HISTORY OF THE U.S. FOOD AND DRUG ADMINISTRATION

Interview between:
Dr. Lloyd C. Miller
Former FDA Pharmacologist
and
Fred L. Lofsvold
Escondido, California
January 27, 1981

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.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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TAPE INDEX SHEET

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GENERAL TOPIC OF INTERVIEW: History of the Food and Drug Administration

DATE: January 27, 1981 PLACE: Escondido, California LENGTH: 147 minutes

INTERVIEWEE	INTERVIEWER
NAME: Dr. Lloyd C. Miller	NAME: Fred L. Lofsvold
ADDRESS: [redacted]	ADDRESS: U. S. Food & Drug Admin.
[redacted]	Denver, Colorado

FDA SERVICE DATES: FROM 1935 TO: 1943 RETIRED? Yes

TITLE: Pharmacologist
(If retired, title of last FDA position)

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Attachment - Excerpt from paper "The Nature of Compendial Standards" by Lloyd C. Miller. Published in "The Physiological Equivalence of Dosage Forms" by Department of National Health and Welfare, Ottawa, Canada 1969. Excerpt describes demonstration of bio-assay for digitalis in courtroom during trial of Yates Chemical Company case.

Attachment - Dr. Miller's comments on transcript of oral history interview with other retired FDA pharmacologists conducted on June 20, 1980.

This is a recording in the FDA's Oral History Project. We are recording today Dr. Lloyd C. Miller at his home in Escondido, California. The date is Jan. 27, 1981. My name is Fred Lofsvold.

FL: Dr. Miller would you briefly outline your academic training and your professional career?

LM: To begin with, I'm the product of California education; Pomona College, with a major in Chemistry and Mathematics, in 1929. That fall I entered the University of Rochester School of Medicine and Dentistry for graduate study towards a PhD in Biochemistry. I had an appointment as an assistant in Pharmacology. The latter resulted in my coming out with sort of a dual capability in both Biochemistry and Pharmacology, the advantages of which were apparent later. From Rochester I went on a research fellowship at the Upjohn Company, where I worked on reproductive hormones. In the spring of 1935, I learned of openings at Food and Drug and was interviewed by Dr. Erwin Nelson, who was the prospective head of the new Division of Pharmacology, which he was organizing. Very shortly after that I received notice of the Civil Service appointment and reported for duty on July 1, 1935. For reasons that were never clear to me, I was assigned to the Bioassay Program, which was part of the regulatory program to check on the potency of such drugs as epinephrine, posterior

pituitary, digitalis, ergot and aconite. At the same time, the Division was tooling up under Dr. Herbert O. Calvery for research on the toxicity of spray residues, particularly lead and arsenic, effluents (from apples, pears and cherries). I think there were four, perhaps half-a-dozen, hired to come in on the first of July, and the others came in during the next two or three months. About half of us were on the regulatory side--myself and Dr. Jack Curtis, who had just come down from Yale, where he had spent a year on a National Research Council Fellowship. He was a product of the St. Louis University group under Professor Edward Doisy. He was assigned to work on estrogens and the other reproductive hormones. Actually, I had just spent two years working in that field, but Jack had the Research Council experience and he took over the testing of products of that sort.

As it turned out, it was very fortunate from my standpoint that I got into a field in which I had had no experience; it didn't take long to make myself at home, and my particular responsibility was the assay of posterior pituitary. I was in association, at that time, with a man by the name of W. T. McCloskey, who had been the nominal head of that unit for perhaps 10 years.

I should start by saying that the Washington laboratory maintained the only biological testing facilities in the whole Administration. The samples were collected all over the

country according to a schedule, as you probably remember very well. Every year we would ask for about 30 samples each of epinephrine and of digitalis per month; the inspectors around the country would try to collect them. Well, enough were coming in so that we'd run epinephrine about once a week, and pituitary at least twice. We only could test ergot perhaps once a week since there was a limit on how often we could reuse the roosters; they were the only animals I used over and over. Dr. Curtis raised his own rats and used the young females weekly for several months.

Posterior pituitary, a solution made from the dried, defatted pituitary glands of cattle, was then assayed by means of a procedure, the official USP assay, that had actually been developed by McCloskey himself as an assistant to a Dr. M. I. Smith at what was then the Public Health Service. So Mac had a lot of experience with the method and he taught me all he knew. The method depended on removing the uterus from a young guinea pig, suspending it in a saline solution so that when any contraction of the muscle fibers (which resulted from adding the posterior pituitary to the saline) was recorded as movement of the tip of a lever as a tracing in the soot on a smoked drum. The method was capricious, time-consuming and not very accurate.

At the same time, Mac taught me another procedure that was truly equally exasperating; it was the biological assay

for ergot. It depended on the use of Leghorn cockerels, because they had a large single comb. When injected with active ergot, the vessels in the comb would constrict and, of course, constricted blood gets blue, which made the comb visibly blue. A large dose of ergot would make the whole comb blue; a smaller dose would result in only partial bluing. Thus, the effect provided a means for judging the potency of ergot. The standard we used was crystalline ergotoxine ethane sulfonate, which is perhaps immaterial to the history that you are interested in. In any event, the procedure involved taking the group of roosters, 6 or 8, injecting some of them with a known dose of the standard. Then, of course, the rest of the roosters were injected with the preparation under test. An hour later, as I recall, we looked at the roosters and judged from the amount of blueness that the combs showed the potency of the test preparation. These results, of course, were highly subjective, and we would end up with only a record in a notebook of what we had observed. Anticipating the possible necessity for testifying in court, it seemed to be important that we get something more tangible, such as photographs of the roosters' combs. Let's see, this had to be back in 1936, prior to the availability of color films. Being a photographic buff I used my own equipment in trying to get a record of the "blueness", as opposed to the redness of the unaffected normal part of the comb. Well, we worked on it, I guess, a

year or so without ever getting results we felt that we could go into court with. Well, to wind up the ergot story, we were fortunate that about that time, a former Food and Drug man by the name of Dr. Marvin Thompson, who had gone to the University of Maryland, succeeded in isolating the water soluble ergot alkaloids. He and others developed a very good colorimetric test, depending on a beautiful blue color that could be developed by a chemical reaction with the ergot alkaloids. Along with work being done by someone in the AOAC, we came out about 1939 with a respectable chemical method for ergot that let us get rid of the roosters. I can assure you we were very grateful for that.

The third line of research that we were working on at that time was the assay of epinephrine, better known as adrenaline, the hormone that the body puts out in times of stress and fear. The test animal for the official (U.S. Pharmacolocia) assay, was a dog. The procedure called for anesthetizing the dog, setting it up to record blood pressure, and then injecting alternatively, at not more than 5-minute intervals, a dose of the USP standard, and doses of one or more of the various test preparations to be assayed with the object of matching the blood pressure increases. When equal responses were observed, we concluded that the dose given of the preparation must have contained the amount of epinephrine in the known dose of the standard.

Actually epinephrine was a pretty stable product and we were having very little trouble with it. This was certainly not the case with ergot. Indeed, there was supposed to be a lot of bad ergot on the market as the result of an incident some two years earlier. This led to a hearing in Congress into the allegation made by a man named Rusby, a Professor of Pharmacognosy at one of the New York Schools of Pharmacy. He claimed, as I recall now, that a Mr. Armbruster had tried to corner the market in ergot, and like all such efforts the maneuver had failed because somebody figured out how to get around it. Professor Rusby alleged that the Food and Drug Administration was allowing the importation of poor ergot when he, Professor Rusby, not Armbruster, had all of the good ergot cornered. McCloskey was involved in that. Actually, I don't think the FDA came out with the hearings with very much to its credit. The record didn't make them look very good, let's say, which doubtless was a reason for creating the new Division of Pharamacology in 1935. But ergot was still a problem, mainly because the assay method was so bad.

Well, to get back to epinephrine, the method using the dogs was working well and perhaps once a week we would run through all the samples that had come from the stations.

The other large program we had going was digitalis. The samples were coming in in the form of tinctures and tablets, and, of course, the imports, all of which were held pending

release from our laboratory. We gave imports priority because we felt that if we were controlling the quality of the drug as it came into the country, particularly the ones where we were depending on imports, we had a lot better chance of controlling the quality that was going out in the market. This was done under an arrangement with the Customs officials whereby samples were submitted to FDA of all drugs arriving at US ports. In the 30's and 40's, these were mostly crude drugs such as dried digitalis leaf, aconite root, and ergot. The samples were examined physically by pharmacognocists to confirm their identity, microsopically for filth, chemically for moisture content and pharmacologically for potency.

Digitalis was then being assayed on frogs by a procedure that involved injecting them at a given time and allowing 60 minutes for the drug to act, followed by opening the frog to see what effect there had been, if any, on its heart. If the digitalis was potent or, as in the case of the standard of which we knew the strength, the heart would be stopped in about half of the frogs. The difference reflected natural variation in individual frogs. This test was pretty routine, but any time that I could schedule outside work on the regular samples, I devoted to research on possible improvements. Dr. Calvery gave me that responsibility; it was a challenge and very interesting.

Fortunately, we made good progress on the assay of digitalis and soon a number of other laboratories were

involved, partly because we lacked confidence that the potency observed on tests on frogs would be the same as seen by doctors on their patients. If there was bad digitalis on the market, pharmaceutical manufacturers were just as concerned with removing it as Food and Drug was. One thing we needed to know was the rate of deterioration. There was a lot of conflicting information as a result of the use of the rather inadequate methods. So one of the things that we looked into first was a report that if one allowed the injected digitalis to act upon the frogs overnight, the next day they would be either dead or alive. Death, of course, was assumed to have been the result of heart stoppage. But with a less-than-lethal dose, some of the frogs would be alive. It is much easier to count dead frogs than to decide, in a frog examined one hour after having been given digitalis, whether its heart had stopped. Sometimes, just about the end of a one-minute observation period, the heart would decide to beat again. Obviously that was a negative reaction. We clearly needed a better method.

In the course of this work, we were encountering what we called actionable samples, usually those of low potency. Any such report was always backed up by another analyst. Dr. Herbert Braun joined the staff in 1936, the year after I came in. He and I worked very closely together on the digitalis assay duplicating testing where necessary. McCloskey and I corroborated on the pituitary assay and we more or less took

turns on the epinephrine assay. We never got any results on ergot in which we had confidence enough ~~ergot~~ to take any action.

Perhaps I should preface these remarks by saying that when the original Division of Pharmacology was organized, those of us who came in were told that the Food and Drug had a very unenviable record with respect to defending its findings of biological assays. I think they'd had 5 trials and had lost every one of them. FDA witnesses just simply had not been able to persuade the courts that their findings were right and that those of the firms wrong. So it became quite fashionable always to go to court when Food and Drug came up with a citation based on a biological assay. Mr. Campbell made it clear that he expected us, as newcomers, to change this situation. Well, the first case that the new people had been involved in, we won. We had at least stemmed the tide.

Our first court case involved a high potency pituitary solution and led to the citing of Sharp and Dohme of Philadelphia. By about 1938 we were preparing to go to court, as witnesses, to present the evidence we had obtained in the laboratory. The case, of course, had been turned over to the Justice Department and involved a sample of posterior pituitary that we at Food and Drug alleged to be at least 150%; this was 50% over USP intended strength, but only 30% over the USP upper limit of 120%. Sharp and Dohme analysts testified at the trial that they had found it about 125%; this, they

said, was only just a little bit above the upper limit of 120, and implied that they should be commended for putting out a product that fully measured up to standard. The trial lasted the better part of two weeks. It ended up with the judge calling Mr. A. G. Murray, who was on hand with Dr. Klumpp for Food and Drug as well as the Assistant District Attorney, and the Sharp and Dohme attorneys to the bench and saying, "Look, we've got a difference of opinion here of two groups of analysts, both of whom, I'm sure, are telling the truth. I can't decide on the basis of the evidence which one is the nearest to the true strength of this product. Why don't the two of you take this sample, go to one laboratory (Food and Drug or Sharp and Dohme) long enough to get a good assay, then go down to the other laboratory -- whatever order you decide upon, and test this sample, further, together. Then you come back to me and report on what you found." This was the choice Mr. Murray and Dr. Klumpp faced and they had to agree to it. It scared me because I -- not that I lacked confidence in our result -- knew that this procedure was just very tricky. But we all agreed to do it and in the course of the next two weeks we got all set up. We first went up to the Sharp and Dohme laboratories and, in a relaxed atmosphere, we all checked the necessary solutions, checked the apparatus to make sure all conformed exactly to what the USP required. I may say that what I learned then stood me in good stead later in writing USP directions.

