: Would this be in the late '20s?

Dr. Woodard: No, it was 1934 or 1935. It was his mission to gather together people to set up his new division, take it out of the Division of Medicine and set up a new Division of Pharmacology. In order to do that he, and I'm not sure who helped him, canvassed many of the universities and brought together the group of people, some of whom you see here. They carried over from the old branch four people that I recall. Harold Morris, who ultimately went to NIH and then became a big cancer specialist. There was a Herman Morris who was no relation, but he eventually went out to the Western Regional Laboratory in the USDA. Howard Lightbody, who was a biochemist and whose specialty was in enzyme work. And W. T. McCloskey, who had done the ergot work which Bert talked about before. McCloskey had done the work. The only other person that I can remember was a gentleman by the name of Scottie, who you will probably hear about later. Scottie was my first introduction to the Division of Pharmacology. He was an animal caretaker. It was 3 weeks before I could figure out the language that he was using. I wasn't used to the Southern

dialect in this area. At any rate, the people that were appointed were Ed Laug, and he was selected, particularly as I understand it, because of the expertise that he had gotten with A. N. Richards at the University of Pennsylvania. There was Lloyd C. Miller, who had trained under Balure at Rochester and was a lipid biochemist. I'm not sure what he was supposed to do, but he eventually went on to become head of the Pharmacopeia Division until he retired. He had years and years in that job. Then there was Herbert Braun, who is deceased. He had trained under Tatum at the University of Wisconsin and he was a pure pharmacologist.

Dr. Laug: And the only one.

Dr. Woodard: I think that's right.

Dr. Laug: It's very interesting that when the Division was formed in '35, the preponderance of people who were there, except E. E. Nelson, and he was only there 2 years, were all biochemists. Larry Grant, Chester Tolle.

Dr. Woodard Who was the fellow who was killed?

Dr. Laug: Edward Wallace.

Dr. Woodard: Ed Wallace, now he was a pharmacologist. I worked for him very briefly.

Dr. Laug: There was a preponderance of biochemists who then changed sails and became pharmacologists.

Dr. Young: Was this because the field of professionally trained pharmacologists was so scanty in number?

Dr. Woodard: No, these people were picked because of special expertise that they had. This was the original idea to bring together people of many diverse interests to focus on the problem of lead and arsenic toxicity. Then he brought in Calvery from the University of Michigan. He was designated as the person to take over the division when Nelson went back. Calvery was supposed to become the head of the division, which, because of vagaries in the Civil Service, was a problem. He was Acting Chief for a couple of years at least, maybe more, because he didn't have an M.D. Somebody thought that the head of that division should be an M.D. Then, before the Cancer Institute was formed, but was in the initial stages, Harold Morris moved to the Cancer Institute and Dr. Fitzhugh was selected as the person to take his place in the chronic toxicology area. But in this group, which originially started with the focus on lead and arsenic, you had people doing analytical work, you had people doing work in enzymology, you had people doing various kinds of animal work. And then, there was a pathologist. The original pathologist was a lady.

Dr. Laugh: Lucille Fenner?

Dr. Woodard: Yes, Dr. Fenner. She was ill most of the time, and for the first year she only worked maybe a couple of months.

Dr. Laug: Nelson didn't come until '39.

Dr. Woodard: Yes, and then they got Arthur Nelson, who was no relation, from the Cancer Institute. He had trained with a pathologist who is now retired and who was head of pathology at NCI. The name escapes me.

Dr. Young: What school was he? Do you remember that?

Dr. Woodard: He came from the University of Minnesota. He had gotten his training under Bell at the University of Minnesota.

Dr. Young: Oh, but the man you mentioned later on.

Dr. Woodard: No. that's Nelson. Arthur Nelson got his M.D. and then he did his pathology training under Bell at the University of Minnesota who was one of the better known pathologists in the ocuntry. So all the people in the original Division of Pharmacology were from very highly qualified

backgrounds and from good schools and had good training and I think made the field of Toxicology what it is today. I can remember in subsequent years that the people who set up the Dow Toxicology Group came here and spent weeks learning about how to do these things from the people in the Division before they set up their lab. Henry Smyth, who set up the group at Union Carbide or at Carnegie spent weeks and weeks here before he set up that Institute, which was one of the better known groups in toxicology in the country. Another, of course, Oser, who was head of the Food and Drug Research Laboratories spent many, as a matter of fact, he practically lived in the Division for about two years.

Dr. Young: What were the characteristics of the Division that gave it this distinction that others later came to see in order to imitate?

Dr. Woodard: Well, I think it was a lot of original thought in toxicology and methodology. There were no methods in toxicology, there wasn't even an LD50. As a matter of fact, the first LD50 that was ever published was published by Ed Laug on the glycols.

Dr. Laug: That was the outgrowth of the Elixin Sulfanilamide matter. The publication was:

"The Toxicology of some Glycols and Derivatives"
Edward P. Laug, Herbert O. Calvery, Herman J. Morris and Geoffrey Woodard
J. Indus. Hyg. and Toxicol., 21:173-201 1939.

This publication formed the basis of much other related work.

Dr. Young: We want to talk about that. So let's don't forget that. Right.

Dr. Woodard: And then John Draize was brought in from Edgewood to do dermal toxicity, of things that applied to the skin because of his background and work there. He was a pharmacologist from Wisconsin originally. He spent a year in Wyoming I believe, before he went to Edgewood. I believe he didn't really care about Edgewood too much. Almost his entire professional career was in the Division of Pharmacology. And I guess Draize probably has got his name on more tests than anybody else in the country. It's still the Draize Eye Test that you use that you use for irritating substances and the Draize Skin Test. Many of these tests were developed, however, either with Ed or Bert or some with myself. Draize was the major and got the credit for it.

Dr. Laug: In connection with the Draize Test. I would consider it a serious omission if Draize's fundamental skin and eye work, now basic for evaluating cosmetics in industry were not given more than passing mention. Recently there occurred a "flap" in the news media over the use of rabbit eyes for evaluating a variety of facial and eye cosmetics. The "Draize Test" was mentioned.

Dr. Young: What formed you into a closely integrated cooperating team? The problem you worked on, this lead and arsenic residue problem, was that it?

Dr. Woodard: Oh no. I think it was just a gung-ho outfit.

Dr. Fitzhugh: It was cooperation between the groups because we were almost all of us working as independent individuals to a certain extent.

Dr. Woodard: I think we were just a really excited group of people working in exciting new areas.

Dr. Young: Exciting, new areas. Now define that.

Dr. Woodard: There was no such thing as toxicology before we started doing this kind of work.

Dr. Young: Therefore, as one looks at the map of this new area, what does one see? There was nothing. What did you create?

Dr. Woodard: Well, to do the work on the lead and arsenic, the procedure was introduced to feed repeated doses over the lifetime of the animal. That had never been done. It may have been done by somebody before, but not on a massive scale

like was planned here. Also, Morris had started a study on sulfur dioxide also on the same basis, of giving this dose every day for the lifetime of the animal which in the case of rats is just a couple of years. In the case of dogs perhaps we had early experiments that ran as much as seven years. The other areas were, and Lightbody I think pioneered in this area, was the effect of compounds on enzyme systems in the body, as a way of measuring toxicity. Ed, I think, did a lot of pioneer work in metabolism and storage and excretion as measures of this. And, of course, you know, we all, as Garth said, worked very closely together. And while we were working independently, each one had a little bit of interest in the major problem.

Dr. Young: So that it was each of these things being a new experimental approach and also that they were all interrelated is what blew it up into a mammoth contribution to a developing field?

Dr. Woodard: I think so.

Dr. Young: Well, that's what I'm trying to - how about letting others elaborate or add to what you've said so far?

Dr. Laug: I'd like to, expanded a little bit on this Elixir Sulfanilamide matter because really that was the thing that got it started. I don't know whether I need to go into that, but you know the company.

Dr. Young: I'd like you to go into that. I know the case, in fact I'm just about to write a chapter on Elixir of Sulfanilamide Revisited for a book in honor of Dr. Aaron Eide, who's retiring. So that your own, not only your own expression of the scientific aspects, but the human interest side of this as far as your involvement is concerned, is something I'm also interested in.

Dr. Laug: Well, we were presented with the problem when this thing broke. I think over 100 people died. A chemist at Massingill had decided that diethylene glycol was a good solvent for sulfanilamide and without the kind of work which now goes behind any drug preparation, and immediately we had to get started. Well we knew that the diethylene glycol did it, but how toxic was it really? And, in those days, if you had two rats and you killed one and didn't kill the other one, then that was called an LD 50. What we did is described in this article, which has been published, called the "Toxicity of Some Glycols and Derivatives". It was by myself, Calvery, Morris and Woodard.

Dr. Young: That is the publication you referred to previously?

Dr. Laug: Yes. I think the most significant thing that we did, and I think that John will certainly agree that in those

days there was not much precision when determining toxicity. And what we did was by the use of statistics, we made it possible that when you treated animals with something toxic, you could create a curve, a slope, and the significance of that was that you could then compare it to something else and that was the point, LD50. In other words, if you gave graduated doses to animals, and you did that with another compound, in a similar manner, you could then compare the two points where it killed half the animals and that's a statistical approach and had really never been done. And that's the part where we led these fellows around by the hand later, the industry people came around and did it. That, I think was a very fundamental piece of work. And I really think that needs to be properly evaluated. It has absolutely nothing to do with ourselves who were on this, because it was then worked up in the Division, and they all used it. Dr. Fitzhugh spent his professional life on that same approach. Usually either acute toxicity or chronic toxicity. But, that point where you can say this is the toxicity of Compound A which I have compared to Compound B. If you don't know that point, you've got nothing.

Dr. Young: Do you remember how you decided to undertake that particular kind of an experiment, in view of the circumstances?

Dr. Laug: Simply because the review of the literature revealed that there was no mechanism. You couldn't look at diethylene glycol or arsenic or anything else and say, well this is twice as toxic as that and so on and so forth. And this is a method, a statistical method which has been successfully refined over the years, so it's really now an accepted tool.

Dr. Young: Did you have group meetings when the deaths began to be reported, at which you said, "Now what is our task going to be, in order to solve this?" Was this a task put upon you by the regulatory agents--"give us evidence so we can go into court?"

Dr. Laug: No, I don't think it had reached that stage, do you think, Geoff?

Dr. Woodard: No, I wouldn't say that. This was -- a lot of these things were the vision originally of Dr. Calvery who died very prematurely. He had, I think to me at least, he had a lot of visionary ideas of what needed to go into this new science. These ideas--well he brought in Chester I. Bliss who had just gotten back from Russia, I believe. And he brought him for a couple of summers as a part-time consultant. And he was here at about the time that this thing happened. Now they had worked out something of this sort for kill in order to compare insecticides. They had worked out some sort of a

statistical method so that you knew which insecticide was better than the other. The old Pete Grady Chamber, as I recall. And so we all recognized that this was a problem. We have all these animals, now how do you go about determining an accurate figure that you can use as a benchmark. So he worked with all the people in the Division.

Dr. Young: What was Bliss's skill?

Dr. Woodard: He was a statistician. Bliss was actually an entomologist and he went to England or somewhere and spent a couple of years on that, I guess three years, and worked with Fisher.

Dr. Young: Fisher was the fellow who was the pioneer.

Dr. Woodard: He was sort of Fisher's protegee.

Dr. Young: So he's sort of the conduit by which the statistical pioneers come to your agency.

Dr. Woodard: And then Bert was very much interested in this.

Dr. Vos: Well I came along much later.

Dr. Woodard: But also he's done a lot of work in statistics.

Dr. Fitzhugh: You know the first experiments in setting up toxicity experiments go back a little while and both Geoff and Ed have mentioned the early '50s. Really nobody had done this except Dr. Sollmann at Western Reserve, who's really the father of Toxicity I suppose. When he used two animals and decided when one animal died that established the LD 50.

Dr. Young: Roughly, when did he do this?

Dr. Fitzhugh: Well it was before this division, I can't... he'd been at Western Reserve a long time.

Dr. Laug: I think it must have been about in the late '20s.

Dr. Fitzhugh: Probably in the '20s. Then when we began the chronic toxicity, in the setting up of experiments, we had to have some method of establishing how many animals. We would talk in terms of lifetime studies on these animals and we had to use some statistical idea of how many animals we should have, how many doses to administer. That was the basis which we used.

Dr. Young: This was going from a sample of two to a big enough sample to be significant.

Dr. Fitzhugh: Yes, at that time you had to plan not only for the acute toxicity, but for the chronic toxicity, for which we

were going over a time of two years in the rats. So we had to have the greater numbers. That has grown over the years from a few doses to many more. But we were the ones who first started to use this method of statistical evaluation in order to set up and start experiments -- what methods to use.

Dr. Young: And so Bliss was there to help. Do you have a feeling that Dr. Calvery had the vision of expanding it numerically or did you all have input into that?

Dr. Laug: I think it's like Topsy, it just growed initially. Then later, when they saw what this was going to be, Bliss was there. After all, Calvery was a biochemist. He had not been in this area at all, but I do agree that he had some thoughts about where this could lead.

Dr. Fitzhugh: He certainly had enough thoughts on it to seek Bliss's information because, when I first came here when Bliss was -- part of the time he was here -- but anyway we consulted with him and got methods by which to start on at least.

Dr. Young: Where was his main base after he got back?

Dr. Fitzhugh: Connecticut. University of Connecticut.

Dr. Vos: No, he didn't even have a job when he first got back. He was unemployed. I have letters from him still from when he was a consultant down in Mexico after he had been here. But he eventually ended up in Connecticut Agriculture Experiment Station as their chief statistician. Bliss is the well known father of bio-statistics in this country, I would believe.

Dr. Young: Well, you see what I am getting at, you are all acknowledging this as a new frontier. And I'm trying to define what's important about it and you're doing well with that and also assign credit. I'm getting the sense from what you say that, as, I guess must be usual in many ventures of this kind, credit is a multiple thing. This was a team. And there was a lot of input that each of you had and that these others had. There might have been a little bit of this in connection with the insecticide residues earlier, but the big experiment was that which was forced upon you by this terrible circumstance.

Dr. Woodard: Well, the insecticide problem was the original basis for having set up a division. Now as Ed said, it was a political football and I remember we worked through '37 or '38 until New Years Eve--right up until midnight on New Years. Because Congress cut off our funds and said there was to be no more work on lead and arsenic.

Dr. Young: What was the gossip about why this happened--why this termination?

Dr. Laug: There was pressure from the growers. Also, in those days, I should say, probably no good feelings between the Food and Drug Administration and the National Institutes of Health.

Dr. Young: The National Institute of Health was set up in 1930.

Dr. Laug: Well, I know. But what was it--Toxicology Division, wasn't it?

Dr. Woodard : Yes, Paul Neil was head of a group, and I don't know just what they called them. They didn't exactly think that this stuff was as toxic as we said it was.

Dr. Laug: That's right, and Congress took the whole thing out of our hands and put it into their lap.

Dr Vos: It started out, didn't it with the seizure of apples and the farmer or the orchardist whose apples were seized because of excessive residues complained to his Congressman and the Congressman then put into the appropriation act of the Food and Drug Administration that none of these funds shall be used for the study of toxicity of lead and arsenic.

Dr. Young: Right, I knew that and you are also saying that there was a sort of intramural tussle based on point of view within the Federal establishment.

Dr. Laug: Very much so. Very much so.

Dr. Woodard: Well, the NIH has always had much political sense, the Food and Drug Administration never had any political sense at all. That was really part of the problem.

Mr. Lofsvold: At about this time were we revising the tolerance?

Dr. Laug: That was the intention, you know.

Dr. Woodard: They had a hearing actually for fluoride. They finally got a tolerance for fluoride which was unconstitutional or something.

Mr. Lofsvold: This was at the time--this was under the new 1938 act.

Dr. Laug: Yes.

Dr. Young: Fred, in our conversation, you indicated that it was your recollection that, though this taboo on the continuation of the lead and arsenic research did come down, that with the war, or at any rate perhaps the defense period before the

war, the Food and Drug resumed research on these things under a military contract.

Mr. Lofsvold: That was the story that I heard either from Ed Laug or Bert Vos.

Dr. Young: Let's get that

Dr. Laug: The prohibition was specific, however, on lead and arsenic, as I recall. But, of course, there are lots of other heavy metals.

Mr. Lofsvold: I thought you said pesticide residues?

Dr. Laug: Well, in those days, that's what it would have been lead and arsenic, of course. But there was a great problem on mercury. It's even more toxic than lead and even more insidious. We got back into the action so to speak, but it was a far cry from the original setting of tolerances for lead.

Dr. Young: Now that was what? The contract with the military was mercury?

Dr. Laug: Yes, that's right.

Mr. Lofsvold: And also didn't we have some effort a little later on DDT?

Dr. Laug: You mean a contract? I think you're right, yes, that's right. We couldn't do it on our own until somewhat later, is that right?

Dr. Vos: Well, as I say, my recollection was that our work on DDT was done on Army funds for fear that if we did it on our own funds that we would be considered in violation of the spirit of our appropriation.

Dr. Fitzhugh: Well the first material we got on DDT was the crude material seized from the Germans. The first material I had to start on, I know -- yes, that was the first material.

Dr. Laug: There's a very interesting little story about that. I guess it can be repeated right now. Dr. Calvery handed me some material--it must have been during the war, maybe 1943. And it was called Gesserol. It was invented actually in Switzerland. And the Germans didn't know that by sprinkling a little of this stuff down the shirt of these people who were infested with lice, that it would kill the lice. They used it against potato bugs first. The Germans at that time were raising nothing but potatoes to keep themselves going. Then it was discovered that it had all these other uses. And he gave me some of that stuff and he said now we want to start

working on this, but unfortunately I can't tell you the formula. And I remember laughing, about two months later the formula or what it actually was, appeared in the Saturday Evening Post. But that is par for some of these.

