*Comment*

Indomethacin is effective in the control of certain cases of rheumatic diseases. The high percentage of good and excellent results in nonrheumatoid benign rheumatic diseases would suggest that it is the treatment of choice. The initial dose may be 25 mg once or twice daily. In this group of diseases, it is seldom necessary for the physician to exceed a total daily dose of 100 mg or 125 mg at the most. However, even with low dosage the physician must be on guard for the occasional patient who might develop gastric upset or even ulceration, as well as the unusual patient who is highly susceptible to cerebral side-effects.

In rheumatoid arthritis, indomethacin is also effective, producing a good and excellent result in an appreciable number of cases, and because of its limited hazards, it should be included among the therapeutic weapons to be used in the treatment of this difficult disease. However, it should not be inferred that indomenthacin replaces or eliminates the need for a sound basic therapeutic program for the patient with rheumatoid arthritis which should include increased rest, salicylates, physical therapy, and other adjunctive or supportive measures. The patient with rheumatoid arthritis who is not responsive to the basic program of therapy may have this supplemented by the cautious prescribing of indomethacin beginning with a dose of 25 mg two or three times daily, best given after meals and at bedtime with a glass of milk. The daily dose may be increased in increments of 25 mg at perhaps weekly intervals. If disease activity persists, the physician would be justified in increasing the total daily dose to 150 to 250 mg daily, according to tolerance. As the higher dosage of indomethacin is approached, the physician must increase his caution regarding the possible development of gastric ulcer and in some patients must be prepared to cope with the distressing symptoms of headache, lightheadedness, and disturbances of sensorium. If the rheumatoid arthritic process continues to remain actively painful and disabling, the physician may cautiously add to the overall program such therapy as gold and low-dosage corticosteroid therapy as recommended in previous reports.[7,8]

*"Dropouts"*

In accordance with the suggestion of Mainland and Sutcliffe,[9] an explanatory note is appended regarding patients who were dropped from the study.

Twenty-three patients who began therapy, for one reason or another, became dropouts. They are grouped in four main categories: (1) Five patients were simply lost to followup for inexplicable reasons. Some were doing well and some were not doing so well. (2) There were four patients in whom the original diagnosis was determined to be incorrect. (3) Six patients were finally determined to be impossible to evaluate, despite the liberal use of placebo. Some of these at one time were considered to yield excellent results and at another time, seemed to be therapeutic failures. However, while honest and objective appraisal was attempted, retrospectively it was decided that there was too much uncertainty regarding their evaluation to permit conclusions in one direction or another. (4) Eight patients were receiving the drug for so brief a time that no conclusions could possibly be warranted. Most of these were too disturbed at the prospect of experimentation, after they had to sign "release form." Two others unexpectedly had to move out of town within a week after therapy was started.

*Generic and Trade Names of Drugs*

Indomethacin—*Indocin.*
Phenylbutazone—*Butazolidin.*
Chloroquine phosphate—*Aralen Phosphate.*
Prednisone—*Deltasone, Deltra, Meticorten, Paracort.*
Probenecid—*Benemid.*
Sulfinpyrazone—*Anturane.*

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[7] Rothermich, N. O.: Local Steroid Injection Therapy in Rheumatic Diseases, *Postgrad Med* 30:283–292 (Oct) 1961.
[8] Rothermich, N. O.: Corticosteroid Therapy in Rheumatoid Arthritis, *Postgrad Med* 36:117–128 (Aug) 1964.
[9] Mainland, D., and Sutcliffe, M. I.: *The General Problem of Dropouts, ARA Coop Clin Committee Bull* 18:6 (Dec 7) 1964

Senator NELSON. We will recess until tomorrow morning at 10 a.m.

(Upon the direction of the chairman, the letter by Mr. T. O. Cron, Assistant Commissioner for Education and Information, FDA, subsequently dated, follows:) [1]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
FOOD AND DRUG ADMINISTRATION,
*Washington, D.C., May 3, 1968.*

Hon. GAYLORD NELSON,
*Chairman, Subcommittee on Monopoly, Select Committee on Small Business, U.S. Senate, Washington, D.C.*

DEAR SENATOR NELSON: You will recall that Dr. Robert McCleery of our Bureau of Medicine testified before your Subcommittee yesterday and noted that an article in *Pageant* magazine misrepresented the safety and effectiveness of Indocin (indomethacin). While Dr. McCleery was testifying, Merck & Co., manufacturers of the drug, distributed a statement of rebuttal.

Three major points were made in the company's release: (1) that the FDA had never discussed this matter with the company; (2) that the company neither encouraged publication of the article nor supplied testimonial letters on unapproved claims; and (3) that the company did not see the text before it appeared in print.

For the record, the *Pageant* article was indeed discussed with the Merck management, including its President, on November 11, 1966. I was present at that meeting. Prior to that, our Agency received letters from the company's Vice-President for Public Relations and its Administrative Vice-President about the article and its creation.

In addition, both Vice-Presidents had acknowledged to us in writing that Merck had supplied "case histories" (another term for testimonials) to the authors of the magazine article. Finally, the letter from Merck's Vice-President for Public Relations enclosed an internal memorandum written to the Administrative Vice-President, dated June 17, 1966, which demonstrated that the company's public relations staff had seen the *Pageant* article and had not registered disapproval. This was, of course, before the July publication date of the magazine.

I hope this letter is helpful to the work of the Subcommittee.

Sincerely yours,

THEODORE O. CRON,
*Assistant Commissioner for Education and Information.*

(Whereupon, at 2:35 p.m., the subcommittee recessed, to reconvene at 10 a.m., Friday, May 3, 1968.)

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[1] See p. 3370, infra.

# COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

FRIDAY, MAY 3, 1968

U.S. SENATE,
MONOPOLY SUBCOMMITTEE OF THE
SELECT COMMITTEE ON SMALL BUSINESS,
*Washington, D.C.*

The subcommittee met, pursuant to recess, at 10:10 a.m., in room 318, Old Senate Office Building, Senator Gaylord P. Nelson (chairman of the subcommittee) presiding.

Present: Senators Nelson, Scott, and Hatfield.

Also present: Benjamin Gordon, staff economist; James H. Grossman, minority counsel; Susan H. Hewman, research assistant; Elaine C. Dye, research assistant; and William B. Cherkasky, legislative director, staff of Senator Nelson.

Senator NELSON. The hearings of the Subcommittee on Monopoly will open. We will hear testimony this morning from representatives of Merck & Co., who will be introduced by the distinguished and very able Senator from New Jersey, Mr. Case.

Senator, I understand you will introduce the representatives of this very fine company, which is located in your State.

## STATEMENT OF HON. CLIFFORD P. CASE, A U.S. SENATOR FROM THE STATE OF NEW JERSEY

Senator CASE. Thank you, Mr. Chairman. It is indeed located in New Jersey, and I guess a lot of other places, too, but we claim it as a citizen. Also, as a citizen of Rahway, N.J., we claim it as a citizen of my hometown. That makes it a special pleasure and privilege to present to you this distinguished citizen of my town, represented by its chief executive and several of its leading scientists.

Two of the witnesses are constituents, New Jersey residents and personal friends of mine: Mr. Henry Gadsden, president of Merck & Co. on my right, and Dr. Max Tishler, who is president of Merck, Sharp & Dohme research laboratories division. As a matter of fact, Dr. Tishler and I were remembering that 31 years ago, when I first ran for public office in the Common Council of the great city of Rahway——

Senator NELSON. That is at the head of the Boy Scouts. I remember that.

Senator CASE. Senator, you are so disarming.

He opened his door to me when I was ringing doorbells in the approved fashion and seeking votes. So if he is a good friend, I think we have good reason to be.

Senator NELSON. Did you check the vote in that precinct?

Senator CASE. This vote was 10 to 1. This was a good, solid, American precinct.

I am glad to say it is more or less in the State, sir.

The other two witnesses, Mr. Chairman, are Dr. Karl Beyer, senior vice president for research, and Dr. Douglas Lawrason.

They are from the State of the senior Senator from Pennsylvania, also on the Senate Small Business Committee, who is here this morning.

Senator SCOTT. I will give you as much time as you want to say something nice about me, although you may defer.

Senator CASE. If it is all right, Mr. Chairman, I shall defer this until the Senator runs again. I have to go over to another committee, unfortunately.

Senator NELSON. He would rather have you say something nice when it counts, I am sure.

Senator CASE. Well, I have this other committee and I have to do my duty there.

The committee has been examining Merck products in its hearings. Now I understand it is Merck's turn. I am glad that they asked for an opportunity to testify and that the committee found it possible to schedule them so soon after the other witnesses had testified. I am pleased to present these witnesses, representative of a company and an industry which occupy an important and valuable role in the life and growth of our State and our Nation.

Thank you very much, Mr. Chairman.

Senator NELSON. Thank you very much, Senator Case.

The committee is very pleased to have you appear here this morning and present these distinguished citizens from your State.

Senator CASE. Thank you.

Senator NELSON. How did you wish to proceed, gentlemen? You have a number of witnesses here. Do you have any particular schedule you want to follow?

## INTRODUCTORY REMARKS OF HENRY W. GADSDEN, PRESIDENT, MERCK & CO., INC., RAHWAY, N.J.; ACCOMPANIED BY LLOYD N. CUTLER, SPECIAL COUNSEL, WASHINGTON, D.C.

Mr. GADSDEN. Mr. Chairman, I would like to make a few opening remarks and introduce Dr. Tishler, who will proceed to introduce Dr. Beyer, and then Dr. Lawrason, who did the clinical investigation. Then I shall return, as the final witness, to present a statement with reference to the company's marketing, advertising, and promotional activities, which, in our opinion, have fairly presented this drug and have positioned it appropriately in the minds of the physicians.

Shall I proceed?

Senator NELSON. Your biographical sketch will be printed at this point. Please proceed.

(The biographical sketch of Mr. Gadsden follows:)

BIOGRAPHICAL SKETCH OF HENRY W. GADSDEN, PRESIDENT, MERCK & CO., INC.

Henry W. Gadsden became president of Merck & Co., Inc., on January 15, 1965, after directing all the company's production, marketing, and research activities for nearly a decade as executive vice president.

Before becoming executive vice president and a director of Merck in 1955, he served as vice president and then administrative vice president. Mr. Gadsden had been a vice president and director of Sharp & Dohme, Incorporated, when the latter company merged with Merck in 1953.

Mr. Gadsden is a director of the Campbell Soup Company, New Jersey Bell Telephone Company, and the New Jersey State Chamber of Commerce. He is a member of the Board of Directors of the Pharmaceutical Manufacturers Association and secretary-treasurer and a director of the PMA Foundation. He is a trustee of the Committee for Economic Development; New Jersey State Safety Council, Inc.; and Seeing Eye, Inc.

Born in New York City April 16, 1911, Mr. Gadsden was graduated from Yale University in 1933, receiving a B.S. degree in economics. He was first associated with Bankers Trust Company in New York City (1933–34), and then with the management consulting firm of R. A. Lasley, Inc. (1934–37), also in New York. He joined Sharp & Dohme, in Philadelphia, in 1937.

At Sharp & Dohme, after two years as an analyst in sales research, Mr. Gadsden became assistant to the executive vice president in 1939; director of production and engineering in 1946; vice president in 1949; and a director in 1952.

During World War II, he served as executive officer of the Philadelphia Ordnance District of the U.S. Army, rising to lieutenant colonel. Returning to Sharp & Dohme in 1946, he served in a civilian advisory capacity as district chief of the Philadelphia Ordnance District from 1948 to 1955. He is a former vice president and director of the American Ordnance Association.

Mr. Gadsden formerly served as a director of the First Pennsylvania Banking and Trust Company; Provident Mutual Life Insurance Company; the Institute for Cancer Research, Philadelphia; and the Philadelphia branch of the American Cancer Society. He was formerly a trustee of Lankenau Hospital, Philadelphia; Overlook Hospital, Summit, N.J.; Episcopal Academy of Philadelphia; and Short Hills Country Day School.

A resident of Short Hills, New Jersey, Mr. Gadsden is married to the former Patricia Parker of Philadelphia. They have four sons: Christopher H., born in 1946; Thomas P., born in 1949; William F., born in 1955; and Robert W., born in 1956. The family formerly resided in Gladwyne, Pennsylvania, from 1949 to 1955.

Mr. GADSDEN. Mr. Chairman, I wish first to express my appreciation and that of my associates for this opportunity to appear before the committee during the 5 days set aside for the examination of various aspects of indomethacin.

As you know, this drug was discovered by Merck scientists and is marketed by the company, for the management of certain arthritic disorders, under the trademark of "Indocid" abroad and "Indocin" in the United States.

We felt it urgently important that we present our testimony now, Mr. Chairman, because although the committee's intent may have been to focus on FDA actions relating to Indocin, the announcement of the hearings suggested a primary concern with the product and the behavior of our company.

The FDA has regulatory authority over all prescription drugs and a broad responsibility to protect the public interest as such drugs are developed, tested, and used. But, in practical terms, the agency cannot be held ultimately responsible for the safety and effectiveness of any specific drug product or for the integrity with which it is brought to the attention of physicians. In the final analysis, it is we who are responsible for both.

It is our purpose to present to the committee and place on the record our assessment of Indocin. In the process, we will also present a record of our performance.

With me today from the company are Dr. Max Tishler, president of our Merck Sharp & Dohme research laboratories; Dr. Karl H. Beyer, Jr., our senior vice president for research; and Dr. F. Douglas Lawra-

son, our vice president for medical affairs. You have statements of their background before you, as you have mine. Let me simply say that they are scientists whose research contributions and professional distinction are internationally recognized.

Also present with us today are two distinguished independent rheumatologists, who are prepared briefly and informally to discuss their own experience with Indocin and their own perception of its place in the management of arthritic disorders. I make this distinction, Mr. Chairman, because I want to emphasize the conditions under which they are here, lest these conditions be misunderstood.

To make the record absolutely clear: when we heard about this inquiry into Indocin and decided that we should ask for an opportunity to testify, we asked Dr. Smyth and Dr. Calabro if they would be willing to appear and use a few minutes of the time allocated to us. They have performed clinical investigations on Indocin under grants from Merck to defray the costs of the work. We offered to pay their expenses in coming to Washington. We are not paying them an honorarium for their appearance here. We would not and could not pay them for their testimony. We asked them to accompany us only because we believed it would be helpful to the committee to hear the views of practicing rheumatologists who have studied Indocin in patients.

We are also accompanied today by Mr. Lloyd Cutler as our Washing counsel.

As I said at the outset, I will submit a closing statement with reference to what we think is the very responsible conduct of the company in the presentation and positioning of the product.

May I now introduce the president of the Merck Sharp & Dohme research laboratories, Dr. Max Tishler, whose curriculum vitae is submitted for the record. He is recognized as one of the great industrial research directors in the Western World. Rather than summarize his long list of achievements and honors here and abroad, I shall mention only two. Dr. Tishler is a life trustee of Tufts University and a member of the National Academy of Sciences. Among its approximately 800 members, I understand the Academy has admitted less than 30 from industry. Dr. Tishler.

Senator NELSON. Doctor, the committee welcomes you and the other representatives of your distinguished company. We have always followed the policy on this committee, and I am sure we will continue to do so, which I have announced a number of times from the Chair, that we would permit any company from the drug industry to come before this committee upon its request. We desire to maintain a balance in the testimony, and I think at least a half dozen times from this chair, I have publicly invited both the companies and the Pharmaceutical Manufacturers Association to appear. So we welcome you here today.

I think I should say to you that you may have based some of your viewpoints about the hearings upon what you have read in some of the medical publications and trade press as well as on statements by the PMA, and you might very well have come to the conclusion that this committee has not intended to receive balanced testimony. In fact, as I read the statements going out in a fair percentage of the medical publications, those that are supported by advertising and those that are not, I do not recognize that I have attended the same hearings that these reports have covered. I say the same thing about the statements

I read coming from the association of which you are a member, the Pharmaceutical Manufacturers Association. So, I wish you to know that your company is welcome to come before this committee at your request at the earliest possible date we can schedule. That has been said repeatedly for every company in the country. I have, and I am sure the committee has no objection, made this statement because we intend to give to the industry an opportunity to respond to anything that is said at these hearings. We have made that position clear from the very beginning, and, as I understand it, your request to appear came a very short time ago and we scheduled it as you desired, forthwith. That has been our practice in the past and is our intent for all future hearings.

Senator SCOTT. Mr. Chairman, may I congratulate the chairman on the promptness in which this company has been given an opportunity to reply to a good many statements, many of which are derogatory to it and some of which, I am sure from having looked over some of their statements, they are prepared to rebutt.

I am aware that medical journals take one point of view on the matter and that the American press generally may be able to report only what it hears in this room and what the chairman or I or other members of the committee say. I do regret that there appears to be some effort to try this case in the press before it has been heard fully in the hearing room. I have not been entirely sympathetic to the position of the American Bar Association in its effort to inhibit the press in its reporting of crime news, but I think it is a crime in itself for the press to put any witnesses under a shadow before he testifies, and it is wrong to do this. I had read in a book once that you should never criticize the press, and I am now doing the worst thing that any politician should do, but I am doing it, I think, under this rather intensive provocation.

My criticism, however, is not directed as much to the press—and I hope they will give the same three-column treatment to your testimony as they gave to your opposition yesterday—but my criticism is fundamentally to the fact that the Food and Drug Administration, which often comes in to us to make recommendations, whom we listen to with a great deal of care, nevertheless seemed with altogether too much eagerness yesterday to have launched themselves into a series of attacks on this company, and the merits of this will develop as we hear all the testimony.

But I do not like the fact that Mr. Goodrich's testimony was so timed yesterday as to carry more than the implication of a threat in saying, as reported in the press, that decisions whether to recommend prosecution to the Justice Department now rests with him, the clear implication being that if you gentlemen and your company do not behave yourselves or if you give him too much trouble, you will pay for it. Dr. McCleery, as acting director of the FDA's Division of Medical Advertising, criticizes the advertising practices as seriously misleading. I am going to examine the entire testimony when we are through, with a particular eye on the credibility of Government witnesses and the motivation of Government witnesses and the timing of the appearance of Government witnesses for the purpose, apparently, of influencing or affecting the testimony of subsequent witnesses. I have been a member of the bar for more than 40 years, and I think I know slanted testimony when I see it. I think I know timing when I see it, and I

think I know the use of the press to create an impression before all the evidence is in when I see it.

I am glad to see that the press is making copious notes of this. I expect to be probably criticized in various columns as the tool of the interests, but after 26 years, I am able to bear that burden, also. I do not know any of you gentlemen, I never met you until this morning, and I am only interested in the fact that you shall have a fair opportunity to appear and to be heard. If you are wrong, I will condemn you just as cogently and incisively as my statement is critical of the apparent effort of a Government agency to gain a certain degree of publicity for its activities, a certain indecency, in my opinion, in rushing to the assault here where your testimony has not been heard. It might have been better if they waited to comment on your testimony.

I appreciate the chairman's giving me an opportunity to say this. Your drug may be a good drug, it may be a bad drug. It may cure or alleviate some of the arthritic disorders; it may not. I hope it will, because I have one of them. But right or wrong, I am pleading simply that, as the chairman has said, we have hearings fairly balanced—and he has been most careful here to see that you are properly brought in. But I plead for the same treatment in the press. I cannot expect it in the planted stories among the columnists, because we all do that. I cannot say non mea culpa. Every politician on the Hill is busy planting his views with some columnist; I have done it myself. So this is not said out of piety, but it is said out of recognition of the facts of life.

Recognizing these facts, I conclude simply by pleading once more for the most careful and fairest presentation of the testimony before the committee. As the chairman has so well demonstrated, he has concern for that. I also plead for the same kind of presentation in the press. I do not think that either Senators or newspapermen really know whether indomethacin is a good drug or not. So let us all join together, press and public and the Government, to find out whether the patient is receiving the kind of thoughtful care from the drug industry and from the medical profession, which we hope he is, which I personally believe he is, and let us keep the patient's concern in mind.

Thank you very much.

Senator NELSON. Thank you, Senator. I think I should comment on what the distinguished Senator from Pennsylvania has said.

One, as to the FDA rushing to the assault before the company has been heard, I would like to say that it is partly my fault. The FDA has not appeared before this committee at any hearing except at the request of the committee. We have requested the FDA to appear on specific problems. After having listened to all the FDA witnesses, having read their testimony very carefully before I came to the hearings and having talked to the witnesses, I think the testimony of these officials has been very carefully prepared and judiciously presented, in balance, and that they have presented their honest opinions. I must say they have been most persuasive in my listening to their testimony as well as listening to those who disagree with FDA. I have been tremendously impressed with the quality of the witnesses and the quality of their testimony.

In any event, they came at the request of the committee. We did not ask the Merck Co. to appear ahead of FDA and for the FDA to come to rebutt them. The purpose of the hearing is to learn about problems in the industry.

As to the press, given the fact that you conduct a 2- or 3- or 4-hour hearing covering very long and complicated testimony, and the fact that the reports of the press must necessarily be condensed because there is not that much space in the paper, I think that the press has done a balanced job of reporting. We have had a series of hearings here, the nature of which is to study what appear to be problems in the industry that are of public concern.

As to publicity of the industry, I do not think there is any doubt in the world that 99$^{99}/_{100}$ percent of the inches in the press are favorable to the drug industry. There is only a tiny percentage that is unfavorable. That part that has been unfavorable with regard to drug pricing is unfavorable because it appears on its face to be an inexplicable pricing structure. We have heard from the industry in great detail, and I for one am not persuaded that it has given an adequate explanation of why a drug like prednisone should sell in competitive bidding in New York City, and to the Defense Supply Agency, and the Veterans' Administration, and hospitals for 45 cents a hundred and in the retail market for $17.90 a hundred, while the Medical Letter, a distinguished publication, says that at least 22 versions of the drug with this vast price range are of equivalent therapeutic value.

This is a matter of important public concern. When you have two drugs of equal value, one selling for 45 cents a hundred to one group and the other for $17.90 a hundred to pharmacists, that is news; and I would have considered the press quite biased if they had not printed it.

The other aspect that has been news is that the same company selling at $17.90 to the pharmacists are themselves offering their drug in the competitive marketplace at $1.20 a hundred; and at the same time, companies that are selling it for $17.90 a hundred to the pharmacists in the retail marketplace in America are selling it for one-fourth that in the marketplace in Bern, Switzerland, and elsewhere. These are matters of news, and I do not think the press has been biased, frankly, in reporting this rather interesting and significant variance in the price structure.

Senator SCOTT. None of which I read in this morning's press, Mr. Chairman. I was not referring to that. I am not making any prejudgment. I wonder if the fact that these witnesses are due to appear had anything to do with the fact that the only news in the paper this morning consists of attacks upon the witnesses before they have been heard. I would be doing less than my duty, even at the peril of a politician being critical of the press, if I did not say that I expect as a member of this committee a balanced reporting of what goes on here, and I think balanced reporting does not include an assault on the witnesses before they have been heard by quoting, after 4 hours of testimony, simply those statements which reflect on one company.

Senator NELSON. I would like to continue on this point. As to the FDA, I would want the Senator to know that there is no fault that rests with them. If there is any fault at all, it rests with the chairman of this subcommittee, because I decided upon the order in which they would appear.

Senator SCOTT. You did not write the story.

Senator NELSON. No, but I thought that perhaps you thought that the FDA volunteered to come in, as you put it, in the indecency to rush to the assault before the company was heard. I am only saying

that I was the one who requested them to appear on that day, and it does not reflect on the FDA.

I think you have a particular problem here. You have congressional committees which conduct hearings. They conduct hearings about problems that exist in the country, and it is these problems that the press report. If there are no problems in the industry, we do not expect the press to spend all its time on research to discover what the industry did that was good.

We had exactly the same situation when I introduced the first legislation for minimum tire safety standards and for uniform auto safety standards, both of which subsequently became part of the law of the land. I had people in my own State, where we have a very distinguished auto company, American Motors, and some distinguished tire companies who attacked me as being antiauto and antitire industry. I am not antiauto industry or antitire industry. I think they are great industries, just as the pharmaceutical manufacturing industry is a great industry and has made a great contribution to the country. But the fact was that there was something wrong in the industry and when the hearings were conducted, and the stories on the front page reported that there were defective and inadequate tires on the market, I think the press was right in reporting these facts. Everybody knows that the auto industry has made a great contribution to this country, but that does not mean that the auto industry is perfect, any more than the pharmaceutical manufacturing industry is perfect or the legal profession, of which I am a member, is perfect, or any other field is perfect.

The point that I make, and I do not think it has been made clear in the press and the drug industry, is that we are going to hear all viewpoints. We want to hear all viewpoints. We want a balanced record. We have been attacked by the Pharmaceutical Manufacturers Association for not hearing all viewpoints, I guess because you cannot hear all viewpoints at once. We have leaned over backward to tell the companies involved that they can testify any time they wish as soon as we can schedule a place and time. We have told the PMA the same, and it has come three times and has presented many witnesses. Other individual witnesses have to wait in line.

If the industry would prefer that they, either PMA or the companies, not have a preferential chance, which I think they are entitled to because we are talking about their business, the committee might very well proceed to listen to individual witnesses for the next 3 years, because we have had that many requests from individual doctors all over the country.

Senator SCOTT. Of course, if you tried that, you would have trouble with me, as you know.

Senator NELSON. My point is that we want balance and all viewpoints here. I say to you, representing the company, that if at any time in these hearings, you think there is a viewpoint that has not been heard from the industry standpoint, let the committee know and you will be heard. If I slip up on it, Senator Scott certainly will not. But I want that well understood from the beginning.

The other aspect I would like to mention is that whenever you conduct a hearing of this kind, members of the committee ask to explore the problem. The fact that you might cross-examine a witness or di-

rect-examine a witness or raise a tough question that sounds prejudicial does not mean anything at all. This is the way to explore an issue to get full information. If you have the information, the record will show the answer. This committee does not make medical judgments. We are trying to get the best professional witnesses we can find, and I think we have had some of the best in the country, as we intend to have, to conduct further hearings with the best witnesses we can find.

Mr. GADSDEN. Mr. Chairman, may I make a comment, please?

Senator NELSON. Surely.

Mr. GADSDEN. As will be evident in the subsequent testimony, while we disagree most deeply with some of the conclusions and statements of the Food and Drug Administration, we nevertheless, credit them with speaking out of sincere conviction. This is the way they saw it, but we do believe that they just happened to be in error as to their conclusions.

Senator NELSON. I think the FDA has very distinguished scientists and administrators and that they are sincere, just as I am sure you are. But that is the purpose of the hearing. If there is a difference in viewpoints, we want to hear yours so that, on balance, the record can be read and people can make a judgment about where the truth lies, whether it is on one side or the other or somewhere down the middle. We have had distinguished medical witnesses here—you are aware of this—from your own industry, from within the companies who will disagree vigorously about the interpretation of some kind of study, about the interpretation of the same set of facts. That is bound to be the case because medical science is still an art to a considerable degree. So there are bound to be differences of opinion. We want to hear all the best opinions we can get, both from those who feel one way and those who differ with them.

Mr. GADSDEN. Should Dr. Tishler proceed, sir?

Senator NELSON. I assume, Dr. Tishler, that if we have some questions while you are testifying, you will have no objection to interruptions?

## STATEMENT OF MAX TISHLER, PH. D., PRESIDENT, MERCK SHARP & DOHME RESEARCH LABORATORIES, DIVISION OF MERCK & CO., INC., RAHWAY, N.J.

Dr. TISHLER. I have no objection.

Senator NELSON. We have your statement and your biographical data. They will both be included in full in the record. If there is something, while you are reading, that you would like to extemporize on or elaborate on that would have taken too much time to write out in detail, you may feel free to do so. If there is anything you would like to eliminate, feel free to do so, but your statement as submitted will go in the record in full, and anything you wish to change in the course of your testimony, you may.

Dr. TISHLER. Senator, I plan to read my statement.

(The biography of Dr. Tishler follows:)

BIOGRAPHY OF MAX TISHLER, PH. D., PRESIDENT, MERCK SHARP & DOHME RESEARCH LABORATORIES DIVISION; MEMBER, BOARD OF DIRECTORS, MERCK & CO., INC., RAHWAY, N.J.

Dr. Max Tishler, who heads the $57-million-a-year research program of Merck & Co., Inc. is not only President of the Merck Sharp & Dohme Research Laboratories but also one of the nation's leading scientists in his own right.

When he was persuaded by the late George W. Merck to leave an academic career at Harvard to join the Merck laboratories, there were no antibiotics, no steroids, and only two vitamins commercially available. Dr. Tishler has contributed significantly in all of these and other fields of medicinal chemistry, having received more than 100 patents and published more than 100 papers. In 1953, he achieved national recognition with his election to the National Academy of Sciences.

In 1937, when Dr. Tishler became a member of the Merck research staff, it numbered fewer than 100 persons. Today he heads an organization totaling nearly 1,800, including representatives of some 35 diverse disciplines. (In addition, 500 persons are engaged in research and development in other divisions of Merck.) At major research centers in Rahway, N.J., and West Point, Pa., and several experimental farms, Dr. Tishler directs extensive research programs in human and animal health.

Major discoveries made in the Merck Sharp & Dohme Research Laboratories since Dr. Tishler assumed leadership in 1956 include drugs for the treatment of heart disease, hypertension, rheumatoid arthritis and other inflammatory diseases, and mental depression; and animal health products for control of economically significant diseases of poultry and livestock.

In addition to membership in the National Academy of Sciences, his honors include election to the American Academy of Arts and Sciences in 1965; the 1964 Chemistry Lecture Award of the Royal Swedish Academy of Engineering Sciences (Stockholm, Sweden); Rennebohm Lecturer, University of Wisconsin School of Pharmacy, (1963); the Julius W. Sturmer Memorial Lecture Award, Philadelphia College of Pharmacy, (1964); the 1963 Chemical Industry Award of the American Section of the Society of Chemical Industry; the 1961 Industrial Research Institute Medal; the 1960 Honor Scroll Award of the New Jersey chapter of the American Institute of Chemists; and the Merck Board of Directors Scientific Award (1951). He has received honorary D.Sc. degrees from Tufts University (1956), Bucknell University (1962), and the Philadelphia College of Pharmacy and Science (1966); and an honorary D.Eng. degree from Stevens Institute of Technology (1966). He is also a member of the honorary societies, Phi Beta Kappa and Sigma Xi. Funds from the Merck Board of Directors Award established the Annual Max Tishler Visiting Lectureship at Harvard and the Max Tishler Annual Scholarship at Tufts.

Born October 30, 1906, in Boston, Dr. Tishler was educated at Tufts University where he received his B.S. degree in chemistry, graduating magna cum laude. In 1929, he became Austin Teaching Fellow at Harvard University, and after receiving the degrees of M.S. in 1933 and Ph.D. in 1934, he became Research Associate with the late Professor Elmer P. Kohler, and in 1936, Instructor in Chemistry.

Joining Merck in 1937 as a research chemist, he served successively as Section Head of Process Research (1941–44) and Director of Developmental Research (1944–53). During this period, Dr. Tishler led the Merck teams which first synthesized hydrocortisone and developed commercial syntheses for vitamin B–2, pantothenic acid, and vitamin K–1. He also headed the development of production processes for penicillin, streptomycin, cortisone, and hydrocortisone.

His work in sulfa drugs included discovery of sulfaquinoxaline, the first effective drug against coccidiosis, a costly disease of poultry, and he developed a number of practical syntheses of amino acids which furthered research in nutrition.

In collaboration with Dr. Selman A. Waksman, Rutgers' Nobel laureate, he isolated the first actinomycin in crystalline form. In recent years, related actinomycins have found use in the treatment of certain types of cancer. He also collaborated with Dr. Waksman on a book entitled *Streptomycin*, and with Harvard's Dr. James B. Conant on *Chemistry of Organic Compounds*, a textbook.

In 1954, he became Vice President for Scientific Activities, and in 1956 was

named to head the Merck Sharp & Dohme Research Laboratories as Vice President and Executive Director, being named President in 1957. He was elected to the Board of Directors of Merck & Co., Inc. in 1962.

Dr. Tishler is active in educational affairs and serves on a number of scientific advisory committees affiliated with the U.S. government, with the numerous professional societies of which he is a member, and with the pharmaceutical industry.

Dr. Tishler and Mrs. Tishler, the former Elizabeth M. Verveer, reside in Westfield, New Jersey, and are the parents of two sons, Peter Verveer and Carl Lewis.

CURRENT AFFILIATIONS (UNLESS OTHERWISE NOTED)

*Civic*

National Research Council of the National Academy of Sciencies: Member, Advisory Committee on Tropical Medicine; member, Committee on Role of Patents in Research.

*Educational*

Columbia University: Member, Scientific Advisory Committee, International Institute for the Study of Human Reproduction.

Harvard University: Member, Visiting Committee (School of Public Health); member, Visiting Committee (Department of Chemistry).

University of Pennsylvania: Associate Trustee (Science); member, Physical and Biological Sciences Board.

Rutgers University: Member, Advisory Committee, School of Medicine.

Tufts University: Life Trustee; member, Executive Committee; vice chairman, Educational Policy Committee; member, Development Committee of Board; consultant, Modernization of Chemistry Department; member, Administrative Board, Tufts-New England Medical Center; chairman, Visiting Committee (Chemistry); member, Board of Advisors, School of Dental Medicine Program.

Union Junior College: Trustee.

The Fund for Overseas Research Grants and Education: Member, Board of Directors.

The Weizmann Institute of Science: Member, Board of Governors.

*Industry*

Industrial Research Institute: Member, Advisory Editorial Board. "Research Management"; former member, Board of Directors (1962); member Awards Committee.

Pharmaceutical Manufacturers Association: Member Research and Development Section.

*Professional*

Agricultural Chemical Society of Japan: Member.

American Association for the Advancement of Science: Fellow.

American Chemical Society: Member; former chairman, Organic Chemistry Division (1953–54); former councillor, North Jersey Section; member, Committee to Study Chemistry in Industry (Project of Committee on Chemistry and Public Affairs).

American Institute of Chemists: Fellow; former councillor (1959–61).

Association of Harvard Chemists: Member; past president (1964).

"Chemical & Engineering News": Member, Advisory Board.

Chemical Society (London): Fellow.

Chemical Society of Japan: Member.

Directors of Industrial Research: Member.

New York Academy of Sciences: Fellow.

"Organic Syntheses": Former member, Editorial Board (1954–59); former Editor-in-Chief (1959).

"Separation Science": Member, Board of Editors.

"Industrial Research": Member, Editorial Advisory Board.

Society of Chemical Industry: Honorary Vice-President (1968–69); member, Executive Committee (1963–68); former Chairman (1966), American Section; Chairman, Nominations Committee (1968).

Swiss Chemical Society: Member.

Dr. TISHLER. My scientific colleagues and I welcome and appreciate the opportunity to tell this committee about the development and introduction of indomethacin. You will forgive me, Mr. Chairman,

if I talk about the Merck Sharp & Dohme research laboratories with pride. But it is pride in others: in the achievements of my fellow scientists, and in the consistent philosophy of a management that believes that the two most important ingredients of research are quality and integrity.

The pharmaceutical industry laboratory, Mr. Chairman, is organized to bring together scientists of widely different disciplines, all needed to carry a program from the conceptual stage through clinical investigation. They comprise men from at least 35 separate disciplines—from chemists to pharmacologists, pathologists, biologists, physicists, engineers, and physicians, who are joined together to seek solutions to medical problems. In our society, pharmaceutical research laboratories have almost unrivaled capacity for such collaborative research in medicine.

This is the way our laboratories are organized at Merck, which considers research to be the vital heart of the company. To the best of our knowledge, there is no sizable company outside the pharmaceutical industry that over the years spends a higher percentage of its own revenues—excluding government support—for research and development.

Our budget for this work is the largest published of any pharmaceutical concern in the free world—$57 million this year, of which less than 2 percent comes from government. We have 2,300 people engaged in this work, of whom more than 500 have advanced academic degrees. Last year they published nearly 150 research papers in scientific journals.

Senator NELSON. Are you saying that $57 million is the figure that you identify as a cost accounting factor for research in your company?

Dr. TISHLER. Yes, it is.

Senator NELSON. Some times we have had trouble trying to get figures on how much is research, because company officials say it is difficult to separate it out, and I suppose it is.

Mr. GADSDEN. I am not aware of your previous discussion on this point, Senator. I would assume that perhaps the problem had to do with the cost accounting principles of allocation to a specific project. However, under our system, we can tell you how much is spent for research throughout the company, and this is the figure to which Dr. Tishler is referring.

Senator NELSON. When you refer to 2,300 people engaged in this work, just so I have it clear in my mind, I am not sure how you distinguish research from something else, but does this involve quality control, too?

Dr. TISHLER. No, this does not involve quality control. If you would like a breakdown on the type of research I am referring to, we have exploratory research, fundamental research, basic research, developmental research, and applied research—five categories of research. It is broken down into these categories. Most of the research is directed toward investigating, searching for new therapeutic agents, trying to find the limitations and scope of therapeutic drugs, developing the processes to make the products, doing all the physical things that are part of the controls that we have to set up for the situation.

Senator NELSON. You have refined these categories a bit since I have been in school. It was pure and applied research in those days.

Dr. TISHLER. We have good reasons for breaking it into five categories.

Senator NELSON. I am sure you do.

Mr. GADSDEN. I would have to tell you that this is Merck terminology, and what this means to us may not be the same as what it might mean in another research establishment.

Dr. TISHLER. That is correct.

Shall I proceed?

Senator NELSON. Please go ahead.

Dr. TISHLER. It is the quality and integrity of research that counts, not its quantity. To illustrate this point, it would be relevant, I believe, to give the committee a brief description of how Merck got into the long and difficult war against rheumatoid arthritis, a war in which indomethacin is one more significant advance.

Thirty-five years ago, a few years before I came to the company, hardly more than a young lecturer from the Harvard Chemistry Department, some Merck scientists became interested in helping to isolate the active ingredient of the yellowish outside layer, or cortex, of the adrenals—those two tiny glands that sit on top of each kidney. An insufficiency of this ingredient—even then thought to be a steroid hormone—causes Addison's disease, a normally fatal illness.

What was the basis for Merck's interest in this field? There was little or no commercial reward at the end of the road. Only 800 Americans were then known to have Addison's disease, and they were kept quite healthy on adrenal extracts. The only possible reward for the effort appeared then to be scientific and medical. The active ingredient of the adrenal cortex was believed to be vital to life. My colleagues were not looking for a commercial drug to cure a specific disease. They were chiefly seeking knowledge to cure ignorance, which is the greatest enemy of human health.

If this seems sententious, it is also practical. In 1933, when George Merck established the pioneer laboratory in our industry, he was persuaded that the long-range success of both our research and the company itself would depend primarily on our ability to make fundamental and lasting contributions to human health. This has been our philosophy and our practice ever since.

It took more than a decade of failures, however, to synthesize cortisone, which had been isolated earlier from the adrenal cortex. The first complete synthesis was achieved in 1944 by a 26-year-old Merck chemist, Dr. Lewis H. Sarett, who had come to us from Princeton 2 years before. Four more years were required to produce enough cortisone to try it in Addison's disease. It was successful for this use, but there was little interest on the part of clinical investigators in exploring uses in other diseases.

Then came the historic letter from Dr. Philip Hench, the great rheumatologist of the Mayo Clinic, explaining a scientific hunch and asking for some of this scarce chemical to try on a carefully studied bedridden rheumatoid arthritis patient. We sent Dr. Hench a single gram of cortisone for his patient. On September 28, 1948, a few days after treatment started, the patient rose from her bed and walked out of the clinic. From his scientific hunch, from one gram of cortisone and one well-studied patient, Dr. Hench made the epic discovery that won him the Nobel Prize.

Several years after he made medical history by using cortisone in rheumatoid arthritis, Dr. Hench told a Senate committee:

> The work of investigators in scientific research is different from that in any other field that I know of. Frequently they are dealing with ideas for which there are no words. Thoughts are chemical processes, and there are times when a chemical process can be felt without any appropriate words.
>
> So that the only way you can really judge the quality of the members of any research organization is, in my opinion, by what they do—by their fruits.

Dr. Hench was referring to our laboratories. Some of what my colleagues there have done is told in a booklet, "By Their Fruits," which I would like, Mr. Chairman, to submit for the record.[1]

Senator NELSON. Yes, it will be received.

Mr. GADSDEN. Is this the appropriate way?

Senator NELSON. Just leave it at the desk here.

Senator SCOTT. Mr. Chairman, I have to leave for the time being. May I have your permission to submit a statement at the end of the testimony if I decide to do it?

Senator NELSON. Yes, it will be printed in the record.[2]

Senator SCOTT. I shall try to get back.

Senator NELSON. Thank you, Senator.

Please proceed, Dr. Tishler.

Dr. TISHLER. This booklet I submitted, Mr. Chairman, describes the contributions, up through 1963, of our company's scientists to some of the landmarks in chemical medicine.

These accomplishments have become part of medical history, but let me remind you that in 1933, while I was still a graduate student at Harvard—and this was not so long ago—there were no vitamins; no sulfas; no antibiotics; no antihypertensives; no antidepressants; no corticosteroids; no polio, measles, or mumps shots; no blood plasma; no anticoagulant therapy; no controllers of gout; and no broadly effective diuretics. Today, these words are part of the layman's language and the tools of our physicians. The work of Merck scientists played a key role in progress in the research and development in these fields.

Therapy in these fields has had an impact on the world around us. Anyone who has been a member of the Merck scientific team during any part of this period is proud of our contributions to these advances which have helped to wipe out or reduce the terror of whole categories of disease and have contributed dramatically to the extension of man's lifespan * * * a gift of years that has been called the greatest technological achievement of the 20th century.

One of the drugs of which my colleagues and I are most proud is indomethacin. It is recognized by our peers in the world of science and medicine as a creative masterpiece. At least a hundred first-rate, technically trained men and women in more than 20 different disciplines at Merck made contributions to this research and development achievement over a period of a decade. They have been rewarded in the only way that counts. Upward of a million people have been able, as a result of indomethacin, to lead happier, more productive, and less painful lives. This is what research at Merck is all about.

[1] Retained in committee files.
[2] See statement, p. 3451, infra.

In 1959, Mr. Chairman, an attempt was made to measure the contributions of industrial laboratories to the growth of fundamental knowledge. A study of the basic research articles printed in scientific journals during the course of 1 year was published in the weekly magazine, Science. Merck stood fifth on the list, right behind General Electric, Bell Telephone, Du Pont, and American Cyanamid. They averaged a third more papers than did we, but they also averaged over 30 times our financial resources.

But if my colleagues have reason for pride, they also have reason for discouragement. I am not referring only to disparagement of our work, though this is sometimes heartbreaking. I am referring to the painful slowness with which we and our counterparts in other pharmaceutical laboratories and our collaborators in the great research organizations of government, universities, and medical schools around the world are able to push back the frontiers of ignorance.

For most illness, such as the degenerative diseases, we have not yet found either the cause or the cure. While we can discover drugs like indomethacin which improve the health and well-being of patients, we are still fighting our way through the dark, and we are often terribly discouraged.

Biomedical knowledge is almost half a century behind that of the physical sciences in the accumulation of knowledge of the kind and depth that leads to major discoveries. The situation stems from the complexity of life. In the human body research is dealing with something like 100,000 or more biochemical processes. When you add to this the tremendous genetic complexities of the human being, the most complicated hybrid on this planet, you can see how difficult it is to make a statistical analysis of his chemical and emotional reactions. The number of unknown variables with which we have to cope is well beyond our present comprehension. We still can and do make significant progress, but it is clear that if research is really to conquer disease, we must never lose sight of our central task: the accumulation of more and more basic knowledge. This will require patience on the part of all, including the Congress, which has been so generous in recent years with appropriations for basic research in medicine.

Turning again to rheumatoid arthritis: in few other fields of medicine is our basic knowledge more deficient than it is in rheumatoid arthritis. Though indomethacin has given relief to many patients who suffer from this disease, there is still a deep dissatisfaction connected with this achievement. It is a dissatisfaction, too, for the medical profession and for the millions of victims of rheumatoid arthritis and related diseases. Neither we nor anybody else has found either the cure, or for that matter, the cause or causes of these diseases. All we have discovered are better ways to relieve painful suffering and return invalids to productive lives. This is important. But we still have before us the challenge to finish the job—namely, to cure and prevent the diseases themselves.

We now want to concentrate on the specific stage of our long research effort in this field—that of indomethacin—that now interests you and your committee. To tell you about this program, I would like to call on Dr. Karl Beyer, Jr., senior vice president for research of our laboratories. He is a distinguished scientist with an international reputation. He has both an M.D. degree, and a Ph. D. degree in physiology. He is a past president of the American Society for Pharmacology and

Experimental Therapeutics, which in its 60 years has honored only one other scientist from industry with this post. He is a member of the Drug Research Board of the National Academy of Sciences, and among his other honors will be the Distinguished Service Award of the University of Wisconsin, which he will be awarded in Madison 2 weeks from today.

Thank you very much.

Senator NELSON. Thank you very much, Dr. Tishler. We appreciated having your testimony.

We shall be pleased to hear from Dr. Karl Beyer, and we are pleased that my alma mater has seen fit to honor you with a distinguished service award, which is eloquent testimony to your qualifications.

Dr. BEYER. Thank you, sir.

Senator NELSON. Dr. Beyer, we have your biography and statement, both of which will appear in the record in full. You may proceed in any way you wish.

(The biographical data of Dr. Beyer follows:)

BIOGRAPHY OF KARL H. BEYER, JR., M.D., PH. D., MERCK SHARP & DOHME RESEARCH LABORATORIES, WEST POINT, PA.

GENERAL INFORMATION

Born June 19, 1914, Henderson, Kentucky; married; two daughters.

SPECIALIZATION

Pharmacologist and Physiologist, with principal research interest being in the fields of renal pharmacology, metabolism of drugs in the body and enzymologic studies on secretory mechanisms of cells.

EDUCATIONAL RECORD

B.S.—1935: Western Kentucky State College.
Ph.M.—1937: University of Wisconsin.
Ph. D. in Physiology—1940: University of Wisconsin.
M.D.—1943: University of Wisconsin.

CAREER SUMMARY

Instructor in Chemistry: Western Kentucky State College, 1935–36.
Instructor in Physiology: University of Wisconsin Medical School, 1939–43.
Assistant Director of Pharmacological Research, Sharp & Dohme, 1943–44.
Director of Pharmacological Research, Sharp & Dohme, 1944–50.
Assistant Director of Research, Sharp & Dohme, 1950–56.
Director of Merck Institute for Therapeutic Research, West Point, Pa. 1956–58.
President of Merck Institute for Therapeutic Research, 1961–66.
Vice President for Life Sciences, Merck Sharp & Dohme Research Labs., West Point, Pa., 1958–66.
Senior Vice President, Research—Merck Sharp & Dohme Research Labs., West Point, Pa., 1966–.

MEMBERSHIPS

Fellow in the American College of Physicians (F.A.C.P.).
Fellow in American Association for Advancement of Science.
Fellow in The New York Academy of Sciences.
Fellow in The Royal Society of Medicine.
Member of the American Chemical Society; American Physiological Society; Society for Experimental Biology & Medicine; Philadelphia Medical Society; Philadelphia Physiological Society; American Society for Pharmacology & Experimental Therapeutics (Secretary, 1959–61; President, 1964–65; Past-President, 1965–66); Federation of American Societies for Experimental Biology (President, 1965–66); Canadian Pharmacological Society; Association of American Medical Colleges; The American Therapeutic Society; Society of Toxicology; Amer-

ican Society of Nephrology; Council on Circulation & Renal Section, American Heart Association; International Society for Biochemical Pharmacology; Board of Trustees, Biological Abstracts (Treaurer, 1965– ); Drug Research Board, National Academy of Sciences, 1964– ; Editorial Committee, Annual Review of Pharmacology; Editorial Board, Journal of Clinical Pharmacology & Experimental Therapeutics; Committee on Biological Handbooks; National Society for Medical Research Board, 1964– ; Who's Who in America; The Newcomen Society in North America.

AWARDS

The Merck Scientific Award (1959).
The Gairdner Foundation Award (1964).
Modern Pioneers in Creative Industry Award, Natl. Assoc. of Mfgrs. (1965).
Modern Medicine's Award for Distinguished Achievement (1967).
American Pharmaceutical Association's Foundation Award in Pharmacodynamics (1967).

OTHER AFFILIATIONS

Lecturer in Physiology: Jefferson Medical College.
Lecturer in Pharmacology: Temple University Medical School.
Lecturer in Pharmacology: Graduate Medical School, University of Pennsylvania.
Special Lecturer in Pharmacology: Woman's Medical College.

PUBLICATIONS (OVER 150 PUBLICATIONS, INCLUDING THESE LISTED)

"Sympathomimetic Amines: The Relation of Structure to Their Action and Inactivation" (Physiol. Rev. *26*: 169, 1946).
"Functional Characteristics of Renal Transport Mechanisms" (Pharmacol. Rev. *2*: 227, 1950).
"Pharmacological Basis of Penicillin Therapy" (Chas. C. Thomas, Publisher, Springfield, Ill., 1950).
"Factors Basic to the Development of Useful Inhibitors of Renal Transport Mechanisms" (Arch. Int. Pharmacody., *98*: 97–117 (May) 1954).
"The Mechanism of Action of Chlorothiazide" (Ann. N.Y., Acad. Sci., *71*: 363, 1958).
"Newer Diuretics in Progress of Drug Research" (E. Jucker, Ed., Basle, *2*, pp. 9–69, 1960).
"Effect of Drugs on Active Transport", in "Enzymes & Drug Action" (Ciba Foundation Symposium, 1962. Ed. J. L. Mongar and A. V. S. deReuck; Pub. by J. & A. Churchill Ltd., London, England.)
"Physiological Basis for the Action of Newer Diuretic Agents" (Pharmacol. Rev. *13*: 517–562 (Dec.) 1961).
"Fetal Malformations" (Arch. Env. Health *5*: 94–96, 1962).
"The Effect of the New FDA Regulations on the Drug Industry" (Clin. Pharmacol. Therap. *5*: 1–5, Jan.–Feb., 1964).
"Method of Inhibiting Gastro-Intestinal Irritation" Patent No. 3,129,137 dated Apr. 14, 1964.
"My Criteria for Acceptable Research in Pharmacology" (Am. J. Pharmaceutical Education *28*: No. 5, Dec., 1964).
"Renotropic Characteristics of Ethacrynic Acid; A Phenoxyacetic Saluretic-Diuretic Agent" (J. Pharmacol. Exp. Ther. *147*: 1–22, 1965).
"From Theory to Therapy" (Proc. Western Pharmacol. Soc. *8*, 1965).
"Perspectives in Toxicology" (Toxicol. & Appli. Pharmacol. *8*: No. 1, Jan., 1966).
"The Federation in Midpassage", Introductory Remarks. Fed. Proc. *25*: No. 5. Sept.–Oct. 1966.

## STATEMENT OF KARL H. BEYER, JR., M.D., PH. D., SENIOR VICE PRESIDENT FOR RESEARCH, MERCK SHARP & DOHME RESEARCH LABORATORIES, DIVISION OF MERCK & CO., INC., RAHWAY, N.J.

Dr. BEYER. Thank you, Senator.

As has been stated by Dr. Tishler, neither the cure for nor the etiology of rheumatoid arthritis is yet within the realm of knowledge of physicians and medical scientists.

However, the development of a multitude of useful medicinal agents over the past 20 years—some of them, like indomethacin, for disease entities still beyond our capability for understanding—provides evidence that one does not need to know all about a biological function to alter it beneficially.

The development of indomethacin does not suggest that we have moved any closer to understanding the factors that precipitate or are involved in the rheumatoid process. What the successful application of the compound does imply is that, with the benefit of accrued knowledge and experience, Merck scientists were able to formulate a working hypothesis as to what initiated and sustained the inflammatory process; and also able to develop methodologies for the discrete examination in laboratory animals of the effects of candidate compounds on the basic factors of the disease.

While the search for more potent corticosteriods continued in the early 1950's, a group of Merck scientists and biochemists started what was to be a 12-year search in another direction—to find a compound that was not hormonal in nature, but that would still provide the benefits of the steriods.

Early in 1957 the attention of the scientists in this program turned to compounds with an indole nucleus. This was because an indole metabolite, serotonin, was thought to play a role in initiating and sustaining inflammation. A number of serotonin antagonists were synthesized by Merck chemists and made available for pharmacologic assessment as anti-inflammatory agents.

The serotonin theory eventually proved to be wrong, but it did provide the first promising chemical lead in our nonsteriod program.

The program began to achieve full focus later in 1957, when Merck scientists observed the first promising indole derivative after evaluating hundreds of unsuccessful agents, but it did not live up to the expectation of Merck scientists and physicians and was dropped.

In March 1961, another promising derivative was finally synthesized. That compound, too, was effective in preclinical studies, but even as clinical trials were being planned, our scientists developed another indole derivative, indomethacin, which appeared to have greater potency with less toxicity than any of the previous compounds.

Before indomethacin could be studied in man, it had to undergo lengthy and comprehensive testing in animals. More than 100,000 animals were used during the nonsteroid anti-inflammatory program leading to the development of the compound.

While animals themselves do not suffer from rheumatoid arthritis as a disease entity, we have been able to utilize a number of animal models to define, reproduce, and control in the laboratory fundamental phenomena involved in arthritic diseases.

Through the capability of developing methodologies for the control of biological phenomena in animals, our pharmacologists achieved the ability to strip arthritis down to its essential elements of inflammation, swelling, pain, and heat or fever, so that the action of potential compounds could be examined unfettered by the imponderables created clinically as patient, disease, and drug interact.

Some examples of animal models to test for antiarthritic activity are the carrageenin assay, which helps in the assessment of a drug's ability to reduce inflammation, pain, and swelling; the granuloma cot-

ton pellet assay, for measuring a drug's ability to inhibit inflammation and fibroblast proliferation; and still other tests which provide an indication of the analgesic and anti-inflammatory properties of compounds.

Additional control of these animal models is afforded by a comparison of the dosage of the drug with the response. Moreover, such dosage-response relationships are further compared with those of compounds commonly employed in the management of arthritic disorders. These comparisons are more than comparisons of potency, for we are able to compare the qualitative characteristics of the compounds as well.

The sizable and comprehensive animal studies with indomethacin provided clinicians with demonstrative evidence of the safety and efficacy of the compound, warranting tests in man.

The anti-inflammatory activity of indomethacin was demonstrated in the cotton pellet granuloma inhibition test in mice in which granuloma inhibition was observed following both oral and local administration. It was also demonstrated in the inhibition of edema induced by injection of the irritant, carrageenin, into the hind paw of rats.

Fever-reducing activity was demonstrated by inhibiting the fever produced by injection of a bacterial endotoxin in both rabbits and rats, as well as yeast-induced fever in rats.

In these and other tests, the potency of indomethacin was significantly greater than that of the anti-inflammatory compounds with which it was compared. It must be noted, however, that these studies comparing indomethacin with other known compounds, though serving as valuable indicators to the clinical investigator, are based on phenomena measured in animals and are not directly translatable to disease in man.

As part of the pharmacologic assessment, indomethacin was examined in the laboratory for its effect on the heart, the cardiovascular system, and autonomic reflex mechanisms, as well as for its effect on excretion, renal function, and animal behavior. Indomethacin did not affect any of these organ systems and processes.

When methodology was needed to examine a specific effect, we devised it if it was not available. Just as the Porter-Silber test, for example, bearing the name of two members of our staff, has become standard procedure in steriod measurement, so we devised new methodology to enhance reliability of metabolic studies with indomethacin. To do this required meticulous knowledge of the physiology of the animals employed in the studies and the synthesis of indomethacin compounds labeled with radioactive carbon. Such advances in methodology not only furthered our own indomethacin studies, but also contributed to the studies of scientists in other laboratories, since much of our methodolgy was published in detail.

Tests in several species to determine the metabolic fate of indomethacin indicated that in the dog, the drug present in the plasma is essentially all unchanged indomethacin. In other animals, metabolism of the drug differs. In the guinea pig, a significant amount of the drug is present in the plasma as a metabolite, with a small amount of indomethacin present in the cerebrospinal fluid. The route of excretion depended on the species and not the dose or the route of administration.

The influence of indomethacin and hydrocortisone on resistance to

infection was studied extensively in mice, rats, and rabbits, both before and subsequent to the initiation of clinical trials.

In the area of bacterial infection, in investigations in mice and rats, 10 different bacterial pathogenic microorganisms were used and the drug was given at several dose levels and treatment schedules. In contrast to hydrocortisone, indomethacin produced no detrimental effects in any of the experimental infections, even when administered in amounts 80 to 330 times the threshold dose for anti-inflammatory activity.

In the area of viral infection, indomethacin neither increased nor decreased resistance, in mice, to infections induced by the influenza A, Columbia SK, or the Eastern Equine encephalomyelitis virus.

In contrast to the adrenal corticosteroids, indomethacin did not depress antibody formation, which is a defense mechanism of the body against infection. These findings undoubtedly accounted, in part, for the contrasting effects of indomethacin and hydrocortisone on experimental bacterial infections, as mentioned above.

Taking all observations into account, it was held to be most probable that indomethacin would have no effect, beneficial or detrimental, on infections in man.

The safety assessment of indomethacin in the laboratory has been the most extensive we have ever undertaken and has included acute, subacute, and chronic toxicity studies in mice, rats, guinea pigs, rabbits, cats, dogs, monkeys, domestic pigs, and chickens. Chronic toxicity studies were continued for 26, 52, and 129 weeks in dogs; 35, 57, and 80 weeks in rats; 18 weeks in monkeys; 22 weeks in rabbits; and 27 weeks in guinea pigs. Acute and subacute toxicity studies were conducted in mice, cats, domestic pigs, and chickens. Reproduction studies included two-generation tests in mice, the recommended two-litter study in rats, and an established pregnancy test in rabbits.

The only toxicity that could be clearly identified as a direct effect of indomethacin was the production of gastrointestinal lesions of the type reported in animals for aspirin, phenylbutazone, and the anti-inflammatory steroids. Where anti-inflammatory potency and gastrointestinal irritation could be tested in the same species, the therapeutic ratio was as favorable for indomethacin as for phenylbutazone or the steroids. This type of potential side effect of antiarthritic dosages of aspirin, phenylbutazone, and steroids is well known to the physician.

Of course, there were other side effects we could not foresee which have occurred in man, but they were primarily of the subjective, sensory type, such as headache and dizziness, which are not usually observed in animals, since animals cannot communicate with man.

In the interest of time, I should like simply to condense the rest to say that the publications from our laboratories clearly disclose the results of the extensive animal studies carried on in the preclinical evaluation of indomethacin. They have not been challenged, even in the face of intensive investigation of the compound by other scientists.

The details of these studies are found in an extensive monograph which was provided each investigator and the FDA before clinical studies were undertaken. Reports of animal data to FDA and investigators were updated regularly to reflect the findings of animal studies continuing after the preclinical phase had been completed and the human studies were underway.

No drug, to my knowledge, has received a more intensive preclinical assessment than indomethacin. Except for the sensory effects, the transposition of the total preclinical assessment to experience in man has been gratifying.

The critical clinical evaluation phase, and the professional review period following the discovery of a new drug, will be covered by my colleague, Dr. F. Douglas Lawrason, a certified member of the American Board of Internal Medicine, and former dean of the University of Arkansas School of Medicine.

May I introduce Dr. Lawrason?

Senator NELSON. Thank you very much, Dr. Beyer, for your very valuable contribution to the discussion of this drug. As I think you perhaps know, I believe all of the witnesses, including the FDA, have commented upon the value of the drug in the treatment of rheumatoid arthritis and some other conditions. What they have differed on is the interpretation of some of the tests that have been made and the place that Indocin has in the medical armamentarium.

But if my memory is correct, there has not been any question in anybody's mind that it has a useful and valuable place in the treatment of rheumatoid arthritis and some other related conditions.

Thank you very much.

Dr. BEYER. Thank you, sir.

## STATEMENT OF F. DOUGLAS LAWRASON, M.D., VICE PRESIDENT FOR MEDICAL AFFAIRS, MERCK SHARP & DOHME RESEARCH LABORATORIES, DIVISION OF MERCK & CO., INC., RAHWAY, N.J.

Senator NELSON. Dr. Lawrason, the committee appreciates having you here today. You did submit, I think, a biographical sketch.

Dr. LAWRASON. That is correct.

Senator NELSON. Your full statement and biographical sketch will be printed as supplied to the committee by you. You may proceed to give your testimony as you see fit.

(The biography of Dr. Lawrason follows:)

CURRICULUM VITAE

I. Name: F. Douglas Lawrason, M.D.

II. Education:
- University of Chicago, 1937-40.
- University of Minnesota, B.A., 1941.
- University of Minnesota Graduate School, M.A., 1944.
- University of Minnesota School of Medicine M.D., 1944.

III. Internship and Postgraduate Training:
- Yale School of Medicine.
- New Haven Hospital, New Haven, Conn., Internship and Residency, 1944–48.

IV. Teaching or Research Experience:
- University of Minnesota, Assistant in Anatomy, 1942–44.
- Yale School of Medicine, Dept. of Internal Med. James Hudson Brown Memorial Res. Fellow, 1949.
- Yale School of Medicine, Dept. of Internal Med., Instructor in Medicine, 1950.
- Yale School of Medicine, Dept. of Internal Med., Assistant Professor, 1951.
- National Academy of Sciences, Washington, D.C., National Res. Council, Div. of Med. Sciences, Professional Associate, 1950–53.
- Univ. of North Carolina School of Medicine, Chapel Hill, N.C., Asst. Prof. of Med. and Asst. Dean, 1953–55.

Univ. of Arkansas Medical Center, Little Rock, Ark., Prof. of Med., Provost for Medical Affairs and Dean of the School of Medicine, 1955–61.
Merck Sharp & Dohme Research Laboratories, West Point, Pa., 1961 to present.
Research studies included—
Research concerned with cancer and leukemia in inbred strains of mice, at the University of Minnesota.
Investigation of new methods for the determination of plasma proteins and investigation concerned with salt and water excretion as related to renal dynamics, at the Yale School of Medicine.
Studies in experimental leukemia in inbred mice with particular reference to immunologic aspects and factors of resistance of transplanted tumors, at the University of North Carolina School of Medicine.
As a United States Naval Reserve Officer, studies in experimental anemia in swine, hematologic studies in animals exposed to atomb bomb radiation (Bikini) and hematologic follow-up studies in Japanese exposed to atomic bomb; done at the Philadelphia Naval Hospital and the Naval Medical Research Institute, Bethesda, Md.

V. Medical Practice:
Medical practice associated with various professional appointments listed.

VI. Medical Publications:
Lawrason, F. D. Studies of Leukemia and Mammary Cancer in Inbred Mice. Thesis for M.A. University of Minnesota, 1944.
Kirschbaum, A., Lawrason, F. D., Kaplan, H. S., and Bittner J. J. Influence of Breeding on Induction of Mannary Cancer with Methylcholanthrene in Strain Dba Female Mice, Proceedings of the Society for Experimental Biology & Medicine *55*:141, 1944.
Lawrason, F. D., Kirschbaum, A. Dietary Fat with Reference to the Spontaneous Appearance and Induction of Leukemia in Mice. Proceedings of the Society for Experimental Biology & Medicine *56*:6, 1944.
Lawrason, F. D. and Cronkite, E. P. Incidental Finding of Megaloblastic-like Cells in Bone Barrow of One of Two Swine with Macrocytic Anemia and Chlorhydrin. Yale Journal of Biology & Medicine *29*:87, 1949.
Lawrason, F. D., Eltzholtz, A. C., Sipe, C. R., and Schork, P. K. Correlation between the Mean Corpuscular Volume and Reticulocytosis in Phenylhydrazine Anemia in Swine. Blood *4*:1256, 1949.
Goodyer, A. V. N., Relman, A. S., Lawrason, F. D., Epstein, F. H. Salt Retention in Cirrhosis of the Liver. Journal of Clinical Investigation *29*:973, 1950.
Epstein, F. H., Lawrason, F. D., Relman, A. S., Goodyer, A. V. N. Studies in Salt Excretion during Quiet Standing. Journal of Clinical Investigation *30*:63, 1951
Erslov, A. J., Iverson, C. K., and Lawrason, F. D. Cortisone and ACTH in Hypoplastic Anemia. Yale Journal of Biology & Medicine *25*:44, 1952
Wagner, R. and Lawrason, F. D. The Production of Fever by Influenzal Viruses. IV. Effects of ACTH and Cortisone.
Lawrason, F. D., Alpert, E., Mohr, F. L., and McMahon, F. G. Ulcerative-Obstructive Lesions of the Small Intestine. Journal of the American Medical Association *19*:641–44, 1965

VII. Present position:
Vice President for Medical Affairs, Merck, Sharp & Dohme Research Laboratories, West Point, Pa.

Dr. LAWRASON. Mr. Chairman, members of the committee:

My major responsibility is the clinical investigation of Merck drugs, as a member of a team of 40 physicians who are devoting their careers to this work. The clinical investigation of indomethacin has been my responsibility.

In this statement, I have four points to make:

First, indomethacin is a useful drug for the treatment of at least four different forms of arthritic disease. It is effective and safe as described to the medical profession.

Second, Merck answers to its own standards of research as well as to the regulatory judgment of this country and other countries throughout the world. Our standards are based upon several decades of notable accomplishments in medical research, and we give ground to no one as to the integrity of our standards and performance.

Third, the validation of the merits of our work since our studies began in 1961 up to the present can be found in the collective judgment of several hundred investigators of recognized authority in this country and abroad.

Fourth, there does not exist in this world today a generally accepted test design for the study of drugs or of any other type of therapy in rheumatoid arthritis. If there were, we would be the first to use it.

Mr. Chairman, I shall explain what we do in the study of drugs in rheumatoid arthritis. In addition, I want to point out what neither we nor others can do to study drugs in this field and why the studies conducted on indomethacin fully warrant its right to be available for physicians who wish to prescribe it for their patients.

The study of indomethacin in man dates back to 1961. At that time the cooperating clinics project of the American Rheumatism Association was still in the primitive stages of its long effort to improve clinical design in this field. We faced the task of studying a new drug shown in animal testing to possess anti-inflammatory activity comparable to steroids. The patients could not wait, nor would we wait for the design of a wholly satisfactory double-blind study for rheumatoid arthritis.

We performed what was the best method of study in 1961, and what still remains the best method in 1968. We took the drug to a handful of expert physicians in rheumatology. They began with very low doses, gradually increasing them. Under careful observation they determined the patients' positive or negative reactions. When these men told us the drug worked—that it provided relief of pain and reduction in inflammation—we accepted their judgment, both because of their knowledge and experience and also because it provided significant confirmation of the laboratory and animal work that had preceded it. After that we put the drug in the hands of additional specialists having particular expertise in a variety of arthritic disorders—rheumatoid arthritis, spondylitis, gout, osteoarthritis, musculoskeletal disorders, and so forth. As experience with the drug accumulated, we obtained the cooperation of investigators in more than 60 major medical centers in the United States and abroad. If the committee wishes, I will provide a list of these institutions for the record.

Senator NELSON. If you would, please.

(The document referred to follows:)

LIST OF INTERNATIONAL INSTITUTIONS WITH WHICH INDOCIN ® INVESTIGATORS (ORIGINAL NDA) ARE ASSOCIATED

Buenos Aires Hospital, Argentina
Institute of Rheumatology, Argentina
Karolinska Institute, Stockholm, Sweden
Marion General Hospital, Manila, Philippines
Medical Institute of Rheumatology, Bogota, Columbia
Military Central Hospital, Lima, Peru
National School of Medicine, Mexico
Norfolk and Norwich Hospital, England
Osaka University Hospital, Japan
Oslo University Hospital, Norway
Okayama University Hospital Japan
Queen Elizabeth Hospital, Adelaide, Australia
Royal North Shore Hospital, Australia
Royal Perth Hospital, England
Royal Prince Alfred Hospital, Australia
Royal Victoria Infirmary, England.
Rheumatology Foundation Hospital, Finland.
Sahlgren Hospital, Gutenberg, Germany.
St. Erik's Hospital, Sweden.
St. Stephen's Hospital, London, England.
Tokyo University Hospital, Tokyo, Japan.
Tokyo Women's Medical College, Tokyo, Japan.
University of Florence, Florence, Italy.
University of Frankfurt, Frankfurt, Germany.
University Hospital of Cork, Cork, Ireland.
University Hospital of Wurzburg, Germany.
University of Paris, Faculty of Medicine, Paris, France.
University of Vienna, Austria.
Westminster Hospital, London, England.
Kyushu University, Japan.

