available to prepare these for publication and we find that a Seminar is a good way to accomplish this.

Which of the procedures that you have developed have been the most helpful to you?

The procedures we developed for organic nitrates such as nitroglycerin and pentaerythritol tetranitrate have been extremely helpful. They are much better than the manual procedures and have helped, not only to speed up the analytical work, but also to provide a greater degree of confidence in the results. The use of a distillation procedure in analyzing amines has also been very helpful for the same reasons. In addition to these two methods for the groups of compounds mentioned, we have also developed procedures for vitamins, various antihistamines such as chlorpheniramine maleate and methapyrilene fumarate, the barbiturates and some other groups of compounds.

You must have many manifolds?

Yes, we have. In this way we get the flexibility which we need. By using these manifolds, we can rapidly switch from one procedure to another when there is a need to do this, and obviously for our type of operation, it is extremely important to have this ability to switch from one assay to another.

Have you found any specific instance where your automated capacity has been extremely helpful?

Yes. Since we possess the capability of performing a large number of assays very rapidy, we have been able to gather analytical data at many stages of our in-process manufacturing, such as the granulating, blending, and mixing stages as well as the tableting and encapsulating stages. From these data, we have been able, by following several batches, to isolate several critical phases. By controlling these phases we have found that the quality of the product can be maintained at a high level. This type of study was made possible only through the use of the automated system.

In about two weeks we are going to visit the FDA lab in St. Louis. Do you have any interest in what they are doing?

Certainly. After we perform all of our tests and get the products out of the house, the FDA is very much in the picture. Of course, we are very confident of our quality and perhaps unlike some other companies, we are not very concerned about our products being tested by the center. In many respects, we are operating similar types of facilities when you consider the variety of items being tested. They also are looking for procedures which can be used to test a variety of dosage forms. I understand that they have developed some good procedures.

Thank you, Dr. Leeper. You have been most generous with your time.

A pleasure. Please come again.

PART II

Interview with Dr. Arthur W. Steers and Mr. Richard F. Heuermann, the Director and Deputy Director of the National Center for Drug Analysis, St. Louis, Missouri

How long has this office been established, Dr. Steers?

DR. STEERS: About three years.

This serves as a national center?

DR. STEERS: Yes, this is the National Center for Drug Analysis, the NCDA.

We are housed in the laboratories formerly occupied by the St. Louis District of FDA. A pilot program for testing feasibility of a National Center for Drug Analysis was started in March, 1967, at this laboratory. The study proved so successful that FDA recommended to the Secretary of HEW that this National Center for Drug Analysis be established. The St. Louis District Office was then abolished and its administrative and inspection functions, as well as its laboratory responsibilities, were distributed among the neighboring FDA Districts.

And this is the only lab of its kind?

DR. STEERS: Yes. There is, in Washington, a similar national laboratory center, but it specializes in antibiotics and insulin.

Oscar Raimondo and Pat Izzi check the manifold on the AutoAnalyzer, which is running an analysis of Amphetamine Sulfate.

How many studies has NCDA done?

MR. HEUERMANN: We've finished or have in progress 20 studies. Initially, we were not set up for automated analysis. Just as we completed the first two studies (anticoagulants and minor tranquilizers) our first deliveries of AutoAnalyzers arrived. Before that we worked on a team basis. As a result of our first studies it became obvious that we would need automation to analyze the large number of samples generated by the drug surveys.

Had there been any change in legislation around that time with regard to what the manufacturer must supply, which accounted for a larger workload on the part of the FDA?

DR. STEERS: Some legislation had been passed in 1962, but in addition, FDA felt that we needed to have a better knowledge of the quality of drugs on the market. The 18 Districts were analyzing a total of about 30,000 drug samples per year. This was done, to a large extent, on a problem-oriented basis and did not permit statistical analysis of results. At NCDA we are on a survey-oriented, random sampling schedule.

How do you get your samples?

