PRECLINICAL AND CLINICAL TESTING BY THE PHARMACEUTICAL INDUSTRY, 1978

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH AND SCIENTIFIC RESEARCH

OF THE

COMMITTEE ON HUMAN RESOURCES UNITED STATES SENATE

NINETY-FIFTH CONGRESS

SECOND SESSION

ON

EXAMINATION OF THE PROCESS OF DRUG TESTING AND FDA'S ROLE IN THE REGULATION AND CONDITIONS UNDER WHICH SUCH TESTING IS CARRIED OUT

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TUESDAY, MARCH 7, 1978

U.S. SENATE,
SUBCOMMITTEE ON HEALTH AND SCIENTIFIC RESEARCH,
OF THE COMMITTEE ON HUMAN RESOURCES,
Washington, D.C.

The subcommittee met at 9 a.m., in the HEW North Building Auditorium, Washington, D.C., Senator Edward M. Kennedy (chairman of the subcommittee) presiding.

Present: Senators Kennedy and Schweiker.

OPENING STATEMENT BY SENATOR KENNEDY

Senator KENNEDY. We will come to order.

Today's hearing focuses on the protection of human subjects of prescription drug research. A prescription drug is, in a very real sense, least safe the day it is approved for marketing by the Food and Drug Administration. For it is then that the product goes into widespread use and is subject to the varying standards and abilities of drug prescribers, as well as the endless variety of clinical situations.

The role of the Food and Drug Administration is to protect the American people from potentially unsafe, ineffective products. In order to do that, the FDA requires extensive animal and human testing prior to marketing. The data from these tests determine whether or not a new drug is to be marketed. If that data is unsound, whether because of sloppy research or fraudulent research, the American people are put at unacceptable risk.

This subcommittee exposed a very serious problem in the quality of animal data in hearings 2 years ago. It was shown that FDA was making decisions on the basis of worthless data—and was not aware of the problem at the time of decision making. As a result of those hearings, additional funds were obtained to develop a monitoring program to detect the magnitude of the problem and to enable corrective action to be taken. I have serious reservations about the adequacy of that effort.

Today we will learn of disgraceful abuses in the human drug testing program. We will hear of unconscionable neglect of basic

research standards of informed consent; outright fraud in the fabrication of data submitted to the FDA; woefully inadequate monitoring of the human drug tests by the companies sponsoring the research.

The result is that human subjects are put to needless risk and that worthless data is submitted to the FDA. It is truly a game of Russian Roulette as to whether the agency or the sponsoring company becomes aware of the problem. The stakes are high—the health of the American people.

The most disturbing thing of all is that, as in the case with the animal test data, the extent of the problem is unknown. There are 2,000 active clinical investigators in any given year in the United States conducting 12,000 studies. If only 10 percent of the data is faulty, if only 10 percent of the human subjects are at unnecessary risk, the problem is enormous. When you consider the potential cumulative effect of faulty animal data coupled with faulty human data, you have the elements of a regulatory nightmare.

Drug testing is one of the important research areas where human test subjects are essential. The protection of those people depends on the quality and integrity of the local institutional review boards. Several years ago, Dr. Bernard Barber, at hearings before this subcommittee, revealed serious deficiencies in the functioning of those boards. Now, years later, FDA's own staff has completed inspections of 100 such boards in the drug testing area, and they have found conditions equally unacceptable. In 63 percent of the cases, informed consent was inadequate. Abuses in this area included use of a so-called "short" consent form without a written narrative; the absence of a fair explanation of procedures to be followed; the absence of a description of attendant discomforts and risks; the absence of a discussion of appropriate treatment alternatives; the inclusion of exculpatory language; the inclusion of misleading language about the safety and efficacy of the drug.

In 44 percent of the cases, continuing review of the clinical investigation was inadequate.

In 19 percent of the cases, the boards' work was done by mail.

This Nation has a biomedical and behavioral research capability second to none. Only in recent years have we, with the help of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, begun to develop a comparable capability to protect the subjects of that research.

Their work has been of high quality. Emotional issues have been successfully depoliticized and the work of the Commission has been generally praised by layperson and scientists alike.

Since its creation, the need to extend its mandate to other Federal agencies has become clear. The abuses in programs of the Defense Department and the CIA were striking examples. Today's hearing shows the continuing need for such a Commission to help HEW improve its policies as well.

Research on human subjects is essential for the protection of the health of the American people. The National Commission, if its mandate is extended, will help assure that the human subjects of

such research will be able to rely on the best system of protection that this or any other nation can devise.

(NOTE: S. 2579, as introduced in the Senate by Senator Kennedy on February 23, 1978, was titled "to amend the Public Health Service Act to establish the President's Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, and for other purposes.")

Senator KENNEDY. Our first witness this morning is Donald Kennedy, Commissioner of Food and Drugs, who has testified frequently before the committee in th past. With him Dr. Michael J. Hensley. Dr. Hensley is a medical officer in the Clinical Investigations Branch of the FDA, Division of Scientific Research. Dr. Hensley is a board-certified pediatrician who has previously served as Associate Director of Clinical Pharmacology for the Saron Pharmaceutical Co.

We welcome you here.

STATEMENT OF DONALD KENNEDY, PH. D., COMMISSIONER OF FOOD AND DRUGS, FOOD AND DRUG ADMINISTRATION, ACCOMPANIED BY MICHAEL HENSLEY, M.D., DIVISION OF SCIENTIFIC INVESTIGATIONS, BUREAU OF DRUGS; AND RICHARD M. COOPER, CHIEF COUNSEL, FDA

Commissioner KENNEDY. Mr. Chairman, on my right is Richard Cooper, Chief Counsel of the Food and Drug Administration.

It is a pleasure to welcome you to the Department of Health, Education, and Welfare.

Let me kind of skip over some points in my submitted statement, which we will ask to be made a part of the record. I am going to do this very informally.

What we are talking about today, Senator Kennedy, is a relatively new program. As you and your colleagues know, the investigation of drugs was essentially unregulated before 1962. It was one of the features of the amendments of that year that put the clinical investigation process under review. Between that time and 1967, when the entire bio-research monitoring program came into existence, partly as a result of the work of you and your subcommittee, FDA's efforts to monitor clinical investigations, I think, can only be described as less than a full program.

We did do about a hundred fairly intensive investigations during that period and, as a consequence of the results that they yielded, in addition to a special survey done between the years 1972 and 1974 on clinical research, we decided to install a full compliance program during the present fiscal year. It is, in a sense, a halfway report on that compliance program that you will be hearing about this morning.

I think it is important to understand the nature of our assessment of clinical research. What we developed and issued to FDA field offices is——

Senator KENNEDY. I think before we get to that, Mr. Commissioner, could you give us some assessment about the resources now? I mean do you have the sufficient resources to do the job so we can

put into some perspective at least what you are going to tell us about the nature of the general conclusions of the research, the review itself?

Commissioner KENNEDY. I think I cannot give it to you in precise terms of positions and dollars, Mr. Chairman. We would be happy to provide that for the record. I can give you an indication, and that is what I am proceeding to do now, of the number of investigators, the number of sponsors, the number of institutional review boards that are involved.

Senator KENNEDY. All right.

Commissioner KENNEDY. I was going to explain first that our programs are of two basic types: "surveillance" inspections in which we are trying to measure procedural compliance with the applicable regulations; and "directed" inspections in which we do data audits of studies submitted in connection with investigational new drugs or new drug applications. Included are "for cause" inspections which are conducted where we suspect that a problem situation exists.

Surveillance inspections essentially are designed to be preventive. Directed inspections are inspections designed to be remedial in nature and, as a consequence, they are much more thorough.

I think it is important to distinguish between two kinds of things that we do. In one of them we are attempting to survey the adequacy of testing of new drugs that the public may be exposed to.

Another type that I will talk about in just a moment has its major purpose trying to insure that the guarantees we think are important to make to human subjects are actually met. The main purpose of that inspectional program is the protection of the subjects of the research themselves.

The first type includes the investigator and sponsor programs, one of which we refer to as the data audit program. In the data audit program headquarters provides to the field districts copies of protocols under which individual clinical investigators conduct their studies, or copies of case reports submitted by these clinical investigators to the drug sponsor. Our investigator then visits the clinical investigator to obtain information on the conduct of the study and performs an onsite audit of the clinician's data to check its reliability. In this case we do not select clinical investigators at random to receive these visits. Instead, they are chosen because we have determined that their work was important in the consideration of drugs for IND's or NDA's. So we are looking at investigators who have been involved in the developmental work on important drugs that are going to receive fairly wide exposure.

Under this program, as of January 31, 1978, 77 assignments had been issued to the field, with 34 inspections completed. Of these, 28 have been reviewed by headquarters and 6 are now under review. We have issued 25 informational letters to clinical investigators where no major problems were found. Three inspections, 10 percent of the very small total, have resulted in intensive "for cause" investigations. Of these "for cause" investigations, one has resulted in the proposal to disqualify the clinical investigator. It is true that this program

may be a promising source of "for cause" inspections in the future.

The sponsor program is essentially a random one and its purpose is to ascertain the adequacy of research monitoring by the sponsor. Our investigators are supplied the names of particular drugs that are under clinical study or in submitted new drug applications. The field investigator then visits the sponsor, generally a drug company, and reviews the sponsor's monitoring procedures. As part of the inspection, the FDA investigator selects two clinical investigators who have studied the drug in question, and conducts further inspections to determine just how well they were being monitored by the sponsoring drug firm. 138 assignments had been issued to the field as of January 31, 1978, and 37 inspections were completed so far, but they have not been received and analyzed yet by the Bureaus.

At the end of the fiscal year, Mr. Chairman, we will have a complete set of reports from all those investigations that I have just mentioned. As I will say more about this in a moment, we hope to use that in designing our strategy for the fiscal year afterwards.

I want to say something briefly about our pilot compliance program for institutional review boards, which you alluded to in your own introductory statement. This is a slightly older program, and hence it has sampled the universe much more completely.

As you know, an IRB is established for each institution in which clinical investigations are conducted, and it is composed of members of various professions in the community, laypersons as well as persons versed in the scientific subject matter of the investigation.

The IRB is charged with reviewing the ethics and risk/benefit decisions made on clinical studies involving subjects at that institution. Regulations promulgated in 1971 require that clinical investigations of new drugs on institutionalized human subjects be initially approved and subjected to continuing review by the IRB.

In each inspection assigned we use a particular drug study as a reference, and under the program FDA field investigators interview the chairperson of the IRB or other responsible individuals at the institution, as well as other staff.

That report of the investigator and records are forwarded to headquarters for evaluation. The results are communicated back to the chairperson of the IRB or administrator of the institution through either of two types of letters—information letters offering suggestions for improvement, or remedial letters requesting positive assurance that specific serious deficiencies noted during the inspection will be corrected.

About 25 percent of the letters issued to IRB's to date have been in this latter category.

I think you have seen, Mr. Chairman, and if it has not been made available to your committee, we will promptly submit it for the record, the analysis of this inspectional program. Although our legal authority to move directly against an IRB is limited, we do have the authority to refuse to permit or to continue to permit clinical studies involving subjects in a particular institution and to refuse to accept completed studies if the studies are not properly reviewed, approved, and supervised by the institutional review board.

We intend to propose regulations that will provide for an additional sanction, the disqualification of an IRB.

As of January 31, 1978, the milestone we are using in all these statistics, we have issued assignments to the field for 329 IRB inspections. One hundred and ninety-eight inspections have been completed, and 142 have been reviewed and analyzed. We found that approximately 25 percent failed to comply in the way described above. Although, as you pointed out, there were more minor deficiencies in a larger percentage than that.

Senator SCHWEIKER. What were the reasons for the majority of the failures, Commissioner?

Commissioner KENNEDY. You can analyze it in a number of different ways. The document that I have in mind is one that I believe was submitted to the committee. There were a number of failures to provide a consent form with the adequate written narrative attached to it. I think that of the total number of institutions, we have it broken down into institutions that have general assurances and those without. Of the total population, 38 percent were defective in that regard.

I think that probably is the largest single violation in terms of proportion of the total. But there were numerous other deficiencies.

For example, some institutional review committees conducted their review of studies by mail instead of by having an adequate number of meetings per year.

In other cases, there was a failure to adequately define a quorum and to make sure that the majority of members was present at all of the meetings of the committee.

There were defects in the consent form of various kinds. Lacking disclosure of alternative procedures is a common defect of consent forms.

If a procedure is represented to have a potential benefit for the subject, you must tell that subject of alternative ways, other than by participating in that experiment, in which that benefit might be produced. Misleading language of a variety of sorts on safety and efficacy of the drug—all of these defects have been found, and all of them in percentages that were a little disturbing, but I think it must be remembered, in fairness to many of those institutions and their review boards, that this is a new process for them. As we inspect and issue letters, we presume that compliance will improve as they learn how to meet their responsibilities.

Senator KENNEDY. I think obviously the point is that these institutional review boards are the primary source for the protection of human beings. That is the very key aspect of this whole kind of process. They are the interface between the researcher and human beings. The initial conclusions of your draft is that you found that in 63 percent of the cases informed consent was inadequate. That has to be a factor which is of very, very deep concern. I am sure it is to you. It has to be to us. I think it is an important factor in terms of the compelling interest we have for continuity in assuring adequate protection with the panel for protection of human subjects and also for initiatives that have been placed forward in the various agencies themselves.

What we find is, in spite of the enormous aspects of publicity for adequate protection of individuals and the stress that has been placed on it in recent times, and the efforts that have been made, there still are glaring gaps in this area and we have to recognize that. You point out that this is an initial process for many of these institutions to deal with, but it is one of great urgency and importance and great significance to this committee, as I know you know, and I know that you are very much aware of it.

So there are some extremely important additional factors about the nature of the research. It seems to me we have got two different issues. One is about the nature of research and scientific viability, and the second thing is the adequacy of the informed consent. Both of these matters are interrelated in the course of our hearings this morning.

As we get into those glaring and obvious deficiencies in the scientific information, we cannot avoid recognizing the very, very significant importance of this issue. I know you believe that. We believe that. I just wanted to underline it.

Commissioner KENNEDY. Mr. Chairman, I was going to describe very briefly some of the problems that we have encountered in our "for cause" inspections of clinical investigators.

As you know, these were usually carried out when there was reason to believe that work of a clinical investigator was faulty or unreliable. These get triggered in a variety of ways. I believe we have submitted for the committee, and if we have not, we will promptly do so, a very brief tabular summary of the ways in which the "for cause" investigations that are under discussion here—there are 26 of them—were triggered by the compliance programs and by other means during this year.

Our drug reviewer sometimes encounters, in a new application, data that appear to have been generated in a way other than orthodox. Occasionally we get complaints from drug sponsors that clinical investigators—that they have asked to do work for them—are turning in shoddy work, and we pursue those. We have got seven of those. It was the second most predominant source of triggering events for "for cause" inspections.

Consumer complaints, IRB investigations, data audits done under the compliance program that I have just described, review of the literature, all of these will sometimes generate a feeling on the part of Dr. Hensley and his colleagues that there is a problem and will trigger "for cause" inspections. We have not completed our evaluations of all these today. I emphasize to you, as we have to the subcommittee staff, these are investigations in progress, of which we have, as it were, a snapshot in midflight.

As you will learn from me in general terms and from Dr. Hensley in more specific terms, there are alarming problems. They fall into the following categories:

Case reports on fictitious subjects, and on subjects who were never administered the investigational drug they were supposed to have received.

Senator KENNEDY. You mean the subjects of the tests were nonexistent?

Commissioner KENNEDY. Yes, Senator.

Senator KENNEDY. You have got a series of these. Let us go through them.

Commissioner KENNEDY. Just to pick them off briefly.

Case reports containing the results of clinical laboratory work which was not actually performed. The purpose of such laboratory work is to assess the safety of the drug in human subjects—for example, if a drug is toxic to the liver, and tests of liver function are not performed, then the drug might not be withdrawn in time to prevent permanent liver damage or death.

False representation of institutional review board approval of a study. A layer of subject protection is removed if uninformative consent forms were used, or if a study of the type done should not have been done in the institution in question.

Misrepresentation of patient diagnosis and demographic data. If a patient does not have the disease to be treated with the investigational drug, then any report of efficacy of that drug is obviously spurious.

Consent of the clinical subject not obtained. Consent means informed consent. Lacking necessary information, the subject might enter a study which he would not have entered if he had been informed of the dangers as well as the possible benefits.

Drug doses given far exceed protocol limitations. This could be dangerous since protocols often specify doses at the upper limit of what has been judged to be safe.

Drugs given to inappropriate subjects. This could be dangerous if drugs aimed at the generally healthy adult population are given to children or the aged where their metabolism might be different. Of particular importance is the administration of drugs to pregnant women where fetal abnormalities might be caused.

Serial use of investigational drugs to the exclusion of accepted therapy. This makes the subject nothing but a guinea pig, and his best interest might not be served.

Administration to subjects of two or more investigational drugs at the same time and the administration of other significant and perhaps interfering drugs with the investigational drug. The point here is that whenever the information obtained from an experiment is valueless, the subject has been placed at risk for no good purpose. Experiments in which some rudimentary code of good sense and adherence to protocol is not followed wastes the experiment and, hence, puts the subject to unnecessary risk.

Inadequate medical attention to the test population, either because of excessive delegation of authority, lack of followup, et cetera.

Finally, representation of investigational drugs as marketed products and/or the sale of such drugs. This is the case we have seen a few times in which an investigational drug is really being administered to patients as a marketed drug, but the investigational status of the drug has conferred on prescribing physician a kind of exclusive franchise that allows the physician to exploit his status as investigator by purveying a product not available to all physicians.

Senator KENNEDY. What you are talking about is a laundry list of really outstanding abuses of perversions of science, are you not?

You have got tests allegedly being done on subjects that were non existent. You have got falsification of various records, misrepresentation of various boards, the inadequate informed consent.

These are all on human beings.

This committee saw this kind of situation concerning the testing of animals. As a result of the testing on animals, we tried to insist with FDA and FDA leadership support for the review on human subjects. Because we saw that many of the laboratories, individuals that were working in these areas also were working on human beings, and although we could not make a determination that they were going to be similar patterns and practice in the areas of human beings, I think you find here in terms of that observation you make that this is also happening in the areas of human beings. What we do not know and what we are going to get into with Dr. Hensley in greater detail and greater specificity is the extent to which it is taking place. How do you react to that as a scientist and as the head of FDA, and what kind of conclusions can we draw about the nature of this kind of a problem as it applies to testing?

Commissioner KENNEDY. I think I would want to try to reach conclusions in two different areas, Senator.

As you know, from the numbers I have just given you, we have been able to mount in this first fiscal year program, which is not complete yet, a set of sampling procedures that we think are going to define a universal problem for us. What you have just heard are the categories of defect, and they are very serious defects, that we have found in some of the 26 "for cause" inspections which represent what we believe to be the worst of the universe and not the average.

The real question is how much sampling do we need, first of all, to know how best to invest our energies to stop this sort of thing and, second, to bring this very large universe of clinical investigation, 12,000 people, into better compliance with procedures that both as scientists and humanitarians we believe ought to be followed.

The sample right now is large enough to be disturbing, but not large enough to tell us, as I think it will at the end of this year, exactly what kind of compliance program we ought to have to adequately sketch the size of the problem and suggest to us ways of attacking it.

Certainly, to respond to your main question though, Senator, each of the kinds of defects that I have just mentioned represents not only a problem with regard to protection of patient rights, but most of them also represent the most egregious kind of scientific errors.

Senator KENNEDY. Although you cannot draw a conclusion about the extent of the particular problem, based upon this kind of review, the conclusion I think we can draw is that with careful review, as we are going to hear from one investigator, working over a period of 6 months, find very, very serious perversion of scientific information. Although on the one hand, we cannot—I would not think it is fair to project that this is either happening across the landscape, I also do not think that we can say that we know as a matter of fact that it is not

happening. We do not want to unduly alarm the American people. But it would seem to me that if this sends signals to the agency and to the Congress, we cannot rest until we know that it is not happening.

I think that we ought to put this in some kind of perspective. It seems to me this is a most serious kind of situation in terms of science and science research to find that when you dig deep, you find some extraordinarily serious abuses.

I think it would be as inaccurate to state that we do not know that it does not exist in other areas, as it is to make a generalization that it does in other areas. But the things that we can conclude are that although that has not been the purpose of our particular review, we started off with other purposes from the legislative investigation, what we have found is when we scratched the surface, we found similar kinds of treatment by some companies or some laboratories in drug testing. And when we scratched around in the area of human testing, which is obviously the most significant and important, we find similar types of disturbing situations. This is why I think it is of such importance in terms of protecting individuals not only in the consent aspect but also in terms of knowing the veracity of the scientific information which is submitted to the companies and submitted to FDA to being accurate.

Commissioner KENNEDY. I certainly agree, Senator, that our present information does not allow us to be reassuring any more than it persuades me that we ought to condemn the whole enterprise.

I might just add that one of the things we see emerging here is some suggesting that there may be patterns to the violations that we encountered in the "for cause" inspections, and by looking over earlier disqualifications of investigators, it may help us do a better job. That is something we will keep on analyzing and of which we will keep the subcommittee informed.

It does appear that certain types of drugs and certain types of investigators tend to be involved in these serious problems more frequently than others, although it is perhaps a little preliminary to say too much about this. A couple of drug classes, psychotrophic drugs and analgesics, appear to be involved with much higher frequency than other drug categories. As we look at the pattern of affiliation of clinical investigators, we see by far the majority of those involved in serious problems are independent practitioners that are not affiliated with group practice or with institutions. So to the extent that these trends hold up, we may find ourselves at the end of the fiscal year with an intelligent framework at least for beginning to dissect the problem and deciding where we ought to concentrate most of our resources and attention in the "for cause" area.

Senator KENNEDY. I would add one more, Mr. Commissioner, you have to call in question the monitoring of some of the major drug companies reviewing the scientific information. It is not going to be just limited to certain types of drugs. I think what you will see in the course of the development of this hearing is that the monitoring process and procedures by some of the companies, even though on

paper, they are very elaborate, very detailed, very extensive and exhaustive, that in the practical application they just have not worked or picked up some of these serious situations which you have outlined.

If that is true with the one or two case studies that we are going to review this morning, how are we sure that they are catching these particular problems as they apply to other case studies as well?

That is obviously something that we have to be concerned with.

Commissioner KENNEDY. Yes; I agree, Senator. Actually the last thing that I was going to touch on in my prepared statement was that we are about to finalize regulations published last September on the obligations of sponsors and monitors. We certainly will also be watching for those kinds of correlations, too.

As you know, our sponsor sample is much smaller than our investigator sample, and so the kinds of trends that one might propose in that universe are not as apparent to us yet as those for the investigators.

Senator SCHWEIKER. Dr. Kennedy, I think it's important for us to try to get some feeling for the magnitude of the problem, in line with what Senator Kennedy was just talking to you about. You say in your statement—I guess I interrupted your testimony there because we began to question you—"I do not want it to leave this subcommittee with the impression the whole world of clinical research is bad."

Could you give us a rough estimate of what proportion of the research we are talking about has the sort of problems you've outlined? In other words, do we have to narrow it down and look hard at 15, 25 percent of the work? How do you see the dimensions of the problem?

Commissioner KENNEDY. I wish I had a clear, simple answer to that question, Senator. I do not. Can I briefly sketch the nature of the difficulty I have with it?

First of all, we are trying to do an objective sampling in part of our program. It is very hard to avoid the temptation to lean toward the "for cause" investigation—I think our investigators know their drug categories and sponsors, and maybe categories of investigators that are more likely to yield hits than others. I think there is some tendency to concentrate on those. I would not want to believe that the 10 percent that we hit even from this very, very small sample is not somewhat skewed from that effect as well as from the very small size of the sample.

The most objective sampling procedure that we have is the one that has not yet yielded very much data. So I will not be able to say anything about that to you until the end of the year. The 10-percent figure comes from investigations that are based on important new drugs, and if that 10-percent figure holds up, and I reiterate that it is a very small sample, I would be quite troubled by it. I think it is too high, much too high.

Senator SCHWEIKER. I have one other question along the same line, again asking for an estimate. I realize I am forcing you to

make an estimate that is just a guess, to serve as some sort of guide to us in thinking about the nature and magnitude of the problem.

Do you see the majority of the problems we've talked about today as resulting from sloppy, careless work, somewhat unintentional, or do you see most of this as deliberate, willful abuse?

Commissioner KENNEDY. Well, of the "for cause" sample that we will be talking about most of this time, the 26, there is a great deal of willfulness. I do not think most of that can be put down as sloppiness.

On the other hand, I think in the case of the IRB compliance data that we talked about, a little sloppiness and a little unfamiliarity contributes much more to the problem than willfulness. In the universe as a whole I continue to believe personally, it is nothing but a personal belief, that the universe is predominantly honest. But I also think the consequence of it not having been regulated for a very long time, and as a consequence of it consisting of people who, by and large, have not received much training in this area in their own education, I think that there is apt to be a fair amount of sloppiness.

Senator KENNEDY. Dr. Hensley, we would like to ask you some questions. We will talk about investigator No. 2.

Will you explain to us for the record why we are not given the names of the particular investigator?

Dr. HENSLEY. As the Commissioner pointed out, these investigations are still just that—they are investigations. For the most part I think these cases will result in administrative sanctions, and very few of them may result—I stress "may"—in criminal procedures. We are using numerical designations for investigators, and I do not intend to reveal location of these.

Senator KENNEDY. Fine. You can understand, we are not interested in the individuals, but we are interested in at least what the patterns are and what the practices are in terms of the type of situation that we may be facing.

Could you tell us a little bit about the investigation done by investigator No. 2, doctor No. 2, on a drug for Bristol Laboratories to enhance mental functions in the elderly.

As I understand it in June 1977 FDA inspectors made a routine random inspection of this study which was conducted at a nursing home. Can you describe for us what the nursing home looked like, what the status of the institutional review committee was, and perhaps what the quality of the particular test was?

Dr. HENSLEY. I can comment at two points in time on the status of the nursing home. At the time of the investigation the nursing home was described as a locked-door facility.

Senator KENNEDY. What does a locked-door facility mean?

Dr. HENSLEY. Well, I thought—I kind of thought you might ask that.

Senator KENNEDY. Just in layman's language.

Dr. HENSLEY. A locked-door facility essentially is a nursing home where the patients are judged not to be capable of protecting themselves in an open environment.

Senator KENNEDY. The importance of this obviously if they are not capable of feeding themselves or caring for themselves in an

open environment reflects I imagine on their capability of granting informed consent?

Dr. HENSLEY. That is correct. Many of these people are without family and wards of the court.

Senator KENNEDY. Well, why don't you continue then.

Dr. HENSLEY. At the time of the investigation we have two insights into that. The inspector that did that investigation and described the nursing home: Smelling of urine, it was a locked-door facility where patients wandered about aimlessly, and the patients were said to be without soap, toilet paper, and basic necessities.

I have spoken with an official of the health department in the city where this was done, and that official described it using the phrase "a rat infested dump." It was a poor situation.

I visited the nursing home several months after that. The health department had taken fairly aggressive action, and the place had been cleaned up somewhat. It smelled about like any institution. Patients were cared for I suppose on the par of most mental hospitals, and I think that might be a more accurate description than nursing home for these patients. Most of these patients, many of these patients were alcoholics, many of them suffering from organic brain syndrome of one type or another.

As far as being rat infested, at the time we only saw one rat. It was rather large.

But with respect to the institutional review committee, there was none. This inspection was keyed on a study as you say done for Bristol. They went to look at the record for that study and found no IRC.

The administrator of the nursing home had just recently been removed. He was facing charges associated with embezzlement of patient funds and a number of other things. Although he had been removed, he was accessible, and he was asked to comment at that point—what about IRC? He essentially said, well, I know there was a study done here. I do not know anything about institutional review. I do not know anything about informed consent. All I can say is we did a study, and I do not know who was on it. That is about it.

Senator KENNEDY. As I understand it, it was represented that there was an institutional review committee?

Dr. HENSLEY. That is correct.

Senator KENNEDY. And effectively there was none.

Dr. HENSLEY. That is correct.

Senator KENNEDY. You have talked about just the physical characterizations of the facility and about the nature of the types of residents that were in the facility, some that had, I gather from what you said, some organic brain disturbances from prolonged use of alcohol or alcoholism, the drug that was being tested was a mind-expanding drug, enhancing drug?

Dr. HENSLEY. Mainly stimulant, a general stimulant in fact for the geriatric population as I understand it. I am not a chemist. I understand it is related to amphetamines in its general class.

Senator KENNEDY. I think you mentioned about Dr. No. 2 not having a license to practice medicine in this State. Did Dr. No. 2——

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Dr. HENSLEY. No. The study was done in a rather unusual fashion. Toward the end of the study, the doctor in question, who was at the time serving a pediatric fellowship at a local hospital allegedly disappeared, and in his office he left behind a number of his personal effects. Among his personal effects was a Xerox of a medical licensure certificate for that State. The name of the original recipient had been whited out and investigator's name written in in ink. The original recipient was about two doors down the hall. He knew nothing about it.

Senator KENNEDY. Was the study completed?

Dr. HENSLEY. We do not know. I do not really believe that it was. There were two studies actually alleged to have been done, a preliminary study on patients that were reasonably in good shape mentally, and a more difficult study on patients who had severe mental impairment. We know laboratory work was done. Hematology work, blood chemistries, and urinalyses for a sufficiently large number of patients, to have accomplished both studies, was performed. But interviews with personnel and physicians whose patients were used led us to believe that the second study may well not have been completed.

Senator KENNEDY. So we have a question of an nonlicensed doctor with an institutional review committee that does not exist in a very questionable—described as rat-infested facility—but certainly from your own visual observations, you characterized it—as one in which serious questions as to the care of the patient, and a study which is virtually nonexistent.

Is that correct?

Dr. HENSLEY. The second study is probably not nonexistent in part. As to what was done with these patients, we really do not know.

Senator KENNEDY. Do you draw any tentative conclusions about monitoring process that would permit this kind of circumstance?

Dr. HENSLEY. Having read the protocol, and patient selection portion of that protocol for initial study, I suspect that had the monitor visited the facility, he would have been alarmed and he would have questioned the conduct of this study.

I think it was obvious, it was obvious to me, it would be obvious to anyone walking in the front door, once they got past the electronic lock, these were not patients with minimal organic dysfunction. They were significantly impaired patients. Conversion with the nursing staff would have revealed that nursing staff disagreed wholeheartedly and violently objected with the descriptions provided by the investigator as to the effect of the drug. The investigator provided a description suggesting the drug was efficacious. The nursing staff said "no."

Senator KENNEDY. Was there any monitoring at all? Does the file in fact show that the company became concerned about not getting the data back from the investigator?

Dr. HENSLEY. They did. There were two people in charge of the monitoring as I understand it. The original monitor—I am not sure of the circumstances—but he was replaced and did eventually leave the company. The second person in charge of monitoring these studies raised serious questions as to the validity of the data.

I have with me a memo. I think his last paragraph is rather revealing:

> Conversations I had with Mr. Blank and Mrs. Blank confirm that this investigation did conduct a study in the nursing home. However, my impression is that the study was poorly conducted and any data we may receive are likely to be inconclusive.

That memo is dated August 7, 1975.

Senator KENNEDY. Did Bristol send any of the information in to FDA?

Dr. HENSLEY. Yes, they did. A little less than a month later, the data were submitted in summary fashion to FDA. I believe the date on their submission was August 27, 1975. They were submitted without comment.

Essentially, 2 years later, following initiation of our inquiry, these studies were submitted in a more complete fashion and comment was made the investigator had been rather uncooperative.

Senator KENNEDY. This is the company's characterization of the investigator's conduct?

Dr. HENSLEY. Yes.

Senator KENNEDY. How did they characterize it—uncooperative?

Dr. HENSLEY. Yes. As I recall, that was their characterization.

Senator KENNEDY. Did they point out any of these other problems?

Dr. HENSLEY. No.

Senator KENNEDY. They did not point out any of the other points that had been brought out about the institutional review board or any of these other problems?

Dr. HENSLEY. No. As I recall, they limited their comments to problems they had with the investigator. They made some statement about the efficacy of the drug, in fact I believe they stated the study did tend to show efficacy. They noted they were having to base a number of their comments on review by their own people, particularly with respect to tolerance because the investigator apparently had not done everything he should have done.

Senator KENNEDY. What is the status of FDA regulatory action with regard to Bristol now?

Dr. HENSLEY. Our division, Scientific Investigations, that is—Dr. Kelsey I believe sent a letter to Bristol essentially asking how this happened. That letter was February 16 of this year. We have not received a reply at this point. They have 30 days to reply to that letter.

Senator KENNEDY. Could we consider Investigator No. 1. Endo Laboratories, Inc. What prompted you to review the test done by Investigator No. 1 on narcotic antagonist in newborn infants?

Dr. HENSLEY. I am a pediatrician by training. In the course of doing a literature review, essentially reading journals, I ran across an article——

Senator KENNEDY. Reading the journals?

Dr. HENSLEY. Yes. The article struck me as being just a bit strange, the procedures used, the conduct of the study seemed unlike anything I had ever seen before. So I initiated an inquiry trying to find out why the study was done and who had paid for it and these kinds of things.

Senator KENNEDY. It was not brought to you as a result of the committee or any other group?

Dr. HENSLEY. No.

Senator KENNEDY. Just your own individually selected investigation. Do you want to describe what that investigator wanted to do and what FDA gave him original permission to do?

Dr. HENSLEY. The story we eventually get was this was done under or for Endo Laboratories, as was pointed out. A protocol was submitted to FDA through Endo, and I reviewed the protocol and compared it to the publication, and comparison of the two revealed there were a number of points medically I thought were questionable that had not been reported to FDA and protocol. The basic problem as I saw it with this study was one of consent. That was apparent when one read the protocol or the paper. The study in essence was one in which mothers were recruited into the study while they were in the delivery room.

Senator KENNEDY. In the delivery room?

Dr. HENSLEY. Yes.

Senator KENNEDY. Under what circumstances in the delivery room?

Dr. HENSLEY. In active labor, as I understand it.

Senator KENNEDY. What tentative conclusions do you draw about trying to gain informed consent when a woman is in labor? Is this not highly unusual?

Dr. HENSLEY. I should think so. I recall having been with my wife through her deliveries and I would imagine she would have signed anything that was put under her nose just to get rid of it. I do not know what the circumstances yet were.

Senator KENNEDY. In any event, that is not an appropriate time for gaining informed consent of an expectant mother?

Dr. HENSLEY. No. It did not seem so. The more reasonable thing to have done would have been to enter mothers into the study well in advance, give them time to understand it.

Senator KENNEDY. Do you want to tell us about the study?

Dr. HENSLEY. Right.

These mothers were mothers who had carried their infants to term—the pregnancy was to have been uncomplicated. The infants were to be divided into two groups. The study was to run something like this:

Mothers would receive a pain reliever, Demerol, Meperidine, a standard analgesic in the delivery room. They would receive it within 1 hour of delivery. That was the protocol as gotten by FDA.

It turns out that if mothers did not get the drug within 1 hour of delivery, they got another dose. Another dose of Demerol that would be sufficient to impair the respirations of the infant at least as measured by respiratory function tests that were being done on these infants. So the dose was initially kind of open ended; they eventually would settle on a dose.

Senator KENNEDY. If I understand, this is a test to depress the respiratory function of the infant through the administration of Demerol just prior to delivery?

Dr. HENSLEY. Right.

Senator KENNEDY. The purpose therefore for the testing is to depress the infant's breathing, respiratory function, at the time of birth; is that correct?

Dr. HENSLEY. That is correct.

Senator SCHWEIKER. How much risk is there in that?

Dr. HENSLEY. That is a very difficult question to answer. Demerol is probably the most common cause of respiratory depression in the newborn, I guess, just based on my experience, that is. There is great individual variation between women as to how much they tolerate and how well their babies do. I think there is significant risk, and I guess the best way to answer that is if one of my kids were a candidate for this study, I would not permit it to be done. I do not think it is a good idea.

Senator KENNEDY. The purpose—so we put it in some context, the purpose for the Demerol was to depress the infant's breathing?

Dr. HENSLEY. Correct.

Senator KENNEDY. In the consent form, it had these words—equipment required for treatment of depressed breathing is routinely—I will put the whole consent form in the record—the sentence above that says, "It is therefore extremely unlikely"—this is the consent form that is shown to the mother who is in labor—"extremely unlikely that the Demerol you receive will have a significant depressing effect on your baby's breathing."

But in fact that is exactly what they are trying to do.

Dr. HENSLEY. That is correct. I suppose the key word is "significant."

Senator KENNEDY. "Significant." You have to evaluate what is significant?

Dr. HENSLEY. Right. It seems to me that is the choice the mother should make. But the investigator in this case chose to make that decision for her.

Senator KENNEDY. And further it says, "Therefore, extremely unlikely the Demerol you receive will have a significant depressing effect on your baby's breathing," when actually, the purpose for the administration of the Demerol is to depress the baby's breathing?

Dr. HENSLEY. That is correct.

Senator KENNEDY. And it continues on: "After breathing the carbon dioxide for 5 minutes, your baby will receive an injection of Narcane or placebo and he will be tested with carbon dioxide again."

It does not say what a placebo is?

Dr. HENSLEY. On the attachment to that, I think it describes or mentions distilled water. It is sort of oblique in there. I agree that "placebo" should have been more clearly explained. Half of these babies were to receive the placebo.

Senator KENNEDY. Half of them, after they are told it is not going to have a significant effect in depressing, and obviously the purpose is to do it, half of those infants are going to get placebo, which is going to have no effect?

Dr. HENSLEY. That is correct.

I point out also that those who received Narcane, received it 30 to 60 minutes after delivery rather than within a few minutes of delivery.

Senator KENNEDY. What is the Apgar score——

Dr. HENSLEY. It comes from the name of a prominent pediatrician who passed away a few years ago, simply a score of how good the baby looks: 10 points, five categories, zero, 1 or 2—there is heart rate, color, tone, muscle tone, reflexes; these kinds of things. The baby gets a score of zero, 1 or 2. In our hospital, Apgar 7 or less was an indication the baby was in significant distress and an intratracheal tube should be put in the baby and artificial means of respiration should have been used.

Senator KENNEDY. What were the scores of these infants?

Dr. HENSLEY. Many of them were 7 and 8. There were a few that were extremely low. I recall one that had Apgar 3. Apgar of 3, I think, would have alarmed us a great deal. That is a baby on the point of cardiac arrest.

Senator KENNEDY. The infants were significantly depressed when they were born?

Dr. HENSLEY. Many of them were, not all of them. I think if one breaks it down, most of them are not. But many were.

I think—more importantly, I think the more important point is not the 1-minute Apgar score, but 5-minute Apgar score. The score is usually done at 1 and 5 minutes in most hospitals, and it was in this case. By 5 minutes, most babies who do not have some basic underlying problem are in pretty good shape. Their Apgars are usually 9 or 10. They are breathing well. The color is good. Fourteen of these infants have Apgar of 8 or less. I think that is the problem.

Senator KENNEDY. Was there a midesophogeal balloon placed in the infants?

Dr. HENSLEY. Yes. In fact, in the article, there is an illustration of a baby sort of spread eagled on the examining table, something of that nature, with esophogeal balloon in place. According to investigators, that was used to measure respiratory effort, measuring changes in pressure.

Senator KENNEDY. You are familiar enough with the consent form to know that was never mentioned?

Dr. HENSLEY. That is correct. I asked the investigator why. He said he did not feel it was significant.

Senator KENNEDY. What? That it was not significant?

Dr. HENSLEY. Yes.

Senator KENNEDY. Where did they place the balloon?

Dr. HENSLEY. It would be in the midesophagus, above the diaphragm, about level with the heart, I guess.

Senator KENNEDY. Is that outside?

Dr. HENSLEY. No. It is in the esophagus.

Senator KENNEDY. You have to open the infant's mouth?

Dr. HENSLEY. Right.

It can be done one of two ways: I think probably they would insert the tube either through the nose or the mouth.

Senator KENNEDY. Given 50-percent oxygen by mask?

Dr. HENSLEY. They were. Apparently for about 5 minutes on four occasions for each of these infants. I think five of these infants actually were entered twice in the study—these infants received twice that——

Senator KENNEDY. What is the significance of giving those kind of doses of oxygen?

Dr. HENSLEY. Well, the Academy of Pediatrics has a clear recommendation on oxygen therapy and newborn. The background on that is that quite some time ago a condition called retrolental fibroplasia, a degenerative disease of the eye, was described in premature infants and in small infants, term infants who were small; and it was related by many people to oxygen therapy.

The American Academy of Pediatrics recommends that one keep the arterial concentration of oxygen at 40 to 60 millimeters of oxygen to prevent that from happening; and the recommendation is not just premature in small babies, but in all newborns. The investigator's response when we asked about this was that this was highly unlikely to happen in term babies; and that is indeed the case. I had to research 15 or 20 minutes to find reported cases in the literature of term babies who have gotten retrolental fibroplasia. It does happen. It does occasionally happen, very rarely happens in adults who get oxygen therapy.

Senator KENNEDY. The point in layman's terms is does it impose certain risks to an infant?

Dr. HENSLEY. It imposes a risk.

Senator KENNEDY. It is not an insignificant one. That is nowhere on the consent form, either?

Dr. HENSLEY. That is correct.

[Information supplied for the record follows:]

June 1977
The Journal of PEDIATRICS 1009

Use of naloxone to reverse narcotic respiratory depression in the newborn infant

Twenty neonates whose mothers had received meperidine (1.0 to 1.5 mg/kg) intravenously within three hours of delivery were studied to determine the effectiveness of naloxone in reversing neonatal respiratory depression. The following measurements were carried out within 20 to 30 minutes after delivery: minute ventilation, end tidal CO_2, and ventilatory response to CO_2. These determinations were repeated after administration of either placebo or naloxone, 0.01 mg/kg intramuscularly. Minute ventilation and $P_{A_{CO_2}}$ were within a normal range before medication in both groups, but the slope of the CO_2 response curve was decreased, indicating mild-to-moderate respiratory depression. After administration of placebo the test results did not change significantly. After administration of naloxone, $\dot{V}_E$ increased significantly ($P < 0.05$) and the slope of the CO_2 response curve doubled ($P < 0.001$). Naloxone effectively reverses narcotic depression of the respiratory center in the newborn infant.