LIST OF DOMESTIC UNIVERSITIES AND HOSPITALS WITH WHICH INDOCIN® INVESTIGATORS ARE ASSOCIATED

Arkansas University Medical Center.
Boston University Medical School.
Buffalo University School of Medicine.
Children's Hospital (University of Iowa).
Colorado University Medical Center.
Columbia University College of Physicians & Surgeons.
Cornell University School of Medicine.
Duke University Medical Center.
George Washington School of Medicine.
Harvard Medical School.
House of the Good Samaritan (Boston).
Johns Hopkins University Medical School.
Long Island College Hospital.
Maryland University School of Medicine.
Massachusetts General Hospital.
Methodist Hospital (Brooklyn).
New York University School of Medicine.
New York University Medical Center.
Ohio State University School of Medicine.
Oklahoma University School of Medicine.
Oregon University Medical School.
Stanford University School of Medicine.
Texas University Southwest Medical School.
Tulane University School of Medicine.
UCLA School of Medicine.
UCLA Medical Center.
University of California Medical Center.
University of Chicago School of Medicine.
University of Miami Medical School.
University of Michigan School of Medicine.
University of Minnesota Medical School.
University of Oregon Medical School.
University of Pennsylvania School of Medicine.
University of Southern California Medical School.
University of Tennessee College of Medicine.
U.S. Naval Hospital Newport, R.I.
Utah University Medical School.
Vanderbilt University School of Medicine.
Veterans' Administration Hospital, Palo Alto, California.
Veterans' Administration Hospital, Philadelphia, Pa.
Washington University School of Medicine.
Western Reserve University School of Medicine.
Yale University College of Medicine.

Dr. LAWRASON. At this point, several of the investigators employed a controlled-study method known technically as placebo substitution. This is a highly useful method of confirming drug action. It is a single-blind study. Here the patient is placed on various medications including placebo at different stages, but does not know when the different drugs, which are identical in appearance, are being added or removed. These studies confirmed that the therapeutic response obtained on indomethacin was due to the drug, since the symptoms rapidly returned when the patient was given the placebo medication.

In the 1961–65 period we are discussing, this method was not only sound but respected. Even though criticized earlier in these hearings, it still remains valid today. The skilled physician, deeply concerned over the patient's comfort and progress, soon learns the characteristic pattern of the fluctuations in the activity of the individual's disease. By his experience he easily recognizes an exacerbation of symptoms of the disease, and he is able to regain control with reinstitution of the effective therapy. To imply that these clinical investigators purposely choose to institute placebo at the point in the patient's disease when the patient is about to experience an exacerbation of his illness is sheer nonsense and is a reflection on the scientific integrity of the observer and also on his moral character.

Mr. GORDON. May I interrupt here just a moment?

Dr. LAWRASON. Yes, sir.

Mr. GORDON. I do not like to be in a position of defending any previous witness, but it seems to me that if a writer points out a flaw in an investigative method, I do not think he is thereby imputing dishonesty, is he?

Dr. LAWRASON. I do not believe this was said, Mr. Gordon. I believe the implication was that one could give a placebo or an active compound, and then at the time one expected an exacerbation to occur or a remission, a change in the cyclic character of the disease, the investigator would change medication. This is what this refers to.

Mr. GORDON. Yes, but it does not necessarily impute dishonesty, does it?

Mr. GADSDEN. Even though I am not a doctor, I think the implied criticism of the single-blind study is that it is open to this kind of variation. If this criticism is implied, then I think Dr. Lawrason's comments are appropriate.

Dr. LAWRASON. I would like to refer to Dr. O'Brien's testimony, in which he said that a study of this type—namely, the single-blind placebo—was designed in such a way that the bias is in favor of the drug.

Mr. GORDON. That is a statistical bias, I would think. At least, that is the way I understood it.

Dr. LAWRASON. He did not say "statistical."

Mr. GORDON. Well, we are talking about statistics. As I said, I do not want to defend anybody, but my understanding is that the bias was a statistical bias rather than a personal bias. But I do not want to read meaning into his words.

Let me ask you this: In referring to the 1961–65 period, are you implying that clinical trials using control groups were not used before 1961?

Dr. LAWRASON. No, the double-blind study is not new. It has been used for many years. However, the difficulties involved in rheumatoid arthritis includes the subjective character of the observations to be made. It is extremely difficult to construct a valid control study under these conditions, where active therapy is usually in the background.

Mr. GORDON. Have you any idea how many years controlled trials have been in use? I am not saying double blind, necessarily, but controlled.

Dr. LAWRASON. Are you referring to clinical controls?

Mr. GORDON. Yes, well-controlled clinical trials.

Dr. LAWRASON. This is nothing new. I would hazard a guess of 20 years or more.

Mr. GORDON. You may be interested to know that as a result of some research, I discovered that well-controlled clinical trials were conducted in the 18th century, about 225 years ago. It is in this book by Lind "On Scurvy," that discusses a wonderful trial he did, and I am going to include it in the record at this point, with the permission of the chairman. It is a short description of this particular trial.

(The article follows:)

[From Lind's Treatise on Scurvy, edited by C. P. Stewart and D. Guthrie, University of Edinburgh Press, pp. 145–146]

OF THE PREVENTION OF THE SCURVY

As the salutary effects of the prescribed measures will be rendered still more certain, and universally beneficial, where proper regard is had to such a state of air, diet, and regimen, as may contribute to the general intentions of preservation or cure; I shall conclude the precepts relating to the preservation of seamen, with shewing the best means of obviating many inconveniences which attend long voyages, and of removing the several causes productive of this mischief.

The following are the experiments.

On the 20th of May 1747, I took twelve patients in the scurvy, on board the *Salisbury* at sea. Their cases were as similar as I could have them. They all in general had putrid gums, the spots and lassitude, with weakness of their knees. They lay together in one place, being a proper apartment for the sick in the forehold; and had one diet common to all, *viz*, water-gruel sweetened with sugar in the morning; fresh mutton-broth often times for dinner; at other times puddings, boiled biscuit with sugar, &c.; and for supper, barley and raisins, rice and currants, sago and wine, or the like. Two of these were ordered each a quart of cyder a-day. Two others took twenty-five gutts of *elixir vitriol* three times a-day, upon an empty stomach; using a gargle strongly acidulated with it for their mouths. Two others took two spoonfuls of vinegar three times a-day, upon an empty stomach; having their gruels and their other food well acidulated with it, as also the gargle for their mouth. Two of the worst patients, with the tendons in the ham rigid, (a symptom none of the rest had), were put under a course of sea-water. Of this they drank half a pint every day, and sometimes more or less as it operated, by way of gentle physic. Two others had each two oranges and one lemon given them every day. These they eat with greediness, at different times, upon an empty stomach. They continued but six days under this course, having consumed the quantity that could be spared. The two remaining patients, took the bigness of a nutmeg three times a-day, of an electuary recommended by an hospital-surgeon, made of garlic, mustard-seed, *rad. raphan.* balsam of Peru, and gum myrrh; using for common drink, barley-water well acidulated with tamarinds; by a decoction of which, with the addition of *cremor tartar*, they were gently purged three or four times during the course.

The consequence was, that the most sudden and visible good effects were perceived from the use of the oranges and lemons; one of those who had taken them, being at the end of six days fit for duty. The spots were not indeed at that time quite off his body, nor his gums sound; but without any other medicine, than a gargarism of *elixir vitriol*, he became quite healthy before we came into Plymouth, which was on the 16th of June. The other was the best recovered of any in

his condition; and being now deemed pretty well, was appointed nurse to the rest of the sick.

Mr. GORDON. So I might point out to you that a well-controlled trial was conducted as far back as the 1700's.

Mr. GADSDEN. I think the thrust of the remarks of the witness, Mr. Chairman, deals strictly with whether, in order to have a well-controlled test, it must be a double blind.

Senator NELSON. Please go ahead.

Dr. LAWRASON. When we take a drug such as indomethacin to the clinic, we go to the expert in the relevant discipline or specialty. We bring him in as an independent but full-fledged member of the research team. He collaborates in the planning and execution of the studies. Such experts are experienced investigators whose judgment is respected. They are independent in their actions and decisions. Their research is supported with grants for studies that often yield negative as well as positive results. I stress this relationship because we rely heavily on these investigators for the acquisition of objective observations and data on the effectiveness and safety of our drugs.

The experience and authority of the physicians who studied indomethacin, and whose judgments provided the basis for the approval of the drug, is evidenced by the following facts. Two-thirds of the indomethacin investigators in this country were Board-certified in their specialty, which is an unqualified endorsement of their training and experience. Three-quarters of them had full-time appointments with a university or a teaching hospital. Over half of them were active members of the American Rheumatism Association. I can say that the major investigations were carried out by some of the most eminent members of the American Rheumatism Association.

I would like to emphasize that we also went to the best clinics and hospitals throughout the world. These institutions are under the direction of distinguished rheumatologists. They came to the same conclusion regarding the effectiveness and safety of indomethacin as did the chemical investigators in this country.

If the cumulative judgment of this body of men is taken into account, the committee and the Food and Drug Administration, and the physicians and patients using indomethacin can be assured that the value of the drug was confirmed in the clinical judgment of an outstanding group of physicians. The criticisms that have been voiced earlier in these hearings about the testing of this drug do not represent the majority of experienced medical opinion.

The clinical program was completed in the spring of 1964. We had collected a large amount of data from 150 investigators here and abroad. The massive amount of evidence supporting efficacy and safety was submitted to the FDA for evaluation. It contained well-controlled studies and met the requirements of the preclinical and clinical standards of the day. It showed indomethacin to be safe and effective for the uses claimed. The application was approved by the FDA in June of 1965, after approximately a year of review, for the four indicated conditions for which it is labeled and promoted in the United States today.

Senator NELSON. Those four are rheumatic arthritis ——

Dr. LAWRASON. Rheumatoid arthritis, gout, rheumatoid spondylitis, and osteoarthritis of the hip.

Senator NELSON. Is it indicated for any other purpose?

Dr. LAWRASON. In this country, it is not.

Senator NELSON. Do you get a different reaction in patients in another country?

Dr. LAWRASON. In some of the other countries some additional conditions for which we believe it is effective and safe for use are allowed. The Food and Drug Administration in this country has not allowed such other indications.

Senator NELSON. Which are the others?

Dr. LAWRASON. Osteoarthritis in general, rather than specifically of the hip, and musculoskeletal disorders, which involve numerous disorders such as bursitis.

Senator NELSON. Why does not the FDA allow you to make these claims in this country?

Dr. LAWRASON. I believe their reason is that they feel we have not presented them with sufficient evidence of its efficacy.

Senator NELSON. Have you presented these other countries with evidence of its efficacy?

Dr. LAWRASON. We have presented them with a great deal of evidence. There are a great many double-blind studies ongoing and completed, and we expect within a very short time to present to the FDA evidence that will be convincing to them for efficacy and safety in these two indications.

Senator NELSON. Well, now, in how many countries do you sell this drug?

Mr. GADSDEN. Perhaps I ought to answer that. I cannot be specific with reference to this drug, Mr. Chairman, but our drugs are sold in approximately 100 countries throughout the world.

Senator NELSON. Is indomethacin sold in these 100 countries?

Mr. GADSDEN. I know drugs of Merck origin are sold in 100 countries. I do not have at the moment information as to whether "Indocid," is the trademark which is used abroad, is sold in all of these countries. I would assume that it was sold in the great majority of them.

Senator NELSON. What proof did you present to these other countries that indomethacin is effective for the additional uses that you mentioned?

Dr. LAWRASON. In the original application, there was substantial evidence of its efficacy in these other indications. Since then, we have submitted a supplement to the NDA which provided additional evidence as to its efficacy and safety. This same evidence has been presented to other regulatory agencies in other countries. When reviewed by these other agencies, they have come to the conclusion that it is safe and effective in these indications and have allowed it use.

Senator NELSON. Do each of these 100 countries have an agency of scientists who evaluate the information you supply and make a judgment?

Mr. GADSDEN. May I respond to that, sir?

Senator NELSON. Yes.

Mr. GADSDEN. The answer, as I think you might know, is that not all do have such an agency. It is the more developed countries, particularly of Western Europe that do, and even there not all of them. But I would agree with you if your point is that there are countries which do not have such regulatory control.

Senator NELSON. This puzzles me a little bit, not necessarily about this drug in particular, but about any drug. If the country does not have a qualified scientific agency to make a judgment, then a drug can be advertised and sold for any purpose the company desires to sell it for, can it not, regardless of whether it is indicated or not?

Mr. GADSDEN. I would have to agree that it could be, but I do not think a responsible company would do so, sir.

Senator NELSON. We had the case here of chloramphenicol being promoted in Great Britain with no precautions being given in the ads at all. At the same time, the firm testified here that it agreed that all the specific precautions in the package insert required here were important and necessary and should be listed. Yet in Great Britain and other countries, the firm said it did not list these because the law of those countries did not require them.

What I am getting at is the claims of the company that they follow a very ethical, high standard. Yet here is a clear-cut case where as soon as there are no regulations, they promote the drug for a purpose which is illegal in this country, and without any precautions, contrary to the best testimony of all the medical experts in America.

Mr. GADSDEN. Sir, I do not want to be put in the position of talking about whether the conduct of a competitor was appropriate or not. But if you like, I have a statement here which I would be happy to read indicating that the British Pharmaceutical Association, working with the appropriate medical and regulatory bodies in England, concluded that—in advertising—it was undesirable to put such contraindications and warnings in the advertisement when it was a so-called reminder advertisement. I think that the earlier witness who was questioned on this, if my memory is correct, was perhaps not conversant with the subject of advertising.

Senator NELSON. What is your definition of a reminder ad?

Mr. GADSDEN. In this case, sir, this is one——

Senator NELSON. In any case, what is, in your industry, the definition of a reminder ad?

Mr. GADSDEN. I shall have to give you several definitions, sir.

In the United States, the Food and Drug Administration has taken a very narrow definition of what is a reminder ad and we comply with that.

In England, with the agreement of the British medical group and the appropriate governmental authority, it was stated that if there was no dosage indication which would be helpful to the physician in prescribing the product, that is a reminder ad. The editor of the British Medical Journal said he considered it an insult to the intelligence of the British physician to include such material.

Senator NELSON. So, that is different from the reminder ad in America, in which you cannot include any language indicating the usage of the drug; is that correct?

Mr. GADSDEN. Yes.

Senator NELSON. But you can in England and you need not put any warnings or precautions about its use in the ad; is that correct?

Mr. GADSDEN. It is a broader definition in England, where the definition of a reminder ad is any advertisement in which information with reference to dosage is eliminated.

Senator NELSON. In this country?

Mr. GADSDEN. No, sir; I said in Great Britain.

Senator NELSON. That is not a reminder ad in this country. In other words, you usually do not put dosages in your ads anyway, do you, in this country or in any country?

Mr. GADSDEN. We frequently do, sir, in this country. I think the basic point, which is perhaps going to crop up on several occasions, is that when you are an international company and doing business in a variety of countries, quite naturally your foreign subsidiaries must conduct themselves in accordance with the local practices, laws, and regulations of that country—which, in many cases, differ from the regulations in this country as promulgated by the Food and Drug Administration.

Senator NELSON. How do you view the problem of a country that does not really have any agency for evaluating drugs at all?

Mr. GADSDEN. Well, I think we get back to the statement of one of our scientific witnesses—I trust you will permit me to speak just for Merck & Co., because I am neither authorized nor competent to speak for anyone else—that we have our own internal code of ethics with reference to what is appropriate. When, in the opinion of our medical research group, it is concluded that a statement is appropriate to make in these countries, the medical research people have the authority to make the decision that it can and should be made.

Senator NELSON. What bothers me about that is that even in this country, there are disputes among the industry and doctors and the FDA about the promotion of drugs. The argument on the part of those who think drugs are overprescribed is that it is the result of this type of advertising and promotion, despite the insistence of the FDA that package inserts contain certain warnings and contraindications and so forth. The consequence of the advertising, in any event, is that many drugs are widely overprescribed for nonindicated cases. At least, the testimony we have had on some drugs from experts is that this is the fact.

So the result of the advertising and the promotion, even with FDA monitoring what is said in the package insert and in the advertising, is overprescription of many drugs for nonindicated uses. If that is the case in this country where you have a regulatory agency, it certainly must be the case in those countries where you do not have one. It seems to me that there should be in that instance, very important internal restraints upon a company advertising in such a country.

Mr. GADSDEN. I would agree with you, sir. But if you have a code of morals and ethics, you must adhere to it and not take advantage of the fact that you may not get caught somewhere.

Senator NELSON. But let me proceed with this. If you have an underdeveloped country, or any country without a sophisticated scientific community and without a regulatory agency so that it cannot protect itself, what is your standard of guidance for advertising in that country?

Mr. GADSDEN. Our standard of guidance, sir, is whatever has been approved by the scientists of Merck as the appropriate medical positioning of the product.

Senator NELSON. Then you do not use the standard of what is approved by FDA in this country?

Mr. GADSDEN. No, we do not.

Senator NELSON. So you feel that your company, or any company, ought to be able to decide on its own what the standard will be in a country which has no scientific community or regulatory agency at all?

Mr. GADSDEN. No, sir, I do not think I have said that.

Senator NELSON. That is exactly what you said, that you decide what the standard is.

Mr. GADSDEN. I beg your pardon, sir?

Senator NELSON. Please repeat what you have said.

Mr. GADSDEN. I said that in this matter, Merck & Co.—and I refer to my earlier statement that I speak only for Merck & Co.—we have a code of ethics and principles. We assume responsibility for the positioning of the product. This reference to this was made in Dr. Lawrason's statement, I believe. We hold our medical staff responsible. They must approve what is said, whether it be in the United States or any country of the world. This, for Merck, is the restraint under which we operate.

Senator NELSON. I did not get the distinction between what you said and what I said. I said you set the standard.

Mr. GADSDEN. Sir, may I paraphrase what I understood you to say? I think you said, if I understand you correctly, that it is appropriate for Merck or any other company, in countries where there are no regulating agencies, to say what it wants in advertising.

Senator NELSON. To set your own standard, I think I said.

Mr. GADSDEN. I am sorry, perhaps I misunderstood you.

Senator NELSON. That is what I intended to say. In other words, you are saying that in another country where there is no scientific community to evaluate the evidence you have, a company sets its own standards without any outside control. Is that what you have said?

Dr. LAWRASON. Mr. Chairman, may I just say that we do not set separate standards for different countries. We have a single standard at Merck.

Senator NELSON. You mean you run precisely the same ad in the Philippines that you run in the British Medical Journal?

Dr. LAWRASON. No, I am referring to how the drug can be used and what indications are to be cited—in other words, the claims made for the drug and which diseases it should be used for.

Senator NELSON. I do not quite follow that. The FDA will not permit you to use it in this county for—what were the indications?

Dr. LAWRASON. Osteoarthritis.

Senator NELSON. And that involves tendonitis?

Dr. LAWRASON. No, sir; that was the musculoskelatal.

Senator NELSON. And that involves tendonitis and bursistis. The FDA says you cannot use it because you have not submitted, as far as they are concerned, satisfactory evidence or proof of its efficacy, for those conditions.

Dr. LAWRASON. That is correct.

Senator NELSON. Now you go to England and you advertise it for that purpose, and the British will say that it is all right for that purpose. Then, you may go to another country and they will say it is all right for all the purposes you use it for in America plus one other, but not two. Then you go to another country, that has no scientific community, and you claim that it is good for some other purposes and you advertise it and sell it for those purposes in that country if your

scientists and you come to the conclusion that it is useful for those purposes, would you not?

Mr. GADSDEN. Perhaps I should explain to you, sir, what is the procedure. In the internal workings of Merck & Co., a scientific and medical evaluation is made which ultimately results in an application for new drug approval. The thing I want firmly on the record, in case there is any question about it, is that we do not sell abroad—I think I am right—anything for which approval has not been requested of the Food and Drug Administration in the United States.

Senator NELSON. I do not understand.

Mr. GADSDEN. Well . . . if we are not willing to report it to the Food and Drug Administration, we are not going to say in an underdeveloped country that it will cure something for which we are not requesting approval in the United States.

Senator NELSON. I understand. But if you request approval in the United States for its use for a certain purpose and the FDA says that so far as they are concerned, your scientific submission of evidence does not support its use for that purpose, and they turn you down, you still will sell it for that purpose in an underdeveloped country that has no scientific community at all?

Mr. GADSEN. Yes, sir; we will.

Senator NELSON. I am not saying that some company may not make a mistake; it may turn out to be right and the FDA wrong. The principle that bothers me is there are lots of companies in this business that may not be as conscientious as Merck, and you will end up with all the companies supplying drugs to other countries that do not have drug standards, so that a drug might be used for purposes that it should not be. We have had testimony here that drugs which could not be sold in this country because they did not meet U.S.P. standards were shipped overseas—not your company. I am just raising the question, because it seems to me that if that testimony was correct on subpotent drugs which could not go on the market here being sold in South America, I think it ought to be explored from the standpoint of some legislation. I do not think anybody ought to have a license to put drugs on any market that do not meet a reasonable standard in this country.

Mr. GADSDEN. I agree with you, but I think you yourself said earlier that there are differences in medical opinion, and this can result in the Food and Drug Administration's concluding in all sincerity that they do not think the evidence complies with the law and regulations under which they operate, and yet in the opinion of the American scientists it is believed that there is substantial evidence.

Senator NELSON. That is bound to be the case; there is no question about that.

While I am on that point, it is agreed, as I understand it, that indomethacin is not indicated for use in children?

Dr. LAWRASON. Indomethacin?

Senator NELSON. That is right. It is not indicated for use in children; is that correct?

Dr. LAWRASON. It is contraindicated in this country at the request of the Food and Drug Administration.

Senator NELSON. Is it indicated in other countries for use in children?

Dr. LAWRASON. There are other countries that feel the indications for the efficacy and safety of the drug warrants its being used in children; that is correct.

Senator NELSON. I think it is an interesting point just to put into the record at this stage on the question of uses of the drug in this country that in a study done by Modern Medicine of August 1, 1966—I will submit it for the record so I do not have to go through it all—it was found that within 1 year after it went on the market indomethacin was used in pediatrics by 9.4 percent, I believe, of pediatricians who answered questionnaires; 9.4 percent of the pediatricians were using indomethacin despite the fact that the FDA has not approved it for pediatric use in this country.

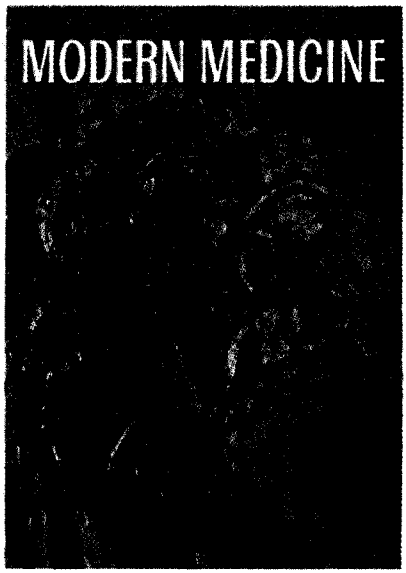
Mr. CUTLER. Could you give us the date, Senator Nelson?

Senator NELSON. Yes, the results of the poll appear in the August 1, 1966, issue of Modern Medicine.

Mr. CUTLER. What was the date of the poll, sir? Does that show?

Senator NELSON. Well, let me see. It was published August 1, 1966. It may be in here, but I do not see the date of the poll.

(The document referred to follows:)




# Poll on Medical Practice

## RHEUMATOID ARTHRITIS

How do physicians treat rheumatoid arthritis today? Are there notable differences from region to region? Between internists and physiatrists? Between large cities and small towns? Some of the answers are on the following pages.

This report contains the most important portions of the analyses carried out on the basis of a questionnaire sent to all *Modern Medicine* readers. No attempt at this time is made to present or detail all of the analyses, or to comment on the significance of these analyses. It is the purpose of this report to present the findings without expression of either approval or disapproval.

The fact that nearly 12,000 physicians took time from their busy lives to answer this questionnaire on rheumatoid arthritis demonstrates a high degree of interest and provides considerable validity to the answers obtained in the questionnaire. Continued reader cooperation with future questionnaires will provide readers and editors with an interesting and revealing series of shared experiences.

IRVING S. WRIGHT, M.D.
*Editorial Consultant*
WYMAN E. JACOBSON, M.D.
*Associate Editor*

*A Special Preprint from* MODERN MEDICINE *August 1, 1966, pp. 75-90*
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**Poll** / RHEUMATOID ARTHRITIS

# 11,603 Respond to Questionnaire

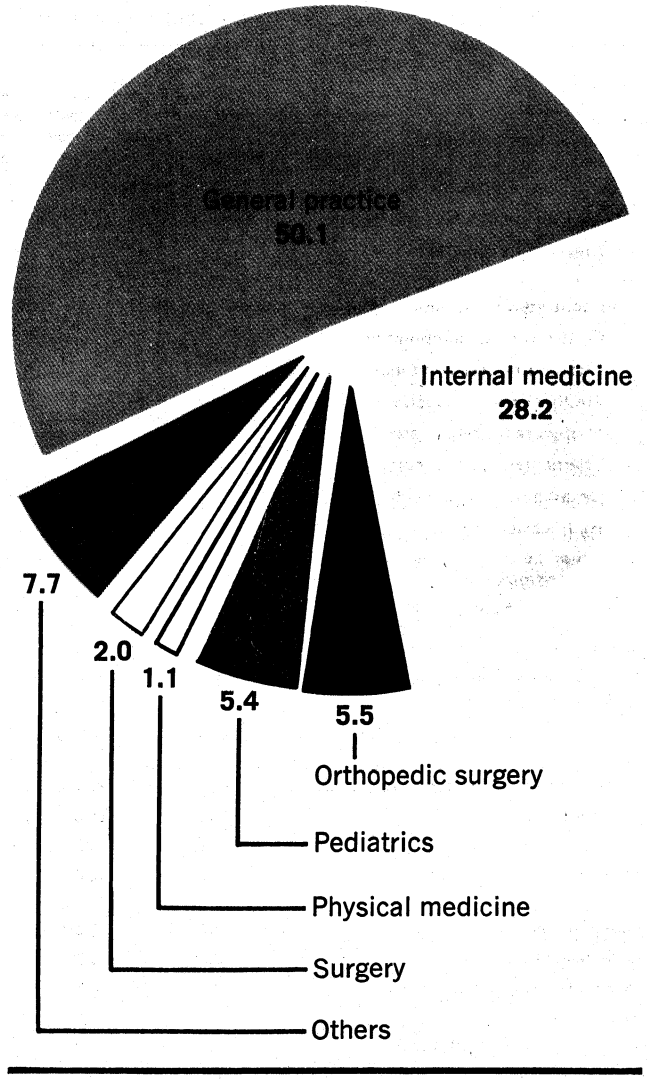
Of the 11,603 physicians who responded to the questionnaire, 5,694 (49.1%) reported that they had treated patients with rheumatoid arthritis within a period of thirty days. Of those reporting treatment, 50.1% were general practitioners, 28.2% internists, 5.5% orthopedic surgeons, 5.4% pediatricians, 2% surgeons, 1.1% physiatrists, and 7.7% other specialists (Fig. 1). Nearly eight out of ten physicians who treated patients with rheumatoid arthritis were either general practitioners or internists.

An "open-end" questionnaire was employed to eliminate or reduce to a minimum the factors which might cause an intrinsic bias or result in responses based on the "correct answer" rather than on the true practice of the physician. Accuracy of the responses was considered best achieved by short recall—thirty days—which in most instances would not require review of patients' charts or lead to unreliable guesses. One-half of the physicians reporting therapy treated no more than one new case and no more than four follow-up cases of rheumatoid arthritis in a thirty-day recall period.

## Analysis of treatment

Table 1 represents the analysis of treatments employed and of patients treated for rheumatoid arthritis during the thirty-day period. The 5,694 physicians used an average of 2.72 methods of treatment and treated a total of 104,010 patients. Major categories of methods used were systemic drug treatment, nondrug treatment, and external drug treatment; in a small sample, method of treatment was unknown or not clearly indicated. The categories of systemic drugs included [1] analgesics and combinations, [2] adrenal steroid hormones and combinations, [3] gold, [4] nonsteroid anti-inflammatory drugs, and [5] a group of miscellaneous drugs, none of which was utilized to any large extent even when the agents were combined in subgroups on the basis of chemical or pharmacological characteristics.

**Fig. 1. Type of practice of physicians who treated rheumatoid arthritis during thirty-day period**



**Poll** / RHEUMATOID ARTHRITIS

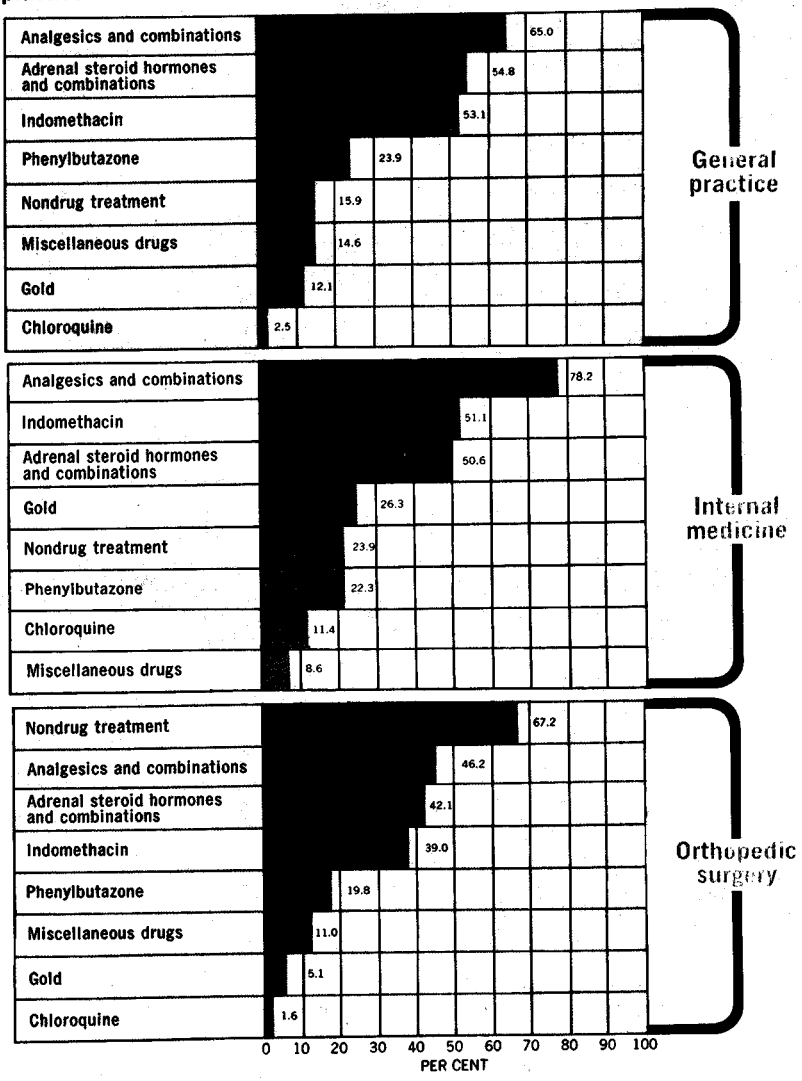
## Table 1. Methods of treatment used for rheumatoid arthritis

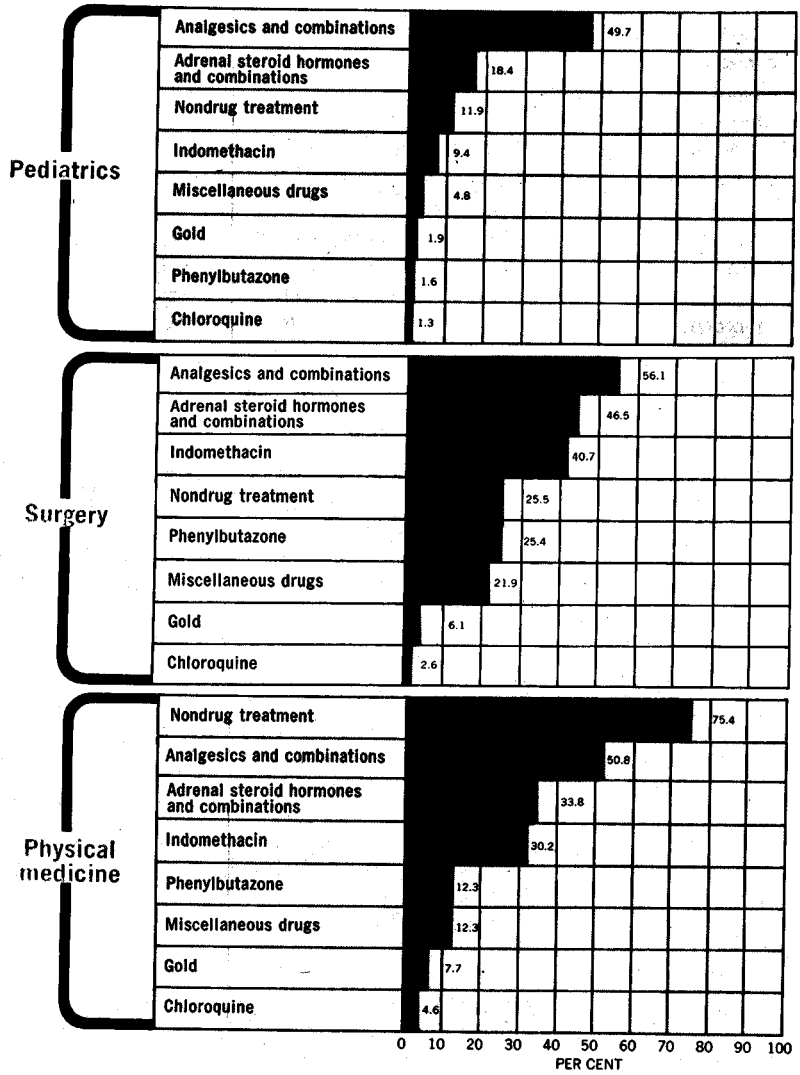
| Category | Percent of treatments mentioned | Percent of patients mentioned | Number of patients mentioned per treatment mentioned |
|---|---|---|---|
| **Systemic drug treatment** | **87.1%** | **79.6%** | **6.13** |
| Analgesics and combinations | 25.9% | 28.4% | 7.37 |
| Aspirin, salicylates, and salicylate compounds | 24.1 | 26.8 | 7.43 |
| Other or unspecified | 1.8 | 1.6 | 6.43 |
| Adrenal steroid hormones and combinations | 22.2% | 16.2% | 4.87 |
| Cortisone and combinations | 1.8 | 1.4 | 5.15 |
| Prednisone and combinations | 5.4 | 3.1 | 3.82 |
| Prednisolone and combinations | 1.9 | 1.4 | 4.73 |
| Methylprednisolone and combinations | 1.5 | 1.0 | 4.36 |
| Triamcinolone and combinations | 1.6 | 1.0 | 4.35 |
| Dexamethasone and combinations | 1.7 | 1.1 | 4.46 |
| Hydrocortisone and combinations | 0.5 | 0.3 | 4.55 |
| Other corticosteroids or unspecified and combinations | 6.6 | 5.9 | 6.03 |
| Adrenocorticotropic hormone | 1.2 | 1.0 | 5.13 |
| Gold | 5.5% | 4.8% | 5.90 |
| Nonsteroid anti-inflammatory drugs | 27.4% | 22.1% | 5.41 |
| Indomethacin | 17.3 | 14.3 | 5.56 |
| Phenylbutazone | 8.2 | 5.8 | 4.74 |
| Chloroquine | 1.9 | 2.0 | 6.97 |
| Miscellaneous drugs | 6.1% | 8.1% | 8.96 |
| Muscle relaxants | 0.6 | 0.7 | 8.53 |
| Tranquilizers and sedatives | 0.6 | 0.7 | 8.68 |
| Vitamins | 1.3 | 2.0 | 10.39 |
| Narcotics and combinations | 0.3 | 0.3 | 8.14 |
| Anabolic agents | 0.1 | 0.2 | 9.71 |
| Vaccines | 0.3 | 0.5 | 10.20 |

| Category | Percent of treatments mentioned | Percent of patients mentioned | Number of patients mentioned per treatment mentioned |
|---|---|---|---|
| **Systemic drug treatment (cont.)** | | | |
| Antibiotics and chemotherapeutics | 0.5 | 0.5 | 6.15 |
| Colchicine and combinations | 0.2 | 0.3 | 9.19 |
| Probenecid and combinations | 0.1 | 0.1 | 5.35 |
| Nonadrenal hormones | 0.3 | 0.4 | 9.56 |
| Others | 1.8 | 2.4 | 9.10 |
| **Nondrug treatment** | **11.5%** | **19.4%** | **11.33** |
| Physical therapy | 9.6% | 16.9% | 11.84 |
| Heat | 2.3 | 3.4 | 10.11 |
| Rest | 1.9 | 3.2 | 11.38 |
| Exercise | 1.3 | 2.3 | 11.62 |
| Other or unspecified | 3.8 | 7.4 | 13.05 |
| Osteopathic manipulation | 0.3 | 0.6 | 13.58 |
| Surgery | 1.0% | 0.8% | 5.46 |
| Miscellaneous nondrug treatment | 0.9% | 1.7% | 12.50 |
| X-ray | 0.1 | 0.0 | 4.56 |
| Diet | 0.6 | 1.4 | 14.21 |
| Psychotherapy | 0.2 | 0.3 | 10.69 |
| Other or unspecified | 0.0 | 0.0 | 3.17 |
| **External drug treatment** | **0.2%** | **0.2%** | **6.42** |
| **Therapy unknown or unclear** | **1.2%** | **0.8%** | **4.60** |
| **Base** | **100.0%** (15,494) | **100.0%** (104,010) | **6.71** |

**Poll** / RHEUMATOID ARTHRITIS

**Fig. 2. Treatment of rheumatoid arthritis according to type of practice**




Pediatrics
Analgesics and combinations 49.7
Adrenal steroid hormones and combinations 18.4
Nondrug treatment 11.9
Indomethacin 9.4
Miscellaneous drugs 4.8
Gold 1.9
Phenylbutazone 1.6
Chloroquine 1.3
Surgery
Analgesics and combinations 56.1
Adrenal steroid hormones and combinations 46.5
Indomethacin 40.7
Nondrug treatment 25.5
Phenylbutazone 25.4
Miscellaneous drugs 21.9
Gold 6.1
Chloroquine 2.6
Physical medicine
Nondrug treatment 75.4
Analgesics and combinations 50.8
Adrenal steroid hormones and combinations 33.8
Indomethacin 30.2
Phenylbutazone 12.3
Miscellaneous drugs 12.3
Gold 7.7
Chloroquine 4.6
0 10 20 30 40 50 60 70 80 90 100
PER CENT

Although the nonsteroid anti-inflammatory drugs were prescribed more often than the other systemic agents, the three drugs included in this category—indomethacin, phenylbutazone, and chloroquine—are different enough to warrant individual consideration. The analgesics and combinations (primarily salicylates) accounted for more than one-quarter of all the treatments, the adrenal steroid hormones and combinations for slightly less than one-quarter, and indomethacin for approximately one-sixth. In the nondrug treatment category, physical therapy was prescribed most often and accounted for about one-tenth of all the treatments.

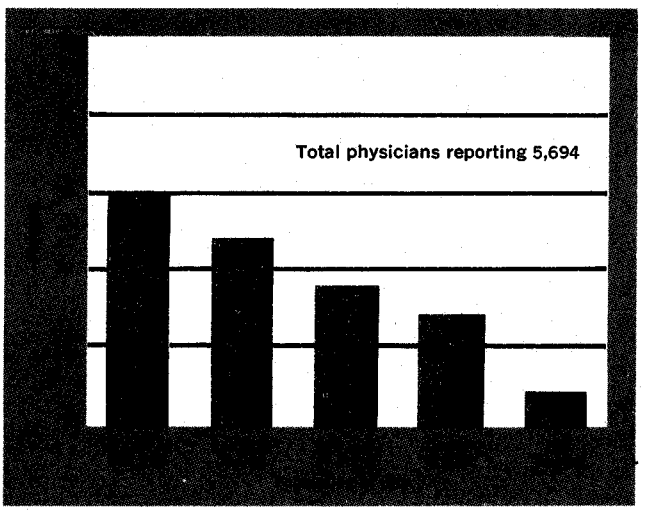
The data on treatment were also processed in relation to the 104,010 patients receiving therapy. Some major differences were noted when the percent of patients mentioned was compared with the percent of treatments mentioned. Although the adrenal steroids were reported in almost one-quarter of the responses, these drugs were used in only one-sixth of the patients. The nonsteroid anti-inflammatory drugs were reported in 27% of the returns but used in only 22% of the patients, salicylates in one-fourth of the returns but in more than one-fourth of the patients, physical therapy in one-tenth of the reports and one-sixth of the patients, and total nondrug therapy in one-tenth of the returns but one-fifth of the patients.

In the data processing, medications combining two or more of the major systemic drugs were included in the group in which the drug was considered to have the strongest pharmacological action in the opinion of the medical editor. Thus, combinations of aspirin and adrenal steroids were included with the adrenal steroid hormones, since the predominant pharmacological action was considered to be due to the hormone.

## Methods of treatment by type of practice

General practitioners and internists utilized analgesics, adrenal steroids, gold, and indomethacin to a greater extent than did the other specialists (Fig. 2). Among the 2,852 general practitioners who reported

**Fig. 3. Distribution of physicians by city size who treat rheumatoid arthritis**




treatment of rheumatoid arthritis during the thirty-day period, 65% prescribed analgesics and combinations, 54.8% adrenal steroid hormones and combinations, 53.1% indomethacin, 23.9% phenylbutazone, and less than 20% any of the other single categories.

Among the 1,606 internists, 8 out of 10 prescribed analgesics and combinations, 5 out of 10 indomethacin or adrenal steroid hormones, 2.5 out of 10 gold, and 2 out of 10 phenylbutazone or physical therapy. This is in sharp contrast to the 310 pediatricians, who relied primarily on analgesics and combinations (5 out of 10) but only infrequently prescribed indomethacin, phenylbutazone, or gold. It is of considerable interest that the surgeons, orthopedic surgeons, and physiatrists used adrenal steroids and indomethacin frequently (3 to 5 out of 10 physicians) but rarely used gold. The internists used gold therapy much more often than did any of the other specialists.

This analysis reveals major differences in treatment based on the type of practice, some of which are directly related to the nature of the specialty; explanations of other variations are less obvious.

## Variations in treatment based on other factors

The data were evaluated in relation to age of the physician, size of the locality in which the physician practiced, and the geographic location on a national basis. Of the 5,694 physicians who reported treatment of patients with rheumatoid arthritis, one-fifth were in cities of 500,000 or more population and one-sixth in communities of under 5,000 (Fig. 3).

Physicians in smaller cities and towns prescribed indomethacin more frequently than did physicians in larger cities: 55% of physicians in areas of under 5,000 persons, but only 38% of those in cities of 500,000 people or more, prescribed indomethacin. On the other hand, physical therapy and surgery were employed more frequently in the larger cities than in communities of under 5,000 population.

The methods of treatment varied with the age of the physician, but only a couple features were rather prominent. Physicians age 65 years or older used gold only about half as frequently as did those age 64 or younger. Physicians 35 to 64 years of age used gold therapy with about the same frequency. Physicians under 35 years of age used adrenal steroid hormones less frequently than did the middle-aged and older physicians. However, the younger physicians used indomethacin and surgery considerably more often than did the physicians age 65 or over.

## Results of treatment

Obviously, the most difficult evaluation is that related to the results of treatment. The questionnaire made no attempt to provide any more than a crude estimate by the attending physicians as to the nature of the response. Physicians were asked to estimate the percentage of patients who apparently recovered, showed improvement, and showed no improvement and in whom the condition was arrested. The results of this evaluation are shown in Table 2. Approximately two-thirds of the patients who were treated either showed improvement or apparently recovered.

**Table 2. Results of treatment of rheumatoid arthritis (estimated percentage of cases)**

| | Mean average percent |
|---|---|
| Apparent recovery | 5 |
| Improvement shown | 60 |
| Condition arrested | 19 |
| No improvement shown | 16 |
| **Total** (Base: 4,477) | **100** |

## Major changes in treatment from 1949 to 1966

In 1949, *Modern Medicine* attempted to evaluate the treatment of rheumatoid arthritis. Results of that survey were compared with those of the 1966 study (Table 3), though the two surveys were not comparable in question form. The 1949 questionnaire listed five specific types of treatment: drugs, vaccines, diet, physiotherapy, and orthopedic procedures. The obvious differences are in relation to medications which were not available in 1949—namely, the adrenal steroid hormones and the nonsteroid anti-inflammatory drugs. The analgesics and combinations accounted for approximately one-third of the treatments in both studies. Gold was used almost twice as frequently in 1949 as in 1966. The large miscellaneous group in 1949 included drugs only. Vaccine was used in 27% of the prescriptions in 1949 but in only 0.9% in 1966.

**Table 3. Comparison of drugs prescribed in 1949 and 1966**

| | 1949 | 1966 |
|---|---|---|
| | Percent | |
| Analgesics and combinations | 32.7 | 29.7 |
| Adrenal steroid hormones and combinations | — | 25.6 |
| Gold | 11.5 | 6.3 |
| Nonsteroid anti-inflammatory drugs | — | 31.4 |
| Miscellaneous | 55.8 | 7.0 |
| **Total** | **100.0** | **100.0** |

**Poll** / RHEUMATOID ARTHRITIS

**Fig. 4. New cases and follow-up cases of rheumatoid arthritis treated during a thirty-day period**

New cases treated

| | Mean | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| All physicians | 2.55 | | | | | | | | | | |
| Physiatrists | 4.44 | | | | | | | | | | |
| Orthopedic surgeons | 3.40 | | | | | | | | | | |
| Internists | 2.61 | | | | | | | | | | |
| General practitioners | 2.59 | | | | | | | | | | |
| Surgeons | 2.51 | | | | | | | | | | |

Follow-up cases treated

| | Mean | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| All physicians | 7.47 | | | | | | | | | | |
| Physiatrists | 9.78 | | | | | | | | | | |
| Internists | 9.11 | | | | | | | | | | |
| Orthopedic surgeons | 8.03 | | | | | | | | | | |
| General practitioners | 7.47 | | | | | | | | | | |
| Surgeons | 5.79 | | | | | | | | | | |

## The physician and rheumatoid arthritis patient population

The physiatrists had the largest mean average (4.44) of new cases during the thirty-day period. The orthopedic surgeons reported a mean average of 3.40 new cases, the internists 2.61, the general practitioners 2.59, and the surgeons 2.51 (Fig. 4). Although the *mean* average of new cases for all physicians was 2.55, the *median* average was 1.00, i.e., 50% of the physicians had more than one new patient and 50% had less than one.

The physiatrists also had the largest mean average (9.78) of follow-up cases of rheumatoid arthritis during the thirty-day period. The internists had a mean average of 9.11 such cases, the orthopedic surgeons 8.03, the general practitioners 7.47, and the surgeons 5.79 (Fig. 4). Although the *mean* average of follow-up cases for all physicians was 7.47, the *median* average was 4.00, i.e., 50% had more than four follow-up cases and 50% had less than four.

## The questionnaire and its validity

The questionnaire on rheumatoid arthritis (Fig. 5) was included in all copies of the March 14, 1966, issue of *Modern Medicine*. Four weeks after release

**Fig. 5. Doctors were asked these questions:**

1. **Do you attend patients with rheumatoid arthritis?**
   **Yes_____ No_____**
2. **How many patients have you seen for the first time with rheumatoid arthritis during the past 30 days?_____**
   **(number)**
3. **How many patients have you seen on subsequent visits for rheumatoid arthritis during the past 30 days?_____**
   **(number)**
4. **How did you treat the patients you saw during the past 30 days?**
5. **What results have you experienced over the past year with your treatment of rheumatoid arthritis? (Estimate by percentage of cases.)**

**Table 4. Type of practice of physicians replying to questionnaire compared with that of total U.S. physician population**

| Type of practice | Physicians replying to questionnaire | | Total U.S. physicians |
|---|---|---|---|
| | Number | Percent | Percent |
| General practice | 3,200 | 27.6 | 34.4 |
| Internal medicine | 1,784 | 15.4 | 12.9 |
| Surgery | 1,005 | 8.7 | 9.6 |
| Obstetrics and gynecology | 776 | 6.7 | 6.9 |
| Pediatrics | 710 | 6.1 | 5.7 |
| Eye, ear, nose, and throat | 639 | 5.5 | 5.8 |
| Psychiatry | 484 | 4.2 | 5.0 |
| Orthopedic surgery | 380 | 3.3 | 2.9 |
| Radiology | 372 | 3.2 | 3.2 |
| Anesthesiology | 340 | 2.9 | 3.4 |
| Dermatology | 299 | 2.6 | 1.5 |
| Urology | 193 | 1.7 | 2.0 |
| Pathology | 192 | 1.4 | 1.4 |
| Neurology | 170 | 1.5 | 1.3 |
| Allergy | 126 | 1.1 | 0.4 |
| Cardiovascular disease | 111 | 1.0 | 0.6 |
| Physical medicine | 70 | 0.6 | 0.2 |
| Thoracic surgery | 66 | 0.6 | 0.6 |
| Preventive medicine | 58 | 0.5 | 0.3 |
| Plastic surgery | 53 | 0.5 | 0.5 |
| Colon and rectal surgery | 52 | 0.4 | 0.3 |
| Gastroenterology | 40 | 0.3 | 0.2 |
| Pulmonary disease | 21 | 0.2 | 0.2 |
| Other | 462 | 4.0 | 0.7 |
| **Total** | **11,603** | **100.0** | **100.0** |

of the questionnaire, more than 11,800 responses had been received. Of these, 11,603 were satisfactory for data processing and tabulation: 3,200 from general practitioners, 1,784 from internists, 1,005 from surgeons, 710 from pediatricians, 380 from orthopedic surgeons, 70 from physiatrists, and 4,454 from physicians of other specialties (Table 4).

Almost all responders, classified according to their specialty or primary type of practice, are represented in about the same proportion in the survey as in the national distribution of the physician population (Table 4). Among the general practitioners, 89.1% reported treating patients with rheumatoid arthritis, among the internists 90%, among the physiatrists 90%, and among the orthopedic surgeons 82.9%.

**Table 5. Regional distribution of physicians replying to questionnaire and of all physicians in the United States**

| Region | Physicians replying to questionnaire | | All physicians in U.S.* |
|---|---|---|---|
| | Number | Percent | Percent |
| New England | 722 | 6.2 | 6.6 |
| Mid-East | 2,291 | 19.7 | 23.0 |
| South Atlantic | 1,413 | 12.2 | 12.7 |
| Great Lakes | 1,816 | 15.7 | 18.0 |
| Mid-South | 481 | 4.1 | 4.8 |
| Plains | 955 | 8.2 | 7.2 |
| Southwest | 856 | 7.4 | 7.9 |
| Rocky Mountain | 549 | 4.7 | 3.8 |
| Far West | 1,793 | 15.5 | 15.5 |
| Pacific | 55 | 0.5 | 0.5 |
| Unknown | 672 | 5.8 | — |
| **Total** | **11,603** | **100.0** | **100.0** |

*Source: Buckley Dement

The large size of the response, the representative distribution by all types of practice, and the geographic distribution of the responders are considered evidence for reliability of the data in this report. With only minor variations, the return on this poll was highly comparable to the distribution of all physicians by states and regions. Table 5 shows this comparison for regions only, but the analysis by the editors included comparison for all fifty states.

Questionnaires are often considered somewhat suspect. It is therefore important that the objectives of the questionnaire which we have presented for your help and ultimate information be restated. The diagnostic and therapeutic measures used by physicians are known to vary considerably. The factors associated with these differences are not known. Teachers in medical schools do not know whether their instructions and recommended forms of treatment have been adopted by their students. Those planning postgraduate training courses do not know what their prospective matriculates have been using in their own practices. Neither the American Medical Association nor the Department of Health, Education, and Welfare can provide detailed information on the actual practices—and the practitioner does not know what his confreres are doing. The purpose of this project is to answer some questions regarding certain leading causes of death and disability. The editors will compile the information which you provide as the practitioners representing different types of practice, all age groups, and wide geographic distribution.

The aim is to determine what is going on. *These findings are not to be considered as endorsement or condemnation of any form of treatment.* The editors of this section will operate with complete independence and detachment in this regard. If others see fit to use this material to strengthen their teaching programs, to read further information into the various forms of treatment which appear to be widely used, or to vent their opinions in the literature regarding these findings, this series will have served some useful purpose.

Senator NELSON. The point I was making is we continue to have cases arise of drugs being used for conditions in which they are not indicated. The dramatic one was brought out in the testimony of several distinguished doctors, including Dr. William Damashek of Mount Sinai Hospital, that chloramphenicol was being used at least 90 percent of the time in nonindicated cases. So, despite the warnings in the package insert, the promotion of the drug or some other factor was causing doctors to prescribe it widely, as the testimony showed, for head colds, minor infections, acne, hangnails, and toe infections. We have cases by the dozens in my files, and testimony of deaths caused by Chloromycetin. All of them resulted from the drug having been given when it was not indicated. All I am pointing out is that we continue to get this kind of evidence. This committee is interested in the question of drug promotion and promotion resulting in the use of drugs in cases which are nonindicated.

The questionnaire I referred to was sent on March 14, 1966.

Mr. GADSDEN. Sir, I think you will appreciate that we are at some disadvantage in trying to comment on this because we do not have it. If you will permit me, I would not like the record to show this juxtaposition between indomethacin and chloramphenicol. I am not qualified to talk about chloramphenicol. I am prepared to talk about indomethacin.

Senator NELSON. I did not use that example to compare them at all. I was just saying that pediatric use of Indocin is not indicated in this country, and in this poll, 9.4 percent of the pediatricians who responded, were using it on occasion for this purpose. I am only pointing out that we hear evidence time after time about drugs that are being used for nonindicated purposes.

I think that part of the cause for such misuse is the dramatic and effective promotion of the drug.

Mr. GADSDEN. Well, sir, as you know, I will be the last witness. I am sure you will have some questions for me on what we have done in the way of promotion for "Indocin."

Senator NELSON. Senator Hatfield has a question.

Senator HATFIELD. Doctor, there are a couple or three questions that come to mind at this point: First of all, as I understand your testimony, you indicated that you submit to the FDA a great mass of material, pretests, research when you are submitting a new drug for approval. Do you feel that the FDA is presently equipped, both with manpower and staff generally, to handle this type of responsibility adequately?

Dr. LAWRASON. I believe that it is generally recognized that this is a terribly difficult job—evaluation of drugs, review of all the information, the data that is submitted on each new application. My opinion is that they need every support and every bit of help, scientific and medical help, they can get to review these applications.

Senator HATFIELD. Now, this mass of material that you submit—I understand, for example, that they have what, a staff of 170 to review 2,000 or more applications? Can they adequately and effectively read and review all of this mass of material that you and each other drug house submits for this New Drug Application?

Dr. LAWRASON. I believe the past 2 or 3 years have been rather difficult times for the agency because they have had a backlog which

they, I believe, have effectively reduced or are effectively reducing. I am not quite sure that the 2,000 you are quoting is an ongoing total amount that is constantly before them.

Senator HATFIELD. I think the figure is about 2,600, the latest figure that I obtained on that. Do you think it is possible in terms——

Senator NELSON. May I interrupt you? I think the record ought to show, Senator, that the 2,600 represents active IND's.

Senator HATFIELD. These are applications.

Senator NELSON. These are active IND's, I believe.

Mr. GADSDEN. I do not have that figure. Just to amplify Dr. Lawrason's remarks, Merck and the industry have, over the years, supported the FDA in their applications for additional funds and additional people, because we are appreciative of the problems which they have in trying to deal with very complex subject matter.

Senator NELSON. Testimony on this subject is in the record as of yesterday or the day before.

Senator HATFIELD. I would like to be sure that we have the exact figure in relation to whether it is NDA or IND at this place in the record.

Do you think there could be a better system devised, such as perhaps utilizing outside consultants, or do you think it should just be a bigger bureaucracy? Of course, you realize I do not have much faith in the bureaucracy that exists there now. But are you indicating to me that we should just add more and more staff to an already rather inefficient operation?

Dr. LAWRASON. Senator, I would hate to make suggestions on how to solve some of these problems of the Food and Drug Administration.

Senator HATFIELD. Would you like to comment on the bill that I have introduced to take all this away from the FDA and put it in the competent hands of the National Academy of Sciences?

Dr. LAWRASON. I would not want to.

Senator HATFIELD. You would not care to?

Dr. LAWRASON. No.

Senator HATFIELD. I understand why perhaps you might not want to at this point.

What would you say as to the second problem that bothers me? That is that you indicate, like your other colleagues in the industry, that you accumulate a mass of material to have the FDA review and study for these approvals, but what kind of continuing research do you have? What kind of continuing program is there to review the effects after a longtime use of these drugs? I have at no point found any satisfactory evidence that there is such a continuing research by industry or of review by Government on the effects that might occur after—not the initial efficacy or the purpose for which it was originally taken, but the side effects or other things that can happen after long term use of the drug?

Dr. LAWRASON. Senator, I can give you some figures on the extent of our continuing investigation of indomethacin which I think will be pertinent to these hearings. As you will recall, seven controlled studies, not all double-blind, were submitted with the New Drug Application.

Since then, four additional double-blinds have been completed. There are now nine others ongoing in rheumatoid arthritis, with an additional four to six with other controls, other drugs. The total,

including these double-blind studies, is 131 studies now ongoing in the various indications.

We have 26 in rheumatoid arthritis, 21 in osteoarthritis, two in osteoarthritis of the hip, 22 in musculoskeletal disorders, and 60 others which involve the investigation of the drug as an analgesic and antipyretic for thrombophlebitis and so forth.

Senator HATFIELD. What is the span of time in which these are continuing? What is your general control period?

Dr. LAWRASON. The general control period extends, for each study, anywhere from 2 weeks to 3 months.

Senator HATFIELD. But what about beyond that point? What if someone has been on some kind of drug for, let us say, 3 years, 2 years, or 5 years? Are there not effects, as has happened in the past, that did not show up maybe in the first few weeks or the first few months, or the first year, or the first 2 years?

Dr. LAWRASON. We have a great deal of evidence for long-term study and treatment in patients. As a matter of fact, each of the two other physicians appearing today before the committee has had long-term studies going in patients for up to 5 years or more.

Senator HATFIELD. Do you use primate centers to any degree in the long-term studies?

Dr. LAWRASON. Only in toxicity. We have our major toxicity effort within our own group, within our own research laboratory.

Senator HATFIELD. Have you thought about the possibility of utilizing these primate centers to a greater extent on the basis of contract?

Dr. LAWRASON. Yes.

Senator HATFIELD. Because here you have a controlled situation. In many of these long-term effects, you cannot have a human control situation, but you can have an animal control situation in these primate centers.

Dr. LAWRASON. You are very right, and we are considering it. As a matter of fact, we have had preliminary discussions with the primate center just outside of New Orleans.

Senator HATFIELD. Let me ask you one other question. What kind of program or system is there for reporting side effects from the use of drugs? Every once in a while, I see something about a side effect, but I read it as something as a result of some individual having had some ill effects and having to initiate the reporting of that, and some physician more or less identifying the cause of it. Is there a system of reporting side effects by the drug manufacturers to the FDA and they in turn to the public, or what does exist in that way?

Dr. LAWRASON. The system involves reporting of both side effects and adverse effects during the investigational stage of a new drug and after the New Drug Application has been approved. During the investigational stage, we anticipate certain side effects even before we go into the clinic as a result of the preclinical information and laboratory data that has been acquired.

Anticipating these, we also watch for anything that is extraordinary. If it is extraordinary to the degree in which it is potentially life-threatening, we report it directly to the FDA. Once the application has been approved, any adverse effects that occur which are not cited in the package circular, or any that are extraordinary and new or of a serious nature, we send this information in directly to the Food and

Drug Administration as an adverse reaction report. This is to be done, I believe, within 15 days of the time we acquire the information.

Senator HATFIELD. This is by regulation?

Dr. LAWRASON. By regulation.

Senator HATFIELD. So that all pharmaceutical houses subscribe to or are required to follow this same procedure?

Dr. LAWRASON. That is right.

Senator HATFIELD. Do you think it is an adequate procedure? Do you thing it is an effective one at the present time?

Dr. LAWRASON. I believe it is working fairly well; yes, sir. I think one of the problems, if I might say so, is the handling of massive amounts of data . . . we are talking about enormous amounts of information.

Senator HATFIELD. What I did understand you to say was the period of time that this system of reporting continues after the initial introduction of the drug?

Dr. LAWRASON. As long as the drug is registered as a new drug, it will continue on for years.

Senator HATFIELD. You mean you are on a continuing research and accumulation of data and facts on the use of this drug all of the life of the drug?

Dr. LAWRASON. It depends on which aspects of research with the new drug we are pursuing and how it relates to the reporting of adverse reactions, but the accumulation of data continues throughout the lifetime of the drug.

Senator HATFIELD. Do you have a pill—the pill? You do not manufacture the pill?

Dr. LAWRASON. No, we do not.

Senator HATFIELD. Well, in my opinion, that is something.

Mr. GORDON. You mentioned the various studies that are going on. Are these conducted, sponsored, or directed by your company?

Dr. LAWRASON. Yes, sir; they are all sponsored—the double-blind studies, the ones I reported. They are all under IND's.

Mr. GORDON. You talked about recent ones, the ones that are going on now.

Dr. LAWRASON. That is correct. They are all established under the IND system and sponsored by us.

Senator HATFIELD. Could I ask you one followup question, Doctor?

Are you satisfied with the kind of reporting you are getting from physicians on their own experiences in the use of these drugs? What kind of conflict does a doctor face in possibly being fearful of malpractice charges if he reports some of most, say, erratic kinds or the most undesirable kinds of reactions? Is there an inhibition on the part of the physician, or what kind of relationship do you have on that?

Dr. LAWRASON. I would say that one of our greatest problems, as it is in most circumstances these days, is communication. However, we have established within our research group, at least, a good working relationship with physicians so that reporting and constant surveillance of ongoing studies are handled as well as we possibly can. We are always attempting to improve this. Distance, time, these are factors. We try to minimize any delay in communications with physicians.

Senator HATFIELD. You are not really, then, fully satisfied with the kind of reporting which you now have from physicians?

Dr. LAWRASON. I do not think we will ever be fully satisfied, sir.

Senator HATFIELD. Do you think this present lack or, let us say, this underdeveloped reporting system that exists now could become a source of difficulty for you in getting some real evaluations in some of these drugs?

Dr. LAWRASON. They have in the past, but we have spent a great deal of time in examining the issues and rectifying the problems. I would hope that they would not.

Senator HATFIELD. There is no role of Government, then, that you see?

Dr. LAWRASON. No; just that it is part of the requirement for adequate supervision and surveillance of the studies.

Senator NELSON. Please go ahead, Doctor.

Dr. LAWRASON. The committee has heard much of the ARA Cooperating Clinics project and of other approaches to the development of controlled studies. When the ARA project offered the opportunity to have our new drug be the first agent employed in a complex study of this design, we were pleased. We consulted with the committee and we supported its goals, even though all previous experience with such studies indicated that no agent of demonstrated anti-inflammatory and analgesic properties had ever successfully been differentiated this way.

Mr. GORDON. I have been informed by Dr. Donald Mainland of the Cooperating Clinics Committee, that they did a trial on hydroxychloroquine sulfate. This was a 6-month trial using the same method as was used with Indocin, with aspirin permitted in accordance with the committee's practices. The trial showed clear cut differences between the drug and placebo.

Dr. LAWRASON. I am not a clinic witness.

Mr. GORDON. This does not fit in with what you were just saying. You said there was no such study, or that this type of study had never shown any differentiation. This particular study apparently did. I just wanted to bring that to your attention.

Dr. LAWRASON. Has this study been published?

Mr. GORDON. I do not know.

Dr. LAWRASON. We are referring to the fact that a similar study was carried out with cortisone almost 10 years ago. It showed that cortisone was no more effective than the placebo. I believe there was another study that has not yet been published, to our knowledge, and that this also failed to show a difference.

Mr. GORDON. I also would like to read into the record the communication I received from Dr. Mainland on April 24, 1966, with respect to that type of study that they did. It says:

In addition to review by the editor and referees of the Journal in which the report was to be published, Dr. Mainland requested a manuscript of this report be reviewed by Dr. Stanley Shor, who has been director of the Department of Biostatics of the American Medical Association * * *. Dr. Shor was very critical and very experienced in reviewing medical journal manuscripts as exemplified by his report on the subject, "statistic evaluation of medical journal articles," volume 195, pages 41123 to 41128. Dr. Shor commented on April 18, 1966, on the indomethacin report as follows—

that is the CCC report—

"It is, I think, the type of analysis that should be kept as a reference by every clinic investigator. Many times I am asked, are there any studies that have been published that you think are really good in terms of drug trials. Of course, every

drug trial has its own bundle of problems, and it is not very useful to set up a step-by-step procedure which is to be used by all drugs in all cases. However, the analysis in this paper brings out so many important points which the usual clinical investigator is either not aware of or simply does not take into consideration that it should be required reading for all the people engaged in clinical trials. I particularly like your method of showing how observed differences could be misleading in the absence of controls. This is especially interesting in your dose response relationship near the end of the manuscript."

I ask that this be included in the record at the proper place.

Senator NELSON. Very well.

Mr. CUTLER. Could we have a copy, Mr. Gordon?

Mr. GORDON. Certainly; I shall have it Xeroxed and give it to you.

(The documents referred to follow:)

[From Bulletin on Rheumatic Diseases, vol. 13, No. 2, October 1962, pp. 287–290]

## HYDROXYCHLOROQUINE SULFATE IN RHEUMATOID ARTHRITIS, A SIX MONTH, DOUBLE-BLIND TRIAL[1]

This trial was conducted by the Cooperating Clinics Committee of the American Rheumatism Association, under the chairmanship of Dr. Charles Ragan. In attempting to create an instrument that can promptly and reliably evaluate a new and apparently promising drug, the Committee is acutely aware of the danger of a controlled trial that is inadequately planned and loosely conducted. The pseudoscientific verdict of such a trial is more misleading than the impression of a single experienced and critical clinician. A report[2] of the Committee's activities from 1958 through September 1961 describes the difficulties it met and the methods adopted to reduce them. Having gained experience in a pilot study ("dry run") and in a three month trial of hydroxychloroquine, the Committee decided to conduct a six month trial of the same drug, partly to obtain more experience and partly to learn more about the behavior of the drug. It recognized that there is considerable evidence that antimalarial compounds benefit certain types of rheumatoid patients to some degree under certain conditions; but it wished to know (1) whether a drug-placebo difference could be demonstrated on the available patients by the methods employed and (2) the magnitude of such a difference.

### CRITERIA OF ADMISSION TO THE TRIAL

The subjects were to be outpatients, of either sex and any ethnic group, with classical or definite peripheral rheumatoid arthritis (A.R.A. Criteria, 1958 Revision[3]) which had become manifest after the sixteenth birthday and had been present for at least one year before the trial. There were to be present at the beginning of the trial at least three clinically active joints, as determined by tenderness on pressure and/or pain on passive movement. Joint swelling was not used as a criterion of eligibility but was recorded and used in assessment of progress.