DR. STEERS: We obtain them from the 17 District offices (18 before St. Louis District was abolished). Under the retail-based program, each District office, through its staff of inspectors, collects a given number of samples per month. The number is based somewhat on population: the greater the population the greater the number of samples. The inspectors collect samples at retail pharmacies.

Are these cooperating pharmacies or have the inspectors the right to walk into any pharmacy?

MR. HEUERMANN: They have the right to enter any pharmacy and purchase a sample. They pay for their samples. The inspector shows his identification and calls for an intact bottle of the latest drug that has been received in the particular study.

Is it geared to a certain study program?

DR. STEERS: Yes, we have a number of different study programs. The first involved anticoagulants, the second minor tranquilizers, the third adrenocorticosteroids, etc.

Are the results of these studies made public?

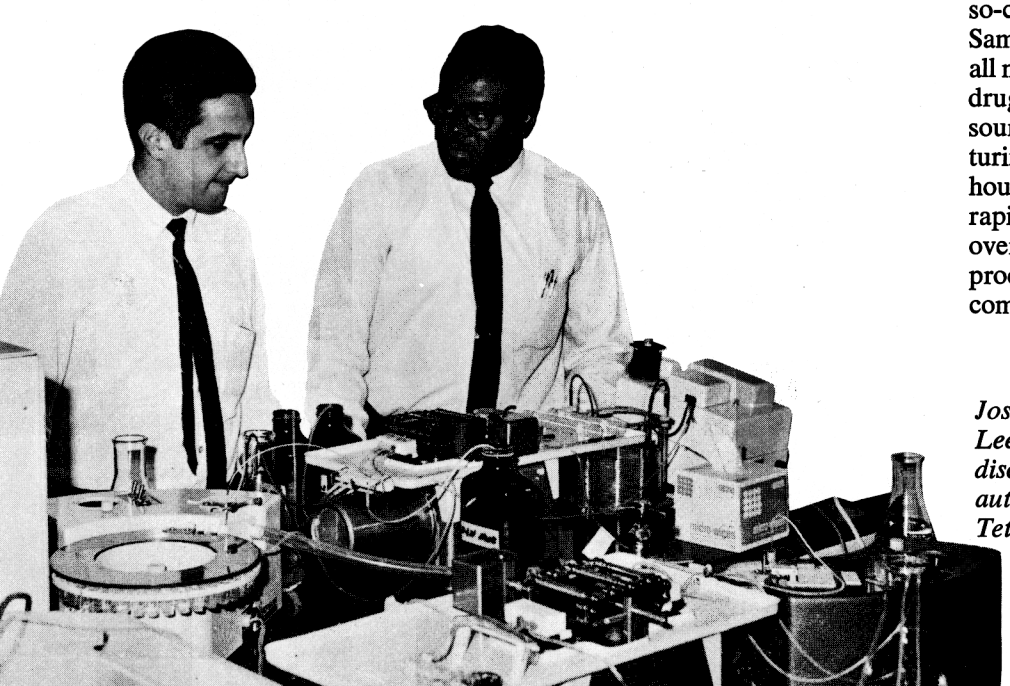
DR. STEERS: We have released no formal reports from NCDA, other than information given in talks to scientific groups such as the Academy of Pharmaceutical Sciences. Results of analyses on all samples are forwarded to Program Analysis Branch, Bureau of Compliance, FDA, where summary reports are prepared. On September 12, 1969, the Administration released the report on the 1969 Reserpine Study. Copies of this report are available from FDA. FDA plans to release analytical summaries of results of surveys as promptly as possible. These summaries will probably be published in "FDA Papers."

MR. HEUERMANN: We feel that the Center is not as well known as it should be. Only a very limited amount of information is commonly known about what is going on here and what we are doing. The release of summary reports on completed studies should help to remedy this.

What kinds of analyses do you do?

