HISTORY OF THE U.S. FOOD AND DRUG ADMINISTRATION

Interview between:
Dr. Daniel Banes, Retired Director
Office of Pharmaceutical Sciences
and
James Harvey Young
Emory University
Robert G. Porter
Food and Drug Administration
Silver Spring, Maryland
June 17, 1980

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.

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

DATE: 6/17/80 PLACE: Silver Spring, Maryland LENGTH: 120 Min.

INTERVIEWEE	INTERVIEWER
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FDA SERVICE DATES: FROM 1939 TO: 1973 RETIRED? Yes

TITLE: Director, Office of Pharmaceutical Sciences
(If retired, title of last FDA position)

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Porter: This is a recorded interview at the home of Dr. Daniel Banes in [redacted] on June 17, 1980. It is one of a series of interviews of retired FDA employees being recorded for the current history project. Present in addition to Dr. Banes are Dr. James Harvey Young, FDA Historian and Robert G. Porter. Dr. Banes, I wonder if you would start our record today with a brief resume of your career with the Food and Drug Administration and since your retirement so that the people who use this material in the future will know who you are.

Banes: I joined the Food and Drug Administration in 1939 during an expansion of the agency following passage of the Food, Drug and Cosmetic Act of 1938. I was a chemist in the Chicago station, as it was then, from 1939 to 1942. In 1942 I joined the Army-Air Force as a trainee in meteorology and later as an officer in the Air Force as a meteorologist. At the conclusion of the war I returned to the Chicago station and served there for 3 years and then was recruited for research work in the Chemistry Branch of the Division of Medicine. I worked as a research scientist from 1948 until the early '60s when I went into administrative work as assistant to the director of the Bureau of Biological and Physical Sciences.

Porter: Was that Bob Roe?

Banes: Bob Roe. Soon afterwards, I was appointed Director of the Division of Antibiotics. For a brief period, until a

reorganization in the Food and Drug Administration put me in as Deputy Director of the -- that was when the Bureau of Biological and Physical Sciences came into operation. I have difficulty in remembering what the units were named following the various reorganizations. Dr. Somerson was brought in as director of that bureau, and Mr. Roe continued as director of those divisions having to do with--directly with regulatory matters.

Porter: Was yours the Bureau of Scientific Research?

Banes: Bureau of Scientific Research.

Porter: And you were deputy to Somerson?

Banes: Deputy to Somerson, that is correct. I am trying to remember the chronology here. It was in 1968 I think that I was appointed Associate Commissioner for Science.

Young: I think that's right.

Banes: And I remained in that post for 2 years and then went back to administration of scientific activities, as a Director of the Office of Pharmaceutical Sciences. That was made a component of the Bureau of Medicine. So that the cycle was that when I first joined what later became the Division of Drug Chemistry, they were the Chemistry Branch of the Bureau of Medicine. That was taken out of the Bureau of Medicine and combined with other divisions, first the Bureau of Biological and Physical Sciences and then as the Bureau of Scientific Research. And the final reorganiza-

tion, which I participated in, brought in those drug activities in the Office of Pharmaceutical Sciences again as a component of the Bureau of Medicine.

Porter: Renamed the Bureau of Drugs, I guess, at that point?

Banes: Renamed the Bureau of Drugs, that is correct. Parallel to the Bureau of Foods.

Porter: Then, did you remain in that capacity?

Banes: I remained as Director of the Office of Pharmaceutical Sciences until my retirement in 1973.

Porter: You've done some interesting things since then, too.

Banes: Following my retirement from the service, I joined the United States Pharmacopoeia as Director of Drug Standards Division. And, at the close of 1978, I retired from the United States Pharmacopoeia. Resigned from that position, but was retained as a consultant for U.S.P. on various projects.

Young: Your own special technical competance as a result of your graduate work and experience would be defined by what bounds?

Banes: My primary activity, as a result of my experience and education, lay in the study of the composition of drugs, the analysis of drugs. Those two, of course, are very closely interrelated. The regulatory monitoring of drugs

and the composition of drug monographs--that is a document which sets forth the characteristics of drugs expressed as standards, and the analytical methods for determining whether a particular product under examination does or does not meet those standards. The process of bringing out satisfactory monographs or regulations for that matter, concerning the composition and analysis of drugs, that process is one of continuing refinement, as the pharmaceutical sciences progress and new information is brought in concerning the application of these standards.

Young: The way that is done now in comparison with the way it was done when you first became associated with the agency must be revolutions apart. Could you speak to the changes of the most significance that you would think of offhand?

Banes: Well, the most significant change in those years was the development of new methods of analysis, primarily with respect to chromatographic methods and measurement of drug properties by the use of spectrophotometric methods, including ultraviolet and infrared spectrophotometry, nuclear magnetic resonance, x-ray diffraction, and other such methods which were not available for application in the late '30s when I joined the Food and Drug Administration. But over the years, and the course of their developments they were applied to the analysis of drug substances.

Young: Did Food and Drug scientists play a significant role -- innovative role -- in these methodological changes?

Banes: I could not say that any of the newer methods were invented by scientists in the Food and Drug Administration. But they were applied very early, and, in some instances, the first application of the newer methods to drugs were brought out by scientists in the Food and Drug Administration. And, particularly in the Research Division of Drug Chemistry or Pharmaceutical Chemistry or the Chemistry Branch of the Bureau of Medicine, whatever it's called.

Young: Do you happen to think of a couple of precise examples of this very early use that are memorable, perhaps?

Banes: In 1943 or thereabouts, during the W.W. II, it was necessary to analyze large numbers of samples of quinine and quinine preparations. Almost all of those analyses were performed in the Chicago Station. Samples collected all over the United States were accumulated in the laboratories of the Chicago Station. Jonas Carol who now is, unfortunately, deceased, was one of those who saw the applicability of ultraviolet absorption measurements to drug analysis and he developed an ultraviolet spectrophotometric method for the determination of quinine in the drug substance itself and in capsules and tablets or other preparations containing quinine. He did all of his exploratory work on an instrument that was in the laboratories of the American Medical Association in Chicago because the Food and Drug Administration didn't have an instrument that was operative

in the range that he needed. And he did work out an analytical method for quinine which permitted him to analyze scores of samples during the course of one working day. Where, using the official methods and those developed for the AOAC would have permitted him to analyze a mere handful. And in checking the ultraviolet method by the conventional method, he found that his results were quite reliable. Since the purpose of the analysis was to distinguish between preparations that had the proper amount of quinine and those that did not, he was able to screen these preparations extremely rapidly. As I said before, this was not a new invention, it was not completely innovative, others had applied ultraviolet absorption to drug analysis, but here was a demonstration that this method could be put to use for rapid analysis of drugs and he then applied it to other substances that absorb ultraviolet.

Porter: So it was innovative in the sense that it was applied to an enforcement problem.

Banes: I think that was the new aspect of the application of that instrument. Jonas was also responsible for investigating the application of infrared spectrophotometry to drug analysis. Because of his activities, the Chemistry Branch secured infrared spectrophotometers and, when Jonas had shown again that this was a unique method for determining the identification of drug substances and also in

some instances for the assay of drugs, the utilization of this instrument was much expanded by the purchase of instruments for the field.

Porter: Are you familiar with the speech Jonas gave sort of looking back on some drug analysis problems. A speech that has been, I suspect, reprinted a number of times? The reason I ask you is that I have a copy of that and he speaks of some of these things that you've been talking about, and I thought that it might be that we could sort of attach it as an appendix to this, if you didn't mind.

Banes: Not at all.

Porter: It's very pertinent to what we've said. I'll do that; I'll get it typed up in the same format.

Banes: He made a speech before the New York Academy of Sciences, that might be the one.

Porter: That might be it, I really can't tell you.

Young: It was a part and parcel of the science of the agency to get its innovations into print wasn't it?

Banes: Yes, when we analyzed samples or someone had solved a drug problem which seemed intractable before, we were encouraged to publish the results of our findings in scientific journals. Many of them appeared in the Journal of the Association of Official Analytical Chemists, because that organization was very much tied in with the activities of the chemists in the Food and Drug Administration. We

also published a number of papers in the Journal of Biological Chemistry and Analytical Chemistry of the American Chemical Society. And in other journals interested in this kind of work. Of course, it was innovative research that most of these journals were looking for, whereas the Journal of the AOAC was devoted to publishing adequate methods of analysis, which is really applied research.

Young: Back in the early years when I mostly did all of my research, in connection with different kinds of assays, it seemed to me that there was a lot of biplay back and forth between the Food and Drug Administration and the U.S.P. The U.S.P. would develop a method and then in connection with its drug research and mainly, back in this period, they were testing botanicals the official method wouldn't be quite sufficient, so then the Food and Drug Administration would push things further and develop some new kind of assay. And then I took it that it would go back to the U.S.P. and eventually become official. So that there was some kind of interaction. You've been with both agencies, does this sort of interaction between the Food and Drug Administration and the U.S.P. with regard to methods continue? Has this been a harmonious thing, or have there been times when there's been tension, because both are, in a sense, involved with the need for standards and the definition of what they should be?

Banes: Well, of course, it is difficult to avoid tension or friction when two different institutions are in the same field of endeavor. But, on the whole, I would say that the relationship between F.D.A. and U.S.P. has been harmonious during the 40 years or so that I have been acquainted with their work and their relationships. You are quite right that in the years in the '30s and the '40s, the Food and Drug Administration did develop methods of analysis that were eventually incorporated in monographs of the United States Pharmocopoeia. That kind of relationship has continued. As a matter of fact, at present, the field is devoting many many years of work to examining monographs of the U.S.P. to determine whether they are satisfactory for their purposes or whether changes are needed. And, if changes are needed, what those changes ought to be. The section of the Food, Drug and Cosmetic Act that says that the Food and Drug Administration should cooperate with the scientific societies for the improvement of U.S.P.--that section is honored by F.D.A., and of course U.S.P. appreciates that.