Dr.Young: Did he tell you where he had gotten it?

Dr. Laug: I don't recall that. They got about 60 lbs, I believe and distributed it among various laboratories. Some of the earlier methods which Geoff worked on were then quite crude. But then they were refined in his hands and by the time we finished with that problem why it was very useful.

Dr. Young: Now could we go back to the ethylene glycol. Diethylene glycol and ethylene glycol are two words for the same thing, is that right?

Dr. Fitzhugh: Oh no.

Dr. Woodard: It's about the same toxicity as ethylene glycol. They are closely related chemical compounds, one is a monomer and the other is a dimer, that's what it amounts to.

Dr. Young: Two different things. Well, now I think that the solvent that this chemist used at the Massingill Plant -- it was diethylene glycol. Now besides the things that have been said so far, is there any other innovative quality about the

research in this project that should be mentioned? Pioneering quality of the research? It was a bigger animal population, it was more...

Dr. Woodard: Well, I would say regarding the concept of the use of multiple species; up until that time usually you did one kind of animal which depended largely on what you happened to have available. So the concept of using multiple species to get these LD-50 figures in different species of animals, I think, was developed about that time. The concept of repeated dosing had started with the lead. I know Garth did a lot of these glycols for two year experiments and he got a lot of wild pathology, stones, and everything else.

Dr. Fitzhugh: We did work on, really, the question of cancer.

Dr. Young: Say that a little more elaborately, will you?

Dr. Fitzhugh: I said when we got those stones and when we were getting cancer from them, we were getting materials that produced so-called cancer.

Dr. Young: Now, as you gave the glycol to two different animal populations--

Dr. Fitzhugh: Particularly rats, you got the stones and then you got the tumors from cancer.

Dr. Young: Right, and this was research that was stimulated by the Elixir Sulfanilamide?

Dr. Fitzhugh: That was the beginning of it, yes--you have the paper on glycols--I don't have mine.

Dr. Young: So this isn't by any means the only paper that eventuated from the research that was triggered?

Dr. Laug: Oh, no. That happened to be the original paper. After that there were lots of them, particularly Dr. Fitzhugh, because he examined the area where it isn't just a single dose that tells you whether the animal is dead or alive, but how is it going to work if you take it for years, which is the problem that faces us at all times.

Dr. Young: And this long dosage with a potentially toxic substance to see it proves to be toxic by small doses over a long period -- this research with the glycol is the beginning of that research. Are there any more comments you want to make about the innovative quality of the long-term studies? I wanted to ask you, generally speaking, what journal these studies were published in if I wanted to go back to that period and try to check them out?

Dr. Fitzhugh: Most of them were in the Journal of Pharamacology and Experimental Theraputics.

Dr. Young: And, will it have glycols in the title?

Dr. Fitzhugh: Yes. The first ones would, and diethyleneglycol.

Dr. Young: And these came out in the late '30s and early '40s?

Dr. Fitzhugh: Yes, early '40s, papers were usually delayed because of writing difficulties.

Dr. Young: I also wanted to ask if the innovative quality of this research, which you all share, was more broadly recognized and taken account of in any way, so that it was noted in any review articles of the field that you can think of or so that it brought to your division or to any of you as individuals any kind of recognition, any awards or prizes that are sort of benchmarks of its importance? (Several: No.) You are in effect saying that perhaps the record hasn't given much credit to the group for this innovation.

Dr. Laugh: I would agree to that, yes.

Dr. Woodard: Because actually the people who've gotten the prizes and the awards are people like Henry Smith, who didn't know the first thing about toxicology before he visited this

division. And the same thing is true of V. K. Rowe and who was his boss? Not Spencer, it was Fassett, who used to be in the Division. In fact he worked directly with a number of us, he set up the Eastman Kodak toxicology group.

Dr. Young: The greatest flattery you got then was imitation.

Dr. Woodard: Well, it was really the people who were trained here or who came here for some kind of help in getting their own organization set-up. If you talk with them, I think most of them will make that point. That what they really learned was what they learned here in the Division, or was the beginning of it. Hazleton is another one. He used to study the toxicity of something or other for industry and he'd call one of us up on the phone and say how about helping me set up this experiment?

Dr. Young: Well, this betokens another thing. That is to say that you were doing this, it was in the public interest, you were finding these things out partly for regulatory purposes, but it was all open knowledge, you published it as soon as you could get it in print. And not only that, you felt that part of your mission was to give counsel and advice to others who wanted to set these things up, particularly in industry. This was done in order to save FDA work later on and to save the public from hazards because they would have done better

background research before they tried to get these things on the market. So this seemed a perfectly natural part of your task, to give advice to these various groups?

Dr. Woodard: Yes, well in addition to the industry groups, I think it's only fair to point out that there were people like Harold Hodge at the University of Rochester who was at one time head of the Atomic Energy Group there. When that support folded, they had to look for other work for his people. So he started doing industrial work and also started teaching toxicology which he had not done before. He used to spend a lot of time here. Arnold Lehman who took the job as Calvery's successor, was another one.

Dr. Young: Where was he, then?

Dr. Woodard: He was in North Carolina.

Dr. Laug: Wasn't Spencer from the Dow Chemical Co. also one that learned a great deal from us?

Dr. Woodard: That's right.

Dr. Fitzhugh: I think it should be known that in the early days, and I think of the early days almost up until 1950 and even afterwards, when the food additive amendment came in, almost all of these people, (particularly industry), if

they had to set up an experiment to prove toxicity I'm thinking primarily of chronic toxicity, those people would come in here. In a conference, 3 or 4 of us would decide on what experiments to perform. Many times, when those experiments were running, they'd come in and show us the preliminary data. They were very anxious for us to guide them all the way through so we were acting as guides all the way along. Not only with industry, but with universities too. At that time, any of them that were doing toxicity work, particularly chronic toxicity work, were under contract to the industry, so they would come in and discuss the preliminaries of what to do, before they brought in the final work. We were guiding them all along all the way through before we got the regulatory data, as a final thing.

Dr. Young: Was part of this consultation consequent to the new drug provision in the 1938 law? Was it concerned with the safety of drugs?

Dr. Vos: Not too much of that on drugs. I mean there was some of that. I would say most of what I remember related to new pesticides that were coming in, the new food additives. Before these Acts were passed requiring their safety to be demonstrated, the more responsible industries would come in and say we have a new thing that we think would be wonderful if we put it in milk or in bread -- what do you think we ought to do. We know that we don't have to do anything unless it's

anything unless it's poisonous or deleterious, but we feel that we ought to. We would then advise them what sort of studies to do, even though we had no authority to set any tolerances.

Dr. Young: Well, the Elixir of Sulfanilamide disaster was what really produced the new drug clause.

Dr. Vos: That was drugs, but that was not...

Dr. Young: I wanted to ask you -- you are answering it in a way, but let me just ask you again. In the early days following the passage of the 1938 law, which I guess went into effect as far as the new drug clause was concerned immediately, did that lead to a group of pharmaceutical researchers coming to your door saying we're about to put out a new drug and we have to prove that it's going to be safe. Will you help us devise the kind of tests that we can later bring back to the agency to show that the drug is safe under the law? What about that new drug clause in the first 5 or 6 years?

Dr. Vos: Well, I would say that in the early days you refer to, that was handled by what was then the Drug Division. And at the beginning there was very very little consultation with the Division of Pharmacology. There was some, but the people that were making those decisions were the medical officers

of what later became the Bureau of Medicine which was then the Medical Branch of the Drug Division. Animal tests were done, but at the beginning there was not too much emphasis put on them in the sense that they were coming in for advice on how to do it. Also, these were pharamaceutical houses who were a little more knowledgeable in these areas than were a food manufacturer or a person who wanted to put some chemical into food.

Dr. Young: Did you say who were a little more knowledgeable?

Dr. Vos: Yes. They knew more. Some certainly came in for advice, but that was not as spectacular as when the pesticides and the food additives developed.

Dr. Young: Well, now the tests required are very elaborate. Did the drug manufacturers in these early days do the kind of toxicity studies with regard to their new drugs that you were doing, testing these various ingredients?

Dr. Laug: No, I don't think so. For one difference in philosophy -- and that is, of course, when it's in food the individual has no choice. If he takes it as a medicine, there is the possibility of measuring the risk against curing the disease. And so the philosophy is a little different.

Dr. Young: I see that, but the risk of chronic toxicity, or even of immediate toxicity is...

Dr. Laug: But it isn't as cogent as it is when you add it to food.

Dr. Young: Yes, I see that.

Dr. Woodard: Well, the explosion in new drug development didn't occur right at that time, anyway. The antibiotic development was the biggest thing that happened. And the antibiotics were being approved with little animal toxicity studies, almost an embarrassingly small amount of toxicity. We didn't have a whole lot to do with that.

Dr. Young: That wasn't a question that the drug bureau raised with you as experts in toxicity when they were looking at these new drug applications or at the antibiotic certification.

Dr. Woodard: They didn't really look at it. I don't think it's fair to say that we didn't do quite a lot, I mean like Carl Beyer from Merck who eventually became vice president of research for Merck Sharp & Dohme, and he used to spend a lot of time in here in consultation. The people at Boston University used to be in. As a matter of fact, the whole area development of the rauwolfia alkaloids, those people spent a

lot of time here, in consultation. The antibiotics, I would say primarily we were not exactly -- well that was considered to be Henry Welsh's area and he didn't really care about having pharmacology monkey with his territory. Others in the antibiotics--I would say that we were brought into it. But then by that time the real explosion in other kinds of drugs developed. The whole field of toxicology then had become much more sophisticated. I don't think there was the need for consultation that there was earliler. The other thing, of course, is that there is a different philosophy in the toxicity of a food additive or a pesticide which you don't know you're getting and you have no medical supervision and a lot of other things, than toxicity of a drug where you presumably are under the care of a physician.

Dr. Young: And you recognized that there may well have to be some there, it's more a matter of balance.

Dr. Woodard: And so in the case of the food additives and pesticides, we were looking for what you might say are more subtle kinds of toxicity than you would in a drug. Because with a drug you are taking a toxic dose to begin with, whereas with a food additive you are taking presumably something that is not a toxic dose. So to find the effect of these very small quantities over a long period of time, you have different kinds of criteria.

Dr. Vos: In the case of the drugs, when a manufacturer is ready to put a new drug on the market, he will be submitting a new drug application, he will have done work in patients so that you have the actual experience in human beings. He will have done animal work prior to that, but you look with greater care at the results in the human beings who have had this drug, and put somewhat less emphasis on the animal. Whereas in a food additive or a pesticide, you ordinarily have no human experience at all. You have to make the whole reliance on the picture in animals.

Dr. Young: You talked about pesticides and moved then into food additives which are a kind of different thing. This was a period of tremendous expansion in food additives as far as industry was concerned. Did you begin to do research on food additives that weren't pesticide residues -- were you in any sense in your division blowing a whistle on food additives that helped lead to the 1950 hearings? Did any of this come from you, or where did the worry about food additives as a part of pesticide residues come that caused Congress in 1950 to have the hearings that were later to lead to the extension of the new drug principle into the area of additives and pesticide residues, colors, etc?

Dr. Woodard: Well, I would say that actually the emphasis on food additives preceded the pesticides, and I would think that perhaps the earliest ones were the ones that Garth got

involved in--the aritificial sweeteners. Where he demonstrated cancer in long term feeding experiments which was far ahead of anybody else ever having really shown this.

Dr. Young: Well, would you speak to that, please. I did an article on the early regulatory history of saccharin and wrote about it.

Dr. Woodard: Well, Garth worked on every sweetener there ever was, including saccharin.

Dr. Fitzhugh: Probably one of the first ones we worked on was selenium as a food additive. We determined there that it caused tumors.

Dr. Young: And this was roughly, if you could find the reference, I'd--what caused you to undertake this research?

Dr. Fitzhugh: Well, we were interested in anything that was in food, certainly. So we were beginning--selenium was probably one of the first ones. In regard to tumors, Bert mentioned the ergot which was one of the first ones. We were very much interested at that time in anything that might cause tumors. The ergot was probably one of the first ones and the peculiarity in that was that the tumors when we were feeding ergot -- the tumors were formed on the top of the ear. And from selenium we found tumors; that, of course, was carcinogenic in any large amount.

Dr. Young: Methodologically, these were the same long-range studies that were triggered by the diethylene glycol experiments?

Dr. Fitzhugh: Well I would say so, yes. Because they were in food. What we were interested in was materials that were in food.

Dr. Laug: You could even add lead and arsenic -- as a food additive, in a way.

Dr. Woodard: And coal tar colors, too.

Dr. Fitzhugh: Well we were interested in coal tar's colors. I distinctly remember the first experiment that I started was with coal tar colors. I thought we were not going to mention colors right now.

Dr. Young: I guess I am trying to get the pattern of what triggered what and when it came even if we don't go into the details of it right now.

Dr. Fitzhugh: We were interested in the long term studies of food additives and actually before we really got into pesticides. We didn't get into pesticides, other than lead and arsenic, until the beginning of the '40s, with the second World War.

Dr. Young: But these food experiments you actually got into--

Dr. Fitzhugh: Immediately after I came in 1939, I began working on these food additives. We fed the sulfites. Remember, the sulfites were studied way back in the early days of the Food and Drug Act after 1906. We studied the long-term effects of sulfites. That was one of the first experiments I got into. It didn't cause tumors, but it did cause dietary effects.

Dr. Young: So you had been almost a decade involved in long term food additive studies before the Congressional hearing.

Dr. Fitzhugh: Yes.

Dr. Young: Were you called to testify on your research at the hearings, eventually, as to what you had found?

Dr. Woodard: I don't believe anybody in that Division--

Dr. Fitzhugh: I can't recall.

Dr. Vos: Was Lehman there in 1950?

Dr. Laug: He came in '47, I think...'46.

Dr. Vos: Would he have been testifing?

Dr. Woodard: If anybody did, it would have been Ben White. He was probably the spokesman for the Food Division and he was quite impressed with the work that this division was doing at every opportunity he was one of the better spokesmen actually for the Division of Pharmacology.

Dr. Laug: Don't you think it was quite possible that the Commissioner may have...we may have furnished him with the background material. I think that is the most likely, but I don't remember any of our people...

Dr. Woodard: No I am sure .....

Dr. Young: What hearing was that?

Dr. Laug: Delany hearings?

Dr. Fitzhugh: Lehman testified in that hearing.

D. Laug: Yes.

Dr. Young: How aware was the Commissioner of what you were doing and the importance of it and how adequately did you feel that, within the budget that FDA had, you were furnished with resources for doing what you needed to do.

Dr. Laug: Well, I can speak for myself at least in the early days the Commissioner had his ear right there. I remember the first day I reported to the Food and Drug in '35 that E. E. Nelson took me down to meet the Commissioner. I wouldn't think it would be that way today. So there was really a very close, well we were all in the same building and we very frequently visited.....

Dr. Young: The different Commissioners asked you about what you were doing?

Dr. Laug: Oh, I think so. If he didn't directly he got it through our Division Chief, but it was a very close business.

Dr. Fitzhugh: I always remember Crawford because he was a -- reminded me as a young man of a real judge. I guess Crawford came after the Second Commissioner, wasn't that right?

Dr. Young: Crawford succeeded Dunbar.

Dr. Fitzhugh: Dunbar was the same way. I think Dunbar was probably closer to us than Crawford, but Crawford would call you into the meetings when you had industry there. He'd always sit in kind of like a corner place, and he would let the industry talk and then he would ask us what we thought about it and whether this material was safe or not or

toxic.....and he would turn to the industry and tell them, "The toxicologist has spoken...that's all."

Dr. Young: He backed you up? You had the feeling that he was backing .....

Dr. Fitzhugh: He was completely behind you. Always 100%.

Dr. Fitzhugh: I think all of the other Commissioners, more or less, did the same thing. As far as safety, the Division was the whole thing. They were very close to the Office of the Commissioner.

Dr. Young: That's a vivid anecdote. Can you think of any other anecdotes that reveal the leadership, the characterists of the Commissioners under whom you served.

Dr. Vos: Well, as a reflection of the growth of the Food and Drug Administration I can give an opposite example from Ed Laug. He was brought down to be introduced when he started. The first time I saw Campbell, the Commissioner, was when he announced his retirement. Calvery told me to come down to the Commissioner's office that something exciting was going to happen. I went down, I was standing in the back row when Campbell announced his retirement.

Dr. Laug: That was only a brief 10 years, or something wasn't it? So it shows how things have snowballed.

Dr. Woodard: I think it is true that when there were really quite important decisions, there were members of this division always there to participate in the conference in the Commissioner's office.

Dr. Laug: No layers between, so to speak.

Dr. Fitzhugh: At that time there were no layers between the Division and the office of the Commissioner.

Dr. Woodard: I remember one day--matter of fact I was drawing those graphs which are in that paper, what is it..."Safe-guarding"...is that the one.

Dr. Fitzhugh: Yes.

Dr. Woodard: I drew those graphs. I was drawing one of these when Dunbar came by and -- I was drawing the original for that (pointing to graph). Dunbar came by and he looked at that, looked at the lettering and turned to Calvery and he said "Does this young man work here?", and he said "yes". Then he said "well you had better keep that young man around, he draws good graphs".

Dr. Young: These are graphs that are in Herbert Calvery's article that is called Safeguarding Foods and Drugs in War Time from the American Scientist in the spring issue of 1944.

Dr. Woodard: Then Dunbar went on to relate that the thing that he was most famous for was a method that he developed, I believe, in analytical chemistry, known as the Dunbar method. I remember he told me that. I don't know what the method was.