Patients with certain specified diseases, such as polyarteritis nodosa, psoriasis, systemic scleroderma, ulcerative colitis and disseminated lupus erythematosus, were excluded, as were patients who, within the previous six months, had experienced pregnancy, childbirth, severe infection or a major surgical operation. Patients who were known or suspected to have ankylosing spondylitis were excluded, but it was not obligatory to screen all patients by sacroiliac radiology. Previous therapies that excluded patients were antimalarials, systemic steroid or phenylbutazone therapy within the preceding two months, and gold therapy within the preceding year, unless a full course within the year had produced no obvious effect.[4]

[1] From the Medical Statistics Unit and the Study Group on Rheumatic Diseases, New York University Medical Center. Mailing address: 112 East 19th Street, Room 1106, New York 3, N.Y.

[2] Mainland, D., *J. New Drugs*, 1:197, 1961.

[3] Ropes, M. W., et al., *Bull. Rheumat. Dis.*, 9:175, 1958.

[4] Probably in all clinical trials there are some implicit restrictions on the type of patient population to which the results can be generalized. Such restrictions are not easy to define and may be overlooked. In this trial, in which the primary objective was a study of the method of opeartion itself, it was desirable to obtain maximum, and willing, cooperation. Therefore it would have been unwise to insist that patients who appeared to be benefiting from another therapy be entered in the trial, or to risk the placebo treatment of patients who, in the opinion of the clinic chief or clinical observer, ought to be available for steroid therapy whenever it might appear desirable.

### THERAPY

The prescribed dosage of drug or corresponding placebo was one 200 mg. tablet four times daily. Assignment of drug or placebo by random numbers was performed at the Coordinating Center at New York University. Approximately equal numbers of drug- and placebo-treated patients were studied at each clinical center. During the trial, systemic steroids, gold and phenylbutazone or related drugs were not permitted, nor were antimalarials. Aspirin was permitted or prescribed at the discretion of the individual observers.

### METHODS OF EVALUATION

Two initial examinations were made, one week apart, and on the second visit therapy was started. Thereafter the patients were examined six times at 28 day intervals (maximum permissible deviation, ±7 days). All observations on any one patient were made by the same observer. The following methods of assessment were used.

*1. American Rheumatism Association functional classifical,*[5] *with reference* to the patient's *usual* occupation (recorded on each visit).

Class I—able to carry on all usual activities without handicap.

Class II—able to carry on all usual activities despite handicap of discomfort or limited mobility of one or more joints.

Class III—able to perform few or none of the usual activities or self-care.

Class IV—largely or wholly incapacitated; bedridden or confined to wheelchair, with little or no ability for self-care.

*2. Duration of morning stiffness*—estimated for an "average" or "typical" day (recorded on each visit).

*3. Number of clinically active joints*—determined by tenderness on pressure and/or pain on passive movement and/or swelling other than bony proliferation (recorded at beginning of trial again after 3 months and after 6 months).

*4. Grip strength*—determined by folded blood pressure cuff attached to mercury sphygmomanometer, with patient's arm unsupported. Read height of column maintained (not initial spurt) by squeezing. Record mean of three readings on each hand (recorded on each visit).

*5. Walking time*—the time, recorded by stop watch, required to walk 50 feet as fast as possible (without running) from a standing start (recorded at beginning of trial, again after 3 months and after 6 months).

*6. Erythrocyte sedimentation rate*—Westergren method, one hour reading (obtained at beginning of trial, again after 3 months and after 6 months).

*7. X-ray films*—postero-anterior, both hands (obtained at beginning and end of trial).

*8. Observer's overall assessment*—the observer's opinion at end of trial regarding the change in the patient's arthritis since the beginning of the trial, recorded as "better," "about the same" or "worse."

*9. Patient's impression*—recorded at end of trial in the same terms as the observer's assessment.

Undesirable signs and symptoms during the preceding four weeks were reported at each visit.

The trial extended from December 1960 through September 1961. It involved 121 eligible patients from 10 clinics (7 to 20 per clinic), including 63 on placebo and 58 on the drug.

### PATIENTS' CHARACTERISTICS AT BEGINNING OF TRIAL

Table I shows the principal characteristics recorded. The distribution by A.R.A. functional classes was: Class I–11; II–68; III–38; IV–4. Rheumatoid factor tests were reported as follows: positive—76; negative—18; doubtful—1; not investigated recently—26. In Table I the range of individual variation represents approximately the middle 90 per cent of the frequency distribution. In none of the characteristics was there any important difference between the placebo and drug-treated patients.

[5] Steinbrocker, O., Traeger, C. H., and Batterman, R. C., *J.A.M.A.*, 140:659, 1949.

TABLE I.—PATIENTS' CHARACTERISTICS AT BEGINNING OF TRIAL

[41 males; 80 females]

| | Median | 90 percent Range |
|---|---|---|
| Age (years) | 53 | 31 to 72. |
| Duration of disease (years) | 6 | 1½ to 21. |
| Duration of morning stiffness (hours) | 2 | ¼ to 7. |
| Number of clin. active joints [1] | 23 | 5 to 54. |
| Grip strength (mm. Hg): [2] | | |
| Males | 95 | 53 to 260. |
| Females | 96 | 44 to 237. |
| 50-ft. walk (second) | 14 | 9 to 34. |
| FSR (mm. in 1 hour) | 40 | 10 to 86. |

[1] Total possible joints (excluding hips): 66.
[2] 2 males and 2 females had maximum registrable strength, 260 mm. Hg.

RESULTS

The data from 8 of the 121 patients presented problems in the analysis; e.g., one patient had received phenylbutazone from a private physician during the trial, one had fractured her hip and one had disappeared entirely. After the analysis of the data from the remaining 113 patients, the 8 problem cases were incorporated in such a way as to avoid bias in favor of the drug. The effect on the main results was negligible. In some instances, however, specific figures were not available for the problem cases; therefore the results given below are from the 113 cases, 60 on placebo and 53 on the drug. In certain analyses some cases had to be excluded; e.g., 11 in the walking test because of inability to walk or absence of lower limb lesions, and 11 in the E.S.R. records because of unreliable laboratory work at one clinic. None of the omissions are due to defective reporting by observers. All comparisons cover the whole six months of the trial.

NOTE: To avoid the statistical term "significant," with its suggestion of "importance," drug-placebo differences are stated to be "adequately accounted for by individual variation" if they would occur in more than 5 per cent of random assignments (such as were used in this trial) when there was no difference at all between treatments. On the other hand, a difference is interpreted as being "associated with the drug" if the frequency of occurrence in purely random assignments would be less than 5 per cent—2 or 3 per cent at most.

*Total group comparisons by individual indexes*

In Table II all the differences appear to favor the drug, but all could be readily accounted for by individual variation. Moreover, the two groups differ very little in the average (median) amount of change, and the individual variation is high in both groups.

TABLE II.—TOTAL GROUP COMPARISONS BY 5 INDEXES

| Index | Placebo (60 patients) | | | | Drug (53 patients) | | | |
|---|---|---|---|---|---|---|---|---|
| | Number | Improved (percent) | Median change | 90 percent range | Number | Improved (percent) | Median change | 90 percent range |
| Duration of morning stiffness. | 56 | 54 | −¼ hour | −3 to +4½ | 53 | 66 | −¾ hour | −4½ to +1½ |
| Number of clin. active joints. | 60 | 62 | −3 joints | −19 to +16 | 53 | 70 | −7 joints | −32 to +6. |
| Grip strength | 56 | 70 | +12 mm | −47 to +55 | 51 | 86 | +29 mm | −17 to +123. |
| 50-foot walk | 54 | 46 | 0 seconds | −6 to +14 | 48 | 50 | 0 seconds | −10 to +8. |
| ESR | 49 | 45 | +1 mm | −34 to +34 | 42 | 64 | −7 mm | −37 to +55. |

*Subdivision by initial severity*

In four indexes (morning stiffness, number of clinically active joints, walking time and E.S.R.) a much more clear-cut drug-placebo difference was found when the data from patients who were more severely affected at the beginning of the trial (a quarter to a third of the total patients) were examined separately (Table III). In the first two of these indexes the differences were clearly associated with the drug. In grip strength, the patients who were *stronger* initially showed the greater drug-placebo difference.

TABLE III.—COMPARISONS AFTER SUBDIVISION BY INITIAL SEVERITY

[P=placebo; D=drug]

| Index | Initial severity | Number of patients | | Median change in group | Percent exceeding group median | | Median change in subgroup | |
|---|---|---|---|---|---|---|---|---|
| | | P | D | | P | D | P | D |
| Duration of morning stiffness. | 3 or more hours | 22 | 18 | —2½hr | 32 | 72 | —1¼hours | —3 hours. |
| Number of clin active joints. | More than 28 joints | 18 | 19 | —10 joints | 28 | 68 | —6 joints | —16 joints. |
| 50-foot walk | More than 16 seconds | 15 | 14 | —2 seconds | 27 | 64 | 0 seconds | —3 seconds. |
| ESR | More than 55 mm | 17 | 13 | —12 mm | 41 | 61 | —11 mm | —17 mm. |
| Grip strength | 75 mm. Hg or more | 34 | 36 | +22 mm | 35 | 64 | +14 mm | +34 mm. |

*Overall assessments*

Three methods of overall assessment showed marked differences associated with the drug.

*1. A.R.A. functional classes*—Of the patients initially in Class II, only 9 per cent of 33 who were on placebo moved to Class I, whereas 50 per cent of 30 drug-treated patients did so. (P approximately 0.001.) Migration of Class III patients to Class II showed no influence of the drug.

*2. Five point scoring system*—Each patient was given a score of one unit for an improvement in any one of the five individual indexes and the scores were then summated. (When a patient could not score on one of the indexes, e.g., through inability to walk, an adjustment was made to bring his total possible score up to 5.) Scores of 3, 4 or 5 were counted as "improvement" (Table IV). This index had shown a drug-placebo difference in the three month hydroxychloroquine trial and is to be explored further as an overall measure.

TABLE IV.—COMPARISONS BY OVERALL ASSESSMENTS

| Parameter | Placebo | | Drug | |
|---|---|---|---|---|
| | Number | Improved (percent) | Number | Improved (percent) |
| Advanced from class II to class I | 33 | 9 | 30 | 50 |
| 5 point scores | 57 | 54 | 53 | 75 |
| Observers' assessments | 60 | 35 | 53 | 64 |
| Patients' impressions | 60 | 60 | 53 | 75 |

*3. Observers' overall assessments*—This was not a "clinical impression" in the ordinary sense because the observers had a summary of their month by month observations; but perhaps it is the most comprehensive summing-up of a patient's progress and it is free from treatment-connected bias in a truly double-blind trial.

The patients' impressions of drug-placebo differences, considered apart from the other data, could have been accounted for by individual variation.

No patient went into remission during the trial.

*X-ray evidence*—assessment (by Dr. Josephine Wells, Columbia University) is not yet finished but an unselected sample of films from 50 patients has shown no drug-placebo difference.

*Undesirable signs and symptoms*

Table V shows that all the recorded phenomena occurred more frequently in drug-treated patients, but the placebo patients showed considerable frequencies that might have been attributed to the drug in a trial without placebo. No patient was removed from the trial because of these occurrences.

TABLE V.—UNDESIRABLE SIGNS AND SYMPTOMS

[Percentages represent patients (out of 60 placebo treated and 53 drug treated) who reported an occurrence on 1 or more visits after therapy started]

| Sign or symptom | Frequency (percent) | |
|---|---|---|
| | Placebo | Drug |
| Pruritus | 38 | 58 |
| Skin rash | 32 | 53 |
| Headache | 48 | 53 |
| Abdominal pain | 47 | 49 |
| Tinnitus | 37 | 47 |
| Nausea | 38 | 45 |
| Dizziness | 35 | 43 |
| Blurred vision | 20 | 43 |
| Diarrhea | 20 | 40 |
| Anorexia | 30 | 38 |
| Stomatitis or sore tongue | 15 | 30 |
| Vomiting | 15 | 23 |
| Photophobia | 10 | 13 |
| Miscellaneous | 63 | 75 |

*Variables other than therapy*—The samples were too small to provide sensitive tests of the relationship between the outcome of the trial and such variables as age, sex, duration of disease at start of trial, presence or absence of rheumatoid factor and differences between clinics. The data did not, however, suggest any close relationship between these variables and the improvement rates or drug-placebo differences.

### CONCLUSIONS REGARDING DRUG EFFECTS

Three overall measures (functional class, observers' assessment and the five point scores) have shown differences in percentage frequency of improvement that were associated with the drug; and so also have certain individual indexes in patients who were severely affected at the beginning of the trial. "Association," however, does not imply causal relationship in a trial that cannot be maintained completely double-blind. It is conceivable that observers, nurses or others might have guessed at the patients' therapy from side-effects and then, probably unconsciously, they might have affected the patients' responses to questions and tests. To detect such an influence, the number of undesirable signs and symptoms reported on the final visit were compared with the observers' overall assessments and with the five point scores. No consistent relationship was found. Perhaps the test was too insensitive; but the magnitude of the percentage frequency differences in Table IV, taken along with other workers' experience with antimalarials, leaves little doubt that the drug-placebo differences were largely cause-and-effect relationships.

One must, of course, beware of accepting percentage differences found in samples of 50 or 60 patients as equivalent to what would be found in a study of much larger numbers of patients of the same kind and under the same conditions. The observers' figures for improvement were placebo—35 per cent, and drug—64 per cent, a difference of 29 per cent. Even if the patients in the trial were strictly random samples of their respective (placebo and drug) populations, all that the 29 percent could tell us would be that the true (population) difference was probably somewhere between 15 and 40 per cent.

### SEROLOGICAL STUDIES

Sera collected from all patients at the beginning and end of the trial were sent to the Rackham Arthritis Research Unit in Ann Arbor, Michigan, for serological, chemical and electrophoretic studies. Complete pairs of sera were available from 50 drug- and 52 placebo-treated patients. We are grateful to Drs. George R. Thompson and Ivan F Duff for permitting us to summarize some of their results here prior to their own publication.

*Latex agglutination tube test*—Thirty-six drug- and 44 placebo-treated patients had positive tests initially. In 7 drug and 2 placebo-treated patients the tests became negative. When changes in titer of more than one tube up or down were examined, the following contrasts were observed: in the 50 drug-treated patients, a fall in 10 and a rise in 3; and in the 52 placebo patients, a fall in 5 and a rise in 6. Although these differences could have been accounted for by individual variation, it should be noted that they are in agreement with results

reported for the sheep cell agglutination test following administration of chloroquine [6,7] and of gold.[8] There was no obvious relationship between the latex test results and the clinicians' overall assessments.

*Changes in serum albumin*—Electrophoretic analyses showed a rise in patients who were reported to be clinically better or unchanged, and a fall in those reported as worse. The difference could not be accounted for adequately by individual variation. The changes did not differ markedly between the two treatment groups.

*Changes in serum gamma globulin*—There was a return toward normal in the drug-treated, but not in the placebo patients.

### PARTICIPATING CENTERS

Lack of space prevents listing the 55 persons (clinic chiefs, observers and nurse-secretaries) who contributed to this trial. The 11 participating centers were: Rackham Arthritis Research Unit, University of Michigan, Ann Arbor; National Institute of Arthritis and Metabolic Diseases and Georgetown University Medical Center, Bethesda and Washington, D.C.; Massachusetts General Hospital, Boston; University of Illinois, Chicago; Southwestern Medical School, Dallas; University of California and Veterans Administration Hospital, Los Angeles; University of Tennessee, Memphis; Jackson Memorial Hospital, Miami; Presbyterian Hospital, New York; University of Pennsylvania, Philadelphia; and University of California, San Francisco.

### ACKNOWLEDGMENTS

The project was supported by Grant A–3252 from the National Institutes of Health, U.S. Public Health Service, and by funds from The Arthritis and Rheumatism Foundation for x-ray expenses. The Committee is indebted to Winthrop Laboratories for generous supplies of the drug (Plaquenil) and placebo, and for cooperation in the special labeling and dispatching of the compounds.

The co-authors wish to express their indebtedness tot their former colleague, Miss Lee Herrera for her invaluable contributions to this work. She participated in all the activities of the project until October 1961 when she moved to California.

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[From Bulletin on Rheumatic Diseases, vol. 16, No. 3, November 1965, pp. 388–391]

## ASPIRIN IN RHEUMATOID ARTHRITIS, A SEVEN-DAY, DOUBLE-BLIND TRIAL—PRELIMINARY REPORT

The time honored place of salicylates in the therapy of the rheumatic diseases as well as their postulated mode of action is being reappraised by many investigators today. This preliminary report of a therapeutic trial of aspirin points up effectively the pitfalls, the tremendous problems and great effort involved in carrying out such clinical studies in order to obtain data which can be meaningfully interpreted. Certainly salicylates are most useful compounds but contrary to the claims of some advertisers their true effectiveness and action has yet to be determined. Attention is called to Dr. Mainland's invitation for readers to submit questions and suggestions regarding this trial to him.

—THE EDITOR.

This trial was conducted by the Cooperating Clinics Committee of the American Rheumatism Association, under the chairmanship of Dr. Charles Ragan. After conducting double-blind trials on an antimalarial compound [1,2] and a seven-day variability study [3] on 499 patients without change in their assigned therapies,

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[6] Freedman, A., and Steinberg, V. L., *Ann Rheumat. Dis.*, 19 :243, 1960.
[7] Popert, A. J., Meijers, K. A. E., Sharp, J., and Bier, F., *Ann. Rheumat. Dis.*, 20 :18, 1961.
[8] Research Subcommittee, Empire Rheumatism Council, *Ann. Rheumat. Dis.*, 19 :95, 1960.
[1] Mainland, D., J. New Drugs, 1 :197, 1961.
[2] Mainland, D., and Sutcliffe, M. I., Bull. Rheumat. Dis., 13 :287, 1962.
[3] Cooperating Clinics Committee of the American Rheumatism Association, Arth. and Rheumat., 8 :302, 1965.

the Committee turned its attention to the scarcity of well-documented information on the clinical effects of aspirin. It decided to study the changes in manifestations of disease activity in patients who were continued on their previously assigned antirheumatic therapies, but were assigned strictly at random to aspirin in a fixed rather high dosage or to placebo, in approximately equal numbers, and were studied by the double-blind technique. In order to avoid excessive distress to patients, and a risk of breakdown of the trial, the period was restricted to seven days.

### CRITERIA OF ADMISSION TO THE TRIAL

The patients were to be outpatients (or domiciliary hospital patients), of either sex and any ethnic group, with "classical" or "definite" peripheral rheumatoid arthritis (A.R.A. Criteria, 1958 Revision [4]) which had become manifest after the sixteenth birthday. In addition to the 20 exclusions in the A.R.A. Criteria, patients were not to be admitted if they had experienced severe infection or major surgical operation within one month before the start of the trial, or if they had a history of toxic reactions to aspirin. Patients who were known or suspected to have ankylosing spondylitis were to be excluded, but it was not obligatory to screen all patients by sacroiliac radiography.

### THERAPY

The drug, acetylsalicylic acid, was administered in capsules, each capsule containing 7.5 grains (approx. 0.5 gm.) and the prescribed dose of drug or corresponding placebo was 2 capsules 4 times a day for 7 days (total daily dose = 60 grains = 3.9 gm.). Assignment of drug or placebo was performed by random numbers at the Biometrical and Coordinating Center. Except for these assignments, patients were allowed to be on any (or no) therapy for rheumatoid arthritis, but it was stipulated that, if possible, no change be made in the type of therapy during the two week preceding the trial or during the trial itself, and also that dosage changes, especially of corticosteroids, be minimal during the trial. Patients were be urged to refrain from aspirin and other salicylates during the week of the trial. Details of types and dosages of all therapies were recorded in the data sheets for use during analysis. The trial extended from April 5 through November 14, 1963.

### METHODS OF EVALUATION

All observations at the initial and final examination (Day 1 and Day 8) were to be made by the same observer who was to have at least the rank of clinical fellow. The maximum allowable departure from the 7-day interval was ±1 day. The following assessments were made in both examinations:

1. *American Rheumatism Association functional classification* [5] with reference to the patient's *usual* occupation.
2. *Duration of morning stiffness*—estimated for an "average" or "typical" day.
3. *Grip strength*—determined by folded blood pressure cuff attached to mercury sphygmomanometer, with patient's arm unsupported. Inflate initially to 20 mm. Hg. Read height of column maintained by squeezing (not initial spurt). Record three successive readings on each hand.
4. *Walking time*—the time required to walk a straight continuous distance of 50 feet as fast as possible (without running) from a standing start.
5. *Number of clinically active joints*—determined by any one of the following: tenderness on pressure, pain on passive movement, swelling other than bony proliferation. Recorded also were heat, redness, ankylosis (determined by clinical examination) and subcutaneous nodules.
6. *Erythrocyte sedimentation rate*—Westergren method; anticoagulant, 3.8% sodium citrate; one hour reading.
7. *Patient's assessment*—the patient's impression regarding his arthritis, recorded as "good," "fair" or "poor"; and as "better," "about the same" or "worse" in comparison with his condition one week previously.
8. *Observer's overall assessment*—recorded in the same terms as the patient's assessment, taking into account not only the impressions gained from the measurement methods (without referring to Day 1 data sheets), but any other available information.

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[4] Ropes, M. W., et al., Bull. Rheumat. Dis., 9:175, 1958.
[5] Steinbrocker, O., Traeger, C. H., and Batterman, R. C., J.A.M.A., 140:659, 1949.

*Blood salicylate levels* were determined on Day 1 and Day 8 at six clinics by the method of Brodie, Undenfriend and Coburn.[6] The interpretation of these data is complicated by the variability of the intervals between the last dose of aspirin on Day 8, the time of clinical examination and the withdrawal of blood for salicylate determination. The more detailed report will include this topic.

The data sheets called for the reporting of *undesirable signs and symptoms*, but no check list was provided. Expenditure of much time on this inquiry did not appear to be justified because no valid population estimate of frequencies could be made from a group that was partly selected by exclusion of salicylate reactors.

### PATIENTS' CHARACTERISTICS

From the 492 patients who were entered in the trial, the data of 51 (28 on placebo and 23 on aspirin) were omitted from the analysis for the following reasons: ineligible by protocol, 19; drop-outs or late for final examination, 14; change in basic therapy, 15; change in observer, 3. If this had been a trial of a new drug it would have been necessary to handle the data from the drop-outs and late attenders in such a way as to avoid bias in favor of the drug. This hardly seemed necessary, at least in a preliminary report on experiences with aspirin.

The remaining 441 patients were considered eligible in all respects, including the interval between assessments (9 were one day late, 1 was one day early). They were provided by 11 clinics (18 to 86 per clinic). Assigned to placebo: 223; assigned to aspirin: 218. Males: 131; females: 310. Median age: 53; range (middle 90 per cent): 30 to 73. Median duration of disease: 7 years; range (middle 90 per cent): 1–27 years.

### THERAPIES

The basic therapies with numbers of patients assigned to placebo (P) and aspirin (A) were as follows: Corticosteroids (P, 59; A, 55); Salicylates (P, 100; A, 93); Antimalarials (P, 14; A, 17); Miscellaneous, i.e., combinations of therapies and some patients who at the beginning of the trial were receiving no antirheumatic therapy (P, 50; A, 53). Thirty-one patients were receiving indomethacin, usually along with another therapy. Except in the salicylate group, all these patients were maintained on their basic therapies during the trial.

In order to permit a search for relationships between intake of the trial therapy and the outcome of the trial, patients were classified rather arbitrarily as "on schedule" if they met all the following criteria: (1) at least 32 capsules during the 5 days following the day of the initial examination; (2) at least 8 capsules on the day preceding the day of the final examination, or 6 capsules if the only dose missed was the breakfast dose; (3) at least 2 capsules on the day of the final examination.

The 117 patients (28% of the P patients, 25% of the A patients) whose reported dosage failed to meet one or more of these criteria were classified as "not on schedule." There was little difference in the proportions of these among the various therapy groups. The data were analyzed as a whole, and also in "on-schedule" and "off-schedule" groups separately. The results from the total 441 patients are shown here, because when a pronounced placebo-aspirin difference in outcome occurred, it did so in spite of the incomplete dosage of some patients.

### COMPARISON OF AVERAGE CHANGES IN FIVE MEASURES OF DISEASE ACTIVITY

Table 1 shows the placebo-aspirin contrast in patients who in the initial examination were recorded as having greater than zero readings in the respective measures of disease activity, because the inclusion of initially "inactive" patients would tend to damp the contrast between the two agents. To estimate how frequently the drug-placebo contrasts in the table would occur solely as the result of the random assignments, the data were arranged in fourfold tables (placebo versus aspirin; improved versus not improved, i.e., deteriorated or unchanged), and the chi-square test (with Yates' correction) was applied. In all measures except morning stiffness the differences would rarely occur in random assignment (P values from chi-square less than 0.01). In morning stiffness the P value was 0.12; which means that, even if there were no difference

[6] Hepler, O. E., Manual of Clinical Laboratory Methods, Charles C. Thomas, Springfield, Illinois, 1953.

in the effect of placebo and aspirin on this measure of activity, differences as great as the observed difference, and greater, would have been produced by the randomization alone.

These results, therefore, appear to have provided a clear demonstration of aspirin effect on all the measures except morning stiffness.

TABLE 1.—COMPARISONS BY 5 MEASURES OF DISEASE ACTIVITY

[Impr. (I.)=improvement. Deter. (D).=deterioration. N.C.=no change.]

| Measure of activity | Placebo | | | | | Aspirin | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Number in group | Impr. (per-cent) | N.C. (per-cent) | Deter. (per-cent) | Median change | Number in group | Impr. (per-cent) | N.C. (per-cent) | Deter. (per-cent) | Median change |
| Morning stiffness | 198 | 33 | 23 | 44 | 0 | 184 | 41 | 32 | 27 | 0. |
| Clin. active joints | 220 | 38 | 10 | 52 | 1 jt. D | 216 | 56 | 9 | 36 | 1 jt. I. |
| Grip strength: | | | | | | | | | | |
| Male | 61 | 31 | 0 | 69 | 15.5 mm. D | 58 | 64 | 0 | 36 | 5.5 mm. I. |
| Female | 152 | 38 | 1 | 61 | 7.5 mm. D | 153 | 59 | 2 | 39 | 7.5 mm. I. |
| 50-foot walk | 214 | 41 | 13 | 47 | 0 | 209 | 55 | 16 | 29 | 0.5 sec. I. |
| E.S.R | 214 | 30 | 5 | 65 | 3 mm. D | 213 | 51 | 8 | 41 | 1 mm. I. |

Note: Patients excluded: (a) Reported absence of disease activity on initial examination: morning stiffness 55; joints 4; grip 10 males and 4 females. (b) Inability to perform test: walking 18; grip 1 male and 1 female. (c) Imperfect data etc.: morning stiffness 4; joints 1; grip 1 female; E.S.R. 14.

Of particular interest was the question whether the salicylate group, about half of whom were suddenly deprived of their basic therapy for the seven days of the trial, showed a larger placebo-aspirin difference than did the other basic therapy groups—particularly a greater frequency of deterioration when on placebo than the corticosteroid group. All the basic therapy groups were analyzed with reference to this question, but no consistent difference could be found attributable to the salicylate deprivation in those who had been on that therapy at the beginning of the trial. It is possible, however, that the conditions of the trial were not suitable to demonstrate such an effect, owing to the variable and uncontrollable time intervals between the clinical examination and the preceding dose of aspirin.

## EXTENT OF CHANGE IN DISEASE ACTIVITY

Table 1, showing overall percentage frequencies and averages, has restricted significance because:

1. A drug-placebo difference in the frequency of improvement may be large but of little practical value if the amount of the improvement is small.
2. The averages of the gains and losses, and the drug-placebo differences in these averages, are trivial; but in certain subgroups the differences may be large. (The records of voluntary aspirin consumption by placebo patients did not suggest that this was the cause of the small size of the differences.)
3. The lack of any conclusive drug-placebo difference in the effect on morning stiffness may have been due to the inclusion of subgroups that were not likely to show much change in a period of seven days.

Much more informative are statements about the ranges of improvement or deterioration, and the Seven-day Variability Study has shown that these differ according to the initial (Day 1) level of activity. In that study those levels were divided, for each measure separately, into classes from A (the mildest) to J (the most severe), each class containing as nearly as possible 10 percent of the total 499 patients in the study.

As examples, Table 2 shows the application of the Variability-Study classification to certain of the data in the present study. In addition to the display of the extent of change, the sub-classification provides a method for increasing the sensitivity of comparisons in drug trials. Thus, although the analysis of the total data showed no convincing drug-placebo difference in the morning stiffness change, the figures in Table 2 show that, when allowance is made for the amount of stiffness recorded on Day 1, the drug-placebo difference becomes more obvious. For example, of the patients who started with 5–25 minutes of morning stiffness, 26 percent of placebo patients reported an hour or more on Day 8, whereas only 5 percent of the aspirin patients reported that amount of deterioration. A later report will show the general application of this simple method of increasing the sensitivity of a trial.

TABLE 2.—EXAMPLES OF RANGE OF VARIATION WITH ALLOWANCE FOR SEVERITY AT INITIAL EXAMINATION

[P=placebo; A=aspirin; VS=variability study; m.t.=more than; l.t.=less than]

| Severity Class at Init. Exam. | Number in group | | | Impr. to: | Percent of number in group | | | Det'n. to: | Percent of number in group | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | P | A | VS | | P | A | VS | | P | A | VS |
| Morning stiff: | | | | | | | | | | | |
| A. zero | 23 | 32 | 57 | | | | | m.t. 25 min | 22 | 6 | 9 |
| B. 5–25 min | 19 | 21 | 20 | zero | 5 | 10 | 10 | m.t. 55 min | 26 | 5 | 10 |
| I. 3.75–4.75 hr | 17 | 18 | 19 | l.t. 30 min | 6 | 11 | 5 | m.t. 4.75 hr | 53 | 1 | 721 |
| J. 5 hr.-all day | 24 | 21 | 48 | l.t. 2.75 hr | 21 | 19 | 4 | | | | |
| No. of clin. active jts.: | | | | | | | | | | | |
| A. 0–3 | 17 | 12 | 44 | | | | | m.t. 8 | 18 | 0 | 7 |
| B. 4–5 | 13 | 9 | 36 | l.t. 4 | 15 | 33 | 39 | m.t. 8 | 31 | 11 | 8 |
| I. 30–36 | 14 | 24 | 45 | l.t. 20 | 0 | 8 | 9 | m.t. 36 | 36 | 25 | 24 |
| J. 37–66 | 25 | 18 | 35 | l.t. 25 | 4 | 6 | 9 | | | | |

Note: Improvement or deterioration implies change from one class to another.

## OVERALL ASSESSMENTS

Table 3 shows the placebo-aspirin contrast in relation to the A.R.A. functional classification. There appeared to be a slightly greater tendency to improve in the drug-treated than in the placebo patients, more especially in the less disabled patients; but it will be noted that numerous changes of class were recorded in the Variability-Study patients who were maintained for one week on their accustomed therapies.

TABLE 3.—COMPARISONS BY ARA FUNCTIONAL CLASSES

[P=placebo; A=aspirin; VS=variability study]

| Class at initial examination | Treatment | Number in class (N) | Class at final examination (percent of N) | | | |
|---|---|---|---|---|---|---|
| | | | I | II | III | IV |
| I | P | 11 | 55 | 36 | 9 | |
| | A | 17 | 71 | 29 | | |
| | VS | 36 | 81 | 17 | 3 | |
| II | P | 121 | 1 | 86 | 12 | 2 |
| | A | 125 | | 94 | 6 | |
| | VS | 205 | 0.5 | 96 | 4 | |
| III | P | 80 | | 9 | 86 | 5 |
| | A | 67 | | 12 | 88 | |
| | VS | 152 | | 5 | 94 | 1 |
| IV | P | 5 | | | | 100 |
| | A | 7 | | | | 100 |
| | VS | 17 | | | 12 | 88 |

From Table 4 it would appear that the patients were somewhat more optimistic than the physicians regarding improvement in general and regarding the benefits of the trial therapy; and a similar observation was made in an antimalarial trial. It appears, also, however, that the patients were more pessimistic regarding deterioration—that they were more ready to report change, in one or other direction, than the physicians. (A more detailed examination of such contrasts is being made in the data from the Seven-day Variability Study.)

TABLE 4.—OBSERVERS' AND PATIENTS' ASSESSMENTS

[Numbers of patients: Placebo, 223; aspirin, 218]

| Assessors and therapies | Changes from initial to final examination (percent of pts.) | | |
|---|---|---|---|
| | Improved | About the same | Worse |
| Observers: | | | |
| Placebo | 17 | 48 | 35 |
| Aspirin | 31 | 54 | 15 |
| Patients: | | | |
| Placebo | 23 | 33 | 44 |
| Aspirin | 45 | 36 | 19 |

FURTHER ANALYSES

Many questions, in addition to those discussed in this report, have been applied to the data from this trial, such as the question of the interrelationships of cumulative effect, recency of last dose and amounts of aspirin consumed—an attempt to see whether the trial could give any clue to an "optimum" aspirin regimen. However, it seemed desirable at this stage to present an overall view, as an invitation to readers to submit questions and suggestions that would help in the preparation of the more detailed report.

PARTICIPATING CENTERS

Lack of space prevents listing the 46 observers and about 16 study-secretaries who contributed to this trial. (Study secretaries did not contribute patient assessments as some of them did in the Seven-day Variability Study.) The 11 participating centers were: Southwestern Medical School, Dallas; State University of New York, Downstate Medical Center, Brooklyn; University of Illinois, Chicago; University of California and V.A. Hospital, Los Angeles; Massachusetts General Hospital, Boston; Jackson Memorial Hospital, Miami; Rackham Arthritis Research Unit, University of Michigan, Ann Arbor; N.I.A.M.D. and Georgetown University Medical Center, Bethesda and Washington, D.C.; Presbyterian Hospital, New York; University of California, San Francisco; University of Tennessee, Memphis.

ACKNOWLEDGMENTS

The Cooperating Clinics' program is supported by Grant AM–03252 from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, U.S. Public Health Service. The Coordinating Center is indebted to Mrs. M. O. Blake, Mr. P. C. Miller and Miss A. C. Powell for assistance in the analyses; and to the Merck Company for its generous and painstaking cooperation in the provision of drug and placebo.

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Senator NELSON. Please go ahead, Doctor.

Dr. LAWRASON. We doubt whether even the authors of this tentative, exploratory, and hopeful experimental design, with all of the complex statistical loose ends that remain to be tied up, would hold it up to the world as a finished and refined tool of biostatistics and control.

Let me make it clear that we at Merck are in no way opposed to the intense desire of experts in rheumatology to take steps forward in clinical design. However, we do not accept the validity of the cooperating clinics study presented to this committee last week as a measure of the value of indomethacin in medical practice. We do not believe a wholly satisfactory double-blind study for demonstrating the effect of a drug in treating rheumatoid arthritis has yet been designed.

From what we know today, no drugs used in rheumatoid arthritis get at the cause of the disease, nor do they appear to halt its ultimate progression. Thus we are talking about drugs which will only give relief of symptoms. Much of this can be determined only by the patient and his physician. At this state of our knowledge there are no really good objective measurements or tests. Those we have, at best, are very crude. The rheumatoid patient manifests no objective laboratory parameters, such as the blood sugar of the diabetic, which the physician can point to and which enable him to know if the patient is improving.

As you know, aspirin has been the backbone of drug therapy in the rheumatoid patient for many years. Therefore it is natural that indomethacin would be compared with aspirin in rheumatoid arthritis, just as any new drug would be compared to an accepted standard therapy of the day. Aspirin is generally accepted by both the medical and lay public as safe. However, there is a great deal of history with aspirin which has never been written. Only in recent years has this drug come under closer scrutiny. In thinking about aspirin, one finds that it really is two drugs—the one that most people take for minor aches and pains in one-, two-, or three-tablet doses, and the second a drug which must be taken in massive doses up to 20 or more tablets (4 to 8 grams a day) to effect a therapeutic benefit in a disease such as rheumatoid arthritis.

In the case where only a few tablets are taken occasionally, as needed, there are few side effects. Most people are able to tolerate aspirin in these amounts, but even with these small doses there are patients who experience gastrointestinal irritation.

However, when one approaches the therapeutic doses of aspirin needed to treat rheumatoid arthritis, there are definite side effects—some very similar to those with indomethacin—which need to be watched carefully by patient and physician. Many patients either cannot tolerate these high doses of aspirin or just will not swallow that many tablets.

On the other hand, most rheumatoid patients who can tolerate aspirin will take it whether it is prescribed or not. If they respond to aspirin and the pain disappears, no further medication, no matter how effective, can make that pain disappear any further. If motion of a joint is allowed up to its maximum by aspirin, then indomethacin, phenylbutazone, or the steroids are unlikely to increase that motion any further. If grip strength, swelling of a joint, and inflammation, for example, have improved in a patient who responds to aspirin, an additional drug, no matter how effective, would probably not provide further improvement in the physical status of the patient.

Although we cooperated in setting up the cooperating clinics study, we did not participate in the design of the study—this was up to the committee. However, I understand there were wide differences of opinion on the study design within the committee itself, particularly with respect to whether or not those patients who were to receive indomethacin should continue to receive aspirin, in the amount the patients desired, as a basic background medication. Obviously the majority of the patients included in the study were responsive to aspirin, and it was decided to allow them to continue to take it. Whether this was the right decision is a matter of opinion, but for the reasons I cited earlier I am not surprised that neither these patients nor the physicians could determine the effect of a second active drug that was being given on top of an already "treated" patient. These studies may not have shown that indomethacin is an effective drug in rheumatoid arthritis by the rigid criteria used, but neither have they shown that it is ineffective. They show nothing as to the effectiveness of indomethacin in patients who do not respond to aspirin or cannot tolerate it in large doses. They do show that during treatment with indomethacin many patients were able to decrease the amount of aspirin they were taking, and when indomethacin was discontinued some of

the patients experienced some degree of clinical relapse. Some statisticians would consider this to be evidence of activity, but the committee chose not to accept these factors as criteria of effectiveness.

The study has yet to be designed which all would agree is the ideal format for a controlled study of such agents. Some double-blind studies were included in our original indomethacin submission to the FDA, and you have heard testimony in criticism of their structure. Dr. Mainland has stated that his study is part of a continuing, long-range effort to eliminate the unreliable factors and variables. More recently, we have been involved with the further development and design of double-blind studies. Many of these are being carried out. But here, too, it is impossible to say whether the principles underlying these studies will be generally accepted as satisfactory.

During the coming years, I am convinced, controlled clinical methodology will be developed so that truly objective data will result. As physicians in medical research at Merck, this is our job and our effort is dedicated to this end. However, it should be recognized that the clinical sciences have not yet reached the scientifically controlled state that has been attained in the laboratory. The patient is not and can never be the exact counterpart of a highly inbred, genetically and environmentally controlled laboratory animal.

If we had to do our clinical research over again with indomethacin, we would do it the same way, by first going to the expert. We would subsequently supplement our basic clinical evaluation with the best double-blind control studies we could devise. This, in fact, is what we are doing today as we take a new anti-inflammatory drug to the clinic. But so long as we do not yet know of a wholly satisfactory double-blind method of proving effectiveness for drugs used to treat rheumatoid arthritis, we do not believe there is any medical basis for postponing the introduction of a drug experts believe to be valuable.

The question of the safety of indomethacin has also been raised. It is important to distinguish between safety for use as contrasted with side effects experienced during use of the drug. The issue of safety deals with the potential threat of serious, life-threatening consequences. The issue of side effects deals with sometimes bothersome, sometimes annoying effects which are not in themselves of serious potential.

These issues have been grouped together in the discussion of indomethacin. In the resulting confusion, the major point—that most of the side effects of indomethacin are of a minor or manageable nature—has been lost. Many disappear in a short time with continuation of the medication or an adjustment of dose. Only 10 to 15 percent of all patients receiving the drug have to discontinue it because of side effects or reactions. In rheumatoid patients the incidence of patient intolerance appears to be greater than in patients with other forms of arthritis. But this is not surprising. It is well known that patients with rheumatoid arthritis have a greater sensitivity or a lower threshold to the adverse effects of many drugs, for reasons which are not known. It should be pointed out also that most of such patients are on multiple drug therapy. This, together with the vagaries of the disease itself, often sets the stage for higher incidence of adverse drug effects.

Sufficient clinical experience was accumulated with indomethacin over the years of investigation before its approval by FDA to assure

its safety for use as directed. I can assure this committee that we would not have requested consideration for approval of this drug if we had thought it was not safe.

The final overall assessment of safety can only be assured after extensive experience. For example, aspirin and related compounds which have been used for over 50 years are even now being reassessed with regard to their potential long-term effects on the kidney.

Information on the safety of indomethacin is outlined in the official product circular. So long as the physician is aware of the effects that have been reported—those that appear more frequently and those only rarely noted—we believe it can be prescribed with the proper assurance that the potential risks can be weighed against the benefits to be obtained.

We are proud of indomethacin. We know through personal experience what it means to many, many people. I am confident, looking ahead, that the scientific teams at Merck that produced indomethacin will develop further advances as they continue to search for the causes of these crippling diseases.

I will be happy to answer your questions.

Senator NELSON. Thank you, Dr. Lawrason. The committee appreciates very much your testimony for our record.

Senator Hatfield?

Senator HATFIELD. I have just one question, Doctor.

On page 6, you were saying in the third full paragraph:

> We do not believe a wholly-satisfactory double-blind study for demonstrating the effect of a drug in treating rheumatoid arthritis has yet been designed.

On page 10, in talking about your clinical research, you say:

> We will subsequently supplement our basic clinical evaluation with the best double-blind control studies we could devise.

I do not quite understand what the hangup is on devising or having now made effective double-blind studies. Why is it so difficult? Why do we not have it now and why do you feel you can devise one that has not yet been done?

Dr. LAWRASON. One of the problems of the studies with rheumatoid arthritis involves the quantification of the subjective measurements; that is, measurement of response in the patient. We do not believe, as I stated, that there is yet an ideal format for design of a double-blind, controlled study, Dr. Mainland and his group in the cooperating clinics point out themselves that their efforts in this direction and their studies with indomethacin are part of a long-term effort to design a truly controlled and adequate study. But we are also in the same process. In the 100 or more such studies that we have developed over the past 2 years and are ongoing now, not all are the same. We do not claim to have the ultimate design. But this is our purpose and this is our job, to find the very best study design that can give objective measurements and results.

Senator HATFIELD. How many drugs are tested by the double-blind study? How broadly used is this technique?

Dr. LAWRASON. Oh, this is a widespread control method, using the the double-blind. It is particularly effective in getting rid of physician or patient bias where measurement is in part subjective. Some diseases are easily studied this way and some are not.

Senator HATFIELD. Should all the drugs be subjected to this kind of test before they are put on the market?

Dr. LAWRASON. Yes, to the extent that they can. But in studying a diuretic, for example, the double-blind is really not necessary to determine whether or not there has been a diuresis within a patient, increase in urine volume.

Senator HATFIELD. What criteria do you use in determining when to use this double-blind study, on which drug, and when not to?

Dr. LAWRASON. In those diseases where there are truly objective measurements—for the most part laboratory measurements, or objective signs within the patient of changes that take place, whether it be with the electrocardiogram or other techniques—the double-blind is of only ancillary and confirmatory value. It is where observations are being made by the physician and patient, where possible bias is interjected, that the double-blind serves the greatest purpose.

Senator HATFIELD. Thank you, Mr. Chairman.

Mr. CUTLER. Mr. Chairman, could I supplement that for a moment? When Dr. O'Brien was testifying, he construed the 1962 Drug Amendments as requiring double-blind studies to prove effectiveness in all future drugs. We have prepared a memorandum on the legislative history of the 1962 amendments, including both the term, "adequate and well-controlled," and the term, "substantial evidence." We would like to submit this memorandum for the record, if we could. It shows that Congress does not believe double-blind tests are essential for "substantial evidence"—that the Congress was well aware that for some diseases and drugs there were at that time no satisfactory double-blind tests.

With respect to "substantial evidence," one of the very illustrations given at the time was the case of rheumatoid arthritis, where doctors continued to disagree as to which drug was the preferred drug, if any, for treating the disease.

Senator NELSON. That memorandum will be accepted for the record.

(The document referred to follows:)

LEGISLATIVE HISTORY

OF THE

DRUG AMENDMENTS OF 1962

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MEANING OF "SUBSTANTIAL EVIDENCE" AND "ADEQUATE AND WELL-CONTROLLED INVESTIGATIONS" AS USED IN SECTION 505(d)(5) OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT.

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Under the Drug Amendments of 1962, Section 505(d) of the Federal Food, Drug, and Cosmetic Act was amended to include a new "effectiveness" test with those which a new drug application must pass before it is approved.

This test is set forth in Section 505(d)(5), which provides that the Secretary shall issue an order refusing to approve a new drug application if he finds that:

"[E]valuated on the basis of information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof. . . ." Sec. 505(d), Federal Food, Drug, and Cosmetic Act, as amended, 21 U.S.C. 355(d).

If the Secretary finds that the above provision, and others, do not apply, "he shall issue an order approving the application."

The 1962 Amendments also added the following definition of the term "substantial evidence":

"[T]he term 'substantial evidence' means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or the proposed labeling thereof." *Ibid.*

There has been some discussion in these hearings about the meaning of the terms "substantial evidence" and "adequate and well-controlled investigations" which were introduced by the 1962 amendments.

The testimony of Dr. William M. O'Brien has particularly focused upon these statutory terms. Dr. O'Brien, in his prepared statement at page 2, stated that:

"The 1962 Kefauver-Harris amendments specifically stated that a manufacturer must support claims of efficacy of a drug with 'subtantial evidence.' The law defines this as 'adequate and *well controlled* investigation by experts qualified by scientific training and experience to evaluate effectiveness.'

"I define the word control as a standard of comparison for checking inferences in an experiment—in other words, in testing a drug one group is treated, and its response is compared to the response of an identical group which receives a standard of comparison—a standard treatment or a dummy (placebo). I believe this was the exact intent of Congress in the 1962 amendments. . . ."

Furthermore, at page 5 of his prepared testimony, Dr. O'Brien stated that:

"The only scientifically sound method for drug testing is the controlled double blind trial which eliminates both positive and negative bias and uses a comparison—either a placebo or a standard drug."

Dr. O'Brien's views on the meaning of the pertinent statutory terms were underscored in his oral testimony before this committee, in response to a quetion by Mr. Gordon.

"Mr. GORDON. Is it your opinion, then, as I understand it, that before a drug is approved by the FDA, controlled double blind studies should be conducted by objective sources? Is that correct?"

"Dr. O'BRIEN. Well, apparently it is not only my opinion but this is what the 1962 amendments said. . . ."

Although Dr. O'Brien conceded in his oral testimony that the 1962 amendments did not specifically require double blind investigations, it is apparent that Dr. O'Brien reads the statutory terms "adequate and well-controlled investigations" as synonomous with, and only with, controlled double blind studies. Dr. O'Brien also concludes that "substantial evidence" can only be produced by controlled double blind studies.

The words in the 1962 amendments of course do not state so precisely what constitutes an adequate and well-controlled investigation. We submit that the lack of such exactitude in the statute was deliberate, and that Congress intended flexibility in interpretation of the statutory terms.

As this submission will show, Congress was well aware of several important points when it enacted the terms "substantial evidence" and " adequate and well-controlled investigations" in 1962. Throughout the legislative debate, it was clear that these terms could have different content, depending upon the kind of disease under consideration. Rheumatoid arthritis received particular attention as a disease about which there is great dispute as to proper methods of diagnosis and treatment. The professional witnesses who testified in the Senate and House hearings did not suggest that there was any particular or exact way to measure the effectiveness of any particular drug. The entire course of the hearings instead established that a wide range of adequate and well controlled investigations and of professional opinion about what they prove can exist with regard to any drug, and that the 1962 amendments were not intended to require an either-or choice between differing schools of thought.

### LEGISLATIVE HISTORY

As introduced by Senator Kefauver on April 12, 1961, S. 1552 would have required the Secretary to refuse to approve a new drug application if he had insufficient information to determine whether the drug is "efficacious in use" under the conditions prescribed, recommended, or suggested in the proposed

labeling. 107 Cong. Rec. 5638. The original Senate bill did not consider the quantum of evidence necessary to establish sufficient information as to "efficaciousness," nor did it consider the manner in which such evidence should be assembled for presentation to the Secretary.

"SUBSTANTIAL EVIDENCE"

During the Senate hearings on S. 1552, the issue of the amount of evidence which would be sufficient to allow the Secretary to determine "efficaciousness" was thoroughly considered.

On July 19, 1962, after the Senate hearings on S. 1552, the Senate Committee on the Judiciary reported out a revised bill. At that time, the previous language regarding "efficacious in use" was amended to provide that the Secretary should refuse to approve a new drug if:

"[T]here is a lack of substantial evidence (including clinical evidence), supported by investigations of experts qualified by scientific training and experience to evaluate the effectiveness of drugs, that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof . . ."

The thorough debate on the issue of what would satisfy "substantial evidence" of effect resulted in a firm consensus, which is illustrated in the Senate Report.

"The term 'substantial evidence' is used to require that therapeutic claims for new drugs be supported by reliable pharmacological and clinical studies. When a drug has been adequately tested by qualified experts and has been found to have the effect claimed for it, this claim should be permitted even though there may be preponderant evidence to the contrary based upon equally reliable studies. There may also be a situation in which a new drug has been studied in a limited number of hospitals and clinics and its effectiveness established only to the satisfaction of a few investigators qualified to use it. There may be many physicians who would deny the effectiveness simply on the basis of a disbelief growing out of their past experience with other drugs or with the diseases involved. Again, the studies may show that the drug will help a substantial percentage of the patients in a given disease condition but will not be effective in other cases. What the committee intends is to permit the claim for this new drug to be made to the medical profession with a proper explanation of the basis on which it rests.

"In such a delicate area of medicine, the committee wants to make sure that safe new drugs become available for use by the medical profession so long as they are supported as to effectiveness by a responsible body of opinion.

"In his testimony supporting new authority for the Food and Drug Administration to pass on the effectiveness of new drugs before they are marketed, Secretary Ribicoff said that questions of 'relative efficacy' are not here involved, and that the requested authority 'would not require a showing of relatively greater efficacy than that of other drugs' (hearings, pt. 5, p. 2585)." S. Rep. No. 1744, 87th Cong., 2d Sess., p. 16.

The views of Senators Dirksen and Hruska, in the same Senate Report, confirm the view that substantial evidence can be less than preponderant evidence, and that room for minority opinions should exist.

"We wish to augment the discussion of the effectiveness of drugs as now provided for in the majority report. Two quotations from the Senate hearings on S. 1552 are especially notable. Eugene N. Beesley, president of Eli Lilly & Co., and chairman of the Pharmaceutical Manufacturers' Association, in his testimony before the Senate Antitrust and Monopoly Subcommittee at page 1998 stated:

" 'Also, it is our understanding that the manufacturer would be required to provide only substantial evidence that a drug produces the effects claimed for it. He would not be expected to prove that scientific opinion was unanimous, or even preponderant, in supporting the effectiveness of a drug. Thus, if a number of tests by competent clinicians show that in well-conducted clinical trials a drug produced the claimed effect on their patients, the drug would not be barred simply because other tests did not produce the identical results with different patients. In other words, a drug should be made available for the benefit of those patients for whom the individual physician thinks it would be useful.

" 'In the entire realm of medical science nothing is more difficult and more subject to honest differences of competent opinion than the determination of the therapeutic merits of drugs in human beings. Experts have sharply opposed

views concerning the proper treatment of many common diseases, and each school of thought has a strong champion. Many highly qualified physicians are convinced of the value of corticosteroid drugs in relieving rheumatoid arthritis; there are others who prefer aspirin; still others are proponents of a variety of other treatments . . .'

"At the completion of Mr. Beesley's statement, Senator Kefauver agreed with Mr. Beesley's determination of effectiveness in the following language found on page 2007 of the printed hearings.

" 'You agree, as we have also recommended, that the Food and Drug Administration should pass upon whether a new drug is substantially efficacious for the claims made for it by the manufacturer, and that is the intent of the language in the bill, although it may need some clarification. Your language was "substantial evidence not only that the drug is safe but also that it produces the results claimed." That is exactly what we had in mind in connection with that.

" 'Mr. BEESLEY. Mr. Chairman, I think we agree in the principle involved. The precise language of the statute is very important, bearing, of course, upon the interpretation that will be given to the statute, and the points which we have made here we think further clarify the statute and are exceedingly important to the way in which it will be administered.

" 'Senator KEFAUVER. I would certainly accept, as far as I am concerned, your further statement on page 10:

" ' "Thus if a number of tests by competent clinicians show that in well-conducted clinical trials a drug produced the claimed effect on their patients, the drug would not be barred simply because other tests did not produce the identical results with different patients," the key words are "well-conducted clinical trials by competent clinicians." I agree with that.

" 'Mr. BEESLEY. Mr. Chairman, the key words here from our point of view are "substantial evidence." What do we mean by efficacy? What do we mean by effectiveness of a drug? And that is the thought, the new thought, that we are producing there, which, may I submit, is exceedingly important.

" 'Senator KEFAUVER. Substantial evidence is required in most Government procedures and that is inherent in what we have in mind with the bills.' " S. Rep. No. 1744, 87th Cong. 2d. Sess., pp. 57–58.

After further consideration, on August 21, 1962, the Senate Committee on the Judiciary issued a second part to its earlier report. At that time, the Senate bill was further amended to include the effectiveness test, including the definition of "substantial evidence" that was ultimately enacted into law. The August 21, 1962, Senate Report further elaborated what was meant by "substantial evidence."

"The proposed committee amendment clarifies and strengthens the previously reported bill by restating and carefully defining the quality and quantum of evidence which the Secretary must find to exist as a basis for clearance of the drug or for withdrawal of a previously approved new-drug application. In the course of committee deliberations a distinction evolved, in this connection, between two tests—the 'proponderant evidence' tests and the 'substantial evidence' test as now specifically defined. Under the former a claim would not be accepted under the new-drug section unless it represented the preponderant view of experts qualified by training and experience in the subject that the claim was supported. The committee recognizes that in the difficult area of drug testing and evaluation there will frequently, if not usually, be a difference of responsible opinion. The committee feels that the existence of such a difference should not result in disapproval of a claim of effectiveness if it is supported by substantial evidence defined in the manner set forth below and evaluated by the Secretary in the light of all the information available to him at the time.

"As the result of subsequent study, a definition of 'substantial evidence' has now been added to the bill concerning what would constitute such evidence. The amendment provides that 'substantial evidence' means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. That is to say, a claim could be rejected if it were found (a) have the investigations were not 'adequate'; (b) that they were not 'well controlled'; (c) that they had been conducted by experts not qualified to evaluate the effectiveness of the drug for which the application is made; or (d) that the conclusions drawn by such experts could not fairly and

responsibly be derived from their investigations." S. Rep. No. 1744, Part 2, 87th Cong., 2d Sess. p. 6.

The Report of the House Committee on Interstate and Foreign Commerce [1] and the Conference Report [2] do not elaborate further on the substantial evidence concept.

The legislative history could not be more clear in establishing that Congress understood the wide range of opinion that exists in the medical profession as to the effectiveness of any particular drug. Thus, Congress provided a definition of substantial evidence which allows the Secretary to find that a drug's effectiveness is supported by substantial evidence even if that evidence is, in volume, outweighed by opposing views.

### "Adequate and Well-Controlled Investigations"

The issue of the manner in which an applicant should assemble evidence necessary to constitute "substantial evidence" was not directly in question during the hearings. The issue, however, was mentioned in debate as a necessary adjunct to the question of how much evidence would be substantial.

The Senate Judiciary Committee, in its second report, recognized that:

"[I]n the difficult area of *drug testing* and evaluation there will frequently, if not usually, be a difference of responsible opinion. The committee feels that the existence of such a difference should not result in disapproval of a claim of effectiveness if it is supported by substantial evidence defined in the manner set forth below and evaluated by the Secretary in the light of all the information available to him at the time." S. Rep. No. 1744, Part 2, 87th Cong., 2d Sess. p. 6 (emphasis added).

In the vast number of pages which the Senate hearings consume, there is only scant reference to the question of the correct methodology for testing drugs. The absence of long debate on this subject is probably best explained by Secretary Ribicoff's observation that the amendments did not "contemplate and basic changes in the established pattern of testing the effectiveness of drugs."

"Secretary Ribicoff. Let me make it absolutely clear that we are not dealing here with what some have called 'relative efficacy.' The claim has been made before this subcommittee that the proposed amendment would enable us 'to decide the relative or comparative efficacy of a new drug in terms of drugs already on the market,' or allow us to refuse clearance for a new drug merely because, in the Food and Drug Administration's opinion, it is 'not the most efficacious drug for the purpose intended or was not as efficacious as one might ideally wish.'

"The bill furnishes no basis for such apprehensions. The proposed amendments would merely require a showing that the new drug described in the application is safe for use and is effective in use, under conditions prescribed recommended, or suggested in the labeling thereof. This would not require a showing of relatively greater efficacy than that of other drugs. It would merely require that a drug claimed to be effective for a particular purpose has been demonstrated *by sound scientific procedures* to be effective for that purpose. In short, it must live up to the claims made for it.

"It should also be pointed out that this proposal *does not contemplate any basic change in the established pattern of testing the effectiveness of drugs. . . .*" Testimony of Secretary Ribicoff before Senate Subcommittee on Antitrust and Monopoly, September 13, 1961, pp. 2585–2586 (emphasis added).

The subject itself is extremely complicated, as the testimony of Dr. David P. Barr illustrated:

"Every one who has tried to test drugs knows how extremely difficult it is to determine whether a drug is or is not effective, and the establishment of its effectiveness requires extensive facilities and team efforts which may require joint services of many participants, physicians, certainly, and pharmacologists, and others." Testimony before Senate Subcommittee on Antitrust and Monopoly, July 19, 1961, p. 259.

That differences of opinion among responsible clinicians as to effectiveness and testing occur frequently was amply demonstrated in the course of the legislative history.

"The committee recognized that legitimate difference of opinion may exist among responsible clinicians with respect to the effectiveness of a particular

[1] H.R. Rep. No. 2464, 87th Cong., 2d Sess.
[2] H.R. Rep. No. 2526, 87th Cong., 2d Sess.

new drug. Experience has shown that a majority of so-called experts has often been wrong in initially condemning a new drug, just as new inventions in other fields are usually regarded with skepticism and often with hostility. The new ground for rejection of a new drug application is therefore expressed in terms of 'a lack of substantial evidence,' evaluated on the basis of all the information before him, that the drug will have the effect claimed for it. The term 'substantial evidence' is defined in terms of the kind and quality of the investigations that must support the claims." Statement by Senator Eastland, 108 Cong. Rec. 16304 (August 23, 1962).

"In the entire realm of medical science nothing is more difficult and more subject to honest differences of competent opinion than the determination of the therapeutic merits of drugs in human beings. Experts have sharply opposed views concerning the proper treatment of many common diseases, and each school of thought has strong champions. Many highly qualified physicians are convniced of the value of corticosteroid drugs in relieving rheumatoid arthritis; there are others who prefer aspirin; still others are proponents of a variety of other treatments." Testimony of Eugene N. Beesley before Senate Subcommittee on Antitrust and Monopoly, December 7, 1961, p. 1998.

"Mr. BEESLEY. . . . By 'substantial' evidence we mean less than preponderant, or conclusive, evidence.

"We mean that, where a reasonable number of clinicians have conducted tests which show that a drug has the claimed effects, FDA should permit the drug to be marketed even though other tests by other clinicians do not show the same effects. This is a case of difference of medical opinions, which, as Dr. Hussey had said, should not be resolved by the fiat of any authoritarian body but by each physician in his own practice.

"Senator KEFAUVER. All right.

"Then we seem to be pretty well agreed all the way around, sir." *Id.*, at p. 2012.

Only at a few points in the hearings was there focus upon "controlled" investigations. When Dr. Charles May, Professor of Pediatrics at New York University, testified, the concept of a controlled examination was used to distinguish the facilities available to the individual physician. See Hearings before the Subcommittee on Antitrust and Monopoly, July 18, 1961, p. 204.

The same distinction was emphasized by the testimony of Dr. Louis Goodman, Professor of Pharmacology at the University of Utah. See *Id.*, at pp. 217, 243.

The one witness before the Senate hearings who stated that he had "often testified to the importance of double-blind controlled trials in clinical research" insisted that his statements did not constitute a demand for such trials on all new drugs. The witness, Dr. Louis Lasagna, asserted that:

"The emphasis should be on scientifically acceptable evidence, of whatever quality and quantity required to give a reliable answer to the questions posed concerning the drug's effects." Hearings before the Senate Subcommittee on Antitrust and Monopoly, July 19, 1961, pp. 282–283.

In discussing the subject of phraseology, Dr. Lasagna concisely stated a view which permeated the hearings: "I would hope that if such a bill were passed, that there would be every opportunity for a flexibility of interpretation." *Id.*, at p. 288.

The legislative history also includes a statement by Dr. I. S. Ravdin introduced into the hearings before the House Committee on Interstate and Foreign Commerce. The statement was signed by a large number of doctors from all parts of the country, including Drs. Michael E. DeBakey and Paul Dudley White. The statement made the following points:

"(1) Medicine is in part an uncertain science. There is at the present time no precise method for determining absolute efficacy or effectiveness. Such a determination must frequently be based upon medical opinion, and medical opinion is not always unanimous.

"(2) Physicians very often have differing opinions about the usefulness of an agent in treating a particular disease. Many eminent physicians, for example, favor the use of the corticosteroids in the treatment of rheumatoid arthritis, but others believe that the corticosteroids are not the drug of choice for this purpose.

"Under such circumstances, it is difficult, if not impossible, to determine the exact effectiveness of the corticosteroids in treating rheumatoid arthritis. . . ." Hearings before House Committee on Interstate and Foreign Commerce, August 20, 1962, p. 207.

Perhaps the most complete discussion of the problems involved in the working of the substantial evidence standard and the methodology of investigating drugs

was by Dr. Theodore Klumpp, the President of Winthrop Laboratories, before the House Committee on Interstate and Foreign Commerce.

Dr. Klumpp testified that:

"Despite advances in scientific techniques, therapeutic representations and claims remain essentially matters of opinion. Different schools of thought with respect to the proper treatment of various diseases are prevalent and sometimes completely contradictory. Not infrequently, it takes years and sometimes decades of widespread clinical experience to evaluate the true or relative merit of a drug in given conditions. From such long experience, a medical consensus generally emerges, but even then some qualified physicians refuse to go along with their colleagues. . ."

"At the present time, there are sharply opposed views among experts concerning the proper treatment of many common diseases. Rheumatoid arthritis is such a condition. There are highly qualified physicians who favor the use of corticosteroid drugs. There are others who feel that the employment of the corticosteroids does more harm than good and that the only meritorious drug is aspirin. Still others are proponents of, respectively, Butazolidin, gold salts, and antimalarial drugs such as quinacrine, chloroquine, and hydroxychloroquine. The use of pyramidon, or large doses of vitamin D, still has adherents, and particularly among clinicians in foreign countries. The reaction of experts to any new drug offered for the treatment of rheumatoid arthritis will inevitably be conditioned by the school of thought to which they happen to adhere. By whose advice is FDA to be guided in the evaluation of a new drug for this condition?"

[Dr. Klumpp then considered similar problems with drugs for epilepsy, mucous colitis, and the common cold.]

The above specific illustrations are only a few of the many that can be cited to show that—

(a) The determination of the effectiveness of a drug is always difficult and sometimes cannot be achieved except by the test of time and widespread use.

(b) Therapeutic representations are essentially matters of opinion.

(c) Differing schools of thought frequently exist concerning therapeutic issues, and the school which favors one theory as to the nature and treatment of disease tends to be skeptical of the drugs advocated in opposing schools. Moreover, medical opinions as to effectiveness of a particular drug can differ widely among equally qualified physicians because of basic differences in opinion relating almost entirely to questions of diagnosis and preferred method of treatment, as well as differences as to the comparative efficacy of one member of a class of drugs in relation to others or the mode of action of a particular drug in the complex body mechanism. Hearings at pages 232–235.

## Conclusions

The legislative history of the 1962 amendments establishes quite clearly that Congress did not intend "substantial evidence" to mean a preponderance of evidence. Nor did Congress expect the medical profession to arrive at single conclusions about drugs and treatments. Rather than enacting standards which would require exact proof and which could leave no room for minority opinions, Congress explicitly favored concepts of flexibility which could accommodate the range of responsible professional opinions.

Had Congress disagreed with Secretary Ribicoff's view that the amendments would not change the established pattern of testing drugs, there would have been more discussion on the subject of the methodology of drug testing. But Congress did not take issue with the Secretary's assessment of the law, and the legislative history shows that Congress intended to maintain flexibility in the area of drug testing, just as it so intended with the concept of substantial evidence.

The substantial evidence standard itself, as enacted, requires a comparable openness with regard to differing opinions in the area of what constitutes adequate and well-controlled investigations. It may well be that certain drugs for some kinds of diseases are better investigated with some techniques than with others. A substantial difference of opinion might exist about which methods of testing should be applied in different circumstances. It would be wholly inconsistent with the clear and unambiguous intent of Congress with respect to the substantial evidence standard to conclude that only certain kinds of tests could produce such evidence when there is a body, however small, of reliable professional opinion to the contrary. An "adequate" test for one situation might be inadequate in others; the kinds of controls possible in one instance might be impossible of achievement, or less meaningful, in aonther; and even the qualifications of

persons performing clinical investigations can be matters for honest differences of opinion.

The substantial evidence standard itself concedes that room must be left open for well-founded differences of opinion. That standard would become rigid, and precisely what Congress expressly intended to avoid, if one point of view about the proper methods of testing drugs were allowed to dominate and exclude other points of view. As long as a sound professional difference of opinion about the merits of different methods of drug investigation exists with regard to particular drugs, it is clear from the legislative history of the 1962 amendments that a single view, especially one which seeks exact answers in inexact areas, cannot properly be considered the "only scientifically sound method for drug testing."

Senator NELSON. I have a letter that I received from the Department of Health, Education, and Welfare, signed by Theodore Cron. Mr. Cutler has a copy of this letter as does the press. I will ask to have it put into the record at the appropriate place after yesterday's testimony.

Mr. GADSDEN. I might ask, are we going to revert for a moment to—you are putting Mr. Cron's letter into the record? I am asking the privilege now or later of talking on the substance of what is going in the record.

Senator NELSON. All right. The appropriate place for this, I would assume, is after yesterday's testimony.[1] If you would like to comment on it now, I will ask that your comments be placed in the record after this letter.

Mr. GADSDEN. Yes, sir.

Senator NELSON. Or, if you wish to submit something later that you will prepare, you may do so.

Mr. GADSDEN. I would like to comment here, and then we can decide into what degree of detail you want to go, sir.

First, I think it is important to record that at the time of the release of indomethacin by the Food and Drug Administration, I, as the chief executive officer of the company, issued an order that under no circumstances were we to seek any lay publicity in connection with it—its benefits, or anything else. I assume, lest we have any confusion here, that you are alluding to the same Mr. Cron letter which I have in front of me?

Senator NELSON. It has no date.

Mr. GADSDEN. The first sentence begins "You will recall that Dr. McCleery."

Senator NELSON. Yes, that was delivered here this morning at about 10:45. I am referring to that letter.

Mr. GADSDEN. I would like to make a statement on that, sir.