Young: Then these standards become official for the Food and Drug Administration under the law as well.

Banes: Yes. The scientific activities in drug chemistry in the Food and Drug Administration are directed toward--- The purpose of scientific research in drug chemistry is to

detect adulterations in drug products and to develop standards and methods of analysis for drug substances. In carrying forward those functions, the Food and Drug Administration, Division of Drug Chemistry have sometimes been involved in actions that can only be described as detective stories. But the episode in which adulterated ipecac was detected illustrates the point of findings with respect to adulteration. And also the question raised about changes in official standards in the United States Pharmacopoeia. The ipecac episode occurred in the '70s, I think, early '70s. Eli Lilly & Company reported to the Division of Drug Chemistry or rather to the Food and Drug Administration that it had been necessary for them to recall a batch of ipecac syrup. Are you acquainted with that?

Young: I was encouraging you to go on. But not saying that I knew a lot about it.

Banes: Eli Lilly & Company reported that they had recalled a batch of ipecac syrup because it did not show the emetic properties that are characteristic of that drug. They sent a sample of that ineffective preparation to the Division of Drug Chemistry for analysis. And also to the Cincinnati District, the home district of Eli Lilly & Company, located in Indianapolis. The preparation met the requirements of the U.S.P. which said that, ipecac syrup shall contain a certain percentage of total alkaloid. The substance was

analyzed by a method developed in the Division of Drug Chemistry, primarily by Joe Levine, who was a very gifted chemist there. The method employed involved column chromatography. By selection of solvents, eluding substances from the column, Joe Levine was able to show that the ipecac alkaloids constituted a fraction of the total--anywhere from about 10 to 80% of the total alkaloids in the product. But there was another alkaloid that is not characteristic of ipecac which would, therefore, contribute to diminishing the potency and emetic effect of the preparation. By application of known methods of analysis, he was able to show that the adulterating substance was elephedrine. Given that hint, inspectors of the Food and Drug Administration working on the premises of the company that had prepared the extract of ipecac to sell to Ely Lilly & Company, were able to show that there were purchases of elephedrine by that firm. So that we had a complete picture of the adulteration of the ipecac.

Porter: It wasn't accidental then, it was intentional?

Banes: It was an intentional adulteration of the substance. Elephedine being much cheaper than extract of ipecac. And Eli Lilly & Company, when they purchased the material, applied the analysis in U.S.P. which was a general method to which elephedrine would respond just as the usual alkaloids of ipecac. Consequently, Eli Lilly & Company didn't catch the adulteration.

Young: But Eli Lilly & Company had had complaints about the medicine not doing the job it was supposed to be doing, that was how...

Banes: Correct. And they came to the Food and Drug Administration and requested assistance.

Porter: I presume there was a recall then.

Banes: There was a recall of several batches of the Ely Lilly & Company material which had been supplied to them by the same firm. And, as I say, the amount of adulteration varied from a small quantity to the major part of the alkaloid. But, this event showed that the standards in the U.S.P. had to be modified in order not only to detect such adulteration, but also to show the proportions of the two major alkaloids in the active drug product. There were two major alkaloids, both of which induce emesis, but in different proportions. That is these two alkaloids haye differing strengths. Cephaeline and emetine are the two substances. And I believe it's the cephaeline that is the more effective in inducing emesis. There are different varieties of ipecac that are shipped from Central and South America, which is their native habitat. And, as a result of our new definition of what ipecac syrup should be, showing cephaeline as the major alkaloid, the U.S.P. eventually adopted the method developed in the Food and Drug Administration and changed the standard to say that it shall

contain the alkaloids of ipecac, but isolated by means of this new method of analysis with a demonstration that cephaeline is a major component.

Young: Did legal action take place against the company?

Banes: I think the recalls were sufficient to impress upon them that there had been a departure from proper activities, but charges were brought against the person who committed the adulteration.

Young: That's what I meant. Not Ely Lilly & Company. So one might find that this case was settled and there was some kind of notice of judgment. If that was so, do you remember the name of the company?

Banes: I believe the name of the company was Curran. And there were charges brought against the individual who was involved.

Young: That would mean a criminal case.

Banes: Yes.

Young: That is a good example of several principles that we were speaking of.

Banes: I think so. First of all, detecting the impurity and identifying it quantitatively. In the course of that work, the Food and Drug Administration developed a new method of analysis for ipecac itself and for ipecac preparations. The study of the composition of various species used to prepare the drug and brought about a modification of

the standards of analysis of the drug and induced the U.S.P. to adopt these standards and analytical methods. So we have here the whole range of activities in drug chemistry.

Young: So the companies who make this preparation, like Lilly, would automatically have to employ these methods in the future so they could meet the U.S.P. standards for the drug to be legal in interstate commerce.

Banes: That is correct. The improvement would be to the benefit of the industry as well as to the consumer. The purpose, again, is to improve methods of analysis, to improve the standards for the benefit of the public including that component of the public which is drug manufacturing establishment.

Young: Was it for audiences in the industry and audiences within the agency that you prepared the various works, various publications that are listed in Who's Who?

Banes: Yes. The publications are for the benefit of all interested parties. Including scientists in industry, scientists in academia.

Young: I would appreciate it if you would define these works so that a layman would understand what you are about as a scientist in preparing them.

Banes: Our scientific approach in determining the composition of drugs would start with awareness of the problem with respect to the composition of the drug. And to resolve that

problem, we collected specimins of the drug in question, both the active ingredients and the finished dosage form. Analyzing according to the conventional methods and determining the source of the problem and going on to develop new methods of analysis which would bypass the problem and lead to a solution of the problem. I think I can illustrate that best by referring to a particular instance, that of digitoxin. Digitoxin is an extremely potent drug used to strengthen the heartbeat and is therefore a very important drug. It is necessary to prepare dosage forms containing digitoxin very carefully because there is a very small margin between the effective dose and the toxic dose. The problem was brought to the attention of the Food and Drug Administration by the U.S.P. in this instance. Lloyd Miller, who was then the Director of Revision for the U.S.P. came to the Division of Drug Chemistry and informed them that, although the method in the U.S.P., which consisted simply of an extraction of digitoxin from the mass, that method worked satisfactorily for just digitoxin itself, but when the specimen of digitoxin was incorporated into tablets and examined by another mode of extraction, the content of digitoxin was found to be quite low. The Food and Drug Administration collected various samples of digitoxin and, analyzing them by a new method developed for this purpose, were able to separate digitoxin

from other components extracted from digitalis leaf, the source in nature of digitoxin. By applying this method, they showed that the samples of digitoxin in the marketplace were really a mixture of two substances, very closely related -- one of them digitoxin, the potent drug, and the other gitoxin, a derivative of digitoxin, very closely related to it -- it contains one more hydroxyl group in the structure of the molecule. But gitoxin is almost devoid of the theraputic effect that is desired with digitoxin. Now, the simple extraction method in the U.S.P. for the durg substance itself, took up both digitoxin and gitoxin. And then when the colorometric tests, to which both of them respond in the same way, was applied to the extract, it appeared as if the declared quantity of digitoxin was present. But, when the more complicated method in the U.S.P. for digitoxin tablets was applied, the gitoxin remained behind, and only the digitoxin was extracted and consequently, the end result was much lower than anticipated. And, we showed by our analyses that the digitoxin samples in the marketplace, contained varying proportions of gitoxin, from about 2 or 3% all the way up to 30 or 40%. After pointing out these differences to the U.S.P., we wrote up our method of analysis for them and induced them to incorporate that method in the U.S.P. The newer method developed for this purpose was to separate digitoxin, to segregate it

in a fairly pure form and then to determine gitoxin by itself using other solvents. In that way we were able to show that when tablets of digitoxin were made up from a so-called digitoxin drug substance, we were able to show that the total of digitoxin plus gitoxin corresponded to the total in the original drug.

Young: This was giving counsel as to how the tablets might be made, also, in order to be in potent form. Or was that a problem the industry had to face?

Banes: No, the important part of the activity was that we induced the U.S.P. to tighten its standards for digitoxin. The new standard says that samples of digitoxin, so-called, must contain the pure active substance to the extent of not less than 90%. And that meant that the gitoxin present could be no more than 10%. It would knock out of the marketplace those samples of digitoxin that had large quantities of gitoxin, the inactive substance. And, consequently, the tablets made from the digitoxin that remained on the market, contained at least 90% of the very active steroid. The tablets made then from the digitoxin permitted in the marketplace, would have their full potency and our analysis would show that.

Porter: Was this so much a group effort or could you pinpoint somebody to more or less credit the scientific work done in that instance?

Banes: Well, the methods of analysis and most of the work involved my effort. Although, I must say that, having gotten the method into the U.S.P., we are now at a point where newer methods of analysis will supercede it. It worked satisfactorily during the time period when the work was done.

Young: And that time period of which you are speaking falls roughly where?

Banes: The method developed in the Food and Drug Administration came in the early 1950's and will be superceded when U.S.P. validates a method using high pressure lipid chromatography. The chromatographic method that was the basis of the test developed in the Division of Drug Chemistry involved a much simpler kind of procedure, column chromatography.

Young: And this is the way of the art?

Banes: This is the way methods of analysis are improved and standards generally are tightened--a continuous process as we develop new information about the shortcomings of methods and standards in Pharmacopoeias. We work toward their improvement.

Young: You mentioned several of these examples in which yourself and other scientists in the Food and Drug Administration have done these things. Would you turn to the matter of the problem of having scientists of this cap-

ability within the Food and Drug Administration when industry, within a relatively limited group of scientists of any discipline, can get higher salaries in industry, can have certain advantages in academia perhaps of picking their own field of inquiry a little bit more freely than might be true in a government bureau. I'm not sure if that's so or not, you can speak to that. What about the problems of maintaining a scientific capacity? You had that task.

