

# History

of the

## U. S. Food and Drug Administration

Interviewee: Herbert L. Ley, M.D.

Interviewer: Ronald T. Ottes  
Robert A. Tucker

Date: December 15, 1999

Place: Rockville, MD

## INTRODUCTION

This is a transcript of a taped oral history interview, one of a series conducted by the Food and Drug Administration's History Office. The transcript is prepared following the *Chicago Manual of Style* (references to names and terms are capitalized, or not, accordingly.)

The interviews are with persons, whose recollections may serve to augment the written record. It is hoped that these narratives of things past will serve as one source, along with written and pictorial source materials, for present and future researchers. The tapes and transcripts are a part of the collection of the National Library of Medicine.

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Herbert Ley, M.D.

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of [REDACTED]

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Page 24, Paragraphs 2 and 3.

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Date: 01 Mar 2000 Signed: Herbert L. Ley, Jr.

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Date: \_\_\_\_\_ Signed: \_\_\_\_\_  
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INTERVIEW INDEX

General Topic of Interview: History of the Food & Drug Administration

Date: December 15, 1999 Place: Rockville, MD

Interviewee(s): Herbert L. Ley, M.D.

Address: [REDACTED]

Last FDA Position: Commissioner of Food & Drugs

FDA Service Dates: 1966 - 1969

Interviewer(s): Ronald T. Ottens & Robert A. Tucker

Address: FDA - Rockville, MD

Number of tapes: Two Length: 110 minutes

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RO: This is another in a series of FDA oral history recordings. Today, December 15, 1999, we are interviewing Dr. Herbert L. Ley, Jr., former commissioner of the Food and Drug Administration. Interviewing Dr. Ley is Robert Tucker and Ronald Ottes. This interview is being conducted in his office in Rockville, Maryland. The transcription of this recording, together with the tapes, will be placed in the National Library of Medicine and become a part of the Food and Drug Administration's Oral History Program.

Dr. Ley, to start this interview, would you give a brief biographical sketch of where you were born, raised, educated, and any relevant work experience prior to FDA?

HL: I was born in Columbus, Ohio, in 1923. The family moved several times in the first few years, but I spent most of my childhood and adolescence in Ashland, Kentucky, on the Ohio River, where I attended high school and one year of junior college. I left Kentucky in the autumn of 1941 to enter Harvard College as a scholarship student. Of course, the war with the Japanese began in December of that year, and things became accelerated, because I took the rapid course to prepare for medical school and entered Harvard Medical School in 1943. I graduated in 1946, spent the next fifteen months interning in Boston, and then entered the U.S. Army in the summer of 1947.

After attending field service school in San Antonio, Texas, I was assigned first to Walter Reed Army Institute of Research in Washington, D.C. While at Walter Reed, I worked in the Infectious Diseases Department. This was very interesting at that time, because a group at Walter Reed was very much interested in testing chloramphenicol on typhus and scrub typhus fevers. I participated in all of those studies, the first in Mexico in the winter of 1947 to study typhus fever, and then three separate six-month field trips to Malaysia where we studied chloramphenicol in the treatment of scrub typhus and typhoid fever.

Following return to the U.S., I entered Public Health School at Harvard School of Public Health and graduated from it in the summer of 1951. I eventually, after further study and residency, became board certified in preventive medicine and public health.

I stayed in the military for a period of eleven years and left it in 1958 to take the position of professor of microbiology and community health at George Washington University in Washington, D.C. I stayed there for three and a half years, then moved to the Army Research Office in Arlington at that time for the next year and a half, from which I was invited to become an associate professor at the Harvard School of Public Health and went to Boston in 1963. My main responsibilities there were teaching and research, again in the tropical diseases category.

That brings me up to the time when I joined FDA in 1966. Is there any further information you wish on the background.

RO: No, that's fine.

HL: Okay. Sometime in the spring of 1966, Dr. James Goddard, the commissioner at that time, visited Boston and asked to speak with me. He had just taken the job of commissioner of the FDA not long before, and we discussed whether I might be interested in a job at the FDA. We also discussed several important projects that were currently before the FDA, including the review for efficacy of drugs marketed in the United States between 1938 and 1962 when the New Drug Amendment to the Food and Drug Law was passed into law.

RO: What position was Dr. Goddard interviewing you for at that time?

HL: I'll get into that in a minute. The Drug Efficacy Study, Goddard felt, would have to be out-sourced. I totally agreed with him after learning a little bit more about the staffing in the medical group within FDA. We even discussed at that time the most suitable agency that could undertake the job and have the stature and scientific position

to give a legitimate set of recommendations, and this was the National Academy of Sciences, long before the Institute of Medicine was created.

Dr. Goddard was interested in having me take the position of director of the Bureau of Medicine in the FDA here in Washington. The current holder, or recent holder, of that position was a Dr. Joseph Sadusk, who had been appointed by Commissioner Larrick, sometime in the period of 1962 through 1965. I tried to find more information about the exact tenure that Dr. Sadusk had at the Bureau of Medicine, looking back into the *Who's Who for 1970-1971*. Interestingly enough, Dr. Sadusk does not list his position at the FDA. He mentions only that he has a faculty position at George Washington University. In any event, Dr. Sadusk had left by the time I joined the FDA in September of 1966. That, in general, brings us up to the time when I became a member of the FDA staff as director of the Bureau of Medicine. Where do you want to go from here?

RO: What were some of the first things that faced you when you took over the Bureau of Medicine.

HL: One of the major chunks of work, of course, was starting to negotiate with the National Academy about how the Drug Efficacy Study was to be implemented and paid for and the method of communication between the FDA and the NAS/NRC (National Academy of Science/National Research Council). That went on over several months until we were, on both sides—Duke Trexler at the Academy and Dr. Goddard and myself—happy with the arrangement which we formalized, I believe, in a *Federal Register* statement. Essentially, it said this: it was addressed to the drug manufacturers, and for all drugs which the manufacturers had marketed in the period from 1938 to 1962 on the basis of safety, principally—efficacy was not a formal requirement—the manufacturers were free to send as much clinical and support information as they wished.

The Academy, in turn, constituted a whole series of panels. My memory is a little dim, but it seems to me it was about thirty panels covering various categories of pharmaceuticals, much as the USP organizes some of its reviews. FDA was to receive the material from the manufacturers, add to the package of data any significant efficacy or safety questions that were in the current file for the drug at the FDA, and forward this material to the National Academy for review by their various panels.