A free-lance writer and TV fellow, Mr. Goldman, called our director of public relations, Mr. Fletcher. Mr. Goldman said his wife had suffered from tennis elbow and had been unable to play and that her doctor prescribed "Indocin" and it worked miraculously. He had checked around and found a lot of doctors who were using it effectively, and said he was going to write a story about it. He was upset with the company, namely Merck & Co., for not telling people about the drug, and he asked the company for background materials, which we sent him.

He was told that tennis elbow is not an approved claim, and he was also told why the company had elected not to publicize the drug.

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[1] See p. 3294, supra.

Several weeks ensued. Mr. Goldman did not visit the company or talk with anyone in the company about the drug or the story he was writing. Then he called Mr. Fletcher again, said his story was essentially finished, said he had a lot of anecdotes to liven it up, and asked if the company could provide additional anecdotal material to personalize it still further.

Mr. Fletcher supplied him with four or five letters from our files, deleting the names of the correspondents. They dealt with approved claims.

There is, as I understand it—and I will check it if this is material—an attribution of a nonapproved claim in the article. This was not among the cases supplied to him by Merck & Co.

Senator NELSON. What is an approved claim?

Mr. GADSDEN. The four that were enumerated earlier, sir, which have to do with various aspects of arthritis.

Senator NELSON. What is an approved claim?

Mr. GADSDEN. When we make a submission to Food and Drug, as we discussed earlier, we request—let us call them indications. Perhaps that is a more precise term than "claims," meaning for what disease conditions use of the drug is indicated. The FDA must approve these indications. The thrust of the criticism is that we were seeking through lay publicity to publicize and popularize the use of this drug for conditions—indications—which had not been approved.

Senator NELSON. I see.

Mr. GADSDEN. I will continue, sir, if I may.

We were altogether unprepared for the appearance of this Pageant article, with the name of the drug as the title of the article, and a subtitle that enumerated its value for a number of conditions for which we had no claim.

Senator NELSON. That will go into the record immediately following this letter so that they will both appear in the appropriate place in the record.

Mr. GADSDEN. Counsel reminds me, sir, that contrary to the statement that is contained in the letter which has gone into the record, Mr. Fletcher did not see the article until after it was printed.

Mr. CUTLER. Also, Mr. Chairman, the article itself, as I understand it, refers to one letter which the author says he got from Merck relating to the use of the drug for an unapproved claim. No such letter was furnished by Merck.

Senator NELSON. Thank you.

Again, thank you, Doctor.

Dr. LAWRASON. Before introducing the two outside witnesses, Dr. Calabro and Dr. Smyth, the two physicians, who will summarize their views and the views of physicians who are treating patients with arthritic disorders, I have with me an even broader representation of medical opinion concerning the values and limitations of indomethacin that we hereby submit to you with the request that it be made part of the official record.

Senator NELSON. Would you identify what it is?

Mr. CUTLER. It is this green folder which you should have up there, Senator Nelson.

Dr. LAWRASON. This exhibit, Mr. Chairman, consists of letters and telegrams from distinguished rheumatologists and experienced physi-

cians across this country and around the world. I want to tell you how they came to us.

When we learned that this committee was planning to hold hearings on indomethacin, we asked a number of investigators who we knew had worked with indomethacin to give us, so we could give to you, their frank appraisal of the drug. Their names and positions and reputations speak for themselves, and also bespeak the fact they would support no drug and no drug company if the facts did not warrant support. We are submitting here every communication we have received, exactly as it came to us. When the committee examines this documentation, it will find it represents the full range of medical and scientific opinion. Some investigators have found indomethacin very useful, some have found it useful in some conditions and not in others; some have found it only marginally useful.

This sample of professional judgment on the part of physicians using indomethacin in their practice reinforces our conviction that when properly used, it is a safe and effective drug that benefits hundreds of thousands of patients. I would like to ask your permission that these letters and telegrams be put in the record.

Senator NELSON. You want it in the record at this point?

Dr. LAWRASON. Yes, sir.

Senator NELSON. They will be put in the record at this point.

(The documents referred to follow:)

RECEIVED FROM DR. F. DUDLEY HART, WESTMINISTER HOSPITAL, ENGLAND

In the light of your extensive experience in the management of diseases for which indomethacin is indicated—

(1) Do you consider that the introduction of indomethacin has contributed to the management of your patients? Yes.

(2) Do you find that indomethacin enables you to obtain results in some of your patients that were difficult to obtain prior to its introduction?

(3) If so, can you define those areas in which the drug has been most helpful?

(a) In acute gout, I would rate it the drug of first choice. Good as are the pyrazoles, we find their action slightly slower, and in this disease a quick result is all-important. Our order of preference is indomethacin first, phenylbutazone and oxyphenbutazone second and colchicine third.

(b) In ankylosing spondylitis, although aspirin is suitable for the mild cases, taken as required, if larger regular anti-inflammatory dosage is necessary, few men doing active work, as are 80% of those attending our clinic, can (or will) take such dosage, and much perfer indomethacin or the pyrazoles. We consider the last two equally effective, but the real but rare danger of blood dyscrasias with the pyrazoles now leads us to try indomethacin first, and only proceed to the pyrazoles if results are unsatisfactory. We try flufenamic acid next, as we find it less effective.

(c) We find indomethacin helpful in half our cases of rheumatoid arthritis, and consider its anti-inflammatory action less than that of the corticosteroids or corticotrophin, but greater than that of the other non-steroidal anti-inflammatory agents. The trial and error method which is necessary in the treatment of rheumatoid arthritis must leave some choice to the patient, who finds large numbers of aspirin tablets tedious to take in many instances, and they will not, and do not, take them. We start with aspirin and only go on to other drugs if therapeutic results are poor to toxic effects troublesome. A number of patients with rheumatoid arthritis prefer indomethacin and do better on it than any other agent. Because of the unwanted endocrine effects, we use corticosteroids only in small dosage in selected patients.

(d) We find indomethacin a useful drug in Reiter's disease.

(e) In osteoarthrosis of cervical spine and hip, we find indomethacin a useful substitute for the pyrazoles, which, though very useful, have the danger of causing blood dyscrasias, though rarely. This is the main reason for preferring indomethacin to the pyrazoles, for in most other respects the drugs are equally effective in the same group of disorders.

LOVELACE CLINIC,
*Albuquerque, N. Mex., April 19, 1968.*

Dr. MAX TISHLER,
*Merck Research Laboratories, Merck & Co., Inc., Rahway, N.J.*

DEAR DR. TISHLER: I understand that there are to be hearings very soon in Washington regarding the efficacy of certain drugs which have been marketed in recent years. Among these I understand that Indocin is one to be considered. I should like to state that I have used Indocin since it first became available, even before it was marketed and that in selected instances I feel that this is a very notably effective and safe drug. I feel that its indiscriminate use, just as the indiscriminate use of any medication without adequate reason, is unwarranted. However, in my opinion, it is the drug of choice in such cases as rheumatoid spondylitis and degenerative arthritis involving the spine and hips especially. Its use in gout is according to literature, very definitely an appropriate measure and with less drastic effects than some of the other medications that are available for treatment for this acutely painful process. My own experience is no extensive enough with this particular problem to warrant comment.

I feel that much of the "poor publicity" which has surrounded Indocin is a result of its indiscriminate use in many instances where it has not been warranted. In my own experience, it is not nearly as effective in peripheral rheumatoid arthritis as it is in the other instances mentioned above. So far as its toxicity is concerned, I feel that the serious problem has to do with gastrointestinal irritability, the symptoms of which are quite readily apparent and if both doctor and patient are aware of this problem, serious trouble can be easily avoided. I have not yet run into any other significant toxic reactions to this drug that would indicate any serious effects on health.

I feel that from the standpoint of all available information in the literature that merits consideration there is adequate information regarding this drug, that further investigational procedures would be a waste of time and a waste of money and would deprive certain patients from the use of a drug that has very definite value to them.

Very truly yours,

C. M. KEMPER, M.D.

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RICHARD W. PAYNE, M.D.
*Oklahoma City, Okla., April 20, 1968.*

DEAR DR. TISHLER: I hear that there is some movement afoot to curtail the use of Indocin. If this news is correct, I would like to put myself on record as finding Indocin indispensable in my practice of rheumatology. The agent has a relatively low order of serious side effects and is of undoubted value in the practical long-term management of many patients with various types of arthritis.

While there are double-blind studies which question the efficacy of Indocin—I am equally prone to question the validity of such studies that I have seen, including my own.

After 6 yrs. experience with Indocin I have no doubt that it is a valuable therapeutic agent in a group of diseases notoriously difficult to treat. That we don't know exactly how it produces its beneficial effects is no fault of the drug.

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MEMORIAL HOSPITAL,
*Charleston, W. Va., April 20, 1968.*

MAX TISHLER, Ph. D.,
*Merck Research Laboratory, Merck & Co., Inc., Rahway, N.J.*

DEAR DR. TISHLER: It is my understanding that you and your associates will be appearing before a Congressional Hearing very shortly to engage in dialogue and data gathering regarding indomethacin and its clinical benefits in the treatment of particularly rheumatoid arthritis, as well as the double blind method of drug evaluation. I thought that you might, therefore, be interested in some of my personal conclusions regarding these two issues based upon my experience with double blind study using Indocin and placebo, as well as experience with indomethacin prescribed to rheumatoid arthritis patients these past three years.

Regarding the double blind method in evaluating drugs for rheumatoid arthritis, I think there is universal agreement that this is still not the answer to evaluation of drugs for this disease, but it is the best we have available at this time. In the first place, rheumatoid arthritis is so variable from day-to-day, week-to-week, and month-to-month that any change short of virtual remission of the disease must be submitted to the mathematical probability wherein the results

are trends and not conclusive evidence. Secondly, in the measurement of activity of disease in rheumatoid arthritis there is also apparent universal agreement that there is still no satisfactory means of doing this. Lansbury's criteria, measurement of the inflammation of the joints, the swelling, mobility, general well-being of the patient, etc., all have a certain subjective element and a wide standard deviation. Typical example is the objective measurement of the knuckle circumference or the knee circumference. This requires no judgment on the part of the patient; however, in order to arrive at a probable accurate mathematical figure, the measurement of his joint must be done by the same person at each observation and several times each observation, even then, the other variables of swelling of the extremities due to causes not related to rheumatic disease are never determinable. This same problem can be applied to all the other objectives and are certainly applicable to the subjective measurements for rheumatic activity. But, I repeat, that this is all that we have at this time and I eagerly search the literature and discuss with my colleagues any developments in this area.

Regarding Indocin and its effectiveness—Indocin is presented as an anti-inflammatory drug and is ranked with aspirin, phenylbutazone, adrenocortical steroids and lesser anti-inflammatory agents. Whether antimalarials are actual anti-inflammatory in the sense of these drugs has never been really determined I think organic gold salts are not considered primarily anti-inflamatory. Of all these drugs, gold in my impression and the impression of the literature has been the one that has stood the test of time and double blind study as being *probably* causative in the induction of remission in rheumatoid arthritis. Thus, indomethacin, an anti-inflammatory drug, cannot offer the promise of remission, but rather a reduction in pain and swelling, and perhaps a delay of the destructive consequences of sustained synovitis. This latter has not been proven even for aspirin and definitely has not been proven for steroids. Steroids may prevent ankylosis and result in a mobile destroyed joint, which is more amenable to surgical therapy. Perhaps a good and consistent use of other anti-inflammatory drugs like Indocin would do the same and have this benefit.

My colleagues in West Virginia, realizing my interest in rheumatology and my experience with the use of indomethacin have asked me—what do I think of the drug? I tell them at this point that indomethacin is a definite anti-inflammatory drug and it is as good as the other anti-inflammatory agents mentioned above. The next question is—why should I use it above the others? I refer them to the serious side effects of phenylbutazone and adrenal steroids, which brings us down to the discussion as to whether it should be used in addition to or rather than salicylates; and this apparently is the issue that has appeared in the literature. I then say that effective salicylate therapy demands the continuous administration of sub-tinnitis dosage of the drug and this means that the patient must be experiencing from time to time tinnitis as well as diaphoreasis, cerebral symptoms, etc., and requires a dosage from 12 to 18 tablets a day. I submit that the problem of getting the patient to take that number of tablets every day for years is in some cases insurmountable; but the same can be accomplished with approximately 6 capsules of Indocin a day. This is then the current pragmatic feeling on my part regarding the use of indomethacin in the spring of 1968. We are currently in the process of retrospective analysis of patients treated 18 months or more with all the above drugs, singly or in clusters, including indomethacin. These are in the hands of our biostatistician and will be made available when completed.

Very truly yours,

DANIEL HAMATY, M.D., *F. A. C. P.*

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MEDICAL COLLEGE OF VIRGINIA,
*Richmond, Va., April 22, 1968.*

MAX TISHLER, Ph. D.,
*Merck & Co., Inc.,*
*Rahway, N.J.*

DEAR DR. TISHLER: It has recently come to our attention that in the near future inquiries will be held concerning the efficacy of Indocin (Indomethacin).

Indocin is no panacea in the treatment of rheumatoid arthritis but it definitely has a place in its treatment and in the treatment of other rheumatic disease such as gout, osteoarthritis, and ankylosing spondylitis.

The management of rheumatic arthritis involves a treatment program of some complexity. No rigid set plan of drug therapy should be followed. A program

which proves beneficial in one patient may not in another. If one medication proved effective in all patients, there would be no need for the long list of available medications. If one method of approach does not prove effective, another should be pursued.

Aspirin or some other salicylate preparation should be given initially in essentially all cases of rheumatoid arthritis. If after several weeks no clinical improvement is experienced, another agent should be added. We frequently use Indocin as the second agent and will continue to use it in this capacity. Also, we have found the drug to be helpful in selected cases of osteoarthritis, acute gouty arthritis, and ankylosing spondylitis.

Sincerely,

DUNCAN S. OWEN, Jr., M.D.,
*Assistant Professor of Medicine, Division of Connective Tissue Disease.*

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MEDICAL COLLEGE OF VIRGINIA,
*Richmond, Va., April 22, 1968.*

DR. MAX TISHLER,
*Merck Research Laboratories,*
*Merck & Co., Inc.,*
*Rahway, N.J.*

DEAR DR. TISHLER: It has come to my attention that there will be a Congressional Hearing regarding the efficacy of Indomethacin (Indocin) in the treatment of rheumatoid arthritis and related rheumatic disorders. My personal feeling about this drug is that it has a definite place in the treatment of rheumatoid arthritis and in certain cases has a very beneficial result. There have been certain side effects which prohibit its use, but none have been of a serious nature in my experience.

Many investigators state that "double blind" and "double blind crossover" studies are the only ways to properly evaluate the effect of a drug. It is my feeling this does not always hold true in the case of rheumatoid arthritis. Patients with rheumatoid arthritis will vary as to their physical abilities throughout the period of day's time and the natural history of rheumatoid arthritis with remissions and exacerbations are two factors which make the double blind study difficult to evaluate in this disease. If there were a more realistic method of evaluating efficacy or lack of same in the rheumatic diseases, this would be most helpful.

Yours sincerely,

ROBERT IRBY, M.D.,
*Associate Professor of Medicine,*
*Medical College of Virginia, Richmond, Va.*

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HOLBROOK-HILL MEDICAL GROUP,
*Tucson, Ariz., April 22, 1968.*

MAX TISHLER, Ph. D.,
*Merck Research Laboratory,*
*Merck & Co., Inc.,*
*Rahway, N.J.*

DEAR DR. TISHLER: Dr. Richard Smith telephoned me this morning asking me to write to you regarding my impressions about Indocin and my thoughts about double blind studies for evaluation of agents for treatment of rheumatoid arthritis.

First, in regard to Indocin, our group did conduct a clinical trial to study efficacy and toxicity before Indocin was marketed. These studies were limited prmarily to rheumatoid arthritis and unfortunately, did not show consistent results. There were a few patients who felt that Indocin gave them much more relief than other analgesics or anti-inflamatory compounds but we did not feel that the drug altered the course of the disease. We continue to use Indocin in a limited number of patients where they feel it has been of help to them. Unfortunately, a number of our patients were unable to tolerate the drug.

In regards to double blind studies with rheumatoid arthritis, it has been most difficult in our experience, to get a true assesment as to its efficacy. This is probably due to the fact that we have such a wide variation, not only in disease activity and extent, but also in patient variability in age, personality, motivation,

etc. We are now in the process of trying to improve our methods of evaluation through a system of gross measurements, correlating the subjective with the objective findings.

Trusting this is the information you desire, I am

Sincerely,

DONALD F. HILL, M.D.

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THE UNIVERSITY OF IOWA,
*Iowa City, Iowa, April 22, 1968.*

Dr. MAX TISHLER,
*Merck Research Laboratory,*
*Merck, Sharp & Dohme,*
*Rahway, N.J.*

DEAR DR. TISHLER: I am enclosing two of the Bulletins that we have written giving our experience with indomethacin.[1] You will notice that the last one was written in 1965.

Since that time we have continued to use indomethacin, particularly in rheumatoid arthritis, and are of the same opinion, namely, that this drug is a safe and effective anti-inflammatory medicament in the management of rheumatoid arthritis. Over the years we have used this drug only in conditions in which we could make a definite diagnosis, and from our past experience knew that it would be effective. These conditions were rheumatoid arthritis, gout, Reiter's disease, and a few cases of degenerative arthritis. We have not prescribed this drug in the conditions that are difficult to accurately diagnose, or in which we are limited only to the patient's response. These include low back pain, fibrositis, painful shoulder, and pains in elderly individuals which are, unfortunately, classified as osteoarthritis.

Most physicians are very impatient and think that an anti-inflammatory drug should relieve or cure a chronic ailment such as rheumatoid arthritis in a short period of time. We have found many patients who were on adequate treatment but still continued to have mild degrees of synovitis. The swelling caused by the synovitis results in pain which is difficult to control. When these people are given indomethacin, in addition to the treatment they are receiving, the synovitis gradually decreases, and improve clinically. This, however, may take several weeks rather than a few days. By the same token when we see a new rheumatoid we usually start them on salicylates and if we cannot hold them with this drug, we usually add indomethacin. A high percentage of the patients that we have do well, but a few continue to show intermittent exacerbations and must be given other drugs as well, including steroids, or gold, etc. If one of our patients has been on steroids, we will add indomethacin in an attempt to reduce the dose of steroids to a safe level. As you know, we believe that rheumatoid arthritics should not receive more than a total of 8 mg. of prednisone, or its equivalent in other steroids, per day. Indomethacin has helped us reduce the steroid dose and prevent many of the side-effects caused by the steroid.

Since 1965, our usual dose of indomethacin is 75 mg. per day. With this dose we see fewer side effects than we reported in the enclosed Bulletin. At times we may give 100 or 125 mg., but cut back as soon as the patient has dizzyness, muzziness, or other irrelevant effects. In our hands, indomethacin is a very safe drug.

I was surprised to hear that a Congressional Committee is investigating indomethacin. I suppose this has been started because of the some of the recent reports on the double blind studies. It is in these studies that one finds many of the loosely defined syndromes being treated, as well as rheumatoid arthritis. Most of these studies depend on the patient's own response to the drug given for a short period of time, usually about two weeks. It is difficult to determine the effect of indomethacin in the ill-defined syndromes. Even in rheumatoid arthritis we have seen severe and relentless progression of the disease despite every type of heroic therapy that we try. It is a well known fact that individuals with a high titer of the rheumatoid factor will have progression despite anything that you do. It is not unusual to see an individual with a very high titer have breakdown of the joints in the wrists and fingers, even though they are getting adequate physical therapy, adequate doses of salicylates, steroids, indomethacin, and/or gold. On the other hand, people who have a low titer may have a remission for long periods of time with little or no destruction of joints. In any double blind study, one has both types of patients, and therefore any drug will not work in

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[1] Retained in committee files.

some arthritics and will appear to be an excellent drug in others. We are very conscious of this as we try to separate these two groups and select the severe ones as candidates for prophylactic surgery (synovectomy, etc.).

In conclusion, our group at Iowa feel that we could not treat rheumatoid arthritics adequately without indomethacin.

Sincerely yours,

W. D. PAUL, M.D.

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PAUL YOUNG, M.D.,
*Asheville, N.C., April 22, 1968.*

Dr. MAX TISHLER,
*Merck Research Laboratory,*
*Rahway, N.J.*

DEAR DR. TISHLER, I have been in the full time practice of rheumatology as a private practitioner since 1958. I believe that I am one of the very few physicians in the country who is in this position of making a full time professional activity out of the treatment of arthritis. Over half of my practice consists of patients with rheumatoid arthritis and I am treating approximately 300 such patients all the time for the last five to ten years.

I have been actively engaged in the evaluation of new drugs for the treatment of arthritis and was doing this in practically all of my patients in the period of 1960 to 1963. I discontinued these endeavors in 1963 because of the enormous amount of paper work which was generated by the law which was passed in 1962 where you had to prove that you were taking the same precautions we had been taking all the time. During the period of 1960 to 1963 I was engaged in the evaluation of 18 different drugs in the treatment of arthritis on some 3000 patient/drug combinations.

I have been quite familiar with the work of the committee on cooperative clinics of the A.R.A. since 1960. It was at my suggestion that the CCC engaged in the study of variability in rheumatoid arthritis in about 1963. I am personally acquainted with well over half of the physicians involved in the CCC studies and I am quite familiar with their drawbacks and limitations.

I am not particularly enthusiatic about the use of Indocin in rheumatoid arthritis because I feel that this has only analgesic and anti-inflammatory effect and prefer to use compounds such as gold and the anti-malarials for the long term treatment of this disease. However it is beyond any reasonable doubt that Indocin does give effective relief of the symptoms of rheumatoid arthritis and in some patients this is the most effective remedy of its type on the market. Probably aspirin would do just as good a job if patients could take 30 aspirin a day, but in my experience most patients cannot take 12 aspirin a day on a regular basis whereas many can take Indocin. It is ridiculous to argue that Indocin is no better than aspirin when many patients cannot take aspirin.

With respect to the recent questions that have been raised by the CCC trials of Indocin, I would like to say that under the circumstances of these trials the types of patients used would not very well demonstrate the effect of Indocin. Due to the nature of the disease, rheumatoid arthritis, Indocin is most effective in patients who have not developed joint deformities and secondary complications of the disease due to anatomical damage. If this study had been confined to patients without deformity and with most of their symptoms being due to the pure inflammatory effects of arthritis there would be in my mind, absolutely no question but that Indocin would have been shown to be an extremely effective drug for relief of inflammatory symptoms due to rheumatoid arthritis.

For physicians who are thoroughly and professionally acquainted with the nature of rheumatoid arthritis it is not necessary to do the "double blind" studies in order to tell whether a drug is effective or not. It certainly is necessary to do this type of study in order to tell whether one drug is more effective than another drug in a *similar* type of patient.

In conclusion, I would like to state that the recent questioning of the value of Indocin in rheumatoid arthritis merely illustrates the ignorance of the people asking the question and the lack of familiarity with the nature of the disease, rheumatoid arthritis, and the proper precautions to be evaluated in judging therapeutic efficacy.

It would be a great disservice to the public at this time to raise any question which could lead to the withdrawal of Indocin for treatment of patients with rheumatoid arthritis. The drugs we have to use in treating rheumatoid arthritis are not as good as we would like to have but there are some patients who desperately need each and every one of them.

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ARTHUR DOBKIN, M.D.
*Akron, Ohio, April 22, 1968.*

Dr. MAX TISHLER,
*Merck Research Laboratories,*
*Merck & Co., Inc.,*
*Rahway, N.J.*

DEAR DR. TISHLER: I am one of a few physicians in this metropolitan area who have been interested in and practicing Rheumatology for a number of years. I have used one of your drugs, Indocin, ever since it was released several years ago. In my experience with this drug, I find that it has a useful place in the therapy of arthritis. I fully realize that it has no curative effects, nevertheless, I have found "Indocin" to be beneficial in a selected and limited number of arthritis patients. It has been effective in relieving the symptoms of a number of patients with Rheumatoid Arthritis, Gouty Arthritis, as well as Osteoarthritis and Rheumatoid Spondylitis.

"Indocin", like many other medications now used in Arthritis, none of which are curative, will therefore have a place in the treatment of the Rheumatic Diseases in selected cases—at least until such time as newer and more effective medications are available.

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MAYO CLINIC,
*Rochester, Minn., April 22, 1968.*

MAX TISHLER, Ph. D.,
*President, Merck Sharp & Dohme Research Laboratories,*
*Rahway, N.J.*

DEAR DR. TISHLER: It is my understanding that a congressional hearing is soon to be held in which the efficacy of indomethacin may be challenged. I do not know the basis for this contest but if the opportunity presents itself, I would be pleased to have you convey my opinion that indomethacin has served a useful function therapeutically. The record clearly shows that it has been adequately tested on an experimental basis prior to its introduction for clinical usage and that widespread clinical trial has indicated an acceptable risk of occasional intolerance on the part of certain patients. It should be noted, however, that all known anti-inflammatory drugs seem to have a tendency to gastrointestinal bleeding but that this does not seem to be an overriding interference to the use of anti-inflammatory drugs in general. As a matter of fact, the public interest would not be served by the elimination of anti-inflammatory drugs.

I feel further that the medical profession has been amply instructed in the proper usage of indomethacin. The challenge to indomethacin on any basis with which I am familiar is in my opinion unwarranted and probably prejudicial.

Sincerely yours,

H. F. POLLEY, M.D.

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VETERANS' ADMINISTRATION CENTER,
*Los Angeles, Calif., April 22, 1968.*

Dr. MAX TISHLER,
*President,*
*The Merck Foundation,*
*Merck & Co.,*
*Rahway, N.J.*

DEAR DR. TISHLER: It is my understanding that there will be a congressional hearing soon to consider, among other things, the current controversy that has been brought forth regarding the antirheumatic efficacy of indomethacin. I would assume that this is somehow related to the results of more recent double-blind evaluations with indomethacin in rheumatoid arthritis (RA).

It is my opinion that while double-blind studies are obviously useful in evaluating new agents, they are also extremely difficult, particularly in such a capricious disease as RA. To this point, I might add that there are few (if any) double-blind trials with other antirheumatic agents that are entirely satisfactory.

Even more appalling are the apparent expectations of many investigators conducting short-term studies in RA that indomethacin would provide objective functional improvement. This is a clinical misconception since all antirheumatic agents are at best palliative. By providing effective relief of joint pain and inflammation, drugs allow patients to undertake therapeutic exercise and other supportive measures. These provide objective improvement. Yet, such measures receive scant mention and do not appear to be an integral part of the reported double-blind studies of indomethacin in RA.

In spite of these controlled trials, many physicians have the impression that indomethacin benefits certain patients with RA. As Healey has recently pointed out in the Bulletin of the Rheumatic Diseases (18, 483, 1967), there may be a sub-group of patients with RA that are controlled by indomethacin, a finding that would not be evident when such patients are included in a general drug trial. To my knowledge, this hypothesis has not been tested.

The result of our long-term evaluation of indomethacin in ankylosing spondylitis (AS), a form of rheumatoid disease affecting young men, has recently appeared in the journal Arthritis and Rheumatism (11, 56, 1968).

In this trial of indomethacin averaging 33 months in 28 AS patients who received an average daily dosage of 100 mg., the response to the drug was good in 21 patients, fair in 5 and poor in 2. Of the 28 patients, 21 improved to ARA functional class I. Before the use of indomethacin, only one of the 28 was so rated. Joint symptoms followed temporary withdrawal of the drug in all but four of the 28 patients. These symptoms were promptly relieved when indomethacin was again taken by the patients.

Clearly, our report parallels the experience of others, such as Bilka, Hart, Kass, Pohl, Rothermich and De Seze, that indomethacin is an essentially safe and effective drug in suppressing the articular manifestations of AS.

I sincerely hope, despite the current controversy and confusion, that investigative pursuits of indomethacin will continue. Only then can we more fully understand the role of this extremely useful and valuable antirheumatic agent. Best wishes.

Very truly yours,

JOHN J. CALABRO, M.D.
*Chief, Rheumatology Section, Wadsworth Hospital.*

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ST. LOUIS UNIVERSITY,
SCHOOL OF MEDICINE,
*St. Louis, Mo., April 22, 1968.*

MAX TISHLER, Ph. D.
*Merck Research Laboratories,*
*Merck & Co., Inc.*
*Rahway, N.J.*

DEAR DR. TISHLER: I understand that indocin is under Federal scrutiny in regard to its effectiveness in rheumatoid arthritis. Since I am presently performing a double blind study with this drug in the treatment of rheumatoid arthritis, I would like to offer the following comments.

The therapy of rheumatoid arthritis, as you know, is very difficult. Fortunately, we have many drugs available today which help the practicing physician control this crippling illness in most patients. Many times we find it necessary to use several medications in the same individual because of a lack of any specific drug which will perform to the degree of satisfaction we desire. Some of these drugs are rather toxic, thereby obviating their routine usefulness. By combining drugs like indocin with some of the more toxic medications, we are thus able to effectively use some of the latter preparations in smaller dosages and, consequently, avoid some of their complications. This would be particularly true of the steroids, the "cortisone-like" drugs. Also, when used alone, indocin may offer significant relief so that the addition of other antiflammatory drugs may not be necessary.

Despite the fact that indocin's value in rheumatoid arthritis has been questioned recently, it is my opinion that this medication certainly has a place in the therapy of rheumatoid arthritis. I do not administer indocin as a drug of first choice; however, I do believe it offers a significant advantage to approximately fifty percent of rheumatoid patients.

Evaluation of any drug for the treatment of rheumatoid arthritis is extremely difficult. Double blind studies, such as those being performed at the present time, seem to be the appropriate method of determining a drug's effectiveness. If a

sufficient number of patients are studied, satisfactory answers should result from such studies. The difficulty in evaluating a drug for the treatment of rheumatoid arthritis arises because of the many patients who will improve with placebo therapy. Also, objective manifestations of improvement are frequently very difficult to measure with any degree of accuracy in rheumatoid arthritis. If there is doubt about indocin in the treatment of rheumatoid arthritis, I believe that double blind studies should give the most reliable information in its efficacy.

Sincerely yours,

JACK ZUCKNER, M.D.,
*Associate Clinical Professor,*
*Director, Section of Arthritis.*

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PITTSBURGH, PA., *April 22, 1968.*

MAX TISHLER, M.D.,
*Merck Research Laboratory,*
*Merck & Co., Inc.,*
*Rahway, N.J.*

DEAR DR. TISHLER: This is in reply to an inquiry from Dr. Richard Smith concerning our findings and results in the clinical therapeutic use of Indomethacin (Indocin).

Although we have not employed double-blind controls, our extensive experience in the management of patients with rheumatic disease has indicated to us over the years that through close clinical observation of our patients under treatment we have generally arrived at conclusions concerning clinical effectiveness of therapeutic agents which closely approximated those reported in controlled therapeutic trials.

Our own experience over an extended period of time has indicated a significant degree of effectiveness of Indocin as an anti-inflammatory agent in a considerable proportion of patients with rheumatoid spondylitis, gouty arthritis, osteoarthritis of the hip, and some patients with rheumatoid arthritis.

The incidence and character of side effects have likewise corresponded with those described in the literature.

In conclusion, we feel that Indocin in appropriate clinical situations offers a useful addition to our therapeutic armamentarium.

Sincerely yours,

H. M. MARGOLIS, M. D.
JAMES H. BARR, Jr., M. D.
BERTRAND L. STOLZER, M. D.
CARL H. EISENBEIS, JR., M. D.
BURTON H. POLLOCK, M. D.

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UNIVERSITY OF MIAMI,
*Miami, Fla., April 22, 1968.*

Dr. MAX TISHLER,
*Merck Research Institute,*
*Merck & Co., Inc.*
*Rahway, N.J.*

DEAR DR. TISHLER: I understand that your company is under investigation by the Subcommittee on Monopoly, chaired by Senator Nelson, in reference to the drug, Indocin.

In our University Clinic we use Indocin, quite effectively, for pain relief in the milder cases of rheumatoid arthritis. Certain patients, particularly males, have better response to Indocin with less side effects than when given large doses of aspirin or mild narcotics. Business men are able to get pain relief without drowsiness. We use Indocin for lowering the dosage of Prednisone. Thus, I think, Indocin is a useful adjunct in the treatment of various arthritics.

Sincerely yours,

DAVID S. HOWELL, M.D.,
*Professor of Medicine,*
*Director, Arthritis Division.*

LOS ANGELES, CALIF., *April 22, 1968.*

Dr. MAX TISHLER,
*Merck Research Laboratories,*
*Merck & Co., Inc.*
*Rahway, N.J.*

DEAR DR. TISHLER: It is my understanding that there are to be some congressional hearings related to the use of indomethacin in the treatment of rheumatoid arthritis. We are all cognizant of the difficulties involved in the evaluation—even double blind studies—of indomethacin or any drug in a disease such as rheumatoid arthritis which is characterized by exacerbations, remissions and the emotional component. However, I have found indomethacin to be a very useful drug in the treatment of rheumatoid arthritis, particularly in milder cases or in patients where one is reluctant to use corticosteroids as patients in the older age group and in those with diabetes, osteoporosis, etc. Furthermore, in the concomitant use of indomethacin with corticosteroids, the dosage of corticosteroids has been reduced in some patients.

Indomethacin has also been a very useful drug in the treatment of other types of rheumatic disease, i.e., episodes of acute gouty arthritis, bursitis, and osteoarthritis. In degenerative arthritis of the hips—for which we have so little to offer therapeutically—I have seen dramatic results from the use of indomethacin.

Sincerely yours,

NATHAN E. HEADLEY, M.D.,
*Associate Clinical Professor of Medicine,*
*U.S.C. School of Medicine.*

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UNIVERSITY OF COLORADO MEDICAL CENTER,
*Denver, Colo., April 22, 1968.*

Dr. MAX TISHLER,
*Merck Research Laboratories,*
*Merck & Co., Inc.*
*Rahway, N.J.*

DEAR DR. TISHLER: I understand that hearings currently in progress, under the chairmanship of the Honorable Gaylord Nelson, are considering the drug Indomethacin (Indocin) and its value in the management of patients with rheumatoid arthritis.

I first undertook clinical investigation of this non-cortisone, anti-inflammatory agent in 1963, and first published our clinical studies of this drug in 55 rheumatoid patients in 1965 in the journal, Arthritis and Rheumatism. These clinical investigations were based upon the best objective measurements of rheumatic activity and at that time it was concluded that, "Indomethacin suppresses joint inflammation and improves function but may require up to 2 to 4 months to obtain maximum therapeutic effects". With three additional years of experience with this drug in more than 100 patients under rigid clinical observation and using similar methods of evaluation, I am still of this opinion.

To state how frequently favorable therapeutic effects occur based upon objective tests, and how often this drug is clinically beneficial is difficult, but in my opinion, between 20 to 25 percent do show objective changes; an additional 20 to 30 percent report subjective benefits.

Among the toxic reactions reported with the use of Indomethacin, the frequency of peptic ulceration has been of major concern to critical, clinical observers. An analyses of more than 700 patients treated with Indomethacin at the University of Colorado hospital and its clinics indicates that this complication seldom occurs. These patients had previously received other anti-inflammatory and analgesic drugs including aspirin, corticosteroids, and phenylbutazone. The incidence of peptic ulcers during the Indomethacin period of therapy was actually less than during similar periods of other anti-inflammatory, anti-rheumatic agents. In my experience, the occurrence of peptic ulceration is not a major obstacle to the clinical use of this drug in patients with rheumatoid arthritis.

In my five years experience based on the practical use of Indomethacin and a careful analysis of the results in all of our patients treated by a staff experienced in the management of patients with rheumatoid arthritis in this University Hospital, I am of the opinion that Indomethacin benefits some patients with rheumatoid arthritis. At present no reliable tests are available to predict which

patients with this chronic disease which is marked by spontaneous remissions and exacerbations, will respond favorable to this drug.

Until more potent and less toxic anti-inflammatory agents are made available for clinical use, I strongly recommend that Indomethacin continue to be available for use in this most crippling of all arthritic conditions. I would not discard a valuable tool although it might have a sharp edge.

Sincerely yours,

CHARLEY J. SMYTH, M.D.,
*Professor of Medicine,*
*Head, Division of Rheumatic Diseases.*

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NORTHWESTERN UNIVERSITY,
*Chicago, Ill., April 22, 1968.*

DR. MAX TISHLER,
*Merck Research Laboratories,*
*Merck & Co., Inc.,*
*Rahway, N.J.*

DEAR DR. TISHLER: As you know, we have been engaged during the last year in evaluating the efficacy of Indocin in patients with generalized osteoarthritis. In addition, we have used Indocin in the treatment of patients with other forms of arthritis particularly those of rheumatoid arthritis.

Although we do not have the results from our osteoarthritis study tabulated as yet, I would like to recall for you some of the difficulties that emerge from this type of work.

First, the cause of these types of arthritis is unknown. This means that one must utilize the symptoms the patient shows as clues concerning the response of the patient to treatment. It is not possible to state that a given causative feature has or has not been altered or changed by the treatment program. Such a statement concerning drug evaluation would of course be the best evidence for determination of an effective program.

This difficulty is further compounded by the variability of the course of these illnesses. It is very difficult to interpret the exact response of the patient to a drug or to no drug.

Therefore, to properly reach a conclusion about the efficacy of a drug requires a careful assessment of a number of signs and symptoms present in the disease and sufficiently large number of patients who are being evaluated.

Although gold treatment for rheumatoid arthritis has been used for almost four decades, it was only in the last few years that a carefully controlled drug study on the efficacy of this compound was completed by a group of British workers.[1] Even here considerable difficulty was encountered. I do not take the view that proper assessment is impossible but it certainly is difficult.

I think that it can be said that Doctor Mainland reached similar conclusions in his careful assessment of role of Indocin in rheumatoid arthritis. He did find it had a beneficial effect although no greater than aspirin. He also points out the real problems that beset any one who does drug evaluation studies.

In ordinary practice in our clinic we have been impressed by patients' response to Indocin in rheumatoid arthritis and other forms of arthritis, including osteoarthritis. We use the drug to help provide relief for patients who require additional medication besides aspirin.

It would be a tragic event if the demands for precision outstrip the methodology available. In our present state of ignorance one must accept less than optimal measure of effect. However, one constantly must try to improve the state of the art.

Sincerely yours,

FRANK R. SCHMID, M.D.,
*Associate Professor of Medicine,*
*Chief, Arthritis-Connective Tissue Section.*

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TUCSON, ARIZ., *April 22, 1968.*

MAX TISHLER, Ph. D.,
*Merck Research Laboratory,*
*Merck Sharp & Dohme,*
*Rahway, N.J.*

DEAR DOCTOR TISHLER: This is a testimonial letter in regard to Indomethacin (Indocin).

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[1] Annals of Rheumatic Diseases, 19:95–117, 20:315–334, 1961.

My experience with this medication began with investigational studies starting in 1961, before this drug was released.

Subsequently, Indomethacin (Indocin) has become a most valuable medication in the treatment of various forms of rheumatic diseases.

Approximately one-half of my patients are receiving Indocin.

Cordially yours,

HARRY E. THOMPSON, M.D.

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COLUMBUS MEDICAL CENTER
RESEARCH FOUNDATION,
*Columbus, Ohio, April 22, 1968.*

MAX TISHLER, Ph. D.,
*Merck Research Laboratories,*
*Merck & Co., Inc.,*
*Rahway, N.J.*

DEAR DR. TISHLER: It is my understanding that you have been invited to appear before a Congressional hearing under the Honorable Gaylord Nelson to discuss the relative merits and clinical value of indomethacin, which is marketed under the brand name of Indocin. Since I originally introduced this drug to humans in November 1961, and have had as long and profound clinical experience with the drug as any physician in the world, I feel constrained to offer some comments.

It may be proper at this point to identify myself to you. As you may or may not know, I have been on the medical faculty of the Ohio State University for more than twenty-eight years and since 1960, have held the rank of Clinical Professor of Medicine. In addition, I am the Founder and Director of the Columbus Medical Research Foundation. I am also senior physician director of The Columbus Medical Center, which is a group-practice clinic of specialists in Diagnosis and Internal Medicine, with a heavy preponderance of rheumatic diseases. Three of the eight physicians (including myself) sub-specialize in the field of Rheumatology to the extent of having more than fifty percent of their practice devoted to that field. We have approximately five-hundred patients with rheumatoid arthritis on continuing active treatment and we regard Indocin as an important part of their overall drug-therapy program.

Not all patients with rheumatoid arthritis are benefited by Indocin, but the same can be said about all other antirheumatic drugs, even including cortisone-derivatives and aspirin. However, more than half of patients with rheumatoid arthritis receive decisive benefit from Indocin and are able to continue taking the drug without undue adverse effects; its record in this respect is superior to aspirin and second only to the benefits derived from cortisone-derivatives.

In over half of the patients who do benefit from Indocin the benefits are striking and decisive and the drug is regard as indispensable to the patients continued well-being and disease-control. This variable, limited, and to some degree unpredictable response of Indocin in rheumatoid arthritis has led to opposite extremes of reaction in the minds of some physicians. Because it is not effective in considerably less than one hundred percent of the patients, some physicians call it a total failure, deny any value to it, and think it should be abandoned. Other physicians regard the striking benefits in some patients as proof that Indocin is a panacea and can be used to the exclusion of all other antirheumatic agents. Both of these extremes of viewpoint are ill-founded and unwarranted. The fact is that Indocin is an excellent adjunct in antirheumatic therapy and should be given a trial, beginning in low doses, in those patients with rheumatoid arthritis who have failed to respond to the so-called basic or conservative program of increased rest, physical therapy, salicylates and so forth.

Evaluation of drug efficacy in rheumatoid arthritis is a most difficult, profoundly complex and often unrewarding endeavor, best carried out by an experienced clinician-rheumatologist who has not only some acumen and scientific orientation, but also patience, understanding, empathy and a keen insight into the complexities of the rheumatoid personality, as well as the rheumatoid disease.

Unfortunately, there are no satisfactory criteria for evaluating rheumatoid disease activity with uniform and reliable consistency. The use of the "single-blind" placebo, by an experienced clinician, in a patient who has been on the drug under evaluation for some period is probably the most reliable method of approach to the problem and enables the clinician to evaluate the drug by

observing the patient's clinical response to the unknown substitution of placebo and to the unknown resumption of the active drug. Where emphasis is needed or where any doubt exists, the placebo trial can be repeated on a number of occasions in the same patient. The use of a placebo can also help the clinician to decide if the appearance of adverse effects or side reactions is drug-related. Oftentimes it is found that an adverse effect, thought to be drug-induced, was in truth the result of the patient's apprehension at taking part in an experiment.

In theory, the "double-blind" technique is the most desirable form of evaluation, but the non-clinician and the statistician fail to appreciate the numerous, often insurmountable difficulties in applying a "double-blind" study to a group of human patients. It is understandable that those who have done most of their work with testing in laboratory animals would want to carry-over this same methodology to the human, but it is becoming increasingly apparent from the reports of such statistician- and laboratory-oriented sources that the pitfalls of the "double-blind" study are manyfold and seem to increase exponentially with the increasing application of further controls and safeguards. Nevertheless, it may be advantageous for an experienced clinician to institute a "double-blind" study during the course of a therapeutic trial of a new drug, and derive important data from it.

In my many years of clinical experience with Indocin, I have used a number of "double-blind" trials, but I have not regarded them as having as much value to me as the hundreds of "single-blind" placebo trials which I carried out. The results of both, however, served further to convince me of the therapeutic efficacy of Indocin in the majority of patients with rheumatoid arthritis.

The Merck Company is to be congratulated for having labored so diligently to produce yet another effective drug for the treatment of this dread disease. I appreciate the opportunity to have developed the earliest clinical experiences with Indocin. However, the most important thing which I personally think makes your company especially deserving of commendation is the wholesome, objective, scientific atmosphere which all of the representatives of your company created and maintained throughout all my studies on Indocin. At no time were any pressures exerted on me in any manner or in any direction which could possibly have influenced my objective approach or created any prejudice or bias in my work or even in my thinking. At all times I felt completely free to report favorably or unfavorably and to state that in my opinion Indocin was good, bad or indifferent. In fact, at several stages I was hyper-critical of the drug and even now emphasize that it is not the last word in rheumatoid arthritis therapy, that improvements can probably be made with derivatives of the drug, that cerebral side-effects are a definite limitation, both in dosage ceiling and in more universal application of the drug. In this atmosphere I have developed the conviction that Indocin is a valuable drug and should not be denied to those patients with rheumatoid arthritis in whom it can and will produce decisive benefits.

Yours truly,

NORMAN O. ROTHERMICH, M.D.

BRONX, N.Y., *April 22, 1968.*

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**DR. MAX TISHLER,**
***Merck Research Laboratories,***
***Merck & Co., Inc.,***
***Rahway, N.J.***

DEAR DOCTOR TISHLER: I am aware that there has been a discussion in the Congress through their appointed Committees to evaluate the evidence with regard to the therapeutic efficacy and the place in our pharmalogic armamentarium of Indomethacin.

The studies that we have performed and our current studies indicate that Indomethacin has an anti-inflammatory action, and through this anti-inflammatory action, a potent analgesic effect in the treatment of inflammatory connective tissue disease, particularly the inflammation associated with traumatic osteoarthritis. It appears to be of use in some patients with acute and chronic rheumatoid arthritis. Of course its effect in acute gout is well known.

The problem with Indomethacin has been the variable response to the drug. This is extraordinarily unusual, but offers a challenge as to the difference between this anti-inflammatory compound and the other which are available. Certainly, further research with Indomethacin and its analogues is warranted, and we are currently actively engaged in this research.

The question of the design of the studies for Indomethacin efficacy has been a challenge to us. A double blind study of Indomethacin against a sugar placebo

would produce no results since patients would be left for prolonged periods of time without medication, and if they were unfortunate enough to have the sugar placebo to continue in the study. In addition, there would be a discrepancy in the results between the possible carry over in the Indomethacin study which might have a greater effect with Indomethacin and a much less effect with the placebo. It would seem that an active medication would be indicated in the placebo capsules. We believe that aspirin answers this need.

With all of these considerations taken into account, I believe that a final evaluation with regard to Indomethacin efficacy should be postponed until all of the data from the studies that are now being carried out is collected. This will not only be more valuable with regard to Indomethacin, but will encourage further studies with Indomethacin analogues which are so important in the future.

Cordially,

JEROME ROTSTEIN, M.D.,
*F.A.C.P., F.C.C.P., Head, Rheumatic Disease Unit.*

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LOUISVILLE, KY., *April 22, 1968.*

DR. MAX TISHLER,
*Merck Research Laboratories,*
*Merck M. Co., Inc.,*
*Rahway, N.J.*

DEAR DR. TISHLER, This is a letter attesting to the efficacy of Indocin in my practice of rheumatology in Louisville, Ky.

This drug has been extremely effective in all of my patients with anklylosing spondylitis. As you well know, this is a very debilitating disease, which affects young men in their prime, and can be ruinous economically if the disease is not checked. In every one of my patients with anklylosing spondylitis, the disease has been checked either partially or completely. All of them are fulfilling, at present, useful lives.

Indocin has further more been effective in selected cases of osteoarthritis. In gout, Indocin has been very effective with minimal side effects. In rheumatoid arthritis, the drug has not been as effective as I would like, and I utilize it very little in these individuals.

For any sort of blind study to be done in individuals afflicted with these crippling diseases, I would consider it inhumane as well as immoral to deny benefits to a selected group of patients.

It would be my feeling, at present, that Indocin is a very effective drug in the conditions named, and there should be no question in its' efficacy in those individuals not only in suppressing their disease, but keeping them useful, productive citizens in our society.

If there is any further information you may require please contact me.

Cordially,

FRANK W. LEHN, M.D.

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BOMBAY, *April 22, 1968.*

We had previously published the results of our experience with Indomethacin in rheumatoid arthritis and still feel that this drug represents a definite advance in treating many rheumatic diseases. Our experience confirms it to be a potent anti-inflammatory, analgesic and antipyretic agent, without many of the severe side effects of corticosteroids and butazones. We have used Indomethacin successfully in many cases who had not responded satisfactorily to aspirin and butazones. In rheumatoid arthritis, there is no doubt that requirements of corticosteroids can be substantially reduced and in a significant percentage of cases, these can be eliminated gradually. Side effects such as headache, giddiness and gastrointestinal irritation have occurred in about 40% of patients but it is not always necessary to discontinue therapy. Such side effects can be managed in the usual manner. We have not come across any case of blood dyscrasia, liver or renal damage.

K. K. DATEY, M.D.,
*F.R.C.P. Honorary Professor of Medicine, Seth G.S. Medical College and King Edward Memorial Hospital; and Director, Department of Cardiology, King Edward Memorial Hospital, Bombay.*

BRUSSELS, *April 22, 1968.*

Q.—In the light of your extensive experience in the management of diseases for which Indomethacin is indicated, do you consider that the introduction of Indomethacin has contributed to the management of your patients?

A.—Yes—in osteoarthritis of the hip, in Bechterew's disease and in rheumatoid arthritis in association with gold therapy.

Q.—Do you find that Indomethacin enables you to obtain results in some of your patients that were difficult to obtain prior to its introduction?

A.—Yes—in osteoarthritis of the hip and Bechterew's disease because the toxicity of Indomethacin on long-term treatment is lower than the toxicity of other available drugs.

Q.—If so, can you define those areas in which the drug has been most helpful to you?

A.—Osteoarthritis of the hip and spondylitis rhizomelica.

Prof. Dr. L. J. Michotte.

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BOMBAY, *April 22, 1968.*

I have been using indomethacin in the form of capsules as well as suppositories since the last five years. In my experience, indomethacin has proved to be a valuable drug for treating rheumatoid arthritis and allied disorders. A number of my patients who had not responded to salicylates, phenylbutazone or oxyphenbutazone were maintained satisfactorily on indomethacin. I have studied the drug's steroid-sparing properties carefully and am convinced that the dosage of corticosteroids can be gradually reduced in a large percentage of cases. I have also tried the drug for prolonged periods in Still's disease where it works most satisfactorily and has excellent tolerance. Indomethacin suppositories have been used in my department in 16 patients for almost two years continuously. Patients having gastrointestinal problems with capsules can be managed remarkably well on indomethacin suppositories.

M. M. DESAI, M.D.
*M.R.C.P., F.C.P.S., Honorary Associate Professor of Medicine, Topiwala National Medical College and B.Y.L. Nair Hospital; Physician In-charge, Department of Rheumatic & Collagen Diseases, B.Y.L. Nair Hospital, Bombay.*

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RHEUMATISM RESEARCH UNIT,
CANADIAN RED CROSS MEMORIAL HOSPITAL,
*Taplow, Maidenhead, Berks, April 22, 1968.*

Dr. MAX TISHLER,
*President, Merck, Sharpe Dohme Research Laboratories,*
*Rahway, N.J.*

DEAR DR. TISHLER, Dr. Carl Pearson of Los Angeles has let me know that there are to be some Congressional hearings in relation to Indomethacin (Indocin). I regret that I shall not be able to come over, but instead he suggested that I might write you in general terms about our experience with this drug both here and at the Royal Postgraduate Medical School. We have not performed any controlled trials, so that what follows is the result of clinical observation.

I feel that this drug is useful in certain patients with rheumatoid arthritis and has about the same potency as aspirin. It is, however, more expensive and we therefore tend to use it when patients cannot tolerate aspirin and sometimes to wean them off steroid medication. This we have been able to do satisfactorily. It seems useful also in ankylosing spondylitis, and we have used it there in such cases who have developed intolerance to phenylbutazone. It appears to be of some value in osteoarthritis of the hip. I have not used it in gout.

We have used Indocin in over 30 children in the first two decades with chronic polyarthritis and it has seemed quite useful here, except perhaps in the youngest children, in whom it has induced vomiting. In general we have not had a great deal of trouble with side effects, apart from headache. We have had one case with perforation of the stomach and two with melaena. Two of our patients have had a rather odd reaction mentally which has ceased on stopping the drug.

Since, however, we have had no control series, it is difficult to evaluate these complications, since, as you well know, some such effects occur even on placebo. We think, however, that these were probably related to the drug.

I hope this is the information you require.

Yours sincerely,

E. G. L. BYWATERS, F.R.C.P.,
*(Professor of Rheumatology, University of London, Hon. Director, Medical Research Council Rheumatism Research Unit).*

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[Telex received in New York from Milan]

APRIL 22, 1968

Dr. M. TISHLER,
*Rahway:*

Prof. D. Gigante—Director of Rheumatological Institute of University of Rome—stated today—The introduction of Indomethacin has greatly contributed to the management of patients with rheumatic disease.

Corticosteroids still remain the most effective drugs for the treatment of many rheumatic patients. However Indomethacin has enabled me to treat effective a large number of these patients because of its marked anti-inflammatory properties which are generally not accompanied by the occurrence of serious side effects.

Indomethacin has been most helpful in the treatment of the following diseases—gout, degenerative disease of the hip and Ankylosing Spondilitis. It has been also very effective in a great number of patients with rheumatoid arthritis.

Copy of above statement signed by Gigante will be airmailed.

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[Message received in New York from Milan]

APRIL 23, 1968.

Dr. MAX TISHLER,
*Rahway:*

Following statement by Prof. C. B. Ballabio, Director of Rheumatological Institute of the University of Milan—"Without doubt the introduction of Indomethacin has contributed to the management of my rheumatic patients. In degenerative disease of the hip Indomethacin gives excellent results which were not possible to obtain with any other medication.

The rheumatic diseases which in my experience can be treated most effectively with Indomethacin alone or sometimes in association with other medications are ankylosing sponylitis and gout. Indomethacin is of some help in the treatment of some rheumatoid arthritis patients especially males."

Copy of above statement signed by Ballabio will be airmailed.

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[Telex received from Hoddesdon in New York]

APRIL 23, 1968.

Dr. M. TISHLER,
*Rahway:*

Indomethacin contributes to the management of rheumatoid arthritis. It enables some patients to be controlled who have not previously been controlled. Watson Buchanan Head of the Centre of Rheumatuc Diseases, Glasgow.

Regards,

HODGKINSON.

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BUENOS AIRES.

Tishler Dr. Romanowicz report head of Rheumatology Rheumatic Disease Center, Rawson Hospital answer first question yes Indocid is of great utility, second, yes, third, rheumatoid arthritis arthrosis gout ankylosing spondylitis unspecific arthritis.

MASANTI.

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CAPE TOWN, *April 23, 1968.*

*Question:* In the light of your extensive experience in the management of diseases for which Indomethacin is indicated, do you consider that the introduction of Indomethacin has contributed to the management of your patients?

*Answer:* Yes.

*Question:* Do you find that Indomethacin enables you to obtain results in some of your patients, that were difficult to obtain prior to its introduction?

*Answer:* Definitely yes.

*Question:* If so, can you define those areas in which the drug has been most helpful to you?

*Answer:* Resistant cases of rheumatoid and osteoarthritis gout.

Dr. R. A. ASHERSON.

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STATEMENT ON INDOMETHACIN BY DR. SELWYN NELSON

This statement is made on the understanding that no use is made of it which is likely to be unethical or embarrassing to the writer.

Indomethacin is a valuable addition to the range of preparations available for the treatment of rheumatic diseases.

All drugs used in the long term management of rheumatic diseases are likely to cause unwanted effects in some patients and Indomethacin is no exception. Most if not all of the toxic effects of Indomethacin are rapidly reversible and also are obvious to the patient.

In the choice of treatment of rheumatic diseases the clinician takes into account the properties of the drug and his experience of its effectiveness in various conditions, its toxicity and the incidence and reversibility of possible unwanted effects. He also takes into account the contra-indications having regard for the expected effect of the drug on a patient suffering from other disorders related or unrelated to the primary condition being treated.

The approach to the prescribing of Indomethacin can be based on a positive or negative assessment of the patient's needs. Experience with Indomethacin has demonstrated its very great effectiveness in gout, rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. It is also very useful in certain miscellaneous non-specific painful disorders of the musculo-skeletal system e.g. Bursitis, "fibrositis" etc. This might be termed the positive approach.

As Indomethacin has a different chemical composition from other non-steroidal anti-inflammatory drugs it can be used where other preparations have been tried and found wanting.

Indomethacin can be used in preference to other anti-inflammatory drugs where there has been a previous toxic effect on the bone marrow caused by another preparation. It is also valuable in the presence of reduced cardiac reserve as it does not cause retention of salt and fluid.

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[Translation]

Dr. Pedro M. Catoggio, Director of the National Institute of Rheumatology, National Institute of Rheumatology, Martínez de Hoz y Marconi—Ramos Mejía, Pcia. Bs. As., Rep. Argentina:

(1) Question: In the light of your extensive experience in the management of diseases for which indomethacin is indicated, do you consider that the introduction of indomethacin has contributed to the management of your patients?

Answer: Yes

(2) Question: Do you find that indomethacin enables you to obtain results in some of your patients that were difficult to obtain prior to its introduction?

Answer: Yes

(3) Question: If so, can you explain those areas in which the drug has been most helpful to you?

Answer: Rheumatoid arthritis, acute inflammatory exacerbations in arthrosis, periarthritis, and in acute gout and rheumatoid spondylitis I have little experience.

Comments: (1) In the last few months we have used suppositories more frequently, (2) We often made the association with ASA, corticosteroids or antimalaric drugs (in R.A.)

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[Translation]

Dr. Raul Houssay, Rheumatologist of the Department of Rheumatology, Ward 20, Rivadavia Hospital, Sanchez de Bustamante 2560, Buenos Aires, Rep. Argentina:

(1) Question: In the light of your extensive experience in the management of diseases for which indomethacin is indicated, do you consider that the introduction of indomethacin has contributed to the management of your patients?

Answer: Indomethacin contributes to the management of rheumatic patients for its analgesic action and when the effective dose is well tolerated.

(2) Question: Do you find that indomethacin enables you to obtain results in some of your patients that were difficult to obtain prior to the introduction?

Answer: Indomethacin enables me to obtain good results in some patients in which the necessary doses of other drugs for the obtention of satisfactory analgesic and anti-inflammatory effects are not tolerated.

(3) Question: If so, can you explain those areas in which the drug has been most helpful to you?

Answer: (a) Osteoarthritis. Arthosis of the hip, (b) Rheumatoid spondylitis, (c) Nonarticular rheumatisms (painful shoulder, bursitis, fibrositis, etc.), (d) Rheumatoid arthritis: Indomethacin is effective in some patients with R.A., especially if it is administered in combination with other medications. Indomethacin is useful for the treatment of morning stiffness.

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[Translation]

Dr. Osvaldo Hübscher, Rheumatologist of the Department of Rheumatology, Ward 20, Rivadavia Hospital, Sánchez de Bustamante 2560, Buenos Aires, Rep. Argentina:

(1) Question: In the light of your extensive experience in the management of diseases for which indomethacin is indicated, do you consider that the introduction of indomethacin has contributed tto the management of your patients?

Answer: Yes; in some patients. Indomethacin has analgesic and anti-inflammatory action. It can be administered for a long time without important danger.

(2) Question: Do you find that indomethacin enables you to obtain results in some of your patients that were difficult to obtain prior to its introduction?

Answer: Yes. In some patients the addition of indomethacin to the previous treatment or its substitution, enables the physician to obtain a better management of the patients. In other patients indomethacin has no action.

(3) Question: If so, can you explain those areas in which the drug has been most helpful to you?

Answer: (a) In rheumatoid arthritis: generally associated to other drugs. Without doubt it has a steroid sparing effect. The use of suppositories at bedtime improves the morning stiffness of the patients, (b) In osteoarthritis with inflammatory signs, (c) In rheumatoid spondilitis, (d) Lower action in fibrositis, tendinitis and other unspecified conditions, (e) No experience in acute gout.

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[Translation]

Dr. Armando Maccagno, Head of Clinics, Rheumatic Diseases Center, Ward 14, Rawson Hospital. Buenos Aires. Republica Argentina:

(1) Question: In the light of your extensive experience in the management of diseases for which Indomethacin is indicated, do you consider that the introduction of Indomethacin has contributed to the management of your patients?

Answer: Yes

(2) Question: Do you find that Indomethacin enables you to obtain results in some of your patients that were difficult to obtain prior to its introduction?

Answer: Yes

(3) Question: If so, can you explain those areas in which the drug has been most helpful to you?

Answer: *Rheumatoid arthritis, Rheumatic spondilitis, Intermittent hydrarthrosis.*

*Arthrosis:* Only in the first and second period. In period 3 I prefer surgical treatment.

In *gout* I have not much experience; in these patients I prefer phenilbutazone because it has uricosuric effect. Only when phenilbutazone is ineffective I use Indomethacin.

I think that the combination Indomethacin-Dexamethasone is very effective because Indomethacin has a steroid sparing effect and the action of both drugs is potentiated.

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[Translation]

Dr. Osvaldo García Morteo, Head of Rheumatology, Rheumatological Department, Ward 20, Rivadavia Hospital, Sánchez de Bustamante 2560—Buenos Aires—Rep. Argentina, Secretary of the Argentine Society of Rheumatology:

(1) Question: In the light of your extensive experience in the management of diseases for which indomethacin is indicated, do you consider that the introduction of indomethacin has contributed to the management of your patients?

Answer: In some rheumatic conditions the introduction of indomethacin has contributed to the management of the patients. In some patients with rheumatoid arthritis it has been able the use of lower doses of corticosteroids and sometimes it was possible the withdrawal of these drugs. In patients with acute inflammatory exacerbations may be a good approach.

(2) Question: Do you find that indomethacin enables you to obtain results in some of your patients that were difficult to obtain prior to its introduction?

Answer: Yes. Some patients have a therapeutic response not obtained previously with other anti-rheumatic drug. Is useful in rheumatoid spondilities and in some inflammatory conditions of the soft tissues. Irregular results were obtained in acute gout. Sometimes indomethacin is ineffective.

(3) Question: If so, can you explain those areas in which the drug has been most helpful to you?

Answer: Its possibility of long time administration made of indomethacin, a drug which is useful in the treatment of R.A. and osteoarthritis. The administration of indomethacin, when the patient goes to bed produce an improvement of morning stiffness. Indomethacin is better tolerated when is administered by rectal route than by oral route.

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[Translation]

Dr. Ana Porrini, Rheumatologist of the Department of Rheumatology, Ward 20, Rivadavia Hospital, Sánchez de Bustamante 2560, Buenos Aires, Rep. Argentina:

(1) Questions: In the light of your extensive experience in the management of diseases for which indomethacin is indicated, do you consider that the introduction of indomethacin has contributed to the management of your patients?

Answer: Yes.

(2) Question: Do you find that indomethacin enables you to obtain results in some of your patients that were difficult to obtain prior to its introduction?

Answer: Yes.

(3) Question: If so, can you explain those areas in which the drug has been most helpful to you?

Answer: (a) In R.A.: Sometimes alone, associated to a basic plan of treatment which includes ASA, exercises and resting. Sometimes it is possible the reduction of steroid drugs.

(b) In Osteoarthritis.

(c) In Rheumatoid spondilitis: In my opinion, phenilbutazone is the selected drug in this condition but, however, I think that indomethacin is more useful in this case.

(d) In non articular rheumatic conditions: specially tendinitis of the shoulder and dorsal and lumbar fibrositis.

(e) In gout: In acute gout the results were not satisfactory; in these patients there were important side effects attributable to the use of high doses. Good results were found in some patients with chronic gout.

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CAPETOWN/KAAPSTAD,
*April 23, 1968.*

I have not had the facilities to conduct controlled studies of Indomethicin, but from 1964 I have had an extensive experience with this drug in the Arthritis Clinic of the Teaching Hospital of the University of Cape Town as well as in private practice.

Side effects were common at the outset because the dosages recommended proved to be too large. Moreover side effects were for the most part unpleasant but were not danger signals. The possible exception in gastero-intestinal complications which are in the first place rare and in the second place it is difficult to establish a cause and effect relationship. More often than not such patients were receiving other anti-rheumatic preparations as well e.g. Salicylates.

Indomethicin has proved of value the treatment of Gout, Osteo-Arthritis and Rheumatoid Arthritis. In the last named it is especially useful as a steroid sparing agent.

T. J. DRY, M.D.

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WIESBADEN, 26.4.1968.

Re Indomethacin.

DR. MAX TISHLER,
*Präsident der Merck Sharp u. Dohm*
*Vis. Laboratories Rahway, N.J.*

DEAR DR. TISHLER: Since 1964, indomethacin has been tested clinically and prescribed regularly at the clinic for rheumatic diseases in the Kaiser-Friedrich Spa Wiesbaden. Indomethacin is indicated in rheumatic and related diseases. In antipyretic therapy indomethacin has proved to be a valuable drug for supplementing already established anti-inflammatory agents. Indomethacin was shown to be useful in certain cases and forms of rheumatoid arthritis, arthrosis deformans, Bechterew's disease (rheumatoid spondylitis) after the other, non-hormonal anti-inflammatory agents had failed. Our experiences are confined to rheumatic and related diseases. The drug, which has meanwhile become a frequently used standard preparation, was not given in other indications.

Very truly yours,

DR. MIEHLKE, *Chief-of-Staff.*

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BALTIMORE, MD., *April 23, 1968.*

DR. MAX TISHLER,
*Merck Research Laboratory,*
*Merck & Co., Inc.,*
*Rahway, N.J.*

DEAR DR. TISHLER: I understand that there are to be hearings on the drug Indocin before a senate subcommittee in the near future.

My letter is to let you know that I have found Indocin very helpful in a limited number of arthritics who have not responded to other medication, such as aspirin, Butazolidin and Tandearil. There are a small number of people with rheumatoid arthritis who do extremely well on Indocin, and if they respond, they respond to doses of 75 mg. a day or less.

Although there is a great deal of emphasis placed on so-called double-blind studies of antirheumatic drugs by the American Rheumatism Association and its Study Group, I have found that this type of study is not essential to determining whether a drug has a beneficial effect in a rheumatoid arthritic who has been under my care for a long time.

To quote Dr. Fuller Albright, under whom I had the privilege of working for one year in 1941–42 in Boston, one patient well studied is worth 100 patients poorly studied. My patients with rheumatoid arthritis are well studied and well followed and I can tell when they receive benefit from a drug.

I believe that Indocin is a valuable addition to our therapeutic armamentarium in managing patients with this disease. I have also found it of value in a few patients with ankylosing spondylitis who have failed to respond to Butazolidin.

Very sincerely,

HARRY F. KLINEFELTER, M.D.

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BUFFALO, N.Y., *April 23, 1968.*

DR. MAX TISHLER,
*Merck Research Laboratory,*
*Merck & Co., Inc.,*
*Rahway, N.J.*

DEAR DR. TISHLER: In view of the impending Congressional hearing concerning the results of Indocin (Indomethacin) treatment of arthritis, I believe that the conclusions of "clinically" oriented rheumatologists and their numerous patients are just as important as the results of "double blind" studies which have been

reported by "statisticians" or "full time" physicians who treat a small number of patients with rheumatic diseases. While I admit that "double blind" studies are desirable, there are many possible errors that are not included in the statistical analysis of these studies and the results are used only to depreciate the potential values of the drug under test. This is especially true in the case of patients with rheumatoid arthritis, where the disease process is extremely variable from day to day, or week to week status; where short term evaluation of drug effect is inaccurate (in a few weeks); when patients are allowed to use a variable amount of aspirin; and where only objective measurements of joints are the decisive criteria. In the majority of rheumatoid patients in any one study, whether "double blind" or "uncontrolled," irreversible changes that determine size of joints, range of motion, and discomfort, have already occurred and do not improve particularly in a period of a few weeks. Such changes are not due to the active inflammatory process of the disease but are the result of long continued disease. The resultant "mechanical" disturbance of joint components cannot be corrected by anti-inflammatory drugs, whether they are salicylates, anti-malarials, phenylbutazone, or indomethacin. However, the statisticians and the "purists" decry the lack of objective measurements of improvement and completely disregard the subjective response of the patient. I will admit that none of the anti-inflammatory drugs mentioned above, have the prompt, dramatic response as the cortico-steroids but they do not have the serious toxicity associated with their "long term use."