Banes: One of the major disabilities in maintaining scientific capacity at high levels in the Food and Drug Administration has been associated with the lesser economic advantages in government as compared with industry. But there are advantages to working in government. And, in some instances, the high-grade scientists would prefer to work in government. One of them is almost free publication. Permission to publish results of findings in journals which might be more limited in industry because of the fear of divulging secrets. So there are advantages to working in government, but I think you are correct in saying that the salary differential would make industry more attractive. And the fact that, very often, government finds itself in a situation where it is impossible to--they are not permitted to recruit scientists. The number of positions are frozen by budgetary considerations and, of course, that makes it difficult to maintain scientific activity on a high level.

Young: How, when you were in positions of responsibility for the science of F.D.A., how did you go about working to keep the scientific level as high as possible?

Banes: The approach is to give the scientists, who have shown the quality of their work, the promotions that they are entitled to as rapidly as possible. That is to argue the merits of getting these people their recognition by awards and by grade promotions, and to encourage them to publish their findings.

Young: You were in F.D.A. at the time the 1962 law was passed and put a lot more pressure on the scientific capacity of the agency, particularly in connection with the review of all drugs in order to be sure that they met the efficacy standard. This must have been quite a crisis to get the larger staff. In fact, wasn't this when scientists were borrowed from the Public Health Service to some extent? Or maybe that wasn't related to your particular part.

Banes: One of the provisions of the 1962 amendments was the certification of all antibiotics, whereas previously only 5 classes of antibiotics were certified. And this expansion of the work of the Division of Antibiotics required the scientific staff of the Division of Antibiotics as it was... At that time we simply went out and recruited rapidly.

Young: There was an expansion in positions given?

Banes: Yes. So, in that instance, we were able to recruit people for the work to be done.

Young: As you look back upon it, you don't give me the impression that you were desperate all the time for manpower to meet the task that you had.

Banes: Well, the tasks are all without limit and I think it's a fact that every scientific administrator always needs more people. I don't think that at any time we had a surplus of scientists, but I don't think we were desperate.

Young: Did you think that the almost alarmist tone of the first and second citizens advisory committee reports about the scientific competence of the agency--from your point of view, might be somewhat exaggerated?

Banes: I think we had competent scientists, but as I say, we always could use more of them because, I'm sure, that many many problems in regulation of drugs went by the boards because we didn't have sufficient staff to take care of all of them. We attempted to resolve the most pressing and the most significant drug problems. And deferred attention to others.

Young: So you rather welcomed this kind of statement that...

Banes: Yes, any kind of a statement that would lead to an enlargement of the scientific staff would have been a benefit to the Food and Drug Administration. From that standpoint we did welcome its findings.

Young: You were in these positions of authority during some of the most important administrative changes that the agency

ever had. The earlier dynasty system came to an end, rather deliberately planned, I guess by the authorities higher than the administration. When Dr. Goddard was brought in to be Commissioner instead of someone from within the Agency, as had been true for many years, and, from that point on, the tenure of commissioners has been shorter than had been true earlier and even before that. Certainly through the period that followed, while you were there, there were different kinds of administrative changes from on high. Did these administrative changes, although they might effect the field and headquarters and so on, did these have much of an impact on you? Or did the work of science proceed unruffled by this somewhat more chaotic period compared with the old days?

Banes: Well, inevitably, the changes that you mentioned, especially the short tenure of the leading officials of the Food and Drug Administration, inevitably these changes did affect the activities of scientists in the Food and Drug Administration. But, I think that the scientific concerns were fairly well insulated. And consequently, they proceeded according to the same kind of outlook in spite of the changes at the time.

Young: So it wasn't quite the same as it was maybe in the regulatory side?

Banes: It wasn't catastrophic. Because as long as the scientists had their assignments and knew the purpose of

their activities, they were able to perform as previously.

Porter: How about in the other direction, did say Goddard's philosophy, for instance, enhance the work, the scientific work?

Banes: I think not.

Young: More attention came to be paid to prescription drugs under him. And because of the law that you were just gearing up to enforce. But it was sort of a turbulent period.

Banes: Yes, it was.

Porter: For some of us, it was very turbulent. For me it was.

Young: I expect to get you on tape another time. And the kind of case histories that you have been giving, then became fodder with much else for the manuals and the books that you prepared, is that right?

Banes: Right.

Young: And so they just, these are broad works that treat drug chemistry pretty much across its whole perimeter.

Banes: Yes, the contents of the books to which you refer were naturally based on my own experiences. But they are applicable to all drugs. Our first approach to writing these books in cooperation with the Education Branch of the Food and Drug Administration was to compose a series of chapters useful in teaching drug analysis to scientists in the field. Our first book published in that field was

Introduction to Regulatory Drug Analysis. The individual chapters were sent out to the field for home study as well as application in the laboratory. With questions provided at the end of each chapter and a list of correct answers sent out to the chief chemist to be used in discussions with those taking the course. I think that program was fairly successful. The field had every chemist doing drug work, taking the course.

Young: It was a true textbook.

Banes: It was intended as a textbook. It had it's faults but I think it was a successful endeavor.

Porter: Well, there was a real need for it.

Banes: Well, there was a need felt and I wrote that manual in response to the...

Porter: What year was that?

Banes: About 1964, perhaps a little bit earlier.

Porter: I was thinking that it hadn't been too many years previously that the drug work had been concentrated in 3 or 4 laboratories, and by the time you are talking about...

Banes: It had been taken over every place.

Young: '65, I think that's when it was.

Banes: In connection with that workbook, there was a touring group from the headquarters, Division of Drug Chemistry, that went out to various field districts and presented a one week seminar with the analytical part and the laboratory

part being devoted to those case histories as you refer to them, as the basis for the course. Now these were problems that were resolved in headquarters and the field was not involved originally in that work. But once the methods were sent to the U.S.P. and became the official methods, then the field districts would have their personnel analyze samples collected in accordance with these analytical methods and standards in the Pharmacopoeia. Consequently, we thought it worthwhile to give the field the background of these methods and indicate to them why they had been developed. What the problems were that we had encountered. And what were the tricks of the trade, so to speak, in applying these methods to the sample. Those seminars were set up before the publication of the manual so they would have been in 1962-'63. The drugs that we were chiefly interested in were sex hormones, estrogens in particular, corticosteroids, digitoxin, and related substances. And a couple of alkaloid drugs.

Young: In the case of digitoxin and then later the ipecac, they are generic drugs?

Banes: Yes.

Young: I take it there were instances of where they were being produced and they showed a need for scientific tightening and even for regulatory action. New drugs are sort of another field from the point of view of your scientific agency. What was the kind of interaction involved

with new drug applications? Would these be brought to you for a review of the pharmaceutical chemistry presented in the new drug application? Are there instances there that you could cite showing the functioning of the scientists in relation to new new drug applications in making the determinations that needed to be made to be sure that the drugs were proper to market?

Banes: The standard approach to new drug applications involves checking the analytical methods provided by the company in both headquarters and the field districts. There were instances where the analytical methods in the new drug application, especially in the earlier years, say the '60's, were defective or were so general that they were unsuitable as a regulatory method. I can't think of any particular instance, but it was a fact that early on the methods provided with the new drug application were useless as regulatory tools. And, in some cases, they were even inapplicable to the drugs manufactured by that company.

Young: And that would just end the application. Or it would go back, at any rate to them for them to...

Banes: Yes, to improve them. But, you're right, the approach is quite different from that in which the Food and Drug Administration itself undertakes to solve a problem. And, in the generic field, in the case of new drug applications, the problems are much more readily resolved. And

it's encumbant upon the manufacturer to improve them.

Young: Sure, you're just holding up a yardstick there. And then the burden is on his shoulder. And that's what the law deliberately intended.

Banes: So the detective work is far more infrequent now than it used to be. But even with new drugs, unforseen, problems are encountered and the Food and Drug Administration is sometimes involved in resolving these new problems. So that the function of the research group in the Food and Drug Administration in Drug Chemistry remains a necessary part of the agency's operation.

Young: Now, let me just hypothesize, you say that in connection with the problem relating to a new drug, the Food and Drug Administration gets sometimes involved in this. Would this mean that it would be a very promising new drug that the Food and Drug Administration, for purposes of society, might be eager to move along the line toward marketing, but there still are problems and therefore it would help resolve some of the problems--is that the kind of thing you meant? Or am I misinterpreting?

Banes: What I meant is that regulatory problems may be encountered with a drug being already in the marketplace. And then it's the purpose of the Food and Drug Administration to resolve those regulatory problems as rapidly as possible. Although the responsibility still rests with the manufacturer.

Young: A drug which may look good, but which in vaster experience shows something like chloromycetin, is that the kind of thing you had in mind? Shows problems that didn't appear in the preliminary evidence before it was marketed.

Banes: Well, that would be unforseen problems, pharmacological problems. I was thinking more of analytical problems. Although the same things are valid for an analytical problem as well as for a pharmacological problem. The purpose is to see why the problem has arisen, what undetected impurity may be the root cause of this problem. And to bring it to the attention of the manufacturer. Sometimes a problem might be resolved in the laboratory of the Food and Drug Administration more rapidly than in the manufacturer's laboratory.

Young: Is this something that you could exemplify? While the tape was off you indicated that, while you were at the University of Chicago, as a Master student, you did observe Ajax Carlson. And we both know that he was an expert witness for the Food and Drug Administration in a host of cases. I've written up a couple in which he was. One of the things that I would like to do sometime is to do a separate article in which I would pay him the tribute which he deserves for being such an effective expert witness for the Food and Drug Administration in a whole broad spectrum of cases. I have gotten certain impressions of him as a

person, but I would appreciate very much if you would speak of him as a person and did you ever witness him on the witness stand yourself?