This was a massive supply of paper to transmit between FDA and the Academy. Dr. Goddard in some way by, I gather, talking to the surgeon general, managed to obtain the services of a number of young Public Health Service commissioned officers who were in training in the Public Health Service. This prevented their being drafted for Vietnam and was quite a favorite occupation for many of the young medical graduates. In any event, they did a wonderful job at both ends in helping FDA staff accumulate the material for the panels, organizing it and distributing to the panel members, and then collecting the panel evaluations and retransmitting them back to FDA.

This process took several years. As a matter of fact, the first public announcements of FDA actions occurred not long before Dr. Goddard left in July of 1968. This was a bioflavonoid drug which was found ineffective. Over the next several years there were approximately, as I recall the figures, three thousand NDA products and probably five more non-NDA "me-too" products for each one of these three thousand. So the total impact on the pharmaceutical industry was really major.

In addition to the DESI (Drug Efficacy Study Implementation) Review, there were several other major policy issues that surfaced shortly after my joining the Bureau of Medicine. One of these was the whole topic of informed consent, which was part of the original legislative history for the 1962 amendments, but had not been implemented in the way of a formal *Federal Register* statement of policy. Goddard was getting pressure from the Hill, and I presume it was from Javits. I don't think it was from Fountain or Nelson. But he was getting pressure to do something about this.

So we talked about it, and he assigned the task to me. We reached an agreement that what we would do is pattern the FDA's position on the Declaration of Helsinki, which was drawn up about ten years after the end of World War II to set guidelines that would make impossible the type of medical experimentation that the Nazi's did on many of their prisoners and slave labor.

RO: So this really came out of the Nuremberg trials. Is that right?

HL: That's right. It was a subsequent add-on to the Nuremberg trials. In any event, the principles are pretty simple: that is, that patients have to give their consent; they have to be informed that they're being given an unapproved, experimental drug; they have to give their consent to such administration of the drug; and there may not be serious conflicts of interest. For example, payment of prisoners in the federal prison system, because money becomes very attractive to these people and they will not necessarily think clearly about the consent process.

This was published as a *Federal Register* proposal. We did a lot of thinking about that and decided to go the proposal route rather than the final route. We got a flood, a torrent of objections to informed consent from the pharmaceutical industry. Most of them, they were very vocal.. "This is going to bring the end to all clinical studies of new drugs in the United States," etc., etc. But we did review the comments that were submitted and from those comments made a few changes, keeping the general principles, but also inserting another element of a local institutional review board (IRB) based on the hospital or clinical entity where the studies were done.

The whole process has continued much in this same way. The institutional review boards have more autonomy today, but basically, informed consent is required. There are still arguments about what constitutes a conflict of interest. But in general, the process

I think is quite fair and reasonable and safe in terms of the patients being informed of the risks as well as they are known at the time.

RO: What authority does the Food and Drug Administration have over the study protocol?

HL: For an IND (Investigational New Drug) it has total authority. I'm not going into all of the details of the '62 amendments, but FDA has a right to object, as I recall, within thirty days to any experimental protocol, which has to be submitted and reviewed by the FDA before the investigator can begin. So it does have that.

RO: There has been quite a bit of discussion recently on gene therapy.

HL: Oh, yes. And that's an interesting question. I don't want to get into it here, but if it were a drug under an IND, the type of information reaching the public on adverse reactions would never have been released by the FDA. It's proprietary. But it has to be reported to the FDA. Apparently, the investigators with the young man that died recently did not report everything promptly to the FDA.

One other thing we can dismiss very briefly . . . At the time I joined FDA, there was among the other bureaus, a Bureau of Drug Abuse Control, abbreviated to BDAC, run by Mr. John Finlater, as I recall. This unit did a lot of undercover and police work dealing with illegal transport of controlled substances. I don't know how Goddard felt about it. I always felt uncomfortable in dealing with BDAC. I do remember that after it was moved to Department of Justice, Goddard, in a joking way one day, said to me as an aside, "Boy, I'm glad we got rid of BDAC," because I think he was equally uncomfortable. Any questions on that?

RO: That was not a part of the Bureau of Medicine. That was a separate bureau.

HL: That was an independent bureau within FDA. We had many employees that had been undercover truck drivers and had participated in stings, and their life in the districts was not very comfortable after that. So many of them were moved to Washington and employed doing good jobs, but not undercover work anymore.

RT: Well, some of those folks actually got into some rather dangerous situations and were not authorized to have firearms or any way of protecting themselves, except their *proWess at talking their way out if they're in too far.*

HL: Okay. So we've taken care of that.

You have down here "Dr. Goddard." What do you want . . .

RO: Well, he brought you into the agency, and he's been rather a controversial commissioner. Would you care to comment about him?

HL: I don't know what gives you that idea. (Laughter)

RO: What's your reaction to him? Probably the fact that he was the first commissioner to come to FDA from the outside.

HL: Yes, yes. I've known Jim since probably the late 1940s. He also, as I recall, went to Harvard School of Public Health—not during the time I was teaching, and not in the year I was a student there. But we crossed paths many times in Washington as members of advisory committees and review panels, and we weren't really close friends, but we were friends. He was always quite a flamboyant guy, and he carried that pattern on to the

Commissioner's Office. Probably, looking back, FDA needed a stimulus, and it sure got one. And I suspect that what happened was that Wilbur Cohen took the head of the U.S. Public Health Service aside and said, "Hey, I've got problems here with FDA, the new law, the commissioner and Dr. Sadusk. We need to shake it up. Who is the most volatile Public Health Service <sup>Officer</sup> that you have to offer." It's just a guess, you know. But I think someone in the Department was looking for that type of flamboyant personality to effect the change. It's rough, but sometimes that's what is needed.

RT: I was in the Legislative Office at that period. Once when in Dr. Goddard's office, I heard him speaking pretty directly to someone in the Department about the need for more SES or high-grade managers for FDA. He made his point by asking how he could effectively run this agency without them? And he got them, apparently.

HL: Yes, he got a number of them. Okay, looking down the list.

RT: Is the cyclamate something that . . . ?

HL: We can get to that eventually. What I think might next be appropriate is comment on the Consumer Protection and Environmental Health Service (CPEHS). This intermediate level of organization between FDA and the Department was introduced in July of 1968. Prior to that time, the FDA had always had fairly direct contact with the Secretary's office, the surgeon general, and the assistant secretary for health.