After more than 20 years of experience in the exclusive treatment of rheumatic patients, I do not subscribe to the conclusions of Short & Bauer that 50% of rheumatoid patients improve with the most conservative treatment. Another frequently quoted "double blind," "cross over" trial with an anti-malarial drug, which was regarded as a masterpiece of drug testing and demonstrated the unquestionable response to the drug, is no longer considered as a "drug of choice" by most clinical rheumatologists. This decision has been determined by the nebulous response of most patients both subjectively and objectively, plus the possible occurrence of irreparable eye damage which was impossible to determine during the short period of the study.

I have used Indomethacin in the therapy of the rheumatic diseases in more than one thousand patients in the past 6 years. In my experience, it has been an effective drug in the majority of these patients and has contributed one more effective drug to the treatment of various rheumatic conditions, which have been a most difficult problem, not only to the physician, but more importantly to the patient. On the basis of carefully controlled animal experiments in the laboratory and also by reduction of fever and inflammation clinically in the patient with acute arthritis, there can be no dispute that Indomethacin is a potent anti-inflammatory drug. There is no question throughout the world that Indomethacin is one of the most effective drugs in relieving such conditions as acute gouty arthritis, acute tendonitis, ankylosing spondylitis, and degenerative (osteoarthritis) joint disease of the hip. The only dispute has centered about the question of response in patients with rheumatoid arthritis, which even the "statisticians," the "purists" and the "reviewers" admit is subject to remissions and exacerbations, difficult to evaluate, and that Indomethacin is at least comparable to phenylbutazone and aspirin.

Indomethacin is of benefit to a variable degree in at least 66% of the patients in my experience. Subjective response has been better maintained with this drug than with either phenylbutazone or salicylates in the chromic arthritic patients (either rheumatoid or degenerative joint disease). The majority of these patients have continued to use the drug (many since 1962) for more than 3 years, which I believe in itself is a testimonial that the drug is effective. Many of this group have been challenged with a placebo or have voluntarily discontinued the drug, even replacing it with a high salicylate dose. However, they have reported a prompt flare of their symptoms and have resumed Indomethacin therapy in practically all instances. The drug has produced functional improvement in many patients, even in patients with mechanical damage to their joints. In early rheumatoid patients with inflammation and joint swelling, I frequently observe decrease (and even complete subsidence in some patients) of the joint inflammation. The results of long term administration in this group of patients will be published in the proceedings of the 2nd Laurentian Conference on Rheumatology (Nov. 1966) which I understand is in press at this time.

It has also, been my experience that 50% of rheumatoid patients on corticosteroid therapy have been able to reduce the steroid when Indomethacin has been added to their therapy. Toxicity remains within tolerable limits in my experience

and I have not encountered any unusual new reactions with its continued use. Side effects on the gastro-intestinal tract, headaches, dizzyness, or a feeling of confusion continue to be the common complaints in my experience.

Sincerely yours,

BERNARD M. NORCROSS, M.D.

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MINNEAPOLIS, MINN., *April 23, 1968.*

MAX TISHLER, Ph. D.,
*Merck Research Laboratories,*
*Merck & Co., Inc.,*
*Rahway, N.J.*

DEAR DR. TISHLER: I am writing this letter to place on record my opinion that Indomethacin is an effective anti-rheumatic agent. Although, my own clinical research published in 1964, plus a fairly extensive experience with Indomethacin since then does not indicate a major anti-inflammatory effect in rheumatoid arthritis, the drug is useful in many such patients. But without doubt Indomethacin is of great benefit in patients with ankylosing spondylitis. Reiter's disease, psoriatic arthritis, and acute gout. It's benefit in these later patients is so unequivocal that a double-blind trial is, I believe, unnecessary and likely redundant. The few negative reports should not out weight the preponderant positive evidence of the usefulness of this drug.

Sincerely,

PAUL J. BILKA, M.D.

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LOUISVILLE, KY., *April 23, 1968.*

DR. MAX TISHLER,
*Merck Research Laboratories,*
*Merck, Inc.,*
*Rahway, N.J.*

DEAR DR. TISHLER: I have been asked to comment on the evaluation of drugs in rheumatoid arthritis, and the question of effectiveness of indomethacin.

I am enclosing a reprint of one of my papers published in the J.A.M.A. Although my remarks related to the difficulty in assessing the effects of drugs in rheumatoid arthritis were written with special regard to corticosteroids, I think they remain pertinent to the present question. (See bottom of page 1254 under heading "Rationale of Procedure" and top of page 1254 as marked.)

Concerning indomethacin, my feeling is that this compound is effective in acute gouty arthritis and ankylosing spondylitis. Response in rheumatoid arthritis is not predictable without clinical trial but certain rheumatoid patients seem to derive benefit.

I hope this information will be useful.

Sincerely,

DAVID H. NEUSTADT, M.D.,
*Associate Clinical Professor of Medicine, Chief, Section on Rheumatic Diseases, University of Louisville School of Medicine.*

[From J.A.M.A., July 11, 1959, p. 1254]

RATIONALE OF PROCEDURE

There is no completely reliable plan or method of evaluating a new agent in rheumatoid arthritis that is not associated with certain shortcomings. To control all variables that come into play in a chronic disease of unknown origin subject to spontaneous fluctuations is a problem which has recently received well-deserved attention.

Short-term observations may be misleading. However, if one omits patients from a study who received a drug for short periods, one may be accused of influencing the final statistical results. Also there may have been some important reason for withdrawing the drug early in the study.

Double-blind and random selection studies are considered by some to disclose results of greater scientific precision than the older and more conventional type of evaluation study. However a double-blind technique also carries with it certain disadvantages that may compromise its value. In conducting studies with a relatively inactive drug (slowly acting agent), such as an antimalarial agent or a gold salt, a double-blind study can be carried out. When employing a corticosteroid which has powerful suppressive capacity, abrupt withdrawal and

placebo substitution is immediately noticed by the majority of patients. Sudden discontinuance also is not without danger because of the possibility of producing a marked degree of adrenal insufficiency. This hypoadrenal state can become an acute and serious medical emergency. Also random selection introduces a number of patients who may be unreliable and are not suitable for testing. Thus, it is almost impossible to carry out such a program without both influencing patients and introducing added difficulties.

For these reasons patients were carefully screened to include only those with well-established rheumatoid arthritis of over one year's duration and to exclude hyperreactors, unreliable patients, and hypersensitive ones.

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OCHSNER CLINIC,
*New Orleans, La., April 23, 1968.*

DR. MAX TISHLER,
*Merck Research Laboratory,*
*Merck & Co. Corp.,*
*Rahway, N.J.*

DEAR DR. TISHLER: Recently it has come to my attention that a Congressional body was considering a recommendation that Indocin be removed from the open market and reclassified so that additional double blind studies could be carried out in attempting to establish its role in the treatment of arthritis.

I had the opportunity to prescribe Indocin in the earlier days when it was available in tablet form, and, of course, was not impressed by the results that we obtained. When the new physical changes were made, and it was furnished in capsule form, I gained the impression that it offered symptomatic relief and in some cases favorable objective changes in a significant number of arthritic patients.

At least 95% of my practice deals with arthritic patients; I have had occasion to prescribe for these sufferers for many years and have now placed Indocin as a valuable drug adjunct in the therapeutic armamentarium.

Patients whom I see comprise a group that I have had an occasion to watch for many years and, as I have maintained in the past, it is only after observing arthritic patients over a minimum of a three year span am I able to gain some insight into what pattern the disease may follow. Realizing this, I appreciate that drug response varies from patient to patient.

My personal conclusions are that Indocin is of definite symptomatic benefit in a large group of patients with arthritis. Gouty patients obtained significant releif from their acute gouty pan when Indocin is administered and the chronic gouty arthritic who is unable to take aspirin medication or Butazolidin will frequently be very thankful because Indocin relieves them of their chronic, nagging joint aches. They can continue to take Indocin without it interfering with uricosuric drugs or where geographcial location makes it unable to obtain blood counts that must be used to guide treatment with Butazolidin. This also is an economic factor when repeated lab studies must be carried out in patients who are given an agent such as Butazolidin.

Ankylosing spondylitis and osteoarthritis of the spine frequently cause patients a considerable amount of pain and incapacitation and Indocin has proven very helpful for these patients, and it is my opinion that it has kept many of these people on the job or in school.

Other types of non-specific rheumatism, such as bursitis, tendinitis, and giant cell arteritis, also seem to respond symptomatically and the patients are thankful for having such an agent available.

In rheumatoid arthritis the drug gives a certain number of patients a significant amount of subjective relief, allowing them to carry out the arthritis exercises and other basic parts of their treatment. Here, too, I feel that the comfort obtained allows them to carry on with their daily obligations and lead a more normal life. It seems to offer an adjunct to aspirin medication, which is our best antirheumatic drug, and does not seem to interfere with other agents, such as gold salts. It also has allowed me to reduce the quantity of adrenal steroids that some patients seem to require to remain functional. I have watched patients use Indocin long enough that occasionally they are under the impression that the drug is no longer giving them any beneficial effect and they discontinue its use on their own, or request permission to discontinue it, and more often than not they find that resuming the drug does give them an added benefit. I find that the symptomatic response to Indocin is often unpredictable for the rheumatoid arthritic patient.

The toxic effect of the agent is appreciated, but to date I do not recognize that it is any more irritating to the stomach than Butazolidin or aspirin and the other annoyances, such as headache, dizziness, etc., are transient and disappear once the drug has been reduced.

I am familiar with the published articles that question the value of Indocin, but I do not feel that double blind studies necessarily reflect the true value of a drug for stages of these diseases change, and only by watching patients for many years can we evaluate a drug response.

In my mind and those of my associates, this drug is of value for the arthritic patient and we would feel that it would do the patients an injustice to remove it from the market at this time, and in my own mind I question how long double blind studies would have to be carried out before they would be effective and meaningful. It seems that any double blind study would take at least ten years and the evidence against the drug does not validate such a move.

Yours truly,

THOMAS E. WEISS, M.D.

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LOUISVILLE, KY., *April 23, 1968.*

Dr. MAX TISHLER,
*Merck Research Laboratories,*
*Merck & Co., Inc.,*
*Rahway, N.J.*

DEAR DR. TISHLER: It has come to my attention that a congressional committee is investigating the drug Indocin (indomethacin).

I should like to state that there are many clincial indications for its use, certain situations where it is the drug of choice and that these comments are borne out by experience with a variety of disease entities.

Sincerely,

WILLIAM P. PEAK, M.D.

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HENRY FORD HOSPITAL,
*Detroit, Mich., April 23, 1968.*

Dr. MAX TISHLER,
*Merck Research Laboratories, Inc.,*
*Rahway, N.J.*

DEAR DOCTOR TISHLER: I have learned the Nelson Committee is investigating the efficacy of Indocin. In view of these developments, I thought you might be interested in our comments.

It has been our experience that Indocin is both antiinflammatory and anti-rheumatic. It has been a useful adjunct in the management of patients with osteroarthritis, rheumatoid arthritis, ankylosing spondylitis, and gout. In some instances of hypercortisonism, it has been a useful antirheumatic agent when steroids were withdrawn.

Although the antirheumatic and anti-inflammatory effects of Indocin may be unpredictable, Indocin has been a welcome addition to our armamentarium.

Sincerely yours,

JOHN W. SIGLER, M.D.,
*Chief, Division of Rheumatology.*

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NEW YORK, N.Y. *April 23, 1968.*

Dr. MAX TISHLER,
*Merck Research Laboratories,*
*Merck & Co. Inc.,*
*Rahway, N.J.*

DEAR DR. TISHLER: I have been informed that the Nelson Committee is considering Indocin, and one of the points under consideration is that it is no more effective than Aspirin in the treatment of rheumatic disease. To date, I have administered Indocin to more than four hundred patients. I have also had the occasion to compare the results of Indocin with a number of Aspirin preparations.

I was doing a double blind test on various preparations of Aspirin and a number of patients were taken off of Indocin to be included in this Aspirin study after two weeks without medication. These patients, after finishing the Aspirin study and another two week period without medication, were again returned to the Indocin. I was aware at the time that there had been a question raised as to whether Indocin was more effective than Aspirin. I, therefore, was interested

in the clinical comparison and, in my opinion, Indocin is definitely superior to Aspirin in the treatment of various forms of rheumatic disease. It, of course, does not control every case but it does help a great many where Aspirin fails to do so.

I am also fully acquainted with the Mainland report, and I think the criteria used are unrealistic and do not give a real evaluation of the drug being studied.

Sincerely yours,

WILLIAM B. RAWLS, M.D.

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ARTHRITIS REHABILITATION CENTER,
*Washington, D.C., April 23, 1968.*

DR. MAX TISHLER,
*Merck Research Laboratories,*
*Merck & Co., Inc.,*
*Rahway, N.J.*

DEAR DOCTOR TISHLER: I am writing you about our experiences with Indomethacin when used as a therapeutic agent in the management of patients suffering from rheumatoid arthritis. First, let me say that our practice is limited to the diagnosis and treatment of patients with arthritis and rheumatic diseases, that we register over one hundred new cases of rheumatoid arthritis every year and that we have not less than two hundred cases of that condition under close observation at all times. I have checked my Diagnosis File and find that since I first opened an office in 1937, a diagnosis of rheumatoid arthritis has been made in 2,043 patients.

Against the above background, it is my opinion that Indomethacin is an extremely valuable agent in the management of this potentially disabling condition and that it has been an important addition to our medical armamentarium. Thus, we have found patients who did not respond to aspirin, phenylbutazone or oxyphenbutazone, who did respond to Indomethacin. By "respond", I mean that the patients would note less pain and stiffness while the physician would observe lessening of the swelling and increase in the motion of involved joints. Furthermore, patients who have originally shown response to aspirin or one of the other drugs, may later become resistant to that drug and then respond to Indomethacin.

Of course, the reverse is also true and some patients who respond to aspirin and phenylbutazone or oxyphenbutazone will not respond to Indomethacin and some of those who do respond to Indomethacin will later become resistant to it.

I confidently hope that the day is not too far off when we will have a "cure" for rheumatoid arthritis. However, no "cure" is known today, and we must therefore use every therapeutic modality available in our fight against this chronic and too often devastating disease. Any drug which will help retard the condition—even if only for a time—is one to be used as long as it brings about relief. In this context, Indomethacin has earned its place as an agent which should be available to any physician treating rheumatoid arthritis.

Very sincerely,

DARRELL C. CRAIN, M.D.

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THE LANKENAU MEDICAL BUILDING,
*Philadelphia, Pa., April 24, 1968.*

DR. MAX TISHLER,
*Merck Research Laboratories,*
*Merck & Co., Inc.,*
*Rahway, N.J.*

DEAR DOCTOR TISHLER: I have been recently advised of the question which has been brought up regarding the efficacy of Indocin. I would like to have the privilege of speaking to this.

Indocin has been extremely helpful in my practice in the management of a multiplicity of problems. I have a large pure rheumatologic practice. A rough estimate of my experience with Indocin would include approximately thirty rheumatoid spondolytics, perhaps 200 rheumatoid arthritics and innumerable osteoarthritics and gouts. I am amused by the remarks I recently read regarding the need to do double blind studies with Indocin. There can be absolutely no equivocation as to the efficacy of Indocin in a host of rheumatic disease. After fifteen years of a practice limited to rheumatology one cannot make mistakes

of this type. This is so emphatically evident in the rheumatoid spondolytic that I consider this observation, though it may not be effective, an enormous joke; however, misleading the public, medical lay is dangerous and grave enough a situation to prompt me writing you.

Indocin is certainly not effective in all, in fact a much smaller percentage of my patients than I had hoped, and it has some unhappy side effects which require careful observation, but it must be perfectly evident that I would find it very difficult to practice rheumotology without this valuable arm.

I should be happy to provide statistics if you care for them.

Very truly yours,

ERNEST M. BROWN, Jr., M.D.

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MAYO CLINIC,
*Rochester, Minn., April 24, 1968.*

MAX TISHLER, Ph. D.,
*President, Merck Sharp & Dohme*
*Research Laboratories,*
*Rahway, N.J.*

DEAR DOCTOR TISHLER: It has been brought to my attention that the matter of the effectiveness of indomethacin may be questioned at a future congressional hearing on drugs. As a rheumatologist, I have had considerable experience with the use of indomethacin in patients with a wide variety of rheumatic diseases and I would be most distressed if this drug were not available for use in appropriate rheumatic diseases. I have found that many patients derive helpful relief of rheumatic symptoms from indomethacin, relief which often has not been obtainable with other simple analgesic medications. As is the case with all of the anti-rheumatic medications, there are some side effects resulting from the use of indomethacin but in my experience proper regulation of dosage and proper observation of the patient has enabled the use of indomethacin without undue risk considering its beneficial effects.

Sincerely yours,

EMMERSON WARD, M.D.

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ORTHOPEDIC AND ARTHRITIS CENTER,
*Oklahoma City, April 25, 1968.*

Dr. MAX TISHLER,
*Merck Research Laboratories*
*Merck & Co., Inc.,*
*Rahway, N.J.*

DEAR DOCTOR TISHLER: This letter is written regarding our work with indomethacin. We first began using this drug in 1961. At that time, a double blind study was carried out with indomethacin on patients with rheumatoid arthritis. It was directed by Dr. Richard Payne who is in charge of our drug evaluation studies. Recently, we have completed a study, again using the double blind technique on the use of indomethacin in patients with osteoarthritis. The results of the first study have been published (Payne, R. W.: Treatment of Rheumatoid Arthritis with Indomethacin, Jour. of Oklahoma State Medical Association, 553–537, December 1965). The results of the study on osteoarthritis have just been completed and the paper is now at the publishers.

The difficulty in evaluating drugs in the treatment of any form of arthritis is well recognized. We have felt that indomethacin is useful in a small but significant group of patients. This would be in the neighborhood of one patient out of four or five. The ones who fail to respond, of course, get no results but those who do respond may develop very desirable effects which, in some instances, would encourage a natural remission of the disorder.

If more details are needed regarding our work with indomethacin, please advise.

Sincerely yours,

WILLIAM K. ISHMAEL, M.D.

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[Cable received in New York from São Paulo]

SÃO PAULO, *April 25, 1968.*

**Mezey Reyour cable following are Dr. Cobra's statements addressed to Dr. Max Tishler quote in the light of my extensive experience in the management**

of diseases for which indomethacin is indicated I have found that: indomethacin has highly contributed to the better management of our rheumatic patients, senso lato, when administered within certain dosage limits, 25 to 75 milligrams orally per day or 100 mg. per day by rectal use. Above these limits there is a high increase in the incidences of side effects which limit the advantage in the use of the drug.

Indomethacin represents a valuable advance in the sense that it facilitated the compensation of certain chronic inflamatory syndromes and permitted the reduction of doses of other drugs such as phenylbutazone and steroids thereby reducing many of their side effects. Indomethacin alone; i.e., without being associated with other drugs or with other therapeutic measures does not seem useful to us because in most of the cases the necessary doses surpass the limits described above. Indomethacin has shown itself efficient as an Adguvant E. "compensation" treatment of patients with rheumatoid arthritis anylosing spondylitis and chronic gout arthritis as well as in the painful stage of osteoarthritis.

Summarizing: As a drug used alone indomethacin is efficient only in large doses but with a consequent high incidence of side effects. Indomethacin represents a drug of decisive efficacy when in moderated doses it is combined with other drugs.

Original statement being mailed today.

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[Cable received in New York from Mexico]

MEXICO, *April 25, 1968.*

DR. K. C. MEZEY, *Merck:*

Robles Gil reply as follows: 1 Since Indomethacin is drug that frequently allow treating patients in best way, 2 Indomethacin produces response in patient on whom previous treatment did not produce therapeutic response and permits the reduction of other drug such as corticosteroids. 3 Principal Indomethacin indication are rheumatoid arthritis. Degenerative articular problems gout. Memo follows.

IBARRA.

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THE UNITED NEWCASTLE UPON TYNE HOSPITALS,
*Newcastle Upon Tyne, April 25, 1968.*

DR. R. HODKINSON,
*Medical Unit,*
*Merck Sharp & Dohme Limited,*
*Hoddesdon, Hertfordshire.*

DEAR DR. HODGKINSON, I understand that the United States Senate is currently reviewing some aspects of the drug industry, including the status of Indomethacin. I have knowledge of articles published in non-medical journals, namely the Wall Street Journal and the Sunday Times, which have contained references to Indomethacin. In my opinion, these articles were inadequate and inaccurate in many aspects, as they failed to mention the properly conducted and controlled clinical trails which were done in 1962 and 1963, and which demonstrated the value of Indomethacin in the management of rheumatic disorders. In fact, Indomethacin was subjected to both the most prolonged and careful scrutiny that any drug had ever received prior to its introduction to clinical usage. Controlled trials and a considerable amount of subsequent clinical experience have fully justified the place of Indomethacin in Rheumatology.

I also feel that unjustifiable emphasis has been placed on side effects which are common to every drug used in medical practice, and in my opinion, the careful administration of Indomethacin constitutes one of the safest and most effective methods of drug treatment in the management of numerous rheumatic conditions. In particular Indomethacin is virtually exempt from the risk of haematopoietic, hepatic and renal side effects which complicate the use of many other drugs in rheumatology.

If you feel it would be helpful to produce this letter and the appended statement of my views on the usage of Indomethacin in rheumatology, you have my permission to do so.

Yours sincerely,

MALCOLM THOMPSON, M.D., M.R.C.P.,
*Consultant Physician.*

Carefully controlled clinical trials have shown Indomethacin to be effective in the treatment of—

Osteoarthritis
Rheumatoid arthritis
Ankylosing spondylitis
Acute gout
Capsulitis of shoulder
Lumbar disk lesion with sciatica

In my experience, Indomethacin has either been the agent of choice or the only agent suitable on many occasions, in the treatment of the above listed conditions.

Dr. LAWRASON. In order to give the committee, Mr. Chairman, the benefit of the expert testimony of men who have thorough and extensive study of this drug, it is my pleasure to present to you first, Dr. John J. Calabro, who is associate professor of medicine at the University of California at Los Angeles School of Medicine and chief of the rheumatology section at Wadsworth Hospital, VA Center, in Los Angeles. It should be noted that Dr. Calabro has been, since 1963, the official representative to the National Society for Medical Research for the American Rheumatism Association.

Senator NELSON. We appreciate your coming here today, Doctor. Do you have a statement?

## STATEMENT OF JOHN J. CALABRO, M.D., ASSOCIATE PROFESSOR OF MEDICINE, DEPARTMENT OF MEDICINE, UCLA SCHOOL OF MEDICINE, CENTER FOR THE HEALTH SCIENCES; AND CHIEF, RHEUMATOLOGY SECTION, WADSWORTH HOSPITAL, VETERANS' ADMINISTRATION CENTER, LOS ANGELES, CALIF.

Dr. CALABRO. I have a letter directed to you, Senator Nelson, and dated April 23.

I would like to begin first by submitting my credentials, my curriculum vitae. I am full-time associate professor of medicine at UCLA School of Medicine and, in that capacity, chief of the rheumatology section of an affiliated hospital, Wadsworth Hospital, VA Center, Los Angeles. I do not engage in the private practice of medicine. I am a full-time teacher and clinical investigator in the field of rheumatology.

(The curriculum vitae of Dr. Calabro follows:)

CURRICULUM VITAE, JOHN JAMES CALABRO, M.D., MAY 1968

PRESENT POSITIONS (SINCE OCTOBER 1967)

Chief, rheumatology section, Wadsworth Hospital, Veterans Administration Center, Los Angeles, Calif. 90073.

Associate professor of medicine, Department of Medicine, UCLA School of Medicine, Los Angeles, Calif. 90024

Born: Buffalo, New York—May 18, 1924.

Marital Status: Married—July 9, 1967—Mrs. Josephine (Puglisi) Calabro.

Medical Licensure: New York (75896) October 5, 1954, New Jersey (196498) June 4, 1958, California (G-14611) May 6, 1968.

Military Service: July 1944–June 1946 USNR, PhM 3/c.

Education: B.S., 1947, Canisius College, Buffalo, New York; Postgrad. Biology, September 1947–June 1948, Canisius College, Buffalo, New York; M.D., 1952, "cum laude" Georgetown University, School of Medicine, Washington, D.C.

Graduate Medical Education: Rotating intern, July 1952—June 1953, Mercy Hospital, Buffalo, New York; Junior Assistant Medical Resident, July 1953–June 1954, Georgetown University Hospital, Washington, D.C.; Senior Assistant

Medical Resident, July 1954–June 1955, Georgetown University, Washington, D.C.; Chief Medical Resident, July 1955–June 1956, Fourth (Harvard) Medical Service, Boston City Hospital, Boston, Massachusetts; Chief Medical Resident, July 1956–April 1957, Jersey City Medical Center, Jersey City 4, New Jersey; Visiting Clinical Fellow in Arthritis, April–June 1957, Hammersmith Hospital, London, England, Juvenile Rheumatism Unit, Taplow, England (under Prof. E. G. L. Bywaters); Clinical and Research Fellow, in Medicine (For study of Arthritis), July 1957–January 1959, Massachusetts General Hospital, Boston, Massachusetts.

Previous Academic Positions: Instructor in Biology, Sept. 1947–June 1948, Canisius College, Buffalo New York; Assistant in Medicine, July 1954–June 1955, Georgetown University School of Medicine, Washington, D.C.; Instructor in Bacteriology, July 1954–June 1955, Georgetown University School of Medicine, Washington, D.C.; Assistant in Medicine, July 1955–June 1956, Harvard Medical School, Boston, Massachusetts; Instructor in Medicine, July 1956–June 1957, Seton Hall College of Medicine, Jersey City 4, New Jersey; Visiting Fellow in Arthritis, April–June 1957, Postgraduate Medical School of London, London, England; Research Fellow in Medicine, July 1957–June 1958, Harvard Medical School, Boston, Massachusetts; Instructor in Medicine, July 1957–June 1958, (on leave of absence), Seton Hall College of Medicine, Jersey City, New Jersey; Assistant Professor of Medicine, July 1958–June 1962, Seton Hall College of Medicine, Jersey City, New Jersey; Associate Professor of Medicine, July 1962–October 1967, New Jersey College of Medicine (formerly Seton Hall College of Medicine), Jersey City, New Jersey.

Past Hospital Appointments: Director, Division of Rheumatology, July 1966 to October 1967, Veterans Administration Hospital, East Orange, New Jersey 07019; Assistant Attending Physician in Medicine for Rheumatic Diseases, January 1967 to October 1967, Newark City Hospital, Newark, New Jersey 07107; Assistant Attending Physician in Medicine for Rheumatology, April 1960 to October 1967, B. S. Pollak Hospital, Jersey City, New Jersey 07304; Attending Physician in Medicine, Chief, Arthritis Clinic, July 1958 to October 1967, Jersey City Medical Center, Jersey City, New Jersey 07304; Consultant in Rheumatology, April 1963 to October 1967 USPH Service Hospital, Staten Island, New York.

Scientific Societies: Diplomate, National Board of Medical Examiners, June 25, 1953; Certified, American Board of Internal Medicine, 1963; Fellow, American College of Physicians; Associate Fellow, American College of Cardiology; American Medical Association; Association of American Medical Colleges; American Association for the Advancement of Science; American Medical Writers' Association; American Heart Association; New York Academy of Sciences; American Rheumatism Association; Southern California Rheumatism Society; Horseshoe Club of England; The DiGamma Society of Canisius College.

Special Activities: American Rheumatism Association: Member, Education Committee, 1961–1962; Member, Committee on Exhibits, 1962–1963; 1964–present; Representative to National Society for Medical Research, 1963–present. The Arthritis Foundation: Delegate, Interchapter Medical & Scientific Committee, 1959–1967. National Association of Broadcasters Scientific Advisory Panel, Member, 1965 to present. Member, Editorial Board (Rheumatology Consultant), International Journal of Industrial Medicine and Surgery, 1967. Southern California Chapter, The Arthritis Foundation, Member, Medical and Scientific Committee, 1967; Chairman, Education Committee, 1967; Chairman, Postgraduate Seminar for SCGP Society, April 20, 1967.

Awards and Honors:

(1) Canisius College, 1947: Graduation honor for excellence in philosophy.

(2) New York State, 1947: War service scholarship.

(3) Georgetown Medical School: Gold medals for highest academic standing in Bacteriology and Obstetrics & Gynecology. Honorable mention in Medicine, Oncology and Psychiatry. Cahill medal for highest academic standing in Surgery. Pediatric Thesis Award. C. V. Mosby Co. Award for highest academic standing in Senior Year.

(4) The Arthritis Foundation, New Jersey Chapter, May 1967: The Robert Wood Johnson Humanitarian Award presented "For his dedication to the betterment of his fellow man and his devoted service to juvenile arthritis patients." This award is made annually to a native or resident of New Jersey who has made an outstanding contribution toward the better-

ment of his fellow man in the fields of medicine, social service or community activity.

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15. Calabro, J. J.: Clinical aspects and medical management of chronic arthritides. J. Am. Phys. Ther. Assoc. *44*:584–591 (July) 1964.

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20. Calabro, J. J., and Amante, C. M.: Prognosis in ankylosing spondylitis. Arthritis Rheum. *11*: (June) 1968.

Scientific exhibits: (Each exhibit has been shown at the Annual Meeting of the American Medical Association, Clinical Session of the American Medical Association, Annual Meeting of the American Academy of General Practice, and the Annual Meeting of the Medical Society of New Jersey)

1959–1960: Wax moulage exhibit: "The feet in rheumatoid arthritis." Portrays clinical and radiologic features of feet of patients with rheumatoid arthritis, with special reference to heel and metatarsal lesions. (Calabro, J. J., Nosenzo, C. J., and Traugott, F.)

1960–1961: Wax moulage exhibit: "Arthritic feet." Utilizing the clinical and radiologic features of arthritic feet in the differential diagnosis of arthritis, including psoriatic arthropathy, rheumatoid arthritis, acute gouty arthritis, diabetic neuropathic joint disease and chronic tophaceous arthritis. (Calabro, J. J., Nosenzo, C. J., and Traugott, F.)

1961–1962: Ectochrome transparency exhibit: "Juvenile rheumatoid arthritis." Ectochrome illustrations demonstrating the protean manifestations of juvenile rheumatoid arthritis. (Calabro, J. J., Catsoulis, E., Nosenzo, C. J., and Traugott, F.)

1963–1964. Wax moulage exhibit: "The foot as an aid in the differential diagnosis of arthritis." (Calabro, J. J., Nosenzo, C. J., Luczynski, E., Jr., Abruzzo, J. L., Mody, R. E., and Traugott, F.) Award: AMA Honorable Mentiton.

1964–1965: Ectochrome tranparency exhibit: "Tietze's Syndrome." (Calabro, J. J., Marchesano, J. M., Mody, R. E., Ruderman, J. E., Abruzzo, J. L., and Traugott, F.) Award: AMA Certificate of Merit.

Presentations of papers at national or international meetings:

June 2–6, 1959 (Washington, D.C.): Second Pan-American Congress on Rheumatic Diseases, in conjunction with the 23rd Annual Meeting of the American Rheumatism Association. Delivered paper on "The Feet in Rheumatoid Arthritis." Co-authored two other papers, one on "Some Observation on the Clinical, Chemical and Serologic Manifestations on Rheumatoid Arthritis. Based on a Study of the Course of 150 Cases." and "X-ray Examination of the Spine of Patients With Rheumatoid Arthritis and Spondylitis: A Correlation with Serologic and Clinical Manifestations of Disease."

September 4–7, 1961 (Rome, Italy): 10th International Congress of Rheumatology. Delivered paper on "The Foot as an Aid in the Differential Diagnosis of Arthritis."

September 13–15, 1962 (London, England): Salicylates: An International Symposium. Sponsored by the Empire Rheumatism Council, with the support of the Nicholas Research Institute, Ltd.: Held at the Post Graduate School of London. Discussor of therapeutic role of aspirin in rheumatoid arthritis.

June 13–14, 1963 (Atlantic City, New Jersey): Annual Meeting of the American Rheumatism Association. Co-chairman of arrangements. Delivered paper on "Observation on the Fever and Rash of Juvenile Rheumatoid Arthritis."

October 15–19, 1963 (Santiago, Chile): Third Pan-American Congress on Rheumatic Diseases. Delivered paper on "The Protean Manifestations of Juvenile Rheumatoid Arthritis."

October 1–3, 1964 (Princeton, New Jersey) : Conference on Gout and Purine Metabolism. Sponsored by the American Rheumatism Association, the National Institutes of Arthritis and Metobolic Diseases, and the Arthritis Foundation. Participant in clinical discussions.

June 17–18, 1965 (Philadelphia, Pa.) : Annual meeting of the American Rheumatism Association. Delivered paper on "Prognosis in Juvenile Rheumatoid Arthritis."

December 5–11, 1965 (Mar Del Plata, Argentina) : XIth International Congress of Rheumatology. Delivered paper on "Patterns of Onset and Course of Juvenile Rheumatoid Arthritis." Arthritis Foundation Travel Grant.

June 6–10, 1966 (New York, N.Y.) : Second International Symposium on Population Studies of the Rheumatic Diseases. Sponsored by NIH and the Arthritis Foundation. Secretary of the Council on Diagnostic Criteria for Juvenile Rheumatoid Arthritis. Member of Committee on Diagnostic Criteria for Ankylosing Spondylitis.

June 13–14, 1966 (New York, N.Y.) : International Conference on Chronic Administration of Salicylates. Sponsored by NIH and the Arthritis Foundation. Delivered paper on "Role of Salicylates in Juvenile Rheumatoid Arthritis."

June 16–17, 1966 (New York, N.Y.) : Annual Meeting of the American Rheumatism Association. Delivered paper on "Idiopathic Hypertrophic Osteoarthropathy (Pachydermoperiostosis) : Onset Before Puberty."

December 2–3, 1966 (Cincinnati, Ohio) : 12th Interim Scientific Session of the American Rheumatism Association. Delivered paper on "The Rash Associated With Juvenile Rheumatoid Arthritis."

June 15–16, 1967 (New York, N.Y.) : Annual Meeting of the American Rheumatism Association. Co-author of paper entitled "Rheumatoid Factor in Ankylosing Spondylitis." Chairman of one concurrent session.

Oct. 22–26, 1967 (Mexico City, Mexico) : IV Pan-American Congress of Rheumatology. Delivered two papers, one on "Indomethacin in Ankylosing Spondylitis," the other on "Prognosis in Ankylosing Spondylitis." Chairman of session on juvenile rheumatoid arthritis and Reiter's syndrome.

November 13–20, 1967 (Rome, Italy) : International Clinical Symposium, sponsored by Rome University in coorperation with the National Academy of Clinicians. Delivered several talks entitled "Situations in Rheumatology."

Dr. CALABRO. In my two-page letter dated April 23, I have summarized my experience and knowledge of the drug indomethacin and its role in patients with various rheumatic diseases.

My first comment pertains to recent reports of double-blind studies of indomethacin in rheumatoid arthritis. Conclusion of such studies have led to some controversy concerning the efficacy of this drug as an antirheumatic agent in patients with rheumatoid diseases. It is my opinion that, while double-blind studies are obviously useful in evaluating new agents, they are also extremely difficult to interpret, particularly in such a capricious disease—I am sure this has been stressed throughout the hearings—as rheumatoid arthritis. To this point, I might add—and I do not think this has been stressed—that there are few, if any, double-blind trials with other antirheumatic agents in rheumatic arthritis that are entirely satisfactory. These would include adrenocorticosteriods, gold compounds, antimalarials, phenylbutazone, and the well-known salicylates—drugs that are generally accepted in the care of rheumatoid patients.

Even controlled crossover techniques of drug testing can be faulty. In that regard, I would like to point to a publication that appeared in the Canadian Medical Association Journal on June 3, 1967. This is an article by a rheumatologist, T. D. Kinsella, and coworkers, MacKenzie, Kim, and Johnson. The title of this article, and I will submit this for the record, from the Journal of the Canadian Medical Association, is "Evaluation of Indomethacin by a Controlled, Crossover Technique in 30 Patients with Ankylosing Spondylitis."

(The document referred to follows:)

[From Canadian Medical Association Journal, vol. 6, June 3, 1967, pp. 1454–1459]

# Evaluation of Indomethacin by a Controlled, Cross-over Technique in 30 Patients with Ankylosing Spondylitis*

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A clinical evaluation of indomethacin employing a controlled, cross-over technique with an inert placebo was undertaken in 30 patients with ankylosing spondylitis. Patients were studied for the frequency and dose relationship of side effects and for the subjective response of morning stiffness, chronic spinal pain, acute exacerbations of pain and peripheral arthralgia. Objective evaluation assessed measured change in movements of the cervical and lumbar spines, in chest expansion and in the range of movement of involved peripheral joints.

Evaluation of the results indicated that a significant number of patients experienced side effects in the form of headache and dizziness while receiving indomethacin in doses above 150 mg. per day. Many other side effects reported by the patients were not found to occur at a statistically significant level. The significance of pulmonary infections encountered in three patients was reviewed. Relief of chronic spinal pain and peripheral arthralgia occurred in 14 and 16 patients, respectively ($p < 0.05$). Relief of morning stiffness and acute exacerbation of pain, and increase in the range of movement of any of the segments of the spine or the involved peripheral joints were not significant ($p > 0.05$). Based on the results of this study, it is suggested that the role of idomethancin in the management of ankylosing spondylitis be re-evaluated and that the daily therapeutic dose of this drug which has been heretofore recommended be decreased.

Indomethancin is a non-steroid anti-inflammatory drug which has been reported to be of therapeutic value in a variety of rheumatic diseases.[1–4] Among the latter, ankylosing spondylitis has been reported to respond particularly well.[5–7] Because a large group of patients with ankylosing spondylitis previously studied[8] was available at Queen Mary Veterans' Hospital, a detailed controlled, crossover trial with indomethacin and a placebo was conducted on some of these patients to assess further the therapeutic efficacy of this agent.

## MATERIALS AND METHODS

All patients in this study conformed to the criteria proposed by Kellgren[9] for the diagnosis of ankylosing spondylitis. Forty-eight patients were chosen at random as possible candidates; all of the latter were specifically advised of the side effects which were known to occur with indomethacin. Table I illustrates the eventual composition of the series. Only those patients who had clearly defined and persistent symptomathology were started on therapy. All patients were continued on their previous forms of medication, and these are indicated in Table II.

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Presented at Second Laurentian Rheumatology Conference, International Symposium on Non-steroid Anti-inflammatory Compounds. Saint Marguerite, P.Q., Canada, October 20–22, 1966.

NOTE.—Numbered footnotes at end of article, p. 3412.

TABLE I.—*Composition of study*

| | *Patients* |
|---|---|
| Originally chosen for study | 48 |
| Started on medication | [1] 38 |
| Lost to study: | |
| Failed to cooperate | 5 |
| Developed side effects | 3 |
| Completed study | 30 |

[1] 10 omitted—inability to cooperate or lack of consistent, well-defined symptoms.

TABLE II.—DISTRIBUTION OF TYPES OF MEDICATION EMPLOYED (OTHER THAN INDOMETHACIN) IN 30 PATIENTS WITH ANKYLOSING SPONDYLITIS

| Type of medication | Daily dosage range (mg.) | Number of patients [1] |
|---|---|---|
| A.S.A.[2] | ≤1,200 | 12 |
| | >1,200 | 9 |
| Phenylbutazone | ≤400 | 10 |
| | >400 | 0 |
| Steroids [3] | ≤5 | 3 |
| | >5 | 0 |
| None | | 5 |

[1] Total exceeds 30, since some patients employed more than 1 type of medication.
[2] A.S.A.=acetylsalicylic acid.
[3] Steroids expressed in equivalents of prednisone.

The range of the duration of illness in these patients was from 13 to 26 years, with a mean of 20.1 years. Capsules of indomethacin (25 mg.) and the placebo for oral use, and rectal suppositories of indomethacin (100 mg.) and the placebo were provided in identical forms. One suppository of the appropriate form was used at bedtime during the first six days of the first period of assessment. This procedure was not repeated during the second period of assessment, since it was felt that the patients would have become aware that substitution or "cross-over" had taken place. The dosage schedule for capsule therapy was 25 mg. twice a day for two days, then 25 mg. four times a day for two days, then 50 mg. three times a day for two days and then 50 mg. four times a day. Although indomethacin and placebo were assigned in a random manner, patients were advised to modify the daily dose, depending upon the occurrence and severity of the side effects experienced.

Reassessment was carried out by the same physician at three, six, nine and 12 weeks after the start of therapy. Cross-over to either indomethacin or placebo was carried out at the end of six weeks, but the assessing physician was not aware of which substance the patient had received. All medication was dispensed in the clinic by one physician who also assessed the frequency and severity of side effects, modification of the dosage schedule was recommended to the patients by this physician when it seemed appropriate. All medication which had not been consumed during each three-week period of assessment was returned by the patients to this physician, who then provided a further supply of a known amount of the appropriate medication.

Assessment of the therapeutic response was based upon both subjective and objective evaluation of the patients. The subjective evaluation was based on patients' opinions, which were graded as to whether the following showed "no change", were "worse" or "improved"; (a) duration and severity of morning stiffness, (b) severity of chronic pain in some or all segments of the vertebral column, (c) frequency and severity of acute exacerbations of pain, and (d) frequency and severity of peripheral arthralgia. Objective response was assessed by the following measurements: (1) movement in the cervical and lumber spines as shown by the range of forward flexion and lateral flexion, extension and rotation, (2) maximal chest expansion, (3) degree of tenderness on "punch" palpation of the sacroiliac joints and (4) range of movement of the involved peripheral joints. The following criteria were employed to designate objective improvement: increase of at least 15° in each of two of the four basic movements in the cervical and lumbar spines, respectively; a sustained increase of at least one-half inch in chest expansion, improvement in the range of movement of two or more peripheral joints, or of at least 25% in a single peripheral joint.

Laboratory tests were done on each patient at each clinic visit in order to assess

both the side effects and the ability of indomethacin to suppress the various laboratory indices of inflammation. The following tests were performed routinely by conventional methods: complete urinalysis, complete hemogram including erythrocyte sedimentation rate (ESR-Wintrobe), blood urea nitrogen (BUN), serum creatinine, serum alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), serum protein paper electrophoresis, latex test for rheumatoid factor,[10] and antinuclear factor (ANF-LE-Test, Hyland). When indicated, chest film, barium meal, electrocardiogram, urine culture and antibiotic sensitivity (if any), and serum protein immunoelectrophoresis were also done. Statistical evaluation of the results was carried out by the chi-square test according to the method of McNemar, using one degree of freedom.[11]

TABLE III.—30 PATIENTS ON INDOMETHACIN AND PLACEBO: FREQUENCY OF SIDE EFFECTS

| Type of side effect | Indomethacin | | Placebo | |
|---|---|---|---|---|
| | Number | Percent | Number | Percent |
| CNS: | | | | |
| Headache | 15 | [1] 50 | 7 | 23 |
| Dizziness | 12 | [1] 40 | 3 | 10 |
| Depression | 2 | 6 | 1 | 3 |
| "Feeling inebriated" | 5 | 16 | 2 | 6 |
| Miscellaneous | 3 | [2] 10 | 2 | 6 |
| Gastrointestinal: | | | | |
| Anorexia and nausea | 7 | 23 | 7 | 23 |
| Symptoms of peptic ulcer | 11 | 36 | 9 | 30 |
| Skin eruption | 3 | 10 | 0 | 0 |
| Anemia | 6 | 20 | 2 | 6 |
| Elevated alkaline phosphatase | 3 | 10 | 1 | 3 |
| Elevated SGOT | 1 | 3 | 1 | 3 |

[1] Significant at the 0.05 level.
[2] Decreased hearing, blurred vision and drowsiness—1 each.

## RESULTS

Twenty-seven patients completed six-week courses of both indomethacin and placebo, while one patient completed three-week courses of each. Two patients whose initial six-week course consisted of indomethacin and who experienced a severe clinical relapse during the first three weeks of placebo administration were subsequently restarted on indomethacin without the knowledge of the assessing physician. These 30 patients represent those who were assessed by the previously described clinical and laboratory parameters. Three additional patients who were lost to the study had received indomethacin only (Table I).

### *Dose tolerated*

The maximum daily dose of indomethacin tolerated without incapacitating side effects by 15 (50%) of the 30 patients was six capsules (150 mg.) per day, and by five others (16%) was four capsules (100 mg. per day). Thus, only 10 patients (34%) tolerated eight capsules (200 mg.) per day; in comparison to the placebo this was a highly significant difference ($p=0.0015$).

### *Side effects*

Three patients who had received only indomethacin were forced to withdraw from the study (Table I). All of these patients experienced severe central nervous system reactions, principally headache and dizziness. One of these also developed extensive right middle and lower lobe pneumonitis which required hospitalization. The occurrence of a pulmonary infection was also noted in two other patients while they were receiving indomethacin.

Of the 30 patients who completed the study, 24 (80%) developed some form of side effect, as demonstrated either clinically or in the laboratory. Thus only six patients (20%) experienced no side effects while receiving indomethacin. On the other hand, 18 patients (60%) experienced some form of side effect while receiving placebo and 16 (53%) of the entire group experienced one or another of the side effects on both indomethacin and placebo. Viewed in this respect, there was no significant difference in the total number of side effects experienced on indomethacin or placebo ($p > 0.05$).

The types and frequency of the various side effects are listed in Table III. It will be noted that reactions involving the central nervous system occurred with the greatest frequency, particularly those manifesting as headache and dizziness.

With respect to both of these symptoms there was a significant difference between the two treatment groups, the p values being 0.027 and 0.015 respectively. A similar difference was not found between the two treatment groups in regard to other complaints referable to the central nervous system, or indeed to any of the other side effects noted in Table III.

It should be noted that four patients whose gastrointestinal symptoms were severe were investigated by means of a barium meal, but in none of these patients was peptic ulceration demonstrated.

*Subjective response*

The results of subjective evaluation of the response to both drugs are depicted in Fig. 1. It will be seen that significant levels of response were noted with respect to relief of chronic spinal pain and peripheral arthralgia, the actual p values being 0.05 and 0.01, respectively. However, there was no significant difference in the responses of morning stiffness and of acute exacerbations of pain.

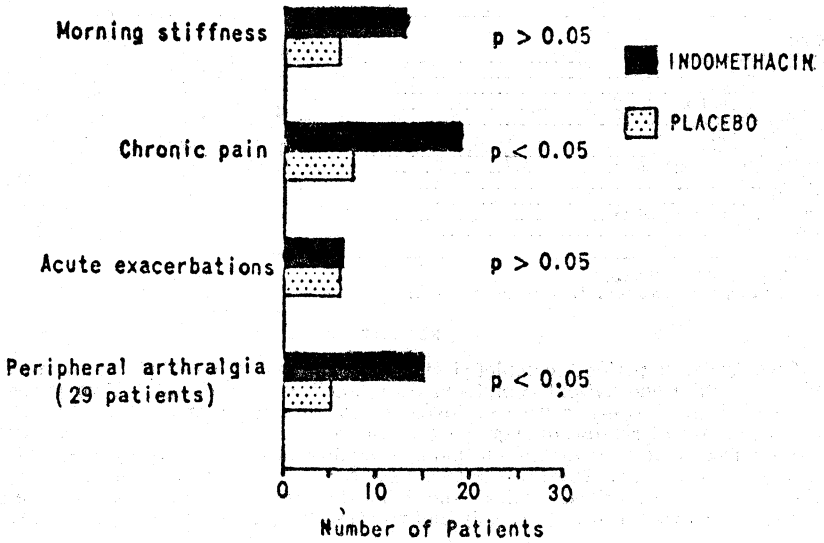



**Fig. 1.—Subjective response to therapy in 30 patients with ankylosing spondylitis.**

*Objective response*

Fig. 2 illustrates the results of objective evaluation of both drugs with respect to the cervical and lumbar spines, chest expansion, and sacroiliac and peripheral joints. It can be seen that in none of these parameters was there a significant difference between the two forms of therapy ($p > 0.05$). Two additional findings should also be noted: first, the very small numbers of patients who demonstrated any subsequent variation in the measurements initially recorded; and second, the lack of correlation between the subjective and objective assessment of the peripheral joints.

TABLE IV.—EFFECT OF INDOMETHACIN AND PLACEBO ON LEVEL OF ESR AND ALPHA-2 GLOBULIN

| | Number of patients | Decreased to normal by: | |
|---|---|---|---|
| | | Indomethacin | Placebo |
| Elevated ESR | 25 | [1] 6 (p>0.05) | 2 |
| Elevated alpha-2 globulin | 26 | [1] 8 (p>0.05) | 3 |

[1] Significant at the 0.05 level.

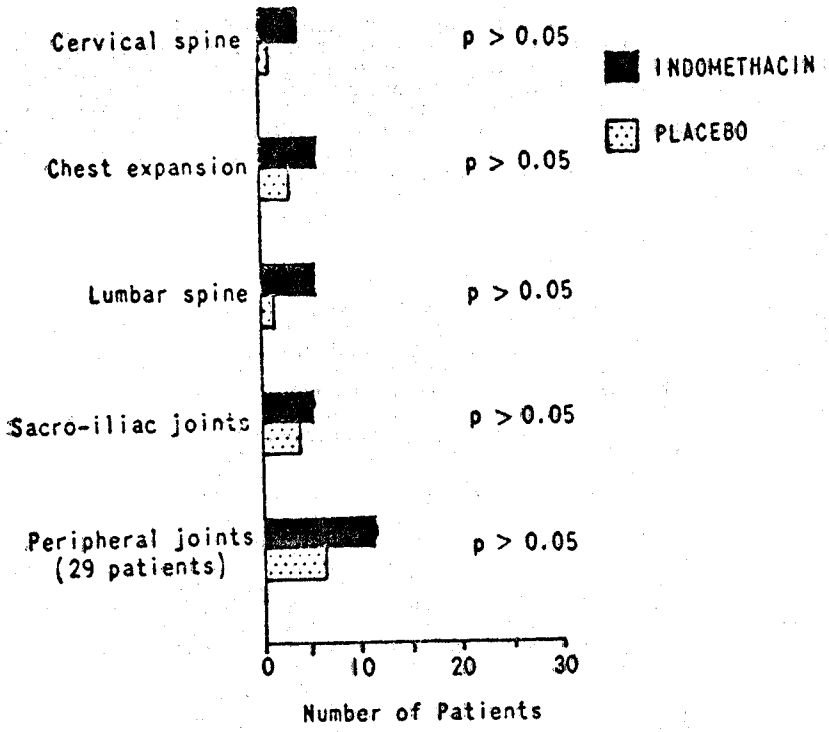



Fig. 2.—Objective response to therapy in 30 patients with ankylosing spondylitis.

*Laboratory results*

No abnormal results were encountered before or during both forms of treatment with respect to the serum antinucleoprotein test, latex fixation test, creatinine and BUN. Similarly, none of the patients exhibited a significant difference in the total white blood cell or differential counts on either drug. It should be noted that two of the three patients who developed a pulmonary infection were able to react with a neutrophilic leukocytosis (range: 11,000 to 21,000 per c.mm.) while the third showed no such response.

Abnormal urine was noted intermittently in eight patients (27%) while taking indomethacin and in 10 patients (33%) while taking a placebo; of the total of 18 patients there were four who had an abnormal urinalysis while receiving both indomethacin and placebo. Thus, 14 patients (47%) in this group showed abnormalities in the urinary sediment. These abnormalities were characterized by minimal proteinuria and microscopic pyuria and were usually not associated with dysuria. Their rate of occurrence could not be related to the administration of indomethacin ($p > 0.05$).

The development of anemia (a fall of hemoglobin of greater than 1 g. %) was noted in six patients (20%) while receiving indomethacin and in two patients (6%) while receiving placebo (Table III): this was not significant at the 0.05 level ($p > 0.05$). It should also be noted that an anemia of less than 13 g. % (range: 9–13 g. %) was present in six other patients before the administration of either drug and remained stable throughout the period of observation. Two patients who complained of symptoms suggestive of peptic ulcer also developed anemia. Investigation of these patients failed to demonstrate occult blood in the stool or, by barium meal examination, an upper gastro-intestinal tract ulceration.

Elevation of the ESR was found at some time during the study in 25 (83%) of the 30 patients, but in only eight, of whom six were receiving indomethacin and two placebo, did the ESR return to nourmal ($p > 0.05$) (Table IV). By

serum protein electrophoresis the alpha-2 globulin was found elevated at some time during the study in 26 (86%) of the 30 patients; in the majority of patients the elevation was slight. The level of the alpha-2 globulin returned to normal values in eight patients (26%) while receiving indomethacin and in three patients (10%) while receiving placebo ($p > 0.05$) (Table IV). Eight (26%) of the patients demonstrated a slight elevation of the serum gamma globulin on paper electrophoresis and none of these showed a significant change in this value during the period of observation. No significant difference at the 0.05 level ($p > 0.05$) was noted with respect to the few patients who developed on abnormal elevation of the level of the serum alkaline phosphatase and glutamic oxaloacetic transaminase (Table III).

## DISCUSSION

The relative value of any medication must be assessed with respect to potentially harmful side effects and the degree of both subjective and objective therapeutic benefits derived from it. The present study was undertaken to assess these factors as they applied to indomethacin in the treatment of ankylosing spondylitis.

In the majority of instances the rate of occurrence of side effects in the present group of patients with spondylitis was not shown to be significant by statistical analysis. It is probable that the many "placebo reactors" in this group resulted because the patients were specifically cautioned regarding these side effects at the onset of the study and because, during the course of the study, considerable attention was directed both to their occurence and to their possible dose relationship. Accordingly, we do not feel that sufficiently unbiased data were obtained from this portion of the study to warrant extensive extrapolation.

Although the data were not shown to be statistically significant, note should be taken of the three patients who developed pulmonary infections while receiving indomethacin. In one patient, resolution occurred only after three weeks of antibiotic administration and withdrawal of indomethacin. In two of these patients a brisk leukocyte response was noted in the blood while in the third, the individual with the prolonged course who did not respond to antibiotics, no leukocytosis was detected. Since some experimental studies with indomethacin [12] do indicate an enhanced susceptibility to infection in animals the recent report by Phelps and McCarty [13] of decreased leukocyte mobility in the presence of indomethacin should prompt close re-evaluation of the incidence of infection in patients receiving this drug.

Abnormal urinalyses were noted intermittently in 14 patients (47%) during this study. Although apparent interference with normal renal function has been reported with indomethacin administration,[14] there was no statistical evidence in the present group of patients that the abnormal urinalyses were related to indomethacin therapy. Similar abnormalities have been previously reported by us [8] and are a recognized accompaniment of ankylosing spondylitis.[15]

The observations relating to the subjective and objective therapeutic responses to indomethacin provided more definitive data than those relating to the side effects. From the point of view of subjective evaluation, only the relief from chronic spinal pain and from peripheral arthralgia were found to be statistically significant responses. The failure of indomethacin to relieve morning stiffness in the spine and, in particular, to decrease the frequency and severity of acute exacerbations of spondylitis in this group of patients is in distinct contrast with the results reported in previous studies which did not employ a controlled, crossover technique.[6,7] From the point of view of subjective response, therefore, indomethacin provided only minor benefit in the management of this group of spondylitis patients.

In none of the objective parameters of assessment was there a significant improvement with the administration of indomethacin. It should also be noted that the subjective improvement reported in peripheral arthralgia was not substantiated by objective assessment of the involved peripheral joints. These data clearly demonstrate the failure of indomethacin to produce objective improvement in the ranges of movement of the spinal and peripheral joints in this group of patients with ankylosing spondylitis.

It was considered possible that the very poor objective responses which were noted did not accurately reflect the anti-inflammatory potential of idomethacin, since, as has been previously indicated, the mean duration of illness in this group of patients was 20.1 years. In other words, it was possible that extensive immobilization of the vertebral column by ligamentous ossification and apophyseal joint fusion would prevent an objective display of improvement in the various ranges of movement. Accordingly, an attempt was made to reassess the data with

this possibility in mind by comparing the radiological changes in the vertebral column with the observed clinical responses.

As might be anticipated, it was virtually impossible to re-evaluate these data without introducing bias. The only definitive data which could be salvaged in this regard related to the cervical spine; employing the previously defined criteria for improvement, it was found that of 21 patients with no functionally significant radiological changes of ligamentous ossification and/or apophyseal joint fusion only one patient improved with indomethacin and none with placebo. On the other hand, of the remaining nine patients who were judged to have functionally significant radiological changes, three improved on idomethacin and one while on placebo. These observations would, therefore, suggest that the failure of these patients to demonstrate objective improvement was not due to mechanical restriction of the cervical spine but rather to failure of indomethacin to decrease or abolish active inflammation. It should also be noted that the latter conclusion is supported by the data which demonstrated the inability of indomethacin to prevent acute exacerbations and to relieve morning stiffness.

The laboratory tests (ESR and alpha-2 globulins) employed to assess the anti-inflammatory effect of indomethacin showed no significant change during this study. Once again these data correlate well with the other parameters used to assess indomethacin in this group of patients.

Although indomethacin has been reported to have both anti-inflammatory and analgesic properties,[16,17] the results of this study would indicate that on ankylosing spondylitis the main effect in indomethacin is as an analegisic, since the only significant responses observed were relief of chronic spinal pain and of peripheral arthralgia. The failure of indomethacin to decrease morning stiffness and the frequency and severity of acute exacerbations, to improve the restricted movements in the spinal and peripheral joints, or to suppress the elevated ESR and alpha-2 globulin levels would also indicate that the anti-inflammatory properties of indomethacin in chronic but active ankylosing spondylitis are minimal.

## CONCLUSIONS

The majority of patients in this study were unable to tolerate the recommended daily therapeutic dose of up to 200 mg. per day of indomethacin. When 15 patients (50%) received a dose in excess of 150 mg. per day and five others (16%) a dose in excess of 100 mg. per day there was a high incidence of side effects. Accordingly, we would suggest that the maximum daily therapeutic dose of indomethacin be reduced below 150 mg. per day. It would also appear that if a beneficial therapeutic response does not occur with a dose between 100 mg. and 150 mg. per day, the probability that such a response will occur with higher doses is slight.

When the frequency and severity of indomethacin-related side effects, particularly those involving the central nervous system, are considered in conjunction with the apparent lack of an anti-inflammatory effect of indomethacin, the role of this agent in the routine management of ankylosing spondylitis should be questioned. Since in our experience[8] a satisfactory therapeutic program for ankylosing spondylitis can be achieved with physical measures, maintenance doses of acetylsalicylic acid and intermittent administration of phenylbutazone, we can discern no preferential role for indomethacin in such a program.

In order to further evaluate the role of indomethacin in the management of patients with ankylosing spondylitis, we would suggest that a cross-over study comparing phenylbutazone and indomethacin might provide more definitive data than were obtained in the present study. It would also seem appropriate to conduct such a study in a group of patients with spondylitis having a shorter duration of illness, so that objective assessment of the anti-inflammatory effects of the drugs would not be obscured by anatomically restrictive changes in the spine.

Appreciation is expressed to Dr. William Dorian of Merck Sharp & Dohne of Canada Limited, Montreal, for his generous support and encouragement, and to Dr. F. Robert MacDonald, Associate Radiologist at the Royal Victoria Hospital, Montreal, for his evaluation of the radiological examinations of this group of patients.

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Dr. CALABRO. This article requires comment, since rarely does any one study violate so many basic tenets of a drug evaluation. For instance, Senator Nelson, as part of the drug trial of indomethacin, all patients continued to take their previous medication, such as aspirin, phenylbutazone, or adrenocorticosteroids. In fact, some patients were even receiving two of these other drugs simultaneously.

Now, how do we test a drug if we allow patients to stay on another worthwhile and effective antirheumatic agent at the same time?

But even before undertaking the study—and this is an inherent difficulty of many crossover studies—unnecessary bias was introduced. All 30 patients, the investigators point out "were specifically advised of the side effects which were known to occur with indomethacin."

In fact, the patients were so well advised that half developed indomethacin side effects while on placebo. In table III of their report, 60 percent of the patients had side effects—not ordinary side effects, but indomethacin side effects—while they were receiving placebo.

Predictably, such a poorly conceived and biased study produced inconclusive results. However, even more appalling—for me as a clinical rheumatologist responsible for the care of patients with rheumatoid spondylitis—even more appalling than their obvious errors of methodology are the apparent expectations by Kinsella and associates that indomethacin would provide "objective functional improvement."

Now gentlemen, this is a clinical misconception, since antirheumatic agents are at best palliative. By providing effective relief of joint pain and inflammation, drugs then allow the clinician to utilize important supportive measures, such as therapeutic exercises and other forms of physical therapy.

To illustrate this point, Senator Nelson, if you had rheumatoid arthritis of the right wrist, and I were to give you an antirheumatic agent, be it corticosteroids or for that matter indomethacin, these drugs could relieve the inflammation and pain in your wrist joint. But if this effect required a number of weeks or a number of months, you would then end up with a joint that would have some restricted motion. No drug in the world is going to bring that motion back. The only measures that will correct this deformity, of course, are well-prescribed, regularly performed therapeutic exercises.

I might ask all of you gentlemen to analyze closely the double-blind studies reported by Dr. Mainland and more recently analyzed by Dr.

O'Brien, in order to question the role of so-called physical measures in these short-term studies. What about these physical modalities that I have just made reference to? Were such physical measures, as therapeutic exercises, standardized in the 11 clinics that were part of the cooperative clinic study of indomethacin? Actually, there was no mention of these in Dr. Mainland's paper. Again, you must realize that no drug will restore motion unless such impaired and limited joints are put through physical measures to increase ranges of motion, and this is obviously an important adjunctive part of the care of the rheumatoid patient.

I will stress again: Antirheumatic drugs do nothing more than remove joint pain and inflammation, and function is restored through supportive measures, such as physical therapy and so on.

Now, in spite of the results of the various double-blind and controlled trials that you have heard much testimony on, many physicians still have the impression that indomethacin benefits certain patients with rheumatoid arthritis. And, you have heard various statistics quoted, anywhere from 25 to 65 percent of rheumatoid patients may be benefited. But as Dr. Healey, a noted rheumatologist from Oregon, has pointed out in the Bulletin of Rheumatic Diseases in December 1967—there may be a subgroup of patients—be it small or large (whatever it is) who may be benefited by indomethacin, a finding that would certainly not be evident if all such patients are included in a general statistical evaluation. What is unique to those patients who do respond to indomethacin? And, to my knowledge, and I quote Dr. Healey, "This hypothesis has not been tested."

Earlier Senator Hatfield had asked about long-term evaluations of indomethacin in various rheumatic disorders. Dr. Charley Smyth, from Denver, Colo., will tell us shortly about his experience with indomethacin in rheumatoid arthritis. I have already submitted to you, Senator Nelson, a reprint of our long-term evaluation of indomethacin in ankylosing spondylitis. This is a form of rheumatoid disease affecting young men. It usually begins between ages 15 and 35. Unlike rheumatoid arthritis, it affects the small (apophyseal) joints of the back—but may also involve the peripheral joints, such as the knee and hip. In many ways, therefore, it is similar to rheumatoid arthritis.

In this indomethacin trial that I have submitted, averaging 33 months, and which is still continuing, actually into its seventh year, there were 28 ankylosing spondylitis patients who received an average daily dosage of 100 milligrams. The response to the drug—using three subjective criteria and three objective criteria, including the erythrocyte sedimentation rate (ESR) as follows: The overall therapeutic rating of all parameters proved to be good in 21 of 28 patients (75 percent), fair in five, and poor in two. (See table I.) Of the 28 patients, three of five patients who had previously been in functional class III improved to class II and two to class I; 21 patients eventually were in the most favorable functional class I, Senator, where only one patient was so rated before the start of indomethacin.

These functional designations are according to the scheme for long-term drug evaluations devised by the American Rheumatism Association, whereby functional class I means the patient is able to carry on all the usual activities of daily living and occupation, and class II means that he may be able to perform in these activities despite joint

limitation or handicaps. Class III means that the patient has difficulty maintaining self-care and occupation, while class IV refers to patients who are bedridden or confined to a wheelchair.

I would like to stress that I wish we had better measures for drug testing. While we have used this classification, and it is as effective as any we have today, it was devised in 1949. The Therapeutic Criteria Committee of the American Rheumatism Association are continuously devising techniques that might sharpen our therapeutic studies of new drugs even more.

I might add that in this study joint symptoms followed temporary withdrawal of the drug in 24 of the 28 patients——

Senator NELSON. You are talking about your study?

Dr. CALABRO. Yes, this has now appeared in the journal, Arthritis and Rheumatism, in February 1968.

Senator NELSON. Did you ask to have this printed in the record?

Dr. CALABRO. Yes.

Mr. CUTLER. It is attached to Dr. Calabro's letter.

Senator NELSON. It will be printed in the record at the conclusion of Dr. Calabro's statement.

Dr. CALABRO. Return of joint pain was then promptly relieved when indomethacin was again taken by the patients. Actually, we could repeat this withdrawal performance periodically.

Clearly, our report of indomethacin in spondylitis parallels the experience of others, such as Bilka from Minneapolis, Hart of London, and European investigators such as Koss and Pohl, and Rothermich, whom you heard yesterday, that indomethacin is effective in ankylosing spondylitis.

That indomethacin has antirheumatic effects in disorders other than ankylosing spondylitis is also apparent, as judged by numerous reports of its usefulness in the management of the majority of patients with gout—Dr. O'Brien puts it up to 80 percent of gout cases in his publication appearing in early 1968 (Clinical Pharmacology and Therapeutics)—and osteoarthritis of the hip.

I might refer to an additional followup publication, since Mr. Gordon has referred to the Katz, Pearson, and Kennedy article of January–February 1965 (Clinical Pharmacology and Therapeutics), but neglected to mention that at the end of that report it was clearly stated that these therapeutic trials were done with an outmoded indomethacin tablet that was never released. He also neglected to mention that Dr. Pearson, the senior investigator—and I would like to submit this also for the record—has since published on the indomethacin capsule, in May–June 1966, Clinical Pharmacology and Therapeutics, the same journal that Dr. O'Brien has his January–February 1968 publication in Pearson, having now used the capsule, has reported greater success in rheumatoid patients, but most notable was the reduction of adverse side effects, from 37 percent in their initial study to 12 percent in their continuation series, with no serious complications.

Finally, again, Mr. Gordon points to a poll on use of indomethacin in medical practice. We should mention very clearly that this is a poll on the treatment of rheumatoid arthritis. It is true that 8 percent of the pediatricians were using indomethacin. The comment is then made, "Unlike the internists, of whom over 50 percent were using indomethacin, this is in sharp contrast to the 310 pediatricians who relied pri-

marily on analgesics and combinations thereof, five out of 10, but only infrequently prescribed indomethacin, phenylbutazone, or gold."

If you look even more critically at this report, you will note that 18 percent of pediatricians were using adrenocorticosteriods for the care of patients with juvenile rheumatoid arthritis. This is a most disturbing situation in young children, because steroids have many more hazards in the child than in the adult. For instance, it will suppress growth in height and weight. It may cause thinning of the bones, notably in the spine, which may then go on to vertebral fracture. Pseudotumor cerebri may also occur in children.

I have recently published all of the notable side effects of steriods that are unique to children. This data can be found in two parts, in the September 28 and October 5 issues of the New England Journal of Medicine in 1967.

We should also note that the pediatricians elected to use simple analgesics in half of their rheumatoid arthritis children. Accordingly, they are using agents that do not have the needed antirheumatic effect. How do they expect to get at joint inflammation with simple analgesics? How do they expect to restore joint motion without first alleviating joint pain and inflammation?

I sincerely hope, despite the current controversy and confusion, that investigative pursuits of indomethacin will continue. Only then can we more fully understand the role of this extremely useful and valuable antirheumatic agent. I have now been working with this agent—this is my seventh year. While I have only published reports of its usefulness in ankylosing spondylitis, I have used it in other disorders. Such data is certainly not scientifically organized and should not be presented, especially since none of it has been published. But I have also watched the growing literature on indomethacin very critically, and I have tried to present my estimation and fair appraisal of this most needed antirheumatic agent.