Banes: I don't think so. My experience of him was as a student when he lectured in physiology. And his manner of presenting the material, his directness and its force, his competence and his humor were what struck me.

Young: Did he retain his accent?

Banes: Yes.

Young: Can you think of a characteristic anecdote that you remember that shows him off?

Banes: Well, there were anecdotes that circulated about his comments in class. There was one about asking a young lady to name an organ that increases remarkably in size when in use, you know that one, don't you? She blushed and said, "oh professor why are you asking me?" He said, "well I can see 3 things about you that are reflected in your answer. In the first place, I'm not thinking of what you're thinking of, I'm thinking of a part of the eye when light is impinged upon the lens. You didn't study your lesson. And, you're going to be very much disappointed when you get there."

Young: That's a good story, I hadn't heard that one. I had heard about how deft he was on the witness stand.

Banes: Well, he knew his field, he was very competent, very confident, and was experienced as a witness. He was extremely effective.

Young: And so you wanted to attend his classes?

Banes: Yes, his classes were extremely popular.

Young: Did you know Ivy in Chicago? Or had he gone on?

Banes: Yes, he had gone on to the University of Illinois. And I saw him testify on the stand on behalf of Krebiozen. Krebiozen, of course, was a big research effort in the Division of Drug Chemistry.

Young: Do you want to speak about the efforts that were made in order to identify it? Because Krebiozen needs to have more attention ultimately in the historical framework, I think.

Banes: Well, Krebiozen was one of those preparations which crop up from time to time as the cure for cancer. There have been many other candidates for that distinction. And although Krebiozen is not as well known now as it was before, we have Laetril, and undoubtedly will have other preparations in the future as a cure for cancer. Krebiozen gained notariety, I think, because of Dr. Ivy's association with it and his endorsement of the material as a cure for cancer. Although, if I'm not mistaken, he said on the stand that he had never seen Krebiozen, had never handled it as it was sold by the Durovic brothers, but that he was doing research along parallel lines and he would discuss his research with the Durovics. And what they were doing would lead to the kind of drug that he was trying to extract from

the serum of innoculated horses. The Food and Drug Administration became involved in the Krebiozen case as a result of the 1962 amendments, which required that all drugs be tested for both safety and efficacy And required that all manufacturers of drugs submit the new drug application for any drug which was not recognized as safe and effective by experts in the field. The Food and Drug Administration then attempted to send inspectors into the premises of the Durovic brothers to witness their manufacturing practices. But, the Durovic brothers somehow managed to evade their attempt and their final statement to F.D.A. was that they were going to engage only in intrastate commerce in the state of Illinois, and that therefore their material was not subject to the provisions of the Federal Food, Drug, and Cosmetic Act. But, in a gesture of cooperation, one of the Durovic brothers gave the inspector a vial of about 10 mg. of crystalline material and said this is Krebiozen. Prior to this time, there had been some negotiations between the Durovics and the National Institutes of Health to monitor a large scale study on the efficacy of Krebiozen in human populations, using double blank studies. There actually were tests, I think, because there was a large number of case histories examined by a group of experts in the vicinity of Washington. Their conclusion, I think, was that efficacy was not demonstrated. But the Food and Drug

Administration was very much interested in the identity of the material handed to the inspector as Krebiozen. And I can recall a meeting of the Food and Drug Representative and the attorney of HEW, the general counsel to HEW, and the various research positions to mull over what we had on hand, what we knew about Krebiozen from the transactions involving the Durovics and the National Institute of Health. In order to come up with an approach to the analysis of these precious 10 mg. The Durovics had given us a formula based on analysis for elements $C_{24}H_{67}$ a very complicated formula with high numbers of atoms in the molecules. And they had a brochure which was similar in appearance to brochures put out by the various drug houses for their materials. It had a discussion of the chemistry of Krebiozen. Said it was soluble in a few solvents like aceto acetic acid, ethyl acetyl acetate, but insoluble in most organic solvents and with a very high melting point. And it was encumbant upon the Food and Drug Administration to weed out those things that seemed factual and those things that seemed entirely fanciful. What seemed fanciful was the complicated molecular formula and the pattern of solubilities in different solvents. The stuff was soluable in water and one organic solvent which was highly non-polar but not in other solvents very closely related to it. So that we rejected and the method of preparation we rejected, but the fact that the

stuff had a high melting point and the fact that NIH had prepared an infrared spectrum of the material. If NIH had been given the same material as FDA did, then we could study the spectrum and determine from the shape of the spectrum what the composition of the substance might be. The high melting point and the shape of the infrared spectrum indicated that the substance might be an amino acid.

Young: This is detective work too.

Banes: Yes, yes, definitely all detective work. And the Division of Drug Chemistry then undertook to examine all of the infrared spectra available to them, especially those amino acids, and eventually they came across the spectrum of creatin-monohydrate and it appeared as if the spectrum obtained by the National Institute of Health was identical with the spectrum of creatin-monohydrate. So that, if the material handed to us gave the same spectrum, then what they had given the government in 2 instances and referred to as Krebiozen, was actually creatin-monohydrate. Now, creatin is prepared from the muscle tissue of horses and other animals. In fact that is a laboratory experiment for the preparation of creatin -- to extract muscle tissue and crystalize out of it creatin-monohydrate.

Young: No injection is necessary?

Banes: No injection is necessary. And innoculation isn't necessary. But here is a substance associated with the

organs of a horse. It is an amino acid and has a very high melting point, and its composition is very closely related to the composition given us, because, if you multiply by 6, the simple formula for the elemental composition of creatin-monohydrate, and add one or subtract one in those large numbers for the carbon, hydrogen and oxygen, then you would get a corresponding formula. So that if we had attempted to analyze the material for the elements, we would have found that the formula ascribed to the substance by the Derovic brothers would seem to be valid. Such an analysis would have taken all of the material given to us and what we wanted at this point was a large number of independent tests which would indicate whether the substance is or is not creatin-monohydrate. So that before we even opened the vials for analysis, we laid out the test that would be done with the largest possible number of independent tests showing what the material is. Now among the methods that require a small quantity of material, would have been an infrared spectrum which was necessary in any case to determine whether the substance we had was identical with the substance that was handed to NIH. At that time mass spectroscopy was just coming into play. One of the experts in the field was Professor Beaman of MIT, I think. He had one of the few instruments in the country and he was one of the leading exponents of that approach and we asked if he would

participate in the study. He said that he would. We brought in experts on microscopic methods of analysis of crystalline materials, both from Food and Drug Administration and from the outside. Our expert was drawn from the University of Maryland. We devised chromatographic methods to compare the behavior of creatin-monohydrate and the substance in the vial. We applied chemical methods. If creatin-monohydrate is treated with hydrochloric acid and is evaporated to dryness it is converted quantatively to createnene. We therefore devised a method, using sub-miligram quantities, experimenting with known creatin-monohydrate first, evaporated with hydrochloric acid and identified the residue by means of infrared spectrophotommetry, chromotography, and other procedures. We then assembled all of the persons who would be involved in the analysis of the vial. Opened the vial, and our expert on infrared analysis took out (Alma Hayden) (Jonas Carol was her supervisor) microgram quantities of the material from the vial, prepared a potassium bromide bisque, that is incorporated the material with the substance, potassium bromide, which is extremely useful in taking infrared spectrum. And determined the infrared spectrum of the material out of the vial comparing it with known spectra of creatin-monohydrate and the material given to NIH, and they matched exactly. So that we were pretty sure from only that evidence that it was creatin-mono-

hydrate, but we wanted to make sure by testing with other independent methods. All of these methods, the mass spectrometric method, the microscopic method of analysis, the chromatographic method, conversion of creatinene quantitatively -- all of them gave results which were exactly like those in the sample handed to us as Krebiozen. We were therefore able to say on the basis of these findings, and said so in court, that the substance given to us as Krebiozen was at least 99% creatin-monohydrate.

Young: Now, this was such an important case that you were anxious to engage in supererogation?

Banes: Yes.

Young: Did Miss Hayden perform this first test in the presence of all the witnesses?

Banes: Yes, all of the experts that were to do their part of the work were gathered together to see that Dr. Hayden was opening the sealed vial, that she had taken a specimen from that vial, and had performed the infrared analytical work, and that she had given portions of that same material to them for their determinations and for their comparisons with the known sample of creatin-monohydrate.

Young: I may find it in the Krebiozen records, it would be possible to find a document that was perhaps signed in a multiple fashion by people who were witnesses to this?

Banes: Possibly.

Young: It would seem to me that you would somewhere have that kind of evidence.

Porter: It was an impressive moment anyway, wasn't it.

Banes: Yes, it was, breathtaking.

Young: Can I ask a kind of speculative question -- when you found that the more simple formula was, if multiplied by a certain factor -- close to the formula that they had supplied -- what did that cause you to think? That these people who had it knew what they had, and in order to confuse the possibilities of analysis, but nonetheless, make the possibilities of analysis show some harmony with the truth, that they had deliberately raised the factor, or would another interpretation be that they were deceived by their own chemistry? Or did you people speculate about what went on in their minds? Did you think it was deliberate fraud, or did you think they might have been gulled by their own pseudo-science?

Banes: Our impression was that the sponsors of this drug knew what they had in hand, and that they did practice deception. But there was always the possibility that...

Young: That was the burden of the case that was brought in Chicago.

Banes: That was the burden of the case. That's right. That there was conspiracy to defraud. You couldn't evade the conclusion that they knew what they had in hand because

they had gathered the creatin-monohydrate from somewhere. They had prepared the material in hand.