DR. STEERS: We do only chemical and physical testing at the Center. We have utilized two different types of sampling and analysis programs. The first is retail oriented and is intended to provide a statistically reliable basis for determining quality of drugs at the retail level. This program provides for collection of samples according to therapeutic categories or "studies" as we speak of them. Often a number of the drugs in a study are closely enough related to permit determination by the same method, which makes for efficiency in analysis.

The second type of sampling program is the formulator-based or so-called "saturation" program. Samples of one particular drug from all manufacturers producing that drug are collected from the best source available including manufacturing plants and distribution warehouses. This type of program will rapidly provide current data on over-all quality of the supply of the product covered. Of the studies completed to date, all have been



Jose Fernandez, left, and Dr. Lemuel Leeper, Director of Quality Control, discuss new approaches for the automation of Pentaerythritol Tetranitrate (P.E.T.N.) in the NYSCO laboratory.

retail oriented with the exception of two reserpine studies. Since we can visualize the need for rapid information about specific drugs we expect most future studies to be formulator-based.

Can you tell us more about how you initiate your studies?

MR. HEUERMANN: Prescription drugs which are medically important and have substantial use are selected for study. In addition, industry or some representative of industry occasionally issues a statement, either to a congressional committee or to the public through their publicity departments, with which we might disagree; or sometimes they make a statement that, although true, is of serious concern to us. In such cases we are interested in following up on it immediately. The first reserpine study was done on essentially a crash basis because of statements made by an industry representative before a congressional committee about the quality of reserpine tablets on the market.

Do you have any direct contact with manufacturers?

DR. STEERS: Whenever the occasion arises manufacturers might be called upon to cooperate directly with NCDA regarding methodology. Many manufacturers who are interested in our work have visited us to discuss our program, the methodology, instruments, and so forth.

Do some of the Districts specialize in drug analysis and others in, say, food analysis?

DR. STEERS: For years it was FDA policy to maintain broad analytical capability at each District laboratory. In the last few years there has been a tendency toward specialization, e.g., if a District Office receives only a few pesticide samples, these are sent for analysis to a nearby District laboratory having a substantial pesticide workload. New York, Philadelphia, Chicago, and Detroit Districts have a substantial number of drug manufacturers, hence they have a heavy drug workload—so heavy that sometimes their laboratories can't keep up. In such cases they send some of their samples to a District laboratory which has a

lighter drug workload, e.g., Kansas City or Denver. This operation is kept separate from the program at the Center.

Do you take part in the work required on new drug applications and clinical trials?

MR.HEUERMANN: No. Clinical trials and work required to support a new drug application are normally done under the direction of the sponsor of the new drug application (NDA). FDA Bureau of Medicine reviews new drug applications for approval. Validation of NDA methods is handled in Washington, D.C., by the Division of Pharmaceutical Sciences; some of the District laboratories also test the NDA methods.

Has there been appreciable withdrawal of drugs since your lab has been established?

MR. HEUERMANN: Under the way in which the program operates, the results on all samples go back to the District in which the manufacturer is located. The Distirct office takes whatever action is necessary. In some cases there have been substantial changes and some new policies.

Drug companies are always aware of quality control. Isn't that true?

DR. STEERS: Of course. The current Good Manufacturing Practice regulations (GMP's) were developed jointly by the drug industry and the Food and Drug Administration. They are a part of Federal requirements under which drugs are made, and they provide guidelines which, if followed, will help assure that only drugs of satisfactory quality are sold to the consumer.

◀ *Mrs. Natalie J. Caplan and Mr. Dave G. Cook, two analytical chemists in the laboratory of the National Center for Drug Analysis in St. Louis, keep a close watch on an AutoAnalyzer. In the background, Mr. Heuermann and Dr. Steers talk with two visitors from Technicon.*

In all the discussion about the use of generic drugs, the obvious question arises whether it is the small company with minimal funds that manufactures generics?

DR. STEERS: Big firms produce generic drugs too, but the smaller companies are primarily in the generics field.

As to content uniformity, that is, single tablet or capsule assay, only 14 monographs required content uniformity in the 1965 compendia but the number is much larger in the forthcoming editions.