Tilo Gerhardt, M.D., Eduardo Bancalari, M.D., Harry Cohen, M.D., and Luis Fernandez Rocha, M.D., *Miami, Fla.*

NARCOTIC ANTAGONISTS are frequently administered to neonates with low Apgar scores who were born to mothers who have received meperidine during labor and delivery. A low Apgar score may indicate an episode of asphyxia in utero rather than depression due to medications administered to the mother. In this situation, the administration of a narcotic antagonist, specifically nalorphine or levallorphan, may place the infant at risk because of adverse agonistic effects of the drug.[1] Naloxone has been shown to be a potent narcotic antagonist without agonistic effects in the adult[2, 3]; it is now used also in the newborn infant without conclusive information about its effectiveness or adverse effects in this age group.

This study was designed to determine the effectiveness of naloxone in reversing respiratory center depression in infants born to mothers who had received meperidine during labor.

From the Division of Newborn Medicine, Departments of Pediatrics, Anesthesiology and Obstetrics/Gynecology, University of Miami, School of Medicine. Reprint address: Department of Pediatrics, University of Miami, P.O. Box 520875 Biscayne Annex, Miami FL 33152.

MATERIALS AND METHODS

Twenty-four women with normal pregnancy and uncomplicated delivery were selected for this study. A written informed consent was obtained from the mothers, after the purpose and the procedures of the study had been explained to them. The research protocol was approved by the committee for the protection of human subjects at the University of Miami. The women received no medication other than meperidine, 1.0 to 1.5 mg/kg intravenously, within a period of one hour prior to delivery; eight mothers who did not deliver within that period of time received a second dose. All labors were terminated vaginally; low spinal or pudendal block with 1% lidocaine was used. The maximal dose used for the spinal block was 30 mg and for the pudendal block, 200 mg. The infants were studied within 30 minutes after

See related article, p. 971.

Abbreviations used
$\dot{V}_E$: minute ventilation
$P_{A_{CO_2}}$: end tidal CO_2
V_T: tidal volume

Table I. Mean ± SE for all ventilatory determinations under basal conditions and during the CO_2 challenge, before and after administration of placebo or naloxone

	Placebo (N = 8)						Naloxone (N = 12)					
	Minute ventilation (ml/min x kg)		$P_{A_{CO_2}}$ (mm Hg)		$\Delta\dot{V}_E/\Delta P_{A_{CO_2}}$ (ml/min x kg x mm Hg $P_{a_{CO_2}}$)		Minute ventilation (ml/min x kg)		$P_{A_{CO_2}}$ (mm Hg)		$\Delta\dot{V}_E/\Delta P_{A_{CO_2}}$ (ml/min x kg x mm Hg $P_{A_{CO_2}}$)	
	B	A	B	A	B	A	B	A	B	A	B	A
Basal values (O_2 50%)												
$\bar{X}$	301	314	43.6	41.2			314	388	42.5	40.7		
±SE	±37	±45	±2.5	±2.6			±35	±40	±2.0	±1.6		
P	NS		NS				< 0.05		NS			
CO_2 response (O_2 50% + CO_2 4%)												
$\bar{X}$	442	460	51.2	50.9	20.1	16.6	466	622	52.4	48.2	16.4	31.4
±SE	±47	±54	±2.4	±2.3	±3.7	±2.6	±42	±54	±1.8	±1.3	±2.0	±2.4
P	NS		NS		NS		< 0.005		< 0.005		< 0.005	

B = Before medication; A = after medication.

birth. By random number 14 infants were selected for the naloxone group and 10 for the placebo group.

Each infant was studied before and after the administration of naloxone or placebo, and the values obtained before and after medication were compared. A placebo group was included for two reasons: (1) to evaluate possible changes in the degree of depression that can occur with progressive postnatal age unrelated to the administration of naloxone and (2) to assess the effect of the stimulus of the intramuscular injection on the degree of respiratory depression. Each study included the determination of respiratory rate, tidal volume, minute ventilation, end tidal CO_2, and the ventilatory response to inhalation of 4% CO_2. The system used to measure these respiratory functions is shown in Fig. 1. The infants breathed from a continuous stream of heated and humidified gas through a nosepiece. The flow of gas was maintained constant at 6 l/minute to avoid rebreathing, and a mixture of 50% oxygen and 50% nitrogen was used in order to prevent possible depression of the central nervous system secondary to hypoxia. Inspiratory and expiratory flows were measured by attaching an infant pneumotachograph (Electronics for Medicine, Inc., 30 Virginia Rd., White Plains, N.Y.) to the outflow part of the system. The flow signals from the pneumotachograph were measured with a Statham PM97 differential pressure transducer (Statham Instruments, Inc., 2230 Statham Blvd., Oxnard, Calif.) and a Gould transducer coupler (Gould Inc., Instrument Systems Div., 3631 Perkins Ave., Cleveland, Ohio). Tidal volume was obtained by electrical integration of this flow signal using a Gould integrator coupler (Gould Inc.). The background flow of 6 l/minute was electrically zeroed and the system calibrated with known volumes of the inspired gas mixture, using a calibrated glass syringe.

End tidal CO_2 was measured with a respiratory mass spectrometer (Statham Instruments, Inc.) calibrated with known concentrations of CO_2. Sampling was done continuously at a flow of 20 ml/minute through a small capillary that was inserted into the nosepiece. With this method all tracings obtained during regular respiration showed an end tidal CO_2 plateau. A latex balloon was positioned in the mid-esophagus to record transpulmonary pressure changes, which were measured with a Statham PM5 pressure transducer (Statham Instruments, Inc.) and a Gould transducer coupler (Gould Inc.). The recordings of flow, tidal volume, esophageal pressure, and end tidal CO_2 were done with a Brush 260 recorder (Gould Inc.).

Dynamic lung compliance was calculated from V_T and esophageal pressure measured at the time of no flow. Minute ventilation and respiratory rate were obtained from the tidal volume tracings.

The ventilatory response to CO_2 was determined by measuring minute ventilation after three minutes of adding 4% CO_2 to the inspired gas mixture. The increase in ventilation, $\Delta\dot{V}_E$, was related to the change in end tidal P_{CO_2}, $\Delta P_{A_{CO_2}}$, in order to determine the slope of the CO_2 response curve ($\Delta\dot{V}_E/\Delta P_{A_{CO_2}}$, ml/kg × minute × mm Hg $P_{A_{CO_2}}$.) Recordings used for the calculations were obtained only during regular respiration. The tests were performed at 20 to 30 minutes of age and repeated 5 to 10 minutes after the infants received either naloxone 0.01 mg/kg (1.5 ml) intramuscularly or placebo 1.5 ml intramuscularly.

Dynamic lung compliance was calculated in order to assure that changes in CO_2 response were not related to changes in lung compliance. Two infants in each group were eliminated from the calculations because their lung compliance values changed more than 25% between the two determinations. All infants were studied under a

radiant warmer maintaining their skin temperature at 36.5° C.

The results were analyzed using t statistics for significance difference in mean, significance limits of the student-distribution, and nonlinear regression analysis by the least squares fit power curve. Results are given as the mean ± standard error of the mean.

RESULTS

The naloxone and the placebo groups were similar in mean gestational age (39.6 ± 0.3 vs. 39.9 ± 0.7 weeks) birth weight (3.200 ± 130 vs. 3.150 ± 170 gm), and Apgar scores (6.5 ± 0.3 vs. 6.4 ± 0.6 at 1 minute, and 8.8 ± 0.2 vs. 8.8 ± 0.3 at 5 minutes). The mean value of lung compliance was also similar in both groups (4.2 ± 0.4 and 4.6 ± 0.3 ml/cm H_2O before and after giving naloxone and 4.2 ± 0.4 and 4.7 ± 0.4 ml/cm H_2O before and after administration of placebo). The age at which the tests were started and ended was 34 ± 5 and 70 ± 5 minutes, respectively, in the naloxone group and 27 ± 3 and 58 ± 5 minutes in the placebo group.

The mean values of the ventilatory determinations for both groups, before and after medication, are given in Table I. Before medication was given, there were no significant differences between the two groups in $\dot{V}_E$ and $P_{A_{CO_2}}$ while breathing 50% oxygen or 50% O_2 plus 4% CO_2.

After administration of naloxone the basal ventilation and the ventilation on exposure to 4% CO_2 increased significantly. This increase in ventilation was accompanied by a significant decrease in end tidal CO_2 during the CO_2 challenge test.

None of the previous values changed significantly after the administration of placebo. The largest difference between the two groups was the increase in the slope of the CO_2 response curve from 16.4 to 31.4 ml/minute × kg × mm Hg $P_{A_{CO_2}}$ with the administration of naloxone, whereas no change was seen if placebo was given.

In Fig. 2 the CO_2 response before administration of naloxone is plotted against the percent change of this response after naloxone was given. The significant correlation of this curve indicates that the more depressed the infants were at birth, the larger was the change of their CO_2 response after the administration of naloxone. This curve also demonstrates no depressant agonistic effect of naloxone; the three infants who had a CO_2 response in excess of 30 ml/minute × kg × mm Hg $P_{A_{CO_2}}$ before medication either increased their response or had no significant change.

No significant changes in any of the test results occurred after administration of placebo, thus indicating that the time elapsed between the two determinations and the stimulus of the intramuscular injection did not influence the results. The CO_2 response curve after placebo was shifted to the left (Fig. 3), reflecting the normal decrease in Pa_{CO_2} observed in the newborn infant during the first hours of life.[4, 5] In the naloxone group there was a significant change in basal ventilation and in the response to CO_2 after medication. As depicted in Fig. 4, the CO_2 response curve showed a similar shift to the left as after placebo, but the most striking change was a doubling of its slope from 16.4 before to 31.4 ml/

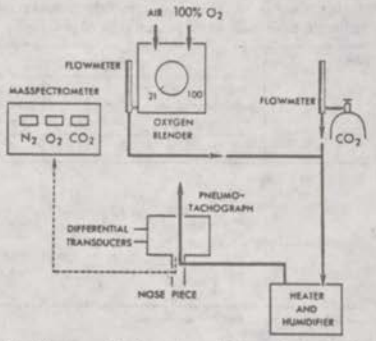

Fig. 1. System used to determine ventilation and end tidal CO_2 concentration in newborn infants.

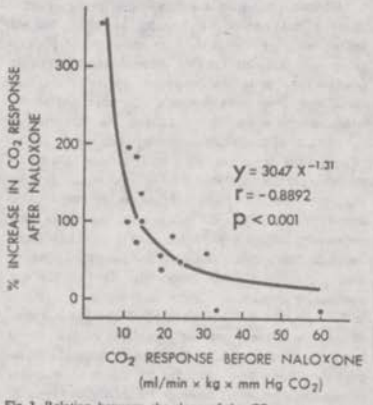

Fig 2. Relation between the slope of the CO_2 response curve before naloxone and percent increase in this slope after medication.

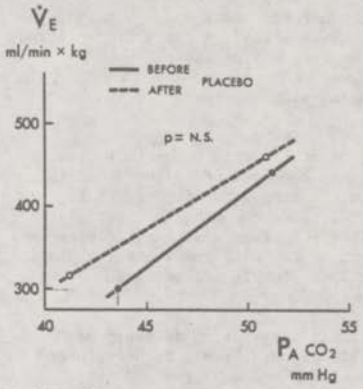

Fig. 3. Mean CO_2 response curves before and after administration of placebo.

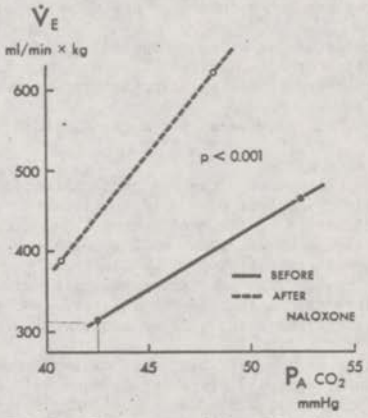

Fig. 4. Mean CO_2 response curves before and after administration of naloxone.

kg × minute × mm Hg $P_{A_{CO_2}}$ after medication. This finding indicates that after naloxone the respiratory center sensitivity to CO_2 increased twofold.

The dynamic lung compliance was the same in both groups before and after medication and, therefore, did not influence the results.

DISCUSSION

Assuming that the effect of naloxone is a complete reversal of the respiratory center depression produced by meperidine, it can be expected that severely depressed infants will change their CO_2 response more than those slightly depressed. This, in fact, occurred in the infants studied.

No data are presently available in the literature regarding the CO_2 response of normal, undepressed neonates during the first hours of life. Rigatto and associates[6] and Avery and associates[7] reported a CO_2 response of 34 and 40 ml/kg × minute × mm Hg $P_{A_{CO_2}}$ respectively, in normal newborn infants during the first days of life. When our results are compared with these values, it would appear that naloxone does reverse the ventilatory response to CO_2 in the depressed infant toward the normal range.

Naloxone in a dose of 0.01 mg/kg will reverse respiratory depression in the newborn infant whose mother has received a moderately high dose of meperidine during labor. This effect is more marked in more depressed infants. No determinations were done after the first hour of life and, therefore, the duration of the naloxone effect on the CO_2 response remains to be defined.

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CONSENT FORM

(Paragraphs which do not apply to you or your baby have been crossed out)

This study is being conducted to determine the effectiveness and appropriate dose of the medication "Narcan" given to a newborn infant in cases of depressed breathing caused by narcotic drugs given to mothers during labor.

You will receive only a regional block for pain relief during labor and delivery.

You will receive the synthetic narcotic drug Demerol during labor to reduce pain. The last dose will be given to you within one hour of delivery. This medication is frequently used along with others during labor for such pain relief. However, you will receive only Demerol since the other medications may effect the study. We feel that this medication alone will be sufficient to relieve any pain you experience during labor. You will receive a regional block for anesthesia for delivery. No general anesthesia producing an unconscious state will be administered.

There is a possibility that giving Demerol within one hour of delivery may cause depressed breathing in your infant. This is more likely to occur when a pregnancy, labor and/or delivery is complicated. However, you and your infant have been chosen because your pregnancy has been normal, and it is anticipated that your labor and delivery will also be completely normal. It is, therefore, extremely unlikely that the Demerol you receive will have a significant depressing effect on your baby's breathing. Equipment required for treatment of depressed breathing is routinely present in each delivery room. An anesthesiologist and pediatrician will be present if treatment is necessary. If treatment is required the investigation will be stopped.

Your infant will receive all the routine infant care that any other infant receives. Your baby will be taken to the nursery within one half hour of delivery, where his rate and depth of breathing will be continuously measured and recorded. He will be given carbon dioxide to breathe which will make him breathe faster and deeper than normal. This is a normal response and will not hurt your baby. This will be recorded. After breathing the carbon dioxide for five minutes your baby will receive an injection of "Narcan" (or placebo) and he will be tested with the carbon dioxide again. "Narcan" is not yet recommended for general use in newborn babies because not enough data has yet been collected to prove its effectiveness or appropriate dose. The aim of the study is to determine its effectiveness and appropriate dose. The limited data available show no bad effects on newborn infants in terms of breathing and heart beat when the dose that your baby will receive is used. In addition, "Narcan" is being used routinely in the JMH delivery room for narcotically depressed infants and at this time has caused no side effects. After the carbon dioxide is given for the second time the experiment is over.

YOU MAY STOP YOUR CONSENT AND DISCONTINUE BEING A PART OF THIS STUDY AT ANYTIME.

INFORMED CONSENT

This study is being conducted to determine the effectiveness of the medication "Narcan" when given to a newborn. This drug is used in cases of poor respiration caused by medication used for relief of pain during labor. Narcan is presently used in most hospitals in this country, and no adverse effects have been reported.

You will receive Demerol during labor to reduce pain and regional anesthesia for delivery. These are standard obstetrical practices in Jackson Memorial Hospital. A small amount of blood will be drawn from you and from the umbilical cord to measure the amount of Demerol in these samples. Your infant will receive the routine care at delivery and then will be taken to the Newborn Center. His respiration will be measured continuously and his respiratory response when breathing carbon dioxide will be tested before and after administering the drug "Narcan" or "Distilled water". While breathing carbon dioxide respiration will increase, but this is similar to what occurs during increased physical activity and is of minimal risk for the infant. The baby will be watched continuously by a doctor and the test will not be performed if any abnormality is detected.

Alternative procedure will be to use the drug Narcan if your infant is born depressed, without measuring his respiration.

YOU MAY STOP YOUR CONSENT AT ANY TIME AND YOUR INFANT WILL BE TAKEN OUT OF THE STUDY.

Senator SCHWEIKER. I'd like to go back to the use of placebo for a moment. Of course, I am disturbed by the study's claim to have gotten informed consent under labor. I have five children, and I have been present in the delivery room for a few of the births. I cannot imagine a worse situation in which to obtain fully informed consent. I certainly would call it anything but informed consent when a woman is in active labor. And in this instance, the consent form doesn't even seem to have been complete.

One other aspect that disturbs me, though, is the use of a placebo. Does not a study like this have to have an FDA-approved protocol before it begins? What I am leading up to is, should FDA be approving a study protocol that says that newborn infants will be depressed and then be given only a placebo? That would bother me if I were the father of one of the babies that wasn't going to get anything to counteract the depression.

Dr. HENSLEY. I think members of Senator Kennedy's staff have asked me that on a couple of occasions. My response has been, first of all, I think if you took 12 pediatricians and put them in the room, probably half of them would say it is a horrible thing to do, and probably the other half would say, I really do not know.

My own personal response is I do not think it is a very nice thing to do at all.

I should add that the protocol was submitted to FDA in February—well, the sponsor, January 29, 1975, and arrived at FDA February 3. The study was actually commenced by the sponsor about 6 months before; it began in June 1974. Standard practice, of course, sponsor's obligation is to submit these things in advance.

Senator SCHWEIKER. I am troubled by this. I cannot imagine that people would give informed consent for their own children to be research subjects if they knew the facts surrounding this experiment.

It seems to me that perhaps the only way the investigator could get consent would be under the stressful conditions of labor.

Commissioner KENNEDY. Senator, could I amplify this response?

Senator KENNEDY. Before that, you mean the experiment started before the protocol was issued?

Dr. HENSLEY. Correct. About 6 months before. I should add, the protocol itself was different from the study as conducted, the business about oxygen, and the subject of the balloon was not in the protocol.

Senator KENNEDY. That does not make any sense.

Dr. HENSLEY. They were not. The investigator considered some things significant and some things not significant. He put things in the protocol he thought were important and omitted certain other things.

Senator SCHWEIKER. How long did the study go on after the protocol was approved?

Dr. HENSLEY. It was several months; I do not know the exact duration. I think it terminated in June. So the difference between February and June.

Senator KENNEDY. What about it, Mr. Commissioner? We are going to run through similar kinds of case studies as we are here.

Do you think it is important, even though there are individuals, these are the 10 percent of these cases; we see this one was basically selected at random by obviously skillful, knowledgeable, committed investigators; if this type of situation exists, how do you react to it?

Commissioner KENNEDY. I find this distressing in a number of ways, Senator.

What I was going to add to Mike Hensley's response to Senator Schweiker's question is the FDA-approved protocol did not contain some of the very important features that have been brought out here, including placement of esophnageal balloon and including oxygen content of the breathing mixture.

Senator KENNEDY. You cannot say that is slipshod or——

Senator SCHWEIKER. FDA did approve using placebo; certainly that was in the protocol.

Commissioner KENNEDY. It did.

The question was, Senator—I am not going to tell you I think FDA should have approved even the protocol it got. I think we should have made that call the other way. But I want to make it clear that that protocol did not have a number of the features that were in the published report. It was a very a much less in labor unacceptable protocol. Because many women are given Demerol, there is a need in normal practice for a drug to reverse the respiratory depression and from the protocol that we received, it did not, I think, even look as though the receipt of the reversing agent was going to be as delayed as it was. So the call was a lot closer in the study actually conducted.

Dr. HENSLEY. One of the most objectionable things about the protocol to me is, or about the study, is that the mothers were given a second dose of Demerol to insure that the babies had some respiratory depression. That also was not in the protocol submitted to us.

Senator KENNEDY. This is not sloppy bookkeeping. This, I would think, is a clear departure from what the review was intended to be. What conclusion do you draw?

If these things are as Dr. Hensley has pointed out, what conclusions do you draw, Mr. Commissioner, on this kind of situation?

Commissioner KENNEDY. I think we have to do a better job.

I would conclude several things:

First: We are probably going to conclude at the end of a year's analysis, this year's analysis of these compliance programs, we are very likely to conclude we will need more effort in this area.

Second: I suspect we are going to conclude that the ways in which we attack the problem routinely are not going to be adequate. That is, we need kind of alert monitoring by highly qualified people who are reading open literature that this case demonstrates. I agree with you it is a good piece of investigation and the question is how much would more literature turn up; and the answer to that question is: obviously we do not know.

I think it is fair to say that for regular readers of the clinical literature, this case is very unusual. One seldom encounters a paper in a distinguished journal of clinical investigation that makes one stop and say, holy smoke, how did anybody let this study go through?

Yet, the disturbing fact is that not only did the Journal apparently publish it without question, but nobody wrote to the Journal afterwards and say, hell, what's going on here?

Dr. HENSLEY. If they did, the comments were not published.

Senator KENNEDY. Let's go to investigator No. 9.

Why did FDA become involved in monitoring the Endo study of new drugs to treat Parkinson's disease in 1976?

Dr. HENSLEY. The involvement really came about because of a complaint from another pharmaceutical company. The story basically is this: The other pharmaceutical company contracted with the same investigator for another study on a drug for Parkinson's disease. They received their data from the investigator and found problems with it. Specifically, they found dates on the laboratory work, and obviously, these had been altered, a very sloppy job. The dates had been crossed out and new ones written in.

The investigator, or whoever altered those dates, neglected to remove identical dates which were present on reverse side of those laboratory slips. This was a 30-patient study that was done. They were aware that Endo had done a study on Parkinson's patients. Representatives of the drug company who gave us the tip went and visited with the people at Endo and compared their data to Endo data. Lo and behold, the Endo study was also a 30-patient study in Parkinson's patients. The patient's names were identical. The sequence was the same. In both cases, patient No. 11 had dropped out of the study. The difference between the Endo study and this study was that the submission that was done or shown to us by the drug company that complained had in it considerably more laboratory data than the Endo submission—I am sorry—than the Endo material that we subsequently did obtain.

Specifically, the submission that we were shown by the complaining drug company had five to seven sets of serum chemistry determinations and CBC's bearing dates in 1974, 1975, dates that corresponded identically to or very similar to dates of alleged clinic visits on the Endo study.

At any rate, based upon the original complaint, we sent investigators to Endo and obtained Endo data, compared the data, and subsequently initiated an inspection. This was a little bit unusual since "for cause" inspections were usually done in IND studies.

Senator KENNEDY. As I understand, the investigator had done an investigation for Endo, and then had used that material in submitting a drug for another laboratory——

Dr. HENSLEY. That is the story as I initially saw it.

Senator KENNEDY. You could not label that by any other name but fraud?

Dr. HENSLEY. It seems a reasonable statement.

Senator KENNEDY. And then there was the actual review of the studies that was done by this investigator for Endo; is that correct?

Dr. HENSLEY. Yes.

Senator KENNEDY. What did you find there, deficiencies in the Endo study?

Dr. HENSLEY. Yes, there were.

We conducted an inspection. What we routinely do is to select at random the number of patient charts that we want to review. In this case, we chose 10. We went to the hospital where the study was allegedly done and asked for those charts. We were only able to obtain six. They did have patient names, identification numbers, identical to the missing four, but just could not locate the charts.

In summary, what we got for the study was——

Senator KENNEDY. Six cases you were unable to get the patient charts?

Dr. HENSLEY. Four. We reviewed six charts, and that gave us enough information to proceed. What we found was the investigator appeared to have filled out the case report using names and demographic information of real patients. However, first, the duration of the disease had been significantly lengthened in three of the patients.

Second, dates the investigational drugs were given were dramatically different from reality in three of the six.

Third, Symmetrel, one of the investigational drugs, was given in only two of the six patients.

Fourth, in only one case does it appear the case report reflects accurately the patient chart. If you want, I could go through those case by case.

Senator KENNEDY. We will put them in the record. If you have that review before you, like in the case of patient No. 18, the six patients that are reported—it says: "Dates reported on study: January 27, 1976, to June 23, 1976." And then patient did not even receive the Endo drug; am I correct in that?

Dr. HENSLEY. That is correct. There is nothing in the patient chart that suggests the patient ever received the drug.

Senator KENNEDY. That is true about patient 19 as well, represented he received the drug from January 27, 1976, to June 1, 1976, and he did not receive the drug either?

Dr. HENSLEY. He did not receive one of the investigational drugs; that is correct.

Senator KENNEDY. Did Endo ever alert FDA to any problems with these studies?

Dr. HENSLEY. No.

We inspected Endo, as I said. Actually, we sent investigators out to acquire records for the study. They felt, as I understand it, that their study was a good study, no matter what the other people had on file. I believe that is still their position.

Senator KENNEDY. Would you indicate whether you believe they withheld any information?

Dr. HENSLEY. I think a better response than yes or no might be to say, or point out, what I said before; specifically, we did in an old submission find large quantities of laboratory data that bore dates of clinic visits, dates that were similar to or identical to clinic visits listed on Endo case reports.

This laboratory data was not included in the Endo response to our request. I think it speaks for itself.

Senator KENNEDY. This is the same investigator, and he did some work for the Hoffman-La Roche Co.; is that correct?

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Dr. HENSLEY. That is correct.

Senator KENNEDY. In 1975, on 30 patients, using a test drug for insomnia?

Dr. HENSLEY. That is correct.

Senator KENNEDY. Now, did you become involved in the inspecting of the records for this case?

Dr. HENSLEY. Well, as I said, we inspected the Endo study and during the course of that investigation, we learned from the investigator that had conducted a study for Hoffman-La Roche.

Senator KENNEDY. Has he conducted studies for other companies, too?

Dr. HENSLEY. Yes. For at least one other company.

Senator KENNEDY. Just one other?

Dr. HENSLEY. As I recall; yes.

Senator KENNEDY. Up to that time of the FDA inspection, had Hoffman-La Roche indicated there were serious problems with the quality of the data?

Dr. HENSLEY. No, they had not. In fact, I believe the data had been submitted into IND without comment, essentially.

Senator KENNEDY. What conclusion did you draw from examining the data?

Dr. HENSLEY. I think it is a fair statement—I better back up—I should explain that this investigator actually did a three-part study. They were regarded in the La Roche correspondence as three separate studies. It is my impression that the first and second study—I am sorry—first and third studies—were probably not done at all, though I do not know. We found no evidence to suggest that they were.

The middle study, the second study, we had found some indication that some of these patients did receive investigational drugs. However, there were a great many discrepancies between the case reports and patient charts and we found a good many patients, in fact, a majority, who were listed by this investigator who, in fact, did not receive investigational drugs. I would say that probably we have reason to believe that two of the three studies had not been done and the second one was poorly done. That is purely a subjective judgment based on what I have got now.

Senator KENNEDY. What do the examination of the case reports with the patient charts reveal? You have done that review?

Dr. HENSLEY. Yes, I did. What we did was to pick five patients at random from each of these three studies and try to obtain patient records.

Senator KENNEDY. It is five patients from each of the three studies?

Dr. HENSLEY. Yes. That is what we intended to do.

Senator KENNEDY. At random?

Dr. HENSLEY. Right. In fact, when our investigator went back to this hospital, the hospital could find no evidence that two of these patients existed—there were no patients listed in the file with names or I.D. numbers similar to these patients. Two of the patients, they could not find the records for. However, for 11 patients we were able to do a fairly extensive chart review.

Of those eleven, we only found one who really appeared to have gotten the drug. A second one may have.

Senator KENNEDY. You made a summary of the finding, is that correct?

Dr. HENSLEY. Yes. I believe you have a better summary than I do.

Senator KENNEDY. Now in reviewing these patients that were selected at random, as you mentioned Veterans Administration Hospital had no records of any kind for 2 of the 15 patients' charts that were selected for review, who had participated in the study, and could not locate current patient charts for two additional patients.

Three patients in addition to the ones previously mentioned were not in the hospital during the period of time covered by the study.

Dr. HENSLEY. That sounds familiar. There may have been more than that.

Senator KENNEDY. Only two of the charts reviewed had any indication that the patient was on the study and taking HLR medication. That is only two of how many?

Dr. HENSLEY. Two of 11. Counting the 2 that never existed, 2 of 13.

Senator KENNEDY. Two they cannot find, 2 were not in the hospital, and so you get 2 out of 11 on the drug. Two patients purportedly participating in study subsequently expired. Their deaths were not reported to the sponsor according to this. The laboratory work allegedly done reported by the Veterans Administration Hospital, according to the laboratory, was not done and reported by the Veterans Administration Hospital laboratory.

Well, they have got a whole series here.

In this last finding that you have, they say you make a serious allegation or charge here that the Hoffmann-La Roche Co. reinterpreted and changed laboratory data submitted by the doctor.

Dr. HENSLEY. I did not make that charge. That was a statement that La Roche made themselves.

Senator KENNEDY. Who made it?

Dr. HENSLEY. Roche made it themselves. That may have been included in our Establishment Inspection Report. But Roche admitted they had gone out on a number of occasions, I think, and had looked at the laboratory data and had altered it. They felt that the—well, I should explain.

Much of this data is printed on what are called SMA–12 forms. These are serum chemistry determinations. The form itself consists of a number of vertical bars with gray zones and there are numbers along these bars. The gray zones indicate the normal range.

What they apparently were doing was to look at where the value appeared to be in the zone and trying to get better designation of it or better localization of it. In other words they felt that the investigator read these forms incorrectly and they were reading them correctly——

Senator KENNEDY. What did you find about the laboratory data?

Dr. HENSLEY. That is an interesting question. The laboratory data—I should drop back for a minute and go back to the Knoll Study—the Knoll Study, the investigator admitted to us he had—he stated

he had lost his original data in a rowboat accident. He had subsequently taken data from the Endo Study and submitted it to Knoll, and then when they complained, he had taken rolls of chart paper, the paper I described to you, and laboratory slips from the lab and put together some new data.

Getting back to the Hoffman-La Roche Study, when we looked at laboratory data associated with the Hoffman-La Roche Study, it looked remarkably like the handcrafted material that had been submitted to Knoll. There were certain characteristics in the format of that data that laboratory personnel were able to point out to us and that identified it as not being genuine.

These characteristics were shared by the Hoffman-La Roche data, much of Hoffman-La Roche data. Not all, but most.

When we looked at the patient chart, we could find no laboratory data in the patient charts that were similar to the data submitted to Hoffman-La Roche, even though these were allegedly hospitalized patients and——

Senator KENNEDY. Did the laboratory officials say they were done in the laboratory or not?

Dr. HENSLEY. They did not believe that they were. They felt that these were most unlike the normal products for laboratory—further, if I might add, if these were hospitalized patients, the format for this hospital is that the floor, the ward gets computerized printouts, and comes up on teletype laboratory information. These SMA forms, these graphs that I have described simply do not go to the floor, so if these were hospitalized patients, the two just do not match up. If they were hospitalized patients, they should have teletyped laboratory data in the charts.

Senator KENNEDY. So laboratory people themselves indicated that it was not down in the laboratory, is that correct?

Dr. HENSLEY. That is correct.

Senator KENNEDY. What does that mean?

What does it mean in terms of the material that is submitted to you?

Dr. HENSLEY. Well, it means either the investigator had it done in an outside lab or that he handcrafted it and it actually was not done.

Senator KENNEDY. How do you change the laboratory data if there is not any laboratory data?

Dr. HENSLEY. Well, apparently what was done is Hoffman-La Roche representatives looked at the SMA forms that the investigator had in his possession, and as I tried to explain, these forms had vertical bars, horizontal lines drawn across the bars, and they felt the investigator had misinterpreted where these lines crossed the vertical bars.

Senator KENNEDY. Where they felt there had been a misinterpretation, they altered it?

Dr. HENSLEY. Yes. And asked the investigator to sign it.

Senator KENNEDY. And he did?

Dr. HENSLEY. Well, I was going to say he wrote a note at the bottom of each page explaining it, but that is not necessarily true. There were a few of those, but not all of them.

Senator KENNEDY. That the tests were not necessarily true or that they were changed——

Dr. HENSLEY. Write a note saying changes were made by Hoffman-La Roche.

Senator KENNEDY. You do not know whether tests were done at all?

Dr. HENSLEY. No.

Senator KENNEDY. Let us briefly go to the charts.

You are familiar with these case studies. Take the case report and then the patient chart, is that the way——

Dr. HENSLEY. That is correct.

Senator KENNEDY. These were the ones selected at random?

Dr. HENSLEY. Yes.

Senator KENNEDY. As we go down, since they were selected at random, if you get study No. 4, for example, on protocol 630, they have patient No. 28. I will review these briefly.

On patient 28, it gives dates of the study, physical description, diagnosis, medication, other problems, and then it has: "Did receive Roche drug" or "Did not receive Roche drug" on the case report.

And in these studies here, patient 28, I think you see the diagnosis is quite a bit different in case after case. Patient 28, it is syncope and diabetes; and on the patient chart, diagnosis, heart disease, emphysema and asthma.

On the case report, it said "Did receive Roche drug."

On the patient chart, it says "Didn't receive Roche drug."

At the top, the dates in the hospital, and there are other things too, 56-year-old male, 5 foot 8, 206 pounds; that is on the case report; and on the patient chart, he is 58 years old, 5 foot 10, 179 pounds.

But additional significance is the date. On the case report, it is 9/3/75 through 9/10/75; and on the patient chart, dates and hospital, it is 9/14/77, 2 years later.

Dr. HENSLEY. Right. He was not in the hospital until after the case report was received. We checked not only the hospital chart but also separate files with this hospital with the head of the administration and could locate no other admissions.

Senator KENNEDY. Patient No. 20. Diagnosis under case report is Parkinson's Disease and tremor.

On the patient chart, it is "Inoperable lung cancer."

And in the case report is "Did receive Roche drug."

And the patient chart is "Didn't receive Roche drug."

As a matter of fact, in the time that they mentioned this particular one that they did the test, this fellow was actually dead.

Dr. HENSLEY. No. He died shortly afterwards. I believe that is one of the patient deaths.

Senator KENNEDY. Well, on patient 20, it says did receive the Roche drug in the case report, and in the patient chart it says didn't receive it.

Patient 33 is did receive Roche drug, case report. And the patient chart is didn't receive Roche drug. It continues along.

In patient 27, different protocol, it gives the physical description, 56-year-old male, former pharmacist, and the physical description of

the patient chart is former deputy sheriff and set painter for Desilu Production. Points out received the Roche drug under case report and "Did not receive Roche drug" in the patient chart.

If you put those on the wall and examine them on a person's desk and compare the case reports versus patient charts, it seems to me it would have to find out that either people did receive it or they did not receive it. I would think that an elaborate monitoring process would catch that pretty easily—or would it not?

Dr. HENSLEY. It would seem so. These patient charts bore little or no resemblance to case reports except in general age of the patient where they were approximately the same.

Senator KENNEDY. The only thing is, would this type of thing be tough to detect in any kind of monitoring process?

Dr. HENSLEY. If the monitor had access to patient charts, it would not.

Senator KENNEDY. If you are doing monitoring, would you have to review patient charts?

Dr. HENSLEY. I would think so. I probably ought to mention briefly how this investigator organized his file. For each patient on this study, and on others, he had a separate—well, there was a little folder, and in this file were case reports and sheets of hospital charts, papers bearing notes and dates that resembled hospital charts. It is entirely possible, I suppose that the monitor might have reviewed those files.

But had the monitor looked at a hospital chart per se, it would have been obvious.

Senator KENNEDY. How is FDA going to know about this unless they went in and investigate on the basis of those submissions?

Dr. HENSLEY. The only way we could pick up on this would be for La Roche to have reported it to us. If this data were submitted, if the case reports are considered on their own, on their own merit, and if data were tabulated and not on laboratory forms, original laboratory forms, I think there's probably no way you could know this was not a good study.

Senator KENNEDY. There was no way they would know, is there? And FDA would make a judgment based upon obviously the case reports submitted to them?

Dr. HENSLEY. Probably so, yes.

Senator KENNEDY. Unless other information was provided to them. Was this other information provided to them on the basis of this?

Dr. HENSLEY. No. I should qualify that and say Roche did make comment about sleep monitor——

Senator KENNEDY. About what?

Dr. HENSLEY. Roche did make a comment about the sleep monitor in the study. This was, as you say, a study of sedative, and there was someone charged with the responsibility of checking the patient at night to be sure they were asleep.

They allowed as how they felt the sleep monitor was biased, that she knew the code. They did make a comment about that.

Senator KENNEDY. That is the only other submission, is it, that you have?

Dr. HENSLEY. Yes. I'm not sure what effect that would have on review at FDA. I think if I were reviewing it, I would probably tend to discount the work. But I do not know.

Senator KENNEDY. We go to No. 10 from McNeil Laboratories.

As I understand former Commissioner Goddard brought to FDA's attention some problems with investigator No. 10. What was the nature of these problems?

Dr. HENSLEY. The company that Goddard was with had contracted to this investigator a study of an anti-arthritic agent, drug. The company had been surprised, initially pleasantly surprised, later with some concern, that the investigator had reported to them the findings on the study very, very promptly. They thought also that laboratory data might not be accurate.

They thought that in fact portions or all of the study might not be real. They have attempted an inspection themselves, much along the lines of the standard FDA "for cause" inspection, I might add—did a reasonably good job of it and brought with them a copy of the inspection.

Senator KENNEDY. Was there any evidence that the laboratory work had been done?

Dr. HENSLEY. For this study?

Senator KENNEDY. Yes.

Dr. HENSLEY. No. The study on that was that the investigator was conducting a two-part study. The initial part was double blind—in other words, neither investigator nor patient knew what he was getting.

The second portion of it was to have been an open study for those who had responded initially. In other words, the investigator would know what the patient was getting in that case.

The story was, as told by the investigator, that the laboratory data was performed by a friend of his at another hospital. Unfortunately, the friend had a rather unusual name. I have sort of a funny memory for things like that, and I recalled having seen the name in an obituary, and it turns out the associate had died half way through the study.

The investigator adhered to the explanation even after we mentioned that——

Senator KENNEDY. You said the one who had done all the laboratory work previously——

Dr. HENSLEY. Yes.

Senator KENNEDY. What evidence was there that the laboratory work had been done?

Dr. HENSLEY. None. The investigator alleged that the messenger would pick up blood samples from the office and deliver them to the office and the laboratory work would be done and reported back to him on a following Friday, all payments were made in cash, no receipts. He was unable to identify the messenger, and of course these pick-ups and deliveries continued long after the death of the associate.

He could offer no explanation, and of course had no original laboratory forms to substantiate this.

Senator KENNEDY. So the work that he did or allegedly did may have been—for McNeil—may have been submitted to FDA without qualification?

Dr. HENSLEY. Yes. I was talking about original study, the one Dr. Goddard complained about.

Senator KENNEDY. So you went to obtain some case reports of the study that he had done for McNeil?

Dr. HENSLEY. Yes. Before we went out to inspect this investigator, we did obtain McNeil case reports, and I did a tabulation of the data just from my own information. I was suprised to see that there was unusual degree of consistency in the data. I believe we have copies of the table.

What we have here is before and after laboratory work for this study. I think you will notice for each patient there is rather an amazing tendency for the before and after values to be identical.

Senator KENNEDY. That is this chart here?

Dr. HENSLEY. That is correct.

Senator KENNEDY. Why do you not represent in layman's language the statistical significance of identical numbers, sort of before and after, what does that mean?

Dr. HENSLEY. Well, maybe we should take, let us take hemoglobin, for example, on the vertical chart here, first column.

If one establishes a normal range for hemoglobin, and being conservative about it, say 12 to 14, and being very conservative, and if hemoglobin determination is reported in tenths, in other words 12.1, 12.2, 12.3, et cetera, there are about 20 possible values one might have there in the normal range, and considering the variation in the way the procedure is done, it is reasonable that these might be considered independent events statistically.

So, for a normal person, for the value to be a normal value, you would have 1 in 20 chances having any one of these values, and for them to be replicated would be a product of those chances because they are independent events, that is 1 in 20. At least, that is my interpretation of it.

Senator KENNEDY. The point is, as I understand it, that there should be a slight variation in all of these factors?

Dr. HENSLEY. Yes.

Senator KENNEDY. And there are identical numbers in all of these numbers in parenthesis which as you point out, I suppose from a scientific point of view, is virtually impossible?

Now, what happened when you confronted them with this?

Dr. HENSLEY. Well, having discussed the Goddard matter with the investigator, having obtained his responses, I showed him these charts.

I also showed to him a chart of other laboratory data that he had submitted to another company at an earlier time. The chart I paralleled with these showed a standard distribution of values. I asked him what his opinion was. He put his head in his hands and said how could this have happened?

Senator KENNEDY. Now, how did he say it? How could this have happened? How did it happen?

Dr. HENSLEY. How could this have happened? This is not any good. I should have noted this. He admitted laboratory data could not be accurate.

Senator KENNEDY. He was saying that about the whole page?

Dr. HENSLEY. About the whole page. I believe there are 45 patients tabulated there.

Senator KENNEDY. He said how could this have happened?

Dr. HENSLEY. He was quite upset. He was not angry—more alarmed.

Senator KENNEDY. What happened? Did they talk to the people at McNeil?

Dr. KENSLEY. The next step was I asked for original laboratory values on these, and I asked who made them—his response was the laboratory work was done by the same individual who had done the other work. This preceded the other study by a year. He said he did not have the original laboratory data. He had sent it to McNeil.

I subsequently called McNeil that same day from the inspection site and asked whether or not the data had been submitted.

The representative who I spoke with got back to me the following day in Rockville and stated, no, they had not received the original. All they got was Xerox copies. I was going to make a comment. Before I could get to it, he said, you know, we went over this with the project monitor. This stuff is just too good. There is too much consistency here.

Then he embarked upon a short dissertation on how much damage this kind of thing did to the pharmaceutical industry. I tried to reassure him at that point, that as of that point this was still under investigation——

Senator KENNEDY. Your comment here is that the company told you what?

Dr. HENSLEY. The company representative said that he admitted that laboratory data could not be real, that it was not good.

Senator KENNEDY. And the investigator?