We ran, I think, three assays that we agreed upon. It took us two weeks or better to do it. So having gotten that, we all came down to Food and Drug and we went through the same thing again. We got another three satisfactory assays and we averaged the six results. As I recall, it was about 140%, clearly higher than the 125% that Sharp and Dohme had claimed, and not quite the 150% that we had claimed. So we went back to the Court. The Judge said, "Well, we accept that. I find Sharp and Dohme guilty of having shipped posterior pituitary that was too strong." What the penalty was, I don't recall, but FDA had won its first case based upon data obtained by biological assay.

Sharp and Dohme had gone to court to protect its reputation, of course. That was always the case. The fine, whatever it was in those days, didn't matter and the firm decided against appealing the decision.

Our next case involved the Yates Chemical Company, a small firm in New York City, that had shipped a tincture of digitalis that we found to be very close to 50%. We checked it and checked it. Yates decided to fight, promising to show that we were wrong.

To begin with, the assay wasn't very good but the main thing that they hoped would win their case was the claim that the USP Digitalis Reference Standard was questionable. We readily agreed to that because we had published the main data

indicating that the standard actually was stronger than it was supposed to be. Well, we went to trial and I've written an account of it to which you can refer.

FL: Yes, I have a copy of the reprint and I will make it an appendix to this recording.

LM: What the reprint describes is what passed for a biological assay in the Court, but actually was only a scaled-down demonstration. However, the Judge thought it was an assay, and since it came out better than it had ever come out in any of the many trials we had had before, the Judge had no problem at all in finding the Yates Company guilty of shipping subpotent digitalis. So, FDA then had a second victory.

As I recall, the next time we were hauled into court was in the Summer of 1941. In any event, the Buffalo Pharmacal Company was involved and the trial was held in Rochester. The product was digitalis tablets, and again we had found quite low potency, namely 50% of labeled strength. In the course of preparing for the case, I was contacted by Professor Clifford Chapman who was a close friend both professionally and socially. He was at the University of Maryland School of Pharmacy, and we had collaborated for a long while on the digitalis assay. He was one of those who had demonstrated that the overnight assay was perhaps more reliable than the USP one-hour procedure. Buffalo Pharmacal had approached him to test its product. He called me up and said, "What goes on

here? I'm finding about 80%, in fact, maybe a little better than 80%. I don't think you would go to court on the basis of an 80% finding." I said, "Well, you've been with the Food and Drug Directorate of Canada, and you know that the rules up there are pretty much the same as down here. I can't say that we wouldn't go to court on the basis of 80%, but I can assure you that we found the product very much lower than that." He replied, "I just don't believe our two laboratories would differ that much. Let's trade samples." So I sent him some of the official sample that we had, and he sent me some that he had. We each found what the other had found on the respective samples. That is, he checked our 50%; I checked his 80%. I became suspicious that we didn't have the same sample. So I took some of both of them over to our Microanalytical Lab, and asked them to look at them under the microscope. To begin with, the samples didn't seem to have the same color. Then under the microscope, sure enough, there was a lot of starch filler in the tablet that I found to be 50%. There was apparently no starch at all in the sample that Dr. Chapman had been asked to test. This was something very interesting, I can tell you. Obviously, the firm was going to argue that they were marketing a product that was practically all right on the basis of tests that they were going to have Dr. Chapman testify to. At the moment I can't recall whether I reported back to Dr. Chapman our findings about the physical

examinations. After all, there was a certain amount of questionable propriety involved in exchanging samples. We may have overstepped the bounds a little bit theoretically, already.

Anyway, the case came to trial and I remember it very well. It was in the middle of the summer, and it happened that I had just gotten out here to California on vacation expecting to have three weeks of leave, when I got a telegram from my Chief, Dr. Calvery, saying that I was needed in Buffalo the 5th of July, let's say, and I was wanted there the 3rd or the 4th to talk to the attorneys ahead of time. I called Dr. Calvery to beg a few days' extension but he explained that he knew I'd just gotten to California, but I was on leave at the pleasure of the government. So I paid my own way back to Buffalo, arriving in a sweltering hot spell, in the days before air conditioning. We met with the U.S. District Attorney on the 4th of July. It was to be a jury trial, my first experience with a jury. The defense attorney, it turned out when we got into court, was the kind that depended upon bullying the witness, being the type who was more at home in the police court. Anyway, he bullragged me throughout my testimony. All the time I had in mind that I was going to testify eventually that the FDA sample and that given Dr. Chapman were different. I had also brought along a little bit of a solution of iodine I expected to apply to a tablet from the FDA

sample containing the starch, expecting it would turn blue. That would contrast to applying iodine to a tablet from the Chapman sample which had no starch and hence would not turn blue. Through, I recall, a day and a half of testimony, I tried to maintain our position. We had agreed not to introduce this starch test evidence until after Dr. Chapman had testified. The Buffalo Pharmacal attorney, tried to establish the credibililty of Dr. Chapman through me. "You know Dr. Chapman?", he asked me. I replied "Yes". His next question: "He's one of the world's finest biological assayists, is he not?" I was not going to fall into that trap so I said, "No." But I hesitated somewhat. After all, Cliff was a good friend of mine and I didn't want to insult him, but I wasn't going to build up their case. As soon as I started to say "No", their attorney turned away from the bench and started back to his table. But when my "No" was drawn out, as if to show some doubt, he whirled around and said, "What do you mean, is Dr. Chapman one of the world's outstanding experts in biological assay?" Well, I knew it worked fine once, so I tried it again answering with slightly more exaggeration. That time the attorney definitely reacted and he asked me a third time. So I made my "No" even longer the third time. The attorney turned to the Judge saying, "Your Honor, this witness says 'no', but he sounds like he means 'yes'." By that time, the whole courtroom was tittering--the jury included--so the Judge

said, "Court is recessed for five minutes or so." As I recall, the courtroom there was on the upper floor of a building that had an hugh open space from ground floor to roof. We all walked out into this thing, and you could hear on all sides, "Noooo, noooo."

When I got back to Washington and reported the incident to Mr. Campbell, he bawled me out, saying, "You weren't respectful; you shouldn't have done that." Well, I can't quarrel with success, but I never tried that again.

We did win the case, and the verdict brought out two very interesting points. The president of the firm was named Dotterweich, and he had a long history (by that I mean 3 or 4 times) of having been found guilty of a Food and Drug violation. He had dissolved his firm and started up a new one. So he never had a second violation, you see. The District Attorney and the Food and Drug Administration decided to fix his wagon. They charged him personally; (it was a rare thing in those days to charge an officer of the firm for anything). Mr. Dotterweich took the stand, and the District Attorney attempted to pin him down. This exchange took place: "Well now, if you were in charge, were you not responsible for the quality of these tablets?" Answer: "Well, I'm not sure." "Well, why, were you not in charge?" "Well, I went out to lunch." "Was somebody else in charge when you went out to lunch?" "No, no, nobody else was in charge."

And he went on with evasive testimony of that kind, which of course was quite unconvincing to the jury which came back with a very anomalous verdict. The Company was not guilty of having shipped this substandard digitalis, but the President was.

And the firm asked how could that be and appealed on the basis of that anomaly up to the U.S. Supreme Court. This was the only case that I was ever involved in which was so appealed. The Supreme Court found that our Courts depend upon the jury system. And the jury may come back with some very strange decisions sometimes, but we're bound to accept them. That was the end of the Dotterweich case. There was another fine point or two with result that U.S. vs. Dotterweich has been cited many times for whatever legal point it was that was settled by the Supreme Court. Actually, the FDA victory was much less a matter of our having strong, clear-cut biological evidence, as it was of chicanery on the part of the Defendant.

FL: Did Dr. Chapman testify in the Dotterweich case?

LM: Yes, he did. His testimony was straight forward and the District Attorney asked him only to identify carefully the samples he had received and tested. I was then recalled to the stand to apply the iodine test that clearly showed the difference in the two samples. So the jury saw immediately that there had been some switching of tablets somewhere along

the line. And, of course, Cliff was completely clear because he had testified only as to tests on what he had been sent.

During the next several years we were carrying out research on the digitalis assay and we published a number of papers. I never published anything on posterior pituitary except a short note on an apparatus that I developed to facilitate the assay somewhat.

We were also, at that time, checking on samples of parathyroid extract. That work was done on dogs we kept in building which had been once used as an engine testing facility on land now occupied by the Pentagon. There was no room for dogs in the FDA space in the Agriculture Building then. The question involved, "What is the dose-response relationship?" It was not called for in the USP assay (which was considered too costly as it was). I worked out the relationship and published it. I also published 2 or 3 papers on ergot; nothing important.

Our most significant work was on digitalis. With the help of a biometrician by the name of Chester I. Bliss, who came in as a consultant, at my request, we applied new statistical procedures to the data obtained in digitalis assays. It enabled us to choose between two competing methods, specifically, the one-hour versus the overnight method. It settled a controversy that had been going on for years between those in the U.S. who favored the shorter (one-hour) USP method and

those including Dr. Chapman at the University of Maryland and others in Ottawa, Canada. The latter all felt that they obtained much better results with the overnight procedure than we were getting with the one-hour assay, which the USP then required and was more popular, partly because it was quicker. Well, with the procedure that Dr. Bliss helped me work out, we clearly showed that the overnight assay was better. So, that method was adopted in the next edition of USP.

However, the controversy did not end there. Just about that time another argument erupted over using frogs and using cats. The so-called cat method was considered better by Dr. Gold, a well known heart specialist in New York. Dr. Gold had testified to that effect in the Yates trial, but the judge ruled that it was irrelevant because the USP set forth the procedure that we were all supposed to use, and that was that. At the end of the trail he said, "I've seen the procedure work right before my eyes and demonstrated that the Yates' product was low and therefore that is my decision." For that work on digitalis, I received the Ebert Medal in 1940, then considered the most prestigious scientific award in pharmacy.

Have you interviewed anyone earlier about the work on the mosquito repellent done at FDA in 1942?

FL: No.

LM: The success with the repellent was one of the more interesting and satisfying stories that came out of the war

that Food and Drug had anything to do with. One day, we had a call from the American Medical Association in Chicago asking whether our Division had any data on the toxicity of the product being supplied our troops, as an insect repellent, that contained a high content of diethylene glycol. It was being used in huge amounts at some airbase in the state of Washington where soldiers were being trained. The mosquitos were bad but the weather was hot and very humid so the men stripped to the waist. They were just lathering this repellent on them in quantity. Someone wondered, "Is this stuff safe, at least used like that?" It turned out that the AMA knew nothing; FDA knew nothing. But we got a sample within 24 hours for testing. Dr. Draize had developed a technique of shaving the fur from the backs of rabbits and applying to small areas the substances to be tested. Thus, he applied the mosquito repellent and found that it was absorbed into the skin very quickly. All he did was put on 1 or 2 ml, rub it with a glass rod, and in a few moments the substance disappeared. Those rabbits showed bloody urine within 24 hours, and they started dying a day or two later. At autopsy, the kidneys literally looked like empty walnut shells. The insides of those kidneys were completely gone. Well, you can imagine the consternation when the word went out to stop using the product. The Army said, "You can't stop, you can't have these men working under these conditions without something to repel the mosquitos,

and nothing else seems to work. You've got to give us some substitute."

As it happened the Department of Agriculture was maintaining a mosquito colony at a facility in Florida. They were in the process of the evaluating of repellents down there, and they may actually have had a candidate or two in mind. Anyhow, they went right to work on it. They succeeded in coming up with the product that we now know as 6-12;6 parts of one thing and one of another, and two parts of a third. They had demonstrated by the end of the week that this was very good for repelling mosquitos. At FDA, toxicity tests were starting. I wasn't involved in it at all, just an interested observer. By the end of three weeks, we knew that the new formula was certainly far safer than the one then in use. At the end of six weeks the Army base in the State of Washington had some of it. From the standpoint of meeting an emergency and coming up with a good answer in a hurry, there was nothing that compared with that project. As I recall, it was a long time before anything better was found.

If you haven't talked to Dr. Draize you should inasmuch as his name is very much in the news right now because of the rabbit eye test that he developed. He came to FDA from Edgewood Arsenal, where he had been working for the Army, about 1939. He joined us after practically all of those who had been working on the spray residue problem had been shifted to

other work. Actually, Draize developed two procedures, the one involving skin application to rabbits whereby much of the back of the rabbit was shaved and divided into squares, called "patches" to which test substances were applied systematically. The patches were observed regularly for a week or more and if a reaction developed, the product that caused it was suspect. The second "Draize Test" involved dropping dilutions of the test substance into rabbits' eyes. The basis for this procedure was the current practice in beauty shops of dyeing and tinting eyebrows and eyelashes. Very often some of the dye got into the customer's eyes and severe damage sometimes resulted. When the '38 Act covered cosmetics, for the first time, nothing was known about the potential hazards of any of the products. Dr. Draize was added to the staff to set up a testing program for cosmetics.