Mr. Janssen: Would you like a Calvery ancedote?

Dr. Young: Surely.

Mr. Janssen: This is a story that was used in some speeches. One day there was a frantic phone call in Washington from Denver, and, at the other end of the wire was a woman whose baby had just swallowed a hair preparation, the whole bottle of this hair preparation. There was a dash to files to see if we could find out anything about what was in that stuff. Well, they found, first of all, that the original formula of this product contained a very toxic ingredient, but that Dr. Calvery had had a conference with the company and persuaded them to take out this ingredient and substitute something else that was satisfactory, which they did. So they were able to assure the mother that the child would not be harmed. Maybe temporarily a little queasy, but not really harmed. And this happened six years after Dr. Calvery had passed away. In

other words, the conscientiousness of this man protected this child six years after his death.

Mr. Porter: I think we should let the record show that the last speaker was Wallace Janssen. We didn't get you introduced at the beginning of the meeting.

Dr. Young: I kept worrying it was an old bottle.

Mr. Janssen: Calvery had a great, I think, reputation of being a very conscientious individual. That was my impression about him.

Dr. Young: Back to the original question, growth of staff and especially staff contributions. Have we covered what is meant by the word protocol, when we were talking about the quantified approaches toward toxicity that you used? Are there other things here in connection with innovation by the Division in the realm of planning, devising and experiment?

Dr. Laug: I might give you one that annoyed a lot of people while I was there. It was called my flyo-assay. Using the same methods that we used for the glycol, it was in the days when Geoff was still working on the chemical method. It wasn't quite still up to snuff. I discovered that you could use a bio-assay method for analyzing for DDT in the tissues of animals that had been poisoned. And you did it by making an

extract of the fat, usually it was in the fat, putting it in a flask and allowing or counting into the flask a hundred house flies. They would walk around on the substance and transfer it to themselves by that process. Then, after a specific time, you counted the number of flies that were living and died. Then you drew a curve and you determined the point at which half of them had died. And that could be related to the quantity of the material that was in the tissues. The humorous part of it was that these were raised in the hoods of the laboratories. I'm no entomologist, but of course there was quite a number of them that escaped, and it was always very amusing because they went all over. That was known as the flyo-assay. It was superceded by chemical methods that were very much more refined. But, at one time, we were able to determine quantities as small as a few micrograms, since the insects were so sensitive to the chemical.

Well, that's an example of how you can still use this method for evaluating something and quantifying. This application of the LD 50 dose is a direct "dividend" of the earlier work on the glycols, relating toxicity to a specified dose.

Mr. Lofsvold: In addition to the things that have been described, Harvey, the Division, I believe, also made an effort to put before the industry and any other interested parties in an organized way, how to test substances for toxicity. Would one of you speak to that? I'm thinking of the publication in

the Journal of the Association of Food and Drug Officials.

Dr. Woodward: Well, I think that this was probably Dr. Lehman's main contribution, well maybe not main, but a major contribution by Dr. Lehman. He recognized that there were all these various industrial groups coming in and asking for consultation and getting advice but, depending on who happened to be in the office or who happened to be at the conference, the advice wasn't always very uniform. And he realized that there ought to be a book or a source that would have all these things spelled out. So he was instrumental in getting all of us to write what was known as the "Bible" in the industry. This was this collection of methods to which you speak.

Dr. Young: Now, it was called the "Bible", what was its official name?

Dr. Woodward: Well, I think in the journal of the Association of Food and Drug Officials of the U.S. Was that the first one or the second one?

Dr. Vos: Well, if I can jump in here, I would say that the very beginning of this was an article by Woodard and Calvery called "Acute and Chronic Toxicity". Here's a copy of it. And that was the first sketching of what were appropriate studies, appropriate protocols.

Dr. Young: Published in Industrial Medicine for January, 1943. That was the first appearance?

Dr. Vos: I would say so, yes. That is addressed simply to methodology. Prior to that, results using these methods had been published, but nothing addressing the reasons for or the actual . . . That was followed then by a series of articles in which the members of the Division contributed their expertise. It went through, I guess, three editions, I think, three revisions. Here is one called "Procedures for the Appraisal of Toxicity of Chemicals in Foods, Drugs, and Cosmetics", which was published in the Food, Drug and Cosmetic Law Journal, Oct. 1955.

Dr. Young: That was the first pulling together.

Dr. Woodard: This was the first paper I ever gave by the way. I presented it at a meeting in Atlantic City.

Dr. Young: At the American Public Health Association in 1941. And it isn't purely technical, because it does include a rationale, set within the broad context of society, for the importance of paying heed to these things.

Dr. Vos: Apparently there was an article that followed that one called, "Procedures for Appraisal of Toxicity of Chemicals

in Food" that was by Lehman, Fitzhugh and others, which appeared in the September, 1949 issue of the Food, Drug, Cosmetic Law Quarterly.

Dr. Woodard: There's one in the Journal of Nutrition, too.

Dr. Young: That you shared in writing?

Dr. Woodard: I think. Do you have one there that was in the Journal of Nutrition?

Mr. Lofsvold: I don't have listed that particular one. I remember very well the one though that was in the Association of Food and Drug Officials because the rights for the reprints were assigned to the Association. They sold copies of it, and it supported that Association for several years, because it was a very popular publication.

Dr. Woodard: I think they still sell that.

Dr. Vos: That was a very interesting phenomenon. The people would come in, and Dr. Lehman would tell them you'd better subscribe to this journal because all the stuff is published there. It seems a little odd that these scientists would be publishing in this obscure Journal of the Food and Drug Officials which had almost no circulation at all, but very quickly the circulatioin zoomed. Some years later, Dr. Lehman

received a blank check for the purchase of a 5 horsepower garden tractor. He displayed it proudly on his wall for a while. This was from the Association of Food and Drug Officials in thanks for his great services in promoting their journal.

Dr. Young: What is the title of the largest volume you have there?

Dr. Vos: Well, if I can go back just a bit, the second one, the first one which appeared in the Food, Drug, Cosmetic Law Journal that was facetiously referred to as "the rogue's gallery article", because there was a picture of each author next to the article. And these pictures, I guess, had to be obtained--some of them were on vacation--they broke into somebody's house, I think to get a copy of a picture. As a result of that, many of the pictures looked very youthful. When the thing appeared, no one could recognize some of these people because they didn't look that way anymore. The final form was the Association of Food and Drug Officials of the United States Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics. That doesn't seem to have much of a date on it. Well, published in 1959, that's the last one. That's the one that was referred to, facetiously, as the "Bible".

Dr. Young: Moving from Dr. Woodard's address at the Public Health Association 2 months before Pearl Harbor to this final volume 18 years later, you have a span of documents. What was the audience and what was the purpose of this whole venture?

Dr. Vos: Well I would say the purpose was two-fold. One was public relations. I mean here people could get out a publication, they didn't have to do any more work, it was simply writing up the methods. But the main object of it, people would come in from industry and say we want to put out a new something in bread, a bread softener--what do we need to do. Well, it got very tiresome telling them -- I mean it was all new to them. But for us to go through all that routine of you need so many animals and half of these people wouldn't even have their--they hadn't decided yet where they were going to have the work done, and these were chemists. You were telling them about animal experiments. They would interrupt you every 30 seconds and say, what kind of an animal was that, so that this became -- you would tell them to go buy this book and this tells all about it.

Dr. Young: So that it was a reducing of methods to print, in order that those who really needed to do this in connection with testing out what was safe, would have, as you say, the "Bible" right at hand and wouldn't have to go to the prophets all the time and ask questions.

Dr. Fitzhugh: I think there's another thing. We think of the development of the hundred-fold margin of safety, which was very much controversial as far as the industry was concerned. Over the years, we developed that. Now that's given in this

same journal. That was developed in "Hundred-fold Margin of Safety," which was by Dr. Lehman and myself. That's in the Quarterly Bulletin of the Association of Food and Drug Officials. A lot of these occurred in this journal and kept the Journal going fine. It kept the industry in touch with what we were doing--this development, along with this whole thing.

Dr. Young: Now, it seemed to me as if you were indicating another benchmark of the art, the hundred-fold. Would you explain that to me?

Dr. Fitzhugh: We were considering how you could evaluate, you might say, in the use of all of these methods which we were discussing. Translating how much material should be allowed in the food and how much would be safe. So we were asking for hundred-fold margin of safety. Between what it showed no effect in the animal and what was going to be used in the food.

Dr. Young: How did you pick the number 100?

Dr. Fitzhugh: Well, we went back and compared what had been safe in many materials, anything that we knew of that had been used in food or had been used sometimes in drugs, and what caused toxicity in the human and what was safe in the animal.

Dr. Young: Did you have a meeting and talk about whether it ought to be 80 or 100, or 500.

Dr. Fitzhugh: Well I guess this just developed over the years. We allowed so much for the difference in the food intake of the animal, we had a mathematical idea there. It's kind of dull in my mind, right at the moment.

Dr. Vos: I think it started out that 100 seemed so extravagant that you couldn't be wrong by worse than that. You judged by an animal, 1/100th of that certainly ought to be safe for humans just by common sense.

Dr. Fitzhugh: That was certainly part of it.

Dr. Young: And you talked it over among yourselves before you got into print?

Dr. Fitzhugh: Oh yes, I suppose we did that many times.

Dr. Young: How can you exemplify that fact that it was so controversial with industry?

Dr. Fitzhugh: The very thing that Bert has said. Because we are requiring such a large factor of safety in the food, that many times seemed to be unreasonable.

Dr. Young: Well, did industry show this by coming in and pounding on your desks, or did they write articles in the trade journals saying these crazy guys over at FDA, or what are examples of industry reaction of opposition? Do you remember conversations at meetings?

Dr. Fitzhugh: They raised questions about it, of course, at meetings of all kinds.

Dr. Woodard: I think we maybe got the figure first, then justified it secondly, didn't we?

Dr. Fitzhugh: Well that probably was part of it.

Dr. Woodard: I think that Bob Smith -- I still have a list of 300 chemicals that he looked at before he got LD 50s in animals and some sort of figure in man. By and large he came up with an average of about 10 fold difference. The average difference between man and animals was something on the order of 10 times from the figures. In order to have a safety factor, you multiply by a nice round number of 10, that gives you 100. So that's really about how it worked out.

Dr. Fitzhugh: That's part of it, certainly.

Dr. Woodard: But I think it's currently gospel in toxicology. That that 100 figure is just like reading straight out of the scriptures.

Dr. Fitzhugh: That's part of the prestige, I think. You mentioned that before. How did industry recompense us for our work and how we were justified in it. They rewarded you, in a sense of the word. In general, we were very -- I think, in my own instance -- I think we were certainly recognized in what we had done, and they recognized that we were scientists, and they followed us pretty good. And rewarded us in a way. Certainly this side of toxicology gave me the award of the year. We haven't mentioned that in the World Health Organization, in the food additives and pesticides section, I was a representative for more than 10 years on each. I was the United States representative and I felt that this was an honor and a reward, in a way. The recognition is what I'm trying to get at, of our work as a toxicologist.

Dr. Young: It certainly was. And this is the kind of thing that I'd like to be concrete about, to be able to say, in trying to make the point. There isn't any doubt in my mind that I've heard things today that, when I write the chapter on Elixer Sulfanilamide Reconsidered, I've got just an utterly new viewpoint compared to the much simpler one I had before.

Dr. Laug: I have no specifics in this area that Garth has just mentioned. But my general feeling, my personal one and all of us who worked, I never got the impression that any of us felt that somebody had picked up the ball and run with it

and that we were left standing, we didn't have that feeling. I think you would all agree with this. Is that right, Geoff?

Dr. Woodard: It's only much more recently that...

Dr. Laug: Yes. In other words, the industry people didn't go out after they copied our notes and go out and say well, this is all our stuff and forget the others. No, we never had that feeling.

Dr. Young: Were there any examples in which you felt vastly aggrieved by something that happened in your interchange with industry? Maybe not.

Dr. Vos: Give us a little time, we'll think of something.

Dr. Woodard: I think it's the other way around. I think that this was a group that was very highly respected. There is another area which we have not talked on -- we've been talking about toxicology, but I think there is also an area in bio-assay that is equally important too. And, as Bert told you about the original thing with the ergot, Eli Lilly is the company that was involved in this particular thing. We brought suit against them and they went to court, and unfortunately I guess we lost the court case. This was done prior to the formation of the Division. This all happened prior to that. As soon as the new division was formed and people like

Lloyd Miller and Bert Vos and Herbie Braun begin getting some of their publications and presentations at meetings, and Jack Curtis, in the estrogenic area, these are all people who are highly respected and they were publishing very competent work and the industry began paying some attention to it. My most recent remembrance was when we were doing a posterior pituitary bio-assay and, amongst other things, we fouund a bad sample of Park-Davis, in '55 or whatever it was that this happened. Park-Davis was a big pharmaceutical company. At first, they were going to -- they said well you people don't know how to do that, and they quoted the back history. But we stayed with it, and they eventually settled out of court, and they fired all the people in their bio-assay group and reorganized the entire operation in that company, as a result of the seizure action we had taken on one of their products. We stuck with our guns. So I would say that, if anything, it was the other way around. We made our weight felt very strongly in the industry, and I think we had a lot of respect from the industry. We also had a lot of peole who had been here who had gone out into industry and they knew that we knew what we were talking about.

Dr. Young: There has been a lot of talk about the revolving door situation through history.

Dr. Woodard: Well, I don't think you would call that a revolving door. The people we had here, they spent anywhere

from three to 20 or 30 years with the government and, for one reason or another, needed to advance further. If there were no opportunities here, you don't have any other choice. So I don't think it's a revolving door. I would object to that.

Dr. Young: It was a wrong phrase and I withdraw it. Beginning with Bigelow, who was Wiley's aide in Food and who went to the American Canners Association. This sort of thing has happened. People trained, who then went out into industry, and I was really going to ask the question about your impressions of this. Do I take it that your impression was, from the implication of your statement, that this really gave a higher tone to industry science. The fact that individuals trained in the Food and Drug went out to different places in industry with the kind of science and the point of view that you had had in the group?

Dr. Woodard: Yes, I would say very definitely and I can give you some concrete examples. Ted Clump, who was in the Bureau of Medicine. We worked together on that Elixir Sulfanilamide thing when he was here. Ted Clump ultimately became president of Winthrop Sterling and also, I guess, was president of the Pharmaceutical Manufacturers Association for a number of years. He was a very strong and outspoken spokesman for the industry. He felt very strongly about the impact of the Food and Drug on the industry. As a matter of fact, when he went to Sterling Winthrop, he organized the Medical Research Group

that they still have there today. And they hired Lloyd Miller from here. They started one of the first big research organizations in the pharmaceutical industry.

Dr. Young: Yes, Merck had had one that started about '34 or '35, I guess the modern campus sophisticated approach. But there was this outflow.

Mr. Janssen: There was Dr. Frederick J. Cullen too. He went to the Proprietary Association. Year after year he ding-donged at them about beefing up their research and tidying up their claims and all that sort of thing. He probably did more good after he got out into the Proprietary Association than he was able to accomplish while he was in the Food and Drug.

Dr. Young: Were you saying, Bob, that we're winding down?

Mr. Porter: We're near the end of the tape and it's lunch time, I was just wondering if we could have a break here?

Mr. Janssen: When was the Division of Pharmacology established?

Dr. Laug: 1935.

(Lunch break.)

Dr. Young: Dr. Laug, would you tell us just a little more about the sudden curtailment in 1937 of the pesticide residue research, about what you could do with what was already done, and the way it was used in the testimony in the California Apple Chop Case.

Dr. Laug: The time of that can be judged by the dates of some of the publications that were made after that time. The stoppage of the laboratory work occurred on the 30th of June 1937. All of our long-term experiments on lead, and our two year experiments on rats, they were all terminated.

Dr. Young: They were only half way through?

Dr. Laug: Essentially, yes. Of course there had been other quicker work like acute toxicity and so on, done to completion, but the long term experiments were only partly completed. But never-the-less we did salvage enough of the data to be able to publish it later. There were - some I'll just mention. We developed a cage in which the animals were housed - it was a glass cage because the animals were ordinarily kept in galvanized cages and the zinc contains lead you see, so running balance experiments we had to use glass cages. That was one small publication just about the time we stopped in 1937.

Dr. Young: In what journal?

Dr. Laug: That was in the Journal of Labaoratory and Clinical Medicine. I don't regard that as a particularly important thing. Then there was the methodology that we worked on. That was in '38. Then another one which is more pertinent to us is the effect of lead on rats -- containing lead arsenic and lead acetate. That was in 1938 also.

Dr. Young: Was that in the same journal?

Dr. Laug: No, that was in Pharmacology and Experimental Therapeutics. Then, in 1938 again Growth and Reproduction of Rats Containing Lead", those were long term experiments and we salvaged what we could out of them. Then there was one again in '38, that was on feeding to dogs, various concentrations. Again, '38, calcium and phosphorus, the influence of these elements on the storage of lead. That's about where it ended, but after that, we had gotten enough expertise that we could be called upon to testify in favor of the Apple Chop case which occurred about 1944, during the war, in Fresno, California. That's the first time that I really got to know Ajax Carlson a little bit more -- and I have to say he was quite a character. A real Swede from way back and a fine gentleman, although he he had a rough exterior. He didn't mince any words if he didn't like something. Well, I heard him on the witness stand and he always made a good witness. He didn't take much guff from any of the smart lawyers within

the limits of courtroom procedure. I respected him greatly. Of course if somebody else like Calvery were here, he'd have a whole book of anecdotes about Ajax. But my knowledge about him was that he was a fine scientist, rough in his exterior. He was highly respected. We saw him quite often. He used to come in to see us. And I believe at one time he was on so many Food and Drug cases during the time that I was around and maybe before that industry seemed to think that he was a special hireling of the Food and Drug Administration. That's about all I can tell you.