There are many conditions in the rheumatic disease field for which we have few agents. You may remember that yesterday, Mr. Gordon, we listed all of the agents we might use in rheumatoid arthritis. We listed, I think, five or six. For ankylosing spondylitis, a not uncommon disease, we can list only three agents. Besides indomethacin, there is phenylbutazone, which has its toxicity. The original report of phenylbutazone in spondylitis cited a 37-percent incidence of side effects.[1] X-ray therapy to the spine has now been generally abandoned because of the increased risk of leukemia. Court Brown, reporting in the British Medical Journal (2:1327–1332, 1965), cites 49 cases of chronic myelogenous leukemia due to radiotherapy. This has increased the hazard of leukemia from X-ray therapy in the spondylitis patient to some 10 times that of the population at large. Leukemia cases did not occur only after the forth, fifth, or sixth years after stopping radiotherapy, as we initially believed, but are occurring even now 14 and 15 years after radiotherapy was stopped.

I need indomethacin to treat my patients with ankylosing spondylitis, as indeed we need it for those patients with rheumatoid arthritis who do not respond to more conservative measures. Indeed, indo-

[1] See Toone, E. C., and Irby, W. R.: "Evaluation of Phenylbutazone (Butazolidin) in the Treatment of Rheumatoid Spondylitis: Report of 50 Cases." Ann. Int. Med., 41: 70–78, 1954.

methacin is a valuable agent in the treatment of acute gouty attacks of arthritis, as it is in patients with osteoarthritis of the hip.

Senator NELSON. Thank you, Doctor. I think the testimony does not differ from what the FDA witnesses said yesterday about the use of indomethacin, except that you went into considerably more detail.

You suggested that the committee evaluate these tests. The committee does not feel competent to evaluate these tests. That is why we call in experts like you and who may well differ with each other. We feel that is the best way to find out what the truth is.

Dr. CALABRO. I hope I have made it apparent that most rheumatologists are unhappy about the methods we have for evaluating antirheumatic agents. As a matter of fact, Dr. Carl Pearson, professor of medicine at UCLA, as well as myself and three other investigators have just received an enormous grant aimed at the pharmacology and testing of drugs in arthritis. I am afraid to even mention the amount.

Senator NELSON. From where?

Dr. CALABRO. From the NIH, for $3.5 million for 5 years. This grant was awarded Dr. Pearson to study the pharmacology of drugs—but more important, to ascertain newer techniques and tools by which we might better objectively evaluate current drugs, or newer drugs, used in the various rheumatic disorders. I hope that this represents at least the beginning of the type of support that many investigators will obviously need in order to evaluate the long term efficacy of antirheumatic drugs.

Clearly, we need a drug like indomethacin, and I hope to test indomethacin with our newer methods of objective evaluation as these become available.

Senator NELSON. Thank you very much, Doctor. We appreciate your coming to testify today.

(The letter and supplemental information submitted by Dr. Calabro follow:)

APRIL 23, 1968.

HON. GAYLORD NELSON,
*Chairman, Subcommittee on Monopoly, Senate Committee on Small Business, U.S. Senate, Washington, D.C.*

DEAR SENATOR NELSON: In anticipation of my participation in the congressional hearing of your committee on May 3, 1968, the following summarizes my experience with the drug indomethacin and the role it has in the management of patients with rheumatic diseases.

Recent reports of double-blind studies of indomethacin in rheumatoid arthritis (RA) have caused considerable controversy concerning the efficacy of this drug as an antirheumatic agent. It is my opinion that while double-blind studies are obviously useful in evaluating new agents, they are also extremely difficult, particularly in such a capricious disease at RA. To this point, I might add that there are few (if any) double-blind trials with other antirheumatic agents that are entirely satisfactory.

Even more appalling are the apparent expectations of many investigators conducting short-term studies in RA that indomethacin would provide objective functional improvement. This is a clinical misconception since all antireheumatic agents are at best palliative. By providing effective relief of joint pain and inflamation, rugs allow patients to undertake therapeutic exercise and other supportive measures. These provide objective improvement. Yet, such measures receive scant mention and do not appear to be an integral part of the reported double-blind studies of indomethacin in RA.

In spite of these controlled trials, many physicians have the impression that indomethacin benefits certain patients with RA. As Healey has recently pointed out in the Bulletin of the Rheumatic Diseases (*18*, 483, 1967), there may be a sub-group of patients with RA that are controlled by indomethacin, a finding that

would not be evident when such patients are included in a general drug trial. To my knowledge, this hypothesis has not been tested.

The result of our long-term evaluation of indomethacin in ankylosing spondylitis (AS), a form of rheumatoid disease affecting young men, has recently appeared in the journal Arthritis and Rheumatism (11,56, 1968).

In this trial of indomathacin averaging 33 months in 28 AS patients who received an average daily dosage of 100 mg., the response to the drug was good in 21 patients, fair in 5 and poor in 2. Of the 28 patients, 21 improved to ARA functional class I. Before the use of indomethacin, only one of the 28 was so rated. Joint symptoms followed temporary withdrawal of the drug in all but four of the 28 patients. These symptoms were promptly relieved when indomethacin was again taken by the patients.

Clearly, our report parallels the experience of others, such as Bilka, Hart, Kass, Pohl, Rothermich and De Seze, that indomethacin is an essentially safe and effective drug in suppressing the articular manifestations of AS.

That indomethacin has antirheumatic effects in disorders other than AS is also apparent, as judged by numerious reports of its usefulness in the management of the majority of patients with gout and osteoarthritis of the hip.

I sincerely hope, despite the current controversy and confusion, that investigative pursuits of indomethacin will continue. Only then can we more fully understand the role of this extremely useful and valuable antirheumatic agent.

Best wishes.

Very truly yours,

JOHN J. CALABRO, M. D.,
*Chief, Rheumatology Section, Wadsworth Hospital,*
*Associate Professor of Medicine, UCLA School of Medicine.*

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[From Arthritis and Rheumatism, vol. 11, No. 1 (February 1968), pp. 56–64]

## INDOMETHACIN IN ANKYLOSING SPONDYLITIS

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Supported in part by Grant 2A–5148 from the National Institutes of Health, United States Public Health Service.

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Among the more promising newer drugs used in the treatment of rheumatic diseases, indomethacin occupies an important place. This nonsteroidal, anti-inflammatory indole compound became available for clinical trials in November, 1961. Studies since then have variously evaluated its potential effectiveness in rheumatoid arthritis [1-9] Reiter's disease, [1-3] psoriatic arthritis, [1-3-6] anklyosing spondylitis, 1 [5-10-12] gout, [1-3-3-4] rheumatic fever [15] and degenerative joint disease. [1-4-6-16]

A number of studies [1-4] have pointed out that the best results with indomethacin were obtained with low dosages, and that even then, the incidence of side effects, such as dizziness, headaches and gastroentestinal disturbance, was unfortunately high Rothermich [1-17] has recently shown that even using dosages as low as 25 mg. daily, the physician must be on guard for the occasional patient who may develop gastric upset or even ulceration, or the unusual patient who is highly susceptible to cerebral side effects.

It is well established now that with indomethacin, as with all antirheumatic drugs, dose-related side effects may appear either early in treatment or when the drug is taken over a long period of time. [3-17]

While our early experience with the drug yielded extremely variable results in peripheral rheumatoid arthritis, far more predictable and satisfactory disease suppression was noted in ankylosing spondylitis (AS). Since then, and after reporting some preliminary results,[18] we have maintained 28 AS patients on indo-

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NOTE.—Numbered footnotes at end of article, p. 3424.

methacin in a clinical study that is now in its fifth year. A battery of laboratory tests was done before and periodically during this drug trial. Thus, we were able to combine a long-term threapeutic evaluation of indomethacin with a continuous monitoring of possible side effects.

## MATERIALS AND METHODS

*The patient group.* Only patients with active AS were selected for this study. They were 25 men and 3 women who attend the arthritis clinics of the Jersey City Medical Center. They have been treated with indomethacin for periods ranging from 5 to 52 months, or for an average of 33 months (Table 1). On alalysis in April, 1967, the age of the patients averaged 41 years, ranging from 20 to 58 years. The duration of disease averaged 19 years, ranging from 3 to as long as 36 years.

The mean age of the patients at disease onset was 24 years. The longest interval between onset and diagnosis was 25 years in one man, but the average interval proved to be 9 years. The mode of onset was insidious in 18 patients and acute in 10. Initial involvement was found to be axial (spinal) in 14 patients, peripheral in 13 and systemic (with recurrent iritis) in one. Of 14 patients with axial onset, 12 had lumbar, one had dorsal, and one had cervical involvement. Of the 13 patients with AS of peripheral onset, 6 had involvement of the hip, 4 of the knee, 2 of the shoulder, and one of the heel.

Serial x-rays have disclosed bilateral sacroiilitis, apophyseal irregularities, and some degree of vertebral demineralization or squaring in all 28 patients. Three patients have associated ulcerative colitis and two have regional enteritis.

Major systemic manifestations in these 28 patients before the indomethacin trial included iritis in 6 patients, aortic insufficiency in 2, angina in 2, while one patient each had vasculitis and cauda equina involvement (Table 2). Persistent EKG abnormalities, chiefly in the form of conduction disturbances, were noted in 10 patients.

Prior to the trial with indomethacin, one patient was in functional class I, 21 in class II, 5 in class III, and one in class IV (Table 1).[19] Previously of the 28 patients, 15 had taken aspirin (daily dosage 1.5 to 6.0 Gm.), 9 had received phenylbutazone (100 to 300 mg.), one oxyphenbutazone (300 mg.), while 3 had taken various types and amounts of adrenocorticosteroids.

*Indomethacin dosage.* The initial dosage of indomethacin administered to each patient was 100 mg. daily, with 25 mg. capsules given after meals and at bedtime. Daily maintenance dosages were then adjusted to the lowest possible required for individual suppression of active articular disease. Adjunctive measures, such as physical therapy, were encouraged. But no medication other than the test drug was administered except in one patient who was gradually being weaned from adrenocorticosteroids.

*The study design.* Each patient was evaluated initially, and again at weeks two, six and 12, and then at three-month intervals. At the initial visit, a detailed work-up, including history, physical examination, x-rays, electrocardiogram and a battery of laboratory studies, was performed on each patient. The patient's functional status was then assessed by means of the ARA Steinbrocker criteria.[19]

At each follow-up visit, careful histories were taken and physical examinations were performed on all patients.

In addition four parameters of disease activity were selected for initial and continued assessment. The parameters were: 1) joint pain, 2) duration of morning stiffness, 3) onset of fatigue and 4) joint mobility including spine extension and flexion chest cage expansion and range of motion of peripheral joints.

To serve as a control phase, temporary withdrawal of indomethacin was carried out in all patients after they had been maintained on the drug for a period of at least three months. The drug was promptly readministered once active disease had recurred.

Laboratory studies performed before indomethacin administration and each time we saw the patients included serum SGOT, SGPT, alkaline phosphatase, cephalin flocculation, thymol turbidity, total bilirubin, total protein and A/G ratio, BUN, uric acid, paper electrophoresis, latex fixation and blood glucose. Of the last 8 patients admitted to the trial, serum studies included only a BUN, SGOT, uric acid, paper electrophoresis and latex fixation test.

Other studies performed initially and on each follow-up visit on all 28 patients included a Westergren ESR, hematocrit, WBC and differential counts, urinalysis and a stool guaiac test.

At follow-up, patients were asked to report any adverse reactions to the drug. Upper G–I series were performed on only those patients who had gastrointestinal complaints. X-rays of axial and involved peripheral joints and electrocardiograms were performed yearly. An ophthalmologic evaluation including slit lamp examination was conducted on all 25 patients who had received indomethacin for more than one year.

*Evaluation of findings.* Therapeutic assessments done at the end of the trial consisted of evaluation of: 1) ARA functional class, 2) the four selected parameters, singly and collectively, 3) calculation of average maintenance dosage, 4) the withdrawal phase of the trial, 5) ESR values, 6) systemic manifestations, and 7) adverse reactions to the drug.

The four selected parameters were rated as improved when joint pain decreased in intensity, duration of morning stiffness diminished by at least one-half hour, onset of fatigue decreased by at least two hours, and the total range of joint motion increased by 25 per cent or more.

We also devised an over-all therapeutic rating scale, whereby improvement in three or four of these selected parameters was graded as good, in one or two as fair, and in none as poor.

TABLE 1.—CLASSIFICATION OF THE 28 PATIENTS AND RESULTS OF INDOMETHACIN TRIAL

| Pt. No. | Sex | Age | AS onset (yr.) | Indomethacin | | Functional class[1] | | ESR | | Individual improvement[2] in | | | | Overall response[3] | Side effects and month first noted |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Daily maintenance (mg.) | Length of Rx (mo.) | Before Rx | After Rx | Before Rx | After Rx | Joint pain | AM stiffness | Onset of fatigue | Joint mobility | | |
| (1) | F | 53 | 25 | 100 | 39 | III | II | 98 | 18 | + | + | − | + | Good | |
| (2) | M | 39 | 15 | 100 | 20 | II | I | 35 | 10 | + | + | + | + | do | |
| (3) | M | 45 | 30 | 75 | 20 | II | I | 54 | 42 | + | + | + | + | do | |
| (4) | M | 42 | 24 | 100 | 18 | II | I | 100 | 71 | + | + | + | − | do | |
| (5) | M | 27 | 14 | 100 | 39 | II | I | 98 | 47 | + | + | + | − | do | |
| (6) | M | 46 | 40 | 100 | 40 | II | I | 34 | 15 | + | − | + | + | do | Nausea, 2d month; dizziness, 2d month. |
| (7) | M | 53 | 33 | 75 | 51 | III | II | 5 | 15 | + | + | + | − | do | |
| (8) | M | 58 | 30 | 125 | 41 | II | I | 23 | 35 | − | + | − | + | Fair | |
| (9) | M | 51 | 17 | 200 | 51 | III | II | 67 | 7 | + | + | + | − | Good | Headache, 6th month; nausea, 29th month; diarrhea, 34th month. |
| (10) | M | 49 | 14 | 25 | 45 | II | I | 61 | 28 | + | + | − | + | do | Headache, 24th month. |
| (11) | F | 23 | 14 | 200 | 27 | II | I | 3 | 6 | + | − | − | − | Fair | Headache, 2d month. |
| (12) | M | 58 | 32 | 100 | 17 | II | I | 4 | 9 | + | + | + | + | Good | |
| (13) | M | 48 | 40 | 100 | 18 | II | I | 37 | 10 | + | + | + | + | do | Dizziness, 2d month. |
| (14) | M | 44 | 24 | 100 | 50 | II | I | 33 | 32 | + | − | − | − | Fair | |
| (15) | M | 30 | 16 | 100 | 29 | II | I | 20 | 15 | + | + | + | + | Good | |
| (16) | M | 21 | 18 | 200 | 49 | III | I | 4 | 4 | + | − | − | + | Fair | Nausea, 22d month; diarrhea, 22d month. |
| (17) | M | 36 | 17 | 100 | 38 | II | I | 22 | 5 | + | + | + | + | Good | |
| (18) | M | 43 | 22 | 200 | 52 | II | I | 27 | 15 | + | + | + | − | do | Nausea, 3d month; headache, 3d month. |
| (19) | M | 32 | 21 | 100 | 40 | II | I | 10 | 12 | + | + | + | + | do | |
| (20) | M | 40 | 20 | 150 | 39 | II | I | 30 | 2 | + | + | − | + | do | |
| (21) | M | 20 | 14 | 75 | 52 | II | I | 42 | 44 | + | + | − | + | do | |
| (22) | M | 47 | 26 | 125 | 21 | II | II | 37 | 53 | + | + | − | − | Fair | |
| (23) | M | 44 | 20 | 100 | 38 | III | I | 20 | 21 | + | + | + | + | Good | |
| (24) | M | 22 | 18 | 100 | 21 | II | I | 2 | 1 | + | + | + | + | do | |
| (25) | M | 55 | 25 | 100 | 6 | II | II | 102 | 82 | − | − | − | − | Poor | |
| (26) | M | 31 | 25 | 50 | 40 | I | I | 5 | 3 | + | + | + | + | Good | |
| (27) | F | 53 | 23 | 100 | 6 | IV | IV[4] | 105 | 105 | + | + | + | − | do | |
| (28) | M | 39 | 36 | 75 | 5 | II | II | 11 | 11 | − | − | − | − | Poor | Nausea, 1st month. |
| Average | | 41 | 24 | 100 | 33 | | | 39 | [5] 26 | − | − | − | − | | 11 months (range 1 to 34 months.). |
| Total | (6) | | | | | (7) | (8) | | | 25 | 22 | 17 | 17 | (9) | 13 side effects (8 pts.). |

[1] American Rheumatism Association classification: Class I—Ability to carry on a llusual duties without handicaps. Class II—Adequate for normal activities despite handicap of discomfort or limited motion of 1 or more joints. Class III—Limited only to little or none of duties of usual occupation or self-care. Class IV—Bedridden or confined to wheelchair; little or no self-care.

[2] The 4 selected parameters were rated as improved when joint pain decreased in intensity, duration of morning stiffness diminished by at least ½ hour, onset of fatigue decreased by at least 2 hours, and the degree of joint mobility increased by 25 percent or more.

[3] Overall therapeutic rating scale, whereby improvement in 3 or 4 of the selected parameters were graded as good, in 1 or 2 as fair, and in none as poor.

[4] This woman, with a 15-year history of diabetes, died following a second episode of myocardial infarction. No autopsy was obtained.

[5] The "p" value obtained from student's "t" table is statistically significant at the $<0.01$ level after testing the average paired differences against zero for the ESR values before and after indomethacin.

[6] Total: Male, 25; female, 3.

[7] Total by classification: Class I, 1; class II, 21; class III, 5; class IV, 1.

[8] Total by classification: Class I, 21; class II, 6; class III, 0; class IV, 1.

[9] Total: Good, 21; fair, 5; poor, 2.

TABLE 2.—SYSTEMIC MANIFESTATIONS OF ANKYLOSING SPONDYLITIS DEVELOPING DURING INDOMETHACIN TRIAL AVERAGING 33 MONTHS

| Systemic manifestations | Number of cases before indomethacin trial | Number of cases during indomethacin trial |
|---|---|---|
| Iritis | [1] 6 | 3 |
| Angina pectoris | 2 | 0 |
| EKG conduction changes | 10 | 4 |
| Aortic insufficiency | 2 | 1 |
| Foot and ankle ulcerations | 0 | 1 |
| Vasculitis | 1 | 0 |
| Cauda equina lesion | 1 | 0 |
| Total | 22 | 9 |

[1] 1 patient had 3 bouts of iritis during the indomethacin trial, but had had recurrent iritis before this trial while receiving other antirheumatic agents. Two other patients experienced their first bouts of iritis while receiving indomethacin.

## RESULTS

Indomethacin proved an effective suppressive agent of the articular manifestations of AS in the present study, as judged by the following:

1. After treatment for an average period of 33 months, 21 of our 28 patients were in the most favorable functional class I,[19] as compared with only one of 28 before utilization of indomethacin (Table 1). Of 5 patients in functional class III before the drug trial, 3 improved to class II, and 2 to class I.

2. Analysis of each of the four selected parameters revealed a decrease in joint pain in 25 of 28 patients (89 per cent), a decrease in the duration of morning stiffness in 22 (79 per cent), delay in the onset of fatigue in 17 (61 per cent), and an increase in joint mobility in 17 patients (61 per cent) (Table 1). Joint pain and morning stiffness diminished promptly after indomethacin was started, usually in 48 hours, or within one to 7 days. Alleviation of fatigue and improvement in joint mobility was less dramatic, taking from one week to 3 months, and occurring on the average within 4 weeks.

After an average treatment period of 33 months with indomethacin, the over-all therapeutic rating of all four parameters was good in 21 of 28 patients (75 per cent), fair in 5 (18 per cent) and poor in 2 (7 per cent) (Table 1).

3. The average daily maintenance of indomethacin required for suppression of articular disease was 100 mg., the lowest was 25 mg. and the highest 200 mg. (Table 1). Only 7 patients needed more than 100 mg. daily, 5 with active hip or other peripheral joint disease, 2 because of marked axial (spinal) involvement.

4. When indomethacin was withdrawn, severe axial pain and morning stiffness recurred on an average within 48 hours in 24 of the 28 patients. Symptoms were promptly alleviated in all 24 patients when indomethacin was readministered.

Of the remaining four patients, two (Table 1, patients no. 25 and 28) did not respond to the drug and therefore exhibited no symptoms when indomethacin was withdrawn. Two patients (patients no. 15 and 17) had achieved remission.

5. The average Westergren ESR values for all 28 patients decreased during the drug trial from 39 mm. to 26 mm. (Table 1). The $p$ value obtained from Student's $t$ table is statistically significant at the $<0.01$ level after testing the average paired differences against zero for the ESR values before and after indomethacin.

ESR values were normal (15 mm. or less) initially and remained so in 8 patients (29 per cent). Eight other patients (29 per cent) attained normal ESR values by the end of the trial. Thus, normal ESR values were noted in 16 patients (58 per cent) while on indomethacin (Table 1).

Only 4 patients had marked ESR values after the trial. Response to indomethacin was good in 2 patients, fair in one and poor in one (Table 1).

6. While articular manifestations of AS were generally controlled with indomethacin, certain systemic manifestations of the disease were not (Table 2). During long-term maintenance on indomethacin, iritis occurred in 3 patients, and multiple recurrent ulcerations of the left foot and ankle in one patient. The murmur of aortic insufficiency developed in one patient, while EKG conduction disturbances developed in 4 patients. Cauda equina involvement of three years' duration in one patient, manifested by nocturnal incontinence, poor stream and diminished bladder and rectal sensation, did not improve with indomethacin.

Despite suppression of articular symptoms in all but two of the 28 patients, serial x-rays of axial and involved peripheral joints disclosed progressive changes in the majority of patients.

7. A total of 13 side effects, often transient and usually observed during latter months of indomethacin administration, occurred in 8 patients on maintenance dosages of 25 to 200 mg. daily (Table 1). Each of the 4 patients receiving the daily maximum of 200 mg. had adverse reactions.

Headache was noted in 4 of the 8 patients. Of the 4 patients with headache, one also had nausea, and another nausea and diarrhea. Two patients had dizziness, one of whom also had nausea. Two other patients had nausea, one of whom also had diarrhea.

All side effects disappeared spontaneously even though the drug was continued at the same dosage, except for 2 patients whose symptoms persisted until the daily maintenance of indomethacin (200 mg.) was temporarily reduced. Side effects did not reccur in these 2 patients when 200 mg. dosages of indomethacin were reinstituted at a later date.

Upper GI series, performed on the 5 patients with gastrointestinal side effects, revealed no abnormalities. Overt gastrointestinal bleeding did not occur, despite the intermittent presence of positive stool guaiac tests in 6 patients.

There was no evidence of any ocular, renal, hepatic or hematopoietic side effects. There appeared to be no increased susceptibility to infection.

Indomethacin was discontinued in three patients. It was withdrawn in one patient (patient no. 25) with regional enteritis and active foot and heel involvemnet because his response to indomethacin was poor, after having been tried on three different occasions over a six-month period. It was discontinued in another patient (patient no. 28) because of a poor response after 5 months on the drug. Both patients have been more adequately controlled with 300 mg. phenylbutazone daily.

Indomethacin was temporarily discontinued in a man with associated ulcerative colitis (patient no. 18) when the patient developed multiple recurrent ulcerations of the left foot and ankle after he had taken 200 mg. of the drug daily for 36 months. But indomethacin was resumed three months later after two biopsies of the lesion proved negative for vasculitis. The ulcer has now healed.

## DISCUSSION

Our most striking observation about indomethacin is the clear-cut benefit it seems to provide in ankylosing spondylitis.

When indomethacin is used in other rheumatic disorders, such as rheumatoid arthritis, psoriatic arthritis, Reiter's syndrome or juvenile rheumatoid arthritis, one cannot predict if a patient will benefit from its use.[1,4,10-12]

But as demonstrated in this study, and as suggested by other reports,[1,3,4,6,9] indomethacin seems to be almost consistently effective in ankylosing spondylitis. Despite this enthusiasm about indomethacin, it must be kept in mind that this drug, like other antirheumatic agents, does not specifically alter the underlying disease process. Thus, while articular manifestations of ankylosing spondylitis are suppressed with indomethacin, systemic features appear not to be affected.

The disease activity of most rheumatic disorders is usually reflected in the erythrocyte sedimentation rate (ESR), but this relationship does not seem to be as precise in ankylosing spondylitis as in rheumatoid arthritis.[20] A possible correlation between disease activity and the ESR was suggested in this study, when more than half or 16 of the 28 patients either maintained or achieved a normal ESR value paralleling a favorable therapeutic response. This finding has not been reported previously.

In most cases, ankylosing spondylitis tends to be relatively stable for long periods, so that the symptomatic effects of a single drug can be evaluated by using the patient as his own control. Consequently, when indomethacin was temporarily withdrawn, articular manifestations usually recurred within 48 hours, and were then promptly alleviated when indomethacin was resumed. Therefore, we agree with Kass [11] that it is not necessary to utilize complicated therapeutic experiments in a disease such as ankylosing spondylitis. But, since we did not use a double-blind crossover approach, including a placebo and other antirheumatic agents, we cannot report any objective comparisons between indomethacin and other drugs useful in AS. Furthermore, we were convinced at the beginning of this study that the long-term administration of a placebo to patients with active disease and its attendant distress and discomfort cannot be justified ethi-

cally. Wallace and Ragan[21] had similar convictions about the use of placebo in patients with active rheumatoid arthritis.

Despite the fact that the world literature now abounds with warnings of the potential side effects of even small doses of indomethacin, none of our 28 patients were forced to discontinue the drug because of side effects. Indomethacin was stopped in 3 patients, in 2 because of a poor therapeutic response, and in the other only temporarily, when he developed infected foot and ankle ulcerations which proved later not to be due to the drug.

Nevertheless, our findings support the view that side effects are most frequent among patients receiving larger amounts of the drug,[1-4] while they are also in agreement with the concept, stressed by Rothermich,[17] that cerebral side effects may occur on low dosages in susceptible individuals. All 4 patients on the highest daily indomethacin maintenance dosage of 200 mg. experienced adverse reactions to the drug, while 4 other patients receiving small daily dosages of 25 to 100 mg. developed headache and dizziness. Most drug reactions disappeared spontaneously, except in 2 patients whose side effects persisted until the dosage of indomethacin was reduced.

The rather *late* occurrence of most side effects, though briefly mentioned elsewhere,[3, 17] has not been stressed prior to this investigation. Annoying headache or gastrointestinal upset were *not* seen soon after patients were started on indomethacin. In fact, the 13 side effects observed in 8 of our 28 patients usually occurred only after months and even a year or more of indomethacin administration. In any case, close attention to minimal individualized dosages needed for disease suppression appears to reduce the occurrence of potential side effects. This has also been the experience of Boardman and Hart.[22]

In conclusion, despite the fact that indomethacin has been found of considerable therapeutic usefulness, we do not mean to give the impression that we are treating patients merely with drugs. On the contrary, we cannot emphasize sufficiently the overriding importance of treating the entire disease, particularly with physical, recreational and rehabilitative measures. All of these are intrinsic parts of the overall management of the patient w ith ankylosing spondylitis.[18]

ACKNOWLEDGMENTS

We are indebted to Dr. Rustom E. Mody, former Fellow in Rheumatology, for his early assistance in this study to Dr. Bertram W. Charap of the Mt. Sinai Hospital in New York City for ophthalmologic studies and to Mr. John Wykert of Science & Medicine Publishing Co., Inc., New York, for his assistance in the preparation of this manuscript.

The indomethacin used in this study was supplied by Dr. Nelson H. Reavey Cantwell of Merck Sharp and Dohme, Research Laboratory, West Point, Pennsylvania.

SUMMARY

Indomethacin was found to be highly effective in the management of 28 patients with ankylosing spondylitis in a clinical trial that is now in its fifth year. As judged by selected criteria, including joint pain, duration of morning stiffness, onset of fatigue and joint mobility, the response to the drug was good in 21 patients, fair in 5 and poor in 2. After receiving indomethacin for n average period of 33 months, 21 of the 28 patients were classified in ARA functional class I. Only one patient had been so classified prior to the drug trial. Joint symptons followed temporary withdrawal of the drug, but were promptly relieved when indomethacin was again taken by the patients. However, while articular manifestations of ankylosing spondylitis were suppressed by indomethacin, systemic features were not.

Therapeutic maintenance doses of indomethacin were carefully individualized. While the average daily dosage proved to be 100 mg., four patients with marked peripheral and axial joint involvement required 200 mg. daily.

A battery of laboratory tests accompanied the entire period of the drug trial. These tests revealed no ocular, renal, hepatic or hematopoietic changes due to the use of indomethacin.

Cerebral and gastrointestinal side effects, generally mild and usually transient, occurred most often after prolonged administration of the drug. Of the eight patients who experienced 13 side effects, 4 were taking 200 mg. of indomethacin daily. Side effects persisted in 2 of these 4 patients until their maintenance dosage was reduced. Otherwise all side effects disappeared spontaneously while the drug continued to be taken.

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Dr. LAWRASON. Mr. Chairman, the second presentation to the committee will be from a man with long experience in the problems of management of rheumatoid arthritis and other arthritic disorders, a man who has addressed himself to drug evaluation and a leader in the professional society, the American Rheumatism Association. I would like to present Dr. Charley Smyth, a professor of medicine and head of the Division of Rheumatic Diseases at the University of Colorado School of Medicine.

Incidentally, he is also past president of the American Rheumatism Association.

Senator NELSON. Doctor, we appreciate your coming here today and your patience in waiting so long to testify. Your curriculum vitae will be printed at this point. Please proceed.

(The curriculum vitae of Dr. Smyth follows:)

CURRICULUM VITAE, CHARLEY J. SMYTH, M.D.

Born: Mart, Texas, February 7, 1909.

Education: University of Michigan, AB Degree, 1931; University of Michigan, MS Degree (Pathology), 1938; Jefferson Medical College of Philadelphia, M.D. Degree, 1935.

Internship: University of Michigan Hospital, 1935–1936.

Residency: University of Michigan Hospital, Medicine, 1936–1938; Pathology, 1938–1939; Fellowship, Arthritis, 1939–1940.

Professional appointments: Assistant Physician—Rackham Arthritis Research Unit, University of Michigan, 1939–1941; Medical Director—Wayne County General Hospital, Eloise, Michigan, 1941–1949; Assistant Director, Graduate and Postgraduate Medical Education, Univ. of Colo., 1949–1950; Director, Graduate and Postgraduate Medical Education, University of Colorado, 1950–1954; Editor, Rheumatism Reviews for American Rheumatism Assn., Part time 1956–1958.

Present position: Professor, Internal Medicine, University of Colorado, in charge of Rheumatic Disease Section, 1967–present.

Academic appointments: Instructor, Internal Medicine, 1939–1942, University of Michigan, Ann Arbor, Michigan; Instructor, Internal Medicine, 1949–1950, Wayne University, Detroit, Michigan; Assistant Professor, Internal Medicine, 1949–1950, University of Colorado; Associate Professor, Internal Medicine, 1950–1967, University of Colorado; Professor, Internal Medicine, 1967–present, University of Colorado.

Certification of specialty board: American Board of Internal Medicine, 1950.

Hospital appointments: Consultant, Internal Medicine, Fitzsimons General Hospital, 1950–present; Consultant, Internal Medicine, Denver Veterans Administration Hospital, 1950–present; Consultant, Internal Medicine, St. Joseph's Hospital, Denver, 1953–present; Consultant, Internal Medicine, St. Luke's Hospital, Denver, 1953–present; Consultant, Internal Medicine, General Rose Memorial Hospital, Denver, 1953–present; Consultant, Internal Medicine, Mercy Hospital, Denver, 1953–present; Consultant, Internal Medicine, Presbyterian Medical Center, Denver, 1953–present.

International, national, State and county organizations: Committee appointments, Board of Directors and Executive Committee, Arthritis Foundation (National), Vice President La Lingue Internationale Contre Le Rheumatisme, 1965–present.

Professional society memberships: Governor for Colorado, American College of Physicians, 1960–present; American Society Internal Medicine, Committee on Academic Membership, 1965–present; Board of Directors and Executive Committee, Rocky Mountain Chapter, Arthritis Foundation, 1950–present; Central Society for Clinical Research, 1939–present; American Federation for Clinical Research, 1942–present; American Rheumatism Association, 1940–present (President 1960); American College of Physicians, Fellow, 1951–present; Society Experimental Biology and Medicine, 1942–present; American Therapeutic Society, 1958–present; Colorado Society of Internal Medicine, 1952–present (President 1957–1958); American Society of Internal Medicine, 1957–1968 (Trustee 1967–present); Denver County and Colorado State Medical Society and the American Medical Association, active member, 1949–present; American Society of Clinical Rheumatology, 1960–present (President 1964).

Honorary scientific societies: Sigma Xi, Michigan, 1939; Alpha Omega Alpha, Jefferson Medical College, 1935.

## STATEMENT OF DR. CHARLEY J. SMYTH, PROFESSOR OF MEDICINE; AND DIRECTOR, DIVISION OF RHEUMATIC DISEASE, UNIVERSITY OF COLORADO MEDICAL CENTER, DENVER, COLO.

Dr. SMYTH. Senator Nelson, it is an honor. I am deeply grateful for this opportunity to present my views concerning the results of treating arthritic patients with indomethacin.

My major responsibilities include the care of patients seeking relief of pain and disability in two large weekly arthritis clinics at the Colorado General Hospital. In addition, I see and examine, as a consultant, patients in the Denver Veterans Hospital, the Fitzsimons Army Hospital, and other unfortunate victims with various types of arthritis in other hospitals in Denver. I estimate in an average week, I pass judgment and recommend treatment upon 75 to 80 individuals affected with one form or another of arthritis.

In the 30 years that I have worked with arthritic patients I have dealt firsthand with many new compounds. The most exciting and promising was cortisone, introduced in 1949. I witnessed the phenomenal rise and slow decline in its popularity as the sad ill effects of its long-term use made their appearance in the clinics, on the hospital wards, and, unfortunately, at the autopsy table.

Therefore, it was with great interest that I and many other of my colleagues in clinical investigations treating rheumatic diseases began studies with the promising new compound indomethacin in 1963.

It had clearly been demonstrated in experimental animals. It looked as though it were more powerful than cortisone or any of the other then commonly used drugs in the treatment of arthritic patients.

It soon became apparent that this drug quickly controlled the pain and inflammation of gouty joints. After treating 30 patients with acute gout and observing uniformly favorable results with minimal side effects we reported our experiences in Stockholm, Sweden, before the European Congress on Rheumatic Diseases in 1965. Other critical clinicians throughout the world have since confirmed these early studies, and today there is general agreement that this drug is as effective and as safe as any other in the treatment of acute attacks of gouty arthritis.

Our next effort in the area was to investigate patients with rheumatoid arthritis of the spine. Dr. Calabro has told you of his investigation of this variety of arthritis affecting healthy young men in which the disease attacks mostly the spine. The results were excellent, and the drug was well tolerated. Many of these patients were confined to bed, but returned to gainful employment within weeks after the beginning of therapy with this new compound. Other investigators have made similar observations, and today there is no debate about the value of indomethacin in patients with rheumatoid arthritis of the spine.

There is still some controversy about the use of indomethacin in rheumatoid arthritis. This is the great crippler and one of the commonest of the rheumatic diseases. It is in this type of arthritis that the clinical investigator has the greatest difficulty in evaluating drugs, or indeed the effect of any procedure.

I refer primarily, Senator, to the procedure called synovectomy that the orthopedic surgeons are now doing; that is, taking out joint membranes for this disease. We have had great trouble in deciding whether these procedures are really justified or not. They are being done throughout the world without any proof that they are actually beneficial to the patient.

So the course of this disease, as you already have heard, fluctuates up and down, notoriously rises spontaneously and suppresses spontaneously, whether you treat the patients or do not treat them. Furthermore, it has been expressed repeatedly before your committee that there is no satisfaction or sense of security in the methods of testing either a surgical procedure (synovectomy) or a new drug that is handed to the clinician with the question: Is this or is this not an effective agent in this capricious, fluctuating illness?

Our group undertook this difficult problem of attempting to evaluate indomethacin in 1963. We devised a series of objective tests—not including the patient's symptom response—with the aim of expressing a reliable opinion. These studies were based upon the best objective measurements available and conducted by an experienced clinician. To control our data further, we included periods of therapy using placebo capsules, during which neither the patient nor the doctor knew whether his patient was actually taking the real drug or a "dud" pill. In 1965 we published our experiences with 55 patients with rheumatoid arthritis treated with indomethacin. In that report we stated, "Indomethacin suppresses joint inflammation and inproves joint function, but may require up to 2 to 4 months to obtain maximum therapeutic

effort." With 3 additional years of experience in treating more than 100 rheumatoid patients under the same rigidly controlled conditions of objective evaluation, I am still of this same opinion.

As I have previously stated, but a point that must be emphasized, the course of rheumatoid arthritis varies continuously with spontaneous flareups and remissions. Therefore, it is extremely difficult to obtain completely reliable data concerning the benefit of any drug or procedure. We are continuously altering our objective tests, and we have recently devised a skin temperature device in which we will put a thermester, which registers joint temperature, directly on the skin over the joint to critically measure skin temperature to see if this can be a more objective measure of gaining reliable information in this area of clinical drug testing.

Now, if I were to express an opinion about the frequency with which responses occur in rheumatoid arthritis, recognizing fully these limitations which all of us agree to, I would say that 20 to 25 percent of rheumatoid patients treated with adequate doses of this drug do show objective improvement; an additional 20 to 30 percent report symptomatic relief.

I think it should be stressed that when a reliable investigator administers this drug to his patients, the results in indomethacin response are definite; you do not need the statistician to tell the experienced clinician that his patient is better. For this reason I am convinced, as are many other reliable observers who care for rheumatoid patients, that indomethacin is effective in some cases when other agents have failed.

It is claimed by some observers who have appeared before this committee that peptic ulcers are common in rheumatoid patients treated with this drug. I would stress that this is true of any effective anti-inflammatory agent. In other words, if aspirin or any other commonly used antirheumatic drug is taken, it is potentially ulcerogenic or potentially an ulcer-forming agent. My colleagues at the University of Colorado and I have analyzed on our own initiative, because of our interest in the scientific question: Is indomethacin ulcerogenic? We have analyzed now 299 patients treated with indomethacin at the University of Colorado Medical Center during the past 5 years. As a control, we took 65 rheumatoid patients in the same clinics who had received aspirin or other commonly used antirheumatic drugs. This statement I would like to emphasize and bear down upon, because I think that it is the first comparative study that has ever been reported. There was no difference in the frequency of peptic ulcers in these two groups of patients. These studies do not support the view that indomethacin is ulcerogenic.

In the final analysis, it is the arthritic patient himself who decides if any drug is worth taking. If he does not get relief from his joint aches, pains, and stiffness, from a prescription, his physician hears about it on the next visit. It is not the advertising campaign of the drug manufacturers that convinces the practitioner of the virtues and safety of a new drug. His judgment of the benefits and reliability of a drug is based upon his own personal experience gained from listening to and examining his patient.

Senator NELSON. Are you referring to all drugs?

Dr. SMYTH. I did not say so, sir. I could broaden that if you wish me to say so.

Senator NELSON. Oh, no. You said that, "It is not the advertising campaign of the drug manufacturers that convinces the practitioner of the virtues and safety of a new drug. His judgment of the benefits and reliability of a drug is based upon his own personal experience gained from listening to and examining his patient."

Dr. SMYTH. I think I will qualify that to arthritic drugs, sir.

Senator NELSON. Thank you.

Dr. SMYTH. As I look at indomethacin from the vantage point of 5 years of practical experience, coupled with my knowledge of the many reports from other parts of the world, this drug has established a place in the treatment of arthritic patients. Furthermore, it has achieved a reasonable degree of both patient and physician acceptance in large-scale clinical use, which, in the final analysis is the only true test of any therapeutic agent or procedure. I would be handicapped in the management of many arthritic patients without this drug.

(The attachment to Dr. Smyth's statement follows:)

MEDICINE—AN ART AS WELL AS A SCIENCE

In spite of the truly miraculous advances in the sciences of chemistry and pharmacology that synthesize and bring from the laboratory to the doctor new drugs for trial, there are still some factors that are unique in determining the true value of a new drug in a human being. The practice of medicine is not a pure science; it is both an art and a science. In men and women with arthritis of rheumatoid type there is no simple magic test that gives us yes and no answers. Unfortunately, as of now, this is not so. Judgment or medical opinion in weighing the effectiveness or the lack of it with a drug like Indomethacin is based upon experience and previous responses using other, better understood anti-rheumatic agents.

Dr. SMYTH. I am extremely grateful to you, Senator Nelson, for permitting me the opportunity to appear before your committee. Thank you very much.

Senator NELSON. Doctor, the committee appreciates your taking the time to come here and testify.

As to your last sentence, I hope you do not have the impression that we have had witnesses from the FDA and elsewhere who said that indomethacin should not be in the marketplace.

Dr. SMYTH. This is my impression, from the testimony of FDA and others included, that this drug should not be used, medical evidence notwithstanding.

Senator NELSON. You mean it is your opinion that testimony has been presented that this drug should not be available to the public?

Dr. SMYTH. Yes.

Senator NELSON. No; I thought in the last sentence, there was an indication that you believed that witnesses before this committee recommended that the drug be taken off the market.

Dr. SMYTH. Senator, these remarks have been prepared in Denver. They appear exactly as printed.

Senator NELSON. I though you had the impression that some of the witnesses were saying this drug did not have any value. But, the general consensus, as I understood it from the witnesses who have testified today and on previous days, is that this drug has an appropriate place in the physician's armamentarium.

Mr. GORDON. Doctor, I just want to ask one question.

I read an article by you in a magazine called Consultant, issue of April 1967. It is entitled, "Treating Rheumatoid Arthritis, What Is Most Apt To Succeed?"

You discuss steroids and the value of short-term treatment. You discuss phenylbutazone as a drug for the management of rheumatoid arthritis, the antimalarials, gold, orthopedic surgery. But except for mentioning indomethacin in passing, you do not discuss that at all. Why?

Dr. SMYTH. There is a limit to which you can go in an article of that type. It is very restricted, was highly edited by the editor of this journal, Consultant. I just did not have enought time to amplify my opinions about indomethacin in that brief report. I think my presentation today before this committee explains my position much more fully than I was able to do at the time this article was written.

Mr. GORDON. Thank you.

Senator NELSON. Thank you, Doctor.

Mr. GADSDEN. Is it your wish that I should continue? I will be the final witness for Merck.

Senator NELSON. Please proceed.

## STATEMENT OF HENRY W. GADSDEN, PRESIDENT, MERCK & CO., INC., RAHWAY, N.J.; ACCOMPANIED BY LLOYD N. CUTLER, SPECIAL COUNSEL, WASHINGTON, D.C.

Mr. GADSDEN. Thank you, sir. I would like again to express my appreciation for my associates and myself for the early opportunity to get this on the record.

I would like first to explain why I plan to focus my remarks before the committee on advertising and promotion. I am a layman, and it seems appropriate that the medical and scientific issues of interest to you should be discussed by the most highly qualified professionals. I do not feel that I could add anything to the profile of "Indocin" that has been drawn today by Dr. Beyer and Dr. Lawrason.

On the other hand, the philosophy that animates our advertising and promotion is not only a subject of continuing concern to me, but also one for which I can properly accept a very direct responsibility.

As president of Merck, I wear many hats—one as chairman of our new products committee. That committee, as one of its major responsibilities, seeks to make sure that the marketing profile of a drug corresponds in every respect to its medical profile.

It is Merck's policy to avoid the possibility of including any questionable statement or theme in any of our advertising or promotion. The mere fact that any point is validly challenged, in or out of the company, leads us immediately to change or remove the point under discussion. I have repeatedly made this policy clear to my associates, as the following excerpts from my memorandum of May 1966 to top executives of the company will make clear:

> We seek to convey through both the parts and the whole of each advertisement a factual message which will be useful and interesting. Never must the ad seek to obscure a blemish for the sake of over all appeal. * * * We seek to provide sharper focus and greater perspective so that the reader, viewer, or listener will make his own decision. These principles are so cardinal to the success of our operations as to warrant periodic re-emphasis. * * * Please take this occasion to re-indoctrinate all of your people who have a responsibility for our advertising, and follow this up with reminders at appropriate intervals.

More specifically, our internal procedures require that every piece of advertising and promotion must have the approval of a physician and a lawyer, who are responsible for its medical accuracy and conformity with law. When it concerns a new product, it also undergoes final review by the new products committee.

The safeguards are necessary and proper. But I would not have you think that I conceive of advertising and promotion primarily in negative or restrictive terms. Properly carried out, it serves an altogether good and socially valuable purpose.

Through the process of discovery we have described for you, making a drug available is only the first long step toward the objective of having it used by those patients who need it. This objective can be attained only if physicians are aware of the availability of the drug, know what it can do, what its limitations are, and what undesirable effects may accompany it. Furthermore, we believe that this information should reach the physician as quickly as possible. The public interest would be poorly served if patients were denied the benefits of a good drug simply because its availability was not known.

Merck's experience with Benemid, a product for the treatment of gout, illustrates how marketing decisions can have social value. When we introduced Benemid in 1951, we felt that it was a major product because it forestalled attacks of gout instead of merely giving relief after an attack. Sales did not approach anticipated levels for years, apparently because there were simply not sufficient cases of gout. We continued to inform physicians about it, however, in the belief that gout was more prevalent than sales indicated. The past 8 years have justified this belief. The estimated number of cases of gout under treatment has risen from fewer than 350,000 in 1959 to approximately 1 million in 1966. Obviously, the incidence of gout has not increased threefold since 1959.

Mr. GORDON. Is this due to your advertising?

Mr. GADSDEN. As I am going to say, Mr. Gordon, in the next sentence, we would like to take partial credit for increasing the awareness of the symptoms of gout.

Recognition and subsequent treatment of gout have increased—due in part, we believe, to our communications program.

I have described the precautions we take with our advertising. Nevertheless, an occasional advertisement does run into trouble with the FDA. I think the reasons can be found primarily in the changing regulatory climate, and in the turnover of officials responsible for interpreting and applying the advertising regulations. As official attitudes have become increasingly critical of the motives and methods behind the advertising of prescription drugs, more and more companies have been embroiled in disputes with the FDA.

However, questions of interpretation to one side, Merck hopes and believes that the agency shares our belief that responsible and effective promotion is a necessity. It is particularly necessary in the case of a drug which offers the possibility of benefits to patients suffering from conditions for which there is as yet no fully effective or satisfactory method of treatment. Arthritic disorders represent just such a condition. Some patients obtain little or no relief from drugs which are available; side effects limit the benefits others may obtain. The availability of a new drug which can help those who cannot obtain relief from other measures becomes important.

As Dr. Donald F. Hill stated in his presidential address to the American Rheumatism Association in June 1967:

> Our patients come to us discouraged. Arthritis is a discouraging disease. Too many of our patients are further discouraged by what the doctor tells them. Too many of them hear him say: "There is not much we can do for you."
>
> Our failure to keep up with, and apply, the latest treatments and medical information in arthritis may not have . . . final and fatal results, but if it means the difference between a useful and productive life, or a life as a cripple, the point may be lost on the patient.[1]

It is true that a company promotes a drug in order to sell it. But such a statement is an oversimplification which ignores the full facts. A drug sells because it is promoted, and because physicians are familiar with it, and finally because they have found that it fills a real need in their practice.

That Indocin does fill such a need in medical practice has been amply demonstrated. The purpose of clinical investigation is to assure safe and effective medicines. Added evidence that we have provided such a medicine in Indocin is to be found in the high refill rate of prescriptions for this drug. Because it is a useful drug, it deserves appropriate promotion.

We have promoted Indocin in many ways, but have consistently sought to follow the principle of supplying accurate and useful information in a manner complying with our understanding of the regulations.

When Indocin was first made available in this country, we had accumulated experience based on nearly 5 years of investigation by more than 300 physicians in the United States and abroad, as well as extensive experience gained from overseas marketing. Our best knowledge was incorporated into our promotional materials.

The initial promotion pieces very clearly stated that in patients with rheumatoid arthritis, ankylosing spondylitis, arthritis of the hip, and gout—the four indications for which the safety and effectiveness of Indocin had been established—overall improvement considered to be excellent or good had been reported in 65 percent of those patients. This not only established the usefulness of the drug to the physician but, equally, it advised him that the drug had limitations and could not be considered effective in all patients.

Furthermore, prominently presented in these promotional pieces was a table showing the incidence of adverse reactions. It not only listed those adverse reactions the physician could expect to encounter, but what their probable incidence would be. And it also included the statement:

> In about 10 to 15 percent (of the patients), adverse reactions may be of a severity requiring dosage reduction or discontinuance of therapy.

After the introductory phase of our promotional efforts, and as physicians became more familiar with the drug, our themes were varied, but our presentations continued to include the limitations of the product. In many of the advertisements the negative aspects of the drug actually consume the bulk of the text.

As my scientific colleagues have stated, many, if not most, distinguished rheumatologists believe that the use of objective measurements alone in arthritic disorders fails to take adequately into account the

[1] "Progress for the Patient," Hill, Donald F., M.D., "Arthritis and Rheumatism," vol. 10, No. 5 (October 1967).

disease process involved. And even more importantly, the use of these measurements alone ignores the subjective benefits enjoyed by the patient. No claim has ever been made that Indocin has any effect on the basic disease processes involved in arthritic disorders. The only claim made has been that in some 65 percent of the arthritic patients who are placed on Indocin, their stiffness, swelling, tenderness, and pain—which are manifestations of their disease—are relieved. These are the reasons that these patients seek medical help, and the relief of these symptoms is an important benefit to the patients and a source of satisfaction to the physicians who have prescribed the drug.

There is nothing new about the purely statistical approach—as opposed to the clinical approach—to the measurement of the effectiveness of a drug such as Indocin in conditions such as arthritic disorders. Few physicians would dispute that the corticosteroids can provide dramatic relief to many arthritic patients in whom all other measures have failed. Yet in 1960, the following statement appeared in the journal, Annals of Internal Medicine: [1]

> Reports of the Medical Research Council and Nuffield Foundation and the Empire Rheumatism Council indicated no significant difference in results of treatment between two groups of patients, one on cortisone and the other on aspirin. However valid these results statistically, purely functional therapeutic effects of steroids in certain individual patients were still impressive. Since none of these drugs affected the disease fundamentally, the question was whether cortisone had not in some instances enabled the patient to "get more out of life," though happiness is not a scientific quality.

The education of the physician is long and intensive. I think it is fair to say that to succeed in the practice of medicine, much more than in most professions, one must be able to make valid judgments of cause and effect. On the basis of his training and experience, the physician tries a drug in a patient. On the basis of his observation of the effect the medicine produces, he decides whether to continue it. His attitude toward the drug, and certainly toward the promotion relating to it, is continuously watchful and thoughtful—just as it is toward his patient. For example, the physician must evaluate the history of the patient's complaints, determine the significance of his findings on physical examination, and assess the results of laboratory tests before he can arrive at a diagnosis. Equally, he must be critical of the results he obtains from any therapeutic regimen. And if for any reason he is not, you can be sure that his patient will be.

I wonder if any of you gentlemen on the committee or its staff ever have suffered from a recurring pain? Speaking as one who has, I venture the opinion that you could not be deceived—certainly not for long—about whether a drug gave you relief. Well, the patient with arthritis comes to his physician for relief. If he does not receive it, he will want an explanation, or else he will seek relief elsewhere—regardless of the drug advertising his doctor may be exposed to.

To suggest that a physician is uncritical is completely to ignore the realities of the situation. Promotion may assure a physician's interest in a drug, but promotion cannot substitute for results.

There is no doubt in my mind that when physicians feel there is a need for a new drug in their practice, promotion can induce them to try one that offers promise. It is equally certain, however, that promo-

[1] "Thirteenth Rheumatism Review": Annals of Internal Medicine, vol. 53, No. 7, Dec. 30, 1960, p. 49.

tion cannot persuade them to continue prescribing the drug unless they themselves find that it fills a real need in their practice. Indeed, the history of medicine is replete with examples of drugs whose early promise was not fulfilled, and whose sales were equally unsatisfactory.

Senator NELSON. I would like to make the point, however, that chloramphenicol is one item which was heavily promoted, and the promotion was very effective; there is no question about that. The promotional activities were effective and there were disastrous results because the drug was prescribed and used for nonindicated cases. That is part of the issue on which we have been conducting hearings here.

Certainly the doctors got dramatic results. One of the distinguished physicians testified—I think it was Dr. Dameshek—that he had a patient who had been taking chloramphenicol prescribed for a cold. His patient told him that the doctor told her to take it home, put it on the bathroom shelf, and take it every time she had a cold. It sure wiped out the cold for all time, but it killed her, too.

This is one dramatic case where the promotion of the drug resulted in a vast overprescription of the drug, which caused Dr. Goddard to say before this committee, "I am at my wits end" as to how to persuade doctors not to use this drug for nonindicated cases.

That is what the hearings are about, the effectiveness of the promotion of drugs. Here is a case where the promotion has been fantastically effective, with disastrous results for many, many patients. I have scads of letters in my office from people about relatives who have died from taking this drug. One doctor prescribed it because he had been told by a detail man that there were no side effects. He prescribed it for his son for a minor infection. The child developed aplastic anema and died.

Well, the evidence is that promotion is effective and very often doctors do not pay any attention to the precautions that are written in the labeling and that very effectively, in their advertising, drug companies manage with the cleverest advertising agents in America, to kind of skip over the side effects.

We had testimony on the advertising of your drug on this exact point. Yesterday we heard testimony that in JAMA, the language used was that Indocin was "(a) drug of choice."

Mr. GADSDEN. Yes, sir.

Senator NELSON. Well, everybody knows that the phrase "drug of choice" are words of art in the medical field and that they have a very special meaning and that to put the word "a" in brackets does not prevent doctors from thinking that it is "the" drug of choice. I think it is misleading.

But in any event, I have seen example after example of the very clever wording which is aimed at playing down side effects, playing down contraindications, and expanding claims for a drug's use.

I am not criticizing your company especially. I think every single company I have looked at that uses ads does not tell the story as accurately in the ad as they tell it in the package insert which has to be approved by FDA.

Mr. GADSDEN. Senator, if I may respond—you can understand, I imagine, my continued sensitivity to perhaps the inadvertent reference to chloramphenicol within the context of our discussions about in-

domethacin. So I would like to read something to that point into the record.

Senator NELSON. The reason I referred to it is that your language was in the most general kind of terms as were used for chloramphenicol or many other drugs. Chloramphenicol happens to be one of the dramatic examples heard before the committee, standing unrefuted by the company or anybody else that I know of, of the wide misrepresentation of a drug because of the type and intensity of promotional activities.

Mr. GADSDEN. But I think there is a differentiation between the point that I was making, which related to effectiveness—the patient and the physician cannot be fooled over an appreciable period of time by an effective drug—and the issue which you raised about whether the physicians did or did not pay attention to whatever might have been known about the safety of chloramphenicol.

Senator NELSON. Well, I would suggest that they were not fooled in this case over any period of time about an ineffective drug. It was a dramatically effective drug, but was being used for the wrong purpose. It no doubt had an effect on infections, but it also may cause fatal aplastic anemia. It was just being incorrectly used.

Mr. GADSDEN. With your permission, may I make a statement on this point?

Senator NELSON. Yes.

Mr. GADSDEN. Chloramphenicol is an extremely potent antibiotic drug with a propensity to cause aplastic anemia which often results in a fatality. Indomethacin has no adverse effect even remotely approaching this condition. Chloramphenicol, although uniquely valuable for some infectious diseases such as typhoid fever and staphylococcus infection, can often be replaced in the case of other infectious diseases by different antibiotics with less severe side effects. Indomethacin, on the other hand, does not have greater adverse effects than most of the other drugs available for treating certain classes of arthritic disease. Moreover, patients suffering from arthritic diseases do not uniformly respond to the same drug. While it may be that aspirin has fewer adverse effects than indomethacin in the massive doses needed to treat rheumatic disorder, although this has not been proved, there are many arthritic patients who cannot tolerate aspirin or who do not respond to it.

Dr. Hodges estimated the number who cannot tolerate aspirin at 25 percent. Many such patients do respond to indomethacin and do not suffer greater adverse effects than those caused by other, alternative treatments.

Dr. Hodges has summarized for you the many severe side effects that result from the corticosteroids, the butazones, the antimalarials, and gold salts, and you can see that indomethacin compares favorably with any of these alternatives.

Accordingly, any suggested parallel between indomethacin and chloramphenicol is, in my opinion, extremely farfetched.

Senator NELSON. Has anybody suggested a comparison?

Mr. GADSDEN. Sir, I am paraphrasing.

Senator NELSON. I have not suggested a comparison?

Mr. GADSDEN. I apologize for my undue sensitivity.

Senator NELSON. I want to make it clear for the record that I was responding to a statement in your testimony that had nothing to do with indomethacin in particular, or any drug in particular. The sentence was: "It is equally certain, however, that promotion cannot persuade them"—that is, the doctor—"to continue prescribing the drug unless they themselves find that it fills a real need in their practice."

Part of these hearings is directed to the question of the promotion. The point I was making is that you, again, persuade them by promotion to use a drug in their practice that is effective for the purpose for which they use it but should, for the sake of safety, be used with much greater discretion. That is my comment. I was not comparing it with indomethacin at all.

Mr. GADSDEN. There is one other point that you made, Senator. Referring to the quote which did, in fact, appear in our ads—this was a factual quote from a recognized authority.

Senator NELSON. Which quote?

Mr. GADSDEN. The one about "a drug of choice." In fact, the actual quote says, "the drug of choice." Under AMA editorial policy, they do not permit you to say "the" drug of choice; so if you check our advertisements, you will find that we ran both advertisements. In the JAMA, we said "a drug of choice"; in the others, we used the language of the quote itself, which is, "the drug of choice."

I would furthermore like to call your attention to a quotation of 1967 from the recognized publication, New Drugs, as published by the AMA. It says that because "Indocin" has produced relief in acute attacks within 48 hours, and because it lacks the untoward effects of Colchicine, some physicians consider it to be the drug of choice for these attacks.

Shall I proceed, sir?

Senator NELSON. Yes, go ahead.

Mr. GADSDEN. Mr. Chairman, Indocin has demonstrated its ability to fill this need in the practice of physicians, both in this country and around the world. If it did not fill a need, the past 3 years of experience with it would have clearly demonstrated this fact.

I do not challenge the sincerity of some who have said that in our promotional efforts we made some errors. Language is not a perfect method of communication, and it may well be the words and phrases that we used in the belief they meant one thing may have been interpreted by some physicians to mean something else. Such are the complexities of semantics. But this was never done purposely, and whenever any possibility of misunderstanding was called to our attention, we moved promptly to correct it. If we have made errors, they were only minor ones, and to the degree that they existed they were hemmed in by the total emphasis given to the relative effectiveness, safety, and limitations of the drug.

We responded immediately to negative comment by the FDA, and the advertisement which they complained of has not appeared since November 1966. We took this action primarily from a prudent desire to cooperate with the Agency. We hope that upon the completion of the computer tabulations of our entire patient data, we can discuss with the Agency the renewed use of such claims as "Extends the margin of safety."

Senator NELSON. What does the phrase, "Extends the margin of safety," mean?

Mr. GADSDEN. In the context in which this was discussed, in the advertisement and as positioned by our scientists and medical personnel based upon their own knowledge and primarily that of clinical investigators, when compared to the drugs which have been mentioned here before, butazones and corticosteroids, it says that more patients can be treated with Indocin with fewer side effects.

Senator NELSON. That is what "extends the margin of safety" means in this case?

Mr. GADSDEN. Yes, sir.

Senator NELSON. Please continue.

Mr. GADSDEN. Indocin has established its place in medical practice because it has demonstrated effectiveness in many patients with certain arthritic disorders, at the same time being relatively safe for most patients to take over the long periods of time they must remain under treatment.

In closing, I would like to make one general point. Merck has been making and marketing a lot of drugs for a long time. It has been a point of pride with us—and an essential element in our success—to provide good, reliable information on these drugs and their proper use. The record will show that out batting average has been very high. And the people who have benefited from them are, I submit, the best evidence of the social values of our products and the way we market them.

Mr. Chairman, thank you again for the opportunity of appearing before you. If you have any further questions, my associates and I are at your disposal.

Senator NELSON. Thank you, Mr. Gadsden, for your very thoughtful contribution to these hearings. I believe the minority counsel has a question.

Mr. GROSSMAN. Yes, Mr. Gadsden. I would like to ask you about the article that appeared in Pageant. I think that the company issued a release yesterday, but I would like to get it clear for the record, because that matter did not go into the record. I would like to know first of all, and I think you can make a general statement if you wish, but first, is it true that Merck & Co. in no way initiated that article or paid for it in any way and that these people were completely acting on their own. Is that correct?

Mr. GADSDEN. We neither initiated nor paid for nor stimulated it, nor did anything except what I referred to in my earlier testimony.

Mr. GROSSMAN. So in other words, for the record, so that we have it clear, there was no dealing with Pageant magazine or with the authors of the article?

Mr. GADSDEN. No, there was not.

Mr. GROSSMAN. May I ask you, is soliciting material from you common procedure among individuals who write these articles? Do you think there is any way of controlling this? Is it an abuse that industry can handle?

Mr. GADSDEN. I think we are into an area here which is very difficult, if I may be presumptuous, for you or for us on what to say or what not to say. In other words, we have a free press in the United States. You have recognized scientific writers who quite naturally wish to inform the public upon what they consider interesting developments. We have to toe a very close line as between deciding that we will withhold

information from the press completely and thereby run the risk that what is printed is completely misleading, as contrasted to using our best judgment as to what we should supply in the interest of a balanced presentation.

Mr. GROSSMAN. What are your general feelings about articles that reach beyond the doctor, such as this one; in other words articles directed at the general public?

Mr. GADSDEN. This is the type of article to which I am referring. So that we may be completely clear, when I say "science writers," I am referring to science writers for lay publications as contrasted to professional journals.

Mr. GROSSMAN. I agree with your point about the freedom of the press. I am just getting a general impression of what you think about this.

Mr. GADSDEN. Well, I guess I am fairly pragmatic on this subject. Regardless of whether we think it is appropriate or inappropriate, the fact remains that the public has become increasingly interested in anything to do with health. There have been any number of articles. I think that within the restraint under which we must place ourselves—one is that we must obviously comply with the food and drug regulations and other laws of the land—within our interpretation of that, we should attempt to see that what appears in print is as factual as possible.

Mr. GROSSMAN. One other question in a different area. There has been some testimony and some inference that there is no truly independent research being done, in the sense that there is an inherent conflict of interest, almost, in that you have firms to do your clinical research and report their objective findings. I wonder what comments you might have on idea that, for example, the Government might select that specific consultant for the company, the company would pay for it, and submit the findings to the FDA for approval?

Mr. GADSDEN. First, as temperately as possible, I would like to resent the implication that a company such as Merck either could or would attempt to doctor the results.

Mr. GROSSMAN. That is not my question.

Mr. GADSDEN. I realize that. I just want to get that on the record, if you will permit me, because we have been in business for a long time and we could not risk our reputation this way, even if we could "buy results."

Now, some of the previous witnesses before this committee have raised a question as to the integrity of the drug companies or the clinical investigators, who in the main are connected with academic institutions. Well, on their behalf and gratuitously, I resent it for them, too.

Also, one of your witnesses before this committee raised some rather serious doubts in his testimony about whether civil servants would assume the responsibility of making a decision if there were a gain-risk balance, and someone had to assume the responsibility.

Mr. GROSSMAN. I think this is the FDA's decision.

Mr. GADSDEN. I think what I am suggesting is that we are pretty soon in a never-never land. There may be a fourth party, but I cannot identify it at the moment. Questions have been raised as to whether the pharmaceutical companies can do it, or whether it can be ap-

propriately done under grant by academic people; now we have finally completed the circle by saying that, in the opinion of at least one witness, there is question as to whether someone who is a Government employee will assume this degree of responsibility. I am frankly lost with this kind of, if I may, sophistry.

In our opinion, the procedures which have been described by my scientific colleagues have, in fact, yielded very good results. This is what I referred to in my statement. We are in the happy position—in regard to these products which Dr. Tishler has described, starting with the vitamins and bringing it up to date—that there have been very rare occasions when the initial positioning of a Merck product had to be seriously modified based upon experience in the marketplace.

Mr. GROSSMAN. Thank you.

Senator NELSON. Thank you very much, Mr. Gadsden. If you have any additional pertinent material which you have neglected to give us for the record today, the record will be open for another week. If at any time in the course of these hearings, you wish to make any contribution concerning any issues raised before the committee we shall be pleased to have your material.

Mr. GADSDEN. Thank you for that opportunity, Senator. Even before these hearings, in the telephone conversations which I had with Mr. Gordon—I think that Mr. Cutler has had subsequent ones—we asked for the opportunity, if it seemed appropriate, to file supplementary statements based upon testimony that was given between the time we prepared our statements and our presentation here, because we had to do this on very short notice and we compressed it within a limited period of time.

(Subsequent correspondence and supplemental statements were submitted by Merck & Co., Inc., and follow:)

MERCK & CO., INC.,
*Rahway, N.J., May 14, 1968.*

Hon. GAYLORD NELSON,
*Chairman, Subcommittee on Monopoly, Select Committee on Small Business, U.S. Senate, Washington, D.C.*

Dear SENATOR NELSON: I am enclosing several supplementary statements for inclusion in the record of the hearings of your Subcommittee relating to 'Indocin'. We appreciate your willingness to permit us to file these supplementary statements and your recognition that we could not deal in our prepared statements with the testimony of witnesses who immediately preceded us.

We believe that the testimony we presented on May 3 and the statements of Dr. Hodges, Dr. Rothermich, Dr. Calabro, and Dr. Smyth constitute a sufficient response to most of the testimony of the academic witnesses who testified on April 23 and 24.

We have prepared, however, and submit herewith supplementary material bearing on two aspects of Dr. O'Brien's testimony: an internal memorandum by Dr. Hurwitz of the FDA, apparently overlooked by Dr. O'Brien, which revises the views Dr. Hurwitz expressed in an earlier memorandum that was critical of the clinical studies with 'Indocin' and that was quoted from at length by Dr. O'Brien; and a statement of Merck's policies and procedures in the support of clinical investigation.

In connection with the May 1–2 hearings, we are also submitting supplementary material related to the testimony of Dr. Jennings and Dr. McCleery of the Food and Drug Administration, who dealt primarily with the content of our labeling and advertising and with our performance in promoting 'Indocin'.

Implicit in Dr. Jennings' and Dr. McCleery's testimony were suggestions that the Company and its executives acted on the basis of motivation to overstate claims, minimize adverse effects, expand use of the drug beyond allowed claims, and resist efforts of the Food and Drug Administration to enforce proper standards of communication to doctors.

It is difficult to present objective evidence in rebuttal of these subjective imputations. We would remind the Subcommittee, however, that there is a common sense and essential logic in our position that any such motivation would inevitably damage our reputation with the doctor and the patient, and would be detrimental to our business interests in the long run. Since our business is uniquely dependent on what the health professions think of or character and reputation, it would make little sense for us to engage in this kind of conduct—and we do not do so.

As I said in my direct testimony, it is not the Food and Drug Administration that is ultimately responsible for the safety and effectiveness of our products, including the information we give to the doctor about them. It is we who must bear that responsibility and who must suffer the consequences of failure. This is the way it should be, and this is the way the Food and Drug Administration should want it to be.

We would appreciate your placing these materials in the record at the end of the testimony of Dr. O'Brien, Dr. Jennings, and Dr. McCleery respectively, and request that this letter be placed at the end of the Merck testimony on May 3.