Young: They had had it prepared hadn't they by some outfit that had horses, I've forgotten.

Banes: Yes, innocluated horses. I think it was in Illinois.

Young: That's sort of fuzzy until I read the record.

Porter: Incidentally, I interviewed Roland Sherman after he retired. He came to see me. While I probably wouldn't have sought him out for an interview, he was there and so I sat him down and we talked about Krebiozen. He did some of the investigations. You do have a copy of that!

Young: Right. You mentioned at the beginning that this was a very important episode. Was it an episode that took a great deal of manpower?

Banes: Yes. It involved analytical work in drug chemistry with about 4 or 5 chemists participating in the work. Because it was necessary for us in completing the case, not only to identify what purported to be Krebiozen. We also analyzed many samples of the so-called solution of the active ingredient that was injected into the patients. We were able to accumulate different batches of Krebiozen. The sponsors of Krebiozen, the Durovic brothers, insisted that we had missed the active ingredient -- that it was the other 1% that we had not analyzed for that was the true Krebiozen,

and that it couldn't be creatin-monohydrate because creatin-monohydrate isn't soluable in mineral oil. Their injection consisted of Krebiozen in mineral oil. We agreed that creatin-monohydrate is not soluble in mineral oil. But we showed that if creatin-monohydrate in a mixture of amyl alcohol and sodium hydroxide is heated with mineral oil, then creatin-monohydrate is converted to another substance that goes into solution in the mineral oil. And that other substance was the end product of a series of conversions in which creatin-monohydrate is first dehydrated to produce creatinene, and the creatinene then undergoes reenclosure to produce an n-methyl hydantoin.

Young: Did you have mineral oil to analyze? I heard that there were analyses of Krebiozen that showed nothing but mineral oil.

Banes: Yes, the composition varied from mineral oil without any additive, that is the mineral oil seemed to be identical with other mineral oils in the marketplace, or at least didn't have derivatives of creatin-monohydrate. The concentration of methyl hydantoin varied from batch to batch. And some of the batches had a quantity of n-methyl hydantoin that corresponded to the concentration of Krebiozen weight for weight, but was alleged to be in the drug. We experimented in the laboratory with mixtures of creatin-monohydrate, sodium hydroxide, amyl alcohol, and mineral oil.

We produced materials that matched some of those sold as Krebiozen. We were able to show that the preparations that contained the larger quantities of the n-methyl hydantoin had larger proportions of sodium hydroxide and amyl alcohol. Those that had small proportions of the hydantoin, had lower proportions of amyl alcohol. That the process of preparation gave varying compositions, but the samples that we had collected showed a progression with... This work required not only preparation of the materials but, of course, development of analytical methods - chromatographic and spectrophotometric methods to demonstrate that we had prepared such mixtures and could analyze them quantitatively. It took many man years and woman years of work to detect the substances in mineral oil and to develop quantitative methods to determine how much of these extraneous substances were present in the mineral oil samples that we had collected as purported to be Krebiozen.

Young: Now, the regulatory purpose of this was, at one point I believe that they did apply for an IND, or maybe it was even an NDA, I'm not sure. And so you had to determine whether or not it could be accepted, and that didn't last very long. They withdrew it with the new laws, I remember. So mainly what you were doing was preparing for the criminal case that was tried in Chicago?

Banes: Yes.

Young: Did you personally testify?

Banes: No, I did not. Because I did not personally do the work.

Young: I'm sure that transcript exists somewhere, but I...

Banes: It's a tremendous transcript. It was one of the longest cases ever tried, I think. I think it's on record as the longest case. So the transcript was many volumes.

Young: And I guess that after the case was unsuccessful, one of the jurors was tried and convicted of contempt of court or something.

Banes: Contempt of court because of collusion with the defendent. We did not gain a victory in the courtroom. The verdict of the jury was that the defendents were not guilty, but Krebiozen, I believe is no longer sold even in the state of Illinois. So, from that standpoint, the action was successful. At least traffic in the drug diminished markedly after that.

Porter: The Durovics really kind of departed from the scene, didn't they.

Banes: One went to Switzerland, and I think the other died.

Young: My medical school dean, whom you may well know, Arthur Richardson, met Ajax Carlson at a convention in Atlantic City right at the very end of his life, Carlson's life. And Richardson told me that one evening that they went on a walk down the boardwalk together and, since

Carlson had been Ivy's professor, Richardson asked Carlson how he explained Ivy. And, first of all Carlson gripped his chest and then he gripped his head and as he did so he said, "Thank God my trouble is here instead of here." And that was his explanation, at any rate, of Ivy. There is a young woman who is writing the history of the University of Illinois Medical School who has just come upon the University of Illinois papers about the Krebiozen case. Maybe we'll get some more light about the case from there. But this is an example of how a great deal of highly expert time goes into a project in order to prove what, on common sense logic, is sort of obvious to start with. Isn't it? You had to do this.

Banes: Manpower went in to resolving a problem that should have been obvious.

Young: But you say it wasn't obvious until the manpower went into it?

Porter: You worked in the Food and Drug Administration under quite a large number of commissioners. I wondered if you would give us your impressions of them in terms of how they operated and their support or lack of it for your work or any other thoughts about them. What kind of personalities they were. Is there anything that you could sort of start with? Start with Larrick or whoever you want to start with. Tell us what kind of people they were.

Banes: My experience with the various commissioners, of course, was different over the course of time. When I first joined the organization I was a chemist in the Chicago Station. But I was impressed by the fact that Dr. Dunbar, who was then commissioner, visited the stations, visited Chicago and sat down with the full staff in Chicago, told us what was going on in Washington, permitted us to ask questions, and answered them, I thought, in a frank manner. I contrasted that attitude with the attitude of the commissioners who had come in from outside the agency, after Larrick died and after Goddard. And had the feeling that there was less of the camaradery and less of the group feelings between the field and headquarters, as between the newcomers into the Food and Drug Administration and those who had been a large part of its history. Of course there are reasons for this kind of change. The Food and Drug Administration has become a much larger agency than it was in those days. In those days there were perhaps a thousand or so -- it dipped below during the war, I think, or shortly after the war. But it was in the vicinity of a thousand or so. You have to contrast that with the Agency as it now exists. It's probably impossible for the Commissioner of the Food and Drug to operate like this. As a general statement, I think that those commissioners who rose through the ranks had a better feel for the problems of the Food and Drug

Administration and how to go about resolving them than those who have come in from the outside and have served just a short period of time. It's difficult to enter a new kind of activity and become acclimated. Operate from the very beginning as a person who has gotten training over a period of three decades or so and has seen the problems from different aspects as they have risen in their careers. So that by the time that they are appointed Commissioner, it's simply a matter of continuing to do what you have done to a lesser degree in the past. So that, without going into individual personalities, I think that there has been a diminution in the insights of the Commissioner, and I think that those who say that as soon as they become trained so that they are beginning to see what the problems are, they leave. I think that kind of statement has some validity.

Porter: Well, isn't it also true that the political considerations were pretty minimal under say Dunbar and Larrick. Of course possibly there were political pressures on them that you and I out in the field didn't realize. But it just seems like there were much less than now.

Banes: I think there have been political pressures throughout the history of the Food and Drug Administration. The question is how have they been met. Have they been resisted? What is the reaction of the Commissioner? Before the arrival of Commissioner Goddard, the FDA high brass was

promoted through the ranks. And there was less of a feeling that political attachments were involved. Whereas Goddard was appointed by a Democratic president, and there was the feeling that he was a part of the Democratic administration. In the time of appointments from within, the feeling was that the Commissioner remains at the helm no matter what kind of administration. He holds the power whether a Republican or Democratic administration -- the Commissioner remained unchanged. But since Goddard's time, the Commissioner has been expected to turn in his resignation when administrations change. Consequently, there seems to be a political connection between the head of the Food and Drug Administration and the Chief Executive. And, on that basis, it would seem that there is a political tinge to FDA activities. Although I do think that the major policies of FDA have remained the same regardless of who has been appointed.

Young: There has almost been more adversarial relationship with the Congress, it seems to me, in the last 20 years than there ever was up to that point. There were, in the '20s, sniper bills in which Congressmen fought to get bills through that would have ended the technique of the multiple seizure, which had been developed in the late teens as an effective way of bringing something to a halt rather quickly. And this upset constituents and so a lot of ripper

bills were put into Congress but I don't really believe that anybody thought they would pass. They were troublesome, but not threatening, I guess. But however much good the 1962 law may have been, it arose out of a period of criticism of the way things were happening. Some of which may well have been justified. It seems to me at any rate, was a period of tremendous rapid change in both prescription drugs and in food additives and chemistry generally. So that maybe a new kind of enforcement that this law did bring in was needed, but whatever that may be, it was a sort of Congressional critique that set a precedent and has led very often to adversary relationships between certain committees of Congress and the Agency, which have been unlike the previous period and occupied a great deal more of the Commissioner's and high level brass's time. Did you testify before Congressional committees very often?

Banes: I testified before Congressional Committees, but not very often.

Young: Were these circumstances in which a problem had arisen or were these circumstances of the normal routine of business?

Banes: These were instances where problems had developed.

Young: Like what?

Banes: Irradiation of food to preserve the edibles for use in the armed forces. The Department of Defense had entered

food additive petitions with the Food and Drug Administration for the irradiation of various foods by radioactive substances to kill off micro-organisms and so extend the lifetime of the food. The data accompanying the petitions seemed to indicate that the irradiation process was both safe and effective, but there were afterthoughts that developed in the Food and Drug Administration. Upon examining samples, it appeared as if there might be residual radioactivity in the tissues of pork and beef. And a Congressional committee investigated the problem, because the Department of Defense argued that their data showed that there were no dangerous levels of radioactivity. So it was necessary that representatives of both the Department of Defense and the Food and Drug Administration testify. I was Associate Commissioner for Science at that time and, after briefing by the scientists, I testified before the Committee chaired by Senator Hruska of Nebraska.