Dr. Young: In that particular case when he was on the witness stand, do you remember any special episode?

Dr. Laug: No, I can't remember any particular episode. The industry drew upon local talent some of whose expertise I think was rather dubious, and Ajax Carlson more or less intimidated them. Of course, he had a national reputation in the subject so that helped our side greatly. But even all of that didn't make it--we lost the case.

Dr. Young: Thank you.

Dr. Woodard: Yes, the lawyers really loved him because he never equivocated. That was his main... And then, of course, he never really spoke English all that well. There is one story about him that I've only heard, but you must get the

exact details of it. There was something about his graduate students. He liked his schnapps. They had these big graduate student parties with the old man and so they thought one time they were going to get him with too much to drink. So what they did was to substitute for seltzer water--they put gin or vodka in the seltzer water. So they gave him a big drink and he put a little bit of seltzer water in it, drank some of it and it was a little too strong, so he keeps going back and putting some more and finally after a couple of drinks, he was getting to feel it a little bit. And this is the punch line, "Yumping Yiminy, that is sure some strong Yuniper Yuice." I'm not good at retelling these, but I know that is probably the most comical story that I know his own graduate students told about him. I don't know where you would go to find one of these. Brewer, I guess is still around. His big thing was animal laboratory medicine. And he actually established what is now known as the animal care panel or what do they call it? The American Association of Animal Laboratory Science. He established that as an outgrowth of his being in Carlson's laboratory. You ought to get him pretty soon, because he's getting along in years.

Dr. Young: I have never even tried to get in touch with his family. I had a paper to give in Sweden once, and I introduced it with some commendation of Carlson, because of what he had done. And it was very favorably received.

Dr. Vos: There was an article in one of the University of Chicago alumni journals or something on Carlson. He started out -- he was a minister. Whatever the Swedish church is -- Lutheran. He proposed to demonstrate proof of God by dividing sick people into groups. One group he would pray for and one he wouldn't. I mean he was sincere about this. He was either a minister or at a seminary or something. And this struck them as being so sacreligious that you would put God to a test, that he was thrown out of the seminary. From there he went on and ended up in Chicago. I don't know what he...eventually getting into the University.

Dr. Young: That clue is worth following up to the Alumni Magazine.

Dr. Vos: I wouldn't be able to give you what year it is. Another anecdote about him which is probably apocryphal is his lecturing to a class of freshman medical students. He's talking about diabetes -- that you don't need any fancy tests to test urine to see if the patient is diabetic. You just put your finger in and lick you finger. He passes the urine around for them all to do. So they look at each other and everybody does it. He says well now what you really should learn from this is observation. If you had watched me closely you would have seen that I put my index finger in the urine and licked my middle finger.

Mr. Porter: I had Dr. Gustavson as a teacher in chemistry who came from Chicago and I heard him tell that story.

Dr. Vos: I guarantee it never happened. It just fits him so well...

Dr. Young: Well, this is relating a man to a specific circumstance that dealt with the pesticides. Is there more about that category that we ought to say? Some of that was involved in our morning discussion.

Dr. Laug: I would like to say that I think Dr. Fitzhugh has some publications on lead and arsenic. See I have only the publications that related to my particular work, but they did work on lead long-term experiments, didn't you Geoff? I think maybe the publication dates of that will show you that it occurred after that was stopped. Isn't that right, Garth?

Dr. Fitzhugh: I didn't work on lead.

Dr. Laug: Well, I'm not sure, but I thought maybe you had.

Dr. Fitzhugh: No, I had no papers on lead at all. I had mercury. I think I started out with mercury, we studied anything -- metal studies.

Dr. Woodard: You know the Food and Drug Administration is doing all that work over now on lead.

Dr. Laug: Oh yes, of course. That's one of the things that turns me off.

Dr. Fitzhugh: FDA isn't doing anything as far as I can tell.

Dr. Woodard: They are putting it out on contract now. I bid on it.

Dr. Laug: That's unbelievable.

Dr. Woodard: I called up the contract office. I said, "There's no point in doing this experiment." I said that they should look back at what you had done. Furthermore the rat was the wrong animal anyway. They said, "Well", it was a woman who was arranging this and she had worked for some professor some where and he said different, the rat was the right animal to use.

Dr. Laug: The whole original study is now 80 years old. The British had a commission on lead in 1900 -- the Imperial Commission on Lead. People were drinking cider and stuff out of pewter mugs and there was a considerable amount of toxicity, particularly when the product was acid, because it tended to dissolve lead out of the alloy.

Dr. Young: That's what really rang the bell of warning in connection with lead as a pesticide.

Dr. Laug: And now they're investigating kids that lick the drops off a porch railing. That's been known more than 50 years now. That's one of the first things that we were asked to do.

Dr. Young: The dangers of arsenic were known even earlier.

Dr. Laug: Well, yes, the arsenic eaters and so on, right.

Dr. Fitzhugh: You have to have something for your graduate students to do so you put them to working over some of the things.

Dr. Laug: It's a painful waste really, it's not that I have any special reason to be offended just because I worked on lead. but you know there is a long history in the work and just to shove it all under the carpet and forget it is really disgraceful.

Dr. Woodard: Well, part of the problem is the rules they lay down. They don't look in literature now more than 20 years back. And you know all that was published more than 20 years ago!

Dr. Young: Well, how about turning to mercury? What was important, what was innovative about the research that was done on mercury? Dr. Fitzhugh, were you here?

Dr. Fitzhugh: Well, Ed and I both did that. I remember now one we were doing involved both inorganic and organic materials, if I remember correctly.

Dr. Laug: We were associated in a mercury paper in which you furnished all the data for the management of the animals and the pathology and all of that. And we then analyzed the tissues that were involved. (Hands copy of publication to Dr. Young.)

Dr. Young: This was published in the Archives of Industrial Hygiene and Occupational Medicine, Vol. 2, 1950. What got you started on this research? Was it speculative concern about it, or was it some actual incident of poisoning?

Dr. Laug: No, it's actually an outgrowth of our war work. That got us into the mercury first of all because it was proposed as a type of venereal prophylactic and there was the problem of whether or not it penetrated the skin and what kind of compounding with excipients and so on would either enhance or retard penetration of mercury. We did a lot of work on skin. And then, of course, the determination on just how

toxic it is and what happens over a long period of time. There's an interesting story about that with mercury. I think I heard Geoff talking about it at lunch time. There are two kinds of lead compounds--the compounds like lead acetate, etc. Then there are certain organic lead compounds which are a hundred times more toxic because of association usually with benzene. The story is the one in Japan, it's an interesting story. I think I heard you talk about that? Anyway, it involved mercury. A company was manufacturing some product where I believe this was a waste product or something and they dumped it into this bay. The name of the bay was Minemata and they called it Minemata disease. The way they discovered it was, there used to be a lot of cats that would eat the pieces of fish that were dumped on the wharf. And these cats died and also the birds died who ate the fish. And the people who lived around there who ate the fish died. It's a cerebral deterioration. And that was known as Minemata disease. It was because they dumped the mercury, accumulated in the sludge, in the bay. Commercial fishing in the bay brought on the investigation. It wasn't just mercury, but it's association with an organic moiety, methyl.

Dr. Young: And that was after this, though, after 1950?

Dr. Laug: Yes.

Dr. Woodard: That whole story on Minemata disease is, as you probably know, an extremely interesting one because they guy who first recorded that--they put him in jail. It was really bad. It was like the Mafia were after him.

Dr. Young: I just vaguely read about it. That's why, with that background, when mercury was later found in swordfish and so on, it proved to be of such a major interest. Was this when you were in the Agency still? When the mercury was found in the swordfish.

Dr. Laug: We had no connection with it, I don't think. That came later.

Dr.Lofsvold: That, I think, came in the late '60s.

Dr. Woodard: I think of one interesting thing about mercury. We were talking about statistics a while ago, they had a cute device one time. Whenever a question came in from the industry or from a consumer, it would be passed around to all of the scientists in the division and we would all put little comments on it and it would go back to either the head of the division or whoever his assistant was. He would put this together in a written response to the person who asked the question. Somebody found that one of these organic mercury compounds was a fair spermaticidal agent. And so they wanted to propose it for use as a spermaticide in birth control.

They passed this proposal around and different people commented on the amount and the dose and whether we may assume it was all absorbed. When they got all through, a couple of us tabulated the results. We each used different frequencies of use of the material as a basis for our comments. It turned out that that frequently was inversely proportional to the age of the person who responded. I think some of the older people said, well, it wasn't a problem at all if they only used it once a week. For the younger ones the dose went up.

Dr. Laug: That was funny then, is it still funny to you? Well, I can say just from direct personal contact, it wasn't in that connection, but I used to make myself up a hair preparation because I suffer from dandruff. And it contained phenylmercuric acetate, just a small amount. But, when I learned what I had in the laboratory, I gave that one up soon. I used to make this stuff up suspended in alcohol. And, incidentally, we even published a paper on the subject. Where we stuffed the vaginas of rats and analyzed the absorption of the mercury by analyzing the rat's kidneys.

Dr. Young: That is to say that this thing that circulated around produced a research project. I wouldn't mind having the reference for that.

Dr. Laug: It's here, "The Absorption of Phenylmercuric

Acetate From The Vaginal Tract Of The Rat." And that was published in the Journal of Pharmacology and Experimental Therapeutics in 1949.

Dr. Young: Thank you.

Dr. Woodard: I think, in all seriousness, again there is an impact here. We knew that DDT was accumulated in the fat, but this was possible the first time we had really appreciated that metals were accumulated in certain organs. And so Ed first did this with the mercury and, at least in those days I can remember pointing out that he called it a biological magnifier. Because it magnified the amount of mercury that was absorbed high enough so, with the analytical methods which were available at that time, we could measure it. Today, you don't have that problem. There are sensitive instruments you could use, but things weren't all that easy analytically 30 years ago.

Dr. Young Well, at that point, didn't science recognize that lead accumulated in the system?

Dr. Laug: Oh, yes. The other shock tissue happened to be the bone.

Dr. Young: But the point is that nobody did realize that mercury accumulated in the system.

Dr. Laug: Except for one isolated publication that I came upon, I forgot, but it was by a German or somebody who suspected that mercury accumulates in the kidneys. And what he did was, he analyzed, I don't know how many consecutive cases of people who were presumably in good health, who were suddenly killed. He analyzed their kidneys. You know what he found. There was a direct correlation with the storage of mercury in the kidney depending on how many silver fillings you have in your mouth. So we're all walking around right now with a measure of exposure right inside of us. Apparently, from what I've been able to gather, it is not medically significant, but then the question arises what about when you're losing some of your kidney tubules above the age of 70, let's say. In that case it could be a problem. They're still using silver amalgrams. After I found that out, I wouldn't even let the dentist get close to me. But I still have some amalgams. No, I went on the gold standard!

Dr. Young: Is that adequate about mercury?

Dr. Laug: Except I'd like to add one more thing. Remember when we started, that we were supposed to determine for the government what was to most efficacious way of applying the mercury. Well then it was necessary to examine a whole bunch of pharmaceuticals which were used as carriers for the mercury to be rubbed in. And it turned out that there were very sig-

nificant differences depending on what you suspend the mercury in.

Dr. Young: In absorbabililty?

Dr. Laug: Yes. Also it makes a very big difference what compound of mercury is used. And so in all the experiments we had been using the kidney as a biological magnifier, applying it to the animal in a test and then analyzing that. And then we were able to determine quite a lot of different things that either enhanced or prevented the penetration of mercury. Then we worked back to the story of the Minemata disease which is caused by a phenyl mercurial, in other words the mercury is combined with the benzene nucleus and then it is terribly toxic. It is so toxic that, for example, if we took a drop of a phenylmercurial and placed it on the shaved belly of a rat, he's had it within a few hours. And it is also the basis of the experiments that were done later when they first came on to tetraethyl lead. You know that the industry had tremendous trouble with these industrial workers who were involved in the manufacture of lead tetraethyl as an anti-knock compound. It turns out that tetra-ethyl lead sizzles through the skin just like mercury and kills the animal like that. These poor fellows not only got it on their skin, but they inhaled it. They found that out very belatedly.

Dr. Young: Did you ever get any feedback from the military to know what kind of advice they gave the soldiers who used mercury ointments?

Dr. Laug: No, no we didn't.

Dr. Woodard: Well, we did a little of that but...

Dr. Laug: There may have been, I don't recall. We simply ground this stuff out as we did it, and then turned it over to them. They made their decisions. Some recommendations were made! If you used certain combinations they were more effective than others. Of course, that's what they wanted to know.

Dr. Young: What puzzled me a little bit is that I had really never heard of this form of contraception.

Dr. Woodard: It's prophylaxis.

Dr. Vos: To prevent disease, you rub the ointment on your penis after intercourse, as opposed to killing the bugs after they get into the body.

Mr. Lofsvold: Was it a calomel ointment?

Dr. Vos: Yes, that was only one formula.

Dr. Young: And so that had been the kind of age old method. When World War II came, the military wanted to check it for safety.

Dr. Vos: To see if it could be improved. And they were going to add other sulfa drugs in with it to prevent gonorrhea.

Dr. Young: I see, I confess my lack of knowledge.

Dr. Woodard: We had a conference with the military group while we were in the middle of this project and I'll never forget that conference. It was held down here in the National Research Council on Constitution Avenue in a huge room. The people who were working on it were sitting around the table about three times as long as this. Sitting around the periphery they had a bunch of people from the Army and the Navy and the Air Force and there were some academic people. There was a big study going on because they were losing more people from venereal disease then they were losing from being shot at. And so, we were talking about all this scientific stuff and there were two people who were from a university. They said they didn't really understand this, "Why don't you just simply make it make it against the rules for these men to go out and get with these women. You wouldn't have any trouble that way." And a couple of the people spoke up and said something along the same lines. There was an old Colonel sitting back there, he's got ribbons from here to here, you

know. He finally got up and he said, "Gentlemen, let me tell you something, we're talking about people out there fighting in the field and shooting at each other. There is something I want you to know, if they can't fuck, they won't fight."

Dr. Young: Well, can I tell a story too? This is from World War I. Our troops got to France and there were no controls over our troops. Whereas the French had official prostitutes with the Army. And our troops were infecting all the villages that they went to. And so the French came to the Americans and said that instead of letting our troops just go anywhere, they wanted to furnish inspected prostitutes for our army. And this word came back to the United States, and the top people in health talked it over and wondered if they ought to make this recommendation to President Wilson. You remember President Wilson's religious and moral background. Somebody said, "We don't dare, if you make that recommendation to Wilson, he'll call off the war." So this kind of thing has been a problem in more wars than one.

Mr. Lofsvold: In this work that you did on mercury, was that then the basis for our actions against ammoniated mercury bleach creams and similar cosmetics?

Dr. Laug: Some of it was, yes. Because we peripherally analyzed some things that either would enhance or retard mercury penetration, aside from the mercury ointment that was used for prophylaxis.

Dr. Woodard: When I closed up the Lab, we had an AEC license for handling radioisotopes. It took an act of Congress and three visits from AEC people, I wrote all kinds of affidavits and we had to have somebody come out there and do swab tests on everything to be sure that I wasn't leaving any radioactivity there at all. I said, "I'm not getting any income, so this is costing me money. I don't understand why I have to go through all of this and you've got people out here in Oklahoma running around in the desert with enough plutonium in them to kill them." That didn't get me a whole lot. So that's the kind of dichotomy we have in the government.

Dr. Young: You had these experiments that dealt with irradiated food. At the time, they seemed to be a more important social problem than in retrospect they have come. How did it get the gun?

Dr. Laug: Two or three years after the end of the war when it became apparent that Russia had our capabilities for atomic bombs with the potential for use against civilian populations, the FDA became alerted to the implications of possible contamination of our food supplies. In 1949, I was sent to Oak Ridge for an intensive course on the basics of radioactivity. With the help of this course, part of which was also oriented toward civil defense, the FDA set up in 1951 several training teams that visited all the field districts.

I was one of the instructors. After 1951 came a succession of U.S.A. tests in the Pacific and also by the Russians in Siberia. Our attention then became focused on two possible impacts on FDA's responsibility for guarding food and drugs: (1) What would happen to foods and drugs stored in depots close to "ground zero"? If they escaped physical damage, what about their potential radioactivity due to induction by neutrons, how about possible chemical changes? (2) To what extent would fallout contamination be significant? What methods would be practicable for decontamination of field crops, packaged food, wrappers, closures, etc.?

FDA addressed these questions by participating in three tests at the Nevada Test Site in 1953, 1955 and 1957. In these, I was designated to plan and direct the experiments.

In the 1953 tests, a variety of drugs submitted by the drug industry were exposed. To mimic a surviving warehouse near "ground zero", the products were exposed by burying the products in trenches, sufficiently deep to prevent physical destruction, yet close enough and unshielded enough from the neutron flux to produce induced radioactivity.

The 1955 tests were done on foods, packaged in a variety of ways, mostly cans of metal or glass (even beer). Exposures were made roughly at about the same distances and conditions as the 1953 tests on drugs. It was a large cooperative effort

involving the National Canners Association, Glass Packaging Institute, packaging industry, all of whom furnished samples and personnel to be at the test sites.

The 1957 tests were far removed from "Ground Zero" and were designed to expose foods, packaged food, raw farm products to the fallout cloud that followed the explosion.

At that time security regulations were so tight that all our results were classified. However, it was possible for me to prepare, with proper adjustments of certain classified data, and to duplicate reports that could be published in the literature without loss of essential scientific value. (Note, in my bibliography are listed various reports on radioactivity: No. 54, 56, 57, 59, 62, 64, 65, 67, 70, and 73).