Dr. HENSLEY. The investigator maintained that he had sent all of his stuff out to his associate, and that it had been done. He had just overlooked it.

Senator KENNEDY. Do you know what McNeil sent on to FDA?

Dr. HENSLEY. Two- or three-page summary of the data, I believe, at that time.

Senator KENNEDY. That was the extent of it?

Dr. HENSLEY. Yes.

Senator KENNEDY. Did they ever point out any of these other problems?

Dr. HENSLEY. Not to my knowledge.

Senator KENNEDY. Now, this particular investigator does investigative work for a series of other companies?

Dr. HENSLEY. Yes. Most of these people have done quite a bit of work.

Senator KENNEDY. For a number of other companies?

Dr. HENSLEY. A number of other companies.

Senator KENNEDY. In this case here, probably seven other companies.

Well, now we will do investigators 7 and 3.

Can you tell us why FDA got involved in monitoring doctor No. 7?

Dr. HENSLEY. This was prompted by an Institutional Review Committee inspection of a community hospital. The study that was keyed on was a study done by this investigator. Of course, the result was that the IRC had no knowledge of the study having been done; however, subsequently, the staff did inform the inspector that they were aware that this investigator had been up to something and they detailed what they knew about it.

Senator KENNEDY. This investigator was an emergency room physician; is that correct?

Dr. HENSLEY. That is correct.

Senator KENNEDY. He did conduct his studies only in an emergency room?

Dr. HENSLEY. He conducted his study in a hospitalized group of patients, the patients of other physicians, according to allegations made by staff.

Senator KENNEDY. What did the other physicians know?

Dr. HENSLEY. According to the staff, they had no knowledge of it. They learned about this only when this investigator was involved in a malpractice suit in the emergency room; and they began looking into his activities, and the nursing staff reported that the investigator had been administering investigational drugs to a number of different patients.

Senator KENNEDY. What eventually happened to him?

Dr. HENSLEY. Well, subsequent to IRC inspection, a "for cause" inspection was issued on this investigator. An FDA inspector, investigator, located this doctor, and at the time the doctor said all his records were packed up and he was in the process of moving and would they please come back later. Of course, that is what they did.

When they tried to come back, they could not locate this investigator.

Subsequently, this was one of the things that I picked upon and we did reissue that assignment and we have located the investigator, and we now have a team looking at it.

Senator KENNEDY. Had he lost his license to practice the previous year in Florida prior to this?

Dr. HENSLEY. He had lost his license to practice in another State by virtue of charges of fraud by the medical society.

Senator KENNEDY. Do you remember specifically, the informed consent——

Dr. HENSLEY. It had to do with an operation for obesity, and as you say, informed consent——

Senator KENNEDY. This is a question I suppose you have to ask: Why a doctor who lost his license on the basis of informed consent ought to be doing research on a drug, experimental drugs on human subjects?

Do you not think that the fact that he lost his license ought to have been established or flagged by any review process in terms of the investigation?

Dr. HENSLEY. Well, the State he was in had given him another license—in fact, until about two or three days ago, he was still

licensed in that State. I do not know how that was accomplished. But as far as the hospital was concerned—I am sure as far as monitor was concerned, this was a licensed practitioner.

Senator KENNEDY. The medical examiners in Florida indicate in their report that this investigator is found guilty of intentional misleading, fraudulent, deceptive or untrue representation. This is a person who is part of an investigative team on a drug, experimental drug on human subjects?

Dr. HENSLEY. Yes.

I should point out he has done quite a bit of other investigational work in the past.

Senator KENNEDY. You mean for a number of other companies?

Dr. HENSLEY. Yes.

Senator KENNEDY. This was for Bristol, as I understand it?

Dr. HENSLEY. Yes.

Senator KENNEDY. The list is 12 different major companies which have sponsored this investigator at one time or another.

Do you know about that?

Dr. HENSLEY. Yes.

Senator KENNEDY. What do you think Bristol should have known from this case that they did not know?

Dr. HENSLEY. That is a hard question to answer. The report that was submitted to FDA stated that study was terminated for administrative reasons. They did not try to use this in support of their IND. I cannot say what they should have known.

First of all, if they looked at the patient chart, they would have seen these were patients that—well, I think without an indepth inspection of the situation themselves, they might not have picked up on this. They would have had to speak with hospital staffs and interview a number of people to pick up on this.

Senator KENNEDY. Well, certainly I suppose as it comes to this company, on the one hand they evidently hired a person that was an unlicensed physician, and on the other they hired somebody who had been found guilty of deceptive practices in terms of informed consent and had his license revoked; and those are, at least the same company hired those two people to do important investigative work in terms of these drugs. I do not know what conclusion you can draw with regard to the monitoring system.

You ought to have monitoring systems that pick that up, I would think.

Dr. HENSLEY. You mean a centralized record system?

Senator KENNEDY. Whatever kind of system you want to have.

It seems to me they ought to be able to give assurance about the quality of the person that is going to be doing the investigative work.

Dr. HENSLEY. That seems reasonable.

Senator KENNEDY. Did investigator No. 3 work for Bristol Laboratories on this same drug?

Dr. HENSLEY. Yes, he did.

Senator KENNEDY. What were the deficiencies of the work done by No. 3?

Dr. HENSLEY. The problems were many. This was a situation where contract monitoring organizations, sort of an independent middle-man group, contracted with investigators to do two studies, in patients with acute pain.

The first study was for another company, was a 1-day study. The second study was for Bristol and it was a 3-day study. The studies were set up to run back to back. In other words, the investigator did the first study, and then the following day took the same patient and entered them onto the Bristol study. They were entered in blind fashion.

He did not know what they had received, nor did they.

In talking with the investigator, I learned that—well, in doing the inspection, we noticed that the dates that patients were entered into the study simply did not correspond to the dates entered into the patient log. In other words, his office records, in other words, the patients, were not there the days they were supposed to have been on the study.

In response to that, the investigator noted that on the instructions of the middle man monitoring the organization he had given the drug to these patients to take home, essentially they had put them in the pocket and they were told when the pain starts, take the drug and give me a call. So a good portion of this study was conducted over the telephone.

Senator KENNEDY. We have a series of others, but I think we will not go into those at this time.

We are going to hear from the companies themselves and give them a chance to make whatever comment they would want.

I just think, again, Mr. Commissioner, I think that obviously we are very much concerned about the nature of the decision-making process within FDA, the basis for the kind of information that they are going to have available to them.

We have seen over the period of the last 2 years instances in terms of testing in animals which was inaccurate, distorted, misrepresented the real fact situation, much of that information was submitted to FDA as the basis for scientific information for a judgment about particular drugs.

We are enormously distressed by what appears to be at least in a preliminary way a similar discrepancy on the basis of scientific information in the areas of human experimentation, as well as the failure to provide the type of informed consent which is absolutely essential in protecting human subjects.

We can draw no conclusion today, whether this is the tip of the iceberg, and there is a great deal more that lies underneath the surface, or whether it is the iceberg. What we can draw the conclusion on is that this abuse and misuse of scientific information is of enormous importance and seriousness. It reflects on the ability of FDA to make balanced and informed judgments about approving various drug materials that can have a wide distribution across the American system.

We just, I think, are unsure as to how deep that goes.

You are going to come back and tell us at the end of this review process, at the end of this year, your own conclusions about this, but

I think we are particularly troubled with the fact that as we develop new drug legislation as to the type of weight that ought to be given to the monitoring system, that either does exist or does not exist in terms of companies themselves, so that we can give the assurances and protections to the consumers that they are entitled to.

I think this is a matter of grave importance to the American people. I am heartened by your statement earlier during the course of the hearings about your distress about this type of situation.

Perhaps you would like to make a concluding comment about this type of problem that we may very well be faced with.

Commissioner KENNEDY. A few observations, if I may, Senator.

I think it is certainly a situation that we want to watch very carefully. I have made a commitment to you that I intend to keep—to share with you the results of this fiscal year's program and the conclusions that we draw from those results, just as promptly as we are able to generate them, together with any plans for developing a future strategy of monitoring.

I do think it is important to reemphasize in concluding that our sample today is inadequate to make in any direction the iceberg determination to which you allude. That is, it could be better than we suppose, or worse.

I think it is important to emphasize that "for cause" inspections, the results of which Dr. Hensley has been talking about, are generated when they think there is reason to be distressed, and therefore they may presumably represent the worst of the universe.

Finally, since some of these involve fraud, I do want to speak to that question for a moment.

First, in terms of our own compliance activities, we are engaged in an exercise here that is an investigation. Like any investigation, we are trying to determine who struck John.

We have a snapshot here in the middle of a series of investigations. They do seem to show up-raised arms. I think it is important to note that there is in any investigation or disqualification proceeding an opportunity for a hearing and cross-examination, and that in none of the cases we have talked about yet has that aspect of due process yet been given.

Finally, just an observation that I cannot resist, because it comes up every now and then:

You know the scientific enterprise has gone along for centuries developing an elaborate set of mechanisms that guard integrity of results against operation of statistical chance; and the scientific enterprise system is terribly good and very sophisticated about that.

For a long time now it has never found it necessary to design internal protections that are part of the way of doing that science that protect not only against chance but against fraud.

If it turns out that we have to design such mechanisms into the scientific as well as the retrospective evaluation investigation process, it is not going to be easy to convert a world in which trust has prevailed into one in which we routinely have to guarantee that a particular outcome is proof against fraud as well as proof against chance.

Senator KENNEDY. I think the matter which I suppose is of very substantial concern to us would be the fact that in some of the situations that have been described today there would be really no cause for alarm as to whether information submitted to FDA was actually accurate. No storm signals going off; no way or means that you could, on the basis of information that was submitted, to cause a sufficient kind of concern to do the kind of investigative examination that we have done in these cases as a result of trails that led back into this situation.

But on the basis of information that was submitted, if it was accepted on the face by some of the major significant drug companies there would be no cause for alarm. Yet, we find in these instances, investigators themselves, who have been doing investigations for a number of companies, in one particular instance for 12, much of their conduct being characterized as fraudulent and in terms of potential criminal investigations—when you have people scratching out names and substituting other names for drugs and using the material that was developed for one and submitting it for another, at least in terms of the protection of the American people, that is fraudulent. Whether in a court of law they will convict, it is another factor. I know you have to deal with this issue.

I cannot underscore enough, given the past review of this problem, the scientific information, the quality of scientific information, and its importance, and the importance this committee has given to that issue, we intend to work very closely with you and your department and insure that you are going to get the resources that you need to be able to make these judgments and to try to get the kind of personnel that can do the kind of review, the type of review, so that we will know the extent of this issue; because I do not think we have a higher responsibility in protecting the health of the American people than to insure that the kind of drugs they are taking are going to be—the judgment as to the efficacy and safety is going to be based upon sound scientific information.

We have enough storm flags out to give us sufficient kinds of warnings.

I know you are going to pursue this in a very vigorous and strong way. We are going to work very closely with you.

We want to be able to give the American people the kinds of conclusions that are drawn, the kind of detailed study, like Dr. Hensley does in these particular cases.

We want to thank you. We want to thank Dr. Hensley. There is so much we have seen over the period of years about people making a difference and doing I think a first-rate job in terms of responsibility.

There are many long, hard days in trying to look into these matters, but I think all of us are very appreciative of your presence and because of dedication and work that you are involved in.

I think it is typical of many of the people in the Food and Drug Administration who are trying to deal with some of the complex problems.

Dr. HENSLEY. I appreciate your kind remarks.

I should point out I do enjoy my work quite a bit.

Senator KENNEDY. That is all right. No one is saying you cannot enjoy doing some responsible and important things.

Dr. HENSLEY. Thank you.

Senator KENNEDY. Our next panel consists of Dr. Ralph Jacobsen, M.D., vice president and medical director, Endo Laboratories; Stanley Crooke, M.D., Ph. D., associate director of research and development, Bristol Laboratories. Dr. Crooke is accompanied by Irving J. Pachter, Ph. D., vice president and director of research and development, Bristol Laboratories; and Mr. Robert Endries, counsel, Bristol Laboratories.

Dr. George I. Poos, Ph. D., vice president of scientific affairs, McNeil Laboratories; Dr. John Burns, vice president of research, Hoffmann-La Roche. He is accompanied by Dr. Milton Willner, director of medical research, Hoffmann-La Roche.

If we could start off with Dr. Crooke. We want everyone to have the time to respond to these matters and to take what time they would. We will include all of your statements in their entirety in the record.

We will obviously permit you, on the basis of what you heard this morning, additional time to make whatever additional comments you want on any of these fact situations.

We will leave the record open for a 2-week period so you can analyze those statements and that material will be included in the record, along with your full and complete statements.

We are interested in developing the dialogue on this. I think it would be best to move through and summarize these statements, but we will let you proceed in any way you would.

Dr. Crooke, would you like to start?

STATEMENT OF DR. RALPH JACOBSEN, M.D., VICE PRESIDENT AND MEDICAL DIRECTOR, ENDO LABORATORIES; STANLEY CROOKE, M.D., PH. D., ASSOCIATE DIRECTOR OF RESEARCH AND DEVELOPMENT, BRISTOL LABORATORIES; ACCOMPANIED BY IRVING J. PRATCHER, PH. D., VICE PRESIDENT AND DIRECTOR OF RESEARCH AND DEVELOPMENT, BRISTOL LABORATORIES; AND ROBERT ENDRIES, COUNSEL, BRISTOL LABORATORIES; AND DR. GEORGE I. POOS, PH. D., VICE PRESIDENT OF SCIENTIFIC AFFAIRS, McNEIL LABORATORIES; DR. JOHN BURNS, VICE PRESIDENT OF RESEARCH, HOFFMANN-LA ROCHE, ACCOMPANIED BY DR. MILTON WILLNER, DIRECTOR OF MEDICAL RESEARCH, LA ROCHE, A PANEL

Dr. CROOKE. We have a prepared statement. It is probably too long to go through at this time. If you would like, I can address the questions of studies of doctors 2, 3 and doctor 7.

Senator KENNEDY. Yes.

Dr. CROOKE. Let me first address doctor No. 2.

Actually, the studies with doctor No. 2 should be considered as a separate set of problems for us, as opposed to the studies for doctor 3 and doctor 7. I would like to address those independently.

As a brief background, let me discuss the drug that was involved. The drug was compound BL–3912A. BL–3912A, as was correctly pointed out, it is similar structurally to a group of psychoactive agents, including amphetamine, and another drug, R–DOM.

Studies employing several species of laboratory animal suggested that 3912 might be a potent performance restorer absent the generalized——

Senator KENNEDY. Could I in terms of the record clarify that we are now talking about a nursing home drug; is that correct?

Dr. CROOKE. That is correct. We are talking about—well, first of all, I will address doctor No. 2 and then doctor 3 and doctor 7.

Doctor 2 is involved in studies on 3912.

Senator KENNEDY. That is nursing home?

Dr. CROOKE. Yes.

This is an agent that is supposed to be a performance restorer for senile individuals.

Now, the hope for 3912 was that it would be a generalized performance restorer, absent the CNS stimulatory and hallucinogenic properties of several of the other agents in this class.

There were reasonable animal data to support this. In fact, it was found to antagonize the R–DOM-induced abnormal behavior in cats, and enhance operant and learned behavior tasks. In experiments with aged rats, BL–3912A was demonstrated to facilitate learning and prolong memory. These effects were tentatively ascribed to the 5-hydroxytryptamine [serotonin] receptor against activity of BL–3912A, and were produced at doses significantly lower than toxic doses.

Thus, based on experimental animal data, experience with compounds of similar structures, and data concerning its mechanism of action, BL–3912A was a promising candidate for clinical trials.

Initial clinical trials included phase I studies in two groups of normal volunteers. In the first study, doses of 1 mg to 80 mg were employed without significant side effects. In the second phase I study, doses of 20 to 120 mg were tested. Many of the volunteers who received 40 mg to 120 mg noted increased mental alertness and demonstrated improvement in a performance test. Obviously, this is not of scientific significance, but a cause for optimism.

At a dose of 120 milligrams, definite euphoria and mild CNS stimulation were observed, but no other toxicities were noted. Studies employing 60 healthy volunteers were performed with BL–3912A before trials in patients were begun.

Study number 8 for which doctor No. 2 was principal investigator was the first study in which BL–3912A was administered to geriatric patients, suffering from senile mental deterioration. It was a double blind placebo comparative study. The initial doses employed were 25 milligrams and 50 milligrams daily for 5 days. If no side effects were observed, the doses were increased to 25 milligrams to 50 milli-

grams twice daily for 7 days, then three times daily for the duration of the study.

The results of this study suggested that doses of 50 milligrams to 150 milligrams daily resulted in statistically significant improvement in mental performance in geriatric patients with no significant toxicities.

Study No. 15 was also performed by doctor No. 2.

This study was an open dose ranging safety and efficacy study in which patients were treated with doses of 25 milligrams to 75 milligrams daily for a period of 60 days. The conclusions from this study were that BL–3912A resulted in improvement in mental acuity with no significant toxicities.

Subsequent to the studies performed by doctor No. 2, several other studies were performed. In these studies, BL–3912A was shown to be non-amphetamine like, but the positive results in geriatric patients reported in studies 8 and 15 were not reproduced.

As a consequence, we did not file an NDA on 3912, and we discontinued additional studies.

That is background on 3912A and studies by doctor No. 2.

I would like to address some general considerations relevant to 3912.

The primary research interests of Bristol Laboratories are antibiotic; anticancer and analgesic drug development. BL–3912A resulted from a collaborative research effort with an extramural scientist. Consequently, the intramural clinical expertise in the area of CNS performance enhancers was not optimal at the initiation of clinical studies on BL–3912A. In fact, since very few drugs for senile mental deterioration have been developed, clinical drug testing expertise is probably substantially less for such compounds than compounds of different classes throughout the academic and pharmaceutical company research establishments. Consequently, the performance of the initial efficacy trials was perhaps suboptimal.

Senator KENNEDY. What does that mean? You say "the performance of the initial efficacy trials was perhaps suboptimal."

You are using that as a kind of explanation for the fact that you have an investigator who does not have a license, no institutional review, no consent forms, virtually no performance in terms of the data itself—"the performance of the initial efficacy trials was perhaps suboptimal" is probably the classic understatement of the year.

Dr. CROOKE. It is early in the year.

Senator KENNEDY. Are you going to respond in greater detail to those particular elements? That is the basis of the information that we have heard during the course of this morning; and your response is that efficacy trials were perhaps suboptimal?

Dr. CROOKE. I would like to amplify on that statement. I think the rest of the statement I prepared will amplify it.

Senator KENNEDY. All right.

Dr. CROOKE. Before I do that, I would like to say that there are relatively few drugs for senile mental deterioration that have been developed. The expertise in the area, the clinical expertise in the area

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I think is perhaps less well developed than in many areas in which drugs are developed.

In addition to what was inexperience on the part of Bristol Laboratories clinical staff at the time, I think you would have to add potential difficulties in finding experienced investigators in outstanding sites to do significant research in this area, and that is an important consideration.

Senator KENNEDY. Sure. But experienced investigators, you do not want to include somebody who has lost their license, or did not have a license?

Dr. CROOKE. Of course, we did not know that at the time the studies were going on. In fact, let me just explain how doctor No. 2 was selected as principal investigator.

Senator KENNEDY. OK.

Dr. CROOKE. At the initiation of studies 8 and 15, doctor No. 2's credentials seemed ideal. After completion of medical school—and let me correct one impression that is not true—doctor No. 2 is a physician. He went to medical school, did postgraduate training in surgery and engaged in the private practice of medicine until joining a major pharmaceutical firm as a monitor for the clinical trials of a psychoactive agent thought to be active in the treatment of childhood hyperkinesis. He subsequently was promoted to associate medical director, then became director of clinical research projects at another pharmaceutical company. During this period, doctor No. 2 generated several publications.

Each of these characteristics of doctor No. 2's background have been documented. Thus, we felt, that is the individuals who were involved felt, that doctor No. 2 had considerable experience in the clinical evaluation of drugs, and more particularly had been involved in research on a psychoactive agent. Moreover, at the initiation of studies 8 and 15, he was associated with a geriatric center, and consequently had access to the appropriate patient population—at least what seemed appropriate at that time.

Senator KENNEDY. Taking one at a time, in spite of this array of credentials, he did not have a license to practice in Florida, did he?

Dr. CROOKE. That is what I have heard today.

Senator KENNEDY. Do you know whether he did on your monitoring process, would you not have a sheet there that says—would there not be on any page a question, I suppose you would ask whether the fellow is doing investigating, whether he is licensed——

Dr. CROOKE. He would have asked, I am sure, although I cannot submit it in the form of a paper.

At the time he was considered a clinical investigator, he was in an acedamic institution in a residency program, which he returned to after being in practice for sometime. So, again, the assumption of truth was probably not an unreasonable assumption at that time. I must state in retrospect that it was a mistake, but I am not sure it was unreasonable.

Senator KENNEDY. Now, are you prepared to characterize that facility as an appropriate facility for certain investigation?

Dr. CROOKE. Well, I've never been there, so I cannot speak directly to the facility.

Senator KENNEDY. What is your report—you're vice president and the medical director was there, was he not?

Dr. CROOKE. Prior to initiation of the study, there was a visit by the vice president and medical director. He was also visited by the person to whom the medical monitor for this study reported and by the medical monitor.

Senator KENNEDY. Did they give any characterization of the facility?

Dr. CROOKE. Not in the information that I reviewed.

Senator KENNEDY. Did they give any characterization of the ability of people to make an informed judgment on this kind of test?

Dr. CROOKE. That is a complicated question. That bears on the problem of doing a study in this kind of drug.

Senator KENNEDY. Probably suggests even a higher degree of real standards, ethical standards?

Dr. CROOKE. Absolutely. I think this is an area where one would need as much experience and as much quality as one could muster to hope to identify an active agent. Diagnosis of this symptom complex—I do not know that I want to call it a disease. The evaluation is largely subjective, much more subjective than many other areas. I think that is one of the reasons that evolution of new agents in this area has proceeded very, very slowly. Not the only reason, but one of the principal areas.

Senator KENNEDY. Obviously, as I am sure you are aware, there are very elaborate procedures which have been outlined and established in case law for notification of people on the issue of informed consent in institutional seatings which are similar to this particular one.

It seems to me that you want to know whether this was either recognized by the company, in trying to get some kind of understanding about your monitoring process or procedures—are your people sensitive to this?

They went down and looked at that facility. Did they inquire about institution review board, which we have heard is basically nonexistent, and what was reported back to you?

Dr. CROOKE. At the time of the initiation of the study, the necessity for human research committee or institutional review board was of course discussed with the investigator and at that time the investigator indicated that there was no institutional review board in that institution. That is not uncommon.

In a geriatric center, one might easily expect that to happen. But subsequently, there was an institutional review board formed and at least the information that Bristol received this was formed and that the study approved and signed——

Senator KENNEDY. In retrospect, we know that it was a phony board, do we not?

Dr. CROOKE. That is correct. But at the time it was not known. Perhaps it should have been, but it was not.

Senator KENNEDY. Do you want to continue.

Dr. CROOKE. The initial studies on 3912 were developed and monitored by a physician employed for the purpose of monitoring this drug. Prior to joining Bristol Laboratories, the medical monitor had performed a number of controlled clinical studies and had published in the medical literature on the effects of drugs in geriatric and younger patients with anxiety neuroses, depressive neuroses, and psychophysiologic disorders. Studies with doctor No. 2 were the first involving patients that he was asked to monitor for Bristol Laboratories. Prior to initiation of studies with doctor No. 2, doctor No. 2 and the facilities were site visited by the monitor, and subsequently by the vice president and medical director for Bristol Laboratories.

My review is based on information contained in the files. As you know, we had a very short time to review all these files. As far as I can attest, these are absolutely accurate from my review.

Study No. 8 was initiated on December 11, 1974, and terminated on April 7, 1975. Study No. 15 was initiated on January 30, 1975, and terminated on April 7, 1975. During this period the medical monitor made two monitoring visits on January 6–7, 1975, and February 17–25, 1975. I think this is an important correction to make: that in fact the medical monitor for this study did go to the site of the study and in trip reports described some of the patients who were treated. He did not describe the facility, but he did describe some of the patients who were seen. Descriptions were positive on the basis of medical monitor's reports.

One other point, and that is this was a double blind study. The discussions with the nurses who were involved in the study occurred nearly 2 years after the study. I'm not clear how the nurses would have known who got drugs, who did not, and how good their memory would have been 2 years later. Suffice it to say, there were monitoring visits, two within a month's period after the study was initiated.

In addition, there were numerous phone calls between monitor and investigator. On April 30, 1975, the monitor's employment at Bristol Laboratories was terminated. On May 5, 1975, a replacement medical monitor joined the medical staff at Bristol Laboratories for BL-3912A. Strenuous efforts by the new monitor and his associates to obtain case reports failed for many months, and when case reports were obtained they were incomplete. Investigation by Bristol Laboratories and the FDA suggested that doctor No. 2 had failed to meet the obligations of informed consent, and failed to follow the protocol in many patients.

Senator KENNEDY. Why did you let it go if strenuous efforts by his——

Dr. CROOKE. No. The studies were terminated. Strenuous efforts to obtain case reports, of course, began before studies were terminated, but studies were terminated as of April 7, 1975, so the duration of the studies is from December 11, 1974, to April 7, 1975. At the time these studies were initiated, it had been planned that a number of other studies would follow with this investigator, and of course those plans discontinued. So the duration of the studies was 4 months—duration of involvement with the investigator—4½ months.

Let me discuss the questions of informed consent and Human Research Committee approval, since this is a matter of concern.

Approval of protocols 8 and 15 by an appropriate human experimentation committee was required by Bristol Laboratories, as this is a requirement for all Bristol Laboratories' clinical studies. In a letter dated November 11, 1974, Bristol Laboratories was informed of Human Research Committee approval. Subsequently, Bristol Laboratories has been informed by the FDA that there is doubt—and probably this committee did not exist.

Bristol Laboratories required and obtained sample informed consent forms at the initiation of studies 8 and 15. However, inasmuch as the case report forms were never completed by doctor No. 2, no informed consent forms were received by Bristol Laboratories. Subsequently, Bristol Laboratories was informed by the FDA that no evidence of signed informed consent forms could be found in the patient's records at doctor No. 2's geriatric center in which the studies were performed.

I would like to address analysis of data generated by studies 8 and 15 and also to correct perhaps one not totally accurate impression.

In the final report on 3912, the problems with the investigator were discussed, perhaps not in depth enough, but they were discussed more than just simply not mentioning it.

The final report was generated on November 30, 1977, and I can explain the reasons for the delay. The reason for the delay in the generation or the final report was that during that time for month after month efforts were made to obtain case report forms. Now, long before that, in August of 1976, a statistical analysis was performed on data we had available to us. What we lacked was demographic information and additional laboratory information that we felt was essential before we wrote a final report.

The reason for delay was our effort to obtain complete data. In the final report, actually what the monitor for Bristol Laboratories said was interpretation of the results obtained with several of the tests was compounded by significant differences between treatment groups at the beginning of the study.

I will skip some of this.

Let me go to conclusions. That is where I want to be. He said complete demographic data, dose schedules, and narrative concerning side effects and laboratory abnormalities were not provided by an investigator. Reviews of the findings presented by personnel lead to the conclusion there were no serious adverse effects which should be contributed to administration of the drug. Because of incompleteness of case reports for this study and lack of cooperation of the investigator, it has been decided that no further work will be assigned to this investigator.

So in fact, perhaps inadequate, but there was a statement as to some of the problems as it occurred.

Back to the analysis: Although the case reports obtained were incomplete, they were evaluated. There is certainly an obligation, we are obligated to evaluate all data we obtain, even if they are unsatisfactory.

In general, the results suggested activity, with only minimal side effects. However, the monitor's reports clearly indicate the lack of demographic data, and the deficiencies in the case report forms. Moreover, because of significant doubts concerning the results of these studies, similar studies were initiated in other institutions under well-monitored and well-controlled circumstances. These studies failed to confirm the results of studies 8 and 15, and the clinical evaluation of BL–3912A was discontinued. In none of the studies on BL–3912 were serious side effects noted in any patient.

That concludes our formal statement about Dr. No. 2. I suppose you may have some questions.

Senator KENNEDY. How do you characterize your monitoring process given what the situation was down there in terms of the facility, described by some as rat infested, with virtually no institutional kind of review, troubles that you had in terms of getting your information, the delays, all of those. There was a complete failure in terms of meeting the requirements of informed consent. No one else has any other responsibility.

You have the prime responsibility in setting up a process for informed consent. How do you characterize your own monitoring process?

Dr. CROOKE. Well, I think as we state here in subsequent sections, it is obvious the monitoring process was not adequate in this case. I think the major problems were in the selection of the investigator and not the monitoring—not the length of monitoring at least. The selection of the investigator was clearly a mistake. The investigator did a poor job and has caused a great deal of problems for Bristol.

Prior to initiating the studies, there were two monitoring visits and there were two visits by the monitor during the conduct of the study. And as the studies progressed, it became clear to the superiors of the monitor that he was doing an inadequate job.

As a consequence, a new monitor was assigned to the study. In direct answer to the question, selection of investigator was inappropriate and monitoring of the study was perhaps—not perhaps—was definitely inadequate. The duration of these studies was four months——

Senator KENNEDY. Before we leave that, given this situation, I cannot understand how it could be more inadequate or more inappropriate, given the failure of the investigator to be a licensed practitioner, the type of facility, the problems that you have with informed consent, the difficulties you had of getting the material, you say, as I understand it, that it failed in this case.

How should we know it is any better in any other case? When we considered your investigator in your other situation, somebody who has lost their license because of violating the basic kind of tenants in terms of informed consent, described by medical examiners in the most grevious kind of way, so we have, and as you respond here, you say well it is basically the investigator that was the problem.

But really our system is not too bad. And then just a little bit later you hire a fellow who has had his license revoked because of

intentional misleading, fraudulent, deceptive, untrue representation of medicine.

How do we know whether the rest of your monitoring system is worth a darn?

Dr. COOKE. First of all, the investigator No. 7 is part of another kind of problem that has to do with third-party monitoring services or extramural monitoring services that I would like to address, and it is——

Senator KENNEDY. Whose responsibility is that?

Dr. COOKE. It is clearly our responsibility.

Senator KENNEDY. That is what I am talking about.

Dr. COOKE. I am not denying responsibility. I'm trying to define some of the problems we have had. It is clearly Bristol Laboratories's responsibility for these studies.

My opinion of the conduct of the monitoring of the studies is that it was poor, obviously, and that the monitor failed to do an adequate job. As soon as it was observed that the monitor was doing an inadequate job, he was replaced. The studies were terminated and additional studies were generated to attempt to confirm the data.

Senator KENNEDY. When it was attempted to be confirmed, it was not confirmable?

Dr. CROOKE. Yes.

Senator KENNEDY. How much did the monitor receive, the investigator receive during this period of time?

Dr. CROOKE. How much what?

Senator KENNEDY. Money.

Dr. CROOKE. $106,000.

Senator KENNEDY. For the whole program——

Dr. CROOKE. That was for studies 8 and 15.

I think the other thing that has happened, of course, is that unrelated to this we did in 1976, Sept. of 1976, generate formalized guidelines for clinical trials in which we attempted to address some of these questions. These are difficult matters of judgment. The selection of an investigator, for example in our guidelines——

Senator KENNEDY. I do not understand that, why this is a problem, to find out whether basic requirements of being licensed or being in good standing, mean it is $106,000, it seems to me that those basic kinds of issues or questions we are talking about—whether we have an institutional review committee and informed consent, whether investigator is in good standing, whether the facility from visual observation is one that this can be done, the types of population you are considering.

Those seem to me to be bread and butter type of issues or questions to deal with.

Dr. CROOKE. Well, there are many institutions, many places where studies are done, where there are not Human Research Committees established. It depends on the kind of question one is asking and the kind of drug.

For example, if one is looking at a new antibiotic in out-patient situation, one might encounter the situation without a research committee. Yet, no Human Research Committee at this geriatric center

is at least to me at this point not terribly surprising, because I doubt that this geriatrics center was involved in clinical drug evaluation. Nonetheless, these were appropriate age group patients for the study.

Senator KENNEDY. What steps were taken to assure adequate informed consent for this type of population?

Dr. CROOKE. There were guidelines for informed consent, informed consent form, the general informed consent form was sent to Bristol Laboratories. Other than that——

Senator KENNEDY. Nothing, because it is targeted in on a special population, locked-door facility——

Dr. CROOKE. Nothing that is in the files.

Senator KENNEDY. Was anything done, to your knowledge, in reviewing those files——

Dr. CROOKE. No. I was just reminded that there were families, I think two, who wrote to Bristol after termination of the study asking that the drug be continued because their family members had responded. So we assume that informed consent had been obtained in at least some of the patients.

There were no efforts to make sure that informed consent was obtained from an individual competent to make the determination. One of the problems with informed consent is that on the one hand we are certainly required to assure informed consent. On the other hand, we often encounter conflicts between rights of privacy and the desire of physicians to not send informed consent because they do not want patient's names and records known on a general basis versus the desire to have accurate information on the informed consent.

Senator KENNEDY. Did the patient's physicians that were in that facility know that this physician was using them in the study?

Dr. CROOKE. I do not know that.

Senator KENNEDY. Just to get back briefly now to Dr. No. 7, were you aware that Florida revoked his license the year before your study?

Dr. CROOKE. Bristol Laboratories was not aware.

Senator KENNEDY. He worked for 12 other pharmaceutical companies as well.

Dr. CROOKE. That is correct. Dr. No. 7 has a long history of working for pharmaceutical companies. Prior to initiating the studies on butorphanol, which was an agent studied by Dr. No. 7, Dr. No. 7 had more than 100 publications and had a number of other credentials which looked attractive. No one at Bristol Laboratories, so far as I know, was aware he had had his license revoked in Florida. At the time, of course, he was not residing in Florida.

Senator KENNEDY. We heard about the fact that physician No. 3 gave two investigational drugs—sometimes he gave two investigational drugs at once, and sometimes failed to maintain records of dispensing the drugs, and it was inappropriate for patient selection and misrepresentation of patients in case report forms.

Dr. CROOKE. Let me explain the studies by Dr. No. 3 and Dr. No. 7.

At the time those studies were initiated, the intravenous new drug

application for butorphanol, which was oral analgetic was being completed. In fact, there was very significant workload with more than 2,000—almost 3,000 case reports on patients who would receive butorphanol intravenously and the NDA was filed with FDA. For that reason, because of the workload, and also because the evaluation of an oral analgetic is a difficult job, because it is rather subjective evaluation again, we chose to employ external monitoring service, a third-party monitoring service, because we felt we wanted to get these studies done and were afraid we had inadequate manpower in the house. Second, we thought it would be useful to attempt to replicate data we had generated by a third party who would obtain investigators and design studies themselves, and avoid any potential for bias by our desire to have a new agent.

As a consequence, we employed this third-party monitoring service. The monitoring service, in fact, assigned the studies to these physicians and monitored the studies. Again, I am not in any way attempting to suggest that our responsibilities are less—I am simply stating what happened, which is that the monitoring service that we employed monitored these physicians.

Now, Dr. No. 7 was selected by the monitoring firm, and what I have to review is this curriculum vita, which is an acceptable CV—he graduated from reasonable places, had done evidently a great deal of work. He had publications in a wide variety of medical journals, from the New England Journal to surgical journals of one sort or another.

At the time the monitoring service had some concern about Dr. 7's ability to perform an in-patient study inasmuch as he is an emergency room physician. However, it was felt by the monitoring service that this was a small hospital, and he had access to all post-surgical patients, and that he would conduct the study.

Now, the study lasted for a very brief period of time, beginning on Oct. 29, 1975, and terminating on Jan. 9, 1976. During the period of the study, there were six monitoring visits made by the monitoring personnel. As a result of the monitoring visits, it became obvious that Dr. No. 7 was not adequately performing the study, and the personnel in the hospital were inadequately trained to perform the study. In addition, Dr. No. 7 experienced administrative difficulties in the hospital. Consequently, the study was terminated after 16 patients were enrolled.

So that is a somewhat different circumstance, at least from our prospective and the situation with 3912.

Senator KENNEDY. Was he fired from that hospital?

Dr. CROOKE. I do not know.

Senator KENNEDY. Well, he was.

Dr. CROOKE. Well, that is not clear to me. I asked the people involved with the monitoring service about it, and they were not clear, and so I am not sure. I assume that is the case, but I do not know.

What we were told was there were administrative difficulties in the hospital. There was a change in hospital administrators and a variety of other things that may have accounted for it.

Senator KENNEDY. That accounted for what?

Dr. CROOKE. He left the hospital.

Senator KENNEDY. He left?

Dr. CROOKE. And during my review of this material in the information that I had, it was unclear what happened there. Therefore, I called the monitoring service that we employed to get information from them, and it was their impression he had been fired from the hospital, but they did not have any clear information as to why he was fired and for sure that he had been fired.

Senator KENNEDY. If that had been brought up earlier, would that not have sent some signals off?

Dr. CROOKE. No. The study was terminated at the time he left the hospital.

I should add that the results of the study have never been used for anything except evaluation of adverse reactions, and these were essentially nonsignificant, but they were included in the analyses. No analysis of efficacy was attempted.

Senator KENNEDY. Dr. Burns, how would you like to proceed.

Dr. BURNS. Mr. Chairman, we have submitted to you a document which has outlined for your information the procedures that we use at Hoffman-La Roche in our monitoring of clinical studies and also in terms of adverse effects reporting, the role and functions of the institutional review committee and informed consent.

I think the best thing to say is that we can let this stand for the record and we can proceed to a discussion of investigator 9. We also have submitted information on that as part of the record.

Senator KENNEDY. Your complete statement will be made a part of the record.

Dr. BURNS. First I would like to say that we share with you the concern for proper monitoring of clinical studies. I feel that our organization has developed a system that is capable of carrying out and carefully monitoring clinical studies. The specific details of how we carry this out are outlined in the document we submitted, and we are prepared to submit additional data as to how we monitor clinical studies.

I would like to commence by saying that I returned from Europe last week and I was presented with this particular question of appearing this morning, so I spent a considerable amount of time reviewing where we are on investigator No. 9.

Senator KENNEDY. The only point that I might add is that we notified the company two weeks ago.

Dr. BURNS. I was away at that time.

Senator KENNEDY. We are always glad to see you, but there was someone else that we wanted to come down here.

Dr. BURNS. The point I wanted to make was that from my review of the case, I think we operated in a responsible fashion in our dealings with investigator No. 9. Let me elaborate on that point.

Investigator No. 9 is a senior staff physician at a Veterans Administration Hospital who is responsible for two clinics and has patient responsibility for several wards in the hospital. We carried out two studies in the evaluation of the efficacy of a hypnotic drug with investigator No. 9. The first study had two parts—that was con-

fused with three studies by the FDA witness but that is incorrect. There were only two studies.

The first study had two parts and then there was a second study.

The first study, I would say, was uneventful in the sense that there were no problems. There were the usual problems that one observes in a clinical study, especially with a clinical investigator that may not have had experience in a study of this particular type but our monitors spent a considerable amount of effort insuring that this particular study was carried out. A case in point: the monitor was present during the time when the first five patients received the drug.

The first indication that there was a problem came in early October of 1976. I would like to discuss what brought this about.

We observed what we refer to as a discrepancy in the lab results on Oct. 1, 1976. This stimulated us to explore further the nature of this particular discrepancy; and, from Oct. 1, 1975, through that month and into the following month, there were a number of visits by various Roche personnel to this particular investigator.

We attempted to obtain as much information as possible from this investigator. One of the problems that we ran into, was the question of securing the patient's records. This varies from hospital to hospital and institution to institution as to how difficult it is to review patient records. We were able to review laboratory records which investigator No. 9 had available in his office; but the actual patient records, the hospital records, in terms of total review, these were not available to us.

In the course of the review of this particular investigator, we were struck by the fact that something surprising was happening. In the first study that we carried out, the results were essentially consistent with the results we obtained with other investigators in terms of the efficacy with the particular hypnotic. The patient received a placebo for two nights and the drug for three nights. The first studies were consistent with the studies carried out by a number of other investigators, but when we reviewed the efficacy data of the second study, we found that during the placebo nights, the patients essentially had no effect of the drug. However, when the patient was switched to the drug, there was a remarkable effect. That alerted us, I should point out that this was a three-way study in which we were comparing our new drug against secobarbital as a reference drug and a placebo, in an attempt to determine the efficacy of our new drug.

We found out that when a patient was switched to the active drug, they had a remarkable efficacy. This made us go back and question investigator No. 5.

We found to our surprise that he had notified the nurse monitor or the person who was carrying out the study with him at the time when the patient was switched from a placebo to an active drug. Those of us who have been involved in clinical studies know that this is a cardinal sin in terms of carrying out clinical studies because the study is no longer a blind study. Therefore based upon this observation, we felt it necessary to terminate the study because of unconscious bias on the part of the investigator.

We felt that this particular study would have no value whatever in terms of determining efficacy of this particular drug.

We notified investigator No. 9 on November 24 of the termination of the study. I should point out the first indication we had about investigator No. 9 was October 1, 6 weeks before and, subsequently, the Food and Drug Administration was notified that we terminated the study for unconscious bias.

I feel that we have operated in a responsible fashion in terms of our dealing with this investigator, in carrying out this study.

I should like to point out something which might give a wrong impression; that was the question pointed out by Dr. Hensley about the reinterpretation of laboratory data.

One of the problems that we get into when you carry out investigational studies is to insure that the studies that you do and the information that you report to the Food and Drug Administration as to the efficacy of the drug is correct. We were permitted to review the lab data from each of the patients in the initial study, study No. 1, and we found that there were certain errors in transcription; in other words, errors going from, you might say, the raw laboratory data sheet over to the case report sheet, case report form.

These corrections were to make sure that these errors would not exist in the case report forms. The only changes that were made by Roche personnel dealt with making sure that the case reports were accurate and reflected data in the patient's records and these changes were made available only with the knowledge of the investigator. So I just want to be sure that there is an understanding of why those changes were made in the case report and that was to bring the case report forms in line with the raw data which was made available to us.

Senator KENNEDY. The point I would make there is that you would have to see the patient's chart in order to bring the case report up to snuff?

Dr. BURNS. This is a difficult problem, Senator. I think this is documented in the material that was submitted to you. We had considerable difficulty in attempting to get information from the investigator and also from some of the lab people at this particular institution relative to the lab data.