One such product that was suspect was Roux Lash & Brow Tint that had caused a lot of injuries to patients in beauty parlors. Dr. Draize used his eye test to check on products like that. It resulted in an enormous improvement in the cosmetic industry because for the first time there was a way to eliminate the products that were real troublesome.

As to my involvement with the war effort, from the time of Pearl Harbor on . . . and I well remember Pearl Harbor Day, December 7, 1941, it was on a Sunday, and I was in the lab that afternoon, which wasn't unusual. I remember a janitor

coming around, the word had just come over the radio that Pearl Harbor has been bombed.

The work I was doing became heavier because the people that had been doing some of the regulatory work were shifted to war testing of the sort we have been talking about. I, myself, was not involved in the war research. As I remember, the hood in my lab was occasionally used to open a thio compound of some kind that was used for a war gas of some kind. Anyhow, we had a sample of it and work on it was a very hush-hush project. Often some of the product escaped outside the hood and smelled like a thio compound always does. And so they called it the SH Compound. One of the girl technicians in there said, "What does SH mean?" And some guy said, "SHSHSHSH". Dr. Lorry Grant was involved in that. He can tell you about it. Obviously, about all I knew about it was what I could smell. The work didn't come out like the mosquito repellent did.

But came the day in 1942, by which time Dr. Klumpp, who had been in as the Head of the Drug Division, was called to the AMA as Secretary of the Council on Pharmacy and Chemistry for a few months. Then he had been invited to become President of Winthrop Chemical Company. He asked me to consider joining the research staff at Rensselaer. I went for an interview but actually did not decide to make the move until July 1943. I stayed there for six years before moving on to be the head of the USP.

But let's go back to the insulin flurry. All during the time that I was working on digitalis, I'd been very, very close to the USP Revision Committee. In fact, my very first recollection of working with USP was during the first weeks at FDA I was being taught the digitalis assay in what was then the old Food and Drug Building, which was located in the center of what soon became a hugh rectangle of buildings of the present complex of the Agriculture Department. The FDA Building, I think, was on 13th Street, which was closed. The Agriculture Building thus extended between 12th and 14th, and eventually consisted of 7 parallel buildings in all. In 1935, the two end wings were already built. But for 3 weeks in July we occupied the building that was scheduled to be torn down. We looked right down on what I recall was a two-story red brick building, which was called the Olive Building. Have you every heard that story? (This is digressing again.) Back in the early '20's the olive industry in the United States suffered a very bad spell with botulism. And with all these people dying from eating olives, people were not buying them.

I wanted to talk about my worst days at Food and Drug, when we were housed in a building that had been used to the point where it was worn out, and we looked down on this brick building that was known as the Olive Building. And I did mention that the olive industry was threatened with extinction because of the botulism scare. Some smart, shrewd fellow

conceived the idea that, if he could build an olive packing factory, beside the Food and Drug Administation, he could honestly put out olives labeled, "packed under the eyes of the FDA." I don't know how long it went on, but it was at least until public confidence was restored in olives--and henceforth that place was known as the Olive Building.

FL: By that time it was no longer used?

LM: No, it was no longer used for packing olives. As a matter of fact, the Food and Drug had taken it over by then. But I was in the old building only about three weeks, until the new quarters were ready for us in the Agriculture Building. When we moved the old quarters were razed. One of the interesting things that disappeared was the water faucet at the corner of the building that was the source of water for the Bonus Army that camped near there in 1931, or whenever it was that the World War I veterans marched to get Congress to vote them a bonus. General MacArthur was called in to restore order and get them home without bloodshed. Anyway, the Food and Drug people had been there and watched the Army camped all around their office and laboratories.

The first USP crisis that I was involved in was in July, 1935, during the 3-week period prior to moving from that building. It involved Tincture of Aconite, then believed useful as a cardiac stimulant. The only known assay for potency was by use of guinea pigs.

The active principle had been crystallized. USP XI was just about to go to press, and Professor Cook came down to see Dr. Nelson about the assay. I was invited to sit in (Dr. Nelson was the chairman of the USP committee involved in biological assays) and listen to the problem. I don't remember the details, but we cleared up some obscure point with respect to the procedure which we then relayed to Professor Cook by telegram. It became part of USP XI and literally that was my first contact with the USP as a member of FDA. From then on I was always involved with USP problems in one way or another --on digitalis, pituitary, and epinephrine, sharpening up the procedures, looking for ambiguous wording and suggesting ways for eliminating it. In 1943 I left FDA to join Winthrop Labs, and at that time I succeeded Dr. Nelson as the Chairman of the Sub-committee on Biologic Assays, a post I held until I became USP Director of Revision in 1950.

To get back to the insulin story. Insulin had been marketed from the time it was first developed for use in the mid '20s under a very practical and workable arrangement dictated by the patents that were held by the Connaught Laboratories in Canada. Connaught licensed Eli Lilly and Company and others including Squibb, Armour, and Burroughs-Wellcome. By 1941 the basic patents were running out. There was a threat on the horizon that substandard insulin would be offer for import.

Professor Cook recognized it, but because insulin was a patented product it had never been in the USP. This reflected a long-standing USP policy not to recognize and provide standards for patented products. The belief was that there was no real reason to include them since generally there was only one producer. So this all blew up in the fall of 1941, as I recall. No one had any clear idea as to what to do, except that it was agreed that there had to be an amendment to the Food and Drugs Act to take care of it. In any event, Dr. Calvery undertook to work with the USP through the Food and Drug with the idea that the United States Pharmacopeia would recognize insulin. This would provide monographs, with standards and assays to enable Food and Drug to control potency and quality. We worked literally every day and way into the night, and some nights all night on the problem for three or four weeks. The insulin amendment went through soon afterwards concurrently with USP recognition of insulin. I was deeply involved because standarization was dependent upon biological assay. We got Dr. Bliss to come down to help on the assay. We were working closely with the manufacturers and yet they didn't trust the FDA because they didn't trust the government. They weren't sure they wanted to trust the USP, but they did feel, I'm sure, that they could, quote, unquote, "manipulate" Dr. Cook with much greater certainty than they could do anything with Mr. Campbell or Dr. Calvery, as far as FDA was concerned.

So the end result was that the Insulin Amendment provided that the USP should provide the standards and the tests for insulin products. But the FDA should have the usual authority, plus certification, which was something new.

The regulations provided for a novel arrangement for obtaining the data required for certification. As I recall, concurring data had to be submitted from two separate laboratories, that is, from any laboratory maintained by one of the several manufacturers and from the Insulin Laboratory of the University of Toronto, which was independent of, but closely associated with Connaught Laboratories.

FDA was to set up its own testing laboratory and had the choice of certifying the insulin on (a) the results from the two outside labs or (b) of supplementing the submitted data with assays of its own.

A result from any two laboratories could be the basis for certification, provided that the standards were met. That was the compromise that we worked out. As I say, I was deeply involved with Calvery in working on all these things, and I still remember, I sort of half expected, very honestly, that Calvery would ask me to head the new laboratory, because I had been the only one involved working on the details. But for reasons that he had which he never explained to me--I remember his calling me in and saying "Lloyd I don't know who of our people to ask, but I know I'm not going to ask you." I said,

"OK". I never did know his reasons. But within a day or two he decided on Dr. Lorry Grant. And so Grant, who actually hadn't been involved in all this prior to that time, started setting up the unit and learning the procedure and from then on he was the insulin Czar until the time he retired. I went back to the things that I had been doing and that's how Food and Drug got into the insulin business.

An important point which I overlooked was that this batch control was really a continuation of what Connaught had exercised. They had started the two-laboratory approach. As the licensor of the patents they insisted on testing every batch which they certified and taking into account, of course, the results from the laboratory of the licensee. So there was a two-laboratory control in existence prior to the expiration of the patents. And really that's what was being continued under the Insulin Amendments and the regs that came out from FDA under the Amendments.

An important difference between certification of insulin and that of the antibiotics was that the latter had been instituted as a wartime exigency measure in order to expedite production and get the Armed Forces the antibiotics they needed. As a curious coincidence, I was involved in the Winthrop antibiotics program. I had just shown up up there, and I was put in charge of releasing penicillin for the military at Winthrop for several months. When the war was over,

FDA went to Congress for an extension of what had been done under a wartime basis, and the resulting Antibiotic Amendment, I think, only covered about five antibiotics: bacitracin, which is no longer used, penicillin, streptomycin, which had come out by then, and perhaps two others. I guess aureomycin was the fourth.

The big difference was that FDA was given the authority for writing the regulations, setting the standards and the USP was out of the picture. I appeared before Congress arguing at the Sub-committees hearings for continuation of the program similar to that of insulin. Pfizer supported me, but all of the rest of the manufacturers felt that they were quite happy then with the government proposal. That's quite another story and that is worth telling although it is part of public record.

The reason that industry was happy with the FDA arrangement was that they had Henry Welch, who was the Czar of antibiotics in the palm of their hand, literally. He established a journal in which the results of research showing the properties and benefits of an antibiotic were published prior to its being certified. In fact, Henry then used those articles as a basis for FDA certification. Henry was getting the regular FDA salary, which in those days wasn't very much, but at the same time Henry was being called to Geneva to advise WHO on tests and standards for antibiotics on the international

scale. Henry was once a semi-pro baseball catcher, a really tough guy. He had the indiscretion to boast in Geneva that, "the salary that I get from FDA just pays my income taxes. I get the rest of my income in other ways." The principal way he got income was in the sale of reprints from this journal that he had set up to the antibiotic firms. I heard one of the representatives of one those firms say, "I think that we are going to have to build a warehouse to store these reprints that we buying from Henry, because we are not getting rid of them." Henry collected thousands of dollars for those reprints. Yet, he was telling George Larrick that he was getting only a "modest honorarium" as editor of his journal. That went on for several years, until finally one day it blew up and the facts came out. Larrick fired Henry Welch on the spot and Henry was out of the FDA by that afternoon. He had grossly deceived Larrick and, of course, had done a lot of other things which were improper. He'd have the work parties out to his home in Hillandale. He built a swimming pool with FDA labor of this sort by having his people take the afternoon off to dig his swimming pool or help around the house. Put simply, they felt obliged to do it in order to keep their job. But Henry was thrown out, quite properly, quite thoroughly, and retired to Florida. His doctor said he had a heart condition, and that prevented his coming to Washington to testify at any of the inquiries that were held.

FL: Do you have any idea how this actually came to the attenton of Larrick?

LM: It got into the Pink Sheet, a weekly newsletter that circulated widely in the industry, or something like that. There was some trade source for it. It was common knowledge to all of us, but no one had gone to tell George about it.

FL: Something in the Trade Press?

LM: I think we can credit the press for bringing it out. But George specifically asked him the question about his actual outside income and that was all it took. Henry didn't try to lie; the truth spelled the end of what we called King Henry's reign.

As far as I know that is the only scandal that ever touched FDA, never any thing like that came up in the years I was there.

FL: It had a very serious effect on everybody in the agency.

LM: Yes, it really must have because he was a likeable guy. But the industry had come to expect favors. The certification of a batch would be pending, the sample would be in, the firm had gone ahead with packaging on the assurance that the lot would be approved, waiting only to ship it until they had the final word. So they would call Henry to ask how the certification was coming along, etc. Henry would just put them on hold, call the lab, and then he would make the decision. The word might be that the tests weren't quite done. "Well, how

do they look?" "Well, they look pretty good. OK." The lab might end up with egg on its face if the final tests didn't come up to standard. But Henry would have already given his approval and Henry would fix up what was needed. Well, then when Henry left, Dr. Don Grove took over for a while. The pressure got to be too much for Don, he just wasn't up to it. He was a lovable chap, competent as a scientist, but just wasn't equal to the pressure of the job, particularly following Henry, you see. He tried to accommodate and at the same time obey his own conscience. So, Don just had to leave; he was ill.

Dr. Dan Banes took over. Of him, Frank Wiley once said, I was up in Dan's office. It was a very considerable promotion for Dan, and new responsibility. So he had this call come in, just like they did with Henry and Dan said, "your lot will be certified just as soon as the tests are done" and bang, down goes the telephone. That was that. No deals with Dan. So, things were different and have been ever since.

I understand now that Food and Drug is anxious to get out of the standards business, and they have actually arranged with USP to take over the standards making. That will be worked out pretty soon, and completed if it hasn't been done already. USP has taken over the distributing and selling of the antibiotic reference standards which FDA has done since about 1950.