In retrospect, the effort of FDA in getting involved in these civil defense exercises, with particular emphasis on its responsibilities here, was very much worthwhile. In broad review: fallout contamination under emergency situations of packaged foods and drugs could be coped with to make most of them immediately available for consumption. Long term use might pose special problems. So, also, unprotected or unharvested farm products. Clean up operations over long term would here apply. With respect to induced radiation caused by close proximity exposure, the degree to which a situation would be desperate (essential drug, necessary food) would

determine the use of such a contaminated product. Judgement should lean toward use, rather than withholding.

One of the first things that we had to determine was what was the baseline. You can go out and determine the radioactivity in anything and you will find it. But what does it mean, where is your baseline? So, as an interesting little sidelight - do you know what they did? They went up to one of those caches - I don't know if it was Perry ...

Mr. Janssen: Shackleton, at the South Pole.

Dr. Laug: Yes, and they brought us down a whole lot of products.

Mr. Janssen: I still have a can of pemmican.

Dr. Laug: We analyzed those to determine what the activity of that was in the days when nobody had even thought of atomic bombs. Any radioactivity there would have been from a natural source. We then were able to use that as a benchmark. I think our biggest contribution was the system that was finally installed for collecting food samples by the districts. The "Marketbasket". That was an attempt to see what the general exposure of population is. I am reminded, perhaps somewhat ruefully, of the early excitement due to radioactive fallout in our environment. When the first baleful prognos-

tications first emanated, no one, including myself, who was in a position to know better, ever thought of the potential damage done to all of us slowly and gradually in the daily routine of our lives, by the pollution of our biosphere by industrial contaminants and automobile exhausts. Except for immediate atomic attack emergencies, it is now clear that the fears of potential fallout from atomic tests conducted anywhere in the world, present a hazard that is not even in the same ballpark when compared to the hazard we have to endure at all times, due to the relentless defilement of the biosphere by our own immediate doing.

Dr. Young: Did you do with this as you did with some other things -- do animal experiments of a massive kind in order to determine how much radiation it took?

Dr. Laug: No, we were never involved in that side of it.

Dr. Young: That would have been other agencies?

Dr. Laug: Right.

Mr. Janssen: I was wondering to what extent the FDA's activities contributed to the action to stop the open testing of atomic weapons?

Dr. Laug: I wouldn't know.

Dr. Woodward: I would guess that the marketbasket survey had a lot to do with it because there was a lot of flack from all that strontium.

Mr. Janssen: Yes, we had many press releases that we put out about the findings. And then the Public Health Service took that over and began to issue regular reports on strontium 90 and other metals that were found on a regular basis. They sort of took over the reporting to the public aspect of it. That did not include the marketbasket.

Dr. Laug: No. The marketbasket was an outgrowth of our first attempt. Then it was expanded since the technique of collecting these and the different things that went into them - they were then used by the Food and Drug Administration to evaluate other things. That is still going on out there.

Dr. Young: The nutritional side.

Dr. Laug: Nutrition and pesticides, that's the main cue.

Dr. Janssen: The public first became actually aware of the radiation threat, whatever it was, from the widespread publication of pictures showing the FDA inspectors monitoring tunafish with Geiger counters. Those pictures were widely

used in newspapers. And there were pictures also of inspectors in grocery stores monitoring things.

Dr. Young: Whatever the many uses of the marketbasket approach, it was to test the radioactivity of the food that caused that project to be launched. That was your baby?

Dr. Laug: Yes. We started that part.

Dr. Young: Do you know a main publication in connection with the very early marketbasket research? Could we pinpoint that?

Dr. Laug: I don't know whether I was involved anymore.

Dr. Young: That would turn up as a topic in the annual reports, wouldn't it?

Dr. Laug: Yes, well there was a report in the Journal of the Association of Official Agrircultural Chemists in 1955 that is entitled "Report on Radioactive Contamination of Foods". That was the report that emanated from our studies in Nevada.

Mr. Janssen: I've got a box of papers and pictures

Dr. Laug: Yes. There is another one here published in Military Medicine, "Radioactive Contamination of Food and Animals". It's a sort of review.

Dr. Young: That's good. What was the date?

Dr. Laug: That is Military Medicine, 1958, Volume 123.

Dr. Young: Thank you. I can see certain innovative aspects to this. But should we move on? Is there anything else?

Mr. Lofsvold: We could just sum it up by saying that the marketbasket started with radiation, pesticides were then added, then some heavy metals, and now they've added other industrial contaminants like PCB's that are now being analyzed for; using that same approach to determine what the food supply is carrying.

Dr. Laug: There are two publications more here that are pertinent. One was "A Survey of Radioactive Residues in Foods Before and After 1945." That's the story about getting the food from Antarctica or wherever it was. That was also published in the Journal of the Association of Agricultural Chemists. And then finally, one which bears on what has just been said about the marketbasket. We did a total diet study. Here we did strontium 90 and Cesium 137 content in the diet of a 19 year old boy in the metropolitan Washington area. And that appeared also in the Journal of Official Agricultural Chemists. 1963.

Dr. Young: Fine, that links up some articles that...

Dr. Laug: I know, well there are some more.

Mr. Janssen: I don't know how it happened, but I was the one to deal with the Navy, Captain Black. He had us to lunch at the Army-Navy Club to talk about this. He was going to Antarctica – which he did, and then be brought back these samples.

Mr. Lofsvold: They came into the Brooklyn Navy Yard and we sent a New York inspector to pick them up.

Dr. Young: I don't know whether you have a unique copy of your publication list here or not.

Dr. Laug: I do.

Dr. Young: I was wondering if it might be possible, you're going to be around next week, would you trust leaving them with Bob Porter to get photoduplicated and then mailed back to you.

Mr. Porter: If I could borrow them now, I could go do it right this minute, so to speak, and then bring them back.

Dr. Young: That might be better. Then you wouldn't be detached.

Dr. Laug: Yes, that's the only copy I have.

Dr. Young: This, obviously, could save a lot of hunting.

Dr. Laug: I guess this is the copy.

Dr. Young: Might we turn to color then, and let me just start off specifically with a question. I was asked -- this comes from a Mr. Hockheiser, who is a graduate student at the University of Wisconsin doing a dissertation, under Aaron Ide, the historian of chemistry, about colors in the United States. He says the question I would like you to ask the pharmacologists for me is this, "It is obvious to me from the records, that sometime between 1950 and 1953, the FDA changed its position from expecting relative freedom from toxicity, to absolute freedom from toxicity for the certifiable colors. What I would like to know is, what factors led to this change and, more importantly, why it occurred.

Dr. Vos: Well, I'd be delighted to address that for starters. You will find in the file somewhere, if you can find it, a memorandum that I wrote on that for Dr. Lehman's signature, which was about 10 or 12 pages, I guess. The law required us to certify food colors as harmless, and suitable for use. And

we had done that for years and gradually we began to -- well there was an outbreak of toxicity with some children eating some candy--Haloween candy called Trick or Treat in Kansas City, which had a tremendous amount of Orange I in it. The kids got sick and vomited. First it was thought that it couldn't possibly be due to the Orange I. We did some experiments of our own. We ate the candy and yes, we vomited. We tried capsules with the amount of Orange I that was in the candy and that made us vomit and have diarrhea. So it was clear that these colors were not harmless in the absolute sense. They were harmless in the amount ordinarily used. But the law did not say harmless in the amounts ordinarily used, the law said harmless. So we began to have second thoughts on this. Really Food and Drug was in an impossible position of saying that any compound was harmless. I mean, you can't talk about harmless in the abstract way, you have to take it in the context of how it is used. And since the thing was certified for use as a coal tar color, there was no limit on it. You could make up a candy that was half coal tar color. That wouldn't violate the law. So we then realized that we were going to have to look over these colors. And we moved, I guess against those ones which looked the worst and decertified them as no longer being harmless. And there were hearings held in which we presented data that we had that showed that these colors could not be regarded as harmless. I guess we took off Orange I, Orange 2, and Red 32.

Dr. Woodard: There isn't much left.

Dr. Vos: Well, that's where it started, I'd say, with those. And eventually we had the law changed so that you were going to set levels at which the colors could be used.

Dr. Young: You changed policy first. Acting policy without changing the rules exactly, the formal rules.

Dr. Woodard: It was really interpretation of the wording of the law itself was what was changed. They didn't change any policy. It was a change in the interpretation of what that language meant. And because we didn't all agree what the law meant the way it was interpreted after '53 or '54.

Dr. Young: Are you suggesting there was internal dissention?

Dr. Woodard: No, disagreement.

Dr. Young: Without getting into personalities, what were the two?

Dr. Woodard: Well, I think you've got it right there--it's a matter of what does the phrase "harmless and suitable for use" mean. Is it the meaning of each word individually or a meaning of the phrase, harmless and suitable for use.

Dr. Young: And how was the debate conducted? Within the Division, as a scientific thing, or was it a debate that went on to broader reaches within the Food and Drug Administration?

Dr. Woodard: I think it was more -- somebody in another Division -- to say whether it was going to go.

Mr. Janssen: It took quite a while for this issue to get sharpened up. It really didn't get absolutely unequivocally clear, I think until Arthur Fleming got involved in it. Before the Color Additive law was passed. They had a whole succession of things that happened. We had the argument with the Florida orange growers, for example. Congress passed a law to allow coloring that we thought was not...

Dr. Young: He detected a practical change in policy from the records he's been reading rather thoroughly between 1950 and 1953. If you found this out first, does that mean, after an episode such as your experiments with this candy, that you began to discuss whether policy ought to be tightened up and some agreed that you should and some agreed that you shouldn't within the Division? Is that what you are suggesting, that it was a kind of natural disagreement between people who interpreted the scientific evidence as meaning different things? I do not quite understand, I guess, your reference to disagreement.

Dr. Laug: Well, may I ask a question since I was in this. Wasn't it true that the food additives -- now which came first? It was the requirement of the law that if you wanted to put X into bread you have to have all the stuff about safety and all that, right? Well, how much different it is in putting in orange-red into the bread and coloring it? If that came later there was no reason to exclude a dye, anymore than it is to exclude any other additive to food, isn't that so? It would be logical to say that, unless there was a separate law.

Mr. Janssen: They couldn't specify conditions of use on colors until after 1960, when the color additive law was passed.

Dr. Laug: Well, then all right. Then that explains it in that sense. Yes.

Dr. Fitzhugh: Color additives was later.

Mr. Lofsvold: Food additives was 1958, color additives, I think, in 1960. I believe that the additive amendments specifically exempted color.

Dr. Laug: It is actually very logical when you think back, whats the difference if it is a dye or something else. Geoff, do you want to address the question of disagreement or some part of it, my memory of it is completely silent on the thing?

Dr. Woodard: Oh, no, I just happened to be the person who was supposed to be responsible for the testing of color in the first place. These people were saying they are not all suitable for use. I know in the original -- the way Calvery and the lawyers interpreted it, at the time the act was passed in '38, was that that phrase includes in it the implication of quantity. I did not think and they did not think at that time that it was necessary to go any further than that. "Suitable for use" would mean that the amount of color which was excess would be like the....good manufacturing practice. You know the way that most of the food additives used to be stated that it could be used, etc., etc., in terms of good manufacturing practice. Well, "suitable for use" in the phrase that relates to the coal tar color, we interpretted as having a kind of connotation that would be similar to good manufacturing practice. It is not good manufacturing to put 33-1/3 % dye in a candy, which is what these idiots did. The people in the Division of Cosmetics along with some people in the division--I don't know who they were in Pharamacology wanted to get some new legislation on the book and have it unequivocally spelled out. I felt that the law was adequate to handle it.

(interruption due to tape change)

Dr. Woodard Who was the head of the Division of Color? G. Albert Clark, along with some people in our division, plus some individuals in the General Counsels Office who wanted a more specific interpretation of the law. In order to precipitate that, it was necessary to create....to get a law through Congress. You don't just do it by asking for it, you have to precipitate some sort of an emergency, or make the point that we can't possible regulate this. It was a lot of nonsense, we had been regulating it since 1938.

Dr. Young: And they did that by testimony before the Delaney Committee?

Dr. Woodard: Yes, before some body in Congress. What ever the Congress was.

Dr. Fitzhugh: We continued to do research on the toxicity of colors. I did it myself. Chronic toxicity of these dyes one after another. We got almost through all of them, all the food dyes and many of the non-food dyes. They showed some toxicity of those. Now the difficulty was that Mr. Goodrich, the General Counsel wanted to get a new law through and he wanted to spell out what the safety was and how to handle it. By petition methods or not. So we just went ahead and, from the toxicity standpoint, we simply said that each one was toxic if you use enough of it. And Goodrich was always wanting to find the toxicity. I used to call him Mr.

Toxicologist, because of this dye question. He always was pushing for that new law that he wanted to get through. He wanted industry to back him. He didn't want to say they were safe for use. So it was almost entirely Goodrich's fault.

Dr. Young: When had you begun to test these dyes?

Dr. Fitzhugh: Well I started testing dyes in 1939. So I tested them all through 30 odd years that I was in the Food and Drug Administration.

Dr. Woodard: You probably inherited the experiments that Herman Morris had started before you even came.

Dr. Fitzhugh: That's right. I inherited those experiments. And I never stopped testing dyes for 30 years.

Dr. Young: Is it within your memory, not your own memory of being there, but of hearing things from those who were there when you came, about when and why the testing had gotten started. Had there been other episodes earlier that are similar to the later candy episode that has been mentioned; that caused the origin of this testing?

Dr. Fitzhugh: The candy situation certainly accelerated it, no doubt about that. But the general feeling of the coal tar dyes going back to Calvery's own background, he felt that those dyes, in general, were not safe.

Dr. Young: Right. In fact very early after the law there were -- well, I mean even under the 1960 law...

Dr. Woodard: The original reason is because they are spelled out specifically in the law which was passed in '37 or '38, which the others are not.

Dr. Young: But they had been worried about them from right at the very beginning and this is just a continuation of that earlier concern.

Dr. Woodard: You should see the toxicology that was on some of the old dyes that were on the market at the time that that law was passed. They used to have the old archives up in the attic of that South Building. Back in the '20s sometime, they did a lot of work on the coal tar colors where they gave one dose to one animal. That kind of thing. And I got into those old records and looked at them and they were atrocious. And also in all that mess of stuff, was the history of how come this country never used butter yellow as a dye in butter as it was originally intended. Dupont had originally developed butter yellow which is a carcinogenic. As a matter of fact, the first compound shown to be carcinogenic by feeding to animals was butter yellow. And butter yellow was developed by the Dupont Company to put in butter so that it always would be the same color year-round. You know in the winter, butter gets white. Dupont had done all this work and had done

some of these acute toxicity studies and the stuff was not toxic at all, and it made a beautiful yellow color. They started producing it, and the people in the Dupont plant all came down with eczema and it scared the people at Dupont. And they did not put it on the market and never used it to color butter. Because all of the people in the plant manufacturing it got eczemas dermatitis where they made the darn stuff. And that's how close this country got to having a mass consumption of a carcinogenic color.

Dr. Young: It was later found out to be carcinogenic?

Dr. Woodard: Yes, it was later found out to be carcinogenic.

Dr. Young: But not by your research.

Dr. Woodard: Not by our research. It was first done by the Japanese, as a matter of fact. And we corroborated it.

Dr. Young: Can you put a date to the story? When did Dupont find out?

Dr. Woodard: Oh, it was in the '20s sometime.

Dr. Young: Had they discovered it, did they develop the formula?

Dr. Woodard: Well, the dye, I expect, goes back longer than that. But they were working on it and the use of it during the '20s.

Dr. Vos: Wasn't it actually listed as a certifiable color, briefly? And then withdrawn?

Dr. Woodard: See there was no real law originally. The only thing they certified it for was for use in a so-called stain, biologic stain. It was under the old Biologic Stain Act.

Dr. Young: But Wiley sort of by fiat certified colors.

Dr. Woodard: It was an unofficially official list. And it was included in that list at one time, for a short period of time, actually.

Dr. Young: Did it have any other name, than the name you're talking about?

Dr. Woodard: Dimethyl-amino-azo-benzene. But that's confused many many people, because of the name, they always thought it was used in butter, but it never really was.

Dr. Vos: Was it used in other countries in butter?

Dr. Woodard: I think so.

Dr. Fitzhugh: Yes, it was used for a while in some of the other countries. I know, when we took it up at the World Health Organization, we discussed that point. It was used in some of the other countries, but very slightly. I think it was used in Holland, just for a very short while.

Dr. Young: Was it relatively soon after that that the Japanese discovered that it was carcinogenic?

Dr. Fitzhugh: I would think so, I don't know.

Dr. Woodard: Well I know that the report from the Japanese was in 1933. And that was the first compound that was ever shown to be carcinogenic in animals by feeding, or maybe any other way. Chimney sweep cancer was known, but that wasn't by feeding. So then I think, I'm sure it's the first compound that was ever shown to be carcinogenic in animals by feeding experiments. And so that led us to repeat it, which was never published.

Dr. Young: You repeated the Japanese experiments?

Dr. Woodard: Yes, when I first went to work for Food and Drug.

Dr. Young: And it proved out the same way?

Dr. Woodard: Yes, it did, it was carcinogenic.

Dr. Young: And that episode would have made you jumpy, that in itself?

Dr. Fitzhugh: Yes, we were concerned about them being carcinogenic, each and every one of them.

Dr. Young: What is this major paper that is a review of the coal tar color research that the Division did?

Dr. Woodard: It was not my paper. I may have written it, just like that "Safeguarding Food and Drugs in War Time", that was my paperbut Calvery's name was on it.