Young: This was an issue of avoiding a problem that lay in the future.

Banes: Yes.

Young: And it was a little bit different from the recent baby food hearings or something where one sometimes gets the idea that Congress is making more of a teeny hazard than the facts warrant. Kind of using FDA as a whipping boy for political purposes, as it might be in some cases inter-

preted. And I truly think there's been a good deal more of this in the last 20 years than there was in the first 50 years of the agency's history.

Banes: Well, I agree that in the years between 1939 and 1960, so far as I can tell, there was far less of summoning the Commissioner to the Hill with his associates and grilling them on various aspects of FDA activity. The Congress has seen in FDA an agency that is of some interest and significance and has taken a larger hand in reviewing the operations of the Food and Drug Administration.

Young: This may well represent the importance of FDA because of the greater breadth and the need for regulation than was true earlier. I didn't mean to put all the onus on Congress, there may be lots of reasons for this having happened. But it does seem to me that, beginning with Kefauver that the headlines in many ways have turned to FDA in a way that they didn't in the whole period from Wiley's retirement in 1912 until Senator Kefauver opened his hearings in the last week of 1959.

Banes: I think that is the case. We rarely appeared in the news in the early days of my work in FDA. In '62, and many times afterward, there has been insistent references to FDA in the press and in Congress.

Young: Right. I remember somebody saying that, during all those 5 years in which the effort was going on in Congress

that led to the 1938 law, that that tussle made the front page of the New York Times only once, and that was when there was a disturbance in the gallery. So it did become a different period.

Porter: Do you have any more questions?

Young: I can't think of anything right now. Are there any things going through your mind that you'd like to say about the history you lived through that might help us interpret?

Porter: Or opinions or advice or anything? Whatever you want to say. Because we are gathering this not only for history, but hopefully to get some training value out of it too.

Banes: Well, I think the Food and Drug Administration is a necessary agency and a very important one as has been recognized. My experience in the Food and Drug Administration was certainly stimulating and worthwhile. I think that most of the people who work in the Food and Drug Administration would have said exactly the same thing, during the period when I was there. There was a feeling that the work we were doing was important. That it was worthwhile, that we were in an activity that was of consequence, was indispensible.

Porter: We were proud of ourselves.

Young: Yes, you felt worthy because you were using your talents in the public welfare.

Banes: Exactly. I'm not sure that feeling is as widespread now.

Porter: Part of it is probably more typical of the world at large too, I think, somehow.

Young: One went into it -- it was the tradition to go into it thinking one would stick with it for a long stretch of time. One committed oneself to the thing.

Banes: That was true of the agency from the top all the way down to the lowest ranks, from the Commissioner downward. We had the feeling that we were insulated from political currents and were encouraged to do our best.

Young: Do you think that the Henry Welch case was a significant incident in a sort of change there? I'm not sure, there never was anything brought in the way of a trial against him, but certainly the Congressional committees made much of those circumstances and certainly there was much disillusionment that I myself found about that in talking with high level people within the agency itself. Because one of the early things that went with all that you were saying -- the loyalty to the Agency and so forth -- was virtually utter integrity. And this case at least raised questions about that. You were close to that. Do you interpret that as a weighty factor in a kind of growing skepticism?

Banes: I don't think it was a major factor, although it was the first instance that I could recall of -- the first instance impuning the integrity of the Food and Drug Admin-

istration. So it did have some effect. I'm not sure it was a major factor.

Young: The kinds of things we're talking about, in a broader sense, would have happened anyhow. But I remember I was there and, in the aftermath, in a sense, everybody's integrity was somewhat questioned because everybody was required to state things about their financial resources which, had always been taken for granted before, were so proper that nothing needed to be raised. And I certainly heard a lot of grousing when I was doing research about the need, on the part of everybody, to come forward and say what stock you owned and all that kind of thing. So that it did have a sort of ruffling effect inside the Agency that I observed. And it made the kind of criticisms that were coming about drug companies and whether FDA was really tough enough Upon them that the Kefauver hearings did present. It gave a kind of credibility that wouldn't otherwise have been there to some of those assertions, it seemed to me. I don't mean a credibility to them, but a plausibility in the audience's mind that charges like that were made. So I felt that that was the worst bad luck for the Agency to have that kind of thing happen right at the time when criticisms on other fronts were beginning to be made. But, here I'm talking instead of you.

Banes: Well, I agree. I was amazed when there was an outburst of criticism of the Food and Drug Administration.

It was at a time when Mr. Larrick was asked to report, I think, on the thalidomide affair, and we were the only major country where a disaster of large proportions was fended off because we never approved the drug appliation for thalidomide. I thought that the Congress would be outspoken in their praise of what we had done. There were very harsh criticisms leveled at Commissioner Larrick at that time by Senator Kefauver and I think also by Senator Douglas.

Young: Exactly. I had a feeling that these other circumstances played their part there and sort of changed the temper. And that it was a sad coincidence and misfortune.

Banes: In order to carry forward its research and the analysis of drugs and establishing analytical methods and standards, the Food and Drug Administration needs the same level of competence and scientific ability, and the same kind of instruments that are available to industry and anywhere else. They must keep up with science as it develops. It must be able to carry on a dialogue with scientists outside the government at their own level. For the purposes of drug analysis and drug regulation, I think that kind of ability has been secured by the Food and Drug Administration. I hope that we can continue to maintain that.

Young: Was that secured in some measure by attendance of scientific conferences?

Banes: Our scientists were permitted to travel to scientific meetings.

(We completed a tape at this point and decided to terminate the interview. This did not give me an opportunity to record our thanks to Dr. Banes, whose cooperation is greatly appreciated - Porter.)

THIRTY-NINE YEARS OF CHANGE AS SEEN FROM WITHIN THE F.D.A.

By Jonas Carol

When John Windheuser called and asked me to be the after dinner speaker for this meeting, I wondered what I could say that would be important enough for the occasion. Since the date was then four months in the future, it was easy to say "yes." Now I feel like Linus in a Peanuts Cartoon, when he was volunteered against his will to sing "Frere Jacque" at a Christmas Party. He kept hoping that something would happen to save him. But nothing did. Finally the fateful day arrives, and Lucy is shown dragging him to school, while Charlie Brown shouts a final encouragement: "Good Luck! You may break a leg on the way." But I didn't.

Seriously, I consider it quite an honor to address you tonight, since I have been associated with many of you for a long time. I have given a lot of thought to what I could say that might be of interest, and would also fit the theme of this conference. I finally decided to review some of the changes, both scientific and administrative, that have occurred in the F.D.A. during the last thirty-nine years in matters relating to drugs. My view, as seen from the inside, will of necessity be a narrow one and will seem almost auto-biographical. Since I have no intention of keeping you here all night, it will have to be quite sketchy. I would also like to relate a few incidents

connected with court cases in which I was a witness for the Government.

To start at the beginning, I was offered a position as an analytical chemist in the F.D.A. after receiving my M.S. in chemistry in 1930. Although I thought that analytical chemistry was about as low as you could go scientifically speaking, the depression was beginning, jobs were very scarce, and $2,000 a year looked like a lot of money, so I accepted. I was assigned to the Chicago Station and reported for duty on July 2, 1930 and was duly sworn in as a government employee. To my dismay, the laboratories were both ancient and dismal, and I remember vividly thinking, "I'll only stay here long enough to find another job." The work, however, proved to be much more interesting than the surroundings. I was soon allowed to spend most of my time on the analysis of drugs, and found this to be unexpectedly challenging.

Let us contrast briefly the F.D.A. of 1930 with the present organization. Then, it was composed of about 800 employees--now it has grown to over 4,500. Its annual budget has made a tremendous growth from about $3,000,000 to over $70,000,000. In another area, there has also been a remarkable change. When I entered the service, few people knew of its existence, since it was rarely mentioned in the papers or on the radio. T.V., of course, was still in the future. As you all know, hardly a day passes now, without large coverage of matters relating to the F.D.A.--

much of it unfortunately hardly complimentary. THAT is the fate of a regulatory agency. We, inside, often remarked that if we seemed easy on INDUSTRY, consumer groups and some in congress complained. If we seemed HARD on industry, industry and others in congress complained, and if we steered a middle course, everyone complained.

But to get back to the F.D.A. of 1930. Actually it was then the Food, Drug, and Insecticide Agency in the Department of Agriculture. It was a close-knit organization in which everyone seemed to know everyone else. This was not too surprising, since many had been in the organization from its beginning in 1907. To me, just out of school, they all appeared to be contemporaries of the original Dr. Wiley. Structurally, there was, as now, administrative headquarters in Washington. The field service was divided into three districts; Eastern, Central, and Western. Each district was further sub-divided into stations located essentially where the present F.D.A. Districts are today. It so happened that the Central District and the Chicago Station occupied adjacent quarters. To a new recruit, the Chief of the Central District appeared to be an absolute monarch--as indeed he was.

In contrast to the situation today, drugs played a secondary role to foods and insecticides in those early days. In fact, drug analyses were done at only one station in each District. Fortunately, for me, Chicago was the drug analyzing station of the Central District. There was

a small group in Washington engaged in research on drug methodology, but it was in no way comparable with the present Division of Pharmaceutical Sciences. In 1930, as today, the U.S.P., N.F., and A.O.A.C. book of methods were our "Bibles". However, the U.S.P. X and N.F. V bear little resemblence to today's revisions; and the Book of Methods has changed just as dramatically. Very few "pure" chemical compounds, with the exception of alkaloids and salts of organic acids were among the monographs in the U.S.P. X. However, tinctures and fluid extracts of natural products such as cinchona, belladonna, stramonium, and nux vomica were well represented. The assay procedures employed were the so-called "proximate" assays.