However, constraints on the service made it a source of annoyance generally since you had to go to FDA for antiobiotic standards and yet you could not get all of them there. Foreign firms that weren't making a product with the anticipation of certifying, couldn't get an antibiotic standard from FDA, they had to get it some where else, usually from USP which was providing the same standards but FDA did not recognize them for purposes of certification. Now that problem no longer exists. USP distributes them to everyone, just as it has done since 1940 for insulin.

There have been many suggestions, as you probably know, for certifying all drugs. The magnitude of the job is just too great. FDA couldn't possibly expand to do it. Furthermore, the existing system hasn't worked all that bad.

FL: And it's probably unnecessary?

LM: It would be, yes, in my view.

FL: It seems that certification should be limited to a very few drugs.

LM: Yes, only for drugs used in life-threatening situations.

FL: I remember a few years ago we got in to sort of an unofficial certification situation with Digoxin, because of problems.

LM: On the basis of the physiological availability. Several other drugs shared that same problem before very long.

FL: I don't believe it still exists.

LM: I don't think so, after the means of avoiding the problem were worked out.

FL: It was discontinued when the problem was solved.

LM: Yes, the USP commitee worked hard in close cooperation with FDA. It was a problem that I thought might force us to go back to biological testing, as much as we would have hated to do it. At one time I suggested an alternative, namely testing a prototype lot of the product on humans as we once had for the liver preparations. You may remember the USP Anti-Anemia Advisory Board, which used a form of certfication in the late '40's and early '50's, prior to the isolation of vitamin B-12 as the thing which alleviated pernicious anemia. We picked five physicians who were experts in this field, one of them served as secretary. The Secretary would receive production records for a liver extract that, say, Wilson or Armour wanted to sell to any number of distributors. All they had to show was that they had followed exactly the process that had yielded earlier an active product. When ways of improving the process were found, the new product had to go through a testing procedure, the results of which were then passed upon by the Anti-Anemia Board. So the USP was instrumental in controlling the quality of a very important therapeutic agent. I can remember Mr. Campbell discussing it one time in a small meeting I attended. He said, "I am very glad that we have the USP Anti-Anemia Advisory Board but I would

sure hate to have to prosecute a case on the basis of it." He was a lawyer of the first degree. I remember shortly after the 1938 Act was passed, his telling us that it would be many years before we would know the full extent of the new law. "We will enforce the things we know and we will feel our way into it, but it will be a long time before really know what Congress has authorized us to do." That certainly was propetic. Now, 45 years later, the law is still in effect, modified only by various amendments.

Well, let see what else might we think about?

FL: You mentioned earlier that a number of other people in the Division of Pharmacology were doing research on lead and arsenic and spray residues.

LM: Oh, yes.

FL: Could you talk a little about that work even though you weren't personally involved in it?

LM: Yes, I was close enough to be able to tell you something about it. It all began in the late 20's, I suppose, with the discovery that insects were making such inroads in the fruit orchards, of all kinds, that the growers were having to increase the use of insecticides. About all they had then was lead and arsenic compounds. Since there was nothing to prevent it, they were using increasing amounts and apples, for example, were appearing on the market with literally a crust of insecticide on it that you could scrape off with your thumb

nail. Pharmacologists have long known that poisons that kill insects are likely also to kill higher forms of life. There was no law limiting the usage although Food and Drug thought that there was a general law against it, but there was no specific law except the *Insecticide Act*.

FL: The Insecticide Act was passed in 1927, and that related more directly to the purity of the insecticide itself, rather than to the residues.

LM: Well anyhow, from that time on, the Food and Drug was involved in it. The problem, as it then existed, was the overuse of toxic materials as insecticides, and the reluctance of the growers to accept any restraints at all. They maintained there weren't any alternatives, that they had to use all that much insecticide to get the fruit and argued that humans, somehow, weren't subject to the same kind of responses to toxic things that lower forms of animals were. FDA, not having any first-hand data of its own, was obliged to do the best it could, and was losing one court case after another. They were approaching the matter by seizure, which of course is a very admirable way of controlling anything because you tie up a shipment until it spoiled, which in the case of apples, wasn't very long. Then there was no longer anything to fight over. But a Congressman named Lea from Missouri was a big apple grower, and he might even have based his candidacy and his campaign on doing something to get FDA off the backs

of the apple growers of Missouri. In any event, he was in Congress and he fought every appropriation bill for the FDA, modest as they were in those days, that included any authorization to work on spray residues. In spite of his opposition, by fiscal year 1935, there was provision in the budget to work on spray residues. FDA decided to use the funds to create a Division of Pharmacology and chose Dr. Nelson, Erwin Nelson, Professor of Pharmacology at the University of Michigan to organize this new division. He picked Herb Calvery, who was in the Biochemistry Department at Michigan, as a biochemist to head up the chemical part and set up the spray residue testing program. All this, of course, was organized with Mr. Campbell's approval. So, during the spring of 1935, Calvery was recruiting chemists and even physicians who would come in to do pathological testing so that by the time I got there in July of 1935, they already had people transferred from other divisions from the original FDA staff to work on spray residues. There was one group working on lead, and another group working on arsenic. The two elements have quite different actions--lead being a poison that is cumulative; it piles up in the bones and in the body and has a very long-term effect. Arsenic is short-term acting, and its toxicity is quite different. So they were two different programs.

Calvery was a very good organizer. He was a dynamic chap, who never worked according to the clock. He was the

only man I ever knew who could work two days and two nights in a row and still keep going with nothing more than a shower in between.

So he had the program going, and he was a doggedly determined chap. I can recall his telling me that when he was getting his degree at the University of Illinois. (He'd had a hard time. There were many of us in those days who had come from poverty stricken homes. We didn't know we were poor, but we didn't have very much money.) So Calvery was working his way through the graduate school, and he had so little money he didn't have enough to eat. He would buy a cup of coffee, stir in about half a cup full of sugar in order to get the food content of the sugar in the cup of coffee. Whether he was not a good student, or simply a case of making a bad impression temporarily on one of his professors--he was told, "Calvery, you'll never make it to get your degree." Well, that's all one needed to tell Herb Calvery. He was determined; he almost literally worked around the clock as a graduate student and did get his degree at Illinois and established quite a creditable record at the University of Michigan. That was the kind of a guy who was running this program. He was a leader in the sense that he knew where he was going, and he could get people working under him to work harder. We all represented new blood. We were all eager to take advantage of the challenge of this new division. We all responded to a leader like

Calvery. Now, Dr. Nelson was quite another sort. He was the professor type. He was contemplative and responded warmly to our psychological needs, but he was not the driving sort. They were a great pair, Calvery and Nelson. So, Calvery was pushing along on the chemical side and was starting to get results by 2 years later, by 1937. The findings frightened some group of congressmen who succeeded in getting a proscription in the FDA appropriation barring the use of any funds for spray residue research. The antipathy, the animosity, toward the FDA prevailed, finally. So suddenly FDA had to get out of the spray residue research. We had animals on test that had been going the better part of two years by then, at least--dogs as well as rats--all sorts of experiments that were just starting to produce results and probably had produced results which Congressmen Lea didn't like. I know that Campbell and Calvery stayed up all one night, at least one night, maybe two, trying to figure out a way to get around this so we could justify carrying these tests to completion and, if not, to salvage what could be done in order to assist the NIH, which then was still in the Public Health Service, and was authorized to continue the work. Everything at FDA had to stop. Well, the last three days of June all hope had run out. So we had to kill the animals. Everyone who could wield scissors and do anything in the way of sacrificing animals was called upon. Most of us got blisters on our thumbs and fingers from

cutting the tissues that we wanted to save, and preserving them in such a way that they could be turned over to the people at the Public Health Service. We did everything possible to salvage as much as possible of what we'd got. It was a terribliy hectic time. We again, most of us worked most of the night so that Mr. Campbell could go before Congress and say, "Work stopped as of midnight, June 30." Mr. Campbell was a stickler for that. He said, "You must not work a minute beyond midnight." And so we didn't. Of course then the so-called transfer took on. All of the animals had been killed. It was really a traumatic period, as you can imagine. The fellows who had worked so hard to get the experiments going--as I said, I wasn't involved only with this business at the end. But there are still several around such as Ed Laug, of those that were involved. Dr. Ed Wallace was one who worked with us. Later he left the FDA, went to work for Merck. He bought a boat and was working on the mast in a boatswain's chair. The rope broke, and he broke his neck in the fall. Two or three others on the medical side stayed only about 2 years, so they were gone. But Arthur Nelson had come in by then, a pathologist, and a very good one. He gained the highest respect in the industry. He came on and stayed on until he retired, and subsequently passed away. Anyhow that was the incident of cleaning up, terminating research precipitiously. Great distress on the part of Mr. Campbell and Dr. Calvery.

By that time I think Dr. Erwin Nelson had returned to the University of Michigan, leaving Calvery in charge. Has anyone talked about Calvery's demise?

FL: No. I was going to ask you about that

LM: Well, at that time I had left FDA, and so I was no longer in close touch with the staff but I got a letter from Dr. Laug saying that Dr. Calvery had been found dead in the basement of his home. The circumstances of his death were clouded and questionable. Ed went on to say in his letter, "They made the funeral arrangements with such haste that they forgot any pallbearers. In the last hour or two they had to recruit six of us to be pallbearers." What I am about to say was told me by those on the scene. Calvery is gone; his wife is gone. There is only one person still living that I know of that was involved in it. Mrs. Calvery discovered Herb dead in the basement and called their very best friend, Frank Wiley. He picked up Dr. Robert Herwick to come along. Bob, now deceased, was one of the most highly trained men I ever knew. The only man I ever knew who was an MD, a PhD, and an attorney. He had also served as a coroner's deputy in Chicago, so that what he said in this case carried great weight. His immediate decision was that it was a classic case of cyanide poisoning. The physical symptoms were convincing. There was no autopsy; I don't know how they managed to get around it. It was wartime, so the rules may have been bent. They

hurried the funeral. Everybody apparently took a pledge of secrecy but one of the chemists, with whom I was acquainted, later told me that a bottle of potassium cyanide had disappeared from a shelf in his lab just about that time.

Calvery had been working under enormous stress. Once when I talked with him during that period he said, "There have been times I've just gotten on a train (this was before the day of planes) and gone to Chicago for a day or two just to get away from the pressure I have here." So he was a wartime casualty without question. His records at the laboratory were up to the minute. His records at home were three years behind. He hadn't filed his income tax return for three years. Everything was in a mess there. So he just sacrificed everything for the job and somehow or other, it just got too much; he snapped. It was a clear case of suicide. He had accomplished a great deal in the dozen years he was at FDA.

Dr. Arnold Lehman was picked to come in as his successor. Some people said that I was considered as one of the candidates. If they did, I never knew about it. I wouldn't have taken it anyway.

FL: Was Lehman from outside?

LM: Yes. He was a Professor of Pharmacology at George Washington University Medical School. As early as 1941 he had wanted, in the worst way, to get into the Federal government and came over to see us about a job. He was having a tough

time at the Medical School getting along with the head of the department. Calvery, I don't think, would ever have hired him. But Lehman sufficiently impressed the search committee that he got the job, and did a very creditable job in his way. He didn't have the drive or the initiative that Calvery had, but he brought something to the unit that was constructive. He expanded on the start that Calvery had made and went on in other directions. He had been in the post about 15 years when the 1962 amendments were passed and were requiring much more testing, as you know, and Lehman was very good at channeling people to do that.

FL: The organic pesticides and the food additives . . . these things came along . . .

LM: For example Lehman was very active in getting standards for the packaging materials covering the adventitious additives that leached out of the packing material into foods.

When Lehman retired he was succeeded by a man brought back from MIT who had formerly been in the Vitamin Division. He was Head for a while, and then died on the job, I believe. I can't remember his name. All that time I was still in fairly close contact with those with whom I had worked when I'd been there, but I was getting so busy with USP that I just didn't get down to Washington all that often.

FL: That Congressman Lea that you mentioned earlier, he was involved also with the drug advertising portion of the bill.

LM: Yes, FDA wanted to bring under control advertising for foods and drugs which was really outrageous. Congress was in the business of considering a bill to give authority to some Federal agency for control over advertising. It was perfectly natural that the place where the labeling was passed upon should also have approval of the advertising. But Congressmen Lea said, "I will give no more authority to an agency that has harassed me so much in growing my apples. In no way will that happen."

Since he was Chairman of the Committee that brought the bill out, the regulation of advertising went to the FTC. And that's why FTC has it still explaining the curious dichotomy of advertising being a part of FTC and labeling approval is FDA authority. It's been a darn nuisance for the industry, I'm sure ever since, but it was a capricious action on the part of the Congressman from Missouri.