Sincerely,

H. W. GADSDEN, *President.*

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## SUPPLEMENTARY STATEMENT OF MERCK & CO., INC. IN RESPONSE TO PORTIONS OF TESTIMONY BY WILLIAM M. O'BRIEN, M.D., ASSOCIATE PROFESSOR OF PREVENTIVE AND INTERNAL MEDICINE, UNIVERSITY OF VIRGINIA SCHOOL OF MEDICINE TUESDAY, APRIL 23, 1968 BEFORE THE MONOPOLY SUBCOMMITTEE SENATE SELECT COMMITTEE ON SMALL BUSINESS

This statement is filed pursuant to permission granted by the Chairman of the Subcommittee to comment on testimony by witnesses who appeared before the Subcommittee on April 23 and 24 and May 1 and 2 with regard to this Company's performance in the development and marketing of its product 'Indocin'. This supplementary statement covers two points.

(a) Dr. O'Brien was permitted, at the Committee's request, to review Merck's indomethacin New Drug Application file at the Food and Drug Administration, including FDA's internal memoranda relating to the application. Dr. O'Brien quoted extensively from a January 25, 1967, memorandum of David Hurwitz, M.D., of the Food and Drug Administration. (Pages 4538–40) Dr. O'Brien failed to mention that the document quoted from was primarily concerned with a review by Dr. Hurwitz of a supplement to the original New Drug Application, filed in May 1966 to cover additional indications. Dr. O'Brien quotes the document as if it dealt only with the approval of the original New Drug Application.

As Dr. Hodges pointed out in his testimony (pp. 4668–70), Dr. O'Brien also appears to have overlooked a subsequent memorandum of Dr. Hurwitz dated August 1967, in which he, after further review of the data, substantially revised the opinions expressed in his memorandum of January 25, 1967. We have appended to this statement a copy of Dr. Hurwitz's August 1967 memorandum, and request that it be placed in the record at this point.

(b) In his testimony on April 23, Dr. O'Brien appeared to cast doubt on the integrity and reliability of clinical investigators selected by Merck and other pharmaceutical companies, and on the method of their selection.

To complete your record, we are setting forth below Merck's policy and procedure in the selection of investigators. (Copies of this statement were, at the request of the Subcommittee staff, submitted prior to Merck's appearance on May 3, 1968, but were not made a part of the record.)

### MERCK'S POLICY AND PROCEDURE IN THE SELECTION OF INVESTIGATORS

After careful review of preclinical evidence of safety and pharmacological activity of a new therapeutic compound, it may be cleared for clinical study. The Company's medical and scientific staff then must decide whether they wish to carry the compound into the clinical investigative process. If they do, a plan for

the clinical program is developed and the clinical objectives—based on the pharmacological and toxicological data derived from animal studies—are established.

Clinical protocols are then prepared. These outline the broad design of the proposed clinical studies and convey the basic information on toxicology and pharmacology with which clinical investigators must be familiar in order to study the drug in man. In developing the protocols, we consult with clinical pharmacologists, biostatisticians, and selected investigators. In this process, we strive for the best possible study design, reconizing at the same time that the new drug can only be studied within the scope of presently available methodology as well as the availability of patients, volunteers, and clinical research facilities.

Once the clinical plan has been completed and submitted to the FDA, clinical studies are initiated in Phase I—which probes the basic pharmacology and metabolism of the drug in man. These studies are carried out only by expert clinical investigators in a few selected clinical laboratories, normally not more than five. These are almost always in university-affiliated medical centers and are carried out in carefully selected individuals.

If Phase I studies provide evidence of safety and pharmacological activity, the clinical program is expanded to include a half dozen or more expert investigators in the field of medicine where the drug promises to be useful (Phase II). An antihypertensive drug, for example, is taken to specialists in cardiology who have had experience in the investigation of such drugs.

By this time the appropriate dosage range for the drug is fairly well established, and the effects of the drug can be studied in various disease states where it is expected to have a beneficial effect. This additional experience, involving studies in depth, adds greater assurance of safety and efficacy and provides the basis for expansion of the studies into Phase III.

The final phase (III) provides still greater evidence of safety and therapeutic benefit which can then be well delineated in the clinical indications for use of the drug. These studies are carried out by carefully selected physicians experienced in the field of study concerned. These are selected by our medical staff based upon knowledge of their prior work in the field, their prior work for us, and in some instances on the recommendation of Phase I and II investigators. A primary purpose is to obtain a deeper insight into how the drug will respond in the hands of physicians generally.

During all three phases, the studies are well controlled. The more sophisticated and complex double-blind studies are undertaken particularly during the Phase III stage. These studies serve as much as possible to eliminate bias and the elusive clinical variables which are ever present. It must be recognized, however, that although data from such studies tend to appear more convincing, their validity may also be subject to question. In most fields of medicine, it has yet to be proved that *all* relevant factors have been accounted for in the control design, and thus we must avoid total reliance on what may be simply a tidier version of an imprecise appraisal of a drug.

The first and ultimate responsibility for drawing conclusions with regard to safety and efficacy of a drug lies within the medical staff and the research organization of the Conmpany sponsoring the studies. We do not and cannot delegate this repsonsibility to a third party.

Financial assistance in the form of grants-in-aid is given to the investigator to cover the expenses incurred in carrying out his research. For the most part a contractual relationship is established between the Company and the university or institution where the work is being carried out. Grants are made on a sound budgeting basis. Clinical research grants are never based on the condition that a certain number of case reports be submitted or that only positive data be provided. Our records clearly show that studies supported by grants frequently fail to support the objectives set forth in the clinical protocol, either because of a shortcoming in the drug itself or failure to anticipate one or more of the numerous variables which arise during the clinical study and result in negative data.

Most grants-in-aid cover the following costs: Laboratory, technical, clerical, hospital, and bed costs; supplies, mtaerials, and overhead. If there are indirect costs assigned to a project as part of the investigator's overall research budget, these too are covered. Should the investigator request that special studies be done—such as radioisotope work, or metabolic balance studies demanding the special facilities of metabolic ward—these are financed to cover all direct and indirect costs.

It is difficult to generalize about the costs of clinical research in the conduct of studies with new drugs. One cannot, for example, correlate the number of

patients or case reports per study with the cost. Where a minimum amount of laboratory work is required and the patients may not be seen by the physician more than three or four times during the course of the study, the cost of studying 50 patients may not be more than $5,000. On the other hand, studying six patients for six weks in the hospital or in a metabolic ward, at the rate of possibly $100 a day, may cost $25,000 or more. Costs vary with the degree of patient or hospital care needed, the extent of laboratory work, and the number of individual technical or professional tests to be done.

Today, when hospital, laboratory, and research costs are skyrocketing, and when the expense of conducting clinical research on a new drug may extend over a period of three to five or more years, the cost of clinical investigation has become substantial. Indomethacin studies extended over a period of three and one-half years, from November 1961 to NDA approval in June 1965—and indeed a large program still continues.

It is rare for a clinical research program involving a new drug to cost less than a half million dollars. Most are closer to one million dollars before an NDA has been achieved. Even after NDA approval, there are aspects of clinical research which may be pursued for years thereafter.

It should be pointed out that a sponsor would be foolish—in this developing age of clinical science—to undertake to "pay" an investigator for positive data which cannot be substantiated. This could not be done with responsible clinicians. In any case, the cost of conducting medical research is already so high that to add a factor of cost to this by trying to buy data which could not be confirmed would be not only bad ethics and bad research but also bad business. A well-established research enterprise such as ours, with its scientific and medical reputation at stake and investing very heavily in obtaining clinical data, has much more to lose than to gain from this inaccurate data.

It is the policy of the Company to seek out the best and most experienced clinical investigators it can find to evaluate its new drugs or to explore new uses of existing drugs. In 1967, we invested to $2,000,000 in the clinical investigative phase of our research effort, supporting the work of several hundred investigators here and abroad. Although averages are not always meaningful or as accurate as one might wish in describing such a program, we estimate our "average" clinical reserach grant to have been approximately $5,000 during 1967.

This compares with the average for an NIH clinical grant of perhaps $15–25,000 during the same year . . . it is recognized, of course, that the NIH grants are more broadly based and for a longer term. But there are other comparisons that can be made with NIH grants as well. Like the NIH grantee, the Merck grantee is free to and encouraged to publish his data, whatever they may be. Like the NIH grantee, the Merck grantee is committed only to the accomplishment of a study, not to results. Like the NIH grantee, the Merck grantee is drawn from a cross-section of the nation's and the world's resources in the health sciences. The excellence of the performance and the quality of the data depend not so much on the sponsoring institution as on the state of the art and the state of the science in a given field. Thus, clinical reserach supported by Merck is and will be qualitatively similar to research supported by Federal funds. At the same time, both companies such as Merck and Federal agencies such as NIH have a responsibility to do what they can to help strengthen the resources for better and ever better research, including clinical research.

The key thing, from the Company's point of view, and the key message it would wish to communicate to a Committee of Congress that has interested itself in this question, is that the objective of the Company is quality performance in clinical reserach yielding reilable data. This represents an ever-present goal. We do not suggest that we are universally successful in achieving this goal; to attain such a level in any human endeavor is perhaps impossible. But our record has been good.

Indeed, there is no other course for a responsible company to take. We are dealing with products related intimately to man's aspiration for health and freedom from pain and suffering. All such products have a great capacity for good or for harm. In the final analysis, we are responsible for our drugs and have nothing to gain and everything to lose by performing inadequately in our own laboratories, or by permitting sloppy performance by outside investigators, or by knowingly—in our evaluation of preclinical and clinical data—ignoring and neglecting the facts as they bear on the safety and effectiveness of a new drug.

[Copy made by Merck from facsimile]

## INDOCIN IN RHEUMATOID ARTHRITIS

(By David Hurwitz, M.D., Metabolic & Endocrine Div./ODS)

Since its introduction in March of 1965, Indocin has enjoyed wide public acceptance as an anti-arthritic agent. Early pharmacologic studies had indicated an unprecedented potency when the drug was used to control inflammation in various animal models. It was hoped, at that time, that Indocin would have a high therapeutic ratio and thus offer a significant advantage over corticosteroids with their multipilicity of serious adverse reactions. Unfortunately Indocin has shown a similar propensity to cause a wide variety of serious and sometimes fatal reactions, and its clinical usefulness has been limited by its toxicity. This toxicity has been well documented and is now well-appeciated by the medical profession, and Indocin has taken its place along side aspirin and phenylbutazone as another useful agent in a group of poorly understood diseases not amenable to any definitive therapy.

At no time, however, was the actual efficacy of Indocin questioned. It was appreciated that the drug worked considerably better in acute inflammatory conditions like gout than in the chronic arthritides such as rheumatoid arthritis, but the drug was believed efficacious in the latter condition. Several new studies published in the first quarter of 1967 in major scientific and medical journals now dispute the usefulness of this drug in rheumatoid arthritis. Chief among them in an exhaustive clinical study carried out by the Cooperating Clinics Committee of the American Rheumatism Association in association with Dr. Donald Mainland, a well-known biostatistician. This exhaustive study involved 141 patients treated for a three-month period and required ten months to be completed. Indomethacin was compared in a double-blind fashion with a placebo, the patients being allowed free use of aspirin as needed. Although many different parameters were measured and studied by sophisticated statistical techniques, the authors were unable to find any statistically significant differences in those parameters between Indocin and the placebo medication.

In the same month, Donnelley et al. published a similar study in the British Medical Journal. The British authors used a double-blind crossover study comparing Indocin with a placebo, and they also were unable to establish any statistically significant difference between Indocin and placebo. In neither study were there any serious reactions to the medications.

In a third article by Pinals and Frank no differences was found between Indomethacin and aspirin in the treatment of rheumatoid arthritis. This study was a double-blind crossover type and was not as thorough or as well planned as the previous two studies. The authors arrived at the conclusion that Indocin and aspirin have no significantly different effect on the parameters measured which is justified by the results of the experiment, but they seem to have missed the obvious conclusion that no therapeutic effect was demonstrated for either of the medications. The measured parameter, while not varying significantly between the Indocin-treated group and the aspirin treated group, also did not vary significantly within each group at two weeks and four weeks. The lack of inclusion of base line data adds a further difficulty to the interpretation of this paper. In contrast to this study, however, the Mainland and the Donnelly studies were well-planned, well-controlled, and seemed to be products of rigorous, thoughtful research.

Indocin's potential toxicity would make its use in rheumatoid arthritis unacceptable if indeed it has no efficacy for this condition. Therefore it was deemed necessary to review the original studies establishing efficacy in this disease. A search of 100 volumes of the NDA revealed six acceptable controlled studies, five of them double-blind the other single-blind. All of these studies claimed efficacy for Indocin but they vary in quality. As a whole, they would seem to indicate efficacy in this condition; results are summarized in the table, below.

In comparing the old studies to the new ones, it is obvious the latter are better-controlled and use more sophisticated methods of evaluation. Because of the extremely variable nature of the disease and the consequent difficulty in evaluating modes of therapy, it is impossible to say that the new studies outweigh the old, particularly in view of the large mass of testimonial data indicating efficacy. While testimonial studies are not in themselves adequate to allow approval of a drug by the FDA, they certainly cannot be disregarded as meaningless when the ultimate usefulness of the drug and its success is determined by individual

patient reaction to the medication. We are therefore faced with the dilemma of a drug whose efficacy has been seriously questioned by excellent studies but which enjoys solid acceptance by the medical community and the patients it treats. At the present time, then, it would seem wise to consider Indocin as probably effective in rheumatoid arthritis pending further studies in this area. The drug is at the present time safe for use in this condition since in the dosages commonly employed there is very little risk of a serious adverse reaction. This author has recommended in the summary of the most recent supplement submitted by Merck, Sharp & Dohme that further studies be carried out to determine the efficacy of Indocin in rheumatoid arthritis.

TABLE I.—INDOCIN REVIEW—CONTROLLED BLIND STUDIES FROM ORIGINAL NDA

| Author | Date | Volume | Number of patients | Type | Results | Comment |
|---|---|---|---|---|---|---|
| Hart, F. D., and Boardman, P. L. (British Medical Journal, 11:1281, 1965). | 1965 | 30 | 18 | Double-blind crossover comparison with Phenylbutazone 56 days. | (1) Little difference between drugs in therapeutic or adverse effects; (2) Indocin had greater effect on reduction of joint swelling; (3) no serious reactions. | Data not included with study (has been published with adequate data). |
| Percy, J. S., Stephenson, P., Thompson, M. (Ann. Rheum. Dis.) (23:226, May 1964). | 1964 | 30 | 24 | Double-blind crossover sequential comparison with Phenylbutazone. | (1) No significant difference between drugs in patient preference or grip strength; (2) Phenylbutazone had lower incidence of adverse reactions (none serious in either group). | Data incomplete as regards grip measurement or preference, it would be desirable to see how parameters were measured and actual figures; without these we are unable to tell if the patients improved. |
| Wenka, J., Jones, L., Wood, P., Dixon, A. | 1964 | 30 | 22 | Double-blind crossover comparison with placebo 6 weeks. | (1) Patients preferred Indocin but no measurable difference in grip strength; (2) no significant reactions. | The ARA Committee has noticed a feelins of well-being in patients on Indocin; ig this the case here? No objective benefit was noted in the single measured parameter-grip strength. |
| Ward, J. R. | 1965 | 30 | Studies: (1) 29; (2) 40. | 2 studies double-blind crossover comparison with placebo. In study No. 1, unlimited and irregular use of aspirin and steroids was permitted. Study No. 2, all patients on fixed aspirin and prednisone, dosage 4 months. | (1) Indocin group had less tenderness and morning stiffness; (2) Indocin group had significant decrease in pain, morning stiffness, swelling, tenderness; (3) no significant reactions. | (1) Results variable, uncontrolled use of aspirin and prednisone in study No. 1 make it invalid. (2) data scant, inadequate placebo effect (nil); validity of statistics, questionable dosage of other medications unspecified (Study No. 2). |
| Smyth, C. J. | 1965 | 47 | 55 | Single-blind variable time several weeks to several months. | Indocin effective in several parameters as compared to placebo. | (1) Well-developed response criteria; (2) large, unwieldy amount of data; (3) poorly controlled, variable dosage and length of administration; (4) results only suggestive to efficacy. |
| Bode, J. J. | | 80 | 27 total, 15 on Indocin. | Double-blind 3 months | (1) Indocin group had decrease joint tenderness and pain, no difference in parameters; (2) no serious reactions. | (1) Did patients use other medications during this long study? |

TABLE II.—INDOCIN—NEW STUDIES QUESTIONING EFFICACY

| | | | | | | |
|---|---|---|---|---|---|---|
| Pinals, R. S., Frank, S. (NEJM March). | 1967 | | 24 | Double-blind crossover comparison with aspirin 2 months. | (1) No difference between Indocin and aspirin; (2) no serious reactions. | (1) No baseline data; (2) neither drug had any clinical effect which makes results difficult to interpret; authors did not discuss this point; (3) 5 patients on steroids. |
| Donnelly, P., Lloyd, K., Campbell, H. (British Medical Journal, January 1967). | 1967 | | 30 | Double-blind crossover comparison with placebo 1 month. | (1) No statistical significant difference between Indocin and placebo; (2) some delay in onset of fatigue on Indocin but not statistically significant; (3) no serious reactions. | (1) Well-designed study, well-controlled; (2) used aspirin in all patients but amount was recorded and evaluated statistically. |
| Mainland et al. (Clin. Pharm. and Therapeutics, January 1967). | 1967 | | 141 | Double-blind comparison with placebo 3 months. | (1) No statistically significant difference between Indocin and placebo; (2) no serious reactions. | Use of aspirin reduces sensitivity of experiment and may mask small differences between placebo and Indocin. |

# SUPPLEMENTARY STATEMENT OF MERCK & CO., INC. IN RESPONSE TO PORTIONS OF TESTIMONY BY JOHN JENNINGS, M.D., ACTING DIRECTOR, OFFICE OF MARKETED DRUGS, BUREAU OF MEDICINE FOOD AND DRUG ADMINISTRATION, GIVEN ON WEDNESDAY, MAY 1, 1968 BEFORE THE MONOPOLY SUBCOMMITTEE SENATE SELECT COMMITTEE ON SMALL BUSINESS

This statement is filed pursuant to permission granted Merck by the Chairman of the Subcommittee to comment on testimony by witnesses who appeared before the Subcommittee on April 23 and 24 and May 1 and 2 during hearings inquiring into this Company's performance in the development and marketing of its product "Indocin".

On May 1, Dr. Jennings, testifying for the Food and Drug Administration, described the negotiations between the Agency and the Company that led to two package circular revisions in the fall of 1966. (Pages 4690–4704) The general impression we receive from Dr. Jennings' testimony is that the Food and Drug Administration tried from July 15 forward to get the Company to add additional warnings, contraindications, and adverse reactions to the package circulars on "Indocin", but that the Company was reluctant, even recalcitrant, in doing so. It is implied that the Company should have voluntarily made the requested changes long before it did so. Thus, "By regulation, these changes could and should have been put into effect by the firm at the earliest possible times, without awaiting approval from the FDA." (Page 4690)

On the other hand, there is in the same testimony an implied criticism of the Company for proceeding voluntarily without FDA approval when it did change the package circular. "Rather than wait for all the recommended labeling changes to be worked out with us, interim revisions of the labeling were put into effect by the company without our advance approval." (Page 4694)

Dr. Jennings concludes that our letter to doctors transmitting the volunteered package insert changes was "promotional literature" in which the original intent to war physicians of additional hazards was "completely lost." (Page 4695)

His concluding testimony on this subject could leave the impression that the Agency was struggling with the massive problem of a recalcitrant firm unwilling to convey to the doctor important new information on hazards of its drug.

This impression is not justified by the actual facts. We submit below a brief review of our communications with the Food and Drug Administration during the spring and summer of 1966 on revisions in the package insert for "Indocin." These are summarized from our internal memos and records of correspondence with the Agency.

1. *April 6, 1966.* Telephone call to our Dr. Shaffer from Dr. O'Grady, FDA investigational Drug Branch. This call dealt with the Company's IND on "Indocin" covering studies in indications not in the then-approved NDA. Dr. O'Grady reported that the Adverse Reaction Bureau, FDA Bureau of Medicine, thought there was an increasing number of side effects associated with the use of "Indocin". Dr. Shaffer told Dr. O'Grady that from our review of reported adverse reactions, the incidence of such reactions was not increasing but decreasing with more widespread use of the drug. A request was made to discuss the entire investigational program with Dr. O'Grady.

2. *April 7, 1966.* Dr. Shaffer telephoned Dr. O'Grady for a date for conference. This was tentatively set for April 15, but later in the day changed to April 18. FDA was asked whether it had adverse reaction data from sources independent of Merck.

3. *April 19, 1966.* Conference between FDA and Company medical representatives. Although the conference related primarily to the investigational studies for added claims, the FDA representatives reported their opinion that the current package insert should be revised to reflect current adverse information reports, including some data they had that we did not have. The Company medical representatives felt Merck should make a complete review of the labeling and

see whether the data available to us suggested the need for package circular revisions.

4. *May 2, 1966.* As a follow-up to the April 19 conference our Dr. Shaffer telephoned Dr. Seife and asked if he would provide us with the type and number of adverse information reports they had received through the FDA Adverse Reaction Reporting Program. Dr. Seife called back the same day and gave us this information, characterizing the reports with regard to the role "Indocin" may have played. He promised to keep us informed as additional reports came in to FDA.

5. *May 5, 1966.* Letter from Dr. Ruskin of the FDA Division of New Drugs, primarily relating to the pending NDA on an "Indocin" formulation. It "recommended that revised labeling be submitted supplemental to your approved application for the capsule form to contain the most recent reports of adverse reactions which are not in the current labeling. . . ." In this letter Dr. Ruskin requested that a statement be added in boldface type to the warning section of the labeling that this was "not an innocuous drug," and should not be used for other than recommended indications, and not be used in women of childbearing age. *"We recommend that these labeling revisions be discussed with the New Drug Surveillance Branch. . . ."* (Italic added.)

6. *May 27, 1966.* Our Dr. Shaffer telephoned Dr. Seife of the New Drug Surveillance Branch to arrange for the requested discussion. We suggested a meeting on June 6, but Dr. Seife was "occupied with another problem" and said he "would like to arrange for such a conference before the end of June." It was left that Dr. Seife would let us know when he was available. Additional adverse information FDA had received from March 24 through May 5 was communicated in this conversation.

7. *July 1, 1966.* Our Dr. Shaffer telephoned Dr. Seife of FDA to ask about the proposed meeting. Dr. Shaffer learned that Dr. Seife was "out of town" and that Dr. Jennings, Acting Director of the Drug Surveillance Branch, should be called.

Dr. Shaffer called Dr. Jennings and learned that the matter had been reassigned to him. He said he would discuss with Dr. Ruskin the May 5 letter we had from Dr. Ruskin, but that if any *urgent changes in labeling were necessary,* these could be made without submitting a new drug application supplement for FDA approval. Dr. Shaffer told Dr. Jennings that *"in order to avoid subsequent changes requiring reprinting etc., we requested an opportunity to discuss labeling revisions with them as requested by the Ruskin letter of May 5, 1966."*

Dr. Jennings asked that we "check back with him in about one week."

8. *July 15, 1966.* Conference in Washington between FDA and Company medical representatives. Dr. Seife was to enter the hospital for surgery and our labeling matter had been assigned to Dr. Standard.

A summary of major labeling changes prepared by Dr. Seife was reviewed in detail. Dr. Seife told us *the recommendations outlined during this discussion would be sent to us in the form of a letter.*

9. *August 4, 1966.* Dr. Shaffer wrote to Dr. Jennings as follows:

"As you know, we met with Dr. Seife, Dr. Bryan, and Dr. Standard July 15 to discuss proposed revisions of the 'Indocin' Package and Direction Circulars. It was our understanding that Dr. Seife's proposed revisions would be submitted to us by letter. *We would appreciate receiving this communication so we may prepare an appropriate revision based both upon your proposals and our evaluation of the available data."* (Italic added)

10. *August 22, 1966.* No further communication from FDA had been received. On this date, the Merck Sharp & Dohme Division Counsel advised that, since we were willing to accept a number of the FDA recommended changes, we should make the changes voluntarily, notify the FDA, and mail the revised circular to physicians.

11. *September 2, 1966.* We submitted a supplemental NDA containing the added contraindications, precautions, and adverse reaction information, stating in the transmittal letter to the FDA: "We feel it important that these changes be placed into effect at the earliest possible time." The majority of the FDA's suggestions were adopted. We gave our reasons in that letter for not adopting all of them.

Our letter ended with the following paragraph:

"We appreciated the opportunity to discuss suggested changes in the Indocin labeling with your staff. We believe that the revised labeling submitted with this supplemental application accomplishes the mutual goal of providing the physician with the most useful information about this drug. To accomplish this goal, we have taken the position that the labeling should be unencumbered by a listing of

every report of an adverse reaction if, in our best judgment, there does not appear to be a reasonable relationship to the drug. An attempt has been made to provide the physician with some guidance as to the relative frequency with which the listed adverse reactions may occur. We are following the clinical experience with this drug closely and will make further labeling revision if and when indicated."

12. *September 30–October 6, 1966.* No reply to our September 2 letter had been received from the Food and Drug Administration. On September 30, we started our mailing to doctors, and on October 6 notified the FDA that the revised circular had "just been mailed." Enclosed in the letter was the circular, the transmittal letter and the envelope which contained in large red letters, "Do Not Discard Before Reading—Drug Safety Information." The revisions were noted in boldface type so that they would not be missed by the readers.

Although the letter sent out to doctors was clearly marked as noted above, and the enclosed revised insert was made easy for the physician to read, and the body of the letter conveyed what it was intended to convey, it did contain first and last sentences that tended to give it a promotional overtone. In retrospect, we think it should not have had those sentences in it. We do not do everything perfectly, and did not do so here. Nevertheless, we think that the essential intent and message of the letter was clear, and that Dr. Jennings' categorical opinion that original intent was "completely lost" (page 4695) is overstated.

During the course of these discussions with the FDA, we found ourselves involved in differences of medical opinion about the implications of the reports of adverse reactions and side effects of the drug. In terms of telling physicians about them, we were of the opinion that placing before them a mass of detail, much of it repetitious, would tend to obscure the really important warnings. As to the reports themselves and their significance, there were not unnatural differences of opinion. Our medical staff felt, and still does, that nothing essentially new was emerging from these reports, that the increasing number of reported reactions reflected the increasing use of the drug rather than an increasing incidence of reactions, and that as more experience was gained what was emerging was an expected refinement of the original essential pharmacologic profile. The Food and Drug Administration people appeared to think differently. It did not—and does not now—follow that they were right in this opinion.

A good example of this difference of opinion is our view of the value and proper use of the drug in cases of juvenile rheumatoid arthritis. Dr. Jennings, during his testimony, refers to reports of deaths in children associated with the use of indomethacin. He disposes of a number of these cases as probably not due to the drug, but reserves opinion as to several. There is a considerable difference between a drug's being possibly linked to a death, and definitely related to it. The FDA is understandably cautious and has consistently singled out pediatric age groups as a patient population bearing risks beyond the adult group.

From the beginning, because the FDA did not accept our pediatric data, our domestic package circular included a specific contraindication against the use of 'Indocin' in children of pediatric ages.

During our discussions with the FDA in the spring and summer of 1966 about the revision of our labeling, the FDA itself *did not request us* to include any statement in the circular referring to fatalities in children. The only difference between us at that time was whether the existing contraindication of 'Indocin' for children was sufficient, or whether it should be strengthened by the addition of a phrase at the beginning of the circular stating "Not for Use in Children."

We did not believe then and we do not believe now that this addition was necessary or desirable. In the light of the FDA's desire for more emphasis, we did italicize the portion of the circular containing the specific contraindication for use in children, so that it would come even more prominently to the attention of doctors. Moreover, we added an additional paragraph, printed in boldface type in the revised circular, calling attention to the fact that 'Indocin' could mask the existence of infection and reminding physicians that it should be used with caution in patients with existing infections. In our scientific opinion, the reported deaths in children were related more to the existing complications of a serious infection in these patients than to the fact that they were children.

FDA insisted in meetings that followed the events summarized above that we make a further amendment adding a specific statement at the beginning of the circular that the drug should not be prescribed for children, and it requested for the first time that we refer in the contraindications to reports of severe reactions, including fatalities, in a few cases of severe juvenile rheumatoid arthritis.

Although we did not agree with this medical judgment, we did include these statements because of the FDA's insistence.

In the judgment of our medical staff, the total prohibition of 'Indocin' in juveniles suffering from acute rheumatoid arthritis is not warranted. Acute juvenile rheumatoid arthritis is a serious and often hopeless disease. If treated with corticosteroids, very serious effects—including loss of calcium in the bones and the disturbance of the endocrine system—can frequently result. In those children who do not respond to aspirin or cannot tolerate it, we believe it is medically preferable to treat them with 'Indocin' than to risk corticosteroids or to leave them untreated. The FDA does not agree with us, and for that reason we have always contraindicated 'Indocin' for this purpose in the United States. But many doctors do administer the drug successfully to children in Europe. The matter presents a question of refined medical judgment, but it is one on which you will find much responsible opinion on our side.

It must be accepted as a truism that the FDA is at all times in a position to bring great pressure on us to adopt every detail of what they want. For our part, we wish to cooperate as much as possible with the Agency. Good relations with it are essential for us.

Subsequently, when at Dr. Goddard's request we met on November 11, 1966, with him and his staff to discuss our labeling and advertising of 'Indochin', we reviewed the differences of opinion about the controversial points and the transmittal letter to doctors. As a result of the meeting, even though our respective medical staffs continued to be in disagreement on a number of issues, we chose to abide by FDA's wishes and sent out a further revised circular containing all the changes FDA requested, including the different typographical and position treatment of the contraindications in children. This revised circular was transmitted to doctors in December, 1966, with a letter which made reference to nothing but the changes in the insert. Both the circular and the letter were worked out with the FDA.

Neither in these meetings nor subsequently was there any recalcitrance on our part. In our opinion, sincere disagreements in medical opinion cannot be equated with recalcitrance. We were deeply concerned at the time at what seemed to be imputations to us of bad motives and lack of integrity. We argued against such imputations most vehemently. But we worked out this particular problem on the basis of a full and frank discussion of where we and they stood on the matter.

Perhaps it is fair to say that the Company and the FDA must share the responsibility for the time it took to issue the first revised circular. The job could have been done faster if we and the FDA officials concerned had been able to arrange more frequent meetings and to obtain prompt decisions. With respect to the wording of the first transmittal letter to doctors, we must and do accept sole responsibility.

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## SUPPLEMENTARY STATEMENT OF MERCK & CO., INC. IN RESPONSE TO PORTIONS OF TESTIMONY BY ROBERT S. McCLEERY, M.D., ACTING DIRECTOR DIVISION OF MEDICAL ADVERTISING, BUREAU OF MEDICINE FOOD AND DRUG ADMINISTRATION GIVEN ON THURSDAY, MAY 2, 1968 BEFORE THE MONOPOLY SUBCOMMITTEE SENATE SELECT COMMITTEE ON SMALL BUSINESS

This statement is field pursuant to permission granted Merck by the Chairman of the Subcommittee to comment on testimony by witnesses who appeared before the Subcommittee on April 23 and 24 and May 1 and 2 during hearings inquiring into this Company's performance in the development and marketing of its product, 'Indocin'. This supplementary statement covers portions of the testimony of Dr. McCleery on May 2.

We do not agree with the allegations of fact, charges, and conclusions contained in Dr. McCleery's testimony on a number of detailed aspects of our advertising of 'Indocin', such as his extensive discussion of the reference in our advertisement to an article by Hart and Boardman in the *British Medical Journal* of October 18, 1963. We have presented to the Food and Drug Administration detailed factual and legal responses to these charges. In our view, the advertising statements the Company used did not misrepresent the status of the drug, intentionally or otherwise. In any event, the criticized statements have not appeared in any Merck advertisement since 1966.

As Mr. Goodrich testified before your Subcommittee, this matter is now pending before him for a decision on whether further legal proceedings should be recommended. While the matter is in this status—and since the issues involved require lengthy analysis and interpretation of the criticized quotations, the scientific data on which they were based, and the articles from which they were taken—we believe it would be inappropriate to comment on the issues in this forum.

We do feel, however, that we should note our exception to one specific point about our advertising raised by Dr. McCleery, since it suggests knowing misrepresentation on our part. In commenting on an advertisement in the July 18, 1966, edition of the *Journal of the American Medical Association*, he said that the advertisement ". . . featured the claim of one of the participants in a Merck-sponsored symposium. This is attributed to Dr. Englund—they featured a claim, quoting from him at this symposium that [he] had had 500 patients on the drug for three years, when Merck's own records would have told them this was not true." (Page 4733)

The advertising to which he referred contained this statement:

"I have had some 500 patients on indomethacin now for about three years. I find it an extremely helpful drug. I think there are certain areas where it will be without question [a] drug of choice. One of these is osteoarthritis of the hip."

This quotation was taken from a statement made by Dr. DeWitt W. Englund in response to a question from the chairman of an international symposium on Non-Steroidal Anti-Inflammatory Drug Therapy in Rheumatic Diseases conducted September 26–28, 1965, in New York City, by the Excerpta Medica Foundation.

We do not believe that Dr. McCleery's criticism of the Company for using the statement "when Merck's own records would have told them this was not true" is warranted. Merck could properly have relied on Dr. Englund's recorded and published statement as the factual observation of an eminent and leading rheumatologist. Our records did show that Dr. Englund had treated at least 500 patients by that time. The information was contained in Merck's first quarterly report to the FDA after the approval of the New Drug Application on June 10, 1965. It was sent to the Agency about the middle of September, 1965, and should also be in its records.

In another portion of his testimony, Dr. McCleery described his understanding of our connection with a lay article about the drug in *Pageant* magazine. (Pages 4716–20) We consider this also to be fundamental because, according to Dr. McCleery, it led the FDA to conclude that this Company "might not be scrupulous in its advertisinng to the medical profession."

We are therefore setting forth in detail what took place with regard to the *Pageant* article:

1. On February 15, 1966, Mr. Robert P. Goldman, who has been a science writer since the late 1940's, telephoned John E. Fletcher, Director of Public Relations for Merck, stating that while in France his wife had been given a prescription for "Indocin" for the treatment of tennis elbow. Mrs. Goldman and her doctor felt that the treatment had been successful. When Mr. Goldman inquired of the doctor as to the source of the drug, he was surprised to learn that it had been originated by an American company, namely Merck. Mr. Goldman chided Mr. Fletcher about the fact that there had been no publicity about the drug. He said he planned to write an article about indomethacin and asked the company to provide him with some background material on it.

2. On February 17, 1966, Mr. M. T. Noar, a member of the Company's public relations staff, at the request of Mr. Fletcher, sent Mr. Goldman appropriate background information, including a "backgrounder" containing medically and scientifically authenticated information about the drug, its genesis, and the disease conditions for which it is approved; a package circular; relevant papers by scientists from Merck and other laboratories; and a bibliography.

3. Sometime within the next month, Mr. Goldman called Mr. Fletcher stating that he would like to have some human interest stories to increase readability

and asked whether we had any letters. Mr. Noar, at Mr. Fletcher's request, sent Mr. Goldman six letters from patients who had voluntarily written to the Company. Identification of the individuals and their physicians was blocked out in the copies sent to Mr. Goldman.

a. The first letter, dated August 1965 from San Diego, California, dealt with osteoarthritis of the hip joint (an approved claim).

b. The second letter, dated December 14, 1965, related in the patient's language to arthritis (there was no reason to suppose it other than rheumatoid—an approved claim).

c. The third letter, dated December 24, 1965, from Morganton, North Carolina, related to osteoarthritis of the hip (an approved claim).

d. The fourth letter, dated January 6, 1966, from Williamstown, Massachusetts, related in the patient's language to arthritis (there was no reason to suppose it other than rheumatoid—an approved claim).

e. The fifth letter, dated January 10, 1966, on the letterhead of the Enterprise City School District, related to rheumatoid arthritis (an approved claim).

f. The sixth letter, dated October 4, 1965, contained the following paragraph: "I am not too sure whether I have bursitis, tendonitis, or just plain arthritis, and also, my doctors don't know. However, I do know that I had to give up playing golf and I do know that after these few days that I have been taking your wonderful capsules, that I am going to play golf again, and soon."

4. On April 14, 1965, Mr. Goldman wrote Mr. Fletcher stating that he had done the piece on 'Indocin' and that it would probably appear in *Pageant* in July, with the magazine to be on the stands about June 16, 1966. According to his records, Mr. Fletcher also received a telephone call in mid-May from Mr. Goldman in which the latter said that he thought his story would appear in a summer issue of *Pageant*.

5. On the morning of June 15, 1966, while driving to work, a member of the Company's public relations staff heard a radio commercial about a story on 'Indocin' in *Pageant*. He stopped by a newsstand and purchased the magazine in which the article appeared. This was the first time anyone from the Company had seen it.

6. On June 21, 1966, a copy of the article was sent to Mr. Cron, then Director of Public Information and Education of the Food and Drug Administration, together with a copy of an internal memorandum explaining the article's origin.

7. Nothing was heard from the FDA about the article or our part in it until a speech was delivered by Mr. William W. Goodrich, Assistant General Counsel of the Food and Drug Administration, before the Pharmaceutical Advertising Club in New York on October 20, 1966, in which he criticized the *Pageant* article and gave his version of the Company's role in it.

This chronology of events demonstrates that:

1. The Company did not stimulate or cause publication of the article; it responded to a request for information from a recognized science writer.

2. Approved claims were named in all of the letters supplied to Mr. Goldman by Merck. No case histories on unapproved claims were submitted. No testimonials on unapproved claims were submitted. In one single letter the patient reported that he and his doctors did not know whether he had tendonitis, bursitis, or arthritis—arthritis being an approved claim.

3. Merck did not see the text of the article before it appeared in print; it first saw the article when the July issue was purchased from a newsstand on June 15, 1966.

4. Analysis of the article shows that, of the nine personal experiences recited by the authors, only four are attributable to the Company. Of these four, three involve approved claims only. The fourth mentions "bursitis." Although the article purports to quote extracts from this fourth letter, the quotations are not accurate and they changed the letter's meaning by omitting the reference to arthritis, an approved claim.

5. The Company voluntarily made the facts known to the FDA shortly after the published article came into Merck's hands.

6. The FDA did not discuss the *Pageant* article with Merck or seek to vertify Merck's role with respect to it prior to the time Mr. Goodrich made a public speech attacking the article and the Company on October 20, 1966.

Senator NELSON. If you have a supplementary comment, it will be printed in the record at the appropriate place.

Mr. GADSDEN. Thank you.

(The subsequent correspondence and statement of Senator Scott follows:)

U.S. SENATE,
COMMITTEE ON THE JUDICIARY,
*Washington, D.C., May 9, 1968.*

Hon. GAYLORD NELSON,
*U.S. Senate, Washington, D.C.*

DEAR GAYLORD: You will recall that at the Monopoly Subcommittee hearing of Friday, May 3rd you granted me permission to submit a statement at the end of that day's hearings.

A copy of that statement is enclosed.

I would like to have it printed in the permanent record of the hearing of May 3, as if delivered personally, immediately following Mr. Gadsden's final remarks and just prior to your statement recessing the hearing.

Cordially,

HUGH SCOTT, *U.S. Senator.*

STATEMENT OF HON. HUGH SCOTT, A U.S. SENATOR FROM THE STATE OF PENNSYLVANIA

Mr. Chairman, it is entirely clear that today's hearings, requested by Merck & Co., have provided a substantial step forward in dispelling the pall of confusion that has accumulated on these issues during the last two weeks. The value of taking testimony from the party most directly involved in a problem was demonstrated today.

The testimony indicates that there is essentially no problem regarding the safety and effectiveness of this drug as it has been determined by a broad group of highly qualified experts. It is also apparent from the testimony that the Food and Drug Administration had ample evidence regarding safety and efficacy to support its action of licensing this drug.

No insurmountable problem exists with the way in which the Company presented product information to the practicing physician except as a matter of semantics—of subtle differences of opinion on the interpretation of words, judgments, and impressions during a time when the Food and Drug Administration itself has been groping with the problem of how to regulate the flow of information to the medical profession. Such differences as exist can more appropriately be resolved by conference rather than by public charges or legal threats. It would appear that the interests of physicians and patients would thus be better served.

After reading the statements and discussions of the hearings on this product, I am more regretful that the circumstances have led to a condition where a good Company, a good performance, and a good drug have so lamentably been characterized by headlines suggesting danger and deceit. The events of the past two weeks only reinforce the need to reexamine the structure of the hearings themselves so that the parties concerned can appear at the outset and provide a factual base against which criticisms can be leveled or improvements proposed. Fair balance has become a watchword in the drug field today. The planning and timing of Congressional hearings might well be so devised as to bring more balance in the final impression left with the public at large.

(A subsequent statement and supplemental information submitted by Senator Nelson follows:)

STATEMENT BY SENATOR GAYLORD NELSON, CHAIRMAN OF THE MONOPOLY SUBCOMMITTEE

The Monopoly Subcommittee of the Senate Small Business Committee to date has held five days of public hearings on indomethacin, which is manufactured and sold under the trade name of Indocin by Merck & Company. Of our witnesses, 3 were independent physicians from the academic field, 3 from the Food and Drug Administration, 6 from (or on behalf) of Merck & Company, and one, a practicing physician who evaluated the drug for Merck.

The testimony highlighted five problems which are very important to the health and welfare of our people. These are: (1) drug evaluation: (2) what is meant or should be meant by "substantial evidence of safety and efficacy;" (3) the use of euphemistic, soft and unclear language in drug warnings; (4) overpromotion

of drugs, and (5) false and misleading advertising. I shall discuss these problems in order.

As I stated in my opening statement on April 23, the FDA does not engage in the clinical testing of drugs. It approves new drugs solely on the basis of information supplied by the pharmaceutical industry. This raises the question of whether it is sound practice for a firm which has a financial interest in marketing a drug, to direct, arrange, and finance its evaluation. It also raises the question of whether it is possible for an evaluator to maintain objectivity when he is dependent on funds from the company.

Is it a good idea for a physician who is testing a drug to send his data to the company for a statistical analysis while at the same time asking for additional financial support?

Is it a good idea to send a rough draft of proposed results to the firm while at the same time asking for additional money?

Wouldn't it be rather difficult to tell a firm that its product is unsatisfactory especially when a grant for your department at your medical school has been suggested? These are actual cases and I am placing into the record several letters which illustrate the points raised here.

(The letters follow:)

STATE UNIVERSITY OF IOWA,
*Iowa City, Iowa, April 18, 1963.*

NELSON H. REAVEY CANTWELL, M.D., Ph. D.,
*Merck Sharp & Dohme Research Laboratories,*
*West Point, Pa.*

DEAR DR. CANTWELL: I received your letter this morning and want to thank you for suggesting a grant for the rheumatology section at the University of Iowa.

Since you were here, we have started a number of new patients on indomethacin (the LX capsules). At least three of the patients complained of severe epigastric distress within 30 minutes after taking the capsule. Therefore, in the next few subjects we started them out on 1 capsule twice a day increasing 1 capsule daily until they reached the maximum 6 capsules and believe it or not we encountered no distress. This is the method we will follow for the time being, with our fingers crossed.

The fifteen year old patient with generalized psoriasis and psoriatic arthritis returned for a check-up and is under excellent control on a total dose of 150 mg. per day. She goes to school daily and is able to walk much better than she has at any time during the past year. Another woman (age 45) was admitted with generalized psoriasis and psoriatic arthritis. Before she was admitted to the hospital she was started on terrific doses of steroids which did not control either the painful hands or the skin eruption. The dermatologist started her on 42 mg. Triamcinelone and a few days later we began the indomethacin, 2 tablets at first then increasing daily until she reached the maximum of 300 mg. By the time that we reached the maximum dose she had little or no pain in her hands, was able to make a partial fist and began to feel much better. This morning we have her down to 16 mg. Triamcinelone. She is able to be up and about, has no fever, the skin lesion is receding rapidly and she can actually close her fingers and grasp objects. We started another psoriatic arthritic who has been on steroids for over five years to determine whether or not we can reduce the steroid dose.

Under separate cover I am sending you another batch of the monthly Bulletins in case you need some of these. I have had several calls from Iowa physicians asking me about the drug and two of them have sent patients to us so that we could evaluate them and give them indomethacin.

Again I want to thank you for your kindness and will see you in June.

Sincerely yours,

W. D. PAUL, M.D.

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PAUL J. BILKA, M.D.,
*Minneapolis, Minn., May 8, 1963.*

NELSON H. REAVEY CANTWELL, M.D.,
*Merck Sharp & Dohme Laboratories,*
*West Point, Pa.*

DEAR NELSON: I have decided to make a preliminary analysis of the patients on the Indocin tablets. Since I started the higher dosage schedule, beginning last summer, there are 63 patients who have been treated from up to eight months, and it certainly looks like we are getting a better result using the minimum dosage

of 100 mg a day, with the vast majority getting 150 mg per day as the minimal dosage.

15 patients had no help.
17 patients recorded slight help (that is less than 25%).
20 patients had significant help (25 to 50%).
11 patients report great improvement (over 50%).

I have not yet analyzed all of the laboratory data, so I cannot give an accurate statement as yet, however certain things are apparent and might be of interest at this time:

18 patients reported severe headache; all but six were able to continue the medication at lower dosage levels or by adding Benadryl; 8 patients reported severe gastrointestinal upset.

One patient (Mr. Jensen) had a history of a DU, but the pretest X-ray was negative. During the third month of 200 mg per day, he developed an active DU. He was continued on the medication in the same dosage and X-rays two and four months later show the ulcer healed.

Another patient (Mrs. Rose) with a known active DU was started on Indocin 150 mg per day and was continued on this for two months because of the marked relief she obtained. At this time however, her GI symptoms increased, the X-ray showed the still active DU and the Indocin was stopped.

A third patient (Mr. Rardin) with a known history of a DU and with signs of activity was given a two month trial of Indocin 75 mg per day. His ulcer symptoms also increased on the medication and the X-ray showed an active DU. All of the other patients had negative X-rays.

I will start going over the charts for the detailed analysis of the laboratory data and will let you know of the results. The work with MK715 is too early to make any comments on except that it seems at least as potent as 615 in the two to one dosage ratio.

I am enclosing the laboratory charges for March and April. Again would you have this made out to St. Barnabas Hospital, Arthritis Research.

I shall soon be enlarging the facilities for out-patient care at the Kenny Institute and we will be in a position to utilize extra funds for our project there. If Merck can make an additional contribution of $3,000 toward this work, it will be useful and appreciated.

Sincerely,

PAUL J. BILKA, M.D.

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THE COLUMBUS MEDICAL CENTER,
*Columbus, Ohio, May 11, 1964.*

NELSON H. REAVEY CANTWELL, M.D., Ph. D.,
*Merck Sharp & Dohme Research Laboratories,*
*Division of Merck & Co., Inc.,*
*West Point, Pa.*

DEAR NELSON: The enclosed letter is from a very fine patient, a 45 year woman who is a Ph. D. and teaches at Dennison University. She is quite intelligent, immensely cooperative and completely un-neurotic. I thought you would be interested in her very vivid and articulate description of the adverse symptoms which she encountered with Indomethacin.

I would emphasize that these do not alarm me nor indicate any evidence of organic damage but I am afraid they will offer some practical problems in marketing this drug.

Needless to say, I am very grateful for all of your kind efforts in regard to my trip to Japan.

I'll look forward to seeing you on my return. I think we must get together and plan on publishing some of the data which we have collected. Best regards always.

Sincerely,

NORMAN O. ROTHERMICH, M.D.

P.S. I sent a copy of Dr. Shepard's letter to Elmer.

CLEVELAND METROPOLITAN GENERAL HOSPITAL,
*Cleveland, Ohio, June 27, 1963.*

NELSON H. REAVEY CANTWELL, M.D.,
*Merck Sharp & Dohme Research Laboratories,*
*West Point, Pa.*

DEAR DR. CANTWELL: This is in answer to our telephone conversation. As I mentioned to you in my letter of 26 January, we have treated 51 patients with acute rheumatic fever. I have discussed the whole situation with Dr. Mortimer and our plans for analysis are as follows. Dr. Mortimer is presently analyzing the data and in September Dr. Correa, who participated in the study in Chile, will come to the United States to spend six weeks here going over the data and preparing it for publication. It is possible that we will have a rough draft before that time and if we do we will forward it on to you. In addition, Dr. Correa is going to bring with him the serum specimens that we collect once a month from these individuals. In October I am going to Chile to collect further specimens from the study group. The final analysis of the effect of the drug on valvular heart disease will be completed in January. One of the problems that we will face will be adding the final evaluation of the effect of the drug on valvular heart disease to the analysis of the effect of the drug on the acute phase symptoms. It is my feeling that the two should go together since there is no indication that the drug would or should be effective on valvular heart disease and it is not likely that a second publication will be justified. We are in the process of training two technicians to help us complete the laboratory work.

In going over our financial situation, we will require the money remaining in the original proposed budget to complete this work in an adequate fashion.

With best personal regards,

Sincerely yours,

CHARLES H. RAMMELKAMP, M.D.,
*Professor of Medicine.*

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DUKE UNIVERSITY MEDICAL CENTER,
DEPARTMENT OF MEDICINE,
*Durham, N.C., July 9, 1963.*

Dr. NELSON H. REAVEY CANTWELL,
*Merck Sharp & Dohme Research Laboratories,*
*West Point, Pa.*

DEAR DR. CANTWELL: I enclose your completed questionnaire with an attached sheet listing a few further observations. We do not plan on making any further formal report of our findings this year. The protocol sheets are available to you at any time, of course. I would emphasize as I did prior to accepting MK615 for use that the data here are in no way to be interpreted as representing a controlled study. Our patients come from distant towns usually and are often under the simultaneous care of a local physician whose prescriptions are seldom known to us. We simply report what we have noted in our particular and transitory clinic setting.

We need a further supply of both 25 mg and 50 mg capsules of MK615, if these are available. I share with you an impression that these are well tolerated.

Sincerely yours,

GRACE P. KERBY, M.D.,
*Rheumatism Clinic.*

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PAUL J. BILKA, M.D.,
*Minneapolis, Minn., July 9, 1962.*

NELSON H. REAVEY CANTWELL, M.D.,
*Merck Sharp & Dohme Research Laboratories,*
*West Point, Pa.*

DEAR DR. CANTWELL: I have made a preliminary analysis of 50 patients with rheumatoid arthritis who have received MK–615 for at least one week. As I am sure it will take some time before I can complete the clinical evaluation forms on each patient, I thought you might be interested in my impression of the drug at this time.

Of the 50 patients 22 recorded no help or else obtained the same degree of help as from the placebo.

Nineteen patients recorded slight help in the range of 10 to 25 percent improvement.

Eight patients reported significant help which I quantitated, at 25 to 50 percent relief of symptoms.

One patient reported great help, that is, more than 50 percent improvement. Eleven patients who were on medication for at least 3 weeks had the laboratory data which you suggested:

There was no evidence of new ulceration or aggravation of previous X-ray findings of the upper G.I. tract.

Urinary tract disturbance was evident in 4 patients: One had a transient 4 plus albuminuria and 3 showed a few casts. One of these patients who is severely hypertensive had a BUN of 36 which fell to 30 two weeks after stopping the MK 615; no prior BUN was recorded.

Some evidence of liver function disturbance appeared in 7 of these 11 patients: The BSP was elevated in 4; the Cephalin floc was 3 or 4 plus in 5 patients; the alktase was elevated in 4. Unfortunately I did not do base line values in most of these patients, therefore it is impossible to say if these were the result of this medication in as much as most of these patients were on other drugs such as small doses of steroids, gold, chloroquin or were recently on Butazolidin. However, one patient might be worth indicating in detail and I have enclosed this work sheet that was filled out by Dr. Schultz at the University. One other patient had a normal ceph floc before therapy.

The symptomatic disturbances were relatively minor: One patient reported nausea after a single 10 mg dose, repeated on 2 occasions; one patient said her stools were somewhat loose while on the medication for one month; one patient reported mild itching and orythema with 2 trials of the drug (75 mg a day for 3 days and again on 30 mg for one week); three patients were slightly stimulated mentally and even felt a little jittery on the medication.

What this all adds up to is difficult to say. Certainly many of the patients were grateful for the added relief the medication seemed to offer even if it was not in the great degree such as with steroids. The apparent evidence of hepatic change might be a cause of concern. I would appreciate your ideas concerning extending this study or changing the procedure. I am just about out of the medication and will conclude the study if you wish.

I am enclosing some statements from the laboratories where the test procedures were done on these patients. There may still be a few coming in yet so I will send them later.

Sincerely,

PAUL J. BILKA, M.D.

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UNIVERSITY OF UTAH, COLLEGE OF MEDICINE,
DEPARTMENT OF INTERNAL MEDICINE,
*Salt Lake City, October 15, 1963.*

NELSON H. REAVEY CANTWELL, M.D., Ph. D.,
*Merck Sharp & Dohme Research Laboratories,*
*West Point, Pa.*

DEAR NELSON: It was pleasant to meet with you again and learn first hand of the current status of MK615. Your offer of assistance in the statistical analysis of our data is greatly appreciated. The data summary sheets are completed and will be forwarded to you under separate cover, along with detailed information as to the method of acquiring and computing the scores on each patient. The relative weight of each parameter will be described. For your information and use, we are submitting a summary of our experiences with indomethacin in a double blind crossover and long-term evaluation study. All of the patients included in the double blind study fulfilled the following criteria:

1. A diagnosis of either definite or classical rheumatoid arthritis, using the A.R.A. classification.
2. Active disease as evidenced by swelling and tenderness and/or the necessity of corticosteroids to control symptoms.

Most of the patients have had moderate to severe disease with continuous activity for greater than five years. The patients were paired as closely as possible in regard to age, sex, duration of disease, severity of disease and stage and class of disease. One of each pair, chosen at random, was started on indomethacin, with the other member of the pair being started on placebo. This was done in such a way that neither the patient nor anyone involved in the evaluation of the patient's response knew which medication the patient was receiving at any time. All patients were started on a dose of 200 mg. a day in four divided doses. At the end of one month, the parameters for evaluation were measured

again and the other form of the drug given. After one month on placebo and one month on indomethacin, all patients were started on known drug for the long-term evaluation. All of the examinations were repeated at monthly intervals, or as close thereto as possible. With the long-term evaluation, dosage of indomethacin was varied according to the patient's response and/or side effects.

The following parameters of disease activity were evaluated at each visit. The patient's evaluation of the amount of pain he had had in the previous month, graded on a scale of no pain, slight pain, moderate or severe pain. The number of aspirin taken; the duration of morning stiffness; the amount of corticosteroids or other medication. A cuff compression test of hand grip and a ring size of each finger were taken each visit. Swelling and tenderness of the shoulders, elbows, wrists, fingers, toes, ankles, knees and hips were evaluated according to the following scales: swelling was graded 1 for slight synovial thickening; 2 for swelling that changed the contour of the joint; 3 was swelling that obliterated the normal joint contour; 4 was the presence of a demonstrable effusion. Tenderness was graded 1 for the patient says it hurts when pressure is applied; 2, the patient says it hurts and winces; 3, the patient tries to withdraw from the stimulus. It was possible for the same observer to evaluate the patients greater than 90% of the time. Sub-totals of the swelling, the tenderness, the grip strength, the ring size, the duration of morning stiffness, the amount of pain, the number of aspirin and the milligrams of prednisone or equivalent were obtained for each visit. The difference between the individual parameters and its base line was obtained so that a negative score indicated worsening of the arthritis, whereas a positive score indicated improvement. In the marameters of swelling, tenderness and number of aspirin (300 mg. tablets) a change of 1 was reflected as a change of 1 in the score. A change in the amount of prednisone was scored as the number of milligrams times two. The duration of morning stiffness, a change of ½ hour was scored as a change of 1. The grip strength was scored as the change in total score of both hands divided by 20, or in other words, a change of 20 mm. of mercury was scored as a change of 1. The subtotals of the changes in each parameter were then totalled to determine a numerical figure for improvement or worsening of the arthritis. By inspection of the changes in the total score of arthritis, we have evaluated the response to indomethacin as good, fair and none. A good response was considered a response of clearly significant improvement, while on indomethacin, with little or no response while on placebo. A grade of fair was given when there was moderate but definite improvement while on indomethacin, again with little or no response to placebo. The grade none represents either worsening of the arthritis while on indomethacin, or no difference between response to placebo and indomethacin.

We had 31 patients who started the double blind study. Of these, 4 were unable to complete the double blind part of the study because of uncontrollable side effects. The side effects requiring cessation of the study were nausea, vomiting and headache in 2 patients; nausea and headache in 1 patient; and dizziness with nausea and headache in 1 patient. Thus, in the short-term double blind experiment, 68% of the patients had a favorable response; 19% had no demonstrable response; and only 13% had side effects requiring stopping the medication.

The long-term evaluation study has now been under way for ten months, with observations on patients ranging from seven months to ten months in length.

Of the 27 patients finishing the double blind part of the study, 2 were withdrawn before long-term evaluation could be done. One of these was for side effects of the drug, specifically nausea and vomiting, and one patient with a history of bronchial asthma expired with an episode of asthma refractory to all treatment. Of the 25 patients left in the study, 15 had a good response; 9 had a fair response; and 1 showed no response. Of this group, 8 patients have had to stop taking 'Indocin' because of side effects that exceeded the benefit they were receiving. These side effects were dizziness in 5 patients; nausea and dizziness in 1 patient; severe refractory ulcer-type symptoms in 1 patient; giddiness and mental fuzziness in another.

In addition to the double blind study, we have used 'Indocin' in 12 additional patients. Two of these patients had progressive systemic sclerosis; 1 has the fibrositis syndrome; and 1 has an unusual form of hereditary degenerative joint disease. The remaining 8 patients have a diagnosis of either definite or classical rheumatoid arthritis, and were started on the known drug because of severity of the disease process. Four of these were hospitalized because of their arthritis at

the time 'Indocin' was started. Of this group, we have had a good response in 9 patients; a fair response in 2; and 1 patient had side effects that required cessation of the drug before any effect could be noted. Of this group, 5 patients have required stopping 'Indocin' because of side effects, even though the response had been fair or good.

In our work with 'Indocin', we have found that headache, while not an infrequent side effect, has not been particularly difficult to control, responding either to antihistamines or to reduction in dosage of 'Indocin'. The dizziness, nausea and vomiting, however, have been refractory to most efforts at control with the exception of stopping 'Indocin'. Using antacids, anti-emetics, etc. has had no effect in stopping this complication. We have found in a few patients that stopping the drug for a period of time, and then re-starting it, has been successful. We have made frequent checks of blood chemistry and hematological studies, and have found no disturbance with hematopoesis or hepatic or renal toxicity. We have had several patients on 'Indocin' develop peptic ulcer disease, and have had two episodes of massive upper G.I. bleeding. However, in the 2 patients with upper G.I. bleeding, 'Indocin' has been continued after their acute episode and these patients are now 9 months and 4 months post-hemorrhage with no symptoms, or only minimal symptoms remaining. All of the patients who have developed ulcers have also been on corticosteroids.

The possibility of obtaining fewer side effects with as good or better results from the use of the capsule form of 'Indocin' has been of interest to us. As we discussed with you, we would be anxious to try the capsules also in a double blind crossover fashion, similar to our study with the tablet form. To run such a study with the number of patients we would have available would require 90 bottles of 25 mg. 'Indocin' capsules, and 90 bottles of placebo capsules. Anticipating the number of patients who will respond favorably to this, and in whom we would like to continue the capsules past the double blind study, we would need approximately 400 bottles of 25 mg. capsules to carry these patients for a total of six months. We feel that there would be certain other studies that should be pursued in the use of 'Indocin'. These would include correlation of blood level with therapeutic effect and with side effects or toxicity. Because of the peculiar mental reactions we have had, we would feel that an attmept to correlate electroencephalographic findings with blood level and with effect should be done. We would like to receive some of the bulk 'Indocin' so that its effect in experimental models of arthritis could be pursued shortly. Ultimately, the determination of Indocin's' place in the therapeutic armamentarium of the rheumatologist should be done. Several of these things will require more detailed planning before they can be accomplished. However, the capsule double blind study and use of the bulk drug in experimental models of arthritis could be accomplished as soon as we can receive the necessary drug.

From our experience with your drug 'Indocin', we feel that you have developed an agent that has a definite place in the treatment of rheumatoid arthritis, even though we have had considerable disappointment in the amount of side effects. We would feel that with further work, maybe the difficulties might reasonably be expected to be overcome. Although it is still too early to tell, we have noticed in 4 or 5 patients, a tendency for the development of remission of their disease activity. Whether they are truly going into remission remains to be seen, but the evidence suggesting that they are is there.

We can discuss the necessary financial support for a double blind study using capsules when the decision is reached to initiate the study.

Very truly yours,

JOHN R. WARD, M.D.

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STANFORD UNIVERSITY SCHOOL OF MEDICINE,
STANFORD MEDICAL CENTER,
DEPARTMENT OF MEDICINE,
*Palo Alto, Calif., August 22, 1963.*

NELSEN H. REAVEY CANTWELL, M.D.,
*Merck Sharp & Dohme Research Laboratories, West Point, Pa.*

DEAR DR. CANTWELL: I am sorry I haven't answered your previous request for information about Indomethacin. For various reasons I have not put our results together yet but will do so in the not too distant future. This was our first effort at drug evaluation, and I am afraid we have been somewhat inefficient in maintaining precise up-to-date evaluations of the patients. Though all the necessary information is in their charts, we have not extracted it all as yet.

Our impression of the drug remains good. It is clearly not the answer to rheumatoid arthritis and has not been helpful in those few instances of connective tissue disease where we have tried it; but in a significant number of patients it is of decisive benefit when other medications have failed.

I am writing to you about a financial question. We have obtained a modest amount of laboratory information on our patients which the patients were guaranteed would not be charged to them. The day of reckoning is approaching with the hospital when they insist that I settle accounts. I am therefore writing to ask what mechanism you would propose that we employ to obtain the money from you to meet these expenses?

Many thanks for your consideration.

Sincerely,

HALSTED R. HOLMAN, M.D.

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SCRIPPS CLINIC AND RESEARCH FOUNDATION,
*La Jolla, Calif., April 29, 1963.*

ELMER ALPERT, M.D.,
*Merck Sharp & Dohme Research Laboratories, West Point, Pa.*

DEAR DR. ALPERT: I thought I would drop you a little progress note as to what we are doing with the MK–615 that you sent to us, and at the same time, ask if you could send me some more.

With the full realization that our clinic material is too limited in numbers for a large double blind study, we have been merely using MK–615 in the management of some of our patients and recording our impressions of it. Today I can merely tell you that we have seen no untoward effects from it although our top dose has been only 250 mgs as per your suggestion. We have also found that patients tolerate MK–615 together with ASA dose of 4 grams a day without signs of salicylate intoxication. I can also say that the persons on MK–615 seem to be doing quite well although it does not seem to be holding one 40 year old lady.

Finally, regarding our equilibrium dialysis study with MK–615 we have found that MK–615 does, indeed, bind to the same site on albumin that is bound by the $I^{131}$ labeled Urokoh. As you recall, sodium salicylate also binds to this site but we think that MK–615 has a stronger bond than does sodium salicylate.

Meantime, with your generosity I would greatly appreciate some more 50 mg MK–615 tablets so that we may continue our few patients on it.

Very sincerely yours,

RICHARD S. FARR, M.D.,
*Head, Division of Allergy and Immunology.*

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NEW BEDFORD, MASS.,
*February 18, 1964.*

NELSON H. R. CANTWELL, Ph. D., M.D.
*Merck Sharp & Dohme Research Laboratories,*
*West Point, Pa.*

DEAR NELSON: I am sending to you the initial MK–615 Clinical Evaluations as I originally submitted them. Under comments, where previously no comments had been made on any of the forms, I have brought my data up to date to the time when each patient discontinued the medication.

As you may see from these comments, I failed to note any beneficial effect on either a decrease in steroid dosage or any relief which may have been obtained from these patients who all were suffering from some allergic disorder.

My initial impression after evaluating the original data therefor held it does not seem to be of any benefit in allergic diseases. I might note that I have had four allergic patients with bursitis in whom I took the liberty of trying this drug and had beneficial result in all four. I was patiently waiting the recurrence of my own gout to see if it would be of benefit but fortunately or unfortunately depending upon your point of view, I myself have not had the chance to evaluate it personally.

Because of the poor data I did obtain, I saw no reason to go ahead and use the capsule form of M–615 and have not done so. If you feel there is a dramatic difference in the therapeutic benefit, which I would doubt, I could try a group of selected patients on this if you so desire.

Edward Joyce was in to see me and informed me that you are considering a topical preparation of this which may help in dermatological disorders. I indicated

to him that I would be willing to carry out a clinical trial if you felt this was promising.

As far as compensation for the work done, I feel a grant of $1500.00 would be fair if you so see fit.

I am sorry you have been too busy to come in to this area. I will be at the American College of Allergy meeting in Miami the first of March. If you have that in your plans I will be happy to see you then. Best regards from Elaine. Hope all is well with you.

Very truly yours,

PAUL CHERVINSKY, M.D.

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MINNEAPOLIS, MINN.,
*June 24, 1963.*

NELSON R. CANTWELL, M.D.,
*Merck Sharp & Dohme Laboratories,*
*West Point, Pa.*

DEAR NELSON: I have gone over the data on the 63 patients I reported to you earlier this month and have extracted the information you recently asked about.

1. 40 patients have been on 150 mg or less of Indocin per day. 20 of these reported no or slight help and 20 reported significant (25% to 50%) or great (more than 50%) help.

2. 15 patients had 200 mg per day and 7 reported no or slight help and 8 reported significant to great help.

3. 8 patients had more than 200 mg per day. 5 reported no or slight help and 3 reported significant or great help.

4. All patients had rheumatoid arthritis.

5. There was a definite increase in GI symptoms and especially headache with increase in dosage. There was very little headache on 100 mg or less per day. Gastric irritation seems to be an increasing problem.

6. I have had little experience with non-rheumatoids so far, but 1 patient with Reiter's disease had an excellent response; 1 patient with chronic gout had a good response and 1 patient with Scleroderma had slight help.

7. Regarding headache and migraine; the very day you called, the first patient I asked the question of stated that she had been a frequent sufferer of migraine before developing her arthritis. She had been free of headache until it recurred with Indocin. However, she stated this headache was different from what she remembered her migraine was like. I haven't had the opportunity to put the question to all patients, but several have denied previous migraine, yet 3 have admitted to prior migraine.

8. 39 of the 63 patients have been on Indocin for 2 months or more, some over 8 months. It is my plan to carry as many on long-term therapy as tolerate and benefit from the drug. New patients are being constantly added as I presume is your desire.

Sincerely,

PAUL J. BILKA, M.D.

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PAUL J. BILKA, M.D.,
*Minneapolis, Minn., August 29, 1962.*

NELSON H. REAVEY CANTWELL, M.D.
*Merck Sharp & Dohme Research Laboratories,*
*West Point, Pa.*

DEAR DR. CANTWELL: During the last month I have been carrying on a new trial with MK–615 using the higher dosage range which you suggested. A preliminary analysis of 22 patients indicates rather significant improvement in the results using this higher dosage. All patients have rheumatoid arthritis, and the majority have been on the lower dosage trial. The results after 2 to 4 weeks therapy are as follows:

Four patients report no significant improvement.
Five patients report 10 to 25 percent subjective improvement.
Twelve patients report 25 to 50 percent improvement.
One patient reports marked, or over 50 percent improvement.

There have been 2 complaints of nausea caused by the higher dosage and one patient who had a previous active duodenal ulcer, and also is on 0.6mg beta dexamethasone per day developed an active DU on 100mg MK–615 per day. One other patient complained of headaches. I have not, as yet, analysed the laboratory data, but will do this shortly when I fill out the regular investigative forms. I thought, however, that you would be interested in these preliminary findings.