The investigator did have data in his laboratory which would enable us to compare it against the case report.

However, we had many other questions that we would like to have answered and we attempted to get those questions answered. We had no reason to support that there was fraud or anything—we could not prove it. The only thing we knew was that the study was no longer a blind study. The study was no longer a controlled study, and it was based upon that that we terminated the study.

Senator KENNEDY. Let me get into it.

If you say you have trouble getting information from the investigator—is that what you are saying here?

Dr. BURNS. Yes.

Senator KENNEDY. If you have trouble getting information from the investigator, why does not that send up flares? If you cannot get

the kind of information that you want, it seems if you are going to alter or change, or make the report, alter it to your conception of what would be accurate, to do it without the patient's chart would not make any kind of sense.

If you were not able to get the patient's chart, it seems to me you would want to raise that point as reflecting a good deal more on the integrity of the study rather than the question of whether the night nurse knew about the switch.

Dr. BURNS. I think I can answer that.

In the initial study, study No. 1, we were able to get——

Senator KENNEDY. Before we get into study 1, the studies that were supplied here in Dr. Hensley's testimony were the at-random selection of those patients involved in the three studies or the two studies—you know, we do not want to get caught up in words.

As Dr. Hensley points out, the three studies. They do not draw a distinction between one, two, and three and in each of those, in the five or six examples in each one of those studies, they still follow the same pattern in terms of receiving the Roche drug or not receiving it and in terms of the other vital information on it.

We ought to settle that kind of issue at the outset, whether that is your understanding or it is not your understanding because, at least in the information that was provided for us, we find a similar pattern in each one of these three studies.

Dr. BURNS. Let me answer that, Senator.

I am surprised to see this information myself.

Senator KENNEDY. If it is accurate, what does it mean to you?

Dr. BURNS. What I see here?

Senator KENNEDY. That is right.

Dr. BURNS. Well, there are several things. I really cannot understand it unless I know more information.

Senator KENNEDY. Just on the information they did receive the Roche drug or they did not; let us take that as a basic.

If that is accurate, what would you say about your monitoring system?

Dr. BURNS. I would say this, Senator, the case report form says that the patient received the Roche drug. To the best of our knowledge, the patient did receive the Roche drug in this particular study.

Senator KENNEDY. But you do not know whether they did or they did not if they have not examined the patient's chart other than taking the word of the monitor?

Dr. BURNS. Examination of the patient's chart presents a problem. We were able to examine lab data which the investigator gave us to examine which he had in his office, the raw data. We were not able to examine the patient's chart.

Senator KENNEDY. We were advised that it was not accurate.

Dr. BURNS. In questioning by our monitor of the investigator, he had explanations for that. We had no way to check that. We had to accept it.

Senator KENNEDY. You mean you accepted their explanations without going behind it or reviewing it further?

Dr. BURNS. We tried to get more information on this particular point. We got a notice from the Veterans Hospital about the

privilege of patients' charts. We are not privy to information in a patient's chart.

Senator KENNEDY. If this is accurate—that they did not receive the Roche drug, with all the elaborate mechanism which we included in the report as part of your testimony, the monitoring process but if in fact Investigator Hensley's testimony in instance after instance, were true, what conclusion do you draw in terms of the monitoring process that is set up by Roche?

Maybe they have problems they just cannot deal with, but what does it say about it at the present time?

Dr. BURNS. I would say that if this is true, it means a patient has not received the drug, then we do not have a study. I think that is a definite statement.

I would think from the standpoint of our monitoring process, I do not think it raises a serious question about our monitoring process. We examined and obtained information. This is the information we got from the investigator.

Senator KENNEDY. I think you are right about your conclusion that if they did not get the drug, the study is meaningless.

What does it say about your monitoring process?

Either you are satisfied with it or you are not satisfied, you have to say how you can change it so it will be able to reflect the kind of information that you ought to be gathering in order to make the scientific information meaningful.

Dr. BURNS. I think the answer to the question is that I think we should have available more readily the full data of the patient in a hospital chart. I think perhaps this should become a guideline that we should become privy to because the investigator had the information in his office. These are the things he showed us. We did not have the privilege of reviewing the hospital chart.

Senator KENNEDY. If this is the circumstance in this case, what do we know about any of the others or the rest of the information, other studies which you have done? We really do not, I think, is the answer.

Dr. BURNS. I am not sure I understand.

Senator KENNEDY. If you have not been able to get the information, if your monitoring system has not caught this or been able to get the information in order to be able to give the assurance to the Food and Drug Administration that what you represent to be an accurate representation is accurate and your monitoring system does not catch this kind of flagrant kind of situation of who got the drug and who did not, then you are not really able to give us or state today that with regard to other drugs that your system is any better for those than it is for this?

Dr. BURNS. I do not think I would accept that as a conclusion. I would say that in our dealings with the investigator, the investigator gives us information. The investigator obtains the information. We make every attempt to make sure this is the appropriate information. This information was examined and all the records which were given to us by the investigator.

I think there are differences that exist in this institution that may not exist in other institutions.

We are dealing with an investigator who obviously, from what I hear today, presents many, many problems. I don't think I would generalize from this particular study to all of our studies.

Senator KENNEDY. Well, could you not find out even with the rules of the hospital certain information? Two of these patients were never in the hospital, or were there 2 years later. Could you not find that out? Two of them did not exist.

Dr. BURNS. As I pointed out, in study No. 1, we asked to look at the lab reports of the 30 patients in study No. 1. We saw the lab reports on 30 patients in study No. 1. If he had two sets of records we were not aware of them. We were not aware he had another set of records completely different from the lab records. We certainly did see the lab records in these patients in study No. 1. They must have been there, or at least the records were there.

Senator KENNEDY. Well, of course, we know now that the lab report was altered, or at least in error, not on the basis of the patient's chart, but for some other purpose.

How are you going to avoid this in terms of the future?

As to the fact situation which is described only for the purpose of this question—there are other issues that—how are you going to deal with it?

How are you going to change your monitoring system?

Dr. BURNS. Let me just point out to you, Senator, as soon as we had an indication that there was something unusual happening—and this only happened in early October—we made a concerted attempt to get the facts, as much as we could, as outlined in the report which was sent to you. Six weeks later, we terminated the study.

It shows that our monitoring system does work. I do not think our monitoring system is in question.

Senator KENNEDY. What are they doing when they have these conversations over the period? They go down and are monitoring and chatting? Do they find out this kind of material? Do they find out through your monitoring system?

Dr. BURNS. What?

Senator KENNEDY. That two patients were not in the hospital; that two of them were dead? Did you people develop that material?

You have one investigator who is out there, and he may have some additional support. I am trying to find out if your company, with the resources it has, finds out this kind of information; and if they do not, why they do not.

If they do, and find out additional information even beyond that, all the much better. That is all we are trying to find out.

Dr. BURNS. We did not have the opportunity to examine the patients' charts as the Food and Drug Administration investigator did in his examination.

Senator KENNEDY. Did the lab people give you any characterization or give your people any characterization as to the accuracy of the information?

Evidently they told Mr. Hensley that there was altering by the Roche people; that the lab work was not done.

What did they tell you?

Dr. BURNS. That there was altering by the Roche people?

Senator KENNEDY. No. That the lab work was not done in their lab?

Dr. BURNS. No.

We were told by the investigator that the lab work was done in the lab there. To the best of your knowledge, that was the fact. We certainly tried, and we had discussions with the director of the lab, in an attempt to get further information.

There were a series of discussions that were outlined in the material submitted to you. We took this matter seriously, and we explored it, and we proceeded in a rapid fashion. By November 24 we terminated the study.

Senator KENNEDY. OK.

Dr. Jacobsen?

Dr. JACOBSEN. Mr. Chairman, if I may, I would like to submit our prepared statement for the record, but to limit my reading of that statement to the two particular investigators about whom certain charges have been made.

Senator KENNEDY. OK. Fine.

It will be received for the record and included at the conclusion of your testimony.

Dr. JACOBSEN. The first study was carried out by an investigator of our choice, investigator No. 9, and involved the use of one of our approved drugs in combination with an approved drug of another company for the treatment of Parkinson's disease.

This study was not intended, nor needed, for use in support of any FDA application. The work performed by this investigator in connection with our drug was monitored, and it appears to have been conducted in a proper fashion with valid results.

Following this study, we were contacted by another drug manufacturer who was working with the same investigator in a similar test for their product, also used in treating Parkinson's disease.

The other manufacturer had become concerned that some of the data they had received from the investigator might have predated the comencement of their test. A more detailed comparison of the earlier test data involving our product, with the data allegedly developed on the other manufacturer's test showed such striking similarity that it raised a question as to whether the investigator was attemping to pass off our data as data from the second test.

This similarity, as well as further inquiries, led us to encourage the other manufacturer's notification of this possible irregularity to the FDA, and to assist in the ensuing investigation. FDA Investigator W. Friedrich made a review of our data in September 1977; he retained copies of those documents he judged pertinent.

We have no reason to suspect that the data developed in the earlier test on our product was in any way invalid, based on the information we had. The study was published by the investigator.

The second study discussing investigator No. 1, mentioned by the committee's staff, involved a neonatal administration of an Endo drug, Naloxone, which counteracts respiratory depression induced by narcotic analgesics.

It had been previously approved for use in adults.

Unlike other antagonists, Naloxone counteracts the effect of narcotics without itself having any narcotic action. It is essentially free of side effects. Naloxone has provided the medical community with a drug useful in life-threatening situations in the emergency room, and also in the management of postoperative patients.

The protocol in this neonate study was developed by a reputable investigator in collaboration with our company and was approved by the institutional review committee at a respected teaching hospital associated with a major university medical school.

Since this was one in a series of tests conducted to support the extension of the use of this drug for younger age groups, a supplement to our investigational new drug application was prepared and submitted to the FDA prior to the commencement of the study; however, I am embarrassed to say, through inadvertence on our part, the protocol for this particular study was not forwarded to the FDA until after the study had been started.

The FDA has raised no objection to our protocol prior to this meeting or to the results obtained. This product has been approved and is now widely used in all age groups, with lifesaving benefits.

Senator KENNEDY. I don't want to leave the record just there.

They indicated that they were not aware that these other steps were going to be taken, the insertion of the balloon, the administration of oxygen and repeated dosages of Demerol.

Dr. JACOBSEN. If you want, I will address myself to that.

Senator KENNEDY. If you prefer to continue all the way through, you may. In terms of representing the position of the Food and Drug Administration, it is important.

Dr. JACOBSEN. My conclusion is "I will be willing to answer any questions you may have."

Senator KENNEDY. Fine.

Dr. JACOBSEN. As far as Demerol is concerned, this is a widely used drug for the relief of pain which occurs during labor. It crosses the placenta and may cause depression in the newborn.

As far as the dosing used in this study, if I can explain a little more of the detail, perhaps there might be a better understanding as to how the dosage was determined.

The subjects of this study were interviewed prior to the administration of any Demerol. Upon delivery of the child, if this patient had received a certain amount of Demerol within the dose range stipulated in the protocol, then this infant would be continued in the study. The important point here is that it is incorrect—the statement that Dr. Hensley made. This protocol did not dictate the amount of Demerol that the mother received.

The mother received Demerol according to her needs. The drug Demerol was not administered to in any way impair the respiration of these children.

In fact, the purpose of the techniques used here is to detect subclinical depression in infants. The type of test used here, the CO_2 response test, is the most accurate index of any drug depression of the central nervous system and its effect on the respiratory system.

It is a standard test that has been used in adults and studied in adults prior to this study.

The protocol stated that the mothers and infants to be included would not have any complications during this pregnancy; that these would be normal children—that excludes all premature infants—that none of these children would require any major resuscitation. I think as Dr. Hensley pointed out, the Apgar scores were used here. They are a very crude measurement, although it is a widely used assessment of the child's condition.

In 5 minutes, these children were in the range of 7 to 10, as I recall. You will find differences of opinion in various texts as to what the significance of these scores are; but there are references which will indicate within the range of 7 to 10 that the child is in excellent health and those in the range of 2 and below have serious disorders.

The other point that was mentioned was the use of the esophageal balloon. The term itself conjures up all sorts of visions of what this is like. This is a soft plastic tube similar to the tubes used for the feeding of infants. At the end is a small latex bag, smaller than the tip of my finger. This type of procedure is frequently used in infants who have any type of respiratory distress syndrome. The purpose is to measure the lung compliance since any abnormalities in lung compliance might affect the child's respiration. The tube is readily passed by the mouth. It is frequently left in infants for a week. It presents no discomfort to the child. The child may sleep with the tube in place.

Another mention is made of the use of oxygen.

To my knowledge, there have been no reports which have associated the use of this amount of oxygen for this period of time as causing retrolental fibroplasia. We are well aware of the connection of oxygen with the retrolental fibroplasia. It is true that both the esophageal balloon and the oxygen were not included in the protocol. The investigator characterized it as an omission and we considered it a significant omission. Nor was it included in the informed consent.

The investigator's position is, the conclusion in his mind, as well as the Institutional Review Committee, that this procedure did not cause any risk to the infant and, therefore, these procedures were not included in the informed consent.

With respect to the purpose of the placebo—Dr. Hensley has said that half of a group of physicians might react to this as a horrible procedure, and the other half, I don't know.

This paper was presented at several meetings. In checking with the investigator, there have been no critical comments of that sort made to him.

The importance of the placebo here is: Without a placebo any effects which may result following the administration of Naloxone may be attributed to the spontaneous elimination of the drug Demerol which produces this depression or due to the injection itself—that is, just injecting a child may in itself stimulate respiration.

We have received no comment on this protocol until about July 28, 1977, as I recall, when we received a letter from Dr. Lisook of the Food and Drug Administration indicating that several questions

were raised regarding the study and would we provide certain materials which we agreed to provide.

We also asked Dr. Lisook if he would forward to us any questions that were raised. We did not hear anything from Dr. Lisook or the Food and Drug Administration on the study.

Those are the comments I have with respect to Investigator No. 1.

If you have any questions, I can answer those now or go on to Investigator No. 9.

Senator KENNEDY. No; let us deal with this current situation.

I have to admire you, Dr. Jacobsen, for attempting to make a very good defense for a very poor case.

You know the facts as they have been represented here—first of all, your central responsibility in this whole program, I think it is comfortable or convenient to point out that it is an investigator's responsibility, but you have very important responsibilities which you glide right through.

One is the early startup of the study prior to the approval of the program.

Two, I don't see how you can justify this meeting your responsibility of informed consent in view of the fact that the woman is in labor when she has to make this judgment. It just defies me to feel that that is the real meaning of what the purpose of informed consent is; that an expectant mother can make an important judgment in terms of the well-being of that infant at that time.

Then to suggest that this drug has any other purpose, as far as you are concerned, than depressing the respiratory function—that is the purpose of the drug; that is what you are doing, to deal with it. That is why it is in the interest of your particular study and review that the drug be administered. It has a depressing factor in terms of the respiratory function and in terms of the infant and offering the expectant mother the use of a Narcan or placebo that is utterly useless.

Can you conceive of any mother in that circumstance who would opt for the situation where you depress the breathing of an expectant child and then go for a placebo, which is virtually meaningless in terms of addressing the physical problems of a child? It is absolutely inconceivable to me that that happened to be the case, let alone the other questions of the implantation of the balloon in the child's stomach with the additional oxygen that may be given the child that has a completely different medical kind of effect. The testimony that was left out you say it is the investigator's judgment on it that you reached a different conclusion.

You are the company. You have the responsibility to make the judgment. You have the responsibility to oversee that investigator and that just was not done.

We have to draw whatever conclusions we want in terms of your monitoring system.

Are you not troubled by all this, quite frankly?

Dr. JACOBSEN. We are troubled by the deletion of certain steps in the preparation of this protocol and that they were not included in the informed consent.

Senator KENNEDY. Here and now, are you not troubled here and now by the fact that this informed consent was given while the mother was in labor?

Dr. JACOBSEN. The informed consent was obtained in discussions with the investigator at the same time they obtained other consents in the hospital.

Senator KENNEDY. What does that say to you? Is that not worse?

Dr. JACOBSEN. These mothers are usually not admitted to the hospital unless they are in labor.

Senator KENNEDY. Why can you not do it in terms of the mothers that are expecting to delivery over any period of time? Any hospital has that.

Dr. JACOBSEN. Part of that——

Senator KENNEDY. It is somewhat more inconvenient? More expensive? What?

Dr. JACOBSEN. Based upon the selection of the patient. The patient has to meet certain criteria and that would not be known until the patient has reached the stage of labor.

Senator KENNEDY. You mean otherwise you could not have tested this drug?

Or why would you not just go for a broad representation? Why not throw out the net in a much broader and wider way and eliminate the ones you do not need?

Dr. JACOBSEN. One could have done it that way.

Senator KENNEDY. In retrospect, what do you think?

Dr. JACOBSEN. I am not sure, with this institution, with that investigator, or whether that would be proper.

Senator KENNEDY. You are the company, too. Are you turning it all over to this Mr. Investigator? You must have some responsibility on this; do you not think that?

Dr. JACOBSEN. Yes. We certainly do. But in this particular case, we have been informed that at the time these consents were provided to the patient, that the patient was not under any particular distress, Labor, as you know, is a series of intermittent periods of discomfort, but there are periods in between.

Senator KENNEDY. But you don't know whether they were given during that period or not?

Dr. JACOBSEN. I do not.

Senator KENNEDY. How do you know whether it was given then or not?

Dr. JACOBSEN. I was told by the investigator I mentioned that at that time they were not under the effects of particular drugs, or under duress.

Senator KENNEDY. You will accept just that investigator's statement on that?

Dr. JACOBSEN. Right.

Senator KENNEDY. At a time when you are talking about virtually the most vulnerable group in the society, the expectant mother and the infant?

Dr. JACOBSEN. I recognize the sensitivity of this area for any clinical testing. Part of that must be balanced by test and whether this

is, in fact, the best way to evaluate that drug. When drugs are indicated for children of that age group, the Food and Drug Administration requires that they be studied in that age group and that as objective a method as possible be employed.

Senator KENNEDY. That is right, but there is no suggestion that the Food and Drug Administration believes that that is an appropriate time for an informed consent in this type of a situation, is there?

Dr. JACOBSEN. The Food and Drug Administration has not discussed this matter with us. I am just aware of the comments made today.

Senator KENNEDY. All right.

Let us go with the other investigator.

Dr. JACOBSEN. The other investigator, number 9; as I have indicated, we were contacted by another pharmaceutical company who was aware we had conducted a study with this investigator on a similar protocol and they noticed that there was some discrepancy in his lab data and they asked for cooperation; and we did meet with them and we did review this material with them.

Senator KENNEDY. The only thing in the question of the data supplied—you must be troubled by the data itself now, are you not? The fact of patient 18 and patient 19; patient 19 did not receive the Endo drug. That was true on patient 19 as well?

Dr. JACOBSEN. I note here that this refers to the patient's charts and dates in the hospital. These are basically outpatients.

Senator KENNEDY. Does that make any difference?

Dr. JACOBSEN. I don't know whether this is only part of the record.

Senator KENNEDY. If they didn't receive the drug, is it important whether they were in or out?

Dr. JACOBSEN. They took the drug.

Senator KENNEDY. I see. They took it outside?

Dr. JACOBSEN. Yes.

Senator KENNEDY. But you would want to flag that if they said they didn't when they were in and you want to be sure they did when they were out?

Dr. JACOBSEN. Right.

Senator KENNEDY. Thank you.

Dr. Poos?

Dr. Poos. Mr. Chairman, I will dispense with any attempt to read this. I will focus my attention on Investigator No. 10 and the involvement of this investigator with one of our experimental drugs.

I would like to state briefly that this experimental drug is a muscle relaxant and we first introduced it in the clinical trial in July, 1974.

A number of clinical investigators have studied McN-3113 in phase I and phase II clinical trials. An investigational new drug exemption, IND, supplement was filed on May 21, 1975, with Investigator No. 10 as the investigator in an open-label dose ranging study.

The object of the study was to determine what the most effective dose of the drug might be.

We were looking at, without getting technical about it, what I would call low back pain that people suffer from after too strenuous a weekend.

This investigator was visited in his office by one of our physician monitors prior to the beginning of the study to discuss the protocol and conduct of the study.

A letter from the physician monitor to the investigator on May 16, 1975, confirmed the discussion about clinical supplies and the requirement for signed patient consent.

Clinical supplies were shipped May 22, 1975, and an updated IND brochure for McN–3113 was sent June 4, 1975.

On August 5, 1975, at the completion of the investigation as called for in the protocol, a clinical research associate, CRA, visited the investigator and picked up 45 completed case report forms, each signed by the investigator.

It was noted that a therapeutic response to the three dose levels was seen and that nine patients had complained of mild side effects.

A letter from our CRA to the investigator on August 7 confirmed that copies of the case report forms were being returned and enclosed a drug return form with instructions for its use as is our usual practice. The unused drug was returned August 11, 1975.

Approximately nine side effects out of 45 patients were shown.

This study was one of many.

About a year later, approximately in the early fall of 1976, as I recall, it was about September, we had assembled the data from a variety of investigations and came to the conclusion that our experimental drug did not have the degree of efficacy that we had hoped for, so our conclusion was that under the test conditions that we had used, the drug was not sufficiently efficacious that we should proceed and we decided to pull back to the laboratory and find out what the problem might be.

It was after that, and the earliest date that I can recall was early October, 1976, that it came to our attention through another company, and this was the company that Dr. Goddard is associated with and it was referred to by Dr. Hensley in his testimony, that they felt they had a problem with investigator 10 and that they had reported this problem to the Food and Drug Administration.

Obviously at that particular point in time, since we felt we had no problem of note with this investigator, we went back and began to assess the study that he had done for us. We did note, in looking very carefully at the study, that the laboratory values perhaps did not have as great a spread as one might expect, although I would not call this unusual. They were not all the same, but they were extremely close.

More often, one finds a greater spread in laboratory values.

However, at this point in time, we had stopped our studies.

We knew the company that Dr. Goddard was associated with had expressed a concern to the Food and Drug Administration, so having closed out our work, we did not take any positive action in reporting this to the Food and Drug Administration. So, very briefly, that would sum up my comments.

I would be pleased to answer any questions that you might have, Mr. Chairman.

Senator KENNEDY. The way that it has been presented here, Dr. 10 was brought to the Food and Drug Administration's attention

by the former Commissioner Goddard, and this is what prompted the Food and Drug Administration to review the reports the investigator found that we heard here, found the possible inconsistency in the data.

I am sure you have gone over it in some detail.

Then apparently, according to Dr. Hensley, the investigator himself agreed that it was pointed out by the Food and Drug Administration in the study that had been submitted by McNeil in a progress report in support of your IND without qualification and that there had been no corrective action.

Evidently, the investigator himself had, in responding to a conversation to Hensley, indicated that he thought there was an overwhelming consistency as did the McNeil person, Dr. Goodard——

Dr. Poos. I beg your pardon?

Senator KENNEDY. I guess it was another person, Dr. Seay. Yet none of that was brought out to the Food and Drug Administration in the IND report?

Dr. Poos. Well, officially, the data had been submitted. I think what we are dealing with here is a subjective evaluation of what constitutes perhaps a not unreasonable, unusual or unexpected or surprising degree of consistency in a series of laboratory data.

Of course, it would take a very large number of laboratory data and a statistical analysis, which we have not done and I am not sure anyone else has, to determine what category this came in or how to define it.

As I pointed out, we felt that in retrospect, in going back after learning about the report by Goddard's company to the Food and Drug Administration and going back and looking—yes, we agree that the data was maybe a bit unusual in its degree of consistency; but all the numbers were not the same. There are variations.

Senator KENNEDY. Many of them are substantially the same. It is difficult to tell. You would say in the first 12 case studies; for example, in the hemaglobin, 12 of them—of the first 12, if 10 are exactly identical, I do not know whether 10 out of 12 identical ones is an extraordinarily high reflection of consistency or whatever it is; but the fact remains when this was brought up, even though it was recognized by one of your own people, Dr. Seay of McNeil, in terms of the remarkable consistency, you did not feel there was any kind of responsibility to communicate that to the Food and Drug Administration?

Dr. Poos. No. 1, at that time, they already knew it.

No. 2, the main reason was that our program had terminated. We did not feel the responsibility to record that perhaps the variations in the clinical laboratory values were not as great as one might expect under normal conditions. This depends upon the laboratory and the number of patients. Obviously there are a number of factors involved in it.

Senator KENNEDY. For the record, our subcommittee is considering some very extensive drug legislation to deal with a variety of different problems that we have seen over a period of time and we also have the issue of the human experimentation that is before the Congress. We passed that in the Senate, extending it to other agencies, to the

Department of Defense, as well as the CIA and it is before the House Committee; but it seems to me as clear as the nose on my face that there is an essential responsibility for the continuing responsibility for establishing the protection of human subjects, and that this issue which was so dramatized to all the American people with the syphilitic studies and the Ralph girls and the experimentations of the CIA and the DOD; it is a continuing issue of great urgency and importance, and one which requires the kind of overview and the protection that the panel can provide.

We welcome the opportunity to work closely with all the agencies so that, hopefully, they will follow the example of HEW in establishing a similar panel.

This has been an issue of great interest to our committee, to Senator Schweiker, to Senator Javits, who called me before the hearings and said that he was enormously interested in the course of today's hearings. He has been a strong supporter on that particular issue.

The second question, of course, is the information that is being made available to the Food and Drug Administration. We mentioned earlier in the course of the hearing that we cannot expect the Food and Drug Administration to do its job if the information it is going to get is faulty and inaccurate; if it is misleading or misrepresents the facts or is scientifically faulty. We just cannot expect them to make the judgment to protect the health of the American people that is essential.

We have seen in the past, over the period of these past few years, where information on drug testing in too many instances was false and inaccurate on animals. That was a matter of great concern to us.

The establishment of the review mechanism within the Food and Drug Administration to review human experimentation in the early and preliminary sense, they again are showing some extraordinarily and disturbing trends.

As I mentioned earlier, we cannot tell the extent of it at this hearing, but we are distressed by what we have found out in the course of this hearing and we are completely committed to insisting that the information that is going to be provided and reviewed by the scientists is going to be accurate and to conform to the scientific evidence, and that those who are going to be making judgments on this are going to be scientifically competent to give the American people the kind of protection that they are entitled to.

We want to work closely with the Food and Drug Administration and the private sector. We believe it is in their interest as well as in the interest of the American public to see that that is achieved and accomplished and the next few days, few months, few years, are going to be critical in terms of this issue.

We are going to need the help and support of all who have a responsibility in this area.

So, gentlemen, we appreciate your presence here this morning. I thank the Food and Drug Administration and Dr. Hensley.

[The prepared statements of Commissioner Kennedy, Dr. Cooke, Dr. Jacobsen, Dr. Burns, Dr. Poos, and other material supplied for the record follows:]

STATEMENT

BY

DONALD KENNEDY

COMMISSIONER

FOOD AND DRUG ADMINISTRATION

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

BEFORE THE

SUBCOMMITTEE ON HEALTH AND SCIENTIFIC RESEARCH

COMMITTEE ON HUMAN RESOURCES

UNITED STATES SENATE

March 7, 1978

Mr. Chairman and Members of the Subcommittee:

We are pleased to have this opportunity to discuss the Food and Drug Administration's (FDA) Bio-Research Monitoring Programs.

In 1975, FDA appeared before this Subcommittee and described its experience with clinical investigators and with the regulation of clinical research on drugs. At that time, we pointed out some of the serious problems we had found in this area, and the lack of adequate resources for monitoring research on human subjects. More recently, your Subcommittee investigated the quality of research being conducted by laboratories engaged in preclinical animal studies, with the useful outcome that enough new money was made available to allow a broad expansion of our efforts to monitor all aspects of biomedical research--from animal toxicity studies through human clinical trials. I will submit within two weeks a detailed response to the recent letter in which you ask for a report on our regulatory activity involving preclinical laboratories.

Today, you have requested that I discuss the current programs designed to assure the quality and scientific validity of drug research involving human subjects. As you well know, just as the quality of preclinical testing in animals is essential for defining the toxicological potential of new drugs before testing in humans, so the quality of the clinical phases of drug testing is essential to an accurate appraisal of a drug's safety

and effectiveness before marketing. The informed consent of participants in these clinical studies is essential; it is intended to assure that the subject is fully aware of the purposes of his or her participation in the study, and the prospects of benefit and injury from the drug.

BIORESEARCH MONITORING PROGRAM

Before 1976, most FDA activity in bioresearch monitoring was aimed at clinical research on drugs. Although attention was given to sponsors, their monitors, and Institution Review Boards, the main emphasis was on the clinical investigator, the quality and integrity of his work, and the care taken by investigators to assure that their clinical subjects gave informed consent to their participation. Although we had cause to believe that some investigators had submitted false data, were not following the protocols or study plans, or had failed to inform the subject participants, no formal regulatory program existed. The FDA staff working in this area was quite small, but in the period from 1962 through 1976, it performed roughly 100 intensive audits of clinical investigators. These audits ultimately resulted in the disqualification of 24 physicians, who thereby became ineligible to receive investigational-use drugs.

As an outgrowth of these audits and of a 1972-74 special survey on clinical research, and because of increased attention to problems of

research ethics, a comprehensive program for the Agency was designed, and an Agency coordinator was established to oversee each Bureau's implementation of individual programs for monitoring biomedical research. We developed and issued to the field offices a series of compliance programs for evaluating the performance of clinical investigators, sponsors, monitors and Institutional Review Boards to determine whether they are living up to their responsibilities. These programs are of two basic types:

-- "Surveillance" inspections, intended to measure procedural compliance with applicable regulations.

-- "Directed" inspections, which include data audits of studies submitted to IND's and NDA's, and "for cause" investigations of suspected problem situations.

Whereas surveillance inspections are preventative, directed inspections are remedial in nature, and consequently more thorough. I would like to briefly describe these programs and some of the findings that have resulted from them.

Investigator/Sponsor Programs

The first we refer to as the "Data Audit Program." Headquarters provides to the field districts copies of protocols under which individual clinical investigators conduct their studies, or copies of case reports submitted by these clinical investigators to the drug sponsor. Our investigator

then visits the clinical investigator to obtain information on the conduct of the study and performs an onsite audit of the clinician's data to check its reliability. Clinical investigators are not selected randomly for visits; they are chosen because it has been determined that their work was important in the consideration of drugs for IND's (Notice of Claimed Investigational Exemption for New Drugs) or NDA's (New Drug Applications).

Under this program 77 assignments had been issued to the field and 34 inspections had been completed as of January 31, 1978. Of these, 20 have now been reviewed by headquarters: 6 are under review. Twenty-five "informational" letters have issued to the clinical investigators where no major problems were found. Three inspections, 10 percent of the total completed and reviewed, have resulted in intensive "for cause" investigations. One of these have resulted in a proposal to disqualify the clinical investigator. It is clear that this program may be our most promising source of "for cause" inspections in the future.

In a second compliance program our investigators are supplied the names of particular drugs under clinical study or in submitted new drug applications. The field investigator then visits the sponsor, generally a drug company, and reviews the sponsor's monitoring procedures. As part of the inspection, the FDA investigator selects two clinical investigators who have studied the drug in question, and conducts further inspections to determine just how well they were being monitored by the sponsoring drug firm. One-hundred and thirty-eight assignments had been issued to the field as of January 31, 1978, and 37 inspections were completed (but not yet received by the Bureaus).

Institutional Review Boards

Before discussing some of the findings of our "for cause" investigations, I would like to describe briefly our pilot compliance program for Institutional Review Boards (IRB). An IRB is established for each institution in which clinical investigations are conducted and is composed of members of various professions in the community. The IRB is charged with reviewing the ethics and risk/benefit decisions made on clinical studies involving subjects at the institution. Regulations promulgated in 1971 require that clinical investigations of new drugs on institutionalized human subjects be initially approved, and subjected to continuing review, by the IRB.

In each assignment to inspect an IRB, a particular drug study is used as a reference in examining the activities of the particular Board. Under the inspection program, our field investigators interview the chairperson of the IRB or other responsible individuals at the institution, as well as other staff. The FDA investigator's report, along with copies of any of the Board's records obtained during the inspection, are forwarded to headquarters for evaluation. The results of the headquarters evaluation are communicated back to the chairperson of the IRB or the administrator of the institution through either of two types of letters: information letters offering suggestions for improvement, or remedial letters requesting positive assurance that specific, serious deficiencies noted during the inspection will be

corrected. Approximately 25 percent of the letters issued to IRB's to date have been of the latter remedial category. Although our legal authority to move directly against an IRB is limited, we do have the authority to refuse to permit or to continue to permit clinical studies involving subjects in a particular institution and to refuse to accept completed studies if the studies are not properly reviewed, approved and supervised by the IRB. We intend to propose regulations that will provide for an additional sanction--the disqualification of an IRB.

As of January 31, 1978, we have issued assignments to the field for 329 IRB inspections. One hundred and ninety-eight inspections have been completed and one hundred and forty-two have been reviewed. We have found that approximately 25 percent failed to meet our requirements for the conduct of clinical investigations and resulted in the issuance of letters mentioned above.

All three of these programs have an important effect in educating the clinical investigator and sponsor/monitor communities, making them more aware of their responsibilities and signalling our concern for the quality of clinical research data and the rights of human subjects.

"FOR CAUSE" Inspections

The programs I have just discussed sometimes uncover situations leading to what we term "for cause" inspections of clinical investigators. These are generally carried out when there is reason to believe that the work of a clinical investigator is faulty or unreliable.

"For cause" investigations occur as a followup to procedural or data audit inspections where problems or noncompliance have been found, from findings by Bureau reviewers of misleading or suspicious materials in reports of clinical studies, from complaints by drug sponsors of shoddy work or problems in clinical investigations, from inspections of Institutional Review Boards, from review of scientific literature, and from consumer complaints.

We are in the process of conducting 26 "for cause" inspections. Although we have not completed our evaluations of all inspections to date, I would like to share some of our findings. Depending upon your perspective, they could be described as "unusual," "horrible," or "inconceivable." Certainly few of the findings can be put down as expected.

We have found:

-- Case reports on ficticious subjects, and on subjects who were never administered the investigational drug. Obviously, dependence on such spurious data might result in expanded testing of a drug or in the possible approval of a drug for use in a condition where it was, in fact, ineffective.

-- Case reports containing the results of clinical laboratory work which was not actually performed. The purpose of such laboratory work is to assess the safety of the drug in human subjects--for example, if a drug is toxic to the liver, and tests of liver function are not performed, then the drug might not be withdrawn in time to prevent permanent liver damage or death.

-- False representation of Institutional Review Board approval of a study. A layer of subject protection is removed if uninformative consent forms were used, or if a study of the type done should not have been done in the institution in question.

-- Misrepresentation of patient diagnosis and demographic data. If a patient does not have the disease to be treated with the investigational drug, then any report of efficacy of that drug is obviously spurious.

-- Consent of the clinical subject not obtained. Consent means informed consent. Lacking necessary information, the subject might enter a study which he would not have entered if he had been informed of the dangers as well as the possible benefits.

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-- Drug doses given, far exceed protocol limitations. This could be dangerous, since protocols often specify doses at the upper limit of what has been judged to be safe.

-- Drugs given to inappropriate subjects. This could be dangerous if drugs aimed at the generally healthy adult population are given to children or the aged where their metabolism might be different. Of particular importance is the administration of drugs to pregnant women where fetal abnormalities might be caused.

-- Serial use of investigational drugs to the exclusion of accepted therapy. This makes the subject nothing but a guinea pig, and his best interest might not be served.

-- Administration to subjects of two or more investigational drugs at the same time and the administration of other significant and perhaps interfering drugs with the investigational drug. Here the information obtained is valueless, and the subject has been put at needless risk.

-- Inadequate medical attention to the test population through excessive delegation of authority, lack of followup, etc. Obviously, this is dangerous to the subject.

-- Representation of investigational drugs as marketed products and/or the sale of such drugs. In this situation the subject cannot have been informed of the nature of the drug and is sometimes inappropriately charged for it. The investigator may profit hugely by his "exclusive franchise" established by his being an investigator of a product not available to all physicians.

I do not want to leave this Subcommittee with the impression that the whole world of clinical research is bad. We have not spent any time here today discussing the excellent quality of research and the integrity of most investigators that we generally find. The great mass of research being conducted is high quality and valid, and the subject participants in most cases are carefully protected. However, the findings above do illustrate the need for continued vigilance and additional educational endeavors.

NEW REGULATIONS

Proposed regulations clarifying our authority over IRB's and defining their functions and responsibilities will be published in the near future. In addition, revised regulations on informed consent are being developed. On September 27, 1977, proposed regulations were published in the Federal Register to establish regulations on the obligations of sponsors and monitors. These proposed regulations outline the procedures for sponsors and monitors of any type of clinical research study submitted to the FDA in support

of any of 22 various applications. In addition to finalizing these regulations as soon as possible, we plan soon to publish proposals on new clinical investigator regulations, which will clarify and expand upon existing regulations governing the conduct of clinical investigations by clinical investigators.

Last Tuesday, February 28, we published in the Federal Register an announcement of the availability of a series of guidelines for clinical evaluation of drugs in various pharmacological categories. This is a major milestone in the conduct of drug research, for it presents for the first time in an official document, acceptable current approaches to the study of investigational drugs in man. The first category in this series is on General Considerations for the Clinical Evaluation of Drugs and discusses all the necessary requisites to proper clinical study, including those areas that are the subject of today's hearing.

CONCLUSION

To summarize, let me say that in great part due to the Subcommittee's continuing intense interest in our bio-research monitoring activities we have been able to establish a comprehensive program which will permit us to more closely monitor the manner in which clinical investigations are conducted and reported. We strongly believe this effort will result in better protection of the rights and safety of human subjects participating in clinical trials and a significant improvement in the quality of the study reports submitted to us.

If you have many questions we shall be pleased to answer them.

ORAL TESTIMONY

I am Irwin J. Pachter Ph.D., Vice-President for Research and Development for Bristol Laboratories. I have asked Stanley T. Crooke M.D., Ph.D., Associate Director of Research and Development to review our current clinical research practices and our continuing efforts to improve the quality of our clinical research. Additionally, because other medical monitors directly responsible for the studies under review are no longer employed by our company, I have also asked Dr. Crooke to prepare an independent appraisal of these studies.

Dr. Crooke joined Bristol Laboratories in 1975 to direct our cancer research effort, and he is a physician and a scientist for whom I have the highest regard. Let me emphasize that Dr. Crooke was not associated with the studies in question in any way. It will be appreciated that Dr. Crooke had limited time to gather, digest and evaluate the available information, but I trust his assessment is essentially complete.

In addition to Dr. Crooke's comments, I would be pleased to comment on the proposed legislation if time permits.

I am Stanley T. Crooke M.D., Ph.D. I am an Associate Director of Research and Development, and prepared the written response previously submitted to the Committee. I will read a summary of the information provided to the Committee in the written response.

Introduction

As a sponsor of clinical trials, Bristol Laboratories assumes several responsibilities. Paramount is that adequate safeguards be established to maximize the safety of the experimental subjects. Although rarely stated, a benefit to risk determination must be made for each subject enrolled in each study, and only the most fastidious care can ensure that each subject has the most positive benefit to risk ratio. Certainly, adequate and accurate data in experimental animals are requisite, and it is essential that clinical development of compounds proceed in a logical order with each study building on data generated in previous studies. To do this effectively, we believe an overall research plan (which we call a clinical operational plan) is essential, as well as well-designed protocols, and adequate clinical investigators.

A second responsiblity is to protect the rights of subjects employed in clinical trials. This can only be accomplished by providing accurate unbiased information to each subject. Clearly, the difficulties encountered in providing meaningful informed consent are substantial, and have been the subject of much discussion. Suffice it to say that we believe it is the sponsor's obligation to provide guidelines for informed consent for each study, and to attempt to assure compliance by adequate monitoring.

A responsibility which is more difficult to define, but certainly of significance is the responsibility to perform clinical experiments generated by rational scientific goals, with meaningful objectives. To perform studies which may have an impact on the scientific development of a particular drug or class of drugs, with a carefully constructed protocol, and excellent investigators with an interest in the science as well as the medicine involved in the studies, assures the subject that he/she is participating in an effort which will generate the most useful information per subject.

To attempt to improve the quality of our clinical trials, and to assure ourselves that each of the clinical trials sponsored by Bristol Laboratories meets the minimum standards necessary to maintain our responsibilities, we at Bristol Laboratories adopted guidelines for good clinical research practice on September 14, 1976. These guidelines were adopted well in advance of publication of the proposed guidelines of the FDA, but with a few minor exceptions exceeded the requirements later proposed by the FDA. The Bristol Laboratories guidelines have been amended during the months since their adoption, and are currently undergoing extensive revision to reflect our reorganization, an effort to strengthen certain aspects such as informed consent, and to improve documentation procedures in compliance with the proposed FDA guidelines. However, we have incorporated relevant portions of those guidelines in our written response to provide to the committee an overview of our practices. We shall be pleased to provide the revised guidelines when the revision is complete.

Current Practices

The guidelines for good clinical research practices in our written response provide detailed information concerning our current practices in clinical research. Perhaps I can best utilize the time by briefly describing the course of a study from inception to completion. I will, of course, be pleased to amplify any point about which a question may exist.

Prior to initiation of any clinical trials on a new compound, a clinical operational plan in which the goals of the clinical research program, the planned studies, timetables and budgets are discussed. Subsequent to approval of the clinical operational plan, a protocol is generated by the medical monitor for the compound. This protocol must conform to the minimum standards established in the guidelines, and may be discussed with potential investigators. It is then submitted to the protocol review committee for review.

I chair the protocol review committee and on it serve the senior members of our clinical staff, the director of toxicology, the director of drug metabolism, and the director of bio-statistics. Since its formation in September, 1975, it has reviewed each protocol, rejected many, and required revisions of most protocols. In short, it is a functional peer review committee.

Only after approval by the protocol review committee, and receipt of all prestudy documentation, including a copy of the informed consent form, institutional human research committee's approval, and a list of members and their titles of the institutional review committee, can studies be initiated.

Selection of an investigator is a complex process involving site visits by our monitor, and other appropriate individuals, evaluation of the potential investigator's credentials, and an evaluation of institution in which the investigator works.