FL: During your service with FDA, you served under Commissioner Campbell, and I'm sure that you knew many of the people who succeeded him. And, of course, afterwards with Winthrop and USP you had contacts with FDA. Could you tell us something about the people who were running the Agency, starting perhaps with Mr. Campbell?

LM: Mr. Campbell was a man who immediately commanded your respect. He was tall, straight as an arrow, always tan because he was a great golfer, and bald as a cueball. He had just a little fringe of hair around his ears. But he had eyes that

just would burn right through you if he had the slightest occasion for disapproval. At the time I knew him, of course, early in 1935; one of the occasions that I was taken down to his office was when I had a manuscript ready for publication on the parathyroid assay probably in 1936. He was interested in everything at FDA. We were a small enough unit that he could be interested in all that went on. He'd read the paper and wanted me to come down and tell me what he thought about it. As I recall, he was pleased to see the results of original FDA research in the field of biological assay. And of course, after each of the FDA trials, we, the witnesses, were called into his office to report on the case. He wanted the first-hand reports that way. There were other occasions that I went down with Calvery and had contact with him. But he mostly was approachable to those at the top echelon and actually was not very approachable otherwise. Because he was aloof, as I said, he was always "Mr. Campbell" to us. I never heard anybody call him Walter. Maybe Paul Dunbar did. But Paul Dunbar, on the other hand, we knew as Paul. George Larrick was always "George" to everybody, partly because we'd grown up with him and Dr. Dunbar before they were commissioners. But Mr. Campbell had been in from the days, in 1906, and he'd frequently tell anecdotes of his early days. He was one of the very first that Dr. Harvey Wiley hired. I can remember his telling one night at an A.O.A.C. meeting.

The 1906 Act had just become effective with Dr. Harvey Wiley in charge of its enforcement and creating an organization for that purpose. Mr. Campbell and Bill Wharton were two of 7 brought in to get the work started. Mr. Campbell recalled how all 7 were assembled for about the first time in Dr. Wiley's office for "indoctrination" and a lecture on the crusade they were embarking upon. The plan Dr. Wiley put to them was the essence of simplicity: The seven as a team, were to fan out into the city, collecting samples of foods and drugs that they, as individuals, regarded as being violaton of the terms of the new law of the land. To make their task easier, Dr. Wiley had purchased and handed to each of them a knapsack of the sort school children used for their books. The idea was that on their return, the seven would each have a bagful of samples that would then be the objects of all sorts of tests and examination not yet decided upon. All seven accepted their bags respectfully without comment or question as they left the meeting at some spot, Mr. Campbell recalled, near the Smithsonian Institute. This resulted in their being obliged to proceed, Indian file, along a hedge. At this point, Mr. Campbell and Mr. Wharton exchanged glances and, as if on command, all seven knapsacks were tossed over the hedge and never hear of again. Some samples were soon collected but not until there had been some discussion, planning and preparation. No doubt, although Mr. Campbell's law degree was

still fresh and new, his training guided the first collection efforts along lines that gave priority to what must soon have become a primary requisite to every FDA staffer. For every sample, there must be an unbroken record of its movement in interstate commerce. We always got together one or two nights when the Association of Food and Drug Officials of the United States met in Washington. I recall one night, somehow or another I got tagged to organize the program. And, being a stag affair in those days, why there weren't very many limits on what we had. So I went to Ben White, and I said, "Dr. White, would you like to take part in what we were doing and give a talk (I've forgotten) and make it humorous?" Anyhow he indicated that he wasn't above taking a broad view with respect to off-color jokes. Whatever we arranged, I can remember Mr. Campbell being near the front, of course, as he would be. We really did crack him up. We had written a skit, two or three of us, and put it on, and he really enjoyed that night.

I suppose you were inducted into the Yellow Dog Society?

FL: No, I wasn't around Washington at that time.

LM: I was a yellow dog, whatever that was. I had my card for a long time. It was sort of a secret society in those days for FDA people.

But Mr. Campbell was very attentive to his job, absolutely above reproach. He had the respect of Congressmen so

that when he appeared before Congress, as he had to do every year for appropriations and all that. He would call many of us in to work up the budget. But he went up there pretty much alone. He wasn't flanked by a bunch of people. He could do it on his own.

So, as I mentioned, Ben White was the Head of the Division of Foods. Elmer Nelson was head of the Vitamin Division at that time. So we had Erwin Nelson and Elmer Nelson and that was a source of some confusion, but they couldn't have been more different in their personalities. For example, Erwin Nelson in Pharmacology readily agreed to my asking Bliss to come in as a consultant when I told him that we just had reached the limit--at least the limit of what I knew. I had been analyzing data, and I knew there were ways that one could use this new science of biometrics to show the limits of confidence, as we called it, of the data. I went to Elmer Nelson in the Vitamin Division and asked him, when we were having Bliss come back for a second time, would he like to have his Vitamin people come up and work with us in Pharmacology because, after all, they were running vitamin tests all the time on animals and going to court on the basis of them. "No", he said, "we don't take any stock in this statistics business. The British do that, you know, and you come out with a recognized error. We don't have any errors in our tests. We do our tests with such precision that we never have any errors."

FL: At that time they were using chickens . . .

LM: Yes. For vitamin D . . . And chicks also for the B vitamins and rats for A, and that sort of thing. All highly subjective. And really, if we had wanted to, we couldn't have, at that moment, figured out any very good way of evaluating the data from those vitamin assays. But Bliss, I think, would have been able to help them. But no, Elmer Nelson wanted no part of it. "We can't admit to any error in our assays." So that was the end of any work between the Vitamin Division and the Pharmacology Division in biometrics.

Let's see, I talked about the Food Division. That's where they tested the liquor. I wish I could remember the name of the man who was the head of the Liquor Section, because he was known all through Food and Drug. You remember Bill Simmons in New York? Who was the head of the Chicago Division in those days?

FL: Garrett, perhaps?

LM: No, no, that was way before that time. He was a character.

FL: J. O. Clark.

LM: Yes, J. O. Clark. He played golf. He always had a pint of liquor in his golf bag. Well, J. O. and Bill Wharton, the head of the New York Division, were great buddies. They'd come into the A.O.A.C. meetings, you know, and would sit up to play poker and drink all night. Yes, it comes to mind now, it was

Dr. Sale, J. W. Sale was head of the Beverage Section. Well, it just killed Jimmy Clark and Bill Wharton of New York--the mere thought that 9/10 of a bottle of bourbon would go down the sink. There were schemes dreamed up how you might tap the sewer for that particular sink. Of course Sale would have caught on and simply used another sink to dispose of it. The people had integrity in the thing, so that when Henry Welch came along, it was a blow to everyone.

Now, about Paul Dunbar, who had been Associate Commissioner all the time I was at FDA, a very, very kindly fellow. I think he got his PhD at Johns Hopkins in Chemistry, a highly qualified chap, very able to assume the duties of Commissioner. Ran it quite differently than Mr. Campbell had, who had always made his decisions from the legal standpoint; he'd ask first, "What does the law let us do?" Of course, at that time, Larrick was the Chief Inspector and became the Associate Commissioner.

FL: Charlie Crawford . . .

LM: Yes, Charlie Crawford was in there, yes. It was during those days that the 1938 act was being incubated, first as Rex Tugwell had been instrumental in getting an act in about 1935. Charlie Crawford had gained the confidence of many of the legislators, both senators and congressmen, who had his telephone number. Any time of the day or night they could call Charlie Crawford to get his comment. Let's say, there

were lobbyists pushing a point of view, they wouldn't hesitate to step out and call Charlie. He would give them the Food and Drug point of view. So he was very instrumental in a quiet way. Actually, he wrote much of the 1938 act personally. Of course, Tugwell left and then Royal S. Copeland came in, so it became known as the Copeland-Tugwell Bill or something, or maybe Tugwell's name was first.

FL: I think Tugwell was Undersecretary of Agriculture and he kind of sponsored it to get it to Congress first. Then when it needed a Senatorial sponsor, Senator Copeland . .

LM: Copeland, who was a homeopathic physician, you remember, and took a very personal interest in it and he depended on Charlie Crawford the whole time. Well, during those days, I was living in McLean, Virginia, and I was riding into the office many times with Larrick and Crawford, who lived close to each other. I lived farther out, and I'd drive my car in to Larrick's place and leave it there and ride on in with them.

Then Dunbar came on. He was a gardener. He loved dahlias and that sort of thing. Somebody else, whose name I've forgotten now, was President of the National Iris Society. He and the Dunbars, Paul Dunbar, I don't know if I ever met Mrs. Dunbar. She had a keen interest in gardening. As was typical of so many who grew up in a job like that which demanded responsibility, when he retired he had nothing else

to do. His gardening by that time had ceased to keep his attention. They said it was pitiful. When he ceased to go to the office, he just was at loose ends. Charlie Crawford, on the other hand, who followed Dunbar for a couple of years, he wasn't gardening much. We knew his wife, she was a charming lady, and his family. When Charlie retired, he moved to San Francisco, got busy building a house, and it was just a tragedy that he lived only a couple of years in retirement. George Larrick then, on the other hand, all the time he was coming up, by the time he was also deeply involved in the Congressional hearings under Senator Kefauver, didn't have anybody like Charlie Crawford to depend upon. He had help from his staff, a staff of Larry Beacham and others who'd come along whose names you probably know and I've forgotten. They were helpful. By the time he retired, he had a bad heart. He was in very considerable trouble. I remember Dr. Klumpp, Ted Klumpp, was advising as of the time, and he and I used to discuss George's problem.

I made a trip to Santiago, Chile, with George. The Pan American Congress of Pharmacy and Biochemistry--I've forgotten what year it was but it must have been 1964. George went down there and so I had a chance to get reacquainted with him as we spent a week there together.

Things were changing. The '62 amendments had come in under George and had been quite controversial in the hearings

under Kefauver and later under Congressman Harris. I appeared both before the Kefauver Committee and before the Harris Committee. I argued for putting the antibiotic certification on the same basis as that of insulin. It had one more chance to try to get it.

Then when Larrick retired, of course, the Secretary went outside to fill the position with Goddard. Larrick was a nervous sort. His movements were quick. He had a quick mind in contrast to Crawford and, well all three, Campbell, Dunbar and Crawford were the more deliberative sort. They never gave the impression that they acted in the slightest way on an impulse. Everything they did was deliberate. Whereas Larrick, at least gave one the impression, that he might act more or less impulsively. The only time I ever really had a confrontation with George Larrick was--it must have been at the time of the '62 amendments when I was trying to get him to see our point of view. I recall his saying, "Well, Lloyd, you know the USP is the cat's paw of the industry." I pounded the arm of my chair asking, "George, how can you say that?" I went on to to tell the things again and again, that we were opposing what the industry wanted in the antibiotics. I related an incident with Ted Klumpp who was well known to both, of course, and then was President of Winthrop Laboratories. There was some product peculiar to Winthrop which one of the Winthrop men called to my attention. He said, "Look, this product is

coming in from Great Britain under the British standards which are more rigid than those of the USP. I know our factory can make the product to meet the British standards, but they don't have to because USP standards are lower." So I went to our committee and checked and, sure enough, by raising the degree of rotation one degree, we could require that it be considerably purer. So we proposed to do that. Well, Ted Klumpp was President of Winthrop. He got on the phone and talked to me 30 minutes arguing that, "it would cost us $125,000 just to install the equipment to do it. It was just no use. This product is good enough as it is." "Well Ted," I said, "You know that the history has always been when we can make a better product, we do. And you can't show that the impurities are doing any good. In fact, they're diluting out this product. Our committee has looked at it very hard and, as far as I'm concerned, they're determined to go ahead with it." We did. When we hung up, I just could have almost have said to myself. . . Mr. Hill, who was then Chairman of the Board of Winthrop must have been sitting at Ted's elbow. Ted just wouldn't give up. For 30 minutes he tried to persuade me, but we went ahead with it. So I told George that he was wrong. We certainly were not the cat's paw of the industry. I don't know what he based his opinion on.

FL: About the relations with industry--did you see a difference in the relationship between FDA and industry say from Campbell's time to Crawford's or Larrick's time?

LM: Certainly from Campbell's time, because Campbell was legally inclined. Well, he had good reason, because industry had learned that they could get away with an awful lot. They were pushing the law to the limit. They were using the courts to subvert the law. Campbell had had enough of it. He had us working on ways to stop this. We did that, before Campbell retired.