DR. STEERS: We believe the number of monographs requiring content uniformity in the 1970 compendia will be in the neighborhood of 200. The biggest reason for single tablet or capsule assay in the monographs (and, incidentally, the establishment of the National Center for Drug Analysis) is probably the rapid growth of the drug industry since the beginning of World War II. Many new drugs came on the market, including much more potent drugs, involving smaller dosage units. Content uniformity testing is a necessity to assure uniformity in potent drugs. The former 18 Districts scattered throughout the United States were analyzing only about 30,000 drug samples a year. The Administration would like to have about 300,000 samples per year analyzed to keep abreast of the situation. With the content uniformity requirement, where a minimum of about ten determinations per sample is made, the work multiplies rapidly. With large volume work, it is possible to increase efficiency greatly with automated procedures.

How large is the laboratory here?

DR. STEERS: We have a very small laboratory. At present we have only 26 chemists and a total staff of 43.

Then there is still a great deal of manual analysis.

DR. STEERS: Some of our work is done manually, but we use automated procedures to the extent practical. We program our work to permit time to develop automated procedures.

Do you find people who are still sensitive to the thalidomide recall? Do you feel that it is best not to have news of recalls in the public eye?

DR. STEERS: The essential thing is to protect consumers. When a potential danger to health is involved, there are many ways to arrange to have the product removed from consumer channels. Steps are taken to remedy the situation as soon as we know what is wrong.

Do you look for an increase in the size of this laboratory and the staff in the next year or two, in view of the need for greater numbers of analyses?

DR. STEERS: We have plans for the construction of new facilities, and when they are completed we will have the capacity for 150 total personnel. This will *not* take place before 1974.

Do you feel that firms like Technicon have a responsibility to make equipment for solving the problems your people have?

DR. STEERS: This is a matter of dollars and cents. We have drawn from the methods that Technicon has published. Some of these work very well and others have required considerable development work.

What about publishing your methods?

MR. HEUERMANN: We want to publish more, but it takes time to prepare scientific articles for publication. Several of our chemists have published automated methods and a number of additional papers are in preparation. We aim to publish all methods that are developed at the Center. Now, one thing we have found at NCDA is that a method we have developed may work for one manufacturer's product yet not work for another manufacturer's product because of the difference in inert ingredients. The method has to be modified so it will work on all products analyzed here. This is one of our

biggest jobs. We are very busy trying to develop new methods.

You are probably concerned with all of these methods being so-called "official methods."

DR. STEERS: When we first develop a method, it is not official because it is not published in the USP or NF and has not been accepted as an official method by the Association of Official Analytical Chemists. If we use this method to analyze a large number of samples, and one result on a sample is outside the limits, we are not satisfied with this. A sample found to be outside of limits is taken out of line and analyzed manually strictly according to the official methodology. In other words, a check analysis.

In many cases, then, the automated procedure might be a screening?

DR. STEERS: Yes, it is a screening procedure but we have confidence in the results because we have determined a standard deviation to establish the precision of the method. But it is not an official procedure; so if we find an out-of-limits sample, we must make a check analysis by the official procedure.

How many drugs do you run a year? The Districts, you said, usually run 30-35,000 samples a year. This was essentially manual and I imagine that number is more than that now.

LEFT:
Mr. Richard F. Heuermann, Deputy Director of the National Center for Drug Analysis: "Our purpose is to protect the consumer, and even an old sample must be up to the limits. If it is outside those limits, action will be taken."

RIGHT:
Dr. Arthur W. Steers, Director of the National Center for Drug Analysis: "At the Center we have been handling six studies concurrently, with each study generating about 200 samples per month."

DR. STEERS: Last fiscal year the District laboratories analyzed about 50,000 drug samples. At the Center we have been handling six studies concurrently, with each study generating about 200 samples per month. We are therefore analyzing about 12,000 samples per year. A number of the studies include drugs with content uniformity requirement, so the number of analyses made is many-fold greater than the 12,000 samples.