At the initiation of a study, the investigator is site visited frequently, case reports are evaluated as submitted, with particular scrutiny directed toward diverse effects. Unexpected or unusually severe toxicities are reported immediately.

Evaluation of the study involves an evaluation by the monitor, by the statistical department, and input from the investigator. A final report is generated, and this is submitted to the protocol review committee for approval. The approved final report is then submitted to the FDA.

Information on studies perfomed by

Dr. #2, Dr. #3, and Dr. #7

Bristol Laboratories has been informed that the Subcommittee on Health and Scientific Research of the Committee on Human Resources of the United States Senate is interested specifically in the conduct, and monitoring of clinical studies 8 and 15 performed under IND 10,127 (BL-3912A), and studies 58A and 59A performed under IND 9,870 (Butorphanol-Oral). The principal investigators for these studies were Dr. #2 (IND 10,127 studies 8 and 15), Dr. #3 (IND 9,870 study 58A), and Dr. #7 (IND 9,870 study 59A). This statement has been prepared to provide information concerning these studies.

BL-3912A

Background

BL-3912A is a substituted phenylisopropylamine similar structurally to a group of psychoactive agents including amphetamine, and 2,5 dimethoxy 4-methylamphetamine (R-DOM). BL-3912A differs from R-DOM chemically by being an ethyl rather than a methyl derivative.

Studies employing several species of laboratory animals suggested that BL-3912A might be a potent performance restorer absent the generalized CNS stimulatory, and hallucinogenic properties of several of the other agents of this class. In fact, BL-3912A was found to antagonize R-DOM-induced abnormal behavior in cats, and enhance operant and learned behavior tasks. In experiments with aged rats, BL-3912A was demonstrated to facilitate learning and prolong memory. These effects were tentatively ascribed to the 5-hydroxytryptamine (serotonin) receptor agonist activity of BL-3912A, and were produced at doses significantly lower than toxic doses.

Thus, based on experimental animal data, experience with compounds of similar structures, and data concerning its mechanism of action, BL-3912A was a promising candidate for clinical trials. Initial clinical trials included phase I studies in two groups of normal volunteers. In the first study doses of 1 mg to 80 mg were employed without significant side effects. In the second phase I study, doses of 20 to 120 mg were tested. Many of the volunteers who received 40 mg to 120 mg noted increased mental alertness and demonstrated improvement in a performance test. At a dose of 120 mg, definite euphoria and mild CNS stimulation were observed, but no other toxicities were noted. Studies employing 60 healthy volunteers were performed with BL-3912A before trials in patients were begun.

Study number 8 for which Dr. #2 was principal investigator was the first study in which BL-3912A was administered to geriatric patients, suffering from senile mental deterioration. It was a double blind placebo comparative study. The initial doses employed were 25 mg and 50 mg daily for five days. If no side effects were observed, the doses were increased to 25 mg or 50 mg twice daily for seven days, then three times daily for the duration of the study. The results of this study suggested that doses of 50 mg - 150 mg daily resulted in statistically significant improvement in mental performance in geriatric patients with no significant toxicities.

Study number 15 was also performed by Dr. #2. This study was an open dose ranging safety and efficacy study in which patients were treated with doses of 25 mg to 75 mg daily for a period of 60 days. The conclusions from this study were that BL-3912A resulted in improvement in mental acuity with no significant toxicities.

Subsequent to the studies performed by Dr. #2, several other studies were performed. In these studies BL-3912A was shown to be non-amphetamine like, but the positive results in geriatric patients reported in studies 8 and 15 were not reproduced.

As a result of the inability to reproduce the positive results obtained initially, further clinical studies were discontinued.

General Considerations Relevant to Studies 8 and 15

The primary research interests of Bristol Laboratories are antibiotic, anticancer and analgesic drug development. BL-3912A resulted from a collaborative research effort with an extramural scientist. Consequently, the intramural clinical expertise in the area of CNS performance enhancers was not optimal at the initiation of clinical studies on BL-3912A. In fact, since very few drugs for senile mental deterioration have been developed, clinical drug testing expertise is probably substantially less for such compounds than compounds of different classes throughout the academic and pharmaceutical company research establishments. Consequently, the performance of the initial efficacy trials was perhaps suboptimal.

Selection of Dr. #2 as Principal Investigator

At the initiation of studies 8 and 15, Dr. #2's credentials seemed ideal. After completion of medical school and postgraduate training in surgery, Dr. #2 engaged in the private practice of medicine until joining a major pharmaceutical firm as a monitor for the clinical trials of a psychoactive agent thought to be active in the treatment of childhood hyperkinesis. He subsequently was promoted to Associate Medical Director, then became Director of Clinical Research Projects at another pharmaceutical company. During this period Dr. #2 generated several publications.

Thus, Dr. #2 had considerable experience in the clinical evaluation of drugs, and more particularly had been involved in research on a psychoactive agent. Moreover, at the initiation of studies 8 and 15, he was associated with a geriatric center, and consequently had access to the appropriate patient population. Having worked himself as a medical monitor, he was well aware of the regulatory obligations of a clinical investigator.

Monitoring of Studies 8 and 15

The initial studies on BL-3912A were developed and monitored by a physician employed for the purpose of monitoring this drug. Prior to joining Bristol Laboratories, the medical monitor had performed a number of controlled clinical studies and had published in the medical literature on the effects of drugs in geriatric and younger patients with anxiety neuroses, depressive neuroses and psychophysiologic disorders. Studies with Dr. #2 were the first involving patients that he was asked to monitor for Bristol Laboratories. Prior to initiation of studies with Dr. #2, Dr. #2 and the facilities were site visited by the monitor, and subsequently by the Vice President and Medical Director for Bristol Laboratories.

Study number 8 was initiated on December 11, 1974 and terminated on April 7, 1975. Study number 15 was initiated on January 30, 1975 and terminated on April 7, 1975. During this period the medical monitor made two monitoring visits on January 6-7, 1975, and February 17-25, 1975. Numerous telephone conversations are alluded to in the correspondence between the monitor and Dr. #2 during this period.

On April 30, 1975, the monitor's employment at Bristol Laboratories was terminated. On May 5, 1975 a replacement medical monitor joined the medical staff at Bristol Laboratories for BL-3912A. Strenuous efforts by the new monitor and his associates to obtain case reports failed for many months, and when case reports were obtained they were incomplete. Investigation by Bristol Laboratories and the FDA suggested that Dr. #2 had failed to meet the obligations of informed consent, and failed to follow the protocol in many patients.

Informed Consent and Human Research Committee Approval

Approval of protocols 8 and 15 by an appropriate human experimentation committee was required by Bristol Laboratories, as this is a requirement for all Bristol Laboratories' clinical studies. In a letter dated November 11, 1974, Bristol Laboratories was informed of Human Research Committee approval. Subsequently, Bristol Laboratories has been informed by the FDA that there is doubt concerning the legitimacy of this approval.

Bristol Laboratories required and obtained sample informed consent forms at the initiation of studies 8 and 15. However, inasmuch as the case report forms were never completed by Dr. #2, no informed consent forms were received by Bristol Laboratories. Subsequently, Bristol Laboratories was informed by the FDA that no evidence of signed informed consent forms could be found in the patient's records at Dr. #2's geriatric center in which the studies were performed.

Analysis of Data Generated by Studies 8 and 15

Although the case reports obtained were incomplete, they were evaluated. In general the results suggested activity, with only minimal side effects. However, the monitor's reports clearly indicate the lack of demographic data, and the deficiencies in the case report forms. Moreover, because of significant doubts concerning the results of these studies, similar studies were initiated in other institutions under well-monitored and well-controlled circumstances. These studies failed to confirm the results of studies 8 and 15, and the clinical evaluation of BL-3912A was discontinued. In none of the studies on BL-3912 were serious side effects noted in any patient.

Oral Butorphanol Studies

Background

Butorphanol is an orally active, totally synthetic non-narcotic analgetic. In experimental animals, butorphanol was shown to be a more potent analgetic than morphine, and had a very low addictive activity. It was also found to be a potent narcotic antagonist, and antitussive. Toxicologic studies in several species demonstrated that butorphanol had a broad therapeutic index in animals, and was devoid of teratologic activity in animals. Consequently, it seemed a promising candidate for clinical development.

Clinical evaluation of parenteral butorphanol has been completed. Prior to initiation of studies 58A and 59A, parenteral butorphanol was evaluated in more than 2500 patients, and these studies demonstrated that parenteral butorphanol is a potent analgetic of value for the treatment of moderate and severe pain of various etiologies. The side effects of butorphanol have proven to be manageable and similar to those reported for other potent analgetics such as morphine and meperidine. They included occasional episodes of lightheadedness, drowsiness, nausea and, very rarely, hallucinations. The effects of butorphanol on respiration have been reported to be less pronounced than those due to morphine

and the liability of butorphanol for producing physical dependence has been reported to be extremely low. A new drug application has been filed on the basis of the parenteral data.

Clinical studies on oral butorphanol are in progress and yielding promising results. It is expected that a new drug application will be filed for oral butorphanol within the next several months.

General Considerations Relevant to Studies 58A and 59A

Bristol Laboratories employs third party monitoring facilities infrequently. During the past few years Bristol Laboratories has collaborated with consultant firms on a total of 16 studies. All of these monitoring groups were employed to study butorphanol.

The decision to employ a third party firm was reached for two reasons. First, because of the work load imposed by extensive research on parenteral butorphanol, at the time of initiation of studies 58A and 59A, it was felt that the analgetic clinical staff at Bristol Laboratories might not be able to monitor additional studies effectively. Second, because the evaluation of an oral analgetic is a difficult endeavor due to the subjective nature of responses, it was considered prudent to employ an impartial monitoring facility to confirm results obtained intramurally.

Thus, the firm undertook primary responsibility for studies 58A and 59A. Its responsibilities included generation of protocols and case report forms, acquisition of investigators, monitoring of the studies, and evaluation of the clinical data. Before studies 58A and 59A were initiated, over 500 volunteers and patients had received oral butorphanol in studies monitored by Bristol Laboratories.

Study Number 58A

Purpose of Study

The protocol prepared by the contract firm was designed to evaluate in a double-blind, randomized, comparative trial the analgetic activity and side effects of butorphanol given for three days at doses of 4 mg or 8 mg four times daily, and compare the effects to codeine, 60 mg, four times daily, and placebo in patients with musculoskeletal pain. The patients were to be outpatients.

Selection of Dr. #3 as Principal Investigator

Dr. #3 was selected as the principal investigator by the contract firm. However, subsequent to Study 58A, Bristol Laboratories has employed Dr. #3 as principal investigator for butorphanol studies 602-16, 603-05 and 802. The continued employment of Dr. #3 by Bristol Laboratories is due to his excellent credentials, and his performance on prior studies.

Monitoring of Study 58A

The monitoring of Study 58A was conducted by the contract firm. No significant problems were reported by the contract firm during the conduct of this study.

Human Research Committee Approval and Informed Consent

Human research committee approval was not obtained since this was an outpatient study. However, each patient enrolled in the study signed an informed consent.

Evaluation of Study 58A

Final evaluation of Study 58A was conducted by Bristol Laboratories personnel. Of the 93 patients enrolled in this study, 93 were evaluable for toxicities; 91 for analgetic activity. The analgetic response to butorphanol at doses of 4 mg and 8 mg was equal to codeine 60 mg. However, all three treatment groups experienced significantly greater pain relief than the patients in the placebo group.

The most frequent of the reported side effects included dizziness, nausea, and sedation. The incidence of butorphanol-induced side effects was slightly, but not statistically, greater than those induced by codeine. The results of this study have been confirmed by Studies 71, 78, and 803.

Study 59A

Purpose of Study

The protocol was designed to determine in a randomized, comparative, double-blind study the activity of butorphanol (8 mg or 16 mg), codeine (60 mg), and placebo in the treatment of post surgical pain. The patients were to be hospitalized.

Selection of Dr. #7 as Principal Investigator

Dr. #7 was selected by the contract firm. However, his credentials appeared to be acceptable. A concern was Dr. #7's ability to perform an inpatient study at a time when he was an emergency room physician, but this was discussed, and Dr. #7 assured the firm's personnel that he could perform the study.

Monitoring of Study 59A

During the brief period during which study 59A was active, all monitoring was performed by the contract firm. The study was initiated on 10/28/75 and terminated on 1/9/76. During the period of the study, six monitoring visits were made by monitoring personnel. As a result of the monitoring visits, it became obvious that Dr. #7 was not adequately performing the study, and the personnel in the hospital were inadequately trained to perform the study. In addition, Dr. #7 experienced administrative difficulties in the hospital. Consequently the study was terminated after 16 patients were enrolled.

Human Research Committee Approval and Informed Consent

The contract firm was informed that no human experimentation committee existed at the hospital. However, they were subsequently informed that a committee was formed, and then the firm received formal approval of the study. Informed consent forms were reported to be completed on all patients.

Analysis of Study 59A

The data generated in Study 59A were analyzed by Bristol Laboratories personnel. None of the cases were considered evaluable for efficacy, but all were included in toxicologic evaluations of oral butorphanol. None of the patients experienced severe toxicities.

Conclusion

It is a matter of concern to Bristol Laboratories that even two of the many hundreds of clinical studies sponsored by us are sub-standard. However, it should be noted that when problems with these studies were discovered, they were corrected.

The Bristol Laboratories monitor for the studies was replaced, and further investigation with Dr. #2 discontinued. Moreover, since sub-acute dosing schedules were employed in these studies, the fact that four months elapsed between the initiation and termination of the research program with Dr. #2 reflects reasonable diligence. The fact that no significant side effects were observed in the course of these studies is another important consideration.

Clearly, the study performed by Dr. #7 did not progress well. But that study too was rapidly terminated when problems were recognized, and no patient experienced significant adverse effects.

The studies performed by Dr. #7 and Dr. #2 are not acceptable, nor do we subscribe to the belief that a few such unacceptable studies are inevitable if enough studies are performed. We recognize our responsibility to provide the more intense efforts to perform ethical, valuable clinical research on drugs of potential benefit.

This also requires the closest scrutiny of studies once they are initiated so that those which are inappropriate may be terminated rapidly. Finally, and perhaps most importantly, it also requires that the safety and rights of volunteer test subjects are well protected.

Bristol Laboratories on September 14, 1976, established Guidelines for Good Clinical Research. These guidelines, with minor exceptions, meet or exceed the standards published by FDA months later.

In essence, we believe that good clinical research requires adequate performance in five broad types of endeavors. The first step in the performance of good clinical research is the careful design of protocols which accurately define the characteristics of the subjects, and the tasks to be performed. Second, it is essential to select a qualified investigator. Third, each study must be carefully monitored to assure compliance with protocol, and to arrange for any necessary revisions. Fourth, the data must be analyzed carefully and without bias. Fifth, accurate records must be maintained to document these activities.

First, we established an intramural protocol review committee which must approve all protocols prior to initiation of studies. Included in these protocols are minimum guidelines for informed consent. We also require that names and titles of all members of a testing institution's human research committee must be provided to Bristol Laboratories.

Second, we have established minimum standards for the selection of investigators. Whenever possible, we attempt to employ academic clinicians with experience in the scientific areas involved. In our opinion, this is one of the best methods of assuring both a competent investigator and a functional human research committee.

However, when questions we must ask cannot be answered by an academician, we must rely on other types of investigators.

Third, we have established standards for monitoring methods, including frequent visits to testing sites at the initiation of studies as a safeguard against continuation of an inadequate study. The Guidelines also require that, when appropriate, registration forms be submitted to the Bristol Laboratories' monitor promptly after enrollment of each patient in a study, and the rapid evaluation of each case report as it is received by the monitor.

Adverse reactions are particularly scrutinized, and investigators are required to report by telephone any unexpected or alarming adverse effects to the monitor within 24 hours. The monitor's home telephone number is provided, should the investigator need to contact the monitor after normal office hours.

The question of whether to employ a professional monitoring firm is complex. Certainly it is of value to employ such a firm if inadequate manpower in-house would result in inadequate monitoring. It may also be of value to occasionally replicate intramural data extramurally. However, the desire to avoid any danger of biasing the monitoring service or investigators must be balanced against the responsibility of the sponsor to assure compliance with the regulations and the conduct of ethical, scholarly studies.

The analysis of data generated by clinical trials is also discussed in the Bristol Laboratories guidelines. To insure that double-blind studies are truly double-blind, randomization schedules are maintained in the statistical department, and are not available even to the monitor. The final reports on all studies must be submitted to the protocol review committee for approval. Thus another peer review is effected at the close of a study.

Finally, it is essential that adequate records be maintained. Our guidelines of September 14, 1976, addressed this question, but we are currently revising the guidelines to require better record keeping.

It is our opinion that the procedures outlined in our Guidelines for Good Clinical Research substantially increase the assurance that informed consent is obtained for each patient, that institutional review is effected for each study, that adverse reactions are carefully monitored, and that each study is monitored effectively.

These guidelines are under constant review for improvements and refinements that result from our experience. However, there are limitations.

It is difficult to demand, for example, that an investigator reveal the names of his test patients. Our concern for the rights of informed consent is tempered by the investigator's concern for the patient's right of privacy and confidentiality -- a concern we share.

As a consequence, we cannot insure that our policies for informed consent are uniformly implemented. This is a complex dilemma and is not addressed in the proposed regulations of the FDA for 1977 nor in the January 1973 report of the National Academy of Sciences/National Research Council.

It is not possible to predict the performance of each clinical investigator. We can check his educational credentials, and we do. We can evaluate his published work on previous studies, and we do. We can inquire as to his professional standing with others in his field, and we do. But these procedures cannot accurately foretell the competence of every investigator in every research program we undertake.

If this committee can fashion the means by which greater insurance can be provided in these or other critical areas, or if the proposed Presidential commission can do so, we in clinical research would welcome such suggestions, for I can assure you that your concerns and your goals are very much our own.

Statement on Behalf of
Bristol Laboratories Division of Bristol-Myers Company
Before the
Subcommittee on Health and Scientific Research of the Committee on
Human Resources of the United States Senate
on March 7, 1978

Prepared by:

Stanley T. Crooke, M.D., Ph. D.
Associate Director of
Research and Development
and
Robert N. Endries
Vice President - Counsel

Bristol Laboratories is a Division of Bristol-Myers Company located in Syracuse, New York. We have been asked to appear, Senator Kennedy, by a member of your staff, Mr. Walter Sheridan. Mr. Sheridan indicated that the Subcommittee is interested in our comments on S.2579, a bill to amend the Public Health Service Act to establish the President's Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and our relations with three investigators whose work has been submitted to the Food and Drug Administration by Bristol Laboratories.

Our statement is divided into three parts: First, comments on S.2579; Second, a description of the practices and procedures followed by Bristol Laboratories personnel in conducting clinical trials; and Third, a presentation of information about the studies conducted by the three investigators.

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COMMENTS ON PROPOSED LEGISLATION, S.2579

As a pharmaceutical firm engaged in research activities which involve the use of human subjects, we are vitally interested in legislation affecting the conduct of research and are pleased to make our views known. Since the President's Commission for the Protection of Human Subjects of Biomedical and Behavioral Research would succeed the National Commission and have broader jurisdiction with expanded membership, the Commission would have a significant impact on the way research is conducted in this country.

We support the expressed objective of helping to assure that human subjects are adequately protected. As you said last year in introducing S. 1893, ".....(T)his Nation has always had a biomedical and behavioral research program second to none. The Commission gives this Nation a policy for the protection of human subjects of research second to none."

We, as a company, believe that the conduct of research carries with it grave responsibility to safeguard the rights of those who receive experimental therapy. It is clear that responsibility is shared by the clinical investigator, the drug sponsor, the institutional review committee and the Food and Drug Administration. Certainly, there are occasions when someone other than those directly involved can make a meaningful statement of standards which society believes should be met if the rights of those receiving experimental drugs and devices are to be fully protected.

We have studied the proposed bill to establish the President's Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and note that the Commission will study requirements, review rules and policies, analyze and evaluate technological advances and their implications, consider resource allocations, publish and disseminate recommendations, consider moral and ethical principles governing use of technology in medical practice and perform other like tasks. In principal we are in favor of the work proposed for the Commission. Its efforts should lead to continual suggestions for improvement of procedures in a field in which our knowledge continues to grow and our standards continue to require change.

We would be pleased to see the Commission also devote a part of its efforts to the subject of assurance of compliance by clinical investigators. The Commission is asked to "undertake a study to identify the requirements for informed consent by patients before they receive any medical treatment" but it is not asked to address the subject of investigator compliance with informed consent. As an industrial sponsor of clinical investigations we have found that probing of matters relative to informed consent compliance frequently runs counter to mechanisms which have been designed and established to "safeguard the privacy of research subjects" and "ensure the confidentiality of patient records".

The question of the adequacy of Institutional Review needs to be addressed. The qualifications of reviewers and documentation of peer review discussions are almost never available to industrial sponsors of new drug studies. Yet we are asked to assume some responsibility for the integrity of the clinical investigator and provide some assurance that a proper Institutional Review has indeed taken place.

BRISTOL LABORATORIES GUIDELINES FOR GOOD CLINICAL RESEARCH PRACTICES

Introduction

As a sponsor of clinical trials, Bristol Laboratories assumes several responsibilities. Paramount is that adequate safeguards be established to maximize the safety of the experimental subjects. Although rarely stated, a benefit to risk determination must be made for each subject enrolled in each study, and only the most fastidious care can ensure that each subject has the most positive benefit to risk ratio. Certainly, adequate and accurate data in experimental animals are requisite, and it is essential that clinical development of compounds proceed in a logical order with each study building on data generated in previous studies. To do this effectively, we believe an overall research plan (which we call a clinical operational plan) is essential, as well as well designed protocols, and adequate clinical investigators.

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A responsibility which is more difficult to define, but certainly of significance is the responsibility to perform clinical experiments generated by rational scientific goals, with meaningful objectives. To perform studies which may have an impact on the scientific development of a particular drug or class of drugs, with a carefully constructed

protocol, and excellent investigators with an interest in the science as well as the medicine involved in the studies, assures the subject that he/she is participating in an effort which will generate the most useful information per subject.

To attempt to improve the quality of our clinical trials, and to assure ourselves that each of the clinical trials sponsored by Bristol Laboratories meets the minimum standards necessary to maintain our responsibilities, we at Bristol Laboratories adopted guidelines for good clinical research practice on September 17, 1976. These guidelines were adopted well in advance of publication of the proposed guidelines of the FDA, but with a few minor exceptions exceeded the requirements later proposed by the FDA. The Bristol Laboratories guidelines have been amended during the months since their adoption, and are currently undergoing extensive revision to reflect our reorganization, an effort to strengthen certain aspects such as informed consent, and to improve documentation procedures in compliance with the proposed FDA guidelines. However, we have incorporated relevant portions of those guidelines to provide to the committee an overview of our practices. We shall be pleased to provide the revised guidelines when the revision is complete.

GUIDELINES FOR GOOD CLINICAL RESEARCH PRACTICE

Prepared by:
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JOB DESCRIPTIONS

I RESPONSIBILITIES

A. Director Medical Research

The Director of Medical Research is responsible for the overall function of the medical research group. The Director of Medical Research reports directly to the Vice President and Director of Medical Affairs.

1. Personnel

The Director of Medical Research is responsible for selecting employees, and for personnel decisions including promotions, assignation of responsibilities, salary determinations, and terminations.

2. Budget

The Director of Medical Research is responsible for developing the yearly budget as well as more protracted budgets. He is also responsible for budget administration.

3. Clinical Operational Plans

The Director of Medical Research is responsible for the generation of clinical operational plans for all new drugs to be developed clinically.

4. Protocol Review

As Chairman of the Protocol Review Committee, the Director of Medical Research is responsible for review, criticism and approval of all protocols for clinical research.

5. Reports of Clinical Studies

The Director of Medical Research is responsible for

(Job Descriptions)

I A. 5. review of all reports on clinical studies. He is responsible for verification of accuracy, and determination of the adequacy of the report. He may of course write reports also.

6. Protocol Design

The Director of Medical Research may design protocols, and is responsible for advising other personnel in the generation of clinical protocols.

7. Clinical Monitoring

The Director of Medical Research is responsible for the supervision of the monitoring of all studies, and may directly monitor some studies.

8. Liaison with the FDA and other Regulatory Agencies

The Director of Medical Research is responsible for preparation of presentations to the FDA, communications with FDA, and assuring that FDA regulations are met.

B. Associate Director of Medical Research

Associate Directors of Medical Research are responsible for the conduct of research within specific pharmacologic classes of drugs. The positions' responsibilities are similar to those of the Director of Medical Research except that they encompass a narrower sphere. Associate Directors report directly to the Director of Medical Research. Reporting to Associate Directors are clinical monitors, and medical research associates. The Associate Director of Medical Research for each class of drugs is a member of the Protocol Review Committee.

(Job Descriptions)

I C. Assistant Director of Medical Research (clinical monitor)

The Assistant Directors of Medical Research are responsible for the conduct of clinical research on specific drugs within a class of drugs. They report directly to the Associate Director for that class of drugs, and may have medical research associates reporting to them. Their responsibilities are primarily the monitoring of clinical studies.

1. Protocol Design

   Assistant Directors of Medical Research are responsible for generation of necessary protocols for specific studies.

2. Investigators

   Assistant Directors must acquire capable investigators for specific studies.

3. Clinical Monitoring

   The clinical monitoring for each study is specifically the responsibility of the Assistant Director assigned to that study.

4. Reports of Clinical Studies

   Assistant Directors must prepare interim and final reports on all studies assigned.

5. Protocol Review

   At the discretion of the Associate Director to whom an Assistant Director reports, the Assistant Director may be involved in review of protocols generated by other clinical monitors.

(Job Descriptions)

I D. Medical Research Associate

The Medical Research Associate works under the close supervision of a clinical monitor. The Medical Research Associate has primary responsibility for the management of clinical studies.

1. Acquisition of Investigators

The Medical Research Associate is required to interest qualified investigators in participating in clinical studies.

2. Monitoring of Clinical Studies

The Medical Research Associate is responsible for supervision of clinical studies, coordination of shipment of supplies and coding demographic data from case reports.

3. Reports of Clinical Studies

The Medical Research Associate participates in the generation of reports on clinical studies.

4. Protocol Design

The Medical Research Associate participates in the development of protocols for clinical studies.

II QUALIFICATIONS

A. Director of Medical Research

The Director of Medical Research must have M.D. or M.D., Ph.D. degrees, and adequate clinical and scientific experience to direct clinical studies. In addition the director must have adequate administrative experience and ability to direct a group of scientists.

II QUALIFICATIONS

B. Associate Director of Medical Research

Associate Directors of Medical Research must have M.D., or Ph.D. or M.D., Ph.D. degrees, and adequate clinical and scientific experience to direct clinical studies on drugs of specific classes. In addition, associate directors must have adequate administrative experience to direct a small group of scientists.

C. Assistant Director of Medical Research

Assistant Directors of Medical Research must have M.D. or Ph.D. or M.D., Ph.D. degrees, adequate clinical and scientific experience to direct clinical studies on one or several drugs of a specific class.

D. Medical Research Associate

Medical Research Associates must have a B.S. or M.S. or Ph.D. in chemistry, microbiology, or biologically related areas, or a Pharm. D. degree, and substantial scientific experience. For persons with a B.S. or B.A. degree, at least six to eight years of post-college experience in a scientific position related to pharmaceutical manufacture, research, or sales, or experience in an administrative position involved in processing products from research to marketing required.

Persons having an advanced degree must have at least two to three years experience in a health science profession, or pharmaceutical research.

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PROCEDURES

I PROTOCOL REVIEW COMMITTEE

A. Objectives

1. The principal objective of the protocol review committee is to assure that all protocols are of adequate quality to assure patient safety, functional clinical studies, and generation of data relevant to corporate objectives.
2. An additional objective is to assure that all protocols meet minimum standards of format.
3. The committee also serves to improve communication between various groups in Medical Research.
4. The committee is responsible for review of final reports of clinical studies, as well as the initial protocols. Thus, the effectiveness of protocols can be assessed, and in addition suggestions for improvement of future studies may be generated.

B. Committee Membership

1. Chairman

The Chairman of the Protocol Review Committee is the Director of Medical Research, or another individual appointed by the Vice President for Medical Affairs.

2. Members

a. Vice President of Medical Affairs
b. Associate Director - CNS Drugs
c. Associate Director - CVS Drugs
d. Associate Director - Antitumor Drugs
e. Associate Director - Antibiotics
f. Director of Biostatistics
g. Director of Regulatory Affairs

(Protocol Review Committee)

I C. Function

1. After being written and thoroughly reviewed by members of the group involved in the study, eg., the CNS group, and the Biostatistics group, the protocol is submitted to the committee.
2. The protocol is then distributed to the members of the committee.
3. Within 5 days each committee member must submit comments and criticisms of the protocol to the chairman and to the author of the protocol.
4. The author of the protocol and each member of the committee discuss the criticisms and agree on changes.
5. A revised protocol is submitted to the chairman of the committee.
6. The chairman determines if the revised protocol meets the criticisms of the committee members.
7. The chairman of the committee signs the appropriate study commitment form to allow initiation of the study (Exhibit 1).

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II CLINICAL MONITORING

A. Protocol Generation

1. Literature review

The initial step in protocol design is the literature review. During this review, published literature relevant to the drug to be studied, as well as in-house data on the drug to be studied, are reviewed. Consultation with experts is encouraged also.

2. First draft

The first draft of the protocol is submitted to the appropriate Associate Director of Medical Research, other members of the group, Biostatistics, and if desired, the potential principal investigator. After revision, the protocol is submitted to the Protocol Review Committee.

3. Protocol Review Committee

The protocol is submitted to the protocol review committee (see Section I). After criticisms are indicated, the final revised protocol may be employed.

II CLINICAL MONITORING

B. Monitoring of Studies

1. Selection of Principal Investigator

The principal investigator is selected after thorough evaluation and several interviews. The principal investigator must have the following characteristics:

a. Competence

The principal investigator must have demonstrated competence to do clinical studies by prior publications, and/or previous experience.

b. Interest

The principal investigator must demonstrate interest in the study drug, and in collaborating on the specific study being considered.

c. Patient population

The principal investigator must have access to adequate numbers of appropriate patients.

d. Facilities

The principal investigator must have adequate facilities to perform the study.

2. Initiation of Studies

The initiation of a study is preceded by conferences with the principal investigator, and key members of his staff concerning the protocol and the conduct of the study. In most cases, the principal investigator is visited by appropriate Bristol Laboratories staff prior to initiation of the study.

The Medical Research Associate is often involved in the preliminary discussions with potential investigators.

II CLINICAL MONITORING

B. 2. Preliminary discussions are often initiated via a telephone call. Subsequently, if the reply of the investigator is favorable, appropriate data are forwarded to the investigator. This is usually followed by a visit to the potential investigator, and discussions concerning the proposed study, the budget, the protocol, and various regulations. This meeting may be attended by the medical monitor. If the potential investigator agrees to do a study, and the medical monitor agrees that the potential investigator is adequate, and the budget is reasonable, the development of the study proceeds.

Necessary FDA forms are compiled and submitted to the FDA in the IND prior to initiation of the study. The necessary forms include:

1. Original Protocol (signed by the principal investigator);
2. FDA form 1572 or 1573;
3. Copy of Patient Consent Form;
4. Curriculum Vitae for principal investigator and any other M.D.'s working with him;
5. Review Committee approval (together with a list of committee members and their titles.

No study drug may be shipped prior to submission and FDA approval of the IND.

During the initial phases of the study, the study is monitored closely by frequent phone calls, and, if necessary, visits with the principal investigator.

II CLINICAL MONITORING

B. 2. The first several case reports are reviewed carefully, and any problems encountered are discussed with the principal investigator. The rate of patient accrual, and the percent evaluable cases are estimated at the earliest possible time.

3. Interim monitoring

Monitoring of studies continues during the conduct of the study. Case reports are coded and forwarded to Biostatistics. Adverse reactions are closely monitored, and reported. The adequacy of the principal investigator is assessed according to the following criteria:

a. rate of Patient accural
b. adequacy of case reports,
c. cooperativeness.

Any modifications made in the protocol are formally added to the protocol as addenda. These addenda are submitted to the Protocol Review Committee with an explanation of the changes and the rationale. Under no circumstances are changes in protocols to be made informally, or verbally without confirmation in writing. Protocol revisions are submitted to the FDA.

When a formal change in the protocol is made, that change is indicated in a letter to the investigator which includes the relevant sections of the protocol, and the addendum submitted to the Protocol Review Committee.

Appropriate interim reports are submitted to the FDA.

II CLINICAL MONITORING

C. Final Reports

1. All completed case reports are submitted to Bristol Laboratories.

2. Each case report is evaluated by appropriate Bristol Laboratories staff.

   a. The Medical Research Associate usually has responsibility for logging case reports, and for initial evaluation.

   b. The evaluability of the case report is determined by rules defined in the protocol.

   c. The Medical Research Associate is usually responsible for encoding the case report.

   d. The evaluation of the Medical Research Associate is checked by the Clinical Monitor, and immediate consultation on all case reports about which there are significant questions occurs.

   e. The Clinical Monitor is responsible for verifying the accuracy of the initial assessment of the Medical Research Associate.

3. Case Reports are entered in the appropriate Data Banks.

   a. The computer program is established such that frequent edits for errors are possible.

   b. Each case report detected in an edit is reviewed by the Medical Research Associate and the Clinical Monitor.

   c. If necessary, the principal investigator is contacted to resolve discrepancies.

II CLINICAL MONITORING

C. 3. d. Should there be differences of opinion between the Bristol Laboratories monitors, and the clinical investigator which are unresolvable, the most conservative opinion will be accepted, eg., should the clinical investigator feel that a patient responded, but the Bristol monitor feel that, on the basis of the case report, no response was induced, the patient will be labeled a non-responder.

4. A Monitor's Report is prepared.

a. The Medical Research Associate may be involved in the development of the monitor's report.

b. The monitor's report will be written, and/or approved by the appropriate clinical monitor.

c. The monitor's report is submitted to the appropriate Associate Director of Medical Research, and then to the Director of Medical Research, the Protocol Review Committee and other appropriate individuals for review.

d. The approved monitor's report is submitted to the clinical investigator.

5. A Statistical Report is completed.

a. The statistical report is submitted to the Director of Biostatistics.

b. After approval of the report the Director of Biostatistics submits the report to the clinical monitor, the Protocol Review Committee, the Director of Medical Research, and other appropriate individuals for review.

II CLINICAL MONITORING

C. 5. c. After approval, the statistical report is submitted to the clinical investigator.

6. The Principal's Investigator's Report is completed.

a. The Principal Investigator's (clinical investigator's) report is reviewed by the appropriate Medical Research Associate, and Clinical Monitor.

b. Any differences between this report, and those generated by Bristol personnel are discussed.

7. All reports are collated, and discussed, and subsequently submitted to the FDA.

III ADVERSE REACTION REPORTS

Adverse reactions are frequently reported for both experimental drugs, and marketed drugs. It is essential that all adverse reaction reports be handled appropriately.

A. Unusual, unexpected, or life-threatening adverse reactions.

1. Definitions

Unusual or unexpected adverse reactions are adverse reactions which are different from those described in the OPC for marketed drugs. For experimental drugs, reactions which are not predicted by animal toxicology, or previous clinical studies are considered unusual or unexpected.

2. If the adverse reaction is reported by telephone, the telephone call is logged.

3. If the adverse reaction is reported by letter, the receipt of the letter is logged, and the letter is filed in the adverse reaction file for that drug.

III ADVERSE REACTION REPORTS

A. 4. The reporting physician is requested to complete a FD-1639 form, and to send details of the reaction, and a complete case history within 5 days (see Exhibit 2).

5. The adverse reaction is discussed with a Bristol Laboratories physician.

6. An adverse reaction report is filed with the FDA within 5 days after receipt of all pertinent data.

7. The reporting physician is encouraged to publish, as a note, the adverse reaction in an appropriate journal if the reaction is deemed novel or significant enough to warrant a publication.

B. Expected, less significant adverse reactions

1. Any adverse reaction reports which are not classified as indicated in Section IIIA are included.

2. If an adverse reaction is reported by telephone, the telephone call is logged.

3. If the adverse reaction is reported by letter, the receipt of the letter is logged, and the letter is filed in the adverse reaction file for that drug.

4. The reporting physician is requested to complete an FD-1639 form, and to send details of the reaction and a complete case history.

5. The adverse reaction is discussed with a Bristol Laboratories physician.

6. The completed adverse reaction report is filed in the adverse reaction file for that drug.

7. All adverse reaction reports are filed with the FDA with the yearly report on the drug.

IV DATA HANDLING

A. All data are considered relevant. No data are discarded.

B. All case reports are filed according to drug and study number.

C. Data are entered in appropriate Data Banks.

D. In the event a Data Bank is not available for a specific study, the data are filed according to drug and study number only.

E. All original case reports are stored for a minimum period of 2 years after NDA approval, or for 2 years after completion of the study.

V DATA PROCESSING

A. Introduction

The Biostatistics group interacts with clinical personnel in the department of Medical Research to assure that conclusions drawn from clinical studies are statistically sound. This interaction extends to the design of studies, all phases of data collection and processing, analysis of data, and interpretation of results.

B. Assignments

1. Professional Staff

The department head shall assign work on a project basis, ie., one statistician shall be responsible for the department's share of work on all phases (I-III) pertaining to a given formulation (for example, Oral Butorphanol). The following information shall be maintained on file:

a. Drug and formulation
b. Study number (see....for assignment of study numbers)
c. Clinical monitor(s)

V DATA PROCESSING

B. 1. d. Statistician(s) assigned

e. Date of protocol approval

f. Study completion

1. expected date

2. date last data received

g. Statistical Report

1. date promised

2. date delivered

2. Secretarial-Clerical

Secretaries will be assigned data handling responsibilities also on a project basis. In case of need to do so, priorities will be set by the department head. General office work, correspondence, filing, etc. will be performed by the department head's secretary.

C. Statistical & Data Handling Functions

1. Study Design

Each clinical study shall be performed according to a written protocol. Guidelines for content and format are given in Section II.

The study monitor(s) shall discuss a proposed study and/or its protocol with the statistician assigned to the drug project.

The resulting draft of the protocol shall then be sent to the Review Committee, of which the Head of Biostatistics is a permanent member. He will review the proposed protocol or ask the statistician assigned to the project to review it.

V DATA PROCESSING

C. 2. Protocol Review

The secretary to the Head of Biostatistics shall date-stamp all transmittal memos and cover sheets of protocols received for review and keep a log of review functions (see below). She/he shall also assign a study number at this time.

The Head of Biostatistics or designee shall review the protocol and submit comments written in memo form and/or on the protocol itself within 5 working days of receipt, to the study monitor and the chairman of the review committee.

a. Log of Review Functions

The log of the review functions shall contain the following information:

1. submission (or re-submission) of protocol (date)
2. individual assigned to review
3. date of submission of comments
4. date of protocol approval.

b. Document Retention

The reviewer shall keep all unmarked pages of the protocol in his files until receipt of final (approved) protocol (marked pages to be sent to monitor, chairman).

The approved protocol shall be filed, together with the preceding comments, by the secretary to the Head of Biostatistics.

V DATA PROCESSING

C. 3. Data Collection

All data obtained in any study shall be recorded on appropriate forms and collected by the study monitor or designee. It is the study monitor's responsibility to ascertain that all forms are completed as requested in the protocol, and forward only completed forms with a covering memo to biostatistics. The covering memo shall indicate whether partial or final data are being submitted.

The secretary to the Head of Biostatistics shall keep a log of data forms received, note the date of final data on the chart mentioned in II A above, and file data forms in consultation with the statistician assigned to the particular study.

4. Data Storage

Xerox copies of original case report forms will be logged in upon receipt by the department secretary and kept in designated file space. They will be removed only for transfer of data onto transmittal sheets or directly to computer files.

The copies and transmittal sheets shall be kept for 2 years beyond NDA approval, or cessation of the drug project under investigation.

a. Transfer of data to transmittal sheets, coding of data and transfer to transmittal sheets involves both, the clinical monitor and one of the department clerks. Each will initial the transmittal

V DATA PROCESSING

C. 4. a. sheet after completion.

Following keypunching and computer input, data are to be listed from the computer file and checked against the transmittal sheet by the data clerk.

All subsequent corrections of the data file must be indicated on the transmittal sheet and initialed by the clinical monitor.

b. Maintenance of Computer Files

Data files will be kept active, ie., in on-line computer storage for 1 year beyond NDA approval or discontinuation of a drug project.

Files will be kept in archival storage thereafter as needed.

c. Log-keeping

The department secretary shall keep a complete log of all phases of the above mentioned operations.

VI DRUGS AND SUPPLIES

A. Personnel

Two individuals will be assigned to functions necessary for the administration of procedures relevant to the daily operation of the Medical Storeroom.

1. Overall responsibility will be assigned to one person, preferably a Medical Research Associate, who will assure compliance with all operational procedures set forth in this section. That individual will also serve as a liaison with Regulatory Affairs and Product Development in order to

VI DRUG AND SUPPLIES

A. 1. maintain an updated knowledge of pertinent regulations affecting the procurement, utilization and accountability of investigational drugs or other clinical supplies.

2. A second individual, with clerical or secretarial capabilities, will serve to initiate, record, file and maintain all documents and records required for ordering, shipping, and inventory of any clinical supplies or returned materials from completed or terminated clinical studies.

B. Non-controlled Substances

Non-controlled substances are defined as those compounds, either investigational or marketed drugs, which are not currently classified by the Drug Enforcement Administration (DEA) as Schedule I through Schedule V substances.

1. Ordering Supplies

All orders for supplies for planned or ongoing clinical studies will be processed through the person(s) who administer the Medical Storeroom. These orders, in turn, are forwarded to Product Development for procurement, manufacturing, and other preparation processes.

a. Requests for "working" stocks (eg., 10,000 vials, 200,000 tablets, etc.) will be placed by completing the "Order Form for Marketed and Investigational Drug Supplies, rev. 7/74", (Exhibit 3) and submitting to the administrator of the Medical Storeroom.

VI DRUGS AND SUPPLIES

B. 1. b. Special studies, to be prepared from either new material or from existing "working" stock, are requested in the manner described in paragraph 1 a.

c. The clerk assigned to Medical Storeroom duties will maintain a chronological file of all "Order Forms for Marketed and Investigational Drug Supplies" submitted to Product Development. This file will be retained for 5 years.