Paul Dunbar continued in, to a certain extent, in Campbell's way of approach. By that time it was all so obvious that you had to negotiate with the industry and make things work.

Larrick, on the other hand, had been an inspector and had had so much success in teaching industry to do better by going into the plant and showing what was wrong and then showing them how to correct it, that his approach was educational much more than enforcement through the courts. So they had far fewer suits. Then they went after the real frauds, the Hoxsey Cures and all the others that we know about. FDA hardly ever got into a lawsuit on the basis of biological assay. Well, they did have sort of a semi-biological assay argument with Hynson, Westcott, & Dunning over a product which was made from corpus luteum to be taken by mouth. No one had ever demonstrated it had the slightest efficacy. We, by that time, had the crystalline progesterone which had been shown to be practically ineffective by mouth, and yet Hynson, Westcott &

Dunning insisted their product had stopped threatened abortions. They brought in a professor of, I guess he was from the University of Maryland, who had a white beard, Professor David Macht. He was an out and out charlatan, really, hired by Hynson, Westcott, & Dunning to testify. He made such a good impression on the judge that the judge said, "Now there's a scientist." He disregarded all the things that these really prestigious people from FDA had testified, and rendered a verdict in favor of Hynson, Westcott, & Dunning. Except for a few instances like that . . .

Cancer trials we had about a 50/50 record because again it was long drawn out, and the scientific evidence took a seat way in the back.

FL: Well, speaking of science, Campbell was a lawyer, dealing largely with a bunch of scientists--was there ever any feeling on the part of the scientists that they weren't getting support from him?

LM: No, never. He listened to us. He was a good listener. We had to have our ducks in a row when we went down to the Commissioner's office. He wasn't known as a Commissioner then, when someone called you to Mr. Campbell's office, we knew we didn't dare waste his time. Those of us who had anything to say had to have it organized when we went down there. I remember one time Calvery came to get me to take me down. I started down in my shirtsleeves, "Get your coat on!

You're going to Mr. Campbell's office." So we didn't have much time to get ourselves prepared, just the time it took to get from the fifth floor down to the third floor, where his office was. But, no, he was exceedingly attentive to a scientific presentation, as far as those of us who were just scientists were concerned. The same with, of course, Dunbar, who was a scientist.

I haven't talked about Mr. A. G. Murray, Alexander Graham Murray, from whom I learned a great deal about the administrative responsibilities I had at FDA, which were not many. He'd call me in, he'd be writing a letter and want some background. He was one of the ableist draftsmen to draft either a bit of regulation or a letter that we had there. He'd been a chemist, and long since had left the lab. When I knew him, he must have been in his 50's and 60's. He was a real wheel horse. He had everyone's respect. He wrote a lot of Mr. Campbell's letters. I remember a messenger boy we had one time, "Gee," he says, "I sure wish I had a job like Mr. Campbell's, all he does is sit in there, look out the window and sign letters." I learned a great deal about how the FDA worked from Murray who had gone with us on the Sharp & Dohme trial. He was the kind that was glad to help youngsters like me. If you were willing to listen, he would give you the benefit of his experience. He came back after he retired, at 70, to work on for quite a long while because they just couldn't do without him.

Mr. Murray was deeply religious and vigorously opposed the suggestion that FDA consider sampling and testing rubber contraceptive devices on the ground that their use was generally immoral. Reports persisted that a goodly proportion of the devices were defective because of small holes, yet Mr. Campbell had such high regard for Mr. Murray that he refused to approve the project in the face of Mr. Murray's objections. However, he agreed to have Dr. Klumpp try to change Mr. Murray's mind on the subject. This approach succeeded on the strength of Dr. Klumpp's argument that the devices were of great benefit for married couples to prevent the transmission of veneral disease from one partner to another. Convinced of that, a new idea to him, Mr. Murray then backed the project as fully as anyone on the staff. The resulting testing and actions reduced the percentage of defective devices to virtually zero.

Another incident was revealing as to the strength of Mr. Murray's will and devotion to principle. In those days, our per diem allowance was $6.00 and about the only incidental additional expense allowed was for phone calls and cab fare. Returning from a trip, Mr. Murray submitted his expense voucher, believing it was wholly correct and justifiable. The Accounting Office disallowed an item for 35 cents. Mr. Murray vehemently disagreed and over the next 2 or 3 years, he and the Accounting Office spent countless hours in memo-writing

over the controversy. Somehow, the 35¢ had been paid to him and the GAO was trying to recover it. Mr. Murray steadfastly refused to pay it back and the matter was finally settled by deducting the trivial amount from his pay check.

I became interested in better ways of recording the results of bioassays that depended on measuring blood pressure changes, shortly before I left FDA. We had depended, up to that time, on measuring the blood pressure of the dogs, chickens or any other animal that we wanted to by following the vertical motion of a float on top of a mercury manometer. It would bob up and down with the pressure, but it was sluggish, because there was a good bit of mercury that had to be moved with every heart beat. One of my former associates in graduate school had come up with a much more sensitive device which consisted mainly of a tiny thin rubber diaphram that would fluctuate with blood pressure, bulging a bit with each increase in pressure and then returing to a flat surface when the pressure dropped. But the trick was to record that. We didn't have the sensitive pressure gauges that are now available, called Statham gauges. Gee, it must be fun to be in a lab now. But then we could only put a tiny mirror on the top of this rubber diaphram, focus a light on it and follow the movement of the reflected light. Now one would use a laser for things like that, but all we had then was a projection light focused on the pulsating mirror. The trick was

to find something that would follow it. I conceived the idea of using a typewriter carriage with a photocell on that that would follow the spot of light. The photocell area was in two separate parts. As long as the spot of light fell on the right half, the carriage would continue going to the right. The moment the spot stopped, with the cell moving, the left half would be activated causing the carriage to reverse and start back. I enlisted the help of Dr. John Wilkie, a physicist in Vitamin Division, in working out an electronic circuit that would control a motor that I put on this typewriter carriage. In that way the photocell could follow the light beam back and forth which, of course, solved our whole problem. I got it working not long before I announced that I was leaving. It seemed that half the people in FDA dropped in to see this curious device that "worked with mirrors". I remember Henry Welch coming in and saying, "Lloyd, you've got it made. Why in the world are you leaving? Here you've got something that works with mirrors and just going beautifully and everything like that, and you go off and leave us." Calvery had asked me, "What do you want to be?" "Well," I said, "I feel as though I'm getting in a rut here, and Winthrop has offered me a chance to be an associate to a very emminent pharmacologist. Even though I really am not very much of a pharmacologist, I just think it's the chance to get ahead, to say nothing of the fact that they're giving me

about $3,000 more salary." So, Calvery gave up and said, "OK". Even though I had had, you might say, a charmed life . . . I had come in as a P-2 at $2600, and just as soon as I was eligible for a raise in grade, I went to the next grade. I shouldn't say this, but one of those who came in a grade ahead of me, I caught up with in two years, passed him, and his wife never forgave me. So, by 1942, I was P-5, which was pretty high in those days, at a salary of $4600. I got, I think, one in-grade raise of $200. So I left the FDA at either $4600 or $4800. I went to Winthrop for $7,000. But the difference between industry and the Food and Drug was that, come the end of the year, if you'd done a good job, you might get a bonus of $1,000; one year I got several thousand dollars. There were also regular increases in salary. There were other attractions; I was Head of the Biology Division, with 60-70 people under me. In fact, it was larger than the Division of Pharmacology that I'd left at Food and Drug. Of course, all that while I continued to work as a volunteer with the USP. Consequently in 1949 when the USP was looking for a man to succeed Professor Cook and to become the first incumbent of the post of Director of Revision, I was approached. They wanted me to put in my name for consideration, but I was rather reluctant for quite a while. Others were considered, one of whom was Bob Herwick another former FDA man. The Board, in its wisdom, decided to offer the job to me, and so

I took it. We moved down from Albany to the New York area in 1950. After 20 years there, I retired. I've never regretted it.

I can't think of anything else. There may be some things that will come to me that we've overlooked.

FL: Thank you, Dr. Miller, for sharing your experiences and opinions with us.

THE NATURE OF COMPENDIAL STANDARDS

LLOYD C. MILLER

United States Pharmacopoeia

It is clearly an honor and a privilege to address this group tonight. If I had been at all inclined to take the honor lightly while putting my thoughts into useful form for the occasion, the inclination was dispelled entirely by the request to provide the draft well in advance to allow for translation into French. Now, it is one thing to try to be understood in one's own tongue, but it is truly awesome to write with the knowledge that someone else has to put one's thoughts into a second language. To use one of the few French expressions I know, "C'est très formidable!"

Considering the occasion and the hour, I feel obligated to take account of a second important constraint, namely, the need for brevity and, to the degree possible, a lightness of touch. Brevity is easy to come by and is said to be the soul of wit. Despite that, I have the feeling that we have had enough of "soul" of late and it might be useful to consider what brevity does to heighten interest. At least, that seems to be the theme behind the current vogue in women's clothing; interest has certainly risen with the hemlines in the past year or two.

In an effort to minimize the specific gravity of these remarks, I shall draw upon a rather close personal identification with drug standards that dates from my joining the Food and Drug Administration in Washington almost exactly 34 years ago. As it happened, my earliest work at FDA brought me into close contact with two members of the forerunner organization of our host tonight; I refer to Dr. C. W. Chapman, who later emigrated to Baltimore, and Dr. C. A. Morrell, who attained great distinction, you will all agree, by staying right here to become the first head of the Food and Drug Directorate.

Reference to Dr. Chapman leads into a digression in the form of an anecdote which will illustrate some important reasons for compendial standards' being as they are.

The stage was set for this incident when Drs. Morrell and Chapman and I discovered that we shared an interest in the assay of digitalis. The U.S.P. procedure at the time involved the use of frogs over a one-hour observation period. Drs. Morrell and Chapman had demonstrated certain advantages in extending the assay to run overnight so that the results were read the next day.

Some two or three years later, using the U.S.P. method in routine regulatory analysis at FDA, we reported a potency of only 53 percent for a sample of tincture of digitalis. This was, of course, grossly substandard, but the firm involved showed some reluctance to accept our report as a fact and chose to put the matter before a federal court. There was, you might say, the existence of "credibility gap" even in those days. It was not unlikely, however, that the manufacturer's incredulity fed somewhat upon two facts, the first of which was that our finding was based on a biological assay. The second fact was a matter of record in that, with a single exception that had occurred too recently to attract much notice, FDA had never won a case in which the evidence had been obtained by such a procedure. In short, on historical grounds alone, the firm thought it had an excellent chance of persuading the court to disregard our report.

In any event, we found ourselves preparing for an appearance in court, and it fell to me, as the senior analyst for the government, to explain the intricacies

1969
Excerpt from "The Physiological Equivalence of Dodge Tohms"
a publication of the Department of National Health & Welfare, Canada

of an assay depending upon a pharmacologic action of digitalis in frogs to the young Assistant District Attorney who was preparing the case. This required explaining such phrases as "inject into the ventral lymph sac," "pith each frog," and "systolic standstill," let alone the basic principle of comparing the suspect product with the U. S. P. Reference Digitalis Powder by the method set forth in U.S.P. XI.

This all was to be done in the District Attorney's office in New York. To make the task easier, I borrowed a few beakers and some frogs from a nearby laboratory and conducted a desk-top demonstration of the assay. The attorney was utterly fascinated, and to my horror, decided on the spot that the way to win this case was to conduct a digitalis assay right before the judge's eyes. Fortunately, it had been stipulated that there would be no jury.

Only those of you who know the vagaries of biological assay under the best of conditions can surmise how hard we tried to shake the attorney loose from this course that, although admittedly dramatic, was fraught with vast risk of failure. We explained, for example, how important temperature control was and that we had no way of holding the frogs at the required temperature prior to and during the two-hour period of the assay, to say nothing of our ignorance of what might happen in case of failure to do so.

It was all to no avail. As a result, I spent the next few weeks assembling apparatus that could be set up and used in the courtroom. This included a thermostatic water.bath sufficient to accommodate a few dozen frogs in a few gallons of water held at 20° Centigrade.

The only chance of success seemed to lie in the choice of a simple assay design. We knew we could set up and inject the frogs on a schedule of one per minute; thus we could handle 60 frogs in the hour between the time of injecting a dose into the first frog and returning to it to observe the effect exactly an hour later. The second frog had to be injected in the second minute, and so on, for the succeeding 58 frogs. This split-second schedule left no time for wondering what came next, court recesses, or conferences between counsel and witness. Once started, the procedure would have to continue as inexorably as clockwork.