Do you set limits?

DR. STEERS: No, we use the tolerance that is specified in the official compendium or New Drug Applications. Generally the bigger the dose, the narrower the tolerance range. Most of the lower dose drugs have a tolerance range of 90-110% of declared. Nitroglycerine tablets have the largest tolerance of any drug we have analyzed, 80-112% of declared.

Would you comment on your feelings on the record of the major pharmaceutical companies?

MR. HEUERMANN: They are in business to serve consumers and if they don't serve them properly, they will go out of business. So, naturally, they are acutely aware that they must make a good product. Even the best of them, though, will make a mistake once in a while. However, some of the drugs collected under the retail-based program that arrive here for analysis have been as much as ten years old. The program is aimed toward getting recently produced drugs, but we got some samples of digitoxin, for instance, that were quite old. So, in addition to what the firms are producing today, we are dealing with a combination of what they produced in the past plus what time has done to the drugs since then. Results also depend upon the nature of the drug. Some drugs are relatively unstable whereas others are stable for a number of years. Our purpose is to protect the consumer, and even an old sample must be up to the limits. If it is outside those limits, action will be taken.

I know you have always wanted to make a tour of some of the drug companies. Do you ever get to do it?

DR. STEERS: I have visited a number of drug companies, but not recently. With technology advancing as rapidly as it is, we must do more of this than we have.

Hopefully, the AutoAnalyzer gives you the opportunity to do isolated tablet assay. Do you ever prepare one tablet and run it?

DR. STEERS: It all depends on what we are looking for. If the compendium calls for a content uniformity test, we will run individual tablet assays on a minimum of ten tablets per sample. If the result is outside of limits we will do additional individual tablet assays. On low-dosage products, even if there is no requirement, we will determine content uniformity if we have the methodology to do it.

How many samples of corticosteroids did you analyze?

DR. STEERS: We analyzed about 2000 samples and did content uniformity tests on essentially all of them, for a total of about 25,000 assays, including the composite assay and the repeated tests for outside limits samples. The study was in progress for about a year.

May I ask what you are now studying?

DR. STEERS: Retail-based studies are in progress on non-steroid estrogens, diuretics, anticonvulsants, cardiotonics, and skeletal muscle relaxants. We are now preparing for a series of formulator-based studies, which will probably be in progress by the time this is in print.

Have you studied oral contraceptives?

MR. HEUERMANN: No. We are now considering multicomponent drugs, and perhaps the oral contraceptives will be in this group.

Vitamins?

MR. HEUERMANN: No, not at all. So far the studies have included only prescription drugs.

Have you done much on timed-release drugs?

MR. HEUERMANN: No. None of these have been included in the studies to date.

Will you eventually analyze those drugs that are more easily available to the public?

MR. HEUERMANN: I presume you mean drugs not requiring a prescription. We will possibly cover them later, but not soon.

How many AutoAnalyzers do you have here?

DR. STEERS: We buy components when we need them rather than complete automated systems. We're flexible in our use of all our equipment. Eventually we want to be able to go to the supply room and get a pump, a liquid sampler, or other component as needed. I want to make it clear that we have other manufacturers' automated equipment at the Center too—automatic titrators, automatic electrobalance, automated recording spectrophotometer, automated GLC, etc.

What are your immediate problems?

DR. STEERS: One of our biggest problems is developing automated procedures that are specific and are not affected by decomposition products, related compounds or excipients. This, of course, takes considerable time for each drug unless a method has already been developed. Sample preparation needs to be automated as well as readout of all results. We expect to have a computer to assist in some of this. We need additional sophisticated instruments such as NMR spectrometer, mass spectrometer, recording polarimeters, etc. And of course we need more people; we could use a staff of about 150 people.

I hope to come back and interview you then. May I?

DR. STEERS: Of course. Come any time!

Thank you, Dr. Steers and Mr. Heuermann.