2. Receipt of Clinical Supplies

a. All clinical supplies, as prepared or processed by Product Development, will be transferred to the Medical Storeroom accompanied by an appropriate memo (Exhibit 4) with copies to 1) Medical Storeroom administrator, 2) Clinical Monitor for Study Drug, 3) Regulatory Affairs and 4) initiator of request.

b. The Medical Storeroom clerk will file these memos by drug name or as a "special study". A new file will be started each calendar year and the individual drugs within the file will be organized sequentially by lot number. Special studies received during that period will be alphabetically arranged by study name. This file will be maintained at least 2 years.

c. The Medical Storeroom clerk will prepare an "Inventory File Card" (Exhibit 5) for each shipment to the Medical Storeroom A file of these cards will

VI DRUGS AND SUPPLIES

B. 2. c. be maintained alphabetically by drug name and sequentially by lot number for each drug section. A carbon copy of each file card will be maintained sequentially by lot number in a separate cross-reference file.

These file cards and cross-reference cards will be maintained as long as an inventory balance remains for each drug lot.

3. Inventory

All inventory transactions will be recorded on each appropriate "Inventory File Card". All transactions will be recorded as they are made and will reflect amount transferred, date, requestor, recipient and current inventory balance.

a. Inventory file cards will be retained in an "Active Drug File" as long as an inventory balance remains for that drug lot or special study.

b. Whenever an inventory is completely utilized so that the file card reflects a "zero" balance, the file card will be removed from the "Active Drug File" and placed in the "Depleted Drug File". The corresponding, carbon copy cross-reference card is removed and destroyed.

The "Depleted Drug File" is organized alphabetically by drug name and appropriate cards in each drug section are filed sequentially by lot number. The "Depleted Drug File" will be maintained for 2 years.

VI DRUG SUPPLIES

B. 3. c. Occasionally, it may be desirable or necessary to destroy certain inventory balances. This usually occurs as a result of the supply reaching its expiration date or upon termination of a study project.

A written memo requesting such destruction and listing drug name, lot number, dosage form, size, and quantity will be sent to Regulatory Affairs, Product Development, and the Research Stockroom. Notation of destruction and date will be made on the appropriate inventory card and it will be placed in the "Depleted Drug File" described in paragraph 3-b, above. The cross-reference carbon copy card is destroyed and a chronological file of "Memos for Drug Destruction" will be maintained.

4. Shipments of Clinical Supplies

a. Requests for shipments of any material assigned to the Medical Storeroom inventory will be submitted to the Storeroom clerk prior to 9:00 A.M. on the day of shipment.

A "Request for Drug Shipment" (Exhibit 6) will be submitted and all data must be complete. No requests will be processed if the form is considered incomplete in any manner. A chronological file of the "Request for Drug Shipment" forms will be maintained for two years.

b. Upon receipt of a "Request for Drug Shipment" form, the Medical Storeroom clerk will examine the "Active Drug File" to assure the presence of suitable material. When satisfied that sufficient material with an adequate expiration date is present, the clerk will prepare an appropriate, typewritten "Requisition For Clinical Material" as shown in Exhibit 7.

VI DRUG SUPPLIES

B. 4. b. The "Requisition for Clinical Material" is then signed by a Medical Research or Medical Services physician, approved for shipment by Regulatory Affairs, and delivered to the Research Stockroom for shipping procedures. Research Stockroom personnel will not ship material without a completed requisition approved by a physician and a representative of Regulatory Affairs. The clerk will then adjust the appropriate inventory file card(s) to reflect shipment of the item(s).

c. Copies of the completed "Requisition For Clinical Material" are included in the appropriate packages shipped. The investigator must sign, date, and return one copy of the enclosed requisition to the study monitor and the monitor must retain that receipt in the proper study file.

5. Return of Clinical Supplies

All unused clinical supplies from completed or terminated studies or projects must be returned to Bristol Laboratories immediately following such termination.

a. As soon as possible, after receipt of these unused materials, the Medical Stockroom will provide the appropriate study monitor with an itemized list of supplies returned. That list will reflect date of return, study number (if any), name and location of investigator, and the drug's name, lot number, potency, size, and quantity returned. These data will be supplied on a suitable memo entitled "Returned Clinical Supplies: Non-controlled substances" (Exhibit 8).

VI DRUG SUPPLIES

B. 5. b. The clerk will maintain a notebook, alphabetically by investigator's name, and will record all drug supplies returned by each investigator. This notebook will be retained for 2 years.

c. The clerk will also maintain a file of Returned Clinical Supply memos alphabetically by drug name. Memos within each sub-section will be filed chronologically as the memos are issued. This file will be retained for 2 years.

d. All returned clinical supplies from completed or terminated studies or projects will be delivered to Product Development for destruction. Under no circumstances will such supplies be returned to active inventory or used in other studies.

6. Accountability

The disposition of all clinical supplies shipped to investigators must be determined.

a. The study monitor, Medical Research Associate, or other person responsible for the immediate supervision of any study or investigator must determine and verify the quantity of any drug(s) used in the study, and the amount of drug(s) returned from that study. If any discrepancy exists, the responsible study supervisor must immediately notify the investigator and reconcile each discrepancy.

b. For each drug shipped, the Medical Stockroom will supply a suitable form entitled "Investigator's Drug Disposition Record" (Exhibit 9). This form, when completed, should become a permanent part of both the study monitor's and the investigator's files for each study.

VI DRUG SUPPLIES

C. Controlled Substances

Controlled substances are defined as those compounds, either investigational or marketed, which are currently assigned by the Drug Enforcement Administration (DEA) to a "controlled" status as Schedule I through Schedule V substances. For administrative purposes, in the Medical Storeroom, the unique characteristic of these compounds is that all handling, shipping, and transfer procedures require signed, witnessed and dated receipts.

1. Ordering Supplies

Supplies of controlled substances are ordered through the Medical Storeroom in the same manner described for Non-controlled Substances, Part B, paragraph 1 in this section.

2. Receipt of Clinical Supplies

Since Product Development has the only vault for storage of Controlled Substances, that department will retain physical possession and maintain the inventory of all clinical supplies containing such compounds.

a. The Medical Storeroom will maintain a second "inventory" listing of controlled clinical supplies as described for Non-controlled Substances, Part B, paragraph 2 in this section.

b. The individual assigned overall responsibility for the Medical Storeroom will carefully review each Drug Transfer memo (Exhibit 4) and each Inventory File Card (Exhibit 5) prepared for controlled clinical supplies.

He will assure that a readily identifiable, red printed Schedule Number is placed on each document. He will also place a suitable statement on each document to alert the storeroom clerk that special procedures are required for that material.

VI DRUG SUPPLIES

C. 3. Inventory

Inventory file cards will be prepared and filed as described in Non-controlled substances, Part B, paragraph 3 of this section. Destruction of unwanted supplies in this category is carried out in the same manner.

4. Shipments of Controlled Clinical Supplies

Requests for shipments of any controlled substance for clinical investigation will be submitted to the Storeroom clerk prior to 9:00 A.M. on the day of shipment.

a. A "Request for Drug Shipment" (Exhibit 6) will be submitted and all data must be complete. No requests will be processed if the form is considered incomplete in any manner. A chronological file of the "Request for Drug Shipment" form will be maintained for two years.

b. Upon receipt of a "Request for Drug Shipment" form, the Medical Storeroom clerk will examine the "Active Drug File" to assure the presence of suitable material. When satisfied that sufficient material with an adequate expiration date is present, the clerk will prepare an appropriate, typewritten "Requesition for Clinical Material" as shown in Exhibit 7.

The "Requisition for Clinical Material" is then signed by a Medical Research or Medical Services physician, approved for shipment by Regulatory Affairs, and delivered to the administrator of the Medical Storeroom. The clerk will also prepare a suitably worded receipt (Exhibit 10) for transfer of the controlled supplies to a representative from the shipping department.

VI DRUG SUPPLIES

C. 4. c. The administrator of the Medical Storeroom will assure that a properly completed DEA "Order Form for Schedule I and II Controlled Substances" (Exhibit 11) is supplied whenever drugs from Schedule I or II are contained in a shipment. He will also write on that form the number of packages shipped and the date shipped. The form is delivered to Regulatory Affairs for further processing.

Absolutely no shipments of such substances made without prior receipt of the properly completed DEA form!

d. The administrator of the Medical Storeroom, after assuring that all required documents are in order and are properly executed, will accompany the respective study monitor to Product Development where the shipment will be obtained under signed, witnessed receipt. (Exhibit 12).

The shipment is returned to the administrator's office where it remains, in his presence, until a representative from Shipping and Traffic Department arrives. That representative then signs a suitable receipt (Exhibit 10) for each shipment and assumes responsibility for delivery to the investigator(s).

e. The Medical Storeroom clerk retains additional copies of all receiptsand appropriate documents (Exhibits 6, 7, 9, 11 and 12). These copies are maintained in the "Controlled Substance Shipment File" and are filed in chronological order of shipment. The copies are retained for 2 years.

5. Return of Controlled Clinical Supplies

All unused controlled clinical supplies from completed or terminated studies or projects must be returned to Bristol Laboratories immediately following such termination. Whenever Schedule I or II controlled drugs are involved, the

VI DRUG AND SUPPLIES

C. 5. responsible study monitor must obtain an appropriately completed DEA "Order Form for Schedule I and II Controlled Substances" (Exhibit 11) from Research Administration. This order must be supplied to the investigator prior to his return of those supplies.

a. As soon as possible, after receipt of these unused materials, the Medical Stockroom will provide the appropriate study monitor with an itemized list of supplies returned. That list will reflect date of return, study number (if any), name and location of investigator, and the drug's name, lot number, potency, size, and quantity returned. These data will be supplied on a suitable memo entitled "Returned Clinical Supplies: Controlled Substances" (Exhibit 13).

b. The clerk will maintain a notebook, alphabetically by investigator's name, and will record all drug supplies returned by each investigator. This notebook will be retained for 2 years.

c. The clerk will also maintain a file of Returned Controlled Substances memos alphabetically by drug name or study title. Memos within each sub-section will be filed chronologically as the memos are issued. This file will be retained for 2 years.

d. All returned controlled clinical supplies from completed or terminated studies or projects will be delivered to Product Development for destruction. Representatives from that department will provide a signed receipt for such material and will assure that the proper storage and ultimate destruction of those compounds is carried out. Under no circumstances will such supplies be returned to active inventory or used in other studies.

VI DRUGS AND SUPPLIES

C. 5. e. If the returned material is of Schedule I or II classification, the study monitor will promptly advise Research Administration of the receipt of same. Research Administration will also be advised of the investigator's name, location, and of the appropriate DEA order form serial number. If any discrepancy exists between the outgoing order form request and the material received, the study monitor must immediately notify the Medical Storeroom administrator and Regulatory Affairs.

6. Accountability

The disposition of all controlled clinical supplies shipped to investigators must be determined.

a. The study monitor, Medical Research Associate, or other person responsible for the immediate supervision of any study or investigator must determine and verify the quantity of any drug(s) used in the study, and the amount of drug(s) returned from that study. If any discrepancy exists, the responsible study supervisor must immediately notify the investigator, Regulatory Affairs, and the Medical Storeroom administrator. The investigator must reconcile each discrepancy.

b. For each drug shipped, the Medical Stockroom will supply a suitable form entitled "Investigator's Drug Disposition Record" (Exhibit 9). This form, when completed, should become a permanent part of both the study monitor's and the investigator's files for each study.

26-828 O - 78 - 10

VII DISQUALIFICATION OF INVESTIGATORS

The FDA has suggested minimum standards to be met by clinical investigators. These are presented here as the minimum acceptable standards, obviously more stringent requirements, and additional requirements are often operant. Failure to meet these minimum standards will result in an investigator being disqualified, and the termination of study(ies) with that investigator.

A. An investigator may be disqualified if he commences a study without the prior approval of the FDA and the appropriate institutional review committee.

B. Significant, unauthorized deviations from protocols may justify disqualification.

C. The violation of the rights of human subjects regarding informed consent may result in disqualification.

D. The administration of the test drug or device to subjects not directly supervised by the principal investigator may result in disqualification.

E. An investigator may be disqualified if he allows drugs or supplies to be given to individuals not directly under his supervision, or that of the sponsor.

F. An investigator who fails to return drugs or supplies upon request may be disqualified.

G. Serious deficiencies in record keeping may result in disqualification.

H. Failure, without adequate explanation, of the investigator to make reports within the allotted time may result in disqualification.

VII I. The refusal of an investigator to allow records to be copied by authorized individuals may result in disqualification.

K. The falsification or withholding of any required records may result in disqualification.

VIII CONDUCT OF FOREIGN STUDIES

A. Studies conducted outside the United States, by Bristol Laboratories domestic personnel, shall be conducted as though they are subject to FDA regulations, ie., under IND conditions.

B. Prior to the initiation of international studies the appropriate individual at Bristol Myers International Division must be notified

C. Bristol Myers International Division personnel must be kept aware of the progress of all international studies.

IX GRANTS AND CONTRACTS FOR CLINICAL STUDIES

A. No commitments for grants or contracts may be made without the following:

1. A protocol approved by the Protocol Review Committee;
2. approval of the Vice President for Medical Affairs;
3. approval of the Director of Research;
4. approval of the project director.

B. Grants and contracts are to be awarded only after the appropriate human research committee approval.

X CONTINUING EDUCATION

A. All employees are encouraged to engage in continuing education in areas appropriate to their responsibilities.

B. Symposia, special courses, conferences, and work shops, are acceptable forms of continuing education.

C. Physician monitors are expected to enroll in adequate numbers of approved refresher courses to maintain licensure and specialty board status.

-40-

EXHIBIT 1.

LOCAL

DEPT. NO. 832

COST CENTER NO.: 41-05

DEPARTMENT OF MEDICAL RESEARCH

COMMITMENT FORM

Date:_____

PRINCIPAL INVESTIGATOR:
Name:
Address:

Social Security No._____

Drug and Bristol Number:

STUDY DATA (include purpose of study, study number, dates of initiation and completion):

FINANCIAL DATA:

Check Payable to:_____

Total Commitment:_____

Project Code No.:

Proposed Payment Schedule:

$_____Date_____

$_____Date_____

$_____Date_____

APPROVAL:

Project Monitor_____Date_____

Project Director_____Date_____

Protocol Review Committee_____(Chairman)Date_____

Vice President, Medical Director_____Date_____

Vice President, Research_____Date_____

Copies: Project Director, A. Z. Lane

EXHIBIT 2.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
FOOD AND DRUG ADMINISTRATION
WASHINGTON, D.C. 20204

DRUG EXPERIENCE REPORT

Form Approved
Office of Management and Budget No. 57-R0004

DATE SENT TO FDA (Mo., day, yr.) | 1. ☐ INITIAL REPORT ☐ FOLLOW-UP REPORT | 2. PATIENT INITIALS AND IDENTIFICATION NUMBER | 3. ACCESSION NO. (For FDA use only)

SECTION I. BASIC REACTION DATA

4. SEX ☐ M ☐ F | 5. HEIGHT (in.) WEIGHT (lbs.) | 6. DATE OF BIRTH (mo. day yr.) | 7. ORIGIN ☐ CAUC ☐ NEGRO ☐ ORIENTAL ☐ AMERICAN INDIAN ☐ OTHER | 8. DATE OF REACTION ONSET (mo. day yr.)

9. SOURCE OF REPORT (MD, Hospital, etc.) (Name of reporting Physician is optional.) | 10. ADDRESS OF SOURCE (Give Street, City, State, and Zip Code.)

11. DESCRIBE SUSPECTED ADVERSE REACTION(S) AND ANY POSSIBLE ASSOCIATION WITH THE DRUG(S) INVOLVED

12. OUTCOME OF REACTION TO DATE
- ☐ ALIVE WITH SEQUELAE
- ☐ RECOVERED
- ☐ STILL UNDER TREATMENT
- ☐ DIED (Give date and cause)

13. LIST ALL THERAPY IN ORDER OF SUSPICION (Manufacturer: List NDA or IND No.)

NAME OF DRUGS TRADE (Generic)	MANUFACTURERS CONTROL NO.	DOSAGE FORM (tab., cap., etc.)	TOTAL DAILY DOSE	ROUTE (po., im., iv., etc.)	DURATION OF THERAPY	DATES OF ADMINISTRATION	14. DISORDER OR REASON FOR USE OF DRUG

SECTION II. IMPORTANT MODIFYING DATA

15. SUBSTANTIATING LABORATORY STUDIES (Clinical Laboratory, Autopsy, X-Ray, etc.) — CLINICAL LAB: ☐ DONE ☐ ATTACHED ☐ NOT DONE; BIOPSY/AUTOPSY: ☐ DONE ☐ ATTACHED ☐ NOT DONE

16. LIST POTENTIALLY NOXIOUS OR ENVIRONMENTAL FACTORS (Include household products, industrial and agricultural chemicals)

17. EXISTING OR PRIOR DISORDERS AND PAST DRUG REACTION OR ALLERGIC HISTORY — PREVIOUS EXPOSURE TO SUSPECTED DRUG OR RELATED COMPOUND ☐ YES ☐ NO

18. (a) IF FEMALE: GRAVIDITY ☐☐ PARITY ☐☐ (b) IF PREGNANT: WEEKS OF GESTATION ☐☐

19. MAY THE SOURCE OF THIS REPORT BE RELEASED TO THE ARMED FORCES INSTITUTE OF PATHOLOGY? ☐ YES ☐ NO

FOR FDA USE ONLY | **FOR MFG USE ONLY**

20. REACTION FACTORS (Check all applicable boxes)
☐ DECOMPOSITION OF DRUG ☐ INTERACTION OF TWO OR MORE DRUGS ☐ DRUG NOT USED ACCORDING TO LABELING ☐ DRUG OUTDATED
☐ DRUG MISUSED BY PATIENT ☐ OVERDOSAGE ☐ DRUG MISLABELED ☐ CONTAMINATION OF DRUG ☐ OTHER DRUG MISUSE (Specify)

FD FORM 1639 (12/72) — SEE INSTRUCTIONS ON REVERSE — Use additional sheet if necessary.

AND INVESTIGATIONAL DRUG SUPPLIES Rev. 7/74

ROM: _____ DATE: _____

O: A. P. Granatek (3)

C: B. C. Nunning
d. E. Kaser R. T. Catherall
A. Z. Lane

☐ IND filed Date _____
☐ Protocol approved
☐ Commitment approved

page ___ of ___ pages

AME OF DRUG: DOSAGE FORM _____

UNIT DOSE _____

NVESTIGATIONAL UPPLIES DL # MARKETED SUPPLIES List #

UMBER OF BOTTLES ___ NUMBER OF DOSES PER BOTTLE _____

VIALS ___

AS THIS FORMULATION BEEN ORDERED PREVIOUSLY?

__NO ___YES, SEE LOT NUMBER _____

ELIVERY:

)RMAL ___URGENT DELIVERED BY: _____

ABELING:

__REGULAR CLINICAL LABEL ___ REGULAR MARKETED LABEL

__STICKER FOR FUTURE USE

__TRI-PANEL LABEL USING ATTACHED RANDOMIZATION SCHEDULE AND DOSAGE INSTRUCTIONS. LABEL AS STUDY NO. _____

EMARKS FOR SPECIAL INSTRUCTIONS

EXHIBIT 3.

PPROVED:

ECTION DIRECTOR: _____ DATE: ___

BRISTOL LABORATORIES

EXHIBIT 4.

PRODUCT DEVELOPMENT DEPARTMENT

TO: A.Z. Lane (2)
C. Blum
W. E. Kaser ✓
B. C. Nunning
H. J. Rinefierd
D. E. Tisch

DATE: August 13, 1975

SUBJECT: Mitomycin Capsules, 10 mg. - DL# 2400.0

Transfer of Material to MEDICAL STOCKROOM

Formulation #: 75R168

Amount of Material: 1 box of 40 bottles each containing 25 capsules = 1,000 capsules

Description: Each #4 size capsule, #33 maroon opaque cap on #38 ivory body, contains:

SEE ATTACHED FORMULA

BRISTOL LABORATORIES
Div. of Bristol-Myers Co. Syracuse, New York
DEPT. OF MEDICAL RESEARCH
25 CAPSULES 10 MG.
MITOMYCIN
Lot 75R168 Exp. Date 8/78

RECEIVED
AUG 18 1975
W. E. KASER

RECEIVED
AUG 1
S. T. Crooke, M.D. Ph.D.

THIS MATERIAL HAS BEEN RELEASED BY CONTROL

Study Desired:

Clinical use requested by W. E. Kaser

A. P. Granatek

A. P. Granatek

EXHIBIT 5.

FORMULATION # CODE: SUBJECT

DESCRIPTION:

AMOUNT REC'D: DATE REC'D:

PHARMACOLOGY RELEASE: CHEM. ASSAY:

CONTROL RELEASE: BIOASSAY:

MEMO FROM PROD. DEV.:

AMOUNT	SENT TO	DATE	BY	BALANCE

EXHIBIT 6.

REQUEST FOR DRUG SHIPMENT

To _____

_____

_____

_____ (Zip Code)

_____

Date _____

Project No. _____

Commitment Verified _____ Doris Millette

Shipment Acknowledged _____ Clin. Monitor

FORMULATION NO.	PRODUCT IDENTIFICATION	NO. DESIRED

(rev. 10/75)

SIGNED _____

(Signature)

EXHIBIT 7.

REQUISITION FOR CLINICAL MATERIAL

SHIP TO (NAME OF INVESTIGATOR)	SHIP VIA	DATE
INSTITUTION	INSTRUCTIONS	
STREET AND NO.		
CITY	AUTHORIZED BY: MEDICAL DIRECTOR/DIRECTOR-CLINICAL TRIALS/ DIRECTOR-CLINICAL PHARMACOLOGY	
STATE # ZIP		

QUANTITY	DESCRIPTION

REQUESTOR - PLEASE CHECK THIS SHIPMENT CAREFULLY - SIGN AND RETURN TO:

RECEIVED BY: DATE

THIS MATERIAL TO BE USED FOR CLINICAL INVESTIGATION ONLY

BRISTOL LABORATORIES
P.O. BOX 657
SYRACUSE, NEW YORK 13201
ATTN:

P-226-00

FROM: W. E. Kaser
TO:
DATE:
SUBJECT: Returned Clinical Supplies - Non-Controlled Substances

BRISTOL LABORATORIES
MEMORANDUM

C.C.

The supplies listed in this memo have been returned by

_____ on _____.

It is your responsibility to maintain a record of supplies used or returned by this investigator and, if any discrepancy exists, to obtain an explanation or accountability from him.

The following returned items were received and have been delivered to Product Development for destruction:

EXHIBIT B.

WEK/hw

_____
W. E. Kaser

BRISTOL LABORATORIES
MEDICAL RESEARCH DEPARTMENT
P.O. BOX 657
SYRACUSE, N.Y. 13201

EXHIBIT 9.

INVESTIGATOR'S DRUG DISPOSITION RECORD

INVESTIGATOR'S NAME M.D.			DATE
NAME OF DRUG	LOT NO.	EXP. DATE	STUDY OR PROTOCOL NO.
DOSAGE FORM AND SIZE	QUANTITY DELIVERED	DATE DELIVERED	

PATIENT IDENTIFICATION	AMOUNT ADMIN. OR DISPENSED	DATE	AMOUNT RETURNED	DATE

_____, M.D. DATE _____
SIGNATURE OF INVESTIGATOR

WHEN YOU HAVE COMPLETED THIS FORM PLEASE RETURN THE DUPLICATE COPY TO BRISTOL LABORTORIES, MEDICAL RESEARCH DEPARTMENT, P.O. BOX 657, SYRACUSE, N.Y. 13201. KEEP THE ORIGINAL FOR TWO YEARS FROM A DATE TO BE SUPPLIED AT THE TERMINATION OF THE STUDY.

8-414-00 (10-75)

BRISTOL | LABORATORIES

Division of Bristol-Myers Company

Date _____

I acknowledge receipt of one sealed carton containing SUPPLIES FOR _____

(Insert Study Identification)

These supplies are addressed to:

(Insert Name and Address as it appears on the DEA form)

These materials are to be shipped to the addressee by a (suitable bonded carrier as determined by the shipper)*.

SIGNED_____DATE_____

SIGNED_____DATE_____

SIGNED_____DATE_____

*Substitute name of other carrier (e.g., Federal Express) or state that it is to be "hand carried" if the monitor so stipulates.

EXHIBIT 10.

-50-

U.S. DEPARTMENT OF JUSTICE
DRUG ENFORCEMENT ADMINISTRATION
OFFICIAL ORDER FORM
FOR SCHEDULE I AND II CONTROLLED SUBSTANCES
BOTH PURCHASER AND SUPPLIER MUST BE PROPERLY REGISTERED BEFORE USING THIS FORM.
THIS IS AN ORDER TO SUPPLY DRUGS SPECIFIED BELOW

NAME AND ADDRESS OF REGISTRANT
CAMBRIDGE HOSPITAL
1493 CAMBRIDGE ST.
CAMBRIDGE, MASS. 02139

01/31/75
DEA REGISTRATION NO. AC4147167
SCHEDULES 2,2d,3,3d,4,5
REGISTERED AS A HOSP/CLINIC
NO. OF THIS OTHER FORMS 1231C1264

STUDY VO 301-05 AB

TO (SUPPLIER) Bristol Labs Div of Bristol-Myers Co
STREET ADDRESS Thompson Road
CITY AND STATE East Syracuse New York 13057
DATE 9/10/75
SUPPLIERS DEA REGISTRATION NUMBER
TO BE FILLED IN BY PURCHASER

ITEM	NUMBER OF PACKAGES	SIZE OF PACKAGE	NAME OF ITEM	NATIONAL DRUG CODE	NO. OF PACKAGES SHIPPED	DATE SHIPPED
1	1 ea	2 ml	Imferon Inj. 50 mg./ml		100	16 Sept 75
2						
3						
4						
5						

THIS ORDER IS FOR EXACTLY 1 ITEMS (NUMBER OF ITEMS MUST BE ENTERED IN WORDS)

NAME OF FIRM IF NOT AN INDIVIDUAL
Cleveland C. Amory Memorial
SIGNATURE OF PURCHASER OR HIS ATTORNEY OR AGENT
Richard P. Bowen

FORM DEA-222C (FEB. 74)

SAMPLE

EXHIBIT 11.

-51-

To: W.E. Kaser
From: Q.P. Granatek
A. Rinefierd

Transmitted to you are the following:

Lot Number	Amount	Formula Title
74K905 (75K5001)	100 vials	Butorphanol Tartrate Injection, 1 mg./ml. — 2 ml./vial
75K17 (75K5003)	100 vials	Meperidine Hydrochloride Injection, 40 mg./ml. — 2 ml./vial

SAMPLE

These are for shipment to Francis Caminale, M.D. Cambridge, M as part of Butorphanol Study # 302

Received By: Davis S. Clearlow
Date: 9/16/75

EXHIBIT 12.

BRISTOL | LABORATORIES

MEMORANDUM

FROM: W. E. Kaser
DATE:

SUBJECT: RETURNED CONTROLLED SUBSTANCES

TO: E. P. Mariani

CC: A. P. Granatek, J. C. LaPiana, F. S. Caruso, W. F. Minor

Investigator:_____

Date Return Order Received:_____Dosage Form:_____

Returned with this memo are unused clinical supplies from _____conducted by the above listed investigator. Using the attached randomization schedule, please decode and identify the contents of this shipment. Please record your findings in the appropriate spaces provided at the bottom of this memo and indicate lot number, drug identity, and exact quantity of tablets, capsules, unopened or partial parenteral vials, or other drug dosage forms contained therein.

Upon completion of decoding and inventory, please arrange for destruction of this material using the appropriate methods prescribed for controlled or non-controlled substances. Your signature on this memo will serve as a receipt for the indicated supplies and will assure that proper storage and destruction of these materials will be carried out.

Thank you.

WEK/hlw W. E. Kaser

The supplies are as follows:

Drug	Lot#	Strength/ Concentration	Package Size	Quantity Returned

EXHIBIT 13.

Received by_____Date_____

Witnessed by_____Date_____

ADDENDUM 1

"PROPOSED GUIDELINES FOR GOOD CLINICAL RESEARCH PRACTICE".

Section VI - Drugs and Supplies

B. 3. d. During the first week of each quarter (i.e. January, April, July, and October) the Medical Storeroom Administrator will examine all Inventory File Cards for Non-Controlled Substances in The "Active Drug File". At that time, all compounds which have aged 2 years or will be aged 2 years during the current annual quarter will be removed from the Medical Storeroom and placed in quarantine by Product Development. Furthermore, supplies with a labeled expiration date which has been reached or will be reached during the quarter will also be removed from active inventory and placed in quarantine by Product Development.

At that time, a physical inventory of those items will be conducted by Research Storeroom Personnel and the Medical Stockroom administrator or clerk. If it is desirable to maintain those supplies in the Medical Storeroom, Product Development will take all necessary measures to obtain an extension of expiration date or proof that stability of the compound(s) can be guaranteed for an additional stated period of time.

Following such actions, Product Development will re-transfer acceptable supplies to the Medical Storeroom as described in Section VI - 2. a.

e. Following any routine transaction within the Medical Storeroom when supplies are removed for shipment or transfer, the Research Stockroom personnel will record the remaining balance of each item on the Requisition for Clinical Material. (Exhibit 7). This Requisition is then delivered to the Medical Storeroom clerk who will then verify inventory balance(s) and adjust the appropriate inventory file card(s) to reflect the shipment or transfer.

C. 3. During the first week of each quarter, The Medical Storeroom administrator will examine all Inventory File Cards for Controlled Substances in the "Active Drug File". These materials, with the cooperation of Product Development and the Narcotic Control Officer, will be handled in the same manner described in Part B, paragraph 3 of this section. Routine shipments or transfers in this category are handled in the same manner.

ADDENDUM #2

BRISTOL | LABORATORIES

MEMORANDUM

FROM: A. Z. Lane
DATE: March 15, 1977

JECT:

TO:

C. T. Braun	L. L. Gordon	J. J. Quigley
C. C. Carmack	A. P. Granatek	R. A. Ricci
F. S. Caruso	P. K. Jones	S. B. Siskin
R. T. Catherall	M. Losada	J. Soler
G. M. Chudzik	R. J. Noveck	R. A. Trompeter
S. T. Crooke	I. J. Pachter	J. R. Vogel
M. D. DeFuria	R. M. Pilson	R. D. Wilkins
P. Eleftheriou	E. G. Porter	G. E. Wright
L. A. Farchione	A. W. Prestayko	E. Yevak
J. C. Godfrey		

Please find attached a description of procedures which will be followed for all double blind studies conducted by the Medical Department. Your conformance with these instructions will aid in documenting maintenance of the double blind design during our clinical studies.

A. Z. Lane

AZL:dw
Encl.

FROM:
TO:
DATE:
SUBJECT:

BRISTOL | LABORATORIES
MEMORANDUM

C.C.

PROCEDURES FOR DOUBLE BLIND STUDIES

The following procedures will apply to all double blind studies in order to document maintenance of the double blind design.

I. GENERAL PRINCIPLES

Bristol's procedures of assignment to treatment and packaging of medication for each individual, identified by a 3 - piece tear-off label will be continued.

A. Assignment to Treatment

Subjects will be numbered consecutively (as they enter the study, within stratifying restrictions, etc.) and assigned at random to one of the study treatments.

B. Treatment Identification

Medication will be packaged for each individual separately, identified by a 3-piece tear-off label (see attached copy). The portion of the label glued to the bottle shows only the (consecutive) subject number and/or dosing instructions. The tear-off portion of the label identifies, sealed internally the medication and dose.

II. IMPLEMENATION

A. Assignment to Treatment

Randomization schedules will be generated by Biostatistics in consultation with the study monitor and in compliance with the protocol. Three (3) copies of the schedule will be made and distributed as follows:

1. Regulatory Affairs
2. Product Development This copy will be forwarded following receipt by Biostatistics of six (6) copies of the study monitor's drug order.
3. Biostatistics

The study monitor may request decoding for completed cases from Biostatistics. Biostatistics will furnish such information without delay.

B. Compliance

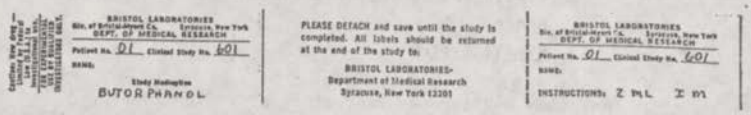
All tear-off portions of the tri-panel labels must be returned by the investigator to Bristol's study monitor, together with full explanations for any broken labels. Preferably labels should be stapled to the corresponding case report forms.

The Bristol monitor forwards all labels and explanations for broken ones to the Medical Stockroom coordinator. Following completion of a study, a report is issued by him, indicating the number of labels released by the Medical Stockroom, the number of lables returned intact, and where applicable, the number of legitimately (explanation) and/or unlegitimately broken labels returned.

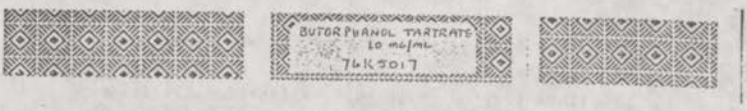
All returned labels and explanations will be filed by the Medical Stockroom coordinator until final NDA approval.

Examples:

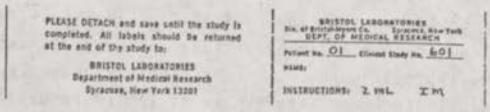
(Front)



(Back)



(Folded)



ADDENDUM #3

BRISTOL LABORATORIES

MEMORANDUM

FROM: S.T. Crooke
DATE: 21 Mar 77

SUBJECT: See below -

TO:
C.T. Braun
C.C. Carmack
F.S. Caruso
M.D. DeFuria
J.C. Godfrey
L. Gordon
M. Losada
R.J. Noveck
R.M. Pilson
A.W. Prestayko
J.J. Quigley
R.A. Trompeter
J.R. Vogel
R.D. Wilkins
G.E. Wright
E. Yevak

CC:
A.Z. Lane
I.J. Pachter
R.D. Smyth

Dr. Robert D. Smyth will serve on the Protocol Review Committee to review pharmacokinetic sections of protocols. It is suggested that pharmacokinetics be reviewed with members of the pharmacokinetic group prior to submission to the Protocol Review Committee.

STC

STC/j

RECEIVED
MAR 24 1977

S.T. Crooke, M.D., Ph.D.

BL-14-70

BRISTOL | LABORATORIES

MEMORANDUM

FROM: S.T. Crooke
DATE: 2 Feb 77

SUBJECT: See below

TO: C.T. Braun, C.C. Carmack, F.S. Caruso, M.D. DeFuria, J.C. Godfrey, L. Gordon, M. Losada, R.J. Moveck, R.M. Pilson, A.W. Prestayko, J.J. Quigley, R.A. Trompeter, J.R. Vogel, R.D. Wilkins, G.E. Wright, E. Yevak

cc: G.H. Hottendorf, A.Z. Lane, I.J. Pachter

Sections of all future protocols which deal with animal toxicology must be submitted to Dr. Hottendorf for his approval prior to submission to the Protocol Review Committee. His approval should be attached to the memo accompanying the submitted protocol.

For protocols which employ a toxicology section previously used and approved, it is necessary only to note that the toxicology section was previously approved by Dr. Hottendorf.

STC

STC/j

ADDENDUM #5 -60-

BRISTOL | LABORATORIES

MEMORANDUM

FROM: S.T. Crooke
DATE: 3 Nov 77

SUBJECT: FDA GUIDELINES RELATIVE TO PROTOCOL REVIEW

TO: I.J. Pachter

cc: Clinical research

CC: C.T. Braun, F.S. Caruso, R.T. Catherall, L.A. Farchione, A. Glick, R.H. Hottendorf, R.D. Smyth

At a recent meeting of the Protocol Review Committee, we discussed recently published proposed FDA guidelines for clinical research, and a number of other matters. In this memo I describe the discussion, and the decisions reached.

1. In general the committee members are in agreement that our procedures are in compliance with the proposed FDA regulations. However, it is clear that it is necessary to revise the guidelines for good clinical research developed several months ago. I was assigned the task of revising the guidelines.

2. Specific deficiencies in record keeping relative to the FDA proposals were identified, and steps to correct these deficiencies are outlined below.

   a. At present adequate records of telephone conversations and site visits with investigators are not maintained. Mr. Catherall was assigned the task of development of forms to record telephone and personal visits with investigators. These will be kept in appropriate study files.

   b. Minimum standards for site visits are to be generated to conform with the proposed FDA guidelines. The necessity of formal site visits, and the general nature of these visits will be included in all protocols. Dr. Glick was assigned the responsibility for development of these minima.

   c. At present no standardized procedures to insure that protocols are in fact submitted to human research committees are in effect. To this end we will in the future require submission of the protocol, or form actually submitted to human research committees, and the memo of acceptance of the protocol from the chairman of the committee.

Memo
STC-IJP
3 Nov 77

d. Standardized guidelines for informed consent are to be amended to include a provision which will indicate that the patients' records may be reviewed by a Bristol monitor to allow quality assurance. Dr. Glick will revise the guidelines for informed consent.

e. Mr. Catherall will obtain lists of approved laboratories. Any unapproved laboratories to be employed in studies must submit documentation of adequacy.

3. The committee reaffirmed the position that a clinical brochure must be approved before any protocol involving a non-marketed agent can be approved. Moreover, the contention that a long introduction in the protocol, or the use of original preclinical reports in lieu of a reasonable clinical brochure, remains unacceptable to the committee.

4. All final reports on all studies are to be submitted to the protocol review committee for review. The usual 5-day deadline for review is extended to 10 days for review of final reports.

5. All revisions of all approved protocols must be submitted to the protocol review committee. No revisions are to be made in approved protocols without informing the committee.

It is our view that the changes in procedures outlined above, and the revision of the guidelines for good clinical research will assure compliance with FDA requirements.

Stc/j
STC

STC/j

ADDENDUM #6

BRISTOL | LABORATORIES

MEMORANDUM

FROM: S.T. Crooke
DATE: 8 December 77

SUBJECT:

TO: PRC Members

C.T. Braun
F.S. Caruso
R.T. Catherall
L.A. Farchione
A. Glick
C.C. Carmack
A.B. Dobkin
M. Losada
J.J. Quigley
R.A. Trompeter
G.E. Wright
E. Yevak
G.M. Chudzik
P.K. Jones
F.V. Macalalad
E. Porter
S.B. Siskin
W.M. Smart
J. D'Aoust
M.D. DeFuria
A.W. Prestayko

In response to a request from the Protocol Review Committee, Dr. Glick has proposed that the attached statements be added to all protocols. The study monitoring section should be inserted in the regulatory affairs section of each protocol, and the informed consent guidelines should be revised to include the statement concerning medical record review.

STC

STC/j

BRISTOL | LABORATORIES

MEMORANDUM

FROM: A. Glick
DATE: December 5, 1977

SUBJECT: Monitoring of Study - Proposed Addition to all New Protocols

TO: S. T. Crooke

cc: C. T. Braun
F. S. Caruso
R. T. Catherall
L. A. Parchione
R. H. Hottendorf
I. J. Pachter
R. D. Smyth

As a result of the Proposed Establishment of Regulations on Obligations of Supervisors and Monitors in the Federal Register of 9/27/77, I was requested at the Protocol Review Committee meeting last month (minutes 11/3/77) to prepare a statement, in conformity with the proposed regulations, on the necessity of site visits and the general nature of these visits which would be included in all future protocols. I propose the following:

Monitoring of Study

A representative of the sponsor's monitor team will visit the investigator at the site of the investigation during the study to assure that the following obligations of the investigator are being fulfilled:

(i) Continued acceptability of the facilities.

(ii) Adherence to the study protocol and applicable FDA regulations regarding obligations of the investigator.

(iii) Maintenance of adequate records of subject identification, clinical observations, laboratory tests, and drug receipt and disposition.

(iv) Reports submitted by the investigator in support of the safety and/or effectiveness of the investigational drug are timely, adequate and accurate.

During the periodic visits to the investigator, the investigator will allow the monitor to review the source documents used in the preparation of the case reports in order to verify the accuracy and completeness of the information contained in those reports.

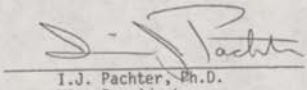
Under Guidelines for Informed Consent, I propose the following insertion:

> The subject should understand that his medical record may be inspected during or after the study by a representative of Bristol Laboratories' monitor team to verify the accuracy and completeness of the data entered in the case report form.

A.G.

AG/sdk

Because the Vice President and Medical Director during the period in question as well as certain other medical monitors directly responsible for the studies under review are no longer employed by our company, I have asked Stanley T. Crooke, M.D., Ph.D., a Bristol physician for whom I have the highest regard and who joined Bristol Laboratories in July 1975 to direct our effort in the cancer area, to prepare an independent appraisal of the record. Let me emphasize that Dr. Crooke was not associated with the studies in any way. It will be appreciated that Dr. Crooke has had limited time to gather, digest and evaluate the information available, but I trust that his assessment is essentially complete.



I.J. Pachter, Ph.D.
Vice President
Research and Development
BRISTOL LABORATORIES

Information on studies performed by
Dr. #2, Dr. #3, and Dr. #7

Bristol Laboratories has been informed that the Subcommittee on Health and Scientific Research of the Committee on Human Resources of the United States Senate is interested specifically in the conduct, and monitoring of clinical studies 8 and 15 performed under IND 10,127 (BL-3912A), and studies 58A and 59A performed under IND 9,870 (Butorphanol-Oral). The principal investigators for these studies were Dr. #2 (IND 10,127 studies 8 and 15), Dr. #3 (IND 9,870 study 58A), and Dr. #7 (IND 9,870 study 59A). This statement has been prepared to provide information concerning these studies.

BL-3912A

Background

BL-3912A is a substituted phenylisopropylamine similar structurally to a group of psychoactive agents including amphetamine, and 2,5 dimethoxy-4-methylamphetamine (R-DOM). BL-3912A differs from R-DOM chemically by being an ethyl rather than a methyl derivative.