As we indicated earlier, the government charge was that the product in question was substantially half-strength. We chose therefore to divide the 60 frogs into three groups of 20 each, one group to receive a full dose of the reference preparation; a second group to receive one-half that amount, namely, a half-dose of the standard; and the third group, naturally, to receive the sample in an amount that would match the full dose of the standard in its effect if in fact it were substantially as potent as its label claimed. On the other hand, if the government claim were to be borne out, the result on the third group would match that of the half-dose of standard.

This routine was rehearsed several times in Washington. On the day before the test in the courtroom, our apparatus and a generous supply of frogs were shipped to New York. The apparatus included the portable water bath, a rather bulky scale for weighing the frogs, and the necessary cages and glassware. We brought along our own Reference Standard tincture, which had to be prepared in advance, but we planned to withdraw the test sample from the bottle of the tincture of digitalis that had already been put into evidence and marked Exhibit A for the government.

The things that went wrong were numerous and agonizing, and I shall cite but three of them. First, in unpacking the scale we discovered that it had been upended in transit so that all of the oil had leaked out of its dash-pot. Consequently, there was absolutely no dampening effect so that the pointer oscillated for minutes instead of coming to rest in seconds. It would have been unnerving to discover this in mid-day when we might have made inquiry and located the proper kind of oil; to discover it after closing time was quite another matter. However, we made a hurried trip to a nearby auto service station and filled the empty dash-pot with light automobile oil. The balance then worked fine and I should not be surprised if that same oil were still in it to this day.

The second crisis arose as a result of our choice of a place to keep the frogs overnight. We accepted the offer of a photographic dark room, although it was located two floors removed from the courtroom, because it had a large sink and ample running water. After one final rehearsal that ended well after 1 a.m., we secured the frogs in the sink, locked the door, and departed for our hotel. You can imagine our dismay upon returning early the next morning to find the floor almost literally alive with frogs. They had found some way to get loose, had taken a long jump in the dark, and had spent *nobody knew how long on the floor out of water.* Perhaps less foolhardy souls would have turned back there; but we felt compelled to go ahead. So the frogs were returned to the water, and when the time came, 60 of them were placed in the cages of the portable water bath and we made our way to the courtroom. This necessitated wheeling the portable bath over several thresholds and into and off the elevator, but at last, well before the time for court to convene, the water bath was in place before the witness stand and the scale was set up on the railing of the jury box.

The court opened and from that time on the proceedings were a matter of record. We explained to the court the workings of the apparatus and our plan. It was not until then, while discussing the apparatus, that I had a chance to check the temperature and discover the third crisis. I was in the process of telling how critical it was that the temperature be kept at exactly 20° and lifted the thermometer in a gesture that was intended to assure the court that we had everything under control. I looked a second time and almost froze when I saw that the thermometer did not read 20°, or even the 20.5° that was permissible, but a nice round 21°!

I must have managed to hide my consternation as I casually dropped the thermometer back in place and continued with the explanation, for no one asked to check the temperature. For my part, it was only one more reason to wonder how the whole thing was going to come out.

We proposed that the frogs be handled in groups of five and that they be assigned at random to the standard or the sample. We invited questions and any change in our plan that might be made provided that it were possible before the first frog was to be injected. Among the consultants for the defense was Dr. Chapman, who understood well that from that point onward there could be no interruption. A few questions were asked, and I recall that one of the medical consultants for the

defense watched closely as the sample was measured into the diluent and remarked, "Miller, you sure can pipet."

The first 60 minutes of the test was devoted, of course, to withdrawing the frogs individually from their cages, drying them, weighing them, and injecting them with the predetermined dose of either the full-strength Standard, the half-strength Standard, or the full strength of the test sample. The transition from the injection to the observation period went smoothly, and we pithed the first frog, which is to say that we destroyed its brain and spinal cord with a darning needle. Thus immobilized but not killed, this and each of the other frogs would lie limply in one of the three trays we had arranged, according to which of the three doses each had been given. Each frog's heart was exposed and examined in turn, and if the heart was still beating, the frog's body was laid at the left-hand side of the tray. If, however, the ventricle was in systolic standstill, indicating that the dose of the digitalis glycoside had been sufficient to produce that characteristic effect, the frog was put at the right.

The process continued with everyone in the court peering over my shoulder. There were occasional sidebar comments on the correctness of my judgment, into which even the judge entered at one time to agree with me that the result was a negative as the exposed heart relaxed and beat again just as time ran out. At last, the entire 60 frogs lay in six heaps before us. I had been vaguely aware of the accumulations in the three trays but had been rather too much preoccupied to keep score.

The official tally was made and it came out this way: the division in the tray for the full dose of the standard was 17 frogs on the right, meaning 17 positives, as against three negatives on the left. In the tray for the half-dose of the Standard the situation was exactly reversed, namely, only three positives and 17 negatives. Turning then to the tray for the sample preparation, the count was four positives and 16 negatives.

I recall that, in a feeling of vast relief, I lifted my eyes to the heavens whence obviously had cometh much help, and the judge declared a recess. Dr. Chapman had meanwhile whipped out his slide rule and calculated that the 60 frogs had given proof that the sample was 54 percent of U.S.P. strength!

Perhaps as a witness, I was guilty of concealing part of the truth, for I made no mention of the fact that never in all of our rehearsals had we obtained such a perfect result.

The defense put in its case, which was based largely on the well-established fact that the U.S.P. Reference Standard that we were using was about 10 percent more potent, in relation to the International Standard, than had been intended. We, as government witnesses, did not dispute this fact, for actually we had been responsible for bringing the discrepancy to light. The court ruled, however, that the error was immaterial to the issue before it. In finding for the government, the judge compared the Standard to a water bucket and asked, "What if the bucket is a pint shy, it is the bucket that both the government and the defendant are directed to use in measuring the quantity of the sample in question. It was demonstrated here before me that the sample does not have the required potency."

This anecdote, which has never been told before under circumstances such as this, illustrates well many of the important facets of good compendial standards.

First and foremost, it will be clear that compendial specifications are intended to be standards in every sense of the word. They constitute "standards of strength, quality, and purity" (a phrase that appears throughout all federal drug standards legislation, and that may be the most than can be said for it) and if they are to have real meaning, the compendia must provide procedures to demonstrate compliance with the standards that are set up. In respect to drug standards, at least, the complementary effect of providing the necessary methods is vital indeed. It would be difficult to imagine a more certain invitation to complete chaos than a situation where all parties at interest were free to choose their own assay methods.

The compendial standards are the bedrock for intelligent use of drugs in the clinic. Dosage instruction would be virtually useless if uniformity from lot to lot could not be assured. Comparisons of clinical effects would be meaningless if the dosage were not standardized.

These points need no emphasis for this audience. Some added word may be helpful on the role of the standards in law enforcement. In this respect they are the yardstick that products on the market must measure up to. This is a yardstick that is equally available both when a drug product is made and later should the government have occasion to check on the product. The same yardstick is available to any other individual or agency that has either reason or responsibility for determining the potency of the product concerned.

The experience in court in the digitalis case illustrated well how the compendia must exercise care and ingenuity in drafting the standards. In this connection, it is relevant to quote from the preface of U.S.P. XV:

> *"It is important that the U.S.P. possess the character of a legal document. As an 'official compendium' under the terms of the Federal Food, Drug, and Cosmetic Act and the counterpart statutes of the states, all of its provisions must lend themselves to the unrestricted use of the regulatory agencies. This creates demands for clarity of context and freedom from ambiguity which frequently preclude conciseness. Occasionally it also denies the adoption of analytical methods that for practical reasons cannot be made equally available to producer and enforcement officer alike."*

In the 30 years since that trial, the product that it involved, digitalis tincture, has declined greatly in stature. It was dropped from the U.S.P. prior to 1955 and has been supplanted largely by the more convenient and more stable crystalline digitalis glycosides, mainly digitoxin and digoxin, both of which are assayed chemically. This brings out the fact that compendial standards undergo constant improvement. In the area of biological testing, with which my own professional interest has been closely linked, we have seen a steady replacement of the costly, cumbersome, and indirect procedures depending on the use of animals by more precise procedures carried out in the chemical laboratory. I, for one, have shed no tears over this evolutionary change.

Frogs have been phased out almost entirely. However, the forthcoming U.S.P. XVIII and N.F. XIII still

COMMENTS ON TRANSCRIPT OF INTERVIEWS HELD JUNE 20, 1980

by Lloyd C. Miller

Herewith are comments evoked by my reading of the transcript which are more or less in the nature of footnotes to the pages to which they refer. The comments are intended to correct the record where my recollection of the facts differs in a substantial way from the transcript. My sole claim for credibility in such cases rests on the fact that I came on the scene July 1, 1935, a month to more than a year prior to the times that those who were interviewed actually reported for work.

Page 9: On the recruiting of personnel for the new Division of Pharmacology, as I recall, this was done entirely by Dr. Erwin Nelson, starting early in 1935. He interviewed me in Detroit at a scientific meeting in March of that year. His first recruit was doubtless Dr. Calvery, a fellow member of the faculty at the University of Michigan Medical School. Another recruit who came July 1, 1935 from Michigan was George E. Farrar, Jr., M.D. who served as pathologist during the year he was in the Division.

Page 10: Dr. Laug mentioned Chester Tolle among those who formed the Division. In fact, Dr. Tolle was in the Vitamin Division during his entire FDA career of perhaps 30 years.

The name of Edward Wallace is mentioned. He was an MD-PhD graduate of the University of Chicago Medical School who was in the Division some 18-20 months from July 1, 1935 and left to join the Medicial Division of Merck & Co. While in the FDA he worked entirely on the chemical methods for determining arsenic in body tissues. Actually, Dr. Wallace was also a biochemist, having taken his PhD under Dr. Koch, Professor of Biochemistry of Chicago Medical School. Thus, Dr. Herbert Braun and Dr. Nelson were the only ones in the Division during the early years who had a degree in pharmacology. I was perhaps a "half-breed" in that my graduate study at the University of Rochester School of Medical and Dentistry was in the Department of Biochemistry and Pharmacology and my research was on the changes of blood sugar and lipids caused by amobarbital anesthesia.

Re Dr. Young's question, it was indeed true that there were far more PhD biochemists available in 1935 than pharmacologists. While Nelson was looking for persons, PhD's and MD's, with specific training in pharmacology and toxicology, in fact, with the exception of Dr. Jack Curtis, none of us who

made up the Division at the start had had any significant experience in the new work planned for the Division or that carried over from its predecessor unit, (whatever it was called). I refer to the bioassays of ergot, posterior pituitary, epinephrine, digitalis, squill and aconite, the latter one of the most potent poisons then known. All of these products were used more or less widely as medicines and their potencies could be measured only by use of laboratory animals.

Page 11, last line: It is of little consequence, but Dr. Farrar was the pathologist for the Division during 1935 and 1936, prior to Dr. Woodard's joining the Division.

Page 13: What Dr. Woodard overlooked is that Dupont had a well-regarded toxicology laboratory in operation prior to 1935. Dr. Frank Wiley, a former associate of Dr. Calvery's at the University of Michigan was there at the time and later, probably at Calvery's urging, came to head a new Section on Pharmaceutical Chemistry at FDA (about 1938). As for Dr. B. L. Oser, he may well have "practically lived in the Division" for a time but he was nationally known as an expert on food and drug problems prior to that. He helped form the Food and Drug Research Laboratory.

Woodard erroneously attributes the LD50 concept to Laug. It was a British idea dating to 1927. We learned it from Dr. C. I. Bliss whom I brought in as a consultant in 1938. We all learned biostatistics and the LD50 concept from Bliss.

Page 14: Dr. Draize was a pioneer in dermal toxicity without doubt; he had a far better understanding of the subject than any of his associates.

Page 15: Woodard inflates the role of the Division in the field of toxicology. Those of us who were not quite "pure pharmacologists" but had been taught pharmalogy in graduate school had learned that, in fact, the science of toxicology had a respectable start prior to 1900. A good case in point is that when lithium chloride was proposed as a salt substitute about 1942, we discovered that its toxic properties had been published about 40 years earlier.

It is quite true that careful excretion studies on lead and arsenic were lacking principally because good analytical methods were lacking. As a graduate student, I took part in nitrogen balance studies on dogs as part of class projects. Also, as a senior in college, I had conducted Vitamin D assays of yeast on rachitic rats as a special research project. Hence the notion of giving graduated doses over the lifetime of an animal was not exactly revolutionary.

Pages 17-18: It is interesting to read, in Dr. Laug's discussion, about the application of the statistical procedures that Braun, Bliss and I worked out first using data from assaying digitalis on frogs and published in a paper for which we were awarded the Ebert Honor Award by the American Pharmaceutical Association in 1939.

