

**History**  
of the  
**U.S. Food and Drug Administration**

**THIRTY-NINE YEARS OF CHANGE AS SEEN FROM WITHIN  
THE FDA**

**By Jonas Carol**



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## 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 Jacques” 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 autobiographical. 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're 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 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 United States Pharmacopeia (U.S.P.), National Formulary (N.F.), and Association of Official Analytical Chemists (A.O.A.C.) book of methods were our “Bibles”. However, the U.S.P. X and N.F. bear little resemblance 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<sub>2</sub>SO<sub>4</sub>.

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 labeling 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 occurred to me that egg white coagulates on heating. Further investigation showed that my guess was correct; the sample proved to be a 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 labeled 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 same time, it eliminated an interesting and often instructive type of 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., N.F., or A.O.A.C. The need for improvisation, 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 320-700 $\mu$ , 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 this 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 expanding, 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 benefitting 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 tested ethical pharmaceuticals for their adherence to label declarations or compendia 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 Pharmaceutical's Manufacturing Association (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 glitoxin 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. SV, 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 and 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 availability, 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 compendiums 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 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 in the analysis of these products for 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 occurred at headquarters. Let me give you an example of change that has occurred 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 Nation 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 contained 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 occurred 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 unraveling 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 substances, 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. had 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 allyl isothiocyanate in the seized product. I failed in this, because this substance proved to be identical with 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 over 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 co-operation 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.