But at the time when I replaced Dr. Goddard—that is in July of '68—I paid a visit to the Secretary's office and talked with both Secretary Cohen and, as I recall, Bill Stewart, who was surgeon general at that time. They were questioning me about my interest in taking on the job of commissioner. We discussed general problems and the need to support FDA, personnel and money-wise. But I said very bluntly to both of them,

“The one thing that I’m really involved with and would not want to leave at this point is the DESI study,” because I had so much to do with creating it, and there were a lot of my friends, scientific friends, that were panel members—not because I had asked for them, but because that’s where they fell out when the Academy selected the panel. And they said, “Well, we don’t see any problem with that, but while we’re on that type of subject, how would you feel if there were another organization placed between FDA and the Department?” They had the Consumer Protection and Environmental Health Service in mind.

In some ways, it makes management sense to consider such an intermediate level, because it should coordinate not only food and drug activities, but water, environmental health and things like that, all of which are health problems basically. I didn’t get into the nitty-gritty about where are the money and personnel slots for this organization coming from. It didn’t seem the time to discuss that. But this was their creation, and there’s no question that the Democrats were responsible and not the Republicans.

As CPEHS, as we used to call it, was made operational, of course, what happened was the Department levied personnel requirements and money requirements, taking those things out of the budget of the subordinate agencies. When Deputy Commissioner Winton B. Rankin spoke very freely—in private—at that time and in his oral history, about the draining effect that this had on the subordinate agencies, I agreed, but the problem I saw with it from FDA’s viewpoint is that none of the people in C. C. Johnson’s offices there were really knowledgeable about food and drug regulation. They may have been about water or environmental health or something like that, but they just didn’t know beans about some of the very fine distinctions in food and drug activities. As such, we had to spend an awful lot of time educating them. If we had a proposal for the Secretary, we’d be called over. “Now, why do you want this? Why do you want that? Why does Food and Drug need this? Why does Food and Drug need that?” It became a real impediment to any effective communication up the line to the Secretary.

There were one or two events where Johnson intervened, probably not an unusual number. I didn't have any particular problem with dealing with him, but what I resented and what eventually came to be something of a problem, was this extra time delay of the papers in his office. And the Secretary further placed a limitation on us at FDA that FDA had to notify the Secretary five days in advance of any drug or product action which was anticipated to cause a public concern. That is touched upon in one of the hearings on Panalba (see Fountain Subcommittee Hearings, Drug Efficacy (Part 2), May 13, 14 and 15, 1969, pp. 173-260).

RO: You were very close to Dr. Goddard.

HL: Yes, reasonably close.

RO: Then the rumor was that the reason Dr. Goddard left government at that time was that he had hoped that he would get to head up this Consumer Protection and Environmental Health Service.

(Interruption)

HL: I have never had in any conversation with Goddard, then or since, any indication that that was his burning ambition as an administrator, so I just can't speak to that. Other possibilities that were rumored, and these are only rumors, are two remarks he made in speeches. One had to do with marijuana, and the other had to do with the corner drug store. Any of these could have been the reason, but I have no knowledge. I wish I did know, but I don't.

RO: But, of course, Herbert Humphrey wouldn't have liked that comment about the corner drug store.

HL: And we've seen other people get in trouble with marijuana since then, too.  
(Laughter)

Anyway, CPEHS was eventually eliminated. Sometime after I left the FDA, Winton Rankin, Maurice Kinslow and I met at Mr. Rankin's house for dinner, and I was given this little memento from the time. It's the *Federal Register* statement abolishing CPEHS as an organization.

RO: Issued by Robert H. Finch.

HL: That's correct. So that I think wraps up CPEHS unless you have any further questions.

Okay. We're beginning to narrow it down. There are three smaller items that I think should be mentioned because of their subsequent importance. I guess the easiest one to begin with is the oral contraceptives, which were under study and being prepared for marketing or just marketed at the time I joined the FDA in September of '66. This was always a very controversial class of drugs in the earlier years, and it's hard to convey at this point how many strong opinions were present. Some people considered them immoral or illegal or causing unnecessary risks to women. Other people felt they were very, very important.

RO: And liberated women.

HL: And liberated women, but not only that, one of the major problems in the world today is population control. Various countries have taken various routes, but oral

contraceptives, in all the variety that are available today, do provide, generally, a convenient method of contraception which is pretty effective, 95 percent plus. So I think looking back historically, the FDA action on oral contraceptives was something that was done carefully as new data became available, but will represent, along with the manufacturers' contributions, really a major advance in population control.

There were some people in Washington, and particularly in some of the media, that took drastic exception to FDA's approval. We were concerned with the need for patients to understand the risks, and in their hurry to get oral contraception, many patients didn't ask their doctor, and their doctor didn't tell them. So as new studies became available showing increases in thromboembolic disease in patients receiving the older, stronger oral contraceptive products, some of the critics of the agency went almost ballistic. "You've got to take them off the market!" was their attitude. What eventually became the practice, and is now present for a number of drugs, is a patient package insert, very abbreviated, very much to the point, delivered to the patient with the product, giving a well-balanced presentation of the risks. And I think this is the way it should have gone, and I'm happy with the end result. I believe Edwards signed the final regulation on patient package inserts, but it has continued and is an important advance that FDA has made.

RO: While we're talking about patient package inserts, drug advertising has been a . . .

HL: Yes. True. I've got an example on Panalba we'll get into in greater length later on. But, it is hard to understand today the unreasonable claims, unsupported claims—as Billy Goodrich would say, puffery—for efficacy that accompanied ads for many drugs and accompanied the handout material from drug detail men in the early 1960s. This was, of course, one of the side effects of Kefauver's initial interest in the economics of the drug industry, because he was attacking advertising as being false and misleading. But

advertising as it existed in the early sixties was unbelievable, and it was certainly, in most cases, very misleading, presenting only one side of the picture, ignoring risks, hazards, side effects.

One of the important parts of the '62 amendments was that FDA's monitoring of advertising had to be increased so that the advertising was consistent with the clinical information in the files. So there are many people who have complained. PDR (*Physician's Desk Reference*) came from a little volume about that thick (indicates one inch) to one about this thick (indicates three inches), because everybody decided they would essentially put the whole package insert in. It's small print, but it's been very helpful to me in the years since FDA. So I certainly agree with all the critics that the drug advertising was not good, and it was very misleading in the early sixties.