Page 20: The "Fisher" mentioned was Sir Ronald Fisher, father of the science of biometry. Dr. Bliss worked with him at Harpenden Hertz, a British government experimental station in England.

Page 21: I came to know Dr. Sollman fairly well and I doubt if he ever used the term "LD50". (He started teaching at Western Reserve shortly after 1900 and kept on giving the same lectures into the 1950's. When he retired, his students approached his successor with this request: "Please plan your lectures on the assumption that we have learned no pharmacology at all."

Page 24: It isn't fair to say or imply that relationships were not good between FDA and NIH. Congress was the culprit and specifically, one Congressman Lee (or Lea) from Missouri, an apple grower, who vowed in 1937 that he would see that "not one cent of FDA money would be spent on spray residue testing". However, there was enough sentiment in Congress to continue testing that the NIH was persuaded, reluctantly, to take the work over from FDA.

The NIH reluctance reflected the fact that the problem had become a messy political issue and there was nothing glamorous at all about feeding rats, dogs or monkeys Pb and As month after month when their scarce scientists might be spending their time finding a cure for cancer or heart disease. Furthermore, providing data on which to base tolerances for spray residues on fruit wasn't the best way in the world to find friends in Congress, a requirement for winning ever-increasing budget requests.

Page 32: What Woodard might have said about the reasons for the advance consultation with FDA on toxicity testing was that the industry toxicologists had learned, by bitter experience, that "those guys at FDA" (i.e., the staff of the Division of Pharmacology) found it hard to recommend approval (to their superiors) of a new drug or food additive that had not been tested exactly as they would have done so and lacking that approval, no drug or additive could be marketed. And the industry had also learned that the FDA attitude could change and make a years' work valueless. Thus, it paid well to keep in very close touch with the few whose decisions could be terribly important. The effect this had on those few can only

be guessed but without exception, there was never a breath of scandal concerning any of the Division of Pharmacology staff members. As much could not be said of the Antibiotics Division.

Page 34: Re toxicity testing of drugs: By the mid-40's, the drug makers had become used to complying with the FD&C Act and had set up their own laboratories (such as the one I headed for Sterling Drug) and were wholly competent in detecting any sort of known toxicity in the drug candidates their chemists had produced. Few compounds having significant levels of toxicity (relative to dosage levels at which their beneficial effects were evident) ever came to the attention of FDA. They (the toxic compounds) had fallen by the wayside.

Page 37: This page is missing (blank) in my copy of the transcript.

Page 41: "Coal tar colors", what a specter those 3 words raise! In fact, the colors may well come from the "tar" left after distilling crude oil rather than from producing coke from coal. Yet we keep on calling the dyes, "coal tar colors"!

Page 45: Another anecdote involving Mr. Campbell you may have missed: It happened during the period Henry Wallace was Secretary of Agriculture and tomato canners were complaining to him that FDA inspectors were interfering with processing tomato puree by using a test that isolated fragments of tomato worm skin from the canned product. Mr. Campbell was asked to attend a small conference in the Secretary's office with canners' representatives and took along the chief microbiologist, a highly regarded scientist in the food industry. (I've forgotten his name but he must be mentioned in every FDA history of that period.) The canners told Mr. Wallace how careful their employees were, etc., and only the best produce was used, etc. Mr. Campbell explained the role of FDA inspectors, their tests and tolerances and called upon the microbiologist to describe how insect fragments could be isolated. This he did, saying that the presence of the fragments in the puree indicated that too often huge green tomato worms had somehow been packed along with the tomatoes picked from the vines on which the worms fed. He only regretted, he said, that he had not yet been able to detect "the green custard" inside the worms as he could see the skin fragments but, of course, he continued, tongue in cheek, there wasn't all that much difference, perhaps, between the "green custard" and the red tomato puree. This recital had the intended effect on Mr. Wallace in that he turned a bit green himself, quickly adjourned the conference and made his way to his private washroom to forestall the urge to retch. The inspectors were never again interrupted in testing tomato puree as the packing plants.

Page 46: Re Woodard's skill in drawing the graphs - I taught Woodard how to use the lettering guides and lay out the figures while he was my lab assistant.

Page 48: Re Calvery's attributes. From the 8 years I worked for him, I learned he was fair, obstinate, and doggedly tenacious in his convictions. More than once he told me of how hard he had worked as a graduate student with no financial support. (For example, to give food value to coffee, at 5¢/cup, he added about 1/3 cup of sugar and stirred til the sugar dissolved.) His major professor in chemistry at University of Illinois tried to discourage him from pursuing study for a PhD, saying he'd "never make it". This served only to make Calvery more determined and he found he could study all night with little or not sleep and thus keep up with his classmates.

Incidentally, Calvery held Dr. Lehman, who in time succeeded him, in very low esteem, saying of Lehman, and in language characteristic of Calvery's usage, "He couldm't carry guts to a bear."

Page 50: Lehman, in his home-spun way, was an effective evangelist for better toxicologic testing and the series of articles he wrote (that came to be known as "the Bible") were very effective teaching tools.

Calvery's articles had led the way with Woodard's active collaboration but Lehman was a more effective teacher as well as a sales representative for the J. Food & Drug officials.

Page 61: Ted Klumpp is the correct spelling. Actually, he went to the AMA, on leaving FDA, as Secretary of the Council on Drugs. After being there 6 months (about 1942) he was more or less drafted to become President of Winthrop Chemical Co. which had been expropriated by the government as "alien property". His task was to oversee the absorption of the formerly German-owned company into the newly-formed American company, Sterling Drug.

Woodard is correct, Dr. Klumpp hired me away from FDA.

Page 76: It is noteworthy that while work on mercury to improve its efficacy for treatment of veneral disease was proceeding in the Division of Pharmacology, on the 5th floor, work on penicillin was well along on the floor above in the Antibiotics Division that made mercurials obsolete for this purpose.

Page 103: Re Woodard's comment on "innovative qualities of FDA contributions. Great credit is due for the persistence

and meticulous attention to the vagaries of natural (eg species-to-species) variation in animals in their responses to toxic substances that the Division exhibited over a 30-year period. The fact that there were few turn-overs in staff from about 1938 on helped greatly in their learning what to look for, how to record and report what we found and to avoid the temptation to cut short an experiment no matter how dull it seemed. But Woodard's experience was limited to FDA and his own laboratory. Advances in analytical chemistry were being made everywhere during that period. The first application of the spectrophotometer to chemical analysis was made at Winthrop Chemical by a modest chap named Morris E. Auerbach about 1941 to assay Atabrine. In recognition of this milestone, Beckman Instruments sent an executive to Auerbach's retirement dinner and presented to him one of the earliest models of the Beckman spectrophotometer, similar to the one Auerbach had used. Laug began using the instrument about 1943-44 by which time its use had spread to nearly every analytical laboratory that could afford it.

Page 106: Dr. Vos mentions a drug "dipanthia" that I don't recognize. One he omitted was parathyroid, the assay of which I studied and published in my first FDA paper in 1937. The work on biosassy of most of the drugs Vos cited are discussed in my interview.

Page 107: Braun, Vos and I tried for 5 years with no success to find a way to apply statistics to the post pituitary assay. There was no such thing as an "LD-50 under another guise".

Page 108: The assay of digitalis (in any of its pharmaceutic forms) represented our first success in applying statistics in that the response was "all-or-none" i.e., as observed, the result (at one hour) was positive or negative and (at 18 hrs.) was either death or survival of individual frogs treated in groups. The methods Bliss taught us as extensions of his classical paper on dose-effect relationships in small numbers of animals enabled us to calculate the potency (and the "standard error" thereof) of a test sample in terms of an accepted standard. It was a simple matter to calculate the LD50 in frogs of both the sample and "reference standard" but we had no use for those values. It was the report of this work in the Journal of American Pharmacology Association that earned the 1940 Ebert Medal Award for me as senior author and merit recognition for Braun and Bliss as co-authors.

Vos is correct in saying that statistics had been applied to digitalis assay data previously by Trevan and Goddum in England using Fisher's basic principles but no no had worked out how to obtain a relative potency for a test sample and the limits of error applicable to that value.

Having succeeded with digitalis and drugs related to it, we then set out to find ways of doing the same for all other bioassays being conducted in the Division of Pharmacology. We offered to help the Vitamin Division improve their assays of vitamins but the offer was rejected by Dr. Elmer Nelson, head of the Vitamin Division with the remark that "We must have our assays absolutely correct for them to hold up in court. We cannot admit to any error whatever."

Page 109: Vos refers to two bioassays in USP IX. I have never checked but certainly USP X had the first assays that gave anything resembling a relative potency and then were for digitalis, posterior pituitary, ergot, aconite and epinephrine. Insulin was not added to the USP until 1940. We were never able to work out a satisfactory statistical method for the insulin assay. Now, it is measured almost entirely by a radio-immuno assay of remarkable sensitivity (i.e., blood levels can be determined) and accuracy.

Page 113: Re the change in animals for the digitalis assay cited by Vos, see comments in transcript of my interview. In brief, the sequence was frogs (first for only a 1-hour observation period and then for 18 hours), cat for perhaps 5 years and finally to pigeons for practical reasons. About 1965 a simple colorimetric chemical method had made the bioassay obsolete for all products then in use except Tincture of Digitalis, the use of which was almost nil.

As to Dr. Young's questions, "why pigeons?" There were reports in the literature on the effects of digitalis on almost every laboratory animal and many tissues such as embryonic heart tissue. I once spend a day observing the latter and concluded that the claims for its use in the digitalis assay were unduly optismistic.

When the so-called "cat assay" went into the USP, ever city in America was overrun with stray cats and collectors could make money selling them at 50¢ each. The demand soon outran supply and when the price went to $3.00, we turned to pigeons which were bred under controlled conditions, were more uniform and much more docile to handle. Their reaction to digitalis was such that a reliable assay took no more of them than of cats. Except for ridding cities of stray cats for a time, we'd have been much better off to have gone to pigeons from frogs, or indeed, instead of ever using a cold blooded animal at all. Re the change from cats to pigeons, it was facilitated by our having developed statistical (strictly speaking "biometric") means of showing that the results on pigeons were certainly no less reliable than those on cats. Dr. Vos mentioned the collaborative testing on each change in assay procedure and of various proposals for refinements. It

is true that we began using collaborative testing as the result of the publication of the Miller, Braun and Bliss article, the thrust of which was to provide a novel means, wholly objective for the first time, of comparing the results obtained by two procedures and thereby choosing the better one. Having published the method, it fell to my lot to analyze the data from as many as a dozen labs at times, at first at FDA and then at Winthrop after 1943. With the help of assistants whom I had trained, I must have compiled and analyzed the data from a dozen collaborative studies on digitalis (at least 5), posterior pituitary, epinephrine and heparin. All the tests were conducted for the U. S. Pharmacopeia, the need for and ways of conducting them having been decided by a group of experts requested to do by the USP. The USP distributed a report on every test, held conferences on the action to be taken in the light of the results, all with full participation and cooperation of FDA.

Concluding comment - what has struck me in two readings of this transcript is the evidence of how little some of those present (regrettably, you only had four) seemed to recall of activity or programs taking place in the Division with which they were not involved. Woodard is an exception because, in part, at least of his special relationship with Calvery. Also, Woodard had moved about from one lab to another which none of the others had done, especially Fitzhugh who spent his entire career doing chronic toxicity. Woodard started in the bioassay program, as my assistant, and ultimately became Calvery's right hand man because he was intelligent, articulate and industrious. He related to me that his decision to leave FDA reflected an inability to get along any longer with Dr. Curtis. Had Calvery been alive and in charge, the problem would have been worked out - probably more to Woodard's satisfaction than otherwise.

The lack of discussion of two areas is a serious gap; I refer to the insulin certification and the endocrine program.

My interview covered the early days - or rather, the hectic period of 4-6 weeks prior to enactment of the Insulin Amendment to the FD&C Act. The best one to tell the entire story is Dr. R. L. Grant who lives in Fairfield, Pennsylvania, 4 Elm Trail N.W., Carroll Valley, Fairfield, PA 17320, a short distance from Gettysburg. His heart is not good but his mind and memory are sound; I last visited him early in February. I'm sure that if you and Dr. Young sent him a few leading questions and a cassette of tape, he would be willing to borrow a recorder and reminisce into the mike. The insulin program was important both in concept and administration; it worked well for various, unrelated reasons.

The endocrine, or rather, the program to control the reproductive hormones was perhaps less exciting and successful in some ways. The loss of the suit against Hynson, Westcott and Dunning was a bitter blow. Dr. Umberger is the only person surviving, to my knowledge, who might cover this area. He still lives in the Washington area.