Dr. Vos: I hope I can come up with the title of the reference to it, but there was an extensive paper that discussed the evolution of the certification of the coal tar colors by the Food and Drug Administration.

Dr. Woodard: That was probably Dan Dahl who wrote that, with Calvery. And I think it was probably published in some obscure journal.

Dr. Young: Could you think of the date?

Dr. Vos: The date would have been about '39, '40, somewhere along there.

Dr. Young: Thank you, very much.

Dr. Woodard: Well I enjoyed it. You know we really haven't dented the surface.

Dr. Young: Yes, I know that.

Dr. Woodard: I don't know what you are going to do.

Dr. Laug: That's what they pay him for.

Dr. Young: I can't dent the surface anyway. I've got 400 pages for all these subjects.

Dr. Woodard: And you have to condense all this nonsense in to two pages, I guess. One thing that I want to leave you with this thought, and that is that I said to somebody here at lunchtime. There are probably 3 areas in Food and Drug which I think are extremely innovative. And I think one we've talked about here is toxology. The other areas are analytical chemistry and instrumentation. And I think that the chemistry is -- I think they have done an extraordinary job.

Dr. Young: Some of that we got from Bill Cook, did we not?

Dr. Losvold: I made notes of the suggestiond that Dr. Woodard has made.

Dr. Young: And the third was?

Dr. Woodard: It's basically instrumentation for the analytical chemistry. There are really two parts to it. One is the development of instruments and the other would be the general pushing back of the analytical chemistry.

Dr. Young: And you would put that in significance?

Dr. Woodard: Those three things were--anything else Food and Drug has done would have probably been done as a result of one of those three things.

Dr. Laug: And you shouldn't forget the analytical biological methods that were developed by all those people before they ever were able to separate the parts of the digitalis.

Dr. Woodard: Well, I think it's all part of the same. The quantitative analytical methods are what makes this Administration possible, and which make it viable. And as long as that can be retained, it will always be a viable organization. I think it's as simple as that.

Dr. Young: That's an editorial, too. What you meant by that really was the earlier bioassay work. I've run across that that in connection with certain of the botannical alkaloids. The Bureau of Chemistry, rather early, found out that the U.S.P. methods weren't sufficient. And then they pushed ahead and developed this in the teens. And they developed more effective method and then they'd be picked up and appear in the next U.S.P.

Dr. Laug: That's right. And they then were constantly being, modified by our people. My interest actually was chemical. But I was very much taken by those methods that they -- a lot of these fellows spent a lot of time on this, isn't that right, Bert--wouldn't you say?

Dr. Vos: Yes, certainly in '39 I would say that half the people in the Division of Pharmacology were working on bioassay.

Dr. Young: Trying to push it along and improve it, the way you talked about the ergot.

Dr. Laug: Didn't they first evaluate those estrogens by biological means? They looked at the lining of the vagina of the rats and they were able to tell whether this stuff was effective. That's long before they had the chemical and sophisticated tests.

Dr. Young: Was the Food and Drug Administration an innovator in the bioassay techniques for the estrogens?

Dr. Laug: Yes. I think so, but I'm not too well informed. Earnest Umberger was associated wiith Jack Curtis starting in the early 40's. He is now retired and lives in the Washington area. He might be able to give you something, I don't know how much. Because the main fellow that ran that was Curtis, and he is dead now.

Dr. Vos: The drugs that were bio assayed in '39, early '40, were digitalis and related compounds that would be ouabain, strophanthin, dipanthin, digitalis tincture, digitalis powder, capsules, posterior pituitary extract, epinephrine, estrogens, pyrogens, ergot, insulin. All those things were routinely bio assayed in the Division of Pharmacology. Now, in addition to the routine assays, I would say that about half the time was spent on research to improve the method, either to refine the method that was currently in use, or to develop an entirely new approach. And a large part of the improvement of old methods consisted in applying statistics. So that you could get more information out of a given amount of work. The old, shall I say traditional bio assay, let's say a pituitary, was to add the drug to an isolated strip of guinea pig uterus and

see how high it contracted. You tried to alternate a standard powder and a commercial sample. And you adjusted the dose until you got equal contractions. With that you could perhaps come in with an accuracy of 20 or 30%. In other words, the thing might assay 80%, and it really might be 105. Well by statistics, instead of matching the contractions, you used the information on all of the big contractions and little contractions and averaged those up and computed what the strength was that should give an equal contraction. Even though you never got two pair of contractions that exactly matched. You could calculate what it should have been that would have made it match. With that you could get an accuracy of perhaps 5% or so.

Dr. Laug: It's the old LD-50 under another guise.

Dr. Young: Is this, the application of statistics you're just talking about. Was that a world first within this Division?

Dr. Vos: Well, I wouldn't say it started in the Division of Pharmacology, no. But is was seized upon, I mean they got Dr. Bliss in then who was a whiz of a statistician. He applied his knowledge to various assays, one after another. Parathyroid, I forgot to mention that, was another one. That was one of the early publications--how to take this very crude parathyroid assay and give it precision by making use of all the information. In other words, not just trying to match re-

sults so that you got an approximate equal response, but to see what the response was after a series of doses.

Dr. Young: Now, each response would be measured on some kind of a scale that was there in the dissertation. And then you got a lot of data and would interpret them with statistics.

Dr. Vos: That's right. I would say that in the example in the digitalis assay there was application of statistics before Food and Drug did, but it was refined in Food and Drug and it was given emphasis and we did collaborative assays with the Pharmacopoeia. First of all, by a collaborative assay you got industry to join in and get familiar with these methods, so it wasn't imposed on them. They then became working partners. Then eventually the new method got into the Pharmacopoeia, so that there was greater precision. You then had less diffi- culty in court. I mean you would have fewer cases that were the result of a misunderstanding or poor technique. The thing was refined to a point where industry was able to put out a good product.

Dr. Young: Now you did the research to improve the method, but the reason that you had this was to test the products on the market. Samples would be brought in--

Dr. Vos: That's right, we had a regular quota--somebody would say you're in charge of epinephrine, how many samples can you

handle a month? So I would say 15, or 10. Then each month 10 samples would come in from various parts of the country.

Dr. Young: And so you would check the products that were actually being sold to physicians.

Dr. Vos: That's right, or in drugstores.

Dr. Young: And improving the technique meant that you had better control over the quality of the product on the market.

Dr. Vos: Yes.

Dr. Woodard: And all of these were highly important drugs.

Dr. Vos: Yes. It's interesting that the first official bio assay in the Pharmacopoeia was in the U.S.P. IX. There were two drugs, one of them was marijuana, the other, I believe was posterior pituitary. So there were only two drugs that were bioassayed. They assayed the marijuana, which is under the pharmaceutical name of cannabis. They assayed it by its effect on dogs. You gave dogs a certain dose and when they staggered, that showed that the drug had certain activity. That was an important drug in those days, so you wanted to have the proper potency.

Dr. Young: Now, what were its indications?

Dr. Losvold: What year approximately is U.S.P. IX?

Dr. Vos: Well, they came out every 10 years, U.S.P. X was effective from January 1, 1926. So U.S.P. IX would have been from '16 to '26.

Dr. Young: In fact cannabis was in proprietary medicine as well as pharmaceutical medicine. And I think the 1906 law required that its presence be labeled in proprietary medicine.

Dr. Vos: Well, U.S.P. X doesn't -- they hadn't started giving the indications yet, but it was a, I guess, a tranquilizer, or something of that sort -- analgesic perhaps.

Dr. Laug: They were very prescient in those days, weren't they?

Dr. Young: When you speak of shifting from bioassay to chemical methods, in the '30s, what are you referring to as chemical methods?

Dr. Fitzhugh: That would be all the heavy metals and those, incidentally, would still be done by chemical methods. Except that they are more refined. Bioassay methods gradually, as chemical methods, and sophisticated gas chromotography and

other things come in, would have been gradually superceded. I don't know how many are still used as a bioassay method.

Dr. Young: Was paper chromotography that Bill Cook was telling us about one of the first chemical methods that replaced the bioassay?

Dr. Laug: No, I wouldn't say that. I would call it a sensitive method for separation of constituents by color. Wouldn't you say, Bert, that's about right?

Dr. Vos: Yes. The reason for the existence of the bio assay, was a drug which had considerable activity. In other words it was not just an indifferent drug but one that could be very potent. It was important, first of all, that the person not get an overdose of it. And that they also not be given an inert drug. You wanted to have a specific dose but the active ingredient was present in such a small amount, that there weren't adequate chemical methods in those days for measuring it. In other words, if you had, let's say a 1% solution of epinephrine, you could measure it chemically. I mean you could isolate it and so forth. But if you had a tenth of one percent solution, you might have trouble making sure that what you were measuring was in fact ephnephrine. I mean your method might not be sensitive to the partly decomposed epinephrine. In other words the breakdown products might also give your chemical reaction. So that, in the case of epinephrine,

there was a pure chemical, but in the dilution in which it was sold, there was, at that time, no chemical way of measuring the strength of the product. So that we gave it to a dog to see how high the blood pressure rose. And compared it with the standard solution. There you were certain that the potency of what you were measuring was active epinephrine. Now, since then, they have chemical methods which are more sophisticated more refined, and there is no longer any bioassay of ephnephrine being done.

Dr. Young: So, in many areas, as the chemical frontier advanced. It became more precise and exact and time-saving.

Dr. Vos: Absolutely.

Dr. Young: So that bioassays shrank out. Are bioassays important at all in any field?

Dr. Vos: Well, the curious thing is that almost as rapidly as they are replaced, new compounds come for which the chemical method is, briefly, inadequate. So that you are using a biological assay. I'm not up-to-date in the field, but many of the antibiotics are assayed by what are biological methods. Or at least were. As I say, I can't speak for what the current practice is. So that you might think it was a dead end profession, but all you've got to do is keep nimble as new things are coming along.

Dr. Losvold: Wasn't it true also, Bert, that for some things like digitalis, the structure or the composition was not exactly known. It was a mixture of active constituents that had not been isolated?

Dr. Vos: That's true. Well digitalis, as you point out-- there are many active ingredients there. You don't just assay for one. There are perhaps 5 or 6 different glycocides in --

Dr. Young: And you want them all there.

Dr. Vos: You want them all there. And whereas you can analyze for them chemically, and measure the more potent ones, and I assume come up with an approximate therapeutic activity. If you do it biologically, you sum these all up automatically in the animal if you pick the right animal.

Dr. Young: Is the Food and Drug Administration a pioneer in what you just said. In picking the right animal? In ways that had been less precise before?

Dr. Vos: Well the example that occurs to me is that initially they used the frog for assaying digitalis. Now that was changed then to the cat, as being a more appropriate -- it measured better the clinical activity. But that work was not done in the Food and Drug Administration. A man at Cornell

University, Dr. Harry Gold, was instrumental in doing that. He measured the effect of different drugs on patients. And he compared the cat assay and the frog assay and found that the cat assay was the more reliable measure of the potency. The change was made subsequently from the cat to the pigeon. And we were able to show in the Food and Drug Administration that the pigeon gave the same response as the cat. And was far cheaper and quicker. So it was an improvement of the assay from the practical standpoint.

Dr. Young: And you would consider that a minor example, but nonetheless an important innovation that the Food and Drug Adminstration scientists came to. Were you always doing that? Were you always trying out new animals? Why would you come to think of using the pigeon instead of the cat?

Dr. Vos: I guess there would be a hint of it in the literature somewhere.

Dr. Young: About some other kind of experiment.

Dr. Vos: Well, that the pigeon might be of some use, I mean somebody had -- it was a proposal. And then the Food and Drug did a comprehensive study and put it up again for a collaborative assay and showed that it was reproduceable so that, as I say, it was not completely out of the blue sky that we said ah, there's a pigeon, let's try it. The problem with the cats

was a shortage of cat population. We were running out of cats. You can't breed cats. You can breed dogs. You couldn't breed cats in the laboratory. I mean there is no commercial source of cats, they were all stray cats that had to be caught and brought in. You can breed pigeons. So this was a practical improvement from that standpoint.

Dr. Young: One other question, forgive me if I'm naive when you gentlemen entered the Agency, what was the state of the concept of a controlled experiment? The emphasis upon the control. You've been talking about experiments that are controlled, it seems to me, but was the concept of control simpler and more naive when you entered than it was rapidly to become? Or not. Do I make myself clear?

Dr. Laug: You are referring to any analytical method, biologic or chemical? Or are you thinking more about biological?

Dr. Young: I suppose biological in the sense that you're testing one thing against another, as you were doing with the bio assay. The mathematics of control, and so on. Now this is something mainly that you read about in connection with a human being in the testing of medicine.

Dr. Vos: Well, I think your question is ambiguous in that the word control has several concepts. In a toxicity experiment you have a group of control animals who are treated exactly like the other group, but don't get any of the toxic material.

Dr. Young: That was recognized as an experimental necessity when you came.

Dr. Vos: I would think that we perhaps gave more emphasis to it as the years went on. There's a tendency to look upon this control group as wasted, they don't tell you anything. If you're looking for toxicity, put on a few controls. I mean that used to be the--I'm not saying that was the attitude at Food and Drug--but, ordinarily, I mean animals cost money and to run controls for two years, that adds to the expense of the experiment. So there is a temptation to put more animals on the drug or on the substance you're testing than on the controls. But Food and Drug, I think from the very beginning, realized that the controls are as important to the experiment as any other group, because each group is going to be compared against the controls. So, you'll have at least as many controls as you will other groups.

Dr. Fitzhugh: We always recommended that and required it in our own laboratory. I've run across that concept very much in evaluating other people's experiments. Particularly in the cases of food additives, requests, petitions, etc. A lot of

people think you're wasting money in putting in so many controls. And we have to emphasize that. That concept has grown, that you need more controls. And certainly the groups of controls had to be as large as any other group.

Dr. Young: Well, when Wiley had the poison squad, you see, which is a good 30 years before you--he was actually using people and his control was the individual person with a preperiod without the drug given and then a period which it was and an afterperiod when it wasn't. But there wasn't any group of people who sat there at the training table and ate something that looked and tasted like sodiuim benzate, but wasn't. In the sense that we think of controls...

Dr. Vos: Well both those methods would be valid. I haven't gone over those Wiley reports for a long time, and I would imagine they were very naive--that would be my presumption. Because you could have the person be his own control, that often is useful. But the important thing is that the person not know, in other words he should use that table every day and never know whether he's getting sodium benzate in his food for a week long or nothing for a week long. And if it had a flavor, you've got to come up with something else that will make him think he's getting it when he isn't. Because much of this can be subjective. If a man says he has a headache, he might not complain about a headache if he thinks he's on the control period.

Dr. Young: But not only that, Wiley told them that if anything serious happened to them the government wouldn't be responsible. And then the Remsem Board told them that they didn't really need to worry. Nothing very serious was going to happen to them. So both the comparative cases by modern standards, I'm sure, would seem to be rather unsophisticated. I did in fact write an article on benzoate of soda in catsup and these experiments. It was easier to see, without asking my scientific friends, that this was a pretty beginning stage of things. And so I was just wondering if the concept of control in this way had leaped from 1902 and 1903 and along in there until 1933.

Dr. Vos: It was a gradual evolution, certainly.

Dr. Young: Until it was very sophisticated, and you are saying that it was much more sophisticated, but nonetheless became even more so as time went on.

Dr. Laug: One thing that I think hasn't received as much emphasis as it should be and that is, when you select the animals, or when they used to select the animals, they weren't very careful whether they were in a homogeneous population. Great strides have been made, particularly in rats and mice, which assure that they come from the same genetic stock.

Because whenever you introduce heterogeneity in a controlled population, right away your chances of not getting as good an assay increase. It's like measuring a chemical into a test tube and using different pipettes for each measurement that you make. There is a little variation. You can get around that by insuring that the animal population is as nearly homogeneous as you can get. That's very important.

Dr. Young: Was homogeneity of animal population recognized as important when you came to work, and did these experiments in the '30s?

Dr. Laug: In our case, I believe even from the beginning, we had a uniform population of animals, didn't we Bert? I don't know whether they came from.

Dr. Vos: I think Curtis raised them.

Dr. Laug: They came from one stock.

Dr. Young: So, by the thirties, this was something that you really were aware of.

Dr. Laug: Oh yes. And we used uniform stock. As a matter of fact, we used it with dogs. We had a dog laboratory, just about where the Pentagon is now. I think they were beagles.

Dr. Vos: No beagles came later -- Irish terriers?

Dr. Laug I think maybe, yes.

Dr. Young: The selenium interests me, Dr. Fitzhugh, because you said that you began experimenting on it and you mentioned this in connection with sweeteners. Is that right?

Dr. Fitzhugh: No, I mentioned it in connection with the early experiments. Chronologically.

Dr. Young: Chronologically. I am interested in sweeteners, and maybe this isn't the place to start.

Dr. Fitzhugh: We started working on sweeteners at very much the same time.

Dr. Young: What sweeteners? I think sweeteners will be a theme, partly because they will have become so important in the future. And I have done that article on the saccharin experiments.

Dr. Fitzhugh: On that first experiment we had four, two of them were not used. They had been used somewhere else. Saccharin and succaryl, and there were two others in that first experiment.

Dr. Young: This first experiment began at what date?

Dr. Fitzhugh: Well, it would have been in the early '40s, but I don't know exactly what date it was.