RO: One of the things as far as television or radio advertising of drugs was direct promotion to patients.

HL: That's new, too.

RO: Yes, right. Because they couldn't in sixty seconds or thirty seconds give all of the information that they needed to.

HL: Well, that's true. I've watched a few of these, including the ads on ED (erectile dysfunction) and generally the ads have to be short, and their presentation is subtle. On the other hand, most of them that I've seen contain reasonable cautions, namely that "Viagra may not be for you. You must see your doctor." This makes sense. They are really very abbreviated, non-medical ads aimed at the consumer. Keeping a fair balance in this information is difficult, but I haven't found anything that I've gotten exercised about in terms of poor promotion. There are many others that are advertised.

Okay. That wraps up my comments on OCs (oral contraceptives).

There was another subject that we became involved with, and I can't recall the exact time. I think it was spring of 1968. I believe it was before Goddard left, and I really can't tie it down closer than that. Parke Davis, the original manufacturer of chloramphenicol, sent us, the FDA, lab data regarding differences between the blood levels achieved in patients with Parke Davis's original chloramphenicol and generic manufacturers' chloramphenicol. There were four or five such generics. In every case, at least in the Parke Davis results, the generic manufacturer product had deficiencies—less area under the curve in terms of blood levels; less total absorption—so that there was a reasonable question whether the generic product was indeed as effective as the original product.

I must say, Parke Davis did their homework and did it very well. And we mulled this over. None of us really wanted to see these four generic products totally removed from the market, and yet something had to be done to stimulate the generic manufacturers to change their product formulation so that it behaved as the original product did.

This is where being in the army for a while helped out, because at that time, for some of the then-conceived biological warfare concerns of the military, vis-à-vis Russia and other Middle Eastern countries, chloramphenicol was one of their last-ditch antibiotics for treatment or prevention of disease caused by some of these horrible bacterial warfare agents. Fort Dietrich still housed the army lab that was doing those studies. So I contacted the Dietrich group and explained the nature of the bioavailability problem to them. They were concerned, concerned enough so that they agreed to run some tests in their own volunteers as subjects—not infected, but as normal subjects—of Parke Davis and the generic manufacturer. This is the sort of thing we couldn't do easily at FDA, but it was a very great concern to the army. Sure enough, they did confirm the difference.

As I recall the generic products were temporarily decertified until, as things worked out, FDA developed a formal policy for bioequivalency comparisons. This is

above and beyond in vitro dissolution tests or anything of that sort. This is actually in human subjects. It was somewhere around twelve or fourteen subjects, crossover with blood levels, urinary outputs of the antibiotic or other drug. As nearly as I know, I think that general policy is still in effect, where there are significant questions of efficacy with generics.

RO: Did they ever come up with an in vitro test?

HL: I don't know. I can't really answer that, because I was only familiar with the problem at that time. But bioequivalency, I haven't heard much about it being a problem lately. But the policy that we set up for the use of normal subjects seems to have solved most of that problem.

A somewhat related problem dealing with other antibiotics was of concern to us both in terms of veterinary medicine and human medicine and the widespread use of antibiotics either as a growth stimulant in animals or as an unnecessary medication in humans. That was commented on at that time. A few of the academic infectious disease people were very much in favor of a more limited use of antibiotics in clinical patients, limiting them only to the patients in whom the antibiotic was clearly needed. But the general medical community was of the opinion, we'll never get antibiotic resistance, and we won't have any problems, and if even though this is a common cold and I want to give an antibiotic because my patient expects it, I will. But we have now learned in the last thirty years that this was a very real problem and is causing difficulties today because practically all of the simple earlier antibiotics have produced severe resistance in microorganisms, particularly in hospitals.

RO: What's the solution?

HL: Well, the solution right now temporarily is new and different antibiotics, but the real solution is in getting the animal feed additives that are in wide human use, replacing them with something simpler which is not of clinical significance today.

RO: And getting the medical profession not to prescribe so freely.

HL: And getting the medical profession to back off in their widespread use of antibiotics.

I think we're now down to cyclamates, congressional hearings, and Panalba, and I need to take a break.

(Interruption)

HL: Okay. One of the things I would now like to discuss is one of the steps in the NAS/NRC DESI Review involving some of the products that were affected adversely. The top staff at FDA, Goddard and I, along with Billy Goodrich and others, planned a strategy, when the Academy (National Academy of Science) began giving us evaluations, of taking initially regulatory action on drug products that were essentially unimportant and about which the scientific community could not argue in any way that they were effective. So this was an intentional thing, and in a second phase we would attack the drug products which were going to be very touchy in terms of the manufacturers' interest in income from these products.

So with that in mind, we chose a bioflavonoid drug product for initial action and published a *Federal Register* proposal to withdraw the NDA (New Drug Application) as it had existed in that '38-'62 period, and there was really essentially no opposition. So we kept taking actions in the form of *Federal Register* proposals on subsequent products which the Academy was by then beginning to forward in fair numbers. Obviously, the

easier evaluations were received first, because the Academy released them first. Some drug products may have had eight or ten indications falling in different panels, and this meant that a total of eight panels had to review this file of data, and those took a little longer. They also were more controversial. They came more toward the end of my stay at FDA.

In any event, by about the spring of 1969, one product that had been reviewed by the Academy landed on the commissioner's desk for action. The product was Panalba, manufactured by Upjohn, which was a combination antibiotic composed principally of tetracycline, but with an added compound of albamycin (novobiocin), a more toxic product than tetracycline with a different spectrum of activity. This had been promoted very successfully by Upjohn to the medical community. I believe the figures are approximately correct that about a third, well, maybe a quarter to a third of Upjohn's total gross sales were Panalba. So it was a very important product from their point of view.

The Academy had come to the conclusion that this was ineffective as a combination product. This takes some discussion because the tetracycline was obviously not ineffective. It was quite an effective drug. The question was whether the albamycin also contributed to efficacy.

My memory may have failed me a bit, but Upjohn, of course, objected to this. They tried to fight it, and they met with me, they met with the Secretary. At one point they requested a hearing, and I spent a total day as a hearing officer reviewing with Upjohn personally all of the clinical data they had provided in the original NDA that was submitted in the '38-'62 interval. As I recall, in the material they had submitted, there was not one single clinical study, and the data were obviously in vitro and there may have been an animal study. But the majority of the information was in vitro, test tubes and culture.