In a proximate assay a portion of the drug was made alkaline, usually with ammonia, and the active components were extracted with an organic solvent. The final determination was made by titration with N/50 acid. All new chemists in the drug laboratory were initiated with an assignment to prepare and standardize a huge batch of N/50 H_2SO_4.

A large part of our analytical work, however, dealt with Patent medicines and not with official drugs. The original Food and Drug Act of 1906 had proven ineffective in curbing the sale of these products, and prior to the 1939 revision of the Food and Drug Act their sale was widespread. Since only alcohol and a few narcotic drugs had to be declared on the label these products were

essentially unknowns to the drug analyst. Usually the only clue to their composition came from a study of the medical claims made on the labelling and in the associated advertising that came with the sample. As you can imagine, experience was a great asset in working with these products. I gained much from the advice and guidance of the chief drug chemist and several of the other "old-timers" in the laboratory.

In 1930, and for a long time afterward, we relied almost completely upon "wet" chemistry in our analytical drug work. Chromatography and spectrophotometry, the mainstays of the modern drug laboratory, were then far in the future. We did use colorimetry in a rather crude way, employing either Nessler Tubes or a Klett Comparator. We also used micro-chemical tests for identity by means of crystal formation. In addition, we had a pH meter.

We were greatly aided in our analysis of unknown drug mixtures by a now little known publication "The Chemistry and Analysis of Drugs and Medicines" by Henry C. Fuller. In this book Dr. Fuller described a systematic separation of drug components based on partitioning between aqueous and organic solvents. By varying the pH of the aqueous phase and the polarity of the organic phase, quite complex mixtures could be separated into their component parts. In a very short time, I knew all of the operations of this system by heart, and employed it to analyze hundreds of samples. Oddly enough, I can't remember specifically a

single example of the many successful analyses I made using this technique, but I remember vividly after about thirty-five years, a case in which it failed.

I had been assigned a sample to analyze that consisted of an essentially colorless liquid. I went through the complete extraction procedure as outlined by Dr. Fuller and found-nothing! On evaporation of a portion of the original sample, however, a white amorphous residue remained that would not redissolve in water. The dry residue burned completely with an odor characteristic of proteins. For a reason I no longer remember, I heated a portion of the drug sample to boiling, and a white precipitate formed that didn't redissolve on cooling. It suddenly occured to me that egg white coagulates on heating. Further investigation showed that my guess was correct; the sample proved to be stabilized solution of egg albumin in water, and it was obvious why Fuller's system had failed.

The non-official drugs that F.D.A. investigated in the early and middle 30's were labelled as if they had the power of curing or mitigating practically every disease known to man. These claims could be wildly extravagant, and many of the samples collected and analyzed resulted in court cases. These cases usually required the testimony of the analyst. Although testifying in Federal Court is far from fun, it did add variety to the chemist's life and frequently gave him a chance to travel. The chief drug chemist at the Chicago Station assigned all incoming

samples to the laboratory personnel. Presumably this distribution was to be made as equal as possible, taking into consideration, of course, the complexity of the sample and the expertise of the analyst. It appeared to me, however, that he reserved those samples for himself that were most likely to be actionable and to result in appearance in court in some desirable and far away location like San Francisco or Miami. If this were true, he slipped up badly in respect to some samples he gave me, as I will explain later. I might point out that in those days the Chief Chemist analyzed samples along with the rank and file members of his staff. NOW, at most field laboratories, the laboratory director not only doesn't analyze samples, but usually makes assignments to a supervisory chemist, who then deals directly with the laboratory personnel.

The enactment of the revised law of 1938 produced many changes within the F.D.A. For one thing, it effectively spelled the doom of the old familiar Patent Medicine. At the sametime, it eliminated an interesting and often instructive type if work in the regulatory drug laboratory. The official and non-official pharmaceuticals remained, naturally, and their assay required skill but usually provided no surprises. The label declaration told the type and quantity of substance to be determined, and normally the method could be found in the U.S.P., NF., or A.O.A.C. The need for improvision, imagination, and experimentation was largely eliminated. Fortunately for me, changes were

beginning to take place in the field of analytical chemistry that would have a profound effect on my career.

In the middle thirties F.D.A. decided to expand its activities in the drug area, and to analyze pharmaceutical preparations at all the field laboratories. This involved a shift of trained personnel and I was sent to the Cincinnati Station where I remained until the fall of 1939. At that time another re-arrangement occurred and I found myself back in Chicago. The F.D.A. had grown somewhat in the meantime, but the same basic salary scale remained, and funds available for supplies and equipment were still meager. I mention this because at that time, the laboratory was able to make the almost unprecedented purchase of a photo-electric filter photometer. The instrument was not intended for drug analysis, but was to be used to determine lead in spray residues on fruit and vegetables. Little did I or any of my colleagues know that this "little black box" was the first of many that would completely change the modus operandi of the analytical chemist. At about this time, I had read a report in a British Journal on the use of ultraviolet spectrophotometry in the analysis of drugs, and when the opportunity arose, and the new instrument was free, I began investigating its applicability in this area. The instrument covered only the spectral range of 320-700u, using a series of broad transmitting filters. Fortunately, I was entirely unaware of its limitations and was delighted to discover that many

drugs could be assayed quickly by this new technique. It proved to be especially useful for the analysis of quinine by absorption spectrophotometry when we were called upon to assay great numbers of samples during World War II.

At that time I made the acquaintance of the Chief Chemist of the American Medical Association Drug Laboratory. He had received his doctorate from the University of Chicago with a dissertation on ultraviolet spectrophotometry. In addition, his laboratory possessed one of the first models of the Beckman DU Spectrophotometer. With great kindness and generosity, he instructed me in the practice and theory of spectrophotometry, and allowed me to use his fine instrument. Armed with examples of its use I tried to convince my superiors at the Chicago Station to buy a DU, but without success. They were shocked at its high cost, about $1,000. Instead they bought a new car which the inspection force needed badly. Years later, when I had to make similar decisions on the allotment of funds in the Division of Pharmaceutical Sciences, I recalled this incident frequently, with more sympathy for these gentlemen than I had felt then.

With the advent of the war years, changes took place in the F.D.A as they did elsewhere. Personnel were lost in increasing numbers to the armed forces and the newly created war industries. Chemists and other scientists were in short supply for the first time since the depression. Consequently, salaries and working conditions improved.

The practice of transferring personnel, wholesale, often to the detriment of the individual's home life and financial status, was curtailed since a prospective transferee could find other employment without moving.

Toward the end of the war, when the manufacture of penicillin was rapidly expending, and its regulation became a new responsibility for F.D.A., Dr. Frank Wiley, then Chief of the Chemical Branch of the Medical Division gave me an opportunity to transfer to his laboratory in Washington to work on the development of analytical methods for the new antibiotics. I accepted his offer immediately, since I had long wanted to devote my entire time to research on the development of analytical drug methods. No such opportunity was then available in the F.D.A. field laboratories.

When I arrived in Washington I was disappointed to learn that my project had been changed because of the unexpected resignation of one of the staff. I was given his job of developing chemical methods for the sex hormones. The use of these substances for human therapy had mushroomed in the late forties. This was a very lucrative field, and it attracted into the manufacture and sale of these products many who apparently knew little of the complex chemistry involved in the isolation and purification of the active components of these substances. A very large percentage of the dosage forms sold were both impure and subpotent. Practically no analytical methods based on

chemical or physical techniques were available for their assay. The F.D.A. did have a small unit in its Division of Pharmacology engaged in the assay of these products using biological methods. But these methods were quite slow, as well as costly, and the unit was unable to cope with the flood of samples being collected.

We thus embarked upon the first of a series of projects of a scope not heretofore attempted in F.D.A. laboratories. This was the assay by chemical and/or physical methods of complex substances of natural origin involving attempts to isolate, separate, and quantitate each physiologically active component. Our hope was to replace biological procedures with rapid and precise chemical or physical methods.

The Chemical Branch soon became the Division of Pharmaceutical Chemistry, and was enlarged by the addition of some outstanding chemists who have in time become eminent in the field of analytical drug chemistry. The addition of these people to our staff, the leadership of Dr. Wiley, new advances in analytical technology and instrumentation, consultation and advice from other scientists within and outside the F.D.A., and a lot of good luck, combined to bring us considerable success in our endeavors. Methods for the estrogenic, androgenic, and progestational hormones were followed by procedures for cardiac glycosides, adrenocortical steroids, and the Rauwolfia alkaloids. Work in related areas led to methods for analyzing complex drug

mixtures by partition chromatography, such as the now classical procedure for APC and finally the comprehensive schemes for separating closely related amines by ion-pairing developed by Joseph Levine and his co-workers. I do not intend to imply that the F.D.A. was making these advances independently and unaided. New methods were being reported almost daily from all over, and we were benefited greatly by the labors of our co-workers both in industry and in academic laboratories.

None of the rapid advances in analytical drug chemistry made by us or others would have been possible without the adoption by the analytical chemist of two essentially physical techniques; chromatography and spectrophotometry. Fortunately for us within the F.D.A., a constantly improving budget, and a growing realization by top administration officials of the need for modern equipment in the laboratory, allowed us to acquire in time, almost all of the supplies and devices we required.

Our first big instrument came in 1947 when the division obtained a single beam non-recording infrared spectrophotometer at a cost of about $5,000. This powerful tool opened new areas to us, and for awhile we did I.R. work for the whole agency as well as for a number of other laboratories. The results we obtained with this equipment, I believe, did much to overcome lingering resistance to the extensive use of instrumentation within the F.D.A. Today every laboratory in the administration is equipped with

recording equipment of every description. Several have mass spectrometers and one laboratory will eventually be computer controlled. We do things now that were entirely beyond our capacity in my early field days, like the isolation and positive identification of microgram amounts of contaminants in a drug product. Then we would have been completely unaware of their presence. I feel, however, that there has also been some loss. Many of the workers in analytical drug chemistry place too much reliance upon the "black box", and not enough upon their own skill and judgment.