Dr. Young: And these were chronic toxicity as well as--

Dr. Fitzhugh: Oh yes, they were chronic toxicity. I guess we also had done the acute toxicity as we did the subacute toxicity. Along at the same time, but not before. Usually we did have the 3 types of experiments. We had acute toxicity, we had the subacute, subchronic as they call it now, which would run about up to 3 months in order to set up the basic dosage levels. And then we did the chronic studies. Usually those three would be done consecutively. The sweeteners study was not a very extensive study as we found out later, but it did show the toxicity of them. And two of them were very toxic, the succaryl and the saccharin were not that toxic. It did not show in our experiments that they were carcinogenic at all. The question has been raised later on about Saccharin, of course. I'm sorry I don't have the date here. That doesn't necessarily show the dates of when they were done, it shows the dates of when they were published. I did have another sheet which I could have brought along, which would have the date. I never thought that you wanted the date.

Dr. Young: Well, I guess just try to pin down things according to date.

Dr. Fitzhugh: But they were fairly early experiments.

Dr. Young: What precipitated your doing them? Were you just covering the waterfront, on all kinds of food additives?

Dr. Fitzhugh: We were picking out, generally, materials that were fairly widely used. You have to remember one thing first, that at this time there weren't so many food additives. It was only after the first World War that they came in by the thousands. No, the second World War. But these materials which we started in the early '40s were really the materials that were used in food fairly widely. Like selenium was in corn and wheat in the areas of Wisconsin and so forth. They were known to be food additives. And the sweeteners were used at that time. That's really what we picked up. As I remember it, we started a number of experiments along about that same time.

Dr. Vos: The first one is in Federation proceedings in 1950, so that would have been perhaps 3 years after it was started, I would guess. That would be a report.

Dr. Fitzhugh: That would be, yes, it wouldn't be any earlier than that.

Dr. Vos: 1950, as I say, would be a time at which you gave a paper on it for a society. Then the publication was the following year, 1951. Journal of the American Pharmaceutical Association, 1951, "Comparison of Chronic Toxicity of Synthetic Sweetening Agents".

Dr. Young: You said that there were a few, selenium and these four sweeteners, and there are probably others, but that the population of additives was small. It was in the period immediately after the second World War that there was such an upsurge. I call that upsurge, in comparison to the "Chemotherapeutic Revolution," the "Chemogastric Revolution." And here you were sitting there watching this happen. Can you tell me about this from your viewpoint, when you suddenly began to be aware that there were infinitely greater number of food additives that were being without any law to prevent it, put into the food supply.

Dr. Fitzhugh: I remember sitting down with Calvery, and he and I, were deciding what we were going to study. We went over the list and got down to maybe less than a dozen. He said, well when we get through these, we really don't know what else to study. Because these are the important things, these and nothing else. After the upsurge came on, I began to

make cards on all the materials that came to the Food and Drug Administration. I'm sorry I stopped it, but I did stop it and when I got up to 10,000; I said, "It's time to stop."

Dr. Young: When you said they came to the Food and Drug Administration, you meant that, they came to your notice, you observed them in the publications and various--

Dr. Fitzhugh: Well, they were actually being used. We haven't touched on that phase of it. But a large number of those materials came in as constituents of packaging. Materials which we considered as to whether they were safe or unsafe, whether we knew something about them.

Dr. Young: They came in--

Dr. Fitzhugh: Either as a request or from information that they were being used or somebody was saying that they were going to use this material, and asked, "Is it safe? We've done acute toxicity and we've done a subacute toxicity for those three months and it doesn't look like it's unsafe, and we're going to use it." Now, we didn't always know they were actually getting into the food. We had a method which was explained to them. We made them use certain solutions and see if they could get it out of the package. And when they said they couldn't get it out, they couldn't find it, we would set a limit and say well if it doesn't come out more than a tenth

of one part per million, go ahead and use it. There was no way of... We were really setting tolerances on those.

Dr. Young: And they were coming in so fast, you were doing them sort of by the seat of your pants.

Dr. Fitzhugh: That's right. And when I said I got 10,000 cards, I said that's enough.

Dr. Young: This was several years after the war. Why do you think the food industry did this? What was there in the total environment that caused the food industry to burgeon in its use of various things in foods, at that time?

Dr. Vos: Well, I think you ought to read the first couple of paragraphs in that article by Woodard and Calvery, which describes what the changes were when there was an increase of people in cities; when the food isn't going just 5 miles from where it's raised to where it's eaten, but it goes first to a processing place and then goes later to the consumer. So you have the problem of keeping it wrapped.

Dr. Young: This was all pretty sophisticated by the '20s. By the '30s. I've been writing about the burgeoning of the processed food industry. This had gotten a long way by the '30s and there had been the fights about saccharin and about the preservatives, the old fashioned preservatives in Wiley's

early years. But here, as you say, it goes in a relatively short time from a list of a dozen that you worry about, that you are actually going to spend your time on in the future, to 10,000.

Dr. Fitzhugh: Many of these may not be used. They may actually not be used--they were questionable to be used. That included pesticides as well as food additives, you see.

Dr. Young: Besides the environment, the urban environment, which has been a factor for quite a while, what is there in the state of the art, in the ingenuity of chemistry that brought that about? Did things happen in the war? War, very often, had a great impact on therapeutics and on different kinds of medical procedures. Were there lots of things that happened, chemically speaking, biochemically speaking, in the war that had something to do with this post-war surge of food additives. It seems to me that it requires more explanation than just the increasing urbanization.

Dr. Fitzhugh: Didn't it develop in the burgeoning of the chemical industry. They were making so many more compounds. When they were developed, they wanted to find a way to use them.

Dr. Laug: I think that's probably true, after all, if some chemist spends a long time synthesizing something, then the

next problem would be, can we make any money out of it? I think there was a lot of that. And I also had the idea that in almost every war it takes about maybe 10 years before the "engine" finally comes to a stop and is only idling, if you know what I mean, economically. And I think that is all carried along with the war effort. That's part of it. Of course, that is rather nonspecific, but I believe it's true even for chemicals and things.

Dr. Young: Well, there you were watching them come in. In hindsight, I have a feeling that you might have thought, why so many? Or just almost felt overwhelmed by the thought of these things. And so, as a social historian, putting this whole thing within as big a framework as possible, what brought about the chemogastric revolution? I can kind of see the thing in the pharmaceutical industry, because you had the sulfas and the penicillin and they were such success stories that they just pushed the industries out to use the same technique to do other things. Maybe the success of the pharmaceutical industry had some kind of impact upon the food industry, to get them to be more ingenious at searching out chemicals that might have some kind of saleable use or make the product easier to market.

Dr. Laug: This is often true, we talked about how many convenience foods there are, for example. We know very well that a huge amount of them may have come out in the last 10 years,

but they also came much earlier. Any time the eating habits of people change, any time you have that, then you've got to have new preservatives, you've got to have ways of making the food look more appetizing, you squirt a little color into it and so on and so forth.

Dr. Young: It may have been that more women got jobs and kept them. This changed eating habits in such a way that this became more important. I don't feel as comfortable about explaining the upsurge in food additives, from the knowledge I have at this point, as I do explaining the increase of drugs.

Dr. Laug: I think it's really a reflection of a great change in our society which started right after the second World War. It's been gradually gaining momentum, as we all know. The number of women, for example, who were employed right after the war was miniscule compared to what it is today. And any time the lady works and comes in at 5:30 in the evening, she's got to have something to plop into the frying pan and that's got to be appetizing.

Dr. Young : Or take it out of the freezer. There's more that needs to come there to me. You were sitting there watching this and I was just trying to get what kind of feel you might have had.

Dr. Laug: I have an idea that we were overwhelmed, but we didn't know it.

Dr. Fitzhugh: Well, at times we were wondering whether the food was going to be food, but then we always thought that all these things were safe and therefore I think we had that feeling.

Dr. Laug: We were naive, very naive.

Dr. Young: What was your reaction to the Delaney hearing? There, a certain amount of criticism began to come to the Food and Drug Administration about not taking some of these new things seriously enough, didn't it? That there ought to be a law that increases your responsibilities in these areas; more than tighter control over coloring, tighter control over food additives, and tighter control over pesticides under more specific laws. Just as in the '60s Kefauver came on and said tighter controls are needed because the thing is roaring so fast it's just hard to put a harness on. Do you remember, did this seem like a big event in your lives, to have Congress getting interested in and holding hearings, and worrying about cancer down the road? The famous Delaney Clause and all that?

Dr. Vos : Well, it seems to me, the amendment, as such, we welcomed, because it was putting the burden of the testing away from the government on to industry. In other words, it's

obvious we weren't going to be able to test all these compounds ourselves. I think, my own personal recollection, I don't know whether I can speak for this Division or not, was that I thought it was presumptuous of Congress to decide that we weren't capable of evaluating--I mean that cancer was too big a problem for Food and Drug to pass judgment on. In other words, this was outside of our realm of competence. We could set tolerances for other things, but this was something beyond. It seemed to me that that was kind of a grandstand play--that was my own reaction to it. But it was something that we were willing to put up with if we got the rest of the package. In other words, if it all went together, why we were glad to have the industry required to do the testing.

Dr. Woodard: We were talking on the way over and I think practically all of us who were in the Food and Drug Administration believe that the Delaney amendment was well meaning, but it has a serious scientific flaw because it says that if we test anything and I include water, that the tolerance is then zero if at sometime in that dosage you're going to get cancer. Of course, scientifically that's nonsense. But nobody has ever come up with the ability to set what that dose is. It can't be 100%. Maybe it's 98% or 85, nobody knows what it is. So he set it at 100%. But scientifically this is not sound.

Dr. Young: Well that clause apart, they welcomed the law because it did require industry to do the kind of testing that you couldn't possibly do.

Dr. Woodard: I think we all agree to that.

Dr. Young: You mentioned that users of these things came in and sometimes they asked you for your advice, sometimes they told you what they were going to do. Do you remember yourself being angered or upset because there were certain food additives that were being used without your consultation which, from what you knew of the science, might well be dangerous to the public? Things that you had no opportunity to control, because the law didn't give you much power to control them. Things that you did turn to and test on animals because you recognized that they were in foods, had been newly introduced into foods, and you were worried about it. Do you remember situations like that before the law came along?

Dr. Fitzhugh: Well, you had to attack them before the law came along. Of course some of those materials were toxic and usually -- I want to say a little bit after what Bert said, but I will answer your question first. I don't recall any particular cases because, if we really had found materials that we considered harmful, we tried to prove that they were harmful under the old law.

Dr. Vos: I guess a good example would be monochloracetic acid. Where we were, I think, pretty well satisfied that the amount that was being used as a preservative, they said a flavor, but that was a gimmick...

Dr. Young: Who were they? You mean several companies?

Dr. Vos: The wine industry in particular. It was being added clearly as a preservative. I think, we had no suspicion that the amounts being used were dangerous. We weren't sure it was safe, but, if we had to guess, we would have said those amounts are probably not hurting anybody. Nevertheless, it was as we tested it, a harmful or deleterious substance that was being added to foods. As I recall, didn't we proceed against that?

Dr. Fitzhugh: I think we proceeded against it.

Dr. Young: Did the law let you do that?

Dr. Fitzhugh: The old law let you proceed against the product.

Mr. Lofsvold: Yes, we did. We had a number of cases around the country and finally ended up, I think, with a recall.

Dr. Young: This would have been in the '40s?

Mr. Lofsvold: Late 40's.

Dr. Fitzhugh: We didn't have too much on that basis, but I was going to say we certainly welcomed the Delaney Amendment, in the early days, all along until more recent years, and we welcomed it and we supported it wholeheartedly. But, as a scientist, when you tried to enforce it down to the miniscule amount, then it becomes unscientific. And, as a scientist, you can't always support that. But even in material such as the nitrites, we knew all along that if you feed them to animals that the mixture of it was carcinogenic. What we said was if it was way down at less than a tenth of a part per million, we didn't think it was in quantities that were large enough. And that's a point that industry and scientists in general oppose in the Delaney Amendment, of course. I have to agree that that is a weak point and, as a scientist, I can't go along with it. But as long as we were able to make a decision, as food and drug regulators, we handled the Delaney Amendment in a very conscientious way, I think. But, in later days, when they have shoved it to the bitter end, by saying that anything that will cause tumors in animals shouldn't be used, because of the Delaney Amendment. So you can shove up the dosage levels and try all kinds of animals, and one of them, on a dosage level somewhere, will produce so-called tumors. That was true of pesticides, any chlorinated compound will do it. Many drugs will, and most of the food additives

will. So all you have to do is to feed it to a sufficient number of animals, species I mean, and adjust the dosage levels high enough, and you will get some kind of tumor. That's where the Delaney Amendment falls down.

Dr. Young: You were just saying that you can reduce the Delaney Amendment to an absurdity, because you can eliminate practically everything if you set the experiment right.

Dr. Laug: And the saccharin business is a classic point in case. Isn't that true, or am I wrong? Didn't they give huge doses in that Canadian study?

Dr. Fitzhugh: Yes.

Dr. Laug: That might be an example of what we're talking about.

Dr. Fitzhugh: That certainly did it with sucaryl and made some assanine decisions on that.

Dr. Young: We have covered a good many of these, is there anything more about food additives, generally, that anyone wants to say? This looms as such a big thing that it's going to have to require certain attention when I get to it. When the law came in and the pressure was put on industry to give the evidence for safety, you were all part of surveying the

documents that were presented. Is that correct, in connection with new additives?

Dr. Fitzhugh: Oh yes.

Dr. Young: Can you talk a little about that process, what happened--did you read them and say yes and no? Was it easy? Was industry on you neck all the time? Did you say yes when it was only sort of a maybe situation? Tell me something about the environment and circumstances of your being in the process of approving or disapproving food additive applica-cations?

Dr. Fitzhugh: Well, yes and no sometimes. It was my responsibility to pass those. I could either turn them down or pass them on. Of course Dr. Lehman had to agree with them most of the time. I don't know whether you ever did or not, Dr. Vos? Did you sign your name to them?

Dr. Vos: Rarely.

Dr. Fitzhugh Anyway, most of the time, when it first started, I think Dr. Lehman signed. Then they became my responsibility and I don't think anybody signed them after I did, until they went to the front office. And usually the scientific part, as I recall it now, I could say they were safe or I could say they weren't safe. Usually nobody raised any objections,

except the industry didn't like it. Usually the front office was very accomodating. Mr. Kirk, one of the last times I saw him, asked me specifically, "Did I ever veto anything you passed"? He said, "I vetoed the chemist and sent that back, but I never bothered with the pharmacologists." And I said, "I think you're right, Ken. I don't think that you ever turned anything back that I said was safe. Maybe you raised some questions, but I don't remember you ever turning anything back." So he was very kind to the scientific toxicologist. It became greatly my responsibility then. I, of course, don't mean that I read all those things. There were too many for that. I had help to do that. I mean, I read most of them. I read the questions that were raised by my staff and I read their reports. If there were any questions in my mind, I went back and read the petitions. But then you did have questions that the industry would raise and they came in--they had a perfect right to come in and talk to you about it.

Dr. Young: In any stage through the whole process?

Dr. Fitzhugh: No, they didn't do that. They usually came in and brought the petitions and discussed them with you and left the petitions or sent them in later with somebody else. And if they raised any questions, they might come in, some of the toxicologists, and discuss it with you. Many of them you had to turn back and ask for more data, at least half of them. Then they would ask you what did you want done? You never

guaranteed that if they did that, that you were going to pass the petition the next time. But you gave them a good reason if they did a good experiment. We went through that process over and over again. Very little controversy with the industry, that is the scientists. If the scientists came in and talked to you, 99 times out of 100, they would see what you were asking and go ahead and do it. Now the lawyers would try to persuade Dr. Lehman that there was something wrong, but that was a different question.

Dr. Young: Generally speaking, what percentage passed, just as you have a feel for it? What percentage did you have to reject, even after new information was supplied? Just a relatively small number or was it a good...

Dr. Fitzhugh: Well I would say that in the first phase of it you would have questions on probably half of them, but later if they performed experiments, that may take several years to get it done, it may never come back. But if they had done the experiments right, I wouldn't think over 10% would be rejected.

Dr. Young: And about the 10% that were rejected, what would be the key reason that the experiments did in fact show some kind of hazard that you regarded as more weighty than industry did?

Dr. Fitzhugh: You didn't always agree with their results. One thing you always had to watch for was that they bring in the raw data as far as they could and that you get your own interpretation, if it's statistical, you ask the statistician to evaluate it. And sometimes, in these long-term experiments there were certain laboratories and certain individuals you always questioned their results. Some you didn't have to question because their interpretation would be the correct interpretation. So you had to watch the points that were questionable on their part such as why don't you interpret the same way we do. Well, if you can get the scientists out of the laboratories, particularly scientists of the industrial laboratories--most of them had good scientists. They would agree with you. They didn't disagree, let's put it that way. Most of the questions that you would raise would be about the interpretation of laboratory studies.

Dr. Young: Did they have any kind of legal right of appeal beyond you?

Dr. Fitzhugh: Oh yes. They had, I mean they would have, of course. When you say, "you," I don't know whether you mean myself or whether you mean the Food and Drug Administration.

Dr. Young: I meant your Division.

Dr. Fitzhugh: Oh the Division. Of course they could appeal. It wouldn't do them any good. They could go to the Administration, yes. They could go to whoever was the Administrator.

Dr. Young: Can you remember, as an example, any major flap in which industry really raised cain, after you said no?

Dr. Fitzhugh: I know they must have had some but at the moment I can't recall.

Mr. Lofsvold: Along this line, Dr. Fitzhugh, when it was proposed to use radiation to preserve food, after applications had been made, we finally turned it down. Was that for pharmacological reasons? Or was that for reasons developed in other Divisions?

Dr. Fitzhugh: Well, I know we raised questions on the destruction of the vitamins, things of that kind--it looked like we never could come to any agreement on that. I don't recall specifically now. We certainly raised questions on the sterilization of food.