Furthermore, there was information that albamycin reduced the efficacy of tetracycline. The Academy panels could find no information or published research or

their own personal experience that indicated that albamycin contributed to the clinical benefit to the patient.

I found in the Drug Efficacy Hearing Committee Report a fact that I had forgotten, that FDA had actually apparently commissioned a study with between fifty and sixty patients who had clinical disease and were treated one group with tetracycline and one group with Panalba. No difference in clinical response. So, as I recall, that was later on.

But we ended up, Upjohn and the FDA, you know, in an impasse. We proposed to decertify the product and to decertify albamycin as a separate product, for which the Academy could not find good reason for efficacy. At this point, it really became a political issue. We sent the letter to the Secretary, as demanded by the five-day rule, proposing three possible courses of action, one of which was decertification and removal from the market, and recommending that course of action. That went on through CPEHS to the Department.

The point that I remember is that I was out of the city at a meeting, I believe with the AMA, and returned to Crystal City offices mid-afternoon or late afternoon. When I got up to the office to see what had gone on during the day, here was Mr. Don Gray from Mr. Fountain's committee in the office, in a terrible humor. Winton had placated him. Gray asked, "When are you going to take action on Panalba? Where's the Panalba action?" We refused initially to give him the papers. It appears that I called Billy Goodrich and Billy said, "Yes, you're going to have to do it. He'll subpoena you and put you under oath if you don't." Then there were some exchanges between Goodrich and the Secretary's office. In the Fountain committee hearing on Panalba, it was also clear that Upjohn was lobbying the Secretary in terms of meetings between Upjohn and the Secretary and that Upjohn had made all sorts of proposals to delay the decertification while they got more data. As it was pointed out in the hearing, they had already had seven years to do so.

RO: Who was the Secretary at that time?

HL: The Secretary at that time was the Honorable Robert Finch.

(Interruption)

HL: The Fountain Committee hearing was held within a few days of that confrontation between Mr. Gray and myself in the Commissioner's Office. It's too detailed for me to remember all of the information. It's very clearly drawn out in the committee report with all the enclosures and everything, so I'm not going to try to go through that. But it was the highest drama I have ever experienced in any job that I've ever done. It was as though it had been written for the stage (see hearing report, Drug Efficacy (Part 2) previously referred to on page 10).

Eventually, Panalba was removed from the market, and I realized then--and I think Billy Goodrich and I have talked about it--that my life expectancy at FDA was probably limited. I had done everything by the book and had drawn on all of the people that were involved in this, both in the FDA and the Department, and I think that what the Administration was really wishing that I would do is to stonewall the whole Academy report, because it was goring too many people. But nobody ever told me to do that, and fortunately, I didn't have to worry about that, but I distinctly had that feeling in the gut.

RO: You mean too many pharmaceutical companies.

HL: Too many pharmaceutical companies were being gored. But it was appropriate. That was the law. Regarding the quality of most data, some of the NDAs were good from that period, but the majority of them were lousy. So I guess that's the story for Panalba.

The other story that we still haven't touched on is the cyclamate issue. I have not had a chance—I haven't found the committee hearing report on the cyclamates. I thought I had it, but I don't have a copy that I can find. But I'll tell the story as I recall.

To set the stage, cyclamates were manufactured by Abbott Laboratories. They were a very popular artificial sweetener incorporated in many so-called diabetic foods and in many dietary products, including diet sodas. Because saccharin didn't suit itself well to cooked or baked products, cyclamate had really moved into the whole area of human foods as an artificial sweetener, so it was in very wide usage.

I don't remember the exact time; it was sometime fall of 1969. I had a request from the pathologist at Abbott Laboratories by the name of Dr. James Price; he requested a private meeting with me in my office. I discussed it with Winton Rankin. As normal policy, we never met any industry rep without a witness. But I had gotten to know Dr. Price, and in other discussions Dr. Price was a reasonable man and I trusted him. So I violated Winton's recommendation for that one time. I learned subsequently, at the time Jim Price was meeting with me in the Commissioner's Office, Abbott was meeting with the Secretary in the Secretary's Office.

But the news that Jim conveyed to me was disturbing and complicated. I noted earlier that I had not found documentation of the cyclamate "problem" before the oral history was taken. Subsequently, I found in my files a reprint of an article published in *Science* (20 February 1970, Vol. 167, pp. 1131-1132), which is attached as Appendix I. This article was jointly authored by Drs. Price and Biava (Abbott), Drs. Oser and Vagin (Food and Drug Research Labs), Dr. Steinfeld (DHEW) and myself (FDA). It provides a regulatory history, protocols and results of the toxicology studies, and overall conclusions of pathologists who reviewed the rat bladder cancer specimens. The reader is urged to review the article at this time.

I did not want to trust my judgment alone or Dr. Price's judgment alone. It so happened there was a committee meeting which FDA had requested of toxicologists at

the NAS/NRC meeting three days later. Although I ruffled some feathers at the Academy and got a mild verbal reprimand from the Academy director, and because the committee was working for FDA anyway, I weaseled my way in, and Jim presented the data to the toxicologists. They agreed this was of enough concern to probably require discontinuation of marketing.

So, having obtained that information, I felt secure in taking a pretty hard hard-nosed approach to cyclamates. I believe I was *summoned* to the Secretary's office. I presented the information that I had, and we discussed in fair length a number of possible actions. The one that we were criticized for later was to leave cyclamate temporarily on the market in diabetic food. Sudden removal of diabetic foods could cause some medical problems and it could cause some severe inconveniences for diabetic patients if they could not stop cyclamates immediately. But other than that, cyclamate should be removed from the market.

Now that was the final position the Secretary adopted. I outlined a number of options, and I wish I had a copy. But collectively, the surgeon general, the Secretary, the Deputy Secretary for Health, Jesse Steinfeld, we all came to the conclusion that we couldn't just sit around and twiddle our thumbs. I was *ordered* by the Secretary, Mr. Finch, not to discuss anything about the cyclamates with a single member of the FDA staff. Period. So I followed his orders. I've heard criticism since that the whole Food Additive section of the FDA should have been involved in the discussion, but that was not the Secretary's wish.

So the following day, the banning of cyclamate in all except diabetic foods was announced by the Secretary. There were a lot of pressures on the Department and FDA at that time. Ralph Nader and (Jim ) Turner were complaining vigorously about FDA's food additive actions. The Secretary, I'm sure, was very sensitive to it as well. There was this unusual form of pressure that was quite concentrated at that time. But the options I set out in my memo to the Secretary really didn't involve that. They were just total

removal, partial removal of all but diabetic foods remaining for a limited time, no action with a public notice or something like that. Obviously, the latter was not a wise course of action.