Before leaving this aspect of the changing scene, let me mention one thing that unfortunately has still not changed. In the U.S.P.X, which was official when I entered the F.D.A., there was a monograph on Thyroid. The present XVII revision, contains essentially the same monograph. Both Lloyd Miller of the U.S.P. and I had hoped to see a really meaningful monograph and assay for this product in the U.S.P. XVIII, but despite much work by us and others, this goal still eludes us.

Let me revert now and consider broadly the scientific changes that have taken place not from a technical standpoint, but from a philosophical one. In 1930 we were concerned almost entirely with establishing the composition of proprietary drugs and relating it to the label claims. In addition we routinely _____ _____ to label declarations or

compendial requirements. Tests for purity were few, and tests for identity were in many cases far from satisfactory.

The sulfanilamide case in the middle 30's had a profound effect on F.D.A. thinking, and seems to have marked the beginning of a more searching look into the purity and composition of all such products. As techniques in general improved, unexpected lack of purity and deficiencies in composition were discovered. The need for ever-tightening specifications was painfully apparent. Both of the compendia, and the drug industry through such organizations as the P.M.A. Quality Control Section worked closely with the F.D.A. to devise new standards.

For example, in the U.S.P. XIII and in previous revisions, the requirements for Digitoxin could be interpreted to allow a mixture of glycosides containing only 51% pure steroid with the remainder comprised of gitoxin and related digitalis glycosides. With the advent of a new and specific assay, the requirements for Digitoxin in U.S.P. XIV were tightened to require not less than 90% pure digitoxin and more than 10% of the accompanying glycosides.

Concern with drug availability is not entirely new, since it prompted the inclusion of the tablet disintegration test in the U.S.P. XIV and N.F. IX, and the concern with tablet and capsule uniformity resulted in the weight variation tests that first appeared in U.S.P. XV, and N.F. X.

As you know, weight variation tests measure dosage variation only if a uniform mixture of drug and excipient is used in the dosage form preparation. This assumption was apparently taken for granted until several rather startling cases proved it was not universally true. As a result, content uniformity tests were devised and appeared in the U.S.P. XVII ad N.F. XII.

When the issue of drug availability, and the related question of generic versus trade name, drugs reached "Front Page" importance in the news media, it became apparent that more meaningful tests than tablet disintegration were required. As a result, the joint U.S.P. N.F. committee on drug avialability, composed of scientists from academic, industrial, and regulatory institutions, began a thorough investigation of this problem. Although their work is by no means completed, it did result in the inclusion in U.S.P. XVIII and N.F. XIII of dissolution tests for a number of drugs.

The use of Reference Standards in the two compendium has grown enormously. This growth came about only after conflicting views over their use were resolved. The standards first mentioned in the U.S.P. X were for use in biological assays only, and were supplied by the Bureau of Chemistry of the Department of Agriculture. By the next revision, the standards were supplied by the U.S.P. With the inclusion of spectrophotometric and chromatographic methods in the compendium, the need for other than

biological assay standards became apparent, and a few were included in the U.S.P. XIV. U.S.P. XVIII will contain over 230 Reference Standards, and the N.F. XIII about 250.

I mentioned earlier the secondary role of drugs in F.D.A. affairs in 1930. The reason is not hard to find. The policies of the F.D.A. are guided broadly by public opinion, by congressional pressure, and by the F.D.A. Commissioner's background and philosophy. In the early 30's money was scarce, and since people buy far more food than medicine, the detection and elimination of economic cheats was of prime importance. In addition, several large foreign countries had threatened to bar the importation of U.S. fruits and vegetables because of excessive spray residue. Hence our strong interest in the analysis of these products for arsenic and lead. Later our interests turned to the problems of filth in foods, and their detection became the major F.D.A laboratory and inspectional job. However, the importance of drugs in the overall regulatory scheme continued to grow; spurred by incidents like the sulfanilamide affair, thalidomide and others. Today, with two successive physician-commissioners and intense congressional interest, drugs have become the major concern of the F.D.A. and more money is allotted to this than to all other F.D.A. activities.

I need touch only briefly on the structural changes that have taken place during my time in the F.D.A. At first it was a small organization, quite stable in

structure, one in which the commissioner appeared to know all of the staff by first name. He often demonstrated this on his frequent visits to the field establishments. Gradually, and after many shifts and reorganizations, the F.D.A. has become a large and much more diffuse organization. I will not attempt to trace the changes that have occured at headquarters. Let me give you an example of change that has occured in the field districts.

In my early days, in the field, there were food analysts, drug analysts, and those who did only spray residue work. In time these distinctions disappeared, and for a number of years each analyst was expected to do all types of work. Gradually, with the increasing complexity of techniques and instruments, specialization returned. Today there are three laboratories that are entirely devoted to a single activity; The National Center for Drugs Analysis in St. Louis, the National Center for Microbiological Analysis in Minneapolis, and the National Center for Antibiotic and Insulin Analysis in Washington. Soon there may be others, and we may eventually see the disappearance of the general purpose Field District as now constituted.

Now I'd like to finish by relating some incidents connected with court cases which I hope you will find of interest.

Before I entered the F.D.A. there had been a serious outbreak of a strange type of paralysis called "Jake Leg", caused apparently by drinking Jamaica Ginger Extract.

This was during prohibition days, and some people drank these products for their alcoholic content. My chief chemist had analyzed many samples involved in these cases and had found that the paralysis cases were associated with an adulterated product in which triortho cresyl phosphate had been substituted for ginger. Not long after I came to work for F.D.A., one of the many samples of this preparation assigned to our laboratory was given to me to analyze, mainly for my training and experience, and I found that it contain the adulterant. The manufacturer of this product was prosecuted and of all the samples analyzed at Chicago, only mine was used in presenting the case in court. My chief chemist wanted to go to the trial very badly and he never forgave me for going in his "place". The trial, held in New York, lasted for over a month, and I had my first experience as a government witness. A strange aftermath of this affair occured about five years later, when I was stationed in Cincinnati. There had been a great flood of the Ohio river in 1936, and after the water subsided, some painters while renovating a store building, had discovered a case of fluid extract of ginger in the basement, and drank it. Unfortunately for them, this was a case of the adulterated product that had been embargoed years before by the Cincinnati Health Department. It should have been destroyed, but it was somehow overlooked and forgotten. I was given the job of investigating the case and had the unpleasant task of interviewing the poor victims in the

hospital, while unravelling the story.

In another case, Daniel Banes, who had been a close associate of mine in the laboratory, accompanied me to the West Coast just before Christmas to testify against the producer of a hormone preparation. The defendant's lawyer put up no scientific defense, but I'll always remember his plea to the jury. It went something like this--"I went to St. John's academy with this man, and our children play together down on the beach. Would you brand my friend a criminal and send him to jail at Christmas time?" Dan and I flew back to Washington defeated, shaking our heads and moaning about science, justice and sentiment.

Then there was the horseradish case that was a source of amusement to my colleagues for a long time. This was the first use by F.D.A. of testimony based on infrared spectrophotometry. Prepared horseradish is sometimes adulterated with cheaper vegetable substance, usually parsnips or turnips, and the lack of pungency is supplied by adding synthetic allyl isothiocyanate. In the case in question, the F.D.A. has seized a shipment of a product adulterated with parsnips and the manufacturer was contesting the seizure. Our evidence was based on microscopic examination. The Administration wished to strengthen its case, and since the Division of Pharmaceutical Chemistry had made good use of its new I.R. spectrophotometer in the identification of drug substances, I was asked to try and establish the presence of the added synthetic ally

isothiocyanate in the seized product. I failed in this, because this substance proved to be identical with the pungent material from true horseradish. However, I did discover that parsnips contain a volatile substance with an extremely distinctive I.R. spectrum; and by this means I was able to calculate the amount of adulterant in the product. My results checked surprisingly well with the microscopic findings. The case--The U.S. versus 50 cases of horseradish, was tried in Boston without jury. The Judge was quite impressed with the I.R. data, and the defense attorney having never seen anything like it, didn't have the least idea what to do in cross examination. The U.S. won; the I.R. had doomed the 50 cases of adulterated horseradish.

The last case in which I was involved as a member of the F.D.A. was by far the biggest and most controversial of all such efforts. This was the Krebiozen affair, which filled many a column in the daily newspapers, and in the Congressional Record. When the F.D.A. began its investigation of Krebiozen, the Division of Pharmaceutical Chemistry was given the task of determining the composition of both crystalline Krebiozen and its dosage form. After a very successful team effort, we established the composition of both products. A large part of the Division was involved and we thought of practically nothing but Krebiozen for many months. The case finally came to court in Chicago, and lasted for nine months. By that time, I had

succeeded Dr. Wiley as Director of the Division, and in that capacity I testified for four days on the overall scientific aspects of our work. We were stunned when we lost the case, for we felt that we had proven without a doubt that this so called cancer cure was nothing more than creatine monohydrate. But at least we had succeeded in revealing the identity of the alleged secret wonder substance and had barred it from interstate commerce.

Now in closing let me mention something that has always impressed me as being of highest importance in F.D.A. work. That has been the close cooperation between F.D.A. scientists and those affiliated with the regulated industries, the colleges and universities and the two compendia. This collaboration has resulted in continuously improving standards of excellence for drugs and has been of great benefit to the consuming public. This is one aspect of activities in the F.D.A. that I hope will never change. THANK YOU.