Mr. Lofsvold: I had a recollection that there was concern about the compounds that would be produced on them.

Dr. Fitzhugh: That certainly was one of them. It was whether these materials were safe or not. These were very tough decisions all along on these materials.

Mr. Lofsvold: There was a lot of pressure, I think, on the Agency, not only on the part of the people who wanted to sell the product, but on the part of the Military who were very anxious to get approved to use that process.

Dr. Young: Now, that would still be in the 40's? or in the '50's.

Dr. Laug: That was in the 50's. One of the best examples was the potatoes; it prevented the sprouting of potatoes. That's a large part of the diet. I don't know how that ever went. Did they finally allow them to do it, or not?

Mr. Lofsvold: No, it has never been approved.

Dr. Fitzhugh: There has never been one passed. The Armed Services supported a number of them, bacon, potatoes, a lot of others.

Dr. Vos: Of course, the story was that the Armed Services wanted to use it. The Food and Drug was unable to tell them differently if they wanted to. They wanted our blessing on it, which we wouldn't give them.

Dr. Lang: I think it can be said though, that as far as the induced radiation was concerned, that that argument, that was

once advanced, is completely dead. It doesn't exist. I mean the only argument you could use is with any authority is the changing of the food product by the radiation or the removal of essential elements.

Dr. Young: To induce radiation means that there would be residual radiation.

Dr. Laug: Yes, but that could never occur unless you, by some strange means, used neutrons. You can't induce anything.

Mr. Lofsvold: Did we ever do any actual experimental work with irradiated products of our own?

Dr. Fitzhugh: No.

Mr. Lofsvold: Just reviewing the data submitted?

Dr. Fitzhugh: Just reviewing the data, there was much amount of data to review each time, great packages of it. And there was always no proof, as I can recall, that you didn't just break down some of the materials into harmful substances. There's also no proof that you don't do the same thing with heat.

Dr. Laug: You know, the interesting thing about it is that it was first brought up by the potato chip people. And you know

why? Well, the public likes a very light yellow potato chips. The potatoes, while those critters, which about the first of January or beginning of February, starts turning part of its starch back into sugar, see. Then when you put that sugar plunges into the hot shot to fry it, it carmelizes part of the sugar and it gets a darker brown. And that is, cosmetically, a no no. That's why they wanted to do it.

Mr. Porter: I remember the Department of Defense had quite an exhibit of irradiated foods at the Museum of Science in Chicago. Probably other places too.

Dr. Laug: I think this whole problem is a boogie that is reflected in the big flap about these nuclear reactors. People have some kind of an inherent fear of this. And that overrides reason in many cases.

Dr. Young: Well, there are so many things to be afraid about that we just, I guess as people, get . . .

Dr. Vos: Ed, if I could answer you briefly. I think the whole problem is that with any other food additive, if you're going to add, let's say, sodium benzoate to food, you can add it in successive amounts and the effect that you are getting is sodium benzoate. Irradiated food, you're going to eat all the food. I mean conceivably your entire diet might be irradiated. How do you decide what margin of safety there is.

You can't irradiate more than your entire diet. You start irradiating it at a higher level, you're not doing the same thing anymore. You're altering the food. They say this isn't realistic, this isn't what we're going to use. In other words, there is no way that you could have a margin of safety that is qualitatively the same, such as you have with most food additives. I think that's the biggest problem.

Dr. Laug: That's true. But I don't think that John Q. Public realizes that.

Dr. Vos: Oh, the public doesn't realize that. But I'm talking about this food additive the reason this never got by -- we had this nagging problem. How do you get a margin of safety on an irradiated product?

Dr. Laug: But then, by the same token, you ought to be able to take potatoes and irradiate them and take them apart and determine the various constituents that changed. I mean, theoretically.

Dr. Vos: Theoretically you can do it. How do you ferret out each constituent?

Dr. Young: Did you folks get involved in your Pharmacology Division at the point at which the supplementation of foods came along? I guess there had been iodine and vitamin D

supplementation, but when the war came and they began rather extensive supplementation of starches and so on, was this a kind of problem like the additive problems? Was the safety of adding the vitamins to flour...

Dr. Vos: I think that was mostly the responsibility of the Division of Nutrition. In other words, these were products which were normal contiituents and it was questioned whether adding it in a certain way was, I mean it might be better if you had whole wheat flour where all the good stuff hadn't been removed from it and then put back. You would probably be better off, because you might be losing something that you didn't know about. But, as far as I know, we never were concerned with.

Dr. Young: You did run safety tests on it?

Dr. Fitzhugh: No, we didn't.

Dr. Laug: Well, I think it's been generally conceded that all that added vitamins do is take a few bucks out of your pocket-book. They make you feel better, but that's about it.

Dr. Vos: Ed, that's not --

Dr. Laug: I'm trying to make a broad point.

Dr. Fitzhugh: Every time you get a cold, don't you take some Vitamin C?

Dr. Laug: After all, Linus Pauling became a Nobel Laureate for doing that.

Dr. Young: I'm not sure it was for doing that.

Dr. Laug: What I am saying is that sometimes I feel a little blush coming on when a good scientist steps out of his field and writes a book in which he and his wife are the subjects. Taking 15 grams of Vitamin C a day! Maybe he is in his dotage, I don't know.

Dr. Young: Well, have we gone on long enough?

Dr. Laug: This question of this flush of chemical in food, I think part of it may be a sophistication of our looking at it. I mean you take bread wrapped in wax paper. Now I'm sure that for the first 10 years of that, no one in Food and Drug gave a second thought to it, as to what the wax might do. Later we began to worry about what all the components of this wax were, whether there were any carcinogenic impurities in it, and so forth.

Dr. Young: And all kinds of containers and what migrated where . .

Dr. Laug: That's right. The can enamels, the antioxidents in the rubber that jar rings are made of. Many of these things had evolved and were used for many years before we became sophisticated enough to worry about them.

Dr. Fitzhugh: All the flavors, we had almost thousands of them -- at first we thought about the natural flavors and didn't worry about the synthetic flavors. Later all of those came under question.

Dr. Young: Which one was the substitute for vanilla that you did recognize and worry about?

Dr. Voss: Coumarin.

Dr. Young: Now that is an example of an early one whose danger made itself evident. Was that not right?

Dr. Fitzhugh: Yes, we could have tested some of the others and they would have probably given the same results.

Dr. Vos: Was the coumarin -- was the problem discovered by us or by industry?

Dr. Fitzhugh: Industry. But we had some of the others.

Dr. Young: So, what you just said, is that also there came to be a heightened level of awareness. And that's what you were saying too.

Dr. Vos: That's part of it, certainly. I wouldn't deny the fact that there was a flush of chemicals.

Dr. Young: Why was there the heightened level of awareness? A few bad examples that caused people to suddenly say, well we've got to look at the rest of them?

Dr. Laug: I don't think so.

Dr. Vos: I think the improved analytical techniques. You couldn't have had it without that.

Dr. Young: It came before a revival of literate consumerism. All of this was a decade and more before Naderism.

Mr. Lofsvold: Wasn't there, though, some public outcry in the press and elsewhere? Something about these strange names that were suddenly appearing on labels when these prepared foods began to hit the market in the '50s? Everybody was used to sodium benzoate and sulfur dioxide.

Dr. Vos: You had to declare only the preservatives, wasn't that all you had to declare?

Mr. Lofsvold: No, you had to declare the preservatives by name, I think.

Dr. Young: That's something to look for in the press.

Mr. Lofsvold: It seems to me that what generated the Delaney select committee was some public interest in the numbers of all these things that all of a sudden were looming up and had not been seen before.

Dr. Young: I've heard it said, and I'm not sure this is true, that the Delaney Clause came mainly because of pressure from the National Health Federation. I thought of that because this was a sort of revival of the natural foods theory which, in some measure at least, went on back in our history. All those chemical names were in contrast to the natural foods that were a sort of ideal that had come on down from Sylvester Graham's day and had a revival under Bernard McFadden and other revivals. This could have been related to that somehow. I think that is something that might be looked in to.

Mr. Lofsvold: Well, I wasn't thinking so much of the Delaney clause which, if I remember correctly, came at the last minute after the hearings had been concluded. I was thinking of the idea of that there was a need for this subject to be explored by the Congress.

Dr. Young: Well, that could be true. But it is true that then, and it continues to be true, complex long chemical names which are incomprehensible produced a sort of anxiety. And it's part of the tussle. There might have been somebody in this period of time who suddenly saw that list and said, "What are we eating?" It's something to check. I'm glad to have it here. I just hope that recalling these days has been a worthy plus to warrant the energy you have expended here in talking with us for our benefit.

Dr. Laug: Well, I'm highly enthusiastic because I always thought that the Food and Drug was really hiding its light under a bushel. When we were working, I guess we didn't feel that way about it. But, since I've retired, I see in the papers where the Food and Drug is being castigated almost every day over something. And anything that can be done to bring out our efforts I think is good. It's not only for us oldsters, but it's for the young fellows that are working there now. It may help make their tenure a little bit more--

Dr. Fitzhugh: Someone should do something if they don't.

Dr. Laug: You know that's the climate now. Look at what they are doing to the Federal Trade Commission, they're berating the hell out of it. Pretty soon there won't be any. That seems to be the philosophy in Congress now.

Dr. Porter: Well, you know I think one reason we're doing this is because the younger people in the organization -- that's really all they see, and they don't -- they're no longer aware of this background of the kind of things that you men did.

Dr. Laug: And it must be dreadful to their morale.

Mr. Porter: We want them to know that. That they are a member of an organization that is very significant and this is really one of the many reasons why we're doing this.

Dr. Young: You had a sense of mission and a pride in a mission and a sense of fruition from what you were accomplishing. And this is perfectly apparent in all the interviews we have, no matter whether they be scientists or inspectors or the administrators in the offices.

Mr. Porter: We found that there is an interest and curiosity. Fred and I found that out in Denver just last month. They asked us to talk at a district conference. So we sat at the table; we made a little outline and kind of traded off stories on how it used to be and things that had been accomplished. It was kind of a mixture of different ways of looking at the past. And they were enthusiastic. I believe nearly everybody in the district at one time or another during the following

two or three days dropped by and said how much they enjoyed it.

Dr. Young: It's apparent from the meeting this morning that the Agency wishes to make the public aware of the positive side of what's happened in connection with the 75th anniversary, which gives an occasion.

Dr. Fitzhugh: I feel like there are lots of young fellows probably in the Food and Drug Administration now who could accomplish a lot more if the morale was better or if their situation was better, if they were working under different conditions. There's a different management. Some of the younger fellows tell me that well, we can't tell if anything is good, we have to always tell them the bad. Then we have our say. They don't object when we tell them it's bad, toxic. They don't turn us down. But when we say it's OK, they turn us down and say they must have someone else look at it again. That's bad for morale. I hope we've said some of the right things.

Mr. Porter: Well, I want to thank everybody and this is the end of the tape.

Vos, Fitzhugh, Laug, Woodard

ATTACHMENT I

Edwin Peuckert Laug

November 9, 1965

Born: Philadelphia, Pennsylvania, October 4, 1902

A. Education:

(1)	Haverford College	B.A.	1925, Chemistry
(2)	Haverford College	M.A.	1926, Chemistry
(3)	University of Pennsylvania	Ph.D.	1930, Physiological Chemistry

B. Professional Experience:

(1) Teaching

(a) Laboratory Assistant: Chemistry, Haverford College, 1926.

(b) Laboratory Assistant and Instructor: Physiological Chemistry, University of Pennsylvania Medical School 1926-1930.

(c) Instructor: Physiology, University of Pennsylvania Medical School 1930-1933.

(2) Research

(a) Biochemist, Physiologist: University of Pennsylvania Medical School 1930-1933, 1933-1934.

(b) Chemist: Marine Biological Laboratory, Woods Hole, Mass. Summers 1932, 1933, 1934, 1935.

(c) Fellow in Nutrition: University of Tennessee Medical School, Memphis, Tennessee, 1933-1934.

(d) Pharmacologist: Division of Pharmacology, Food and Drug Administration, 1935 to date.

(3) Administrative and Supervisory

(a) Chief, Physiochemistry Branch, Division of Pharmacology, Food and Drug Administration, 1951-1960.

(b) Chief, Radioactivity Branch, Division of Pharmacology, Bureau of Physical and Biological Science, 1960-1964.

(c) Chief, Special Investigations Branch, Division of Pharmacology, Bureau of Scientific Research, Food and Drug Administration, 1964 to date.

C. Professional Societies:

(1) Membership

(a) American Society of Biological Chemists.

(b) American Society for Pharmacology and Experimental Therapeutics.

(c) Society for Experimental Biology and Medicine.

(2) Posts Held

(a) Chairman, National Membership Committee, Society for Experimental Biology and Medicine.

(b) Chairman, D. C. Chapter, Society for Experimental Biology and Medicine.

Vos, Fitzhugh, Laug, Woodard

D. Standing Committees:
Member, representing the Food and Drug Administration on the Working Group, Federal Radiation Council, 1959 to date.

E. Superior Service Award 1956:
For the conduct of tests to determine the effect of nuclear explosions on drugs.

F. Administrative and Advisory Responsibilities:

(1) The Radioactivity Branch was set up with a complement of 7 professionals and one subprofessional in 1960. At the time when the Bureau of Physical and Biological Science was reorganized, the branch contained 14 professionals, 2 clerical and 2 subprofessional personnel. The Scientific disciplines represented were: Pharmacology, Biochemistry, Chemistry, Physics and Electronic Engineering. The grade structure was as follows: GS-15 (1), GS-14 (1), GS-13 (2), GS-12 (4), GS-11 (1), GS-9 (2), GS-7 (1), GS-5 (2).

(2) In the reorganization of the Bureau of Scientific Research 1964 a new branch, the Special Investigations Branch was created in the Division of Pharmacology. This branch still contains the personnel and expertise of the old Radioactivity Branch and continues to exercise some of its responsibilities. However, the new branch has changed its posture and direction and considerably broadened its research base. The complement of personnel is now 36. The grades and number of individuals in each scientific disciplines are as follows:

Pharmacologist:	GS-15, (1);	GS-13, (1);	GS-9, (2).	
Biochemist:	GS-14, (1);	GS-13, (1);	GS-12 (1).	
Physiologist:	GS-11, (1).			
Veterinarian:	GS-11, (1).			
Chemist:	GS-13, (2);	GS-12, (3);	GS-11 (4);	
	GS-9, (5);	GS-7, (2).		
Physicist:	GS-14, (1).			
Electronic Engineer:	GS-12, (1).			
Biological Technician:	GS-5, (1);	GS-4, (3);	GS-3, (1).	
Clerical:	GS-6, (1);	GS-4, (1).		
Subprofessional:	(2).			

Vos, Fitzhugh, Laug, Woodard

Edwin P. Laug November 9, 1965

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A. Period 1930 to 1935 antedating career with the Food & Drug Administrati

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(568) 4. Observations on Lactic Acid, Total CO_2, and pH of Venous Blood During Recovery from Severe Exercise
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(566) 6. A Reinvestigation of the Phenomenon of a First Acid Change in Whole Blood
Edwin P. Laug
J. Biol. Chem., 106:161-171 1934

(565) 7. Some Observations on the Nature of the Reducing Substances in Normal Dog Urine
Edwin P. Laug and Thomas P. Nash, Jr., with technical assistance of Louise A. Garavelli
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Edwin P. Laug and Thomas P. Nash, Jr., with technical assistance of Louise A. Garavelli
J. Nutrition, 10:81-92 1935

(563) 9. A Study of the Availability of Bread Carbohydrates
Edwin P. Laug, Louise A. Garavelli, and Thomas P. Nash, Jr.
Cereal Chemistry, 12:356-364 1935

(562) 10. The Excretion of Bromide Iodide and Thiocyanate by the Perfused Frog Kidney
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13. The Influence of pH Upon the Elimination of Hemoglobin by the Perfused Frog's Kidney
M. Dorothy Webster, Frank L. Engel, Edwin P. Laug and William R. Amberson
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B. Period 1935 to date (career with the Food & Drug Administration

(548) 14. An Improved Glass Metabolism Cage for Small Animals
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(547) 15. Application of the Dithizone Method to the Determination of Lead In Biological Materials
Edwin P. Laug
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(546) 16. The Effect of Lead on Rats Fed Diets Containing Lead Arsenate and Lead Acetate
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MONTH	VOL.	PAGE	ARTICLES
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Dec. 1960	I	49	Sr-90 Content of Animal Fodders.
Jan. 1961	II	18	Food, Other Than Milk - Survey of Radioactivity in Food.
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Aug. 1962	III	270 390	Sr-90 in Raw Foods. Survey of Radioactivity in Animal Feeds.
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Jan. 1963	IV	18	Teen-Ager Diet Survey May 1961 - August 1962.
Feb. 1963	IV	81	Cs-137 and Sr-90 in Foods (1960-1962).
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April 1964	V	181	Radionuclides in Diets for Teenagers May 1962 - Nov. 1963.
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MONTH	VOL.	PAGE	ARTICLES
Nov. 1964	V	547	Strontium-90 Content of Human Food and Animal Feed in 1962 and 1963.
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(a) Preliminary Report - ITR 1163 (Classified)
(b) Preliminary Report - ITR 1159
(c) Final Reports
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2. Effects of Nuclear Explosions on Canned Foods-WT 1212.
3. The Effects of Nuclear Explosions on Commercially Packaged Beverages-WT 1213.
4. The Effect of Nuclear Explosions on Meat and Meat Products-WT 1216.
5. The Effect of Nuclear Explosions on Semi-perishable Foods and Food Packaging-WT 1214.
6. Effects of Nuclear Explosions on Frozen Foods-WT 1215.
(d) Summary Report - WT 1222

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