RO: What was to be done with the products that were on the market, other than the diabetic category?

HL: Well, I don't recall whether they were to be recalled from the shelves. I don't know the level of recall which was done. I do know that many of my friends, not FDA, went out and bought cases of diet sodas before they disappeared. So it was taken as a joke by some people, but the pathology was no joke.

RO: Did you ever find out what Abbott had discussed with the Secretary? Was it different than your meeting with James Price? Or had they really bared their soul as far as the actual study results?

HL: I think they bared their soul. I don't think they were really fighting the action. They knew they were in serious trouble. Can't you imagine what a malpractice or a liability lawyer would do with that? I don't think Abbott was fighting it. It was totally different than the Upjohn situation.

RO: Interesting.

HL: But those were the facts as I remember them, and I'm absolutely positive that I was *ordered* not to discuss what happened in the Secretary's Office or any proposed action with a single FDA member. So I didn't discuss it with Winton. He only learned it after they made the announcement.

RO: And of course shortly after that, you left the agency.

HL: That's an interesting way to put it. Yes! (Laughter) I was just going to draw some conclusions from these . . . I never will know for certain. I've been told by one person who will remain nameless, although he was given the same heave-ho out the door, I was told by him—and he should have known—that the cyclamate issue was what did me in. I'm not so sure. Looking back, a little more philosophically, you know, I don't see how the Secretary could have blamed me for cyclamates. It was such a complicated problem, delivered so suddenly, and Abbott wanted to get this to the commissioner and to the Secretary, I'm sure for product liability reasons. So I'm not so sure that my friend is right. I don't know what additional information he has. I am suspicious that cyclamate may have been the second straw, and that what really got Finch upset was the Panalba action, which was not my doing. It appears that someone within FDA, and I know not where, but I could name two or three names, leaked this to Don Gray. I would place my suspicions mainly on somebody in the Bureau of Medicine . . .

RO: Who will remain unnamed. (Laughter)

HL: Oh, I don't know. I don't want to name names in that regard. But the real point in discussing this is that the Panalba situation would be very embarrassing to the Secretary—much more so than the cyclamate issue—because Fountain really made a stage production out of the whole Panalba incident. So I suspect that, you know, Panalba had a lot to do with it. The cyclamate may have been the last straw, but I don't find sufficient reason in the cyclamate affair. There was nothing I could have done, there was nothing I did do to irritate or to make the Secretary's task more difficult than it normally would be.

And there's one other thing. You're right, I did, as you know, depart the FDA not too long after the cyclamate episode. However, there were three actions taken that day. Ken Kirk, Winton Rankin and myself were all given the opportunity to be employed in the Department, in Budget and Fiscal, as I recall, which is not my cup of tea under any circumstances. You know, what happened. Ken had enough time to retire and did. Winton did not, so he went to his exile in Siberia in the Department for a while. And I, although . . .

One other thing has happened that, you know, makes me rethink whether Panalba or cyclamate was the stimulus for Finch's action, and that is that in 1973, I got a call from a friend of mine, a lawyer, who had been listening to Chuck Colson's testimony in the Watergate hearings. My friend told me that Colson had testified that there was a White House political enemies list which was submitted to the chairman of the hearing, and that my name was on the political enemies list. And sure enough, it was published in the *Post* the following day, and my name was there, and Dr. Michael DeBakey, and of course, Jane Fonda, bless her soul, and Henry Fonda, but the rest of them were all activists.

And I still don't know why I was included in that list. But I had very seriously offended someone in the Administration, and I have no idea who. I was, and still am, registered an Independent. I'm neither a Republican nor a Democrat. I have never participated in any political action group. So I am at a loss to explain why this should be, but if either of you ever find out, please tell me.

I think that's about it, gentlemen.

RO: One of the things, while you didn't have user fees during your stay there, would you care to comment about user fees as far as the Food and Drug Administration is concerned? Because, of course, now they have user fees.

HL: Yes. I really can't say. I really haven't looked at it in detail. There are a couple ways you can go at it, and you're performing a service for a pharmaceutical manufacturer, which is part of the drug development cost, really, and in that sense a user fee makes sense. You're performing a service for the manufacturer which eventually will benefit the American public, so in that sense, it would appear more logical to take it out of general taxes. I can argue it either way.

RO: I'm sure when you came in to the Bureau of Medicine, you were pressured to have quick approval of drugs. As I remember, that's always been a problem.

HL: Oh, yes. When Goddard got another one of these senior positions and appointed Robert Hodges to what was then the Office of New Drugs—it was a subsidiary under the Bureau of Medicine—Bob used to give the commissioner and me a weekly tally on number of new applications in, number of applications completed, backlog, you know, all that work. He even broke it down into pre-clinical study section, Phase I, Phase II, Phase III. The backlog was really a serious worry. The number of people you would have to have to bring it down within the six months the regulations call for, would be awfully high. I don't think a lot of physicians would really enjoy that kind of work. I think you'd have a hard time recruiting. Harry Dowling has made the same point in his book, which is a very well-balanced book as of 1969. So it would have been great to find some really good method of reducing the backlog in those days. What's the backlog like today?

RO: I don't know. The other thing, there's been talk of third-party review.

HL: Yes. Well, it depends. It has all sorts of different levels. The director of the NIH suggested that the NIH do the job back in 1968. And in some of the discussions about government operations ten years or so ago, they were talking about a Good Housekeeping seal of approval given by a third party. Frankly, I'm afraid that I'm cynical. From what I saw in some situations while I was at FDA, I would not really trust a manufacturer to pass judgment on his own work, and I would be concerned about conflicts of interest in inviting a third party to do it—even NIH.

RO: Or Dr. Ley & Associates doing it.

HL: That's been suggested, too. It would depend. It's hard to find people who are really knowledgeable about what is important. They're present most commonly in the pharmaceutical industry, and there's a real conflict. The academic group is not oriented that way most of the time.

RT: Well, Dr. Ley, you've now been away from the agency for a number of years and probably have some retrospective thoughts about it, and/or would you care to briefly outline some of the interests you've had since being commissioner?