Studies employing several species of laboratory animals suggested that BL-3912A might be a potent performance restorer absent the generalized CNS stimulatory, and hallucinogenic properties of several of the other agents of this class. In fact, BL-3912A was found to antagonize R-DOM-induced abnormal behavior in cats, and enhance operant and learned behavior tasks. In experiments with aged rats, BL-3912A was demonstrated to facilitate learning and prolong memory. These effects were tentatively ascribed to the 5-hydroxytryptamine (serotonin) receptor agonist activity of BL-3912A, and were produced at doses significantly lower than toxic doses.

Thus, based on experimental animal data, experience with compounds of similar structures, and data concerning its mechanism of action, BL-3912A was a promising candidate for clinical trials. Initial clinical trials included phase I studies in two groups of normal volunteers. In the first study doses of 1 mg to 80 mg were employed without significant side effects. In the second phase I study, doses of 20 to 120 mg were tested. Many of the volunteers who received 40 mg to 120 mg noted increased mental alertness and demonstrated improvement in a performance test. At a dose of 120 mg, definite euphoria and mild CNS stimulation were observed, but no other toxicities were noted. Studies employing 60 healthy volunteers were performed with BL-3912A before trials in patients were begun.

Study number 8 for which Dr. #2 was principal investigator was the first study in which BL-3912A was administered to geriatric patients, suffering from senile mental deterioration. It was a double blind placebo comparative study. The initial doses employed were 25 mg and 50 mg daily for five days. If no side effects were observed, the doses were increased to 25 mg or 50 mg twice daily for seven days, then three times daily for the duration of the study. The results of this study suggested that doses of 50 mg - 150 mg daily resulted in statistically significant improvement in mental performance in geriatric patients with no significant toxicities.

Study number 15 was also performed by Dr. #2. This study was an open dose ranging safety and efficacy study in which patients were treated with doses of 25 mg to 75 mg daily for a period of 60 days. The conclusions from this study were that BL-3912A resulted in improvement in mental acuity with no significant toxicities.

Subsequent to the studies performed by Dr. #2, several other studies were performed. In these studies BL-3912A was shown to be non-amphetamine like, but the positive results in geriatric patients reported in studies 8 and 15 were not reproduced.

As a result of the inability to reproduce the positive results obtained initially, further clinical studies were discontinued.

General Considerations Relevant to Studies 8 and 15

The primary research interests of Bristol Laboratories are antibiotic, anticancer and analgesic drug development. BL-3912A resulted from a collaborative research effort with an extramural scientist. Consequently, the intramural clinical expertise in the area of CNS performance enhancers was not optimal at the initiation of clinical studies on BL-3912A. In fact, since very few drugs for senile mental deterioration have been developed, clinical drug testing expertise is probably substantially less for such compounds than compounds of different classes throughout the academic and pharmaceutical company research establishments. Consequently, the performance of the initial efficacy trials was perhaps suboptimal.

Selection of Dr. #2 as Principal Investigator

At the initiation of studies 8 and 15, Dr. #2's credentials seemed ideal. After completion of medical school and postgraduate training in surgery, Dr. #2 engaged in the private practice of medicine until joining a major pharmaceutical firm as a monitor for the clinical trials of a psychoactive agent thought to be active in the treatment of childhood hyperkinesis. He subsequently was promoted to Associate Medical Director, then became Director of Clinical Research Projects at another pharmaceutical company. During this period Dr. #2 generated several publications.

Thus, Dr. #2 had considerable experience in the clinical evaluation of drugs, and more particularly had been involved in research on a psychoactive agent. Moreover, at the initiation of studies 8 and 15, he was associated with a geriatric center, and consequently had access to the appropriate patient population. Having worked himself as a medical monitor, he was well aware of the regulatory obligations of a clinical investigator.

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Monitoring of Studies 8 and 15

The initial studies on BL-3912A were developed and monitored by a physician employed for the purpose of monitoring this drug. Prior to joining Bristol Laboratories, the medical monitor had performed a number of controlled clinical studies and had published in the medical literature on the effects of drugs in geriatric and younger patients with anxiety neuroses, depressive neuroses and psychophysiologic disorders. Studies with Dr. #2 were the first involving patients that he was asked to monitor for Bristol Laboratories. Prior to initiation of studies with Dr. #2, Dr. #2 and the facilities were site visited by the monitor, and subsequently by the Vice President and Medical Director for Bristol Laboratories.

Study number 8 was initiated on December 11, 1974 and terminated on April 7, 1975. Study number 15 was initiated on January 30, 1975 and terminated on April 7, 1975. During this period the medical monitor made two monitoring visits on January 6-7, 1975, and February 17-25, 1975. Numerous telephone conversations are alluded to in the correspondence between the monitor and Dr. #2 during this period.

On April 30, 1975, the monitor's employment at Bristol Laboratories was terminated. On May 5, 1975 a replacement medical monitor joined the medical staff at Bristol Laboratories for BL-3912A. Strenuous efforts by the new monitor and his associates to obtain case reports failed for many months, and when case reports were obtained they were incomplete. Investigation by Bristol Laboratories and the FDA suggested that Dr. #2 had failed to meet the obligations of informed consent, and failed to follow the protocol in many patients.

Informed Consent and Human Research Committee Approval

Approval of protocols 8 and 15 by an appropriate human experimentation committee was required by Bristol Laboratories, as this is a requirement for all Bristol Laboratories' clinical studies. In a letter dated November 11, 1974, Bristol Laboratories was informed of Human Research Committee approval. Subsequently, Bristol Laboratories has been informed by the FDA that there is doubt concerning the legitimacy of this approval.

Bristol Laboratories required and obtained sample informed consent forms at the initiation of studies 8 and 15. However, inasmuch as the case report forms were never completed by Dr. #2, no informed consent forms were received by Bristol Laboratories. Subsequently, Bristol Laboratories was informed by the FDA that no evidence of signed informed consent forms could be found in the patient's records at Dr. #2's geriatric center in which the studies were performed.

Analysis of Data Generated by Studies 8 and 15

Although the case reports obtained were incomplete, they were evaluated. In general the results suggested activity, with only minimal side effects. However, the monitor's reports clearly indicate the lack of demographic data, and the deficiencies in the case report forms. Moreover, because of significant doubts concerning the results of these studies, similar studies were initiated in other institutions under well-monitored and well-controlled circumstances. These studies failed to confirm the results of studies 8 and 15, and the clinical evaluation of BL-3912A was discontinued. In none of the studies on BL-3912 were serious side effects noted in any patient.

Oral Butorphanol Studies

Background

Butorphanol is an orally active, totally synthetic non-narcotic analgetic. In experimental animals, butorphanol was shown to be a more potent analgetic than morphine, and had a very low addictive activity. It was also found to be a potent narcotic antagonist, and antitussive. Toxicologic studies in several species demonstrated that butorphanol had a broad therapeutic index in animals, and was devoid of teratologic activity in animals. Consequently, it seemed a promising candidate for clinical development.

Clinical evaluation of parenteral butorphanol has been completed. Prior to initiation of studies 58A and 59A, parenteral butorphanol was evaluated in more than 2500 patients, and these studies demonstrated that parenteral butorphanol is a potent analgetic of value for the treatment of moderate and severe pain of various etiologies. The side effects of butorphanol have proven to be manageable and similar to those reported for other potent analgetics such as morphine and meperidine. They included occasional episodes of lightheadedness, drowsiness, nausea and, very rarely, hallucinations. The effects of butorphanol on respiration have been reported to be less pronounced than those due to morphine

and the liability of butorphanol for producing physical dependence has been reported to be extremely low. A new drug application has been filed on the basis of the parenteral data.

Clinical studies on oral butorphanol are in progress and yielding promising results. It is expected that a new drug application will be filed for oral butorphanol within the next several months.

General Considerations Relevant to Studies 58A and 59A

Bristol Laboratories employs third party monitoring facilities infrequently. During the past few years Bristol Laboratories has collaborated with consultant firms on a total of 16 studies. All of these monitoring groups were employed to study butorphanol.

The decision to employ a third party firm was reached for two reasons. First, because of the work load imposed by extensive research on parenteral butorphanol, at the time of initiation of studies 58A and 59A, it was felt that the analgetic clinical staff at Bristol Laboratories might not be able to monitor additional studies effectively. Second, because the evaluation of an oral analgetic is a difficult endeavor due to the subjective nature of responses, it was considered prudent to employ an impartial monitoring facility to confirm results obtained intramurally.

Thus, the firm undertook primary responsibility for studies 58A and 59A. Its responsibilities included generation of protocols and case report forms, acquisition of investigators, monitoring of the studies, and evaluation of the clinical data. Before studies 58A and 59A were initiated, over 500 volunteers and patients had received oral butorphanol in studies monitored by Bristol Laboratories.

Study Number 58A

Purpose of Study

The protocol prepared by the contract firm was designed to evaluate in a double-blind, randomized, comparative trial the analgetic activity and side effects of butorphanol given for three days at doses of 4 mg or 8 mg four times daily, and compare the effects to codeine, 60 mg, four times daily, and placebo in patients with musculoskeletal pain. The patients were to be outpatients.

Selection of Dr. #3 as Principal Investigator

Dr. #3 was selected as the principal investigator by the contract firm. However, subsequent to Study 58A, Bristol Laboratories has employed Dr. #3 as principal investigator for butorphanol studies 602-16, 603-05 and 802. The continued employment of Dr. #3 by Bristol Laboratories is due to his excellent credentials, and his performance on prior studies.

Monitoring of Study 58A

The monitoring of Study 58A was conducted by the contract firm. No significant problems were reported by the contract firm during the conduct of this study.

Human Research Committee Approval and Informed Consent

Human research committee approval was not obtained since this was an outpatient study. However, each patient enrolled in the study signed an informed consent.

Evaluation of Study 58A

Final evaluation of Study 58A was conducted by Bristol Laboratories personnel. Of the 93 patients enrolled in this study, 93 were evaluable for toxicities; 91 for analgetic activity. The analgetic response to butorphanol at doses of 4 mg and 8 mg was equal to codeine 60 mg. However, all three treatment groups experienced significantly greater pain relief than the patients in the placebo group.

The most frequent of the reported side effects included dizziness, nausea, and sedation. The incidence of butorphanol-induced side effects was slightly, but not statistically, greater than those induced by codeine. The results of this study have been confirmed by Studies 71, 78, and 803.

Study 59A

Purpose of Study

The protocol was designed to determine in a randomized, comparative, double-blind study the activity of butorphanol (8 mg or 16 mg), codeine (60 mg), and placebo in the treatment of post surgical pain. The patients were to be hospitalized.

Selection of Dr. #7 as Principal Investigator

Dr. #7 was selected by the contract firm. However, his credentials appeared to be acceptable. A concern was Dr. #7's ability to perform an inpatient study at a time when he was an emergency room physician, but this was discussed, and Dr. #7 assured the firm's personnel that he could perform the study.

Monitoring of Study 59A

During the brief period during which study 59A was active, all monitoring was performed by the contract firm. The study was initiated on 10/28/75 and terminated on 1/9/76. During the period of the study, six monitoring visits were made by monitoring personnel. As a result of the monitoring visits, it became obvious that Dr. #7 was not adequately performing the study, and the personnel in the hospital were inadequately trained to perform the study. In addition, Dr. #7 experienced administrative difficulties in the hospital. Consequently the study was terminated after 16 patients were enrolled.

Human Research Committee Approval and Informed Consent

The contract firm was informed that no human experimentation committee existed at the hospital. However, they were subsequently informed that a committee was formed, and then the firm received formal approval of the study. Informed consent forms were reported to be completed on all patients.

Analysis of Study 59A

The data generated in Study 59A were analyzed by Bristol Laboratories personnel. None of the cases were considered evaluable for efficacy, but all were included in toxicologic evaluations of oral butorphanol. None of the patients experienced severe toxicities.

Conclusion

It is a matter of concern to Bristol Laboratories that even two of the many hundreds of clinical studies sponsored by us are sub-standard. However, it should be noted that when problems with these studies were discovered, they were corrected.

The Bristol Laboratories monitor for the studies was replaced, and further investigation with Dr. #2 discontinued. Moreover, since sub-acute dosing schedules were employed in these studies, the fact that four months elapsed between the initiation and termination of the research program with Dr. #2 reflects reasonable diligence. The fact that no significant side effects were observed in the course of these studies is another important consideration.

Clearly, the study performed by Dr. #7 did not progress well. But that study too was rapidly terminated when problems were recognized, and no patient experienced significant adverse effects.

The studies performed by Dr. #7 and Dr. #2 are not acceptable, nor do we subscribe to the belief that a few such unacceptable studies are inevitable if enough studies are performed. We recognize our responsibility to provide the more intense efforts to perform ethical, valuable clinical research on drugs of potential benefit.

This also requires the closest scrutiny of studies once they are initiated so that those which are inappropriate may be terminated rapidly. Finally, and perhaps most importantly, it also requires that the safety and rights of volunteer test subjects are well protected.

Bristol Laboratories on September 14, 1976, established Guidelines for Good Clinical Research. These guidelines, with minor exceptions, meet or exceed the standards published by FDA months later.

In essence, we believe that good clinical research requires adequate performance in five broad types of endeavors. The first step in the performance of good clinical research is the careful design of protocols which accurately define the characteristics of the subjects, and the tasks to be performed. Second, it is essential to select a qualified investigator. Third, each study must be carefully monitored to assure compliance with protocol, and to arrange for any necessary revisions. Fourth, the data must be analyzed carefully and without bias. Fifth, accurate records must be maintained to document these activities.

First, we established an intramural protocol review committee which must approve all protocols prior to initiation of studies. Included in these protocols are minimum guidelines for informed consent. We also require that names and titles of all members of a testing institution's human research committee must be provided to Bristol Laboratories.

Second, we have established minimum standards for the selection of investigators. Whenever possible, we attempt to employ academic clinicians with experience in the scientific areas involved. In our opinion, this is one of the best methods of assuring both a competent investigator and a functional human research committee.

However, when questions we must ask cannot be answered by an academician, we must rely on other types of investigators.

Third, we have established standards for monitoring methods, including frequent visits to testing sites at the initiation of studies as a safeguard against continuation of an inadequate study. The Guidelines also require that, when appropriate, registration forms be submitted to the Bristol Laboratories' monitor promptly after enrollment of each patient in a study, and the rapid evaluation of each case report as it is received by the monitor.

Adverse reactions are particularly scrutinized, and investigators are required to report by telephone any unexpected or alarming adverse effects to the monitor within 24 hours. The monitor's home telephone number is provided, should the investigator need to contact the monitor after normal office hours.

The question of whether to employ a professional monitoring firm is complex. Certainly it is of value to employ such a firm if inadequate manpower in-house would result in inadequate monitoring. It may also be of value to occasionally replicate intramural data extramurally. However, the desire to avoid any danger of biasing the monitoring service or investigators must be balanced against the responsibility of the sponsor to assure compliance with the regulations and the conduct of ethical, scholarly studies.

The analysis of data generated by clinical trials is also discussed in the Bristol Laboratories guidelines. To insure that double-blind studies are truly double-blind, randomization schedules are maintained in the statistical department, and are not available even to the monitor. The final reports on all studies must be submitted to the protocol review committee for approval. Thus another peer review is effected at the close of a study.

Finally, it is essential that adequate records be maintained. Our guidelines of September 14, 1976, addressed this question, but we are currently revising the guidelines to require better record keeping.

It is our opinion that the procedures outlined in our Guidelines for Good Clinical Research substantially increase the assurance that informed consent is obtained for each patient, that institutional review is effected for each study, that adverse reactions are carefully monitored, and that each study is monitored effectively.

These guidelines are under constant review for improvements and refinements that result from our experience. However, there are limitations.

It is difficult to demand, for example, that an investigator reveal the names of his test patients. Our concern for the rights of informed consent is tempered by the investigator's concern for the patient's right of privacy and confidentiality -- a concern we share.

As a consequence, we cannot insure that our policies for informed consent are uniformly implemented. This is a complex dilemma and is not addressed in the proposed regulations of the FDA for 1977 nor in the January 1973 report of the National Academy of Sciences/National Research Council.

It is not possible to predict the performance of each clinical investigator. We can check his educational credentials, and we do. We can evaluate his published work on previous studies, and we do. We can inquire as to his professional standing with others in his field, and we do. But these procedures cannot accurately foretell the competence of every investigator in every research program we undertake.

If this committee can fashion the means by which greater insurance can be provided in these or other critical areas, or if the proposed Presidential commission can do so, we in clinical research would welcome such suggestions, for I can assure you that your concerns and your goals are very much our own.

1/78

CURRICULUM VITAE

Stanley T. Crooke

Born: March 28, 1945, Indianapolis, Indiana

Education:

B.S.	1966 (Pharmacy)	Butler University Indianapolis, Indiana
Ph. D.	1971	Baylor College of Medicine Houston, Texas
M.D.	1974	Baylor College of Medicine Houston, Texas

Committees:

National Director SAMA Drug Abuse Committee, 1973-1975

Chairman Protocol Review Committee, Bristol Laboratories, 1976-1977

Awards:

1968-1971	Public Health Service Predoctoral Fellowship
1971-1972	Public Health Service Postdoctoral Fellowship
1973-1974	Southern Medical Association Research Award
1973-1974	Institutional Research Award, National Cancer Institute
1974	Outstanding Graduating Medical Student in Pharmacology
1974+1975	Outstanding Lecturer in Basic Science, Baylor College of Medicine
1977	NCI Grant No. CA-10893-10

Affiliations:

American Association for the Advancement of Science
American Association for Cancer Research
American Society for Microbiology
Cancer and Acute Leukemia Group B
American Society for Clinical Pharmacology and Therapeutics

Licensure:

New York State Board of Medical Examiners
Texas State Board of Medical Examiners
Texas State Board of Pharmacy
Indiana State Board of Pharmacy

1977	-	Associate Director of Research and Development Bristol Laboratories;
1977	-	Clinical Assistant Professor, Department of Medicine, Upstate Medical Center;
1976-1977	-	Associate Director of Medical Research, Bristol Laboratories;
1976-1977	-	Clinical Instructor, Department of Medicine, Upstate Medical Center;
1976	-	Assistant Professor, Department of Pharmacology Baylor College of Medicine;
1976	-	Director, Bristol-Baylor Molecular Pharmacology Laboratory, Baylor College of Medicine;
1975-1976	-	Assistant Director Medical Research Bristol Laboratories;
1974-1975	-	Internship, Baylor Medical School, St. Luke's Program;
1971-1975	-	Instructor, Department of Pharmacology Baylor College of Medicine;
1971-1972	-	Postdoctoral Fellow, Department of Pharmacology Baylor College of Medicine;
1971	-	Member, Cancer Research Center, Baylor College of Medicine;
1968-1971	-	Predoctoral Trainee, Department of Pharmacology Baylor College of Medicine

Invited Presentations:

- Bleomycin, A Review presented at the Topics in Clinical Oncology Symposium March 18, 1976, Portland, Oregon.
- New Studies on Bleomycin, Upstate Medical Center, Syracuse, New York, October 25, 1976.
- Structure Activity Relationships of Anthracyclines, Upstate Medical Center, Syracuse, New York, March 28, 1977.
- Antitumor Antibiotics presented at the ACP Medical Oncology Review Course, October 6, 1977, Pasadena, Calif.
- Recent Advances in Cancer Molecular Biology presented at Eastern ACP, October 13-14, 1977.

Invited Presentations (cont'd)

- Co-chairman of the NCCP-Bristol Laboratories Bleomycin Symposium, October 20-21, 1977, Oakland, California.

- BU-2231, A Third Generation Bleomycin, Bleomycin Symposium, October 20-21, 1977, Oakland, California.

- Bleomycin Clinical Pharmacology, Bleomycin Symposium, October 20-21, 1977, Oakland, California.

- Studies on Several New Anthracyclines, Louisiana State University, August, 1977.

- Studies on the Clinical Pharmacology of Bleomycin, Proc. of U.S./Japan Joint Cancer Symposium, May 12-13, 1977, San Francisco, California.

Teaching Experience:

Medical School Pharmacology Course Lectures Given

- Adrenergic Agents
- Anti-Adrenergics
- Anti-Cholinergies
- Anti-Cholinesterases
- Anti-Parkinson Drugs
- Central Muscle Relaxants
- Drug Resistance
- Fetal Drug Effects
- Drug Interactions
- Clinical Toxicology
- Pharmacogenetics
- Prescription Writing

Graduate School Courses Taught

- Molecular Pharmacology

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TESTIMONY OF DR. RALPH JACOBSEN, MEDICAL DIRECTOR, ENDO LABORATORIES, INC.,

BEFORE THE U.S. SENATE HUMAN RESOURCES SUBCOMMITTEE

ON HEALTH AND SCIENTIFIC RESEARCH

MARCH 7, 1978

Mr. Chairman and members of the Committee, my name is Ralph Jacobsen, I am a physician and have been affiliated with Endo Laboratories, Inc., in its Medical Department since 1965. I have been a Vice President and its Medical Director since 1973 and am responsible for the clinical testing of Endo's drugs.

Endo Laboratories, Inc., located in Garden City, New York, has been a manufacturer and distributor of pharmaceutical products in New York for over fifty years. Its products are sold throughout the United States and several foreign countries.

You have requested that we appear here this morning to testify about Endo's procedure for clinical testing of its investigational drugs with particular emphasis on the matters of 1) informed consent, 2) adherence to protocol, 3) adverse effects reporting, 4) institutional review committees and 5) the monitoring of its studies.

Endo performs clinical testing of investigational drugs for several reasons. First and foremost the testing is performed to study the safety and efficacy of these investigational drugs. Second, there may be a need to study additional indications or use in different age groups for FDA approved drugs that have already passed their initial safety and efficacy examinations. Third, different dosage forms may need to be studied for determination of biological equivalency.

PRIOR TO COMMENCING ANY INVESTIGATIONAL PLAN, THE DIRECTOR OF REGULATORY AFFAIRS OF ENDO SUBMITS TO THE FOOD AND DRUG ADMINISTRATION A NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION FOR A NEW DRUG (FORM FD-1571). THIS INCLUDES DETAILED INFORMATION ON PRE-CLINICAL STUDIES WITH THE DRUG ON LABORATORY ANIMALS, INFORMATION RELATING TO QUALIFICATIONS OF INVESTIGATORS, COPIES OF THE WRITTEN INVESTIGATIONAL PLAN AND PROTOCOLS FOR EACH INVOLVED STUDY AND OTHER REQUIRED INFORMATION.

ALL INVESTIGATORS WHO ARE TO STUDY ENDO INVESTIGATIONAL DRUGS EXECUTE THE REQUIRED FDA FORM FD-1572 OR 1573. THE CURRICULUM VITAE AND PROTOCOL ARE SUBMITTED TO THE FOOD AND DRUG ADMINISTRATION. THE INVESTIGATOR ALSO SIGNS A SEPARATE AGREEMENT WITH ENDO COVERING HIS FEES AND THE REQUIREMENT TO ADHERE TO PROTOCOLS AS WELL AS OTHER MISCELLANEOUS MATTERS RELATING TO THE PROPOSED INVESTIGATIONAL PLAN.

PROFESSIONALS UNDER MY DIRECTION MONITOR CLINICAL INVESTIGATIONS. IT IS THEIR RESPONSIBILITY TO MONITOR THE WORK CARRIED OUT BY CLINICAL INVESTIGATORS USING ENDO'S INVESTIGATIONAL DRUGS. INFORMATION OBTAINED FROM CLINICAL INVESTIGATORS WHICH IS REQUIRED FOR FILING WITH THE FDA, SUCH AS ADVERSE REACTION REPORTS, AND PROGRESS REPORTS ARE COLLECTED AND REVIEWED BY THE MONITOR AND THEN TURNED OVER TO ENDO'S DIRECTOR OF REGULATORY AFFAIRS FOR SUBMITTAL TO THE FDA.

WITH THIS BACKGROUND IN MIND, I WOULD LIKE TO REVIEW WITH YOU THE FIVE SPECIFIC AREAS ABOUT WHICH YOU HAVE REQUESTED US TO COMMENT.

1. INFORMED CONSENT

It is Endo's policy to ascertain that a given investigator's institutional review committee has approved the proposed "Patient Consent Form". Additionally, a copy of the proposed consent form is reviewed by Endo. After all approvals are obtained, the investigator is so notified. Items specifically required by Endo in "Patient Consent Forms" are a recitation of known adverse effects from the drug, an explanation to the patient of the nature of the study, the name of the physicians involved, and a recitation that the patient can retire from the study at any time without prejudicing himself or herself from receiving further treatment. The patient or his guardian is required to sign the Patient Consent Form.

2. ADHERENCE TO PROTOCOL

Each investigational study sponsored by Endo has as a vital component of that study a full explanation of the steps to be taken in the study, the nature and dosage of the drug to be administered to the patients, a description of the type and number of patients and a description of the medical techniques to be employed. This explanation is known as a protocol. A copy of this protocol is submitted to the FDA with their form FD-1571. It is also reviewed in detail by the Endo monitor and by the investigator's institutional review committee. It is Endo policy not to allow its investigators to deviate significantly from this protocol. If any material change is necessary to the

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PROTOCOL, IT IS AMENDED AND IS AGAIN APPROVED BY THE INVESTIGATIONAL REVIEW COMMITTEE AND ENDO'S MONITOR. A COPY OF THE AMENDED PROTOCOL IS SUBMITTED TO THE FDA.

3. ADVERSE EFFECTS REPORTING

IF ANY ADVERSE EFFECTS ARE OBSERVED BY THE CLINICAL INVESTIGATOR WHICH CAN BE REASONABLY ATTRIBUTED TO THE EXPERIMENTAL DRUG, THE INVESTIGATOR IS CHARGED BY ENDO WITH THE DUTY OF REPORTING THAT INFORMATION PROMPTLY TO HIS INSTITUTIONAL REVIEW COMMITTEE AND TO ENDO'S MONITOR. ENDO REPORTS THAT INFORMATION PROMPTLY TO THE FDA. IF THE ADVERSE REACTION IS CONSIDERED TO ENDANGER THE PATIENT, THE INVESTIGATION IS TERMINATED.

4. INSTITUTIONAL REVIEW COMMITTEE

ENDO CONSIDERS INSTITUTIONAL REVIEW COMMITTEES TO BE A VITAL PART OF ITS DRUG CLINICAL INVESTIGATION PROGRAM. ENDO CONTRACTS WITH CLINICAL INVESTIGATORS AT INSTITUTIONS MAINTAINING QUALIFIED REVIEW COMMITTEES. ONLY AFTER COMPLETE APPROVAL OF THE PROTOCOL BY THE REVIEW COMMITTEE IS A GIVEN STUDY RECOMMENDED FOR APPROVAL BY THE MONITOR.

5. MONITORING OF STUDIES

ENDO'S PROFESSIONAL CLINICAL MONITORS ARE EACH RESPONSIBLE FOR CERTAIN DESIGNATED CLINICAL INVESTIGATIONS. THE MONITOR SELECTS THE INVESTIGATOR WITH MY APPROVAL, WORKS UP THE PROPOSED PROTOCOL WITH THE INVESTIGATOR, IS RESPONSIBLE FOR ASSURING THAT THE INVESTIGATOR IS QUALIFIED, HAS ADEQUATE

FACILITIES, HAS THE REQUIRED AMOUNT OF EXPERIMENTAL DRUGS AND ADHERES TO THE PROPOSED PROTOCOL DURING THE INVESTIGATION. FURTHER, THE MONITOR GATHERS DATA FROM THE INVESTIGATOR TO PREPARE PROGRESS REPORTS. THE MONITOR NORMALLY VISITS THE INVESTIGATOR BEFORE AND SEVERAL TIMES PER YEAR DURING THE ACTUAL CARRYING OUT OF THE STUDY. THE MONITOR IS CHARGED WITH THE DUTY OF ASSURING THAT PROTOCOLS HAVE BEEN REVIEWED PRIOR TO FILING WITH THE FDA, THAT THE DRUG SUBSTANCE IS DELIVERED TO THE INVESTIGATOR, THAT ANY ADVERSE REACTIONS ARE PROMPTLY REPORTED SO THAT THEY CAN BE TRANSMITTED TO THE FDA, AND FOR ANY OTHER MATTER RELEVANT TO THE INVESTIGATION.

YOUR TELEGRAM ALSO REQUESTED TESTIMONY RELATIVE TO TWO MATTERS IDENTIFIED BY THE STAFF REGARDING TWO SPECIFIC DRUG STUDIES.

THE FIRST STUDY WAS CARRIED OUT BY AN INVESTIGATOR OF OUR CHOICE AND INVOLVED THE USE OF ONE OF OUR APPROVED DRUGS IN COMBINATION WITH AN APPROVED DRUG OF ANOTHER COMPANY FOR THE TREATMENT OF PARKINSON'S DISEASE. THIS STUDY WAS NOT INTENDED, NOR NEEDED, FOR USE IN SUPPORT OF ANY FDA APPLICATION. THE WORK PERFORMED BY THIS INVESTIGATOR IN CONNECTION WITH OUR DRUG WAS MONITORED AND IT APPEARS TO HAVE BEEN CONDUCTED IN A PROPER FASHION WITH VALID RESULTS. FOLLOWING THIS STUDY, WE WERE CONTACTED BY ANOTHER DRUG MANUFACTURER WHO WAS WORKING WITH THE SAME INVESTIGATOR IN A SIMILAR TEST FOR THEIR PRODUCT, ALSO USED IN TREATING PARKINSON'S DISEASE. THE OTHER MANUFACTURER HAD BECOME CONCERNED THAT SOME OF THE DATA THEY HAD RECEIVED FROM

THE INVESTIGATOR MIGHT HAVE PREDATED THE COMMENCEMENT OF THEIR TEST. A MORE DETAILED COMPARISON OF THE EARLIER TEST DATA INVOLVING OUR PRODUCT, WITH THE DATA ALLEGEDLY DEVELOPED ON THE OTHER MANUFACTURER'S TEST SHOWED SUCH STRIKING SIMILARITY THAT IT RAISED A QUESTION AS TO WHETHER THE INVESTIGATOR WAS ATTEMPTING TO PASS OFF OUR DATA AS DATA FROM THE SECOND TEST. THIS SIMILARITY, AS WELL AS FURTHER INQUIRIES, LED US TO ENCOURAGE THE OTHER MANUFACTURER'S NOTIFICATION OF THIS POSSIBLE IRREGULARITY TO THE FDA, AND TO ASSIST IN THE ENSUING INVESTIGATION. FDA INVESTIGATOR, W. FRIEDRICH, MADE A REVIEW OF OUR DATA IN SEPTEMBER, 1977; HE RETAINED COPIES OF THOSE DOCUMENTS HE JUDGED PERTINENT. WE HAVE NO REASON TO SUSPECT THAT THE DATA DEVELOPED IN THE EARLIER TEST ON OUR PRODUCT WAS IN ANY WAY INVALID. THE STUDY WAS PUBLISHED BY THE INVESTIGATOR.① ~~HE TERMINATED A SUBSEQUENT STUDY WHICH WE HAD INITIATED WITH THE SAME INVESTIGATOR CONCERNING A NEW USE FOR OUR DRUG.~~ based upon the information we had.

THE SECOND STUDY MENTIONED BY THE COMMITTEE'S STAFF INVOLVED A NEONATAL ADMINISTRATION OF AN ENDO DRUG, NALOXONE, WHICH COUNTERACTS RESPIRATORY DEPRESSION INDUCED BY NARCOTIC ANALGESICS. IT HAD BEEN PREVIOUSLY APPROVED FOR USE IN ADULTS. UNLIKE OTHER ANTAGONISTS, NALOXONE COUNTERACTS THE EFFECT OF NARCOTICS WITHOUT ITSELF HAVING ANY NARCOTIC ACTION. IT IS ESSENTIALLY FREE OF SIDE EFFECTS. NALOXONE HAS PROVIDED THE MEDICAL COMMUNITY WITH A DRUG USEFUL IN LIFE-THREATENING SITUATIONS IN THE EMERGENCY ROOM, AND ALSO IN THE MANAGEMENT

OF POST-OPERATIVE PATIENTS. THE PROTOCOL IN THIS NEONATE STUDY WAS DEVELOPED BY A REPUTABLE INVESTIGATOR IN COLLABORATION WITH OUR COMPANY AND WAS APPROVED BY THE INSTITUTIONAL REVIEW COMMITTEE AT A RESPECTED TEACHING HOSPITAL ASSOCIATED WITH A MAJOR UNIVERSITY MEDICAL SCHOOL. SINCE THIS WAS ONE IN A SERIES OF TESTS CONDUCTED TO SUPPORT THE EXTENSION OF THE USE OF THIS DRUG FOR YOUNGER AGE GROUPS, A SUPPLEMENT TO OUR INVESTIGATIONAL NEW DRUG APPLICATION WAS PREPARED and submitted to the FDA PRIOR TO COMMENCEMENT OF THE STUDY; HOWEVER, I AM EMBARRASSED TO SAY, THROUGH INADVERTANCE ON OUR PART, THE ~~SUPPLEMENT~~ protocol for this particular study WAS NOT FORWARDED TO THE FDA UNTIL AFTER THE STUDY HAD BEEN STARTED. ~~APART FROM THIS TARDY FILING, I AM NOT AWARE OF ANY SIGNIFICANT IRREGULARITY IN THIS STUDY;~~ THE FDA HAS RAISED NO OBJECTION TO OUR PROTOCOL OR TO THE RESULTS OBTAINED. THIS PRODUCT HAS BEEN APPROVED AND IS NOW WIDELY USED IN ALL AGE GROUPS WITH LIFESAVING BENEFITS. (2)

prior to this meeting

I WILL, OF COURSE, BE WILLING TO ANSWER ANY QUESTIONS YOU MAY HAVE.

THANK YOU.

STATEMENT OF JOHN J. BURNS, Ph.D.
HOFFMANN-LA ROCHE INC.
Nutley, New Jersey

BEFORE THE SUBCOMMITTEE ON HEALTH AND SCIENTIFIC RESEARCH
OF THE SENATE COMMITTEE ON HUMAN RESOURCES
March 7, 1978

Mr. Chairman and other Members of the Subcommittee:

My name is John J. Burns and I am Vice President for Research at Hoffmann-La Roche Inc. Thank you for allowing me to share our thoughts with you on the important topic of clinical research.

Clinical research is a vital component of the drug approval process. It allows scientists and doctors to gain necessary understanding and knowledge of the action of therapeutic agents within the human system. Such research, then, is indeed essential to insuring that the drugs taken by the public at large will be safe and effective. It is imperative, however, that at each step of the clinical research process, the welfare of the subjects of such research is properly safeguarded. Roche has always been acutely aware of this important responsibility. Accordingly, we have implemented stringent procedures designed to protect the health, safety, and welfare of the subjects of our clinical research and also to insure the integrity, accuracy, quality, and reliability of the data resulting from this research. Clinical research is critical, but the accomplishment

within these overriding considerations is a key prerequisite. The Subcommittee has asked for general comments on four major aspects of our clinical research program: These are:

- Clinical Research Monitoring
- Adverse Effects Reporting
- Role and Functions of Institutional Review Committees
- Informed Consent

Our monitoring of clinical research actually commences before the research itself even begins. Prior to administration of a drug to subjects in the study population, a Roche monitor (a physician or a para-medical person) will make a personal visit to the testing facility and discuss important points with the investigator and staff. The monitor will either come from Nutley headquarters or from one of our regional medical offices located throughout the country. At this pre-study visit, the monitor reviews with the investigator the details of the protocol to assure mutual understanding and, in addition, stress the need to follow the protocol in detail. He will also discuss pertinent information on the test drug, including dosage, adjustment of dose, dosing intervals, warnings, potential adverse effects, etc., with all individuals involved in drug administration and evaluation.

The monitor will emphasize the need to maintain proper records and the necessity of filing periodic reports. The monitor will review the adequacy of the facilities and determine that the laboratory is properly certified and discuss the need for patient consent and for Institutional Review Committee approval of appropriate matters, including the reporting of adverse reactions to the Committee. He will also review drug storage and dispensing procedures with appropriate individuals. A "Pre-Study Visit Report" will be completed by the monitor after this initial visit, which must then be reviewed and initialed by the principal medical monitor and, again, by a section head at Nutley.

Once a study is underway, we generally monitor each study by personal visit with the investigator every six to ten weeks and supplemented by telephone calls between these visits. At each personal visit, current case reports are reviewed with the investigator, whether completed or in progress, and a determination is made as to whether the protocol is being followed. Drug supplies are checked to assure that the medications are being dispensed in proper sequence and stored in an adequate and safe manner. The investigator is asked specifically whether patient informed consent was obtained in all cases, whether any unusual and/or serious adverse effects were observed, and whether any significant observations other than those recorded on the case reports were made. Dropouts and the reasons for the withdrawal from the study are discussed in detail. Any deficiencies are discussed with the investigator, and

remedial action is outlined. The requirement of Institutional Review Committee progress reports is also reviewed. A "Monitoring Report" is completed following each visit and is reviewed again by both the principal medical monitor and a section head at Nutley.

Telephone monitoring contacts are designed to determine whether the investigator is encountering any problems, whether he has seen any unusual and/or serious adverse effects, and whether a personal visit may be required prior to the scheduled routine monitoring date. A "Monitoring Report" is also completed following each telephone contact.

It may be instructive to note that we emphasize to all our monitors the need to ascertain periodically from their investigators whether they are obtaining the required informed consent from their patients and whether they are retrieving unused medication from the study subjects for return to Hoffmann-La Roche at the conclusion of the study.

Upon completion of a study, the monitor will make a final visit and prepare a "Final Monitoring Report." At this final visit, the monitor discusses retention of the investigator's study records, later confirmed in writing, insures that all case reports have been collected and all unused drugs have been returned, and that the investigator has completed an Investigational Drug Disposition form.

Such files include copies of the complete case reports for each patient/subject. Again, the principal medical monitor, as well as his section head, must review and initial the Final Monitoring Report.

As can be noted, this monitoring is done on a per-study basis. To supplement this review and to provide Roche medical officers with an overview of all ongoing Roche clinical research monitoring, monthly and bi-monthly "System Monitoring Reports" are compiled by computer. These reports set out the monitoring which has taken place on a monthly basis with respect to each ongoing study and over the previous two years. They indicate when a study was started and whether a personal visit or a telephone contact was made. In effect, the report ensures that our monitors are in fact monitoring. These overviews are reviewed by senior medical management at Nutley and allow us to keep an accurate track record of our monitoring activities.

It should be emphasized that as a standard component of all Roche protocols, all adverse reactions encountered during a study must be reported on a Case Report Form. The side effects are graded on a 3-point scale (mild, moderate, or severe) and discussed in detail. Any death, any unusual or serious reaction, or unusual frequency of reactions must be reported promptly by telephone to Roche headquarters, even though the experience may not appear to be drug-related. For this purpose, Roche maintains a number which can be reached 7 days a week, 24 hours a day. Such reports are then promptly forwarded to FDA.

The Company requires assurance that written consent is to be obtained for Phase I and Phase II, prior to any therapy. It is the responsibility of the principal investigator to obtain that consent. In Phase III it is the responsibility of the investigator, taking into consideration the physical and mental state of the patient, to decide whether it is preferable to obtain consent in writing or verbally. If written consent is not obtained, the investigator must record the fact that oral consent has been obtained in the medical record of the person receiving the drug. During personal visits to the testing facility, the Roche monitor is required to ask the investigator whether informed consent has been obtained in all cases.

When pharmaceutical companies utilize special populations (such as prison inmates) in drug experiments, they must exercise extra care in protecting the rights of subjects because of the subjects' special disabilities caused by their environment. In such circumstances, their responsibility for insuring that ethical standards of experimentation are adhered to should rest with private, outside parties who are answerable neither to the company nor to the institution in charge of the subjects.

All Roche clinical research conducted in institutional settings conforms in all respects to the Declaration of Helsinki and the rules, regulations, and policies contained in the Federal Food, Drug, and Cosmetic Act and its amendments.

In all clinical research studies--Phase I through Phase III- conducted on institutionalized subjects or being conducted by an investigator affiliated with an institution which agrees to assume responsibilty for the study, Roche requires written evidence of Institutional Review Committee approval. No shipment of a Roche drug will be authorized until such evidence is obtained, other than in serious emergency illnesses.

The institutions with which we are familiar and where the bulk of our clinical research is conducted require that the study be approved by their Institutional Review Committees. This approval requires that the senior investigator of a certified project keep evidence of the patients' informed consent. The investigator is also usually required to present to the Institutional Review Committee all written information provided to subjects in obtaining informed consent. In the institutional settings that we deal with, no research is initiated by the investigator until the Committee has given written approval.

No alteration or changes in the study design are allowed without Committee approval, except where necessary to eliminate apparently immediate hazards. Such Institutional Review Committees require the reporting of serious adverse reactions. Also, these Committees conduct reviews of the study at intervals appropriate to the degree of risk, but not exceeding one year, to assure that the research project is being conducted in compliance with the understanding and recommendations of the Committee.

The institutions where our clinical research projects are conducted restrict the participation of the investigator in the deliberations of the Review Committee to providing information to the Committee.

The need for Institutional Review Committee approval is discussed with the investigator during a pre-study visit. As mentioned above, during this visit, Roche's monitor will discuss with the investigator full details of the protocol, the need to maintain adequate records, the necessity of filing periodic reports, as well as other subjects of importance to the study.

The monitor will also emphasize the need for reporting serious adverse reactions to the Institutional Review Committee. He will further discuss with the investigator the need for periodic reporting to the Committee.

During regular monitoring visits, the status of Institutional Review Committee progress reports also are carefully checked and noted. Again, the monitor's report is examined by the principal medical monitor, as well as by the section head in Roche/Nutley offices. All clinical studies must be reviewed by the Institutional Review Committee at least once a year.

We have available copies of all company monitoring forms used by us and will submit them for the records if you desire.

It has been brought to our attention that certain questions have been raised about clinical investigations performed on one of our investigational compounds. As suggested by the Subcommittee, we are not identifying specific individuals or institutions in this statement. As requested, we will identify the investigator as Investigator 9. I would like to take the next several minutes to show you how the clinical monitoring system we have devised worked in this case and what the Company does when we see a problem developing in the course of our monitoring of clinical investigations.

Investigator 9 first came to our attention when he contacted us in 1974 concerning his interest in performing studies with Levodopa. We told him at that time that we had few current ongoing clinical investigations with Levodopa. In subsequent contacts and considering that he has been employed since 1966 by a well-recognized VA hospital that is also a teaching institution affiliated with a medical school, we advised him that we would keep him in mind in the event that a need for studies of mutual interest might arise at a later date.