HL: Hmmm. Well, first of all, I'd like to say that at the time I left the FDA, even though I was not expecting to stay there forever, the immediacy of the decision to leave was painful, as I'm sure it was to Winton and Ken, too, but Ken was already ready to retire. And now, thirty years later, you can look at the events a little more philosophically and chuckle sometimes about part of it. I'm not sure how much longer I would have been effective as commissioner.

We had terrible difficulty in recruiting capable people in this interim situation with a Republican Administration and a Democratic Congress. It's like walking into a hornet's nest in that case, and a lot of people, academics, whom we would generally prefer because they're more scientifically oriented, didn't want to leave their nice, safe little professorship. And you can't blame them. So, looking back, I'm sure that that sort of pressure would have fairly soon stimulated me to look elsewhere myself.

I'd had a few invitations, which were probably stimulated by the Republican group, hoping to ease me out that way, and maybe I should have taken them, but I was very deeply and personally committed to that DESI Review process. I felt it was a very important job, and it was a job that FDA should do, not just because of the law but because of some of the obvious non-efficacious drugs that were in that package and still approved as a new drug before the efficacy provisions. So I thought that was very

important. I'm glad that we succeeded in getting as many of those products out and published and action taken before I left. We knew that some of them were going to be strongly contested.

(Interruption)

HL: As I was saying, before we changed tapes, I was happy that we got as many of those DESI drug reviews properly implemented and actions taken before I left. It's just one of those things, and I was personally committed, and I would have been very unhappy if I had left earlier or been forced to leave earlier. And remember, we all submitted a pro forma resignation to the new Administration when Nixon's group came in. So, looking back, I've joked with friends, I've said . . . Well, it's usually stimulated by a comment, which I've gotten a couple of times, "Well, wouldn't you like to be commissioner again?" I say, "Hell, no! I've spent my four years in purgatory."

RO: I wonder if you have any comments on the agency taking on tobacco?

HL: That's been around for thirty years too—in one form or another. It's a horribly difficult job. It's more a job of public health education than it is of food and drug. I think it would be great for the Public Health Service surgeon general to take it on, but that's caused a few casualties in the past. So I'm not sure anybody has the guts to do it. The only thing that would be comparable would be Thomas Perrin's fight against venereal disease in the mid- to late-thirties, which was a taboo subject but which he personally took on as a public education effort sponsored by the Public Health Service and did more to wipe out VD than anyone has done before or since.

RO: We want to thank you very much, Dr. Ley.

HL: You're most welcome. We have only one piece of tape that I have restricted, just to review that.

RO: You'll have an opportunity to review the transcript.

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# SCIENCE

## **Bladder Tumors in Rats Fed Cyclohexylamine or High Doses of a Mixture of Cyclamate and Saccharin**

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## Bladder Tumors in Rats Fed Cyclohexylamine or High Doses of a Mixture of Cyclamate and Saccharin

**Abstract.** *Papillary transitional cell tumors were found in the urinary bladders in 8 rats out of 80 that received 2600 milligrams per kilogram of body weight per day of a mixture of sodium cyclamate and sodium saccharin (10:1) for up to 105 weeks. From week 79 on, several of these rats received cyclohexylamine hydrochloride (125 milligrams per kilogram per day, the molecular equivalent of the conversion of about 10 percent of the cyclamate dosage to cyclohexylamine) in addition to the sodium cyclamate and sodium saccharin. In another study in which 50 rats were fed daily 15 milligrams of cyclohexylamine sulfate per kilogram of body weight for 2 years, eight males and nine females survived. One of the eight males had a tumor of the urinary bladder. In neither study were bladder tumors found in the control rats or in rats treated with lower doses of the compounds.*

Numerous requests have been made for the information which was presented to the National Academy of Sciences-National Research Council (NAS-NRC) ad hoc Committee on Nonnutritive Sweeteners on 17 October 1969, and which led to the order by the Secretary of Health, Education and Welfare that cyclamates be removed from the list of substances generally recognized as safe (GRAS). In this preliminary report we present the pertinent experimental findings in the context of some relevant historical information.

The enactment of the Food Additives Amendment of 1958 made it necessary to establish at least a partial list of substances generally recognized as safe since such substances generally were exempted from the application of this statute. Food and Drug Administration (FDA) scientists prepared such a list, which included cyclamates, and this was sent to over 900 qualified scientists for comment. Of the 355 scientists who responded, only one commented on cyclamates stating that he was unfamiliar with the data on these sweeteners. Thus, cyclamates were included in the published list, as set forth in the Code of Federal Regulations (Section 121.101).

In 1962, the Food and Nutrition Board of the NAS-NRC issued a revised policy statement which said that artificial sweeteners could be safely used in limited amounts as a nonnutritive substitute for sugar in special purpose foods.

In 1965 and again in September 1967, scientists of the FDA reexamined all available information about cyclamates and concluded that there was no

evidence that the amounts of cyclamates then being used presented a hazard to health. In 1967, the joint FAO/WHO Expert Committee on Food Additives established an acceptable daily intake of 50 mg of cyclamate per kilogram of body weight. In 1968, the NAS-NRC recommended the limitation of daily intake to be 70 mg per kilogram of body weight. On the basis of these two reviews, in April 1969, the FDA proposed steps to achieve revised product labeling that would limit the daily intake to the level recommended by WHO.

The above reviews included an examination of studies in which rats were fed diets containing 1 and 5 percent saccharin or sodium cyclamate for 2 years. These compounds produced no effects at the lower dose and no distinct toxic effects at the high dose (1). Toxicological studies in rats fed diets containing 1 and 2 percent sodium cyclamate for periods up to 11 months indicated no significant adverse effects of this compound (2).

Allen *et al.* (3) reported in 1957 that surgical implantation of pellets containing 4 parts of cholesterol and 1 part of saccharin into the urinary bladder of mice induced one papilloma and three carcinomas of the bladder among 13 animals that survived 40 to 52 weeks. In 1966, a similar study with sodium cyclamate was initiated by one of us (J.M.P.) at the University of Wisconsin. On 5 June 1969, a preliminary verbal report (4) of this study was given to Abbott Laboratories, stating that a significant incidence of bladder tumors had been found in white Swiss mice in two separate experiments with the pel-

let implantation technique. Representatives of Abbott Laboratories had several discussions about these findings with representatives of the National Cancer Institute and the Food and Drug Administration during June and July. It was the judgment of all concerned that tests for carcinogenicity by the pellet implantation technique (3) were not suitable for evaluating the hazard of orally ingested compounds. A similar position regarding data obtained by this technique had been taken by the NAS-NRC ad hoc Committee on Nonnutritive Sweeteners in 1968. Plans for additional toxicity studies of cyclamates, cyclohexylamine (CHA), and saccharin were then agreed upon. It was also decided to pay special attention to the urinary bladders of rats in two toxicity studies sponsored by Abbott Laboratories which had been initiated in 1967 and were nearing completion.

One of the last-mentioned experiments, conducted at Industrial Bio-Test Laboratories, Northbrook, Illinois, was a 2-year toxicity study of cyclohexylamine in rats which was designed to ascertain whether or not the CHA which could be present in minute amounts in commercial cyclamates might be toxic. Charles River strain albino rats in groups of 25 males (125 g) and 25 females (123 g) were given daily doses of either 0, 0.15, 1.5 or 15.0 mg of cyclohexylamine sulfate per kilogram of body weight. During the first year of the study, there was only a slight depression in the weight gain curves observed in male animals fed the highest dose (5). There were no significant differences between test and control animals as to food consumption, mortality, blood chemistry, or hematologic parameters. At the end of 2 years, eight males and nine females were alive in the high dose group. There were 13 to 16 survivors in each of the other three groups at the end of the study. No drug-related changes were found in any of the organs examined except in the urinary bladder. A bladder tumor was found in one of the eight male survivors in the high dose group which was diagnosed as invasive transitional cell carcinoma, grade 2. The tumor did not invade the muscular wall of the bladder, and no metastatic lesions

Table 1. Summary of the preliminary data obtained in the long-term feeding study of sodium cyclamate and sodium saccharin (C/S). At the 79th week groups B, C, and D were each divided into two subgroups each containing approximately half the surviving number of converters and nonconverters. Subgroups 1 and 2 continued to receive C/S at the stated dose and subgroup 2 received in addition the indicated dose of CHA (the molecular equivalent of the conversion of about 10 percent of the cyclamate to CHA).

Group	Daily dose (mg/kg day)		No. of animals alive at week								No. converters† No. tested		No. tumors‡	
			0		56*		78		104		M	F	M	F
	C/S	CHA	M	F	M	F	M	F	M	F				
A	0	0	35	45	25	35	20	35	13	26	11/23	5/33	0	0
B	500	25	35	45	25	35	20	30	10	19	9/24	9/32	0	0
C	1120	56	35	45	25	35	20	31	8	23	23/25	32/35	7	1
D	2500	125	35	45	25	35	20	30	12	22				

\* Ten males (M) and ten females (F) died or were killed for interim study by the 56th week. There was one death in each group except for group B females (none) and group D males (two). † Rats excreting CHA in the urine in amounts equivalent to more than 0.1 percent of the cyclamate fed (see text). ‡ Urinary bladder tumors agreed upon by all of the pathologists on the basis of the slides available to date. Four to eight of these tumors were diagnosed as carcinomas by different pathologists.

were present. Spontaneous bladder tumors have never been recorded in control rats at Industrial Bio-Test Laboratories (5) or at Abbott Laboratories and are reported to be very rare (6).

The second experiment, conducted at Food and Drug Research Laboratories, Maspeth, N.Y., was a 2-year toxicity study of a 10:1 mixture of sodium cyclamate and sodium saccharin (C/S) which was added to the diet of Wistar strain rats in concentrations providing a daily intake of 0, 500, 1120, or 2500 mg per kilogram of body weight (Table 1). The concentrations required to provide the stated daily doses of the mixture were determined from data obtained by biweekly weighing of the animals and biweekly measurements of their food intake. The rats were maintained throughout the 2-year period in individual cages in air-conditioned and humidity-controlled quarters, with water and food freely available.

During this study many of the rats were found to convert cyclamate to cyclohexylamine (7). The rats were considered to convert cyclamate to cyclohexylamine if more than 0.1 percent of the cyclamate was accounted for as urinary CHA. The extent to which individual rats converted (or whether they converted) was variable. The maximum conversion rate was 12.6 percent (7).

In the 79th week, one-half of the animals in each of the treated groups were given supplemental amounts of cyclohexylamine hydrochloride mixed in the diet and calculated (as the base) to provide daily intakes of 25, 56, or 125 mg per kilogram of body weight. All major organs and tissues, including the urinary bladder, were examined histologically in the surviving animals as well as in those animals that died or were killed in the course of the study. Among the 240 rats receiving C/S, seven males and one female of the

group fed 2500 mg per kilogram per day showed papillary tumors of the urinary bladder (Table 1) which were diagnosed by seven pathologists (8). In all but one instance, the tumors developed in rats that had been found to convert cyclamate to CHA. There were three bladder tumors in animals that received supplemental CHA and five in those that did not. Macroscopically, tumors were seen in only two animals. Of the eight tumors, four to eight were diagnosed as carcinomas by the different pathologists. No gross bladder calculi were found in the eight rats with tumors. Three of the tumors were found between weeks 78 and 83, and the remaining tumors were found in animals which were killed between 100 and 105 weeks of the study.

On 8 October 1969, Abbott Laboratories was first notified by telephone of the presence of bladder lesions in rats fed the C/S mixture. On 9 October Abbott pathologists observed the presence of bladder tumor in one of the rats fed CHA. On 13 October Abbott representatives reviewed the microscopic slides and other data from the study of the C/S mixture at Food and Drug Research Laboratories and on the same day reported the findings to scientists of the National Cancer Institute. On 14 October these findings were discussed in a joint meeting of representatives of Abbott Laboratories, the National Cancer Institute, FDA, and the Department of Health, Education and Welfare, and it was decided to report the findings to the NAS-NRC ad hoc Committee on Nonnutritive Sweeteners. The slides of the urinary bladders of the rats from the two studies were reviewed on 15 and 16 October by additional staff and consultant pathologists of the National Cancer Institute. All the available data from these experiments were presented on 17 October to the NAS-NRC Committee which

recommended the removal of cyclamates from the GRAS list.

The development of bladder neoplasms had not been reported in other species or in other strains of rats fed cyclamate or saccharin. There is no evidence that the use of cyclamate or saccharin has caused cancer in man, malformations in children, or any other abnormality in humans other than a rare skin hypersensitivity. However, in view of the requirements of the Delaney clause of the Food Additives Amendment, the removal of cyclamates from the classification of substances generally recognized as safe resulted in the prohibition of their use in general purpose food products.

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