After this, we had other contacts with Investigator 9 concerning his desire to perform a clinical study for us. Subsequently, when we began to initiate clinical studies on a new drug--studies which had to follow a rigid protocol--we thought

that Investigator 9 might be a suitable investigator. Investigator 9 had clinical responsibilities in two outpatient clinics in the VA hospital and was also responsible for patient care in several wards in the hospital which provided a large potential patient population that could be used for the study. We thus inquired if he was interested in performing such a study.

I believe it is relevant to describe the manner in which we implemented our Company policy concerning our monitoring of clinical investigations in respect to the initiation of the first study by Investigator 9. Several pre-study telephone calls and visits were made by the medical monitor responsible for the study in Nutley, New Jersey, as well as personnel from our regional medical office. On these dates, we pointed out to Investigator 9, as we would to any investigator, the requirements of the protocol, the need for patient consent and Institutional Review Committee approval, as well as other matters relevant to the study and to FDA requirements for clinical investigations. As required by the FDA regulations, Investigator 9 submitted a Statement of Investigator Form, Form FD-1573, for the study which stated, among other things, the need to obtain patient consent and Institutional Review Committee approval. Thereafter, a letter from the Institutional Review Committee (Research and Education Committee at the VA hospital) indicating approval of the study was submitted to us.

The letter of approval from the Institutional Review Committee set forth specific requirements of written patient consent and stipulated that signed copies of such consent be sent to the Office of the Associate Chief of Staff for Research at the hospital. When we received a copy of the Institutional Review Committee approval, attached to it was a copy of the patient consent that the Review Committee had approved for use in the study. In most instances, when we receive copies of the Institutional Review Committee's approvals, these consents are not provided to us.

After Institutional Review Committee approval and the pre-study monitoring reviews and meetings, the study was initiated by Investigator 9 in the summer of 1975. This study involved our drug and placebo. Our medical monitor from Nutley as well as our monitor from the regional medical office were present with Investigator 9 on the first night of drug administration in the study. They observed treatment administration to five patients as well as the careful manner in which Investigator 9 and the staff paid attention to the details of the protocol. Our representatives were there in the evening during drug administration and into the early morning hours for conferences with various staff members of the VA hospital, including the nurse sleep monitor involved in the study.

Upon completion of the case reports, Investigator 9 forwarded them to our regional medical office. At our regional offices the case reports underwent an initial detailed review to determine whether they were properly filled out and otherwise accurate. The case reports were also reviewed in Nutley by the medical monitor. In reviewing these case reports, our regional personnel noted a number of obvious errors. The errors were basically errors in transcription or omission of information and were not unusual when one considers that Investigator 9 was a new investigator for Roche performing a study under a rather stringent protocol and requiring the completion of detailed and involved case reports. Some of the problems also dealt with the fact that the VA laboratory had, during the study, changed the laboratory normal values, and the normals differed from the laboratory normals that had been provided to us prior to the institution of the study.

In order to resolve these points, we asked Investigator 9 to review with us the patient records. While we certainly recognize the need for an individual's right of privacy, we are at the same time, on occasion, faced with the need to clarify apparent errors or validate data obtained from clinical investigations. In some instances, when questions arise, the only way to confirm or validate data obtained in a clinical study that is to be submitted to the Food and Drug Administration in

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support of the marketing of a new product is to compare the case reports with the raw data in the patient charts.

In some instances in working with the investigator and the institution these questions on the case reports can be appropriately resolved. In other instances, however, the institutions and personnel will not permit drug sponsors to review patient charts. However, we were permitted to review the laboratory data for each of the patients in this initial study and, with Investigator 9, make appropriate corrections in the case reports. When I say "corrections," what I mean is that some laboratory values recorded on our case reports differed from those in the patients' hospital charts suggesting transcription errors. In other instances, the dates indicated in the patient records differed from the dates in the case report or certain points as, for example, the patient's occupation was omitted from the case report. Accordingly, the only changes that would have been made by Roche personnel dealt with making sure that the case reports were accurate and reflected the data in the patient records. These changes were made only with the knowledge of the investigator.

Following this review, we soon received from Investigator 9 a copy of the VA policy regarding examination of patient records, indicating that, based on federal

privacy legislation, only certain specifically listed persons have access to patient records.

After our meetings with Investigator 9 and our review of the data, we were able to satisfactorily resolve the various inconsistencies that appeared in his case reports. At no time was there any reason to question either the integrity of the study or the individuals involved.

We then decided to run a second phase of this study involving 30 additional patients. We asked Investigator 9 to submit the first five case reports to us so that we could review them with him to make sure that they were correct. Thereafter, we reviewed with him the first case reports noting some very minor discrepancies, such as the failure to include the occupation of the patient. I would also like to add that, in the second phase of this study, certain changes were made in the protocol, basically decreasing the duration of the study from 7 to 5 nights. Investigator 9 confirmed to us by letter that Institutional Review Committee (Research and Education Committee at the VA hospital) approval was obtained for the initiation of this second phase as well as the changes in protocol.

Upon completion of the second phase of the first study, we discussed with Investigator 9 the possibility of another study which would include secobarbital, placebo,

and our investigational drug. As we had done in the first study and prior to the initiation of this second study, we had a number of meetings and contacts with Investigator 9 acquainting him with protocol requirements and the need for patient consent and Institutional Review Committee approval. Investigator 9 then submitted the protocol and other study documents to the Institutional Review Committee for their approval, and such approval was transmitted to us by Investigator 9 prior to the commencement of the study. I would like to point out that the approval again sets forth the requirement of written patient consent and that copies of the executed consent should be forwarded to the Office of the Associate Chief of Staff for Research. The letter of approval to Investigator 9 also notes that patient consents were attached and apparently reviewed by the Research and Education Committee at the VA hospital.

We had no indication that there was any question or cause for concern until October 1, 1976, when we completed our review of the first 21 case reports. In reviewing these case reports, our regional medical office personnel noted that they appeared to be accurate with one noticeable exception, and that concerned a Patient No. 9. When Investigator 9 submitted the case reports to us, he apparently inadvertantly included a copy of the laboratory slip for this patient. A review of the laboratory slip against the laboratory data entered in the case report disclosed a definite discrepancy. While the laboratory data in the case

report indicated no abnormality, the hospital laboratory report for Patient 9 indicated a one-day difference in dates and grossly abnormal values. Immediately, the head of our regional medical office called Investigator 9 expressing our concern and inquiring about the discrepancy. Investigator 9 responded that there were two patients in the hospital at the same time with the same initials. In light of the discrepancy and explanation, we requested that Investigator 9 provide us with the original laboratory data for all 21 patients. Investigator 9 indicated that he did not have the time to do this but, after much conversation, agreed to obtain the data and meet with us so that they could be compared to the data entered on the case reports.

On October 8, Investigator 9 met with a representative of our regional medical office. At this time, our representative noted that the graphs of the laboratory reports appeared to be irregular as if possibly drawn by hand rather than machine. He also noted that the hematology reports had been filled out by hand and not by machine as had usually been the case during the first study. Investigator 9 sought to explain this by saying that the machines were not in operation and that this was not unusual for the hospital. Investigator 9 showed us what he stated was the original laboratory work for Patient 9, and this now matched what was in the case report. We questioned him about the other patient with the same initials as Patient 9 and asked to see this patient's chart. Investigator

9 stated that the patient in question had left the hospital, entered some nursing home, and the records could not be found.

Having notified Nutley of their concerns about the second study, our regional medical personnel discussed the study with us when they visited our offices on October 18. At the same time, the Nutley monitor began an independent investigation of the clinical efficacy data that had been submitted by Investigator 9 in the study. Our analysis of the efficacy data contained in these case reports by Investigator 9 disclosed a very unusual situation. The data from the first two nights of the study which were placebo nights indicated total ineffectiveness of the placebo, whereas data from the next three nights indicated overwhelming effectiveness for the drug--whether it be the investigational drug or secobarbital. These data were unusual by themselves but increased our suspicions even more, since they were too consistently positive compared with the data being generated by other investigators and by the data that Investigator 9 had submitted in the first study.

After review of the situation with our regional medical people, on October 18 it was decided that our monitor would meet with Investigator 9 for a further explanation. Our Nutley monitor visited Investigator 9 at the VA hospital on October 20 and 21. At this time, the Nutley monitor determined that in a pre-study discussion of the protocol Investigator 9 had inadvertantly informed the

nurse observer of the night on which the patients changed from placebo to active medication. Her efforts to review the labortatory files on the laboratory data in question were met with some hostility.

Our monitor contacted Nutley by telephone on the 20th expressing her concern about the attitude and the refusal of certain people in the laboratory to cooperate. A supervisory physician then placed a call to the head of the VA hospital laboratory and discussed our concerns. This person indicated that, if we could provide him with a copy of the Research and Education Committee letter of approval, he would be able to obtain for us laboratory and other data concerning the study. Our regional medical office mailed a copy of this approval to him the next day. None of these data were ever provided to us.

When the Nutley monitor returned, it was decided that this supervisory physician as well as his superior, the Director for Medical Research, should meet with Investigator 9 to discuss this situation.

On November 3, 1976, a month after the problem concerning Patient 9 had first arisen, our medical people met with Investigator 9. Mr. Chairman, I would like to refer the Subcommittee to a memorandum of November 8, 1976, concerning this

visit which was provided to the Subcommittee staff last week. Essentially, as described in the memorandum, after much discussion, Investigator 9 confirmed that he had provided to the nurse observer a copy of the investigator's protocol which indicated that the placebo administration would occur on the first two nights and drug administration on the next three nights of the study. We expressed our concern to Investigator 9 about the possibility of unconscious bias of the nurse observer.

In response to questions concerning the laboratory data, Investigator 9 again indicated that the machines were not working and were often "down." We asked if we could see a patient chart for a patient who was not included in the study. Investigator 9 left the room and returned with a patient chart. Upon examination, we noted that "irregular lines" on the SMA graphs and hand entries on the laboratory charts were also present in this patient's chart even though this was purportedly a patient not in our study.

We then asked Investigator 9 to show us a chart for one of the patients in the study and, upon review, noted the absence of any patient consent. We asked to see a signed consent form for this patient, and after looking through the patient chart, he stated that it must have been misplaced. We then asked to see a patient consent form that he was using in the study, and he provided us with a blank copy of the consent form that was used in the first study and which did not deal

with the use of secobarbital. We immediately advised Investigator 9 that this was unacceptable for that reason and he must immediately bring these consent forms up to date and that a copy of the signed form be retained in the patient's file.

Upon return of our medical people to Nutley, it was decided that we would terminate the study with Investigator 9 because of the possibility of unconscious bias of the nurse observer. Investigator 9 was notified of this decision by our letter of November 24, a copy of which was provided to the Subcommittee staff last week. In our final report on this study to our IND, we noted that we were eliminating the study as a consideration for effectiveness of the drug in light of the possibility of unconscious bias. We reevaluated the first study performed by Investigator 9 and, considering that we had witnessed the first night of drug administration, reviewed approximately 35 patient charts, and that the data were consistent with data generated by other investigators, we decided that no further action was required concerning this study.

In summary, Mr. Chairman, after a thorough review, the only points that we knew for certain were that there was a possibility of unconscious bias and Investigator 9 had failed to show us an effective patient consent for the second

study. We terminated the study and eliminated it from consideration in support of effectiveness of the drug because of this possible bias.

In conclusion, I would like to say that, while we are concerned about what we have heard here today involving Investigator 9 and other clinical investigators, we believe that our procedures and monitoring efforts as evidenced by the fact that we, ourselves, discovered problems with this study and, on our own initiative decided to eliminate the study from efficacy consideration and delete the investigator, demonstrate that we diligently perform our responsibilities as sponsors of clinical investigations and that the present system works effectively.

Thank you very much, Mr. Chairman.

McNEIL

McNEIL LABORATORIES, 500 OFFICE CENTER DRIVE, FORT WASHINGTON, PA 19034, (215) 628-5000

March 7, 1978

I am George I. Poos, Ph. D., Vice President, Scientific Affairs of McNeil Laboratories, a prescription pharmaceutical manufacturer. I have the overall responsibility for Research and Development at McNeil Laboratories.

In response to a request from the Subcommittee, I am prepared to discuss the policies and practices of McNeil Laboratories pertaining to clinical investigational work and in particular a study by an investigator on one of our investigational new drugs.

At the outset, Mr. Chairman, permit me the liberty of expressing my personal respect for the Subcommittee's thoughtful involvement in the manner in which pre-clinical and clinical drug testing is conducted in this nation. I have devoted the better part of my professional career to researching and developing new drugs -- the task is at once immensely sophisticated, often laborious, frequently providing therapeutic benefit while at the same time potential risk to the subjects involved, but always necessary to provide new and improved medication.

During the hearings you have conducted over the past few years, you heard testimony indicating cause for concern about clinical drug investigation. No thoughtful person can disregard the issues raised during these sessions. While our knowledge, development and appropriate use of medications must progress if we are to attack yet untreatable diseases or improve our therapeutic techniques, this must not be a result of undue, unfair or uninformed risk to those subjects in whom investigational drugs are introduced. All parties involved in conducting and sponsoring drug investigations must constantly be vigilant for those investigators who cannot or will not produce high quality work while maintaining the strictest ethical standards. Development of medications would be a far easier task if we could develop strict and uniform objective criteria by which safety and efficacy of all investigational drugs could be readily determined. Unfortunately, science is not always given to such convenient standardization.

With this understood, I would offer the following observation -- the vast majority of clinical investigators I have worked with over the years are dedicated, highly qualified, truly humane individuals. Their efforts have been an integral part of the drug development process, a process which has produced significant, at times dramatic, improvements in our

ability to provide health care. Through years of experience with many clinical studies and investigators at McNeil, we have continuously improved our policies and practices to protect patient safety and privacy while developing reliable clinical data which can be used to make sound decisions by ourselves and the Food and Drug Administration. We are commited to continue to improve our policies and practices.

Senator, the bill you have introduced, S. 2579, is a helpful step in assisting the nation to better understand and manage the complexities of clinical drug investigations. The study authority provided in the legislation should provide an opportunity to better define the parameters of these concerns and, hopefully, lead to appropriate methodologies for assuring thorough, safe and scientifically valid investigations. I support this effort.

It is pertinent to the subject of this hearing to discuss, if but briefly, four key elements of the drug clinical investigation process. These elements are (1) protocol development, (2) selection of clinical investigators, (3) monitoring of investigations, and (4) processing and evaluation of data.

In order to produce dependable results, studies must be conducted pursuant to well designed protocols. At McNeil the protocol development process is initiated by a physician with

expertise in drug investigation protocol design. The proposed protocol is then channeled for review by specialists in a broad range of scientific disciplines. Physicians, clinical pharmacologists, toxicologists, laboratory researchers, statisticians and finally the Director of Research and Development are required to comment on, and where necessary, modify the proposed protocol. This process is repeated until all specialists within McNeil are satisfied that dosage levels and forms are safe and practical when measured against carefully determined study objectives. Further, the reviewers must determine that the patient population meets strict criteria for the disease state being treated, excluding those persons inappropriate for the study due to factors such as presence of other disease states, use of other drugs which might interfere with the study results, women of childbearing potential, and age generally. The parameters being measured must be quantifiable and subject to statistical analysis.

All protocols must be approved by our internal review mechanism in the manner indicated above. It is likely though, given the specific nature of certain compounds, that the participants in the review process will vary slightly to accommodate the need for applicable areas of expertise.

Selection of appropriate clinical investigators is accomplished through a variety of mechanisms. McNeil professional staff is continually reviewing medical, pharmacological and scientific literature. Through this process, and through attendance at

and participation in, a range of professional meetings, we are able to identify clinicians with established expertise in areas of interest to us. Additionally, we give serious consideration to professional referrals from clinicians, investigators and academicians with whom we have an established relationship or from individuals with recognized expertise in applicable disciplines. Given our many years of experience in drug research and development we have established a series of ongoing relationships with many excellent clinical investigators.

Once an investigator has been identified, a McNeil physician monitor or clinical research associate (if we have had previous experience with the investigator) will meet with a perspective investigator -- at the investigator's office -- prior to final designation of the investigator. The purpose of this meeting is to permit the McNeil representative to assess the investigator's interest and ability to adequately conduct the proposed study. Beyond the investigator's professional qualifications -- which have been previously reviewed by McNeil -- it must be determined that there is a sufficient patient population with the disease condition to be treated. This will assure that an adequate number of patients will be studied during the investigation. The investigator's professional support personnel, and facilities are observed, discussed and evaluated.

During this visit a summary of preclinical and clinical data is reported to the physician being considered to conduct the study. The summaries are contained in an IND brochure which is updated as new and significant data becomes available to McNeil and provided to the investigators so that they are knowledgeable about the most recent safety and efficacy data to best treat their patients participating in the study.

After it has been agreed that an investigator will conduct the proposed study and appropriate administrative requirements have been executed, the investigator is supplied with clinical supplies and case report forms.

Immediately preceeding inception of the study, a McNeil physician monitor or clinical research associate will usually meet with the investigator at the investigator's office. The purpose of this session is to permit final inspection of the clinical supplies and a thorough review of the approved protocol. All relevant regulatory requirements are again discussed.

At this point it is relevant to note that if an investigation involves introduction of a drug into humans for the first time -- the McNeil physician monitor will remain on the investigator's premises for an appropriate period of time to personally observe the initial stages of the investigation.

In the majority of circumstances, a McNeil monitor will visit an investigator at intervals of from two to eight weeks during the course of a study. The duration of the intervals is determined in large part by the size of the patient universe under observation and the frequency of the patients scheduled visits to the doctor. During each McNeil-Investigator meeting, applicable case report forms are reviewed in detail with particular emphasis on side effects, laboratory abnormalities and drug inventory control.

Because side effects are always a paramount concern during clinical investigations, patients are routinely monitored for side effects. In addition, McNeil instructs all investigators to notify the physician monitor immediately by telephone in instances where serious side effects occur, which are rare. If warranted, a physician familiar with the drug will be dispatched to assist in treatment or observation of the effected patient. In these circumstances, a review is immediately conducted by all relevant scientific disciplines to determine an appropriate course of action including discontinuance of the study if indicated.

Data generated from each individual study is evaluated as it is received by McNeil. Depending upon the length of the study, some data may be reported to McNeil before the study has been fully completed. Whether interim or final, data are carefully reviewed and analyzed by McNeil experts and upon occasion by independent expert consultants. As stated earlier, science is

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not always given to convenient standardization; therefore the review process for each drug may vary depending upon the protocol, study objective and type of therapeutic drug. The following is a general statement of our data evaluation process.

I should note that this entire process is the result of design and review by internal and independent expert consultants, experience and improvements and rigorous FDA standards, It is an amalgamation of medical judgment, basic science, government regulation, common sense and good science.

All data generated from the study are meticulously reviewed by the CRA and the physician monitor. Patient eligibility for inclusion in the study, adherence to protocol, any side effect or adverse reaction, efficacy, laboratory test results, x-ray or other diagnostic measurements are among the many items especially reviewed. Age, sex and other relevant patient characteristics are also analyzed. The physicians and other highly qualified scientists who developed the drug and the protocol also review the data at various stages of this process. Questionable or incomplete data, unless specifically validated with the investigator, will be discarded at some stage of the analysis process. Skilled statisticians analyze the data. In many instances, study results are entered into a sophisticated computer data file. Individual patient response, side effect profile and other parameters are further evaluated for trends or patterns. Each clinical study undergoes a similar

review and then becomes part of the total review of data from all the other clinical investigators.

The entire evaluation process produces a carefully prepared and thorough summary which is scrutinized by physicians, clinical pharmacologists, toxicologists and basic scientists all of whose education, training and experience qualify them as experts. Decisions as to safety and efficacy are made through joint efforts of many highly skilled, responsible individuals.

At appropriate points in time all these data and evaluations are reported to the Food and Drug Administration where its independent experts conduct further review. The drug may be approved for use, subjected to further study or not approved.

Now to return to the specific investigational drug and clinical investigation identified by the Subcommittee Staff.

After extensive preclinical testing, McN-3113, a promising skeletal muscle relaxant discovered in our laboratories, was introduced into clinical trial in July, 1974. A number of clinical investigators have studied McN-3113 in phase I and phase II clinical trials. An investigational new drug exemption (IND) supplement was filed on May 21, 1975, with investigator number 10 as the investigator in an open label dose ranging study. The object of the study was to determine the most effective dose for the relief of muscle spasm and pain associated with muscle spasm in patients with acute exacerbations of chronic pain syndromes such as acute lumbar strain and lumbar sacral strain.

This investigator was visited in his office by one of our physician monitors prior to the beginning of the study to discuss the protocol and conduct of the study. A letter from the physician monitor to the investigator on May 16, 1975, confirmed the discussion about clinical supplies and the requirement for signed patient consent. Clinical supplies were shipped May 22, 1975, and an updated IND brochure for McN-3113 was sent June 4, 1975. On August 5, 1975, at the completion of the investigation as called for in the protocol, a clinical research associate (CRA) visited the investigator and picked up 45 completed case report forms each signed by the investigator. It was noted that a therapeutic response to the three dose levels was seen and that nine patients had complained of mild side effects. A letter from our CRA to the investigator on August 7 confirmed that copies of the case report forms were being returned and enclosed a drug return form with instructions for its use as is our usual practice. The unused drug was returned August 11, 1975.

This particular study was only one of many. In the Fall of 1976, one year later we decided to suspend clinical trials on McN-3113 due to a lack of sufficient efficacy found for the drug under the test conditions employed.

This concludes my prepared statement. I hope it has been helpful to the Subcommittee and I will be pleased to answer any questions you may have.

SUBMISSION FOR THE RECORD

Hearing Held Before
Subcommittee on Health and Scientific Research
Committee on Human Resources
United States Senate

March 7, 1978

For Kennedy Hearings of March 7, 1978

As of 3/1/78 our list of "For Cause" investigations of clinical investigators contained 26 names. The source of the leads which led us to initiate investigational action on these was:

NDE suspicion of data	8
Sponsor complaint	7
Consumer complaint	4
IRC investigation	2
Data audit (7348.811)	2
Procedural compliance (7348.810)	1
Special survey follow-up	1
Literature review	1

Of these 26 individuals, it appears that there is an overwhelming liklihood that at least 15 will be subject to official regulatory action, i.e. disqualification and possibly criminal prosecution.

A review of the location of studies done by the 15 persons noted above reveals that the studies of 8 of these were covered or should have been covered by institutional committee review.

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A. Comparison of Case Reports with Patient Charts

1. Study #4 Protocol 630

a) Patient #28

Case Report
Dates reported on study: 9/3/75-9/10/75
Physical Description: 56 years old, male, 5'8", 206 lbs.
Diagnosis: Syncope & diabetes
Medication:
other: no alergies
Did receive Roche drug

Patient Chart
Dates in hospital: 9/14/77 (two years later)
Physical description: 58 years old, male, 5'10", 179 lbs.
Diagnosis: Heart disease, emphysema and asthma
Medication:
other: alergic to penicillin
Didn't receive Roche drug

b) Patient #20

Case Report
Dates reported on study: 8/27/75-9/3/75
Physical Description: 58 year old male
Diagnosis: Parkinson's disease, tremor
Medication: L Dopa & artane
other: DOB-37 yrs. old crossed out and initialed by 9
Did receive Roche drug

Patient Chart
Dates in hospital: 1/27/75-2/11/75, 8/14/75-9/9/75 (deceased)

Diagnosis: Inoperable lung cancer
Medication: Chemotherapy
Other: readmitted with terminal lung cancer 8/14/75

Didn't receive Roche drug

c) Patient #33

Case Report
Dates reported on study: 9/10/75-9/16/75
Physical Description: 51 yr. old male
Diagnosis: Tremor, hypertension
Medication: Tylenol, malox
other:
Did receive Roche drug

Patient Chart
Dates in hospital: 4/29/75-5/2/75, 2/14/77-2/20/77
Physical description: 51 yr. old male
Diagnosis: Diabetes, seizures, status post head injury

Didn't receive Roche drug

d) Patient #5

Case Report	Patient Chart
Dates reported on study: 8/20/75-8/27/75	Dates in hospital: 8/20/75-8/25/75 (2 days before completed study)
Physical description: 56 yr. old male, 162 lbs.	Physical description: 57 yr. old male, 188 lbs.
Diagnosis: Parkinson's disease	Diagnosis: Parkinson's disease
Medication:	Medication:
other:	Other: admitted by Dr. 9 himself to change medication from L Dopa to Sinamet
Did receive Roche drug	Didn't receive Roche drug

e) Patient #9

Case Report	Patient Chart
There was no patient in hospital with this name and patient identiy number.	There was another patient about same time with this name and different identity number.
Dates reported on study: 8/27/75-9/3/75	Dates in hospital: 8/13/75-8/29/75
Physical description: 56 yr. old male	Physical description: 56 yr. old male
Diagnosis: Bells palsy	Diagnosis: alcoholism, alcoholic cerabelum degeneration, neuropathy, tremors
Medication:	Medication: Dalmane every night
Other:	Other:
Did receive Roche drug	Didn't receive Roche drug

2. Study #5, Protocol 630B

a) Patient #16

Case Report	Patient Chart
This one appears to be legitimate	
Dates reported on study: 2/22/76-2/26/76	Dates in hospital: 2/22/76-2/26/76
Physical description: 62 yr. old male	physical description: 62 yr. old male
Diagnosis: chronic bronchitis	Diagnosis: chronic bronchitis
Medication:	Medication:
Other:	Other:
Received Roche drug	Received Roche drug

b) Patient #26

Case Report

Dates reported on study: 3/14/76-2/12/76
Physical description: 65 yr. old, 200 lbs.
Diagnosis: Heart disease, high blood pressure

Medication:
Other:
Received Roche drug

Patient Chart

Dates in hospital: 2/25/76-7/9/76
Physical description: 64 yr. old male, 220 lbs.
Diagnosis: acute alcoholic intoxication, psychosis, hallucinating on admission, and continued halucination. Disoriented as to persons, places and times. Declared mentally incompetent 3/19/76
Medication:
Other:
Did not receive Roche drug

c) Patient #9

Case Report

This one also appears legitimate
Dates reported on study: 2/8/76-2/12/76
Physical description: 44 yr old male
Diagnosis: Diabetes & high blood pressure
Medication:
Received Roche drug

Patient Chart

Dates in hospital: 1/28/76-3/15/76
Physical description: 44 yr. old male
Diagnosis: Diabetes and high blood pressure
Medication:
order for Roche drug on separate sheet of paper

3. Study #9, Protocol 824

a) Patient #24

Case Report

Dates reported on study: 9/20/76-9/24/76
Physical description: 46 yr. old male
Diagnosis: residual of nephrectomy
medication: valium before study, Tetrocyclin after study
Received Roche drug

Patient Chart

Dates in hospital: 9/15/76-10/29/76
Physical description: 46 yr. old male
Diagnosis: anemia
medication: dalmane & valium 2/22,23,24/76 (during study time)
Did not receive Roche drug

b) Patient #30

Case Report
Dates reported on study: 9/29/76-9/30/76
Physical description: 33 yr. old male
Diagnosis: hypertension, diabetes
Medication: aldomet, diabonese

Received Roche drug

Patient Chart
Dates in hospital: 9/20/76-9/30/76
Physical description: 33 yr. old male
Diagnosis: atopic dermititis
Medication: penicillin, atarax for sedation, valium for sleep, tetracyclin & dalmane.
atarax, dalmane & valium all given during dates of study
Did not receive Roche drug

c) Patient #27

Case Report
Dates reported on study: 9/26/76-9/30/76
Physical description: 56 yr. old male, 201 lbs.
former pharmacist

Diagnosis: high blood pressure, post nephrectomy

Medication: aldomet, valium
Received Roche drug

Patient Chart
9/15/76-10/6/76
Physical description: 56 yr. old male, 233 lbs.
former deputy sheriff & set painter for Desilu Production
Diagnosis: hypertension, recovery from stroke, admitted for treatment of obesity
Medication: Aldomet, Lasix, Catapres, apresoline
Did not receive Roche drug

Attachment E

SERUM CHEMISTRY DETERMINATIONS, McNEIL.

Subject Number:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
A.Phos.	42	40	52	39	60	50	39	30	60	31	39	34	51	36	58	59	39	50	62	38	63	51	35
	44	38	50	40	54	43	35	32	54	31	40	35	49	34	39	61	41	49	60	39	59	49	
LDH	170	109	170	120	141	139	111	109	147	110	120	106	106	101	111	108	139	131	154	109	154	146	150
	164	120	166	120	136	132	119	111	145	112	120	110	102	101	114	110	142	130	144	110	160	139	146
Glu.	96	94	102	68	69	88	68	66	90	70	90	84	80	76	69	83	69	89	78	82	90	90	98
	94	92	97	66	72	82	70	70	86	71	87	84	89	80	70	80	88	90	80	81	85	90	94
SGOT	34	21	24	17	31	20	16	28	19	30	17	21	31	27	20	33	27	20	33	17	27	31	18
	34	24	27	18	35	17	21	30	20	19	24	19	29	19	22	32	32	19	33	20	27	30	16
Chol.	200	206	197	159	226	175	159	198	204	170	179	190	176	169	191	178	190	186	182	163	198	246	191
	195	211	194	163	211	171	161	190	192	168	191	191	179	171	195	190	203	179	194	160	195	241	201
BUN	11	12	13	11	14	10	11	14	12	10	10	10	11	9	16	17	11	14	10	12	12	15	17
	11	13	12	11	14	10	12	14	13	10	14	10	12	10	12	16	12	13	10	13	12	15	12
TP	7.1	7.1	7.4	7.3	7.3	7.6	7.3	7.0	7.2	7.0	7.4	7.3	7.3	7.6	7.4	7.4	7.4	7.2	6.9	7.0	7.4	7.2	7.3
	7.1	7.1	7.5	7.5	7.2	7.6	7.2	7.1	7.3	7.1	7.4	7.3	7.3	7.6	7.1	7.1	7.3	7.3	6.9	7.0	7.3	7.2	7.0
Alb.	4.2	4.1	4.4	4.4	4.3	4.7	3.9	3.9	4.2	4.0	4.3	4.3	4.0	4.3	4.0	4.3	4.2	4.1	4.0	4.5	4.3	4.3	3.9
	4.1	4.1	4.5	4.4	4.3	4.7	3.9	3.9	4.2	4.2	4.4	4.3	4.0	4.4	4.3	4.0	4.2	4.1	4.0	4.6	4.3	4.0	3.9
UA	3.8	5.0	5.2	3.8	5.4	3.9	4.4	4.2	6.0	4.4	3.9	4.4	4.9	6.0	3.9	3.9	5.9	3.9	6.3	3.4	5.1	6.0	5.3
	3.9	5.2	5.2	5.7	5.5	4.0	4.0	4.3	6.0	4.1	4.0	4.0	3.9	5.7	4.0	3.7	6.2	3.5	6.2	3.4	5.3	6.0	5.2
IP	4.3	3.8	3.9	4.2	4.2	4.3	4.2	4.1	3.4	2.9	2.8	3.0	3.5	2.8	2.7	4.2	4.3	4.0	3.9	4.0	3.7	4.1	3.8
	4.3	3.8	3.9	4.1	4.1	4.3	4.3	4.0	3.2	2.9	2.8	3.0	3.5	2.8	2.7	4.2	4.3	4.0	3.9	4.0	3.7	4.1	3.8
Ca	8.9	8.9	9.2	10.0	10.0	10.3	10.1	9.7	9.2	9.6	9.3	9.6	10.0	9.8	10.2	9.3	9.1	9.6	9.4	9.2	9.3	9.7	10.0
	9.0	9.3	9.2	10.0	9.9	10.0	9.7	9.7	9.4	9.8	9.5	9.6	10.0	9.8	10.2	9.2	9.3	9.4	9.4	9.1	9.9	9.8	10.0
T Bil.	0.4	0.3	0.6	0.3	0.7	0.7	0.3	0.8	0.4	0.3	0.6	0.3	0.4	0.6	0.3	0.4	0.6	0.4	0.6	0.3	0.8	0.8	0.5
	0.4	0.4	0.6	0.4	0.9	0.7	0.4	0.7	0.4	0.4	0.6	0.3	0.3	0.4	0.5	0.5	0.7	0.5	0.8	0.4	0.7	0.8	0.5

Subject Number:	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45
A.Phos.	44	51	40	40	38	60	62	59	44	53	52	43	50	40	41	46	55	60	53	40	57	60
	43	49	40	40	38	61	61	60	44	52	53	47	48	49	40	44	57	62	63	41	56	60
LDH	130	160	141	124	126	141	149	161	139	151	130	124	134	120	170	129	139	149	160	121	141	130
	132	150	139	120	130	151	149	164	143	139	139	109	134	144	169	130	140	145	149	120	135	131
Glu.	79	86	88	69	71	94	96	73	76	83	100	90	91	71	69	70	84	88	94	76	86	99
	80	85	85	69	70	99	94	75	77	76	95	82	85	79	71	70	83	86	93	76	86	100
SGOT	24	39	27	21	20	33	41	40	19	30	41	40	41	29	31	31	29	36	36	23	24	40
	24	41	29	22	20	34	34	39	20	25	39	26	39	40	33	30	32	35	32	24	25	38
Chol.	200	240	216	180	179	196	200	178	216	166	206	192	197	173	188	188	190	206	206	220	188	191	231
	194	283	211	174	184	194	190	180	211	161	214	190	194	183	190	195	194	199	224	190	190	226
BUN	9	12	19	9	11	15	18	20	14	10	14	13	18	11	10	13	9	18	11	10	14	17
	9	12	18	10	12	15	18	20	13	10	12	13	19	13	10	13	9	16	12	10	15	17
TP	6.4	7.5	6.6	7.3	7.3	7.3	7.3	7.3	6.6	6.3	7.3	6.9	7.4	7.5	7.2	7.0	6.9	7.5	7.4	7.3	7.6	7.5
	7.4	7.6	7.6	7.3	7.7	7.0	7.1	7.3	6.7	6.3	7.2	6.9	7.1	7.5	7.2	7.1	7.0	7.5	7.6	7.2	7.6	7.5
Alb.	4.3	4.5	4.3	4.1	4.6	3.8	4.2	4.9	3.8	3.9	4.3	4.3	3.9	4.5	4.3	4.2	4.0	4.6	4.3	4.4	4.5	4.4
	4.3	4.5	4.3	4.2	4.8	3.9	4.0	4.9	3.8	3.9	4.4	4.3	3.9	4.5	4.3	4.2	4.0	4.5	4.5	4.4	4.5	4.4
UA	5.7	5.9	6.3	3.9	3.9	5.4	6.3	4.7	3.4	3.8	5.7	3.9	5.4	3.8	5.0	3.4	5.1	5.9	6.1	5.6	6.1	7.0
	5.6	6.0	6.4	4.0	3.9	5.5	6.3	4.7	5.9	4.0	4.1	4.0	5.3	4.1	5.7	3.9	5.3	6.0	6.0	5.8	6.1	6.9
IP	3.3	4.0	3.1	2.8	3.3	3.9	3.0	3.8	4.1	4.1	4.0	3.8	4.1	3.9	4.0	3.2	3.3	3.4	3.1	3.4	2.9	3.1
	3.2	4.0	3.1	3.0	3.4	2.9	3.0	3.9	4.1	4.0	4.1	4.0	4.0	4.1	3.9	3.3	3.3	3.3	3.2	3.5	2.9	3.0
Ca	9.9	10.0	10.0	9.6	9.8	9.9	9.8	9.9	9.3	10.0	9.6	9.8	9.5	9.7	9.8	9.5	9.8	9.9	9.8	9.9	10.0	9.7
	9.9	10.0	9.9	9.7	9.8	9.9	9.9	9.9	9.7	9.7	9.6	9.7	9.5	9.9	9.8	9.5	9.7	9.9	9.8	9.9	9.9	9.8
T Bil.	0.6	0.9	0.8	0.4	0.6	0.9	0.6	0.6	0.4	0.4	0.6	0.6	0.9	0.3	0.7	0.6	0.7	0.9	0.6	0.7	0.6	0.9
	0.4	0.8	0.8	0.4	0.4	0.8	0.9	0.6	0.6	0.6	0.4	0.6	4.0	4.1	0.7	0.7	0.7	1.0	0.9	0.6	0.7	1.0

Attachment F

LABORATORY DETERMINATIONS, MCNEIL STUDY.

	test	Hemoglobin	Hematocrit	Urine SG	Urine pH.
subjects	1	14.1 14.1	41.5 41.0	1.025 1.025	5.0 5.0
	2	16.2 16.2	54.0 54.5	1.030 1.029	6.0 6.0
	3	16.8 17.0	47.5 48.5	1.028 1.029	6.0 6.0
	4	16.0 16.0	47.0 47.0	1.026 1.026	5.0 5.0
	5	16.9 16.9	52.0 52.0	1.029 1.029	5.0 5.0
	6	15.8 15.8	47.0 47.5	1.028 1.029	5.0 5.0
	7	12.9 12.9	39.0 39.0	1.023 1.024	6.0 7.0
	8	13.3 13.2	40.5 41.0	1.021 1.022	8.0 8.0
	9	14.9 14.9	46.5 46.5	1.029 1.030	5.0 6.0
	10	15.0 15.0	47.0 47.0	1.024 1.024	6.0 6.0
	11	13.5 13.5	40.0 40.0	1.029 -	5.0 5.0
	12	14.0 14.0	42.0 42.0	1.025 1.025	6.0 6.0
	13	15.0 14.8	45.0 45.0	1.024 1.024	5.0 5.0
	14	16.3 16.3	47.5 47.5	1.030 1.030	6.0 6.0
	15	16.0 16.2	47.0 47.0	1.022	7.0
	16	13.2 13.0	39.0 39.0	1.023 1.024	8.0 7.0
	17	14.6 14.8	42.5 43.0	1.028 1.029	5.0 5.0
	18	14.9 14.9	44.5 44.5	1.030 1.028	5.0 5.0
	19	16.3 16.1	50.0 50.0	1.025 1.025	6.0 6.0
	20	13.0 13.0	40.0 40.0	1.024 1.024	8.0 8.0
	21	16.4 16.3	49.5 49.5	1.027 1.027	6.0 6.0
	22	15.2 15.2	45.5 46.0	1.027 1.027	5.0 5.0
	23	16.0 16.1	47.0 47.0	1.030 1.029	7.0 7.0
	24	14.7 14.7	46.5 46.5	1.030 1.029	7.0 7.0
	25	16.5 16.5	50.0 50.5	1.028 1.028	7.0 7.0
	26	15.8 15.8	48.0 48.5	1.026 1.026	6.0 6.0
	27	13.0 13.3	40.5 40.5	1.022 1.021	7.0 7.0
	28	15.9 16.0	48.0 48.5	1.030 1.030	5.0 5.0
	29	16.2 16.2	50.0 50.0	1.026 1.026	7.0 7.0
	30	14.8 14.8	45.0 44.5	1.025 1.026	7.0 7.0
	31	15.9 15.8	48.5 48.5	1.027 1.027	6.0 6.0
	32	15.9 15.9	50.0 50.0	1.028 1.029	6.0 6.0
	33	12.9 13.1	38.0 39.0	1.024 1.026	5.0 5.0
	34	15.3 14.9	45.0 45.0	1.026 1.028	7.0 7.0
	35	14.9 15.0	44.5 44.5	1.028 1.028	7.0 7.0
	36	12.5 12.7	38.0 38.0	1.023 1.023	8.0 8.0
	37	13.9 14.5	42.0 43.0	1.024 1.023	8.0 8.0
	38	17.0 17.0	50.0 48.5	1.025 1.025	7.0 7.0
	39	15.2 15.2	46.0 46.0	1.025 1.025	7.0 7.0
	40	12.9 13.0	39.5 39.5	1.021 1.021	8.0 8.0
	41	14.9 15.0	47.0 47.0	1.029 1.028	5.0 5.0
	42	12.7 12.7	38.5 38.0	1.027 1.026	5.0 5.0
	43	15.1 15.2	45.0 45.0	1.027 1.024	6.0 6.0
	44	14.3 14.3	42.5 42.5	1.021 1.022	8.0 8.0
	45	17.0 17.0	50.5 50.5	1.029 1.029	6.0 6.0

ENDO LABORATORIES

CASE REPORT	PATIENT CHART
Patient #1	
Dates reported on study: 1/6/76-5/18/76	Dates in hospital: started 5/18/76
Physical description: 55 yr. old male	Physical description: 54 year old male
Diagnosis: Parkinson's disease (15 year history)	Diagnosis: Parkinson's Disease (3-4 year history)
Other:	Other:
Patient #2	
No discrepancies between Case Report and Patient Chart. However, on 12/31/76 the Neurology Clinic stated that the patient did not have Parkinson's Disease and Parkinson's Medication was discontinued on that date.	
Patient #15	
Dates reported on study: beginning 2/10/76	Dates in Hospital: beginning 8/24/76
physical description: 56 year old male	Physical description: 61 year old male
Diagnosis: Parkinson's Disease (10 year history)	Diagnosis: Parkinson's Disease (2 year history)
Other:	Other:
Patient #16	
Dates reported on study: 12/23/75-5/4/76	Dates in hospital: beginning 10/21/75; drug for study not ordered
Physical description:	Physical description: until 12/4/75
Diagnosis: Parkinson's Disease	Diagnosis:
Other:	Other: False replicas of patient charts submitted to Endo with Case Reports _ _
	5/10/77 Diagnosis changed from Parkinson's disease to tremor
Patient #18	
Dates reported on study: 1/27/76-6/23/76	Dates in hospital: Did not receive Endo drug
Physical description: 59 year old male	Physical description: 65 year old male
Diagnosis: Parkinson's Disease	Diagnosis: 6/6/77 changed from Parkinson's Disease to tremor
Other:	Other:

CASE REPORT

Patient #19
Dates reported on study: 1/27/76-6/1/76
Physical description: 58 year old male
Diagnosis: Parkinson's Disease (6 year history)
Other:

PATIENT CHART

Dates in hospital: Did not receive Endo drug
Physical description: 55 year old male
Diagnosis: Parkinsons's Disease (2 year history)
Other:

Senator KENNEDY. The hearing is now adjourned.

[Whereupon, at 12:57 p.m., the subcommittee adjourned, to reconvene subject to the call of the Chair.]

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