Sincerely,

PAUL J. BILKA, M.D.

DUKE UNIVERSITY MEDICAL CENTER,
DEPARTMENT OF MEDICINE,
*Durham, N.C., December 10, 1963.*

Dr. NELSON H. REAVEY CANTWELL,
*Merck Sharp & Dohme,*
*West Point, Pa.*

DEAR DR. CANTWELL: Enclosed are the original data sheets for patients who received Indocin tablets. You will note that some are continuing on capsules. Another 24 patients started on capsules since August 1963, and these data sheets are retained here at present. The presently enclosed sheets represent for the most part those patients covered in the June 1963 summary which I sent to you.

Sincerely yours,

GRACE P. KERBY, M.D.,
*Rheumatism Clinic.*

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DUKE UNIVERSITY MEDICAL CENTER,
DEPARTMENT OF MEDICINE,
*Durham, N.C., December 8, 1963.*

Dr. NELSON H. REAVEY CANTWELL,
*Merck Sharp & Dohme Research Laboratories,*
*West Point, Pa.*

DEAR DR. CANTWELL: I am sorry to have missed seeing you at the recent Boston meeting. However I do want to mention two patients in regard to Indocin, one for your own information and one to raise a question re contraindication to use of Indocin.

A 19 year old CF with unequivocal SLE manifesting most strikingly as acute nephritis with good renal function was admitted in October while I was out of town. Because she was not sufficiently critically ill to require immediate ACTH or steroids, my colleagues started her on Indocin, 50 mg per day increasing over about one week to 150 mg per day, at which time I first saw her on return to town. An originally normal BUN rose slightly in the first few days and then to 47 mg% by the time I first saw her. On the chance that this was the phenomenon you have noted with Indocin in the presence of pre-existing renal disease, Indocin was discontinued. The BUN returned to normal over the next few days.

A young WM with chronic rheumatoid arthritis, on phenylbutazone, was admitted recently to the V.A. hospital here with GI symptoms. Two gastric ulcers near the cardia were demonstrated. He was to be discharged this past weekend with ulcers healing well and promptly, to come to the Rheumatism Clinic at Duke for the first time either this Thursday Nov. 12 or Nov. 19, referred specifically for Indocin. However, recalling the report at the June meeting of patients with previous peptic ulcer/developing multiple gastric ulcers, I question whether Indocin may not be contraindicated in this patient. If it is at all possible to have your comments on any further information concerning the GI tract during Indocin therapy prior to this patient's scheduled first visit to the clinic, I shall most appreciate having them. He has to travel 150 miles from his home, doing his own driving despite severe rheumatoid arthritis. Had I realized that I would be unable to get your comments in Boston, I would not have suggested such an early appointment for the patient.

Following our recent telephone conversation, I sought and obtained permission from NIH to use up to $3600 from my research grant for the proposed work with Dr. Luscher. I am therefore proceeding with my plans as related earlier. I also contacted Dr. Stead, to ask if funds of the sort you proposed were permitted by the department. He was entirely agreeable and felt that such uncommitted funds offered greater latitude in opportunity to work and visit in other laboratories, as well as provide enjoyable contact with the commercial firm. From my own point of view the added advantage of being able to conserve my NIH funds in greater part for the operations in my own laboratory which would continue on a limited scale in my absence. Therefore I am free to accept any research funds from Merck, if you still feel as before that the type of informal report sent you last June on our experiences with Indocin constitutes a valid basis for such funds. This type of informal report on our experience can continue to be furnished, although as I recounted earlier, formal reports from here will never be proper due to the long distances our patients travel, making closer supervision impossible. In answer to your inquiry as to institutional and departmental requirements in addressing funds, the funds from Sandoz three years ago were addressed as follows, and this would be the preferred method now:

Name of Payee: Anna H. Hanes Research Fund, Department of Medicine, payable to Dr. Grace P. Kerby.
Street Address: Duke University School of Medicine.
City: Durham, N.C., 27706.
Sincerely yours,

GRACE P. KERBY, M.D.

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UNIVERSITY OF OREGON MEDICAL SCHOOL,
DEPARTMENT OF PHARMACOLOGY,
*Portland, Oreg., February 25, 1964.*

Dr. NELSON H. REAVEY CANTWELL,
*Merck Sharp & Dohme Research Laboratories,*
*West Point, Pa.*

DEAR DR. CANTWELL: Herewith are the special case reports for 11 cases who have had trial of the "Indocin" capsules. The number of the cases are from 3518 to 3528. For the record, I am retaining the additional case record forms that you sent and numbered from 3529 to 3567. These unused forms will be used for any additional cases that are placed on "Indocin" capsules. However, if you wish these blank case forms returned, I can do that.

As you know, I sent you a copy of the individual case records for all the patients (21 cases) who have received both the tablets and the capsules of "Indocin". I am currently writing this up as a short report for possible publication as a research note in CURRENT THERAPEUTIC RESEARCH. When I complete this short note, I shall forward you a copy for your inspection.

I hope that your case reports for the capsules are coming in satisfactorily and you can get off the material to the FDA. Good Luck!

With best wishes,

NORMAN A. DAVID, M.D.
*Professor of Pharmacology.*

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STATEMENT OF SENATOR NELSON—Resumed

One of our witnesses, Dr. Donald Mainland, a medical doctor and one of the most famous biostatisticians in this country, has recommended that the evaluation of drugs be taken entirely out of the hands of the pharmaceutical industry, an idea which merits study. Even if the drug firms continue to do animal, and to some extent clinical studies, approval for marketing by the FDA should be based, at the very least, on studies under its direction. Perhaps it may be a good idea to establish a national drug institute, the purpose of which would be to evaluate drugs, in-house and/or by contract. In other words, it seems reasonable that there should be an independent, careful and scientific evaluation of a drug to secure FDA's approval. We are studying this problem and may be prepared to propose legislation in this field sometime soon.

The second problem is FDA's requirements for evidence of safety and efficacy. The statute requires "substantial evidence" of safety and efficacy which means "evidence consisting of adequate and well-controlled investigations." On December 7, 1964, the medical officer in charge of the New Drug Application for Indocin stated in her summary that "There is a paucity of controlled studies in this massive NDA." On March 15, 1967, Dr. David Hurwitz, M.D. of the FDA's Bureau of Medicine in referring to claims of efficacy in osteoarthritis of the joints, other than the hips and muscular skeletal disorders, found that "136 out of 137 studies are deficient in technique and incapable of standing up to critical examination; it is unfortunate that the company and its investigators do not use the more sophisticated investigative techniques that have been evolved to evaluate new drugs."

Dr. Hurwitz also stated that:

"In view of the wide-spread acceptance of Indocin and its seeming benefit in Rheumatoid Arthritis, it is an unwarranted conclusion to say at this time that the drug is of no usefulness in this disease. However, since these excellent studies by Cooperating Clinics Committee and by Donnelly et al. in the British Medical Journal cast considerable doubt on the efficacy of Indocin, further studies of equal or better quality and of longer duration are in order to determine the place of this drug in the physician's Armamentarium. This re-evaluation is particularly necessary given the toxicity of Indocin which renders the drug totally unfit for use if a significant therapeutic benefit cannot be established."

The question then arises whether a "significant" therapeutic benefit has been

established for rheumatoid arthritis, which presents the largest potential market for indomethacin, Indocin).

Perhaps an answer can be found in Dr. Hurwitz's memorandum of August 25, 1967, in which he stated that: "At the present time, then, it would seem wise to consider Indocin as probably effective in rheumatoid arthritis pending further studies in this area." The word "probably" should be emphasized.

How can we reconcile the FDA medical officers' opinion that there is a "paucity of controlled studies" and that the drug is "probably effective" with the statutory requirement of substantial evidence of efficacy?

How can we reconcile the requirement of "substantial evidence" of safety with the opinion of an FDA medical officer that "* * * Indocin has shown a similar propensity to cause a wide variety of serious and sometimes fatal reactions, and its clinical usefulness has been limited by its toxicity."

The American Medical Association's New Drugs, 1967 edition, states that:

"Central nervous system effects (headaches, usually severe in the morning; vertigo; light headedness; mental confusion) occur during the early weeks of therapy in about 20% to 30% of patients taking indomethacin. Drowsiness, convulsions, depression and psychic disturbances such as depersonalization have also been reported. * * * Indomethacin should be regarded as being potentially ulcerogenic. It may produce single (or) multiple ulceration of the esophagus, stomach duodenum or small intestine. Cases of perforation and hemorrhage, a few of them fatal, have been reported."

I am inserting at this point a summary of side effects reported by Merck's investigators.

(The summary follows:)

SIDE EFFECTS—INDOCIN

"The patient complains of a distressing lightheadness, a feeling of being in outer space, a feeling of the head being foggy and a feeling of difficulty in concentration or in cerebration. There may or may not be an associated violent headache and in a few cases, the headache was so violent that it was predominant or alone. In a few instances, these symptoms have been so severe as to be totally incapaciting and even prostrating" (Oct. 9, 1962).

Dr. NORMAN O. ROTHERMICH,
*Columbus Medical Center, Research Foundation, Inc., Columbus, Ohio.*

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"The greatest deterrent to increasing dosage to an effective level is the appearance of cerebral toxicity. This manifests itself clinically in excruciatingly severe headaches, dizziness, lightheadedness, disturbances of sensorium, a feeling that the head is floating away or even separating from the body and feelings of detachment from reality" (June 12, 1963).

Dr. NORMAN O. ROTHERMICH.

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"As higher dosage levels are approached, it is to be expected that the incidents of cerebral toxicity goes up proportionately and this, in my opinion, represents a not insignificant disadvantage to the drug for it reduces the number of arthritics who can be benefited by the drug. . . . on the other hand some patients have developed disabling cerebral toxicity . . . on comparatively low dosages" (Oct. 12, 1963).

Dr. NORMAN O. ROTHERMICH.

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"I am sorry to report but I am sure you should know, that we saw rather severe dermatitis in one patient after taking four tablets (100 mg) of MK-615 over a 24 hour period. We sincerely hope we will have better results to report in the future" (Apr. 24, 1962).

Dr. H. M. MARGOLIS,
*Pittsburgh, Pa.*

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"We had 31 patients who started the (short term) double-blind study. . . . 13% had side effects requiring stopping medication." "In our work with Indocin we have found that headache while not an infrequent side effect, has not been particularly difficult to control, responding either to antihistamines or to reduc-

tion in dosage of Indocin." "We have had several patients on Indocin develop peptic ulcer disease, and have had two episodes of massive upper GI bleeding." "We feel that there would be certain other studies that should be pursued in the use of Indocin. These would include correlation of blood level with therapeutic effect and with side effects or toxicity. Because of the peculiar mental reactions we have had, we would feel that an attempt to correlate electro-encephalographic findings with blood level and with effect should be done." "We have had considerable disappointment in the amount of side effects" (Oct. 15, 1963).

Dr. JOHN R. WARD,
*College of Medicine, University of Utah, Salt Lake City, Utah.*

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"I would be very anxious to receive further information from you concerning other clinical experiences with Indocin. Our experience to date with the material you supplied us has been limited because of the significant incidence of headaches and gastrointestinal complaints. This has made me reluctant to use it in a number of instances where I might wish to have done so. I would therefore greatly appreciate any further data you have relating to this drug that might influence our use of it" (Jan. 9, 1968).

Dr. KURT J. ISSELBACKER,
*Harvard Medical School,*
*Massachusetts General Hospital, Boston, Mass.*

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"Toxic Manifestations: Only 6 of the 27 failed to show some evidence of toxicity, but in 2 others showing GI toxicity and 1 with rash the medication was continued. Only 1 of the 6 males showing 'excellent' therapeutic response showed clinical toxicity—GI pain" (Jan. 2, 1964).

Dr. WM. C. KUZELL,
*San Francisco, Calif.*

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"I believe you have an excellent skeletal analgesic but I am worried about the headache, nausea and emesis and mental confusion" (Mar. 20, 1963).

Dr. HAROLD M. ROBINS,
*Delaware Avenue Medical Center, Buffalo, N.Y.*

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"In brief, the acute data indicate that indomethacin is approximately as effective as aspirin in the control of fever, joints and other acute manifestations" (Sept. 4, 1963).

Dr. EDWARD A. MORTIMER, Jr.,
*Cleveland Metropolitan General Hospital, Cleveland, Ohio.*

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"Dr. Gum continues to find that Indocin is an interesting and effective agent in rheumatoid arthritis. The incidence of headaches, however, is between 85% and 100%. This is causing him real concern. He commented that this would also seriously impair any presentation to FDA. * * * Dr. Burch . . . refuses to do further clinical investigations and is not too happy that any of his staff continues to do them" (May 6, 1963).

Memo R. R. Robert to Dr. N. H. R. Cantwell on "Progress of Study of Indocin" Merck Co.

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"The side effects occur in about ten percent of the patients and in nearly one-half of this group, the drug had to be discontinued. The side effects are nausea, headaches and lightheadedness" (Oct. 3, 1963).

Dr. W. D. PAUL,
*University Hospitals, University of Iowa, Iowa City, Iowa.*

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"We also discussed with Dick Rebert we definitely feel that you should set up a double blind on the drug. . . ." "It is with some disappointment that we are reaching the conclusion that the effect of the drug is largely subjective and

would most clearly be assigned to the category of analgesics rather than antiphlogistic agents according to our present experience" (Oct. 1, 1963).

DR. R. W. PAYNE,
*McBride Clinic, Inc., Oklahoma City, Okla.*

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"In the fall of 1962, I submitted data on the tablet form of Indocin on the government forms. I have no additional data. My results were generally unsatisfactory and so I discontinued use of the drug" (Jan. 7, 1964).

Dr. JOSEPH E. GIANSIRACUSA,
*San Jose, Calif.*

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"I don't believe I will continue to use Indomethacin until some other reports are available from people in this country . . . the only possible use that I think we might make of it sometime would be in the treatment of acute gout. . . . I think a study of Indomethacin compared with Placebo might be something the house officers might like to undertake sometime in the future. . . . We have no plans at this time" (Jan. 9, 1964).

Dr. J. W. HOLLINGSWORTH,
*School of Medicine, Yale University, New Haven, Conn.*

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"I have learned that two other patients on Indocin have developed peptic ulcers, one with perforation necessitating operation. This now, in our series of approximately 100 patients, makes at least six, and perhaps seven, ulcers. Certainly this agent is ulcerogenic to a degree that will make it difficult to continue to advise its use" (July 9, 1963).

Dr. CARL M. PEARSON,
*School of Medicine, University of California Medical Center, Los Angeles, Calif.*

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"My incidence of headaches in this group has been about 33%. I have discontinued the drug as soon as headaches occur because I have not known how to evaluate this from a toxic point of view. Until we know more about its causes, I don't think we should continue it in the presence of headaches" (June 21, 1963).

Dr. EDWARD E. ROSENBAUM,
*Portland, Oreg.*

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"However, the incidence of side effects that we have more recently encountered seems to us to be at the present time too great to have this medication used as therapy in general office practice" (June 11, 1963).

Dr. CARL M. PEARSON.

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STATEMENT OF SENATOR NELSON—RESUMED

In the December 17, 1965 issue of Medical World News, Dr. Charley J. Smyth is reported to have claimed that indomethacin is the most promising antirheumatic agent since cortisone. Yet, less than two years later in an article in the April 1967 issue of Consultant with the title, "Treating Rheumatoid Arthritis: What's Most Apt to Succeed?" Dr. Smyth mentions indomethacin only in passing. Steroids, phenylbutazone, antimalarials, gold treatment and surgery are discussed, but not indomethacin. Dr. Smyth's explanation to the Subcommittee is that space was limited. Would it not be reasonable to assume that if space is limited, the most important items would have been included and the marginal ones left out?

Doctors Calabro and Smyth presented their personal views of the drug on behalf of the manufacturer. The only independent doctor who had the opportunity of inspecting the NDA file was Dr. O'Brien of the University of Virginia Medical School. His judgment was that although there was considerable testimonial evidence, there was relatively little scientific evidence. Dr. L. A. Healy in the article which Senator Scott has kindly put into the record, stated that:

"In a chronic disease such as rheumatoid arthritis, which is marked by spontaneous remissions and exacerbations, where both the patients and physicians naturally are hoping for improvement, the subjective impression of the efficacy

of any drug is inadequate to judge its value. It is apparent that more reliable information on effectiveness of indomethacin can be obtained from the third group, the controlled studies."

Four independent, well-controlled studies have shown that indomethacin is not more effective in rheumatoid arthritis than is aspirin, which is still the drug of choice according to the AMA.

The third problem is the use of euphemistic language in warnings and contraindications when strong language is required. The reviewing medical officer recommended that the following wording be included as a contraindication: "Indocin should not be administered to children."

This is clear and strong, but this essential warning ended up as follows:

"Since the experience with Indocin in children is limited, it is recommended that this drug should not be administered to pediatric age groups until the indications for use and dosage have been established."

There is quite a difference in clarity and conciseness between the version recommended by FDA's medical officer and the one adopted by the firm and finally approved by the FDA. The result was that the message did not get through. In a poll by Modern Medicine which was reported in its August 1, 1966 issue, almost 10% of the pediatricians who reported treatment of rheumatoid arthritis prescribed indomethacin during a thirty day period in the first year of its marketing life. During this time (first year of its marketing life by July 1966), five deaths in children being given this drug were reported. Up to the beginning of 1968, 9 deaths in children were reported. A stronger warning was adopted later at the insistence of the FDA.

Why didn't the FDA insist on a strong warning in the first place? The reason given by Dr. Hodges was that there wasn't enough data to show that it was dangerous or safe for children. Yet, even though the statute insists that substantial evidence of safety and efficacy should be presented for uses of a drug, it appears that the FDA modified the requirements and used soft warnings for children because the drug was tested in only 55 children and there was not enough evidence to show lack of safety and efficacy.

The fourth problem is that of the overpromotion of Indocin. Here is a drug with very limited uses and yet, it is reported that it has a wholesale sales volume of over $40 million per year and is one of the 200 most frequently prescribed drugs.

The New Drug Application for Indocin was originally approved for use in only the following 4 conditions:

(*a*) Rheumatoid arthritis.
(*b*) Rheumatoid (ankylosing) spondylitis.
(*c*) Degenerative joint disease (osteoarthritis) of the hip.
(*d*) Gout.

The most frequently occurring illness is Rheumatoid Arthritis, for which, according to AMA's NEW DRUGS, aspirin is the drug of choice, and Indocin should be used only when aspirin fails or cannot be used.

The FDA testified that Indocin is being used beyond its approved indications and that some physicians regard the drug as a general purpose analgesic, antipyretic, anti-inflammatory agent and the 1966 promotion of the drug featured this effect.

The fifth problem is that of false and misleading claims which, the FDA testified, have been made for this drug and which necessitated a remedial "Dear Doctor" letter and a Bureau of Medicine recommendation of prosecution under the Food and Drug Act.

I am also inserting at this point a staff memorandum dealing with Merck's advertisement of Indocin in the British Medical Journal of 1967–68.

(The memorandum follows:)

MEMORANDUM

To: Senator Gaylord Nelson, chairman, Monopoly Subcommittee
From: Benjamin Gordon, staff economist
Subject: Comparison of ads for Indocin in the British Medical Journal and the Journal of the American Medical Association, 1967–68

None of the advertisements for Indocin in the British Medical Journal (BMJ) in the years 1967–68 included any prescribing information. Some of these ads say, "Detailed information is available to physicians on request." Others do not even make this reference to indicate the desirability of obtaining information on the drug prior to prescription and administration.

The ads quote from papers favorable to Indocin. But, they do not, at any time, mention warnings, precautions, contraindicatfons, or side effects. Not one of these ads refers to deaths of children from Indocin—a subject which is required to be mentioned in all ads run in the U.S. None of the ads warns against use of the drug in pregnant women or people suffering from peptic ulcer.

The fact that Indocin may cause reactions of the central nervous system, gastrointestinal reactions, skin reactions, blood disorders or eye-ear problems as reported by Merck's clinical investigators, is not even mentioned. But, because of FDA regulations with respect to advertising, all U.S. ads do carry these warnings.

Furthermore, almost every ad which has appeared in the BMJ in the last 18 months has promoted Indocin for bursitis and other muscular problems for which the FDA has not approved claims in this country. Thus, although Merck is not allowed to promote Indocin for these conditions in the U.S., the firm is actively promoting it for them abroad. If the scientific, clinical evidence of the value of Indocin in the treatment of bursitis is not sufficient to recommend it for consumption by Americans for this purpose, is there any reason to believe that it would benefit the British people?

Thus, by praising Indocin, and pointing to its benefits, but by failing to call attention to the drug's negative aspects, Merck is presenting an unbalanced picture to the British Medical profession.

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STATEMENT OF SENATOR NELSON—RESUMED

In summary, FDA's criticism of Merck with respect to Indocin is as follows:

1. Merck made a promotional letter out of a remedial letter to doctors. An additional letter had to be sent out at the insistence of the FDA to correct the first one.

2. Merck used an older article as a testimonial when a more recent but less favorable article was available well before the ad was created and published. In addition, the second article favored a competitive product to a great extent: 15 patients preferred phenylbutazone: 10 found them equally effective; and one preferred indomethacin.

3. Claims of effectiveness were based on dosages far in excess of the upper approved safe limit when the drug was marketed in this country in capsule form.

4. Promotion over the first year of its approved marketing improperly presented the drug to the medical profession—both as to the range of its effectiveness and margin of safety.

The testimonial letters submitted by Merck & Company for the hearings record reflect in general a lack of enthusiasm for the potentialities and safety of Indocin and appear to confirm the testimony of the Food and Drug Administration, with respect to the limitations of Indocin and the unwarranted claims made for it in its advertising and promotion.

Some significant statements from Merck's submissions follow:

Dr. Kemper: Drug of choice rheumatoid spondylitis and degenerative arthritis. Not nearly as effective in peripheral rheumatoid arthritis as in others.

Dr. Hamaty: "Regarding the double blind method in evaluating drugs for rheumatoid arthritis . . . it is the best we have available at this time."

Dr. Duncan S. Owen, Jr.: "Indocin is no panacea in the treatment of rheumatoid arthritis but it definitely has a place in its treatment. * * *"

And what is the place?

Dr. Owen says that aspirin should be given first "in essentially all cases of rheumatoid arthritis. If after several weeks no clinical improvement is experienced, another agent should be added. We frequently use Indocin as the second agent and will continue to use it in this capacity. Also, we have found the drug to be helpful in selected cases of osteoarthritis, acute gouty arthritis, and ankylosing spondylitis."

Dr. Donald F. Hill: "* * * our group did conduct a clinical trial to study efficacy and toxicity before Indocin was marketed. These studies were limited primarily to rheumatoid arthritis and, unfortunately, did not show consistent results. There were a few patients who felt that Indocin gave them much more relief than other analgesics or anti-inflammatory compound, but we did not feel that the drug altered the course of the disease. We continue to use Indocin in a limited number of patients where they feel it has been of help to them. Unfortunately, a number of our patients were unable to tolerate the drug."

Dr. Arthur Dobkin: "I have found 'Indocin' to be beneficial in a selected and limited number of arthritis patients."

Dr. Jack Zuckner: "If there is a doubt about Indocin in the treatment of rheumatoid arthritis, I believe that double blind studies should give the most reliable information in its efficacy."

Dr. E. G. L. Bywaters: "I feel that this drug is useful in certain patients with rheumatoid arthritis and has about the same potency as aspirin. It is, however, more expensive and we therefore tend to use it when patients cannot tolerate aspirin and sometimes to wean them off steroid medication. . . . It seems useful also in ankylosing spondylitis and we have used it there in such cases who have developed intolerance to phenylbutazone. * * *"

Dr. Harry F. Klinefelter: "* * * I have found Indocin very helpful in a limited number of arthritics who have not responded to other medication, such as aspirin. Butazalidin and Tachearil. There are a small number of people with rheumatoid arthritis who do extremely well on Indocin, and if they respond, they respond to doses of 75 mg. a day or less."

In addition, Mr. Gadsden, during the course of his testimony, made the following statement:

"I would furthermore like to call your attention to a quotation of 1967 from the recognized publication, NEW DRUGS, as published by the AMA. It says that because 'Indocin' has produced relief in acute attacks within 48 hours, and because it lacks untoward effects of Colchicine, some physicians consider it to be the drug of choice for these attacks."

The complete paragraph from the AMA 1967 publication from which the excerpt was taken and which presents a more limited picture of the drug's uses is as follows:

"Indomethacin produces anti-inflammatory effects in patients with gout and may be as effective as phenylbutazone in its promptness of action an the degree of relief it provides. Because it has produced relief in acute attacks within 48 hours, and because it lacks the untoward effects of colchicine, some clinicians consider it to be the drug of choice for these attacks; however, controlled trials are needed to determine how its effectiveness compares with that of colchicine. Indomethacin may be useful as a supplement to colchincine in the management of severe cases of gout. Whether it is useful as a prophylactic agent in gouty arthritis remains to be established."

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[From the Medical Letter, vol. 10, No. 10, May 17, 1968]

INDOMETHACIN (INDOCIN)

Indomethacin (Indocin-Merck) is widely used as an anti-inflammatory analgesic drug in the treatment of rheumatoid arthritis and spondylitis, osteoarthritis, and gout (Medical Letter, Vol. 7, p. 89, 1965). Enthusiastic reports of its effectiveness followed the introduction of the drug in 1965, but many of the reports published since that time have been much less enthusiastic, some even questioning whether the drug was more effective than placebo.

In the mass of conflicting studies of indomethacin, not many have been controlled and very few of the controlled studies have been so designed as to give clear answers about the usefulness of the drug. Frequently other drugs were used simultaneously and doses varied widely. The numerous uncontrolled studies have generally ignored the variable course of rheumatic disorders and the effectiveness of placebos in many patients. On the basis of both published reports and their own experience, Medical Letter consultants believe that indomethacin is a useful drug, but that its usefulness is limited by its frequent and sometimes severe side effects.

*Rheumatoid arthritis.*—Indomethacin appears to have about the same anti-inflammatory and analgesic effectiveness as aspirin in patients with rheumatoid arthritis (R. S. Pinals and S. Frank, New Eng. J. Med., 276:512, 1967). Aspirin is better tolerated by most patients and it remains the drug of first choice for rheumatoid arthritis. Indomethacin is not as hazardous as the corticosteroids, gold, or phenylbutazone (Butazolidin), however, and it is worth a trial in patients who cannot tolerate aspirin. Some investigators have observed additive effects when indomethacin was given along with aspirin; other investigators have observed no additive effects (The Cooperating Clinics Committee of the Amer. Rheum. Assn., Clin. Pharmacol. Ther., 8:11, 1967).

*Rheumatoid (ankylosing) spondylitis.*—Although adequate trials are lacking, indomethacin appears to be as effective as phenylbutazone in ankylosing spondylitis. For patients in whom aspirin is ineffective, some clinicians prefer indomethacin to phenylbutazone because its side effects, while frequent, are not likely to be as serious as they may be with phenylbutazone; many deaths from blood dyscrasias have followed prolonged or repeated use of that drug.

*Gout.*—Indomethacin is often effective in the treatment of acute gouty arthritis (P. L. Boardman and F. D. Hart, Practitioner, 194:560, 1965), with some reports indicating that it acts more rapidly than colchicine or phenylbutazone. Some clinicians prefer a brief course of phenylbutazone, and consider both drugs preferable to colchicine because of the frequency and severity of gastrointestinal side effects with colchicine. Trials comparing indomethacin with phenylbutazone are too few to permit a confident choice between the drugs.

*Osteoarthritis.*—The manufacturer claims that indomethacin is effective in osteoarthritis of the hip. While the evidence is not conclusive, one controlled short-term trial does support this claim (J. Wanka and A. St. J. Dixon, Ann. Rheum. Dis., 23:288, 1964). Present evidence does not adequately support the results of early studies showing the drug to be effective in other joints affected by osteoarthritis.

*Adverse effects.*—The incidence of adverse effects has varied, in different studies, from a few per cent to about three-quarters of the patients. Gastric side effects have been less frequent with the capsule formulation which replaced the early tablet formulation. Most of the studies have shown a high incidence of such side effects as headaches, vertigo, and gastrointestinal disturbances, including nausea and vomiting. Peptic ulceration has occurred, sometimes with bleeding, and cholestatic jaundice has been reported. Mental depression has also been reported (M. Thompson and J. S. Percy, Brit. Med. J., 1:80, 1966). There have been a few reports of leukopenia, thrombocytopenia, and agranulocytosis. A number of deaths have been associated with the use of indomethacin, some of them the result of ulceration and bleeding. Both the incidence and the severity of side effects have usually been dose-related. Indomethacin may interfere with resistance to infection, particularly in children (J. C. Jacobs, JAMA, 199:932, 1967), or may activate latent infections. For the persent, indomethacin should not be administered to children.

*Dosage.*—The manufacturer recommends an initial dosage of 50 to 75 mg a day with gradual increases up to 200 mg a day. Because of the high incidence of adverse effects at 200 mg many clinicians limit dosage to 100 to 150 mg a day.

*Conclusion.*—Indomethacin appears to be no more effective than aspirin in the treatment of rheumatoid arthritis; all Medical Letter consultants agree that aspirin is the drug of choice and that indomethacin should be used only in patients who cannot tolerate aspirin. There is some belief that the combination of indomethacin and aspirin may be beneficial in a few patients with rheumatoid arthritis not satisfactorily controlled on aspirin alone, and that a trial of the combination in such patients is worthwhile. Indomethacin appears to be as effective as phenylbutazone in the treatment of ankylosing spondylitis and is probably less hazardous. It is also effective in acute gouty arthritis, and it may be helpful in the treatment of osteoarthritis of the hip. Despite frequent minor side effects and occasional serious effects, indomethacin appears to be less hazardous for long-term use than corticosteroids, gold, or phenylbutazone.

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[From the Medical Letter, vol. 7, No. 22, Oct. 22, 1965]

INDOCIN

Indomethacin (Indocin—Merck) is a nonsteroid indole derivative offered for the treatment of rheumatoid arthritis, ankylosing (rheumatoid) spondylitis, osteoarthritis and gouty arthritis. Like other drugs used in arthritis—aspirin, phenylbutazone, and the corticosteroids—indomethacin has analgestic and anti-inflammatory effects. The drug is not free of serious side effects, and its effectiveness is much more limited than many of the early claims would indicate; nevertheless, it appears to be a useful addition to the group of drugs available; for the treatment of arthritic disorders.

*Rheumatoid arthritis and spondylitis.*—In a number of clinical trials, mostly uncontrolled, about 40 to 50 per cent of patients with rheumatoid arthritis showed some improvement when given indomethacin. In one study, doses of 150 to 200 mg of indomethacin daily were found to be effective in most patients with mod-

erately severe rheumatoid arthritis, though they had little effect when the disease was severe (A. M. Marmont et al., in International Symposium on Non-Steroidal Anti-Inflammatory Drugs, Amsterdam, Excerpta Medica Foundation, 1965, p. 363). In ankylosing spondylitis, indomethacin has appeared to relieve pain more consistently than in other types of arthritis (F. D. Hart and P. L. Boardman, Brit. Med. J., 2:965, 1963). How it compares with aspirin and phenylbutazone in the treatment of spondylitis is not yet known.

Indomethacin has been used in combination with prednisone in a number of studies on patients with rheumatoid arthritis. The use of indomethacin permitted reduction of dosage of the steroid with all the patients in some studies, with fewer than half in others. The side effects of corticosteroids are much more serious than those thus far observed with indomethacin, and the combination, with reduced dosage of steroids, is well worth a trial where steroids cannot be eliminated altogether. It is not yet known whether indomethacin can be safely and effectively used in combination with such other anti-rheumatic drugs as phenylbutazone, gold salts and chloroquine.

*Gouty arthritis.*—In the treatment of acute gouty arthritis with indomethacin, many patients have shown improvement within about 48 hours (P. L. Boardman and F. D. Hart, Practitioner, 194:560, April, 1965). How the drug compares in effectiveness with colchicine and phenylbutazone can be determined only by better-controlled trials than those so far reported. The usefulness of indomethacin combined with a uricosuric agent such as probenecid (Benemid—Merck) in the treatment of chronic gouty arthritis is being investigated.

*Osteoarthritis and other conditions.*—In uncontrolled trials, indomethacin has been reported to be effective in relieving pain in osteoarthritis. A valid judgment of its usefulness must await further trials. It is not recommended by the manufacturer for such acute musculoskeletal disorders as bursitis, tendinitis, and synovitis.

*Adverse effects.*—Adverse effects, often severe, and requiring discontinuance of the drug in many patients, are common, and a few fatalities have been attributed to indomethacin. Among the most frequent adverse effects are headache, dizziness, gastrointestinal disturbances (nausea, anorexia, vomiting, diarrhea, bleeding and ulceration), and psychic disturbances. Whether significant hematologic, renal hepatic, or neurologic reactions occur is not clear. A fuller assessment of adverse effects will be possible only after longer use; indomethacin appears to be too hazardous to be substituted for aspirin when that drug is effective, but it may prove less hazardous than other anti-arthritic drugs.

*Precautions and contraindications.*—The manufacturer warns that indomethacin is contraindicated in patients with active peptic ulcer, gastritis, ulcerative colitis, and regional ileitis. Whether it crosses the placental barrier is not yet known, nor are its effects on the human fetus; therefore, indomethacin should not be used in pregnant women. The manufacturer also warns that there has been insufficient experience to warrant its use in children. Because of the frequency of dizziness, lightheadedness, and feelings of detachment, patients on indomethacin should be cautioned against operating motor vehicles or other machinery, climbing ladders, etc., and the drug should be used with great caution in patients with psychological difficulties, epilepsy or parkinsonism, since it sometimes aggravates these conditions.

*Dosage and administration.*—The recommended initial dose is 25 mg twice daily, with gradual increase as needed. Good response is often obtained with 100 mg daily, divided into four doses. Further improvement rarely occurs when the dose is increased above 150 or 200 mg a day. The drug should be given with food to reduce gastric irritation.

*Conclusion.*—Early clinical trials indicate that indomethacin is a useful addition to the group of drugs available for the treatment of rheumatoid arthritis and ankylosing spondylitis. Its place in the management of acute gouty arthritis and osteoarthritis is less clear; properly controlled trials are needed.

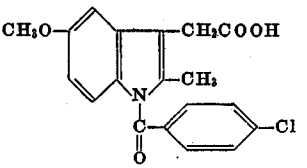
In the treatment of rheumatoid arthritis, aspirin is still the drug of first choice (see The Medical Letter, Vol. 7, p. 75, 1965, for a discussion of the side effects of aspirin). When effective doses of aspirin are not well tolerated, indomethacin may be used with lower doses of aspirin or, if necessary, substituted for it, before resort is had to corticosteroids. In patients already on corticosteroids, reduction of the steroid dosage and a decrease in steroid side effects can often be achieved by the addition of indomethacin.

If gastric ulceration occurs with either aspirin, phenylbutazone, or corticosteroids, indomethacin cannot be considered a safe substitute since it, too, causes gastric ulceration. In such cases, gold salts or chloroquine can be tried; these also have serious side effects, but they do not cause gastric ulceration.

[From New Drugs, 1967, pp. 539–542]

## INDOMETHACIN

[INDOCIN]




1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid

### ACTIONS AND USES

Indomethacin is a new type of nonsteroidal chemical compound that has anti-inflammatory, antipyretic, and analgesic properties.

Present clinical experience indicates that this drug is as effective as the salicylates in patients with rheumatoid arthritis. However, its use is not necessary when salicylate therapy is effective. Although aspirin is still considered the drug of first choice, indomethacin may be tried if aspirin ceases to be beneficial or is no longer tolerated. Doses of aspirin may be taken in between regular doses of indomethacin if necessary.

When given alone, indomethacin is more effective in active rheumatoid arthritis than in the inactive "burnt-out" type. In about two-thirds of the patients, pain, tenderness, and stiffness decrease and ambulation increases in two to three days. However, some clinicians have found that maximal benefits are not obtained until indomethacin has been given for a month or more. With prolonged administration, 10% to 15% of the patients who responded initially must stop taking indomethacin because of its untoward effects.

It has been reported that indomethacin reduces joint swelling and edema in some patients with rheumatoid arthritis. However, results have been equivocal in the few studies in which objective measurements of joint size were made. The erythrocyte sedimentation rate was not affected.

When given alone, indomethacin is less effective than the corticosteroids in the treatment of rheumatoid arthritis. When given concomitantly, however, the dose of the steroids often can be halved and in some patients completely withdrawn. Thus, indomethacin may be especially useful in patients who have been receiving long-term therapy with corticosteroids. However, the hazards of combined therapy with steroids and indomethacin have yet to be fully evaluated.

Indomethacin has been particularly useful in the treatment of mild to moderate osteoarthritis of the hip joint, a condition that is resistant to all other anti-inflammatory agents. It also appears to relieve the pain of ankylosing spondylitis as effectively as does phenylbutazone.

Indomethacin produces anti-inflammatory effects in patients with gout and may be as effective as phenylbutazone in its promptness of action and the degree of relief it provides. Because it has produced relief in acute attacks within 48 hours, and because it lacks the untoward effects of colchicine, some clinicians consider it to be the drug of choice for these attacks; however, controlled trials are needed to determine how its effectiveness compares with that of colchicine. Indomethacin may be useful as a supplement to colchicine in the management of severe cases of gout. Whether it is useful as a prophylactic agent in gouty arthritis remains to be established.

This drug should not be used in children until the indications for use and appropriate dosage have been established.

### ADVERSE REACTIONS

Central nervous system effects (headaches, usually severe in the morning; vertigo; light-headedness; mental confusion) occur during the early weeks of therapy in about 20% to 30% of patients taking indomethacin. Drowsiness, convulsions, depression, and psychic disturbances such as depersonalization have also been reported. Generally, these effects are dose-related and are less likely to appear if the daily dosage is 100 mg. or less given in divided amounts. The symptoms may occur within the first few hours after administration or may be

delayed for two or three days; they frequently disappear with continued use but, if they are severe, the drug should be discontinued.

Gastrointestinal reactions (nausea, indigestion, epigastric burning, stomatitis, diarrhea), which have been observed in about 25% of the patients, often are transient and can be minimized by giving the drug after meals and with milk at bedtime. These symptoms are severe enough to require discontinuing the drug in less than 10% of the patients but, even in these, the adverse effects may not recur when administration of the drug is resumed.

Indomethacin should be regarded as being potentially ulcerogenic. It may produce single or multiple ulceration of the esophagus, stomach, duodenum, or small intestine. Cases of perforation and hemorrhage, a few of them fatal, have been reported. Some patients with a history of peptic ulcer have tolerated the drug without experiencing gastrointestinal symptoms or having evidence of an active ulcer; other patients have developed ulcers after having taken the drug for 1½ to 3 years. Since most patients who developed ulcers had received doses of 150 to 300 mg. a day, dosage may well be a contributing factor. Occult bleeding and resulting anemia may occur in the absence of an ulcer, and persistent indigestion may be a symptom of this. Although measurements indicate that the occult blood loss associated with indomethacin is less than that produced by clinically equivalent doses of aspirin, hemoglobin determinations should be made regularly and the drug should be discontinued if any evidence of gastrointestinal bleeding develops.

Leukopenia, purpura, and thrombocytopenia may develop. Agranulocytosis has been reported rarely, but its relationship to indomethacin administration has not been established. Reports of jaundice and hepatitis have also appeared.

Dermatologic or hypersensitivity-type reactions (pruritus, urticaria, rash, angioneurotic edema, loss of hair, acute respiratory distress) and reactions affecting the eye or ear (tinnitus, blurred vision, orbital and periorbital pain) have occurred infrequently.

No significant alterations in the glucose tolerance test, electrolyte balance, or kidney function have occurred after administration of indomethacin for periods as long as three years. However, more long-term studies are needed to completely assess the effects of its prolonged use.

### PRECAUTIONS

Patients who require larger dosages of indomethacin must be observed more closely for the possible occurrence of toxic effects. The patient may accept the untoward effects of indomethacin if he is told of their possible occurrence. Indomethacin, like aspirin, should be administered on a regular schedule and not used indiscriminately in the treatment of rheumatoid arthritis.

Indomethacin is contraindicated in patients with active peptic ulcer, gastritis, regional enteritis, or ulcerative colitis, and it should be used wth caution in patients with a history of these disorders. These patients may tolerate the drug if small doses are used. Indomethacin also should be used with care in patients who have epilepsy, parkinsonism, or emotional or psychiatric problems, since the drug may aggravate these conditions.

Because of the possible occurrence of central nervous system effects, patients being given indomethacin should avoid activities requiring mental alertness, judgment, or physical coordination (e.g., driving a car, operating dangerous machinery), particularly during the early weeks of therapy.

Indomethacin is contraindicated in patients with asthma who are sensitive to aspirin.

It is now known that indomethacin can mask the signs and symptoms which usually accompany infectious disease. Therefore, the physician must be aware of this possibility to avoid delay in the treatment of an infection, and should use the drug with caution in the presence of existing, controlled infections.

No teratogenic effects have been demonstrated in animal studies. However, it has been shown that indomethacin does cross the placental barrier. Thus, the possibility of risk to the fetus must be weighed against the expected therapeutic benefits if indomethacin is considered for administration to a pregnant woman.

A few deaths in children with severe juvenile rheumatoid arthritis who were receiving indomethacin with other drugs have been reported; in two of these cases, death was attributed to intercurrent infections of possibly unrecognized severity. Clinical studies have been insufficient to establish any recommendation for the use of indomethacin in infants and children and, at the present time, the drug is considered to be *contraindicated in infants and children* because safe conditions for use have not been established.

PHARMACOLOGY

In man, indomethacin is absorbed promptly following oral administration, and peak plasma levels occur within two hours. About 90% of a single dose is excreted in 24 to 48 hours; approximately two thirds of this amount is excreted in the urine as the glucuronide and the remainder is excreted in the feces.

DOSAGE AND PREPARATIONS

*Route of administration.*—Oral.

*Dosage.*—To minimize adverse reactions, small doses of indomethacin are given initially; when necessary, the size of the dose is then gradually increased until an effective level is reached.

In *rheumatoid arthritis, ankylosing spondylitis,* and *degenerative joint disease of the hip,* the initial dose is 25 mg. two or three times daily. If the patient does not respond, this dose is increased at weekly intervals by increments of 25 mg. a day until a satisfactory response is obtained or until a daily dose of 150 to 200 mg. is reached; larger doses are not recommended. If adverse reactions occur, the drug should be discontinued or successive adjustments in dosage should be made until the best possible response is obtained. After an acute phase or exacerbation of rheumatoid arthritis is controlled, the dose of indomethacin should be reduced to a satisfactory maintenance level. No reports on its occasional intermittent use for short periods are available.

When indomethacine is added to a regimen of corticosteroid therapy, it is often possible to reduce the dose of the steroid by as much as one half or to discontinue it entirely. However, this reduction should be made gradually in order to avoid the effects of steroid withdrawal.

Acute attacks of *gout* may be controlled with a dosage of 50 mg. three times a day until the attack subsides. During the intervals between attacks, a dose of 25 mg. twice a day may be sufficient.

*Preparations.*—Capsules 25 mg.

*Supplied by.*—Merck Sharp & Dohme [Indocin].

Year of introduction: 1965.

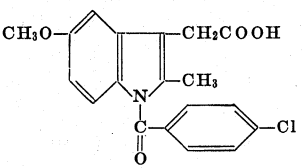
Evaluated for *N.D.* 1966. Reviewed: 1967.

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[From New Drugs, 1966, pp. 531–534]

INDOMETHACIN

[INDOCIN]




1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid

ACTIONS AND USES

Indomethacin is a new type of nonsteroidal chemical compound that has anti-inflammatory, antipyretic, and analgesic properties.

Present clinical experience indicates that this drug is as effective as the salicylates in patients with rheumatoid arthritis. However, its use is not necessary when salicylate therapy is effective. Although aspirin is still considered the drug of first choice, indomethacin may be tried if aspirin ceases to be beneficial or is no longer tolerated. Doses of aspirin may be taken in between regular doses of indomethacin if necessary.

When given alone, indomethacin is more effective in active rheumatoid arthritis than in the inactive "burnt-out" type. In about two thirds of the patients, pain, tenderness, and stiffness decrease and ambulation increases in two to three days.

However, some clinicians have found that maximal benefits are not obtained until indomethacin has been given for a month or more. With prolonged administration, 10% to 15% of the patients who responded initially must stop taking indomethacin because of its untoward effects.

It has been reported that indomethacin reduces joint swelling and edema in some patients with rheumatoid arthritis. However, results have been equivocal in the few studies in which objective measurements of joint size were made. The erythrocyte sedimentation rate was not affected.

When given alone, indomethacin is less effective than the corticosteroids in the treatment of rheumatoid arthritis. When given concomitantly, however, the dose of the steroids often can be halved and in some patients completely withdrawn. Thus, indomethacin may be especially useful in patients who have been receiving long-term therapy with corticosteroids. However, the hazards of combined therapy with steroids and indomethacin have yet to be fully evaluated.

Indomethacin has been particularly useful in the treatment of mild to moderate osteoarthritis of the hip joint, a condition that is resistant to all other anti-inflammatory agents. It also appears to relieve the pain of ankylosing spondylitis as effectively as does phenylbutazone.

Indomethacin produces anti-inflammatory effects in patients with gout and may be as effective as phenylbutazone in its promptness of action and the degree of relief it provides. Because it has produced relief in acute attacks wihin 48 hours, and because it lacks the untoward effects of colchicine, some clinicians consider it to be the drug of choice for these attacks; however, controlled trials are needed to determine how its effectiveness compares with that of colchicine. Indomethacin may be useful as a supplement to colchicine in the management of severe cases of gout. Whether it is useful as a prophylactic agent in gouty arthritis remains to be established.

### ADVERSE REACTIONS

Central nervous system effects (headaches, usually severe in the morning; vertigo; light-headedness; mental confusion) occur during the early weeks of therapy in about 20% to 30% of patients taking indomethacin. These symptoms may occur within the first few hours after administration or may be delayed for two or three days; they frequently disappear with continued use and are reversible when the drug is discontinued. Generally, these effects are dose-related and are less likely to appear if the daily dosage is 100 mg. or less given in divided amounts.

*Gastrointestinal reactions* (nausea, indigestion, epigastric burning, stomatitis, diarrhea), which have been observed in about 25% of the patients, often are transient and can be minimized by giving the drug after meals and with milk at bedtime. These symptoms are severe enough to require discontinuing the drug in less than 10% of the patients but, even in these, the adverse effects may not recur when administration of the drug is resumed.

Indomethacin should be regarded as potentially ulcerogenic, although the available evidence on this point is contradictory. Some patients with a history of peptic ulcer have tolerated the drug without experiencing gastrointestinal symptoms or having evidence of an active ulcer; other patients have developed ulcers after having taken the drug for 1½ to 3 years. Since most patients who developed ulcers had received doses of 150 to 300 mg. a day, dosage may well be a contributing factor. Occult bleeding and resulting anemia may occur in the absence of an ulcer; persistent indigestion may be a symptom of this. Although measurements indicate that the occult blood loss associated with indomethacin is less than that produced by clinically equivalent doses of aspirin, hemoglobin determinations should be made regularly and the drug should be discontinued if any evidence of gastrointestinal bleeding develops.

No significant hematologic reactions or alterations in the glucose tolerance test, electroylte balance, or liver and kidney function have occurred after administration of indomethacin for periods as long as three years. However, more long-term studies are needed to completely assess the effects of its prolonged used.

Other adverse effects reported infrequently are edema; psychic reactions such as depression; angioneurotic edema; drowsiness; tinnitus; blurred vision; and dermatologic reactions such as pruritus, urticaria, and rash. Indomethacin should be discontinued if these reactions occur. Leukopenia has been reported in a few patients.

PRECAUTIONS

Patients who require larger dosages of indomethacin must be observed more closely for the possible occurrence of toxic effects. The patient may accept the untoward effects of indomethacin if he is told of their possible occurrence. Indomethacin, like aspirin, should be administered on a regular schedule and not used indiscriminately in the treatment of rheumatoid arthritis.

Although there is no definite evidence that indomethacin causes peptic ulcers, *it is contraindicated in patients with active ulcers.* In addition, because of its potential for causing bleeding in the gastrointestinal tract, the drug should be used with caution if there is a history of ulcer, regional ileitis, gastritis, or ulcerative colitis. Patients with these conditions may tolerate the drug if small doses are used. Indomethacin also should be used with care in patients who have epilepsy, parkinsonism, or emotional or psychiatric problems. Since the drug may cause aggravation of these conditions.

Because of the possible occurrence of central nervous system effects, patients being given indomethacin should avoid activities requiring mental alertness, judgment, or physical coordination (e.g., driving a car, operating dangerous machinery), particularly during the early weeks of therapy.

No teratogenic effects have been demonstrated in annual studies. However, it has been shown that indomethacin does cross the placental barrier. Thus, the possibility of risk to the fetus must be weighed against the expected therapeutic benefits if indomethacin is considered for administration to a pregnant woman. Clinical studies have been insufficient to establish any recommendation for the use of indomethacin in *infants* and *children.*

PHARMACOLOGY

In man, indomethacin is absorbed promptly following oral administration, and peak plasma levels occur within two hours. About 90% of a single dose is excreted in 24 to 48 hours; approximately two thirds of this amount is excreted in the urine as the glucuronide and the remainder is excreted in the feces.

DOSAGE AND PREPARATIONS

*Route of Administration.*—Oral.

*Dosage.*—To minimize adverse reactions, small doses of indomethacin are given initially; when necessary, the size of the dose is then gradually increased until an effective level is reached.

In *rheumatoid arthritis, ankylosing spondylitis,* and *degenerative joint disease of the hip,* the initial dose is 25 mg. two or three times daily. If the patient does not respond, this dose is increased at weekly intervals by increments of 25 mg. a day until a satisfactory response is obtained or until a daily dose of 150 to 200 mg. is reached; larger doses are not recommended. If adverse reactions occur, the drug should be discontinued or successive adjustments in dosage should be made until the best possible response is obtained. After an acute phase or exacerbation of rheumatoid arthritis is controlled, the dose of indomethacin should be reduced to a satisfactory maintenance level. No reports on its occasional intermittent use for short periods are available.

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*Preparations.*—Capsules 25 mg.

*Supplied by.*—Merck Sharp & Dohme [Indocin].

Year of introduction: 1965.

Evaluated for *N.D.* 1966.

[From the Washington Post, Jan. 21, 1967]

## FDA Is Probing Merck Division

### FIRM COULD FACE CRIMINAL PROSECUTION OVER AD FOR ARTHRITIS DRUG

(By Morton Mintz)

The maker of Indocin, a drug widely prescribed for arthritic disorders, has appeared at a closed hearing to show cause why the company should not be criminally prosecuted for an Indocin advertisement.

The firm, Merck, Sharp & Dohme, a division of Merck & Co., Inc., confirmed that an informal hearing was held recently by the Food and Drug Administration's district office in Philadelphia. The company said comment on the substance of the discussion would be inappropriate.

The advertisement appeared several times last year in the Journal of the American Medical Association. Its headline said Indocin (indomethacin) "extends the margin of safety in long-term management of arthritic disorders."

#### CITED BY FDA COUNSEL

That headline was cited last October by William W. Goodrich, FDA's chief counsel, in a speech in Manhattan.

"There is not yet enough experience to support the claim for greater long-term safety," he told the Pharmaceutical Advertising Club. "To the contrary, the longer the drug is used, the more side-effect information appears."

Goodrich mentioned Indocin in the course of criticizing promotions of the "Big Eight" prescription drugs—a group of drugs and antibiotics, including indomethacin, that entered the market in 1965 and within 12 months had become among the 200 drugs most frequently prescribed.

Like most new drugs, the official said, Indocin was asserted to be safer and more effective than existing products in the same therapeutic group. But as experience has accumulated, he said, "more side effects have been noted and more warning information has been required."

In response to an inquiry, FDA said it knows of 16 deaths and 303 side reactions among Indocin patients.

#### ASSOCIATION WITH DRUG

Seven of the dead were children, the agency said. Only one of these deaths was said to have had a clear-cut association with Indocin. In another, the association was regarded as questionable. In the remainder, it was regarded as dubious, because the children had had severe illnesses and had been treated with other medicines.

The nine adults had had long-standing rheumatoid arthritis and were, FDA said, in an age group over 50. The deaths of three of them were said by FDA to have had a "possibly clear-cut" relation with Indocin. Such a relation was doubted in the others, all of whom had had major, pre-existing complications.

In another complaint about the AMA Journal ad for Indocin, Goodrich told the Advertising Club that the ad quoted "authoritative sources, without the full impact of the actual articles."

He pointed to a claim of usefulness for Indocin in arthritis of the spine ("anklosing spondylitis"). The claim is supported by a reference. A physician who checked it out. Goodrich said, would find that the reference was to a 2-inch abstract of a speech made in 1964.

In addition, Goodrich said, the ad failed to cite this statement in the abstract: "Excellent results have also been obtained in some cases of rheumatoid arthritis . . . there have been some striking failures as well."

A third complaint made by the agency counsel was that the ad "omits some very important warning information that is required" in the authorized prescribing instruction—the brochure enclosed with every package of a drug.

In West Point, Pa., a Merck, Sharp & Dohme spokesman said:

"It is our judgment, based on the facts of Indocin use, that this new anti-arthritic agent does not suffer from certain disadvantages such as the production of hormonal side effects and certain blood dyscracias which do occur with some of the other agents previously available. In this way it has extended the margin of safety in the long-term management of arthritic disorders."

Since the Goodrich speech FDA has refused to comment on the closed hearing or on the possibility of prosecution. Except where data are requested by Congress,

the agency customarily makes no disclosure to the medical or lay public when it calls and holds such hearings or takes certain other steps against drug ads that it considers misleading.

POSSIBLE ACTIONS

In the pending case, FDA's Philadelphia office could recommend anything from concurrence with a company position that it had done nothing wrong to prosecution. A recommendation for a criminal proceeding could be vetoed at headquarters in Washington or by the Justice Department if the case were to be sent there.

Goodrich disclosed in his October speech that a few days earlier Indocin's maker had mailed "a new revised brochure to the profession with new cautionary information in heavy print." The fatalities among Indocin patients were mentioned neither in the brochure nor in the accompanying "Dear Doctor" letter signed by Dr. Frederick K. Heath, vice president for professional communications.

Displayed on the envelope, however, was a prominent box saying "Safety/Drug Safety Information."

Generally, Dr. Heath blended an alert to "important changes" in prescribing instructions for Indocin with statements marked by a promotional tone.

His letter said that "144,000,000 patient days of therapy in 99 countries" had been accumulated with Indocin since its introduction about 16 months earlier.

He also said that Indocin "has become, next to aspirin, the most frequently prescribed antirheumatic drug." The characterization of indomethacin as an "antirheumatic drug" is no longer allowed by FDA.

In addition, the agency found the letter inadequate and insisted on a new one, which the manufacturer mailed in December. Above the "Dear Doctor" salutation the words "Drug Safety Information" were printed in deep blue. Promotional plugs for Indocin were absent.

In addition to directing attention to new precautions, Dr. Heath's December letter emphasized that Indocin "should not be prescribed for children because safe conditions for use have not been established."

That same warning appears three times in boldface type in the new prescribing circular enclosed with the letter.

Also in boldface, the circular says that severe and even fatal reactions have occurred in a few cases of severe juvenile rheumatoid arthritis in children who received Indocin along with other drugs. The precaution in the October circular about the use of Indocin in children was found by FDA to be too mild.

ARTICLE CRITICIZED

The Goodrich speech also contained criticism of an article by freelancers Phyllis and Robert P. Goldman in the July Pageant. The title was "INDOCIN," the trade name of the drug.

The FDA counsel said the article "featured" Indocin "for 'bursitis,' 'trick knee,' 'tennis elbow' and 'a host of other less common disorders characterized by pain and swelling in and around the joints.' "

"The only support for these claims," Goodrich said, "was user testimonials which, according to the article, were made available to the writer by the sponsor of the drug."

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[From the Washington Post, Mar. 19, 1967]

## FDA Begins a Restudy of Arthritis Drug

### SOME AUTHORIZED CLAIMS FOR INDOCIN ARE NOW IN DOUBT

(By Morton Mintz)

The Food and Drug Administration is reevaluating a drug that has been taken mainly for arthritic disorders by millions of persons here and abroad.

The drug is Indocin (indomethacin). In the United States FDA-authorized instructions to physicians prescribing the drug indicate that it is useful in rheumatoid arthritis, arthritis of the spine, degenerative joint disease of the hip and gout.

It is one or more of these authorized claims that the FDA is now reevaluating.

The FDA disclosed its action yesterday in response to a Washington Post query about articles in three prestigious medical journals about Indocin's efficacy against rheumatoid arthritis. Two of the reports indicate that aspirin is as

effective as Indocin; the third indicates the drug to be no more effective than a placebo, a pill containing an inert substance.

The reports raise questions not only about the agency's handling of Indocin, which was approved in June, 1965, but also about the law's strict requirement that "substantial evidence" of efficacy be demonstrated.

Merck & Co., the manufacturer, said Thursday that Indocin's safety and efficacy were established "by more than 300 clinical investigators" and by "a wealth" of experience.

The three journal reports were prepared by experts who performed well-controlled clinical investigations. And only selected patient groups got Indocin; other groups got aspirin, Indocin and aspirin, or aspirin and/or a placebo. These were highly sophisticated double-blind studies.

Neither patients nor physicians knew what was being administered until a code was broken at the end of the trials. Some patients were crossed over, that is, switched without disclosure from one group to another.

But Merck said some of the studies in behalf of Indocin it had submitted to the FDA also were double-blind. It also protested that Indocin worked with some rheumatoid arthritis victims with whom aspirin failed; and that in the other diseases for which Indocin is approved it allows successful control while aspirin does not.

VALUES IRREGULAR

In addition, the relative value of drugs in rheumatoid arthritis is hard to measure objectively, Merck said. Many patients are relieved of pain by aspirin; investigators are unwilling to substitute a placebo for test purposes, the company said.

Last October, Merck revised its prescribing brochure and mailed a copy accompanied by a letter to the Nation's practicing physicians. The letter cited "new cautionary information" but made no mention of fatalities.

By December, FDA knew of 329 adverse reactions, including seven deaths in children and nine in elderly persons. It termed the relation to Indocin clearcut in one fatality, "possibly clearcut" in three others and highly questionable in the rest.

The October Merck letter said that "144,000,000 patient days of therapy" had been accumulated with indomethacin, and that it "has become, next to aspirin, the most frequently prescribed antirheumatic drug." The characterization of Indocin as "antirheumatic" was later disallowed by the FDA.

DEATHS CITED

In November, a jolting warning letter was sent Canadian physicians by the Food and Drug Directorate, the FDA's north-of-the-border counterpart. The letters told of several indomethacin deaths in children and of a number of unexpected adverse reactions.

These included "not uncommon" and sometimes severe effects on the central nervous system, and blood diseases and blurred vision.

In upper case, The Canadian government letter said in capitals "That Indomethacin Should Not Be Used in Children . . ." In addition, doctors were warned that the drug "can mask the signs and symptoms of an infectious process or activate a latent bacterial infection."

In Washington, the FDA called in Merck. In December the company sent out a 2-paragraph letter which warned against Indocin use in children and called attention to the enclosed prescribing brochure which had again been revised to emphasize that warning.

Several months before the FDA approved Indocin in 1965, warnings against its use were published in the Medical Journal of Australia by physicians who "detailed an imposing list of side effects."

SUGGESTION'S ROLE

The double-blind study, reported in the British Medical Journal last Jan. 14 involved 28 persons for 10 weeks.

Although side effects "occurred more often with indomethacin" than with a placebo, the report inferred that "suggestion played a large part in determining both the incidence and variety . . ." The authors were three Welsh physicians, Phelim Donnelly, Kenneth Lloyd and Hubert Campbell.

The New England Journal of Medicine study, published March 2 by Drs. Robert S. Pinals and Sumner Frank of Boston, was done on 24 patients for a month. Two

on Indocin, including one also taking aspirin, dropped out with "intolerable side effects." Another dropped out for an unrelated reason.

Among the remaining 21, one-third preferred aspirin and one-third indomethacin; one-third was unable to detect a difference. The physicians rated Indocin superior in five patients and aspirin in six.

10 WERE THE SAME

No difference was found in 10. "Side effects did not differ in frequency or severity," but headache was noted more commonly with indomethacin and auditory symptoms with aspirin, they said.

The study reported in the January-February Clinical Pharmacology and Therapeutics was sponsored by the American Rheumatism Association and was done by biostatistician Donald Mainland, primarily to establish objective standards for judging rheumatoid arthritis drugs.

No significant differences were found among patients taking Indocin and others taking a placebo. Patients in both groups were allowed to take as much aspirin as desired. Merck cited this in asserting that the study does not show that the relative effectiveness of Indocin and aspirin used separately.

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[From the Washington Post, May 21, 1968]

DRUG AD EXPORTS POSE A PROBLEM

(By Morton Mintz)

In Animal Farm, the satirical fable by the late George Orwell, all the animals were equal, but only for a time. Then some animals asserted themselves to be more equal than others. A parallel may exist in the attitudes businessmen in one country take toward citizens of another when it comes to advertising prescription drugs.

American pharmaceutical companies hold a commanding position in the non-Communist world, and in promoting drugs it might be presumed that they would treat doctors abroad the same as doctors here. If a promotional claim is prohibited in this country because it might mislead a physician (and kill, injure, or at least exploit his patient), the same claim presumably would not be made in other countries. But that this is not always the case is suggested by a recent disclosure concerning Abbott Laboratories of North Chicago, Ill.

In March, 1967, this firm ran an advertisement in the *Journal of the American Medical Association* for Enduron, Abbott's trade name for a thiazide diuretic called methyclothiazide. The ad claimed that in removing excess fluids, Enduron caused a lesser depletion of potassium than rival prescription products. This claim was deemed by the Food and Drug Administration to be misleading. Under pressure by the FDA, the company then sent a letter individually to every prescribing physician in the Nation acknowledging that the loss of potassium with Enduron was not seen by experts as significantly different from the loss with other thiazide diuretics.

But a year later—in April, 1968—substantially the same claims were being made to physicians in Canada for the same product, which there is called Duretic. One ad in which this occurred was published in the *Canadian Medical Association Journal* by Abbott Laboratories Limited. Whether the claims which the parent company had repudiated were carried in other publications and in other countries, a spokesman in North Chicago refused to say.

Other incidents raising ethical questions in the same ballpark have cropped up in hearings held by the Senate Monopoly Subcommittee and troubled its chairman, Sen. Gaylord Nelson (D-Wis.). A recent one concerned indomethacin, a rheumatoid arthritis drug which Merck & Co. sells in the United States as Indocin and elsewhere as indocid. In this country, the FDA has refused to let Merck claim that the drug has been demonstrated to be safe and effective in certain additional medical conditions.

But these same medical conditions are freely promoted as appropriate for Indocid in about 100 other countries. To be sure, a few of these are highly developed Western nations which, it might be fairly argued, could have effective drug regulation if they do not now have it. What especially bothered Nelson, however, was that in countries with no regulation and no significant scientific community, drug promotion can be entirely free-wheeling, with resultant overprescribing at the expense of the health and pocketbooks of innocent patients. In such countries, Nelson asked Merck president Henry Gadsden, "What is your standard of guidance for advertising?"

Gadsden said that his firm's standard "is whatever has been approved by the scientists of Merck as appropriate," and for which evidence has been submitted to the FDA, even if the agency has not been persuaded by that evidence. Nelson did not remind Gadsden of FDA testimony the day before that the agency's counsel was considering whether a criminal prosecution of Merck for misleading advertising of Indocin in the United States should be recommended to the Justice Department. Instead, the Senator said in regard to drug promotion in less-developed countries, ". . . there are lots of companies in this business that might not be as conscientious as Merck . . ."

Surely a difficult and delicate problem is posed. Americans may be uneasy about how American firms promote medicines abroad; they may doubt the wisdom of applying the adage about doing in Rome as the Romans do. But they cannot lightly try to arrogate unto themselves power to tell other countries what to do. Maybe other countries could require as a condition of import that advertising and promotion conform to United States requirements. Maybe it's a problem for the World Health Organization. Maybe even there is no solution.

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[From the Washington Post, Mar. 3, 1968]

LETTER MISLEADING, DRUG FIRM ADMITS

(By Morton Mintz)

For the second time since May, Geigy Pharmaceuticals has conceded that it engaged in a prescription-drug promotion that the Food and Drug Administration criticized as "potentially misleading."

A promotional letter to physicians, the company said, "presented only favorable information" about Persantine, which is used in long term therapy of patients with the intense chest pain known as angina pectoris.

Actually, the firm acknowledged, "there is a substantial body of opinion that does not support the claimed effectiveness" of Persantine, the Geigy brand of dipyridamole. This is one of the drugs marketed before 1962 for which claims of usefulness have been neither approved nor disapproved by FDA, pending an efficacy review by the National Academy of Sciences.

The promotional letter for Persantine claimed that several studies document its effectiveness "in extending walking distance and generally increasing exercise tolerance." The claim was backed up with an enclosure—a reprint of a study reported last March in the Journal of Chronic Diseases.

The claim was knocked down in September, the Geigy Chemical Corp. division has recognized, by a report in the Journal of the American Medical Association. There, telling of a six-month, so-called double-blind study that was designed to eliminate possible bias, two researchers said:

"The study failed to detect a statistically significant difference between the improvement in patients receiving dipyridamole and the improvement in patients receiving a placebo," or inert, dummy pill.

This conclusion was relayed by Geigy in a "corrective letter" sent individually on Feb. 15 to each of the country's prescribing physicians.

Geigy went on to recall that the AMA's Council on Drugs had said last year in its primary publication that double-blind studies comparing dipyridamole with a placebo "have shown equivocal results . . . the drug has not been shown to be effective in the long-term treatment of angina pectories . . .

"Our future promotion will express the range of expert medical opinion on the effectiveness of Persantine when any segment of that opinion" is cited in promotional material, the company said.

The earlier case involved two Geigy prescription drugs used to lower blood pressure. They are Hygroton (chlorthalidone), which the FDA said was misleadingly advertised in MD Medical News Magazine, and Regroton, (chlorthalidone plus reserpine), which was advertised in Circulation Magazine in a way also condemned by the agency.

In the earlier case the firm sent its first "corrective letter." Various firms have sent a total of 21 of them since February, 1967. Had they not been sent, FDA was prepared in each case to seize interstate shipments and announce the action in a press release.

Senator NELSON. We are adjourned subject to call of the Chair.

(Whereupon, at 1:55 p.m., the hearing adjourned subject to the call of the Chair.)

# COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

**TUESDAY, SEPTEMBER 17, 1968**

U.S. SENATE,
MONOPOLY SUBCOMMITTEE OF THE
SELECT COMMITTEE ON SMALL BUSINESS,
*Washington, D.C.*

The subcommittee met, pursuant to call, at 9:40 a.m., in room 318, Old Senate Office Building, Senator Gaylord, P. Nelson (chairman of the subcommittee) presiding.

Present: Senator Nelson.

Also present: Benjamin Gordon, staff economist; James H. Grossman, minority counsel; Elaine C. Dye, research assistant; and William B. Cherkasky, legislative director, staff of Senator Nelson.

Senator NELSON. Today the Monopoly Subcommitee of the Senate Small Business Committee resumes hearings first begun in May 1967 as part of its study of the pharmaceutical industry.

Our primary concern, during the next 4 days of hearings,[1] will be to explore the impact of the drug manufacturers' salesmen, commonly called detail men, upon the prescribing practices of the physician.

A study which appeared in the Canadian Medical Journal in April 1968, the American Medical Association's study conducted some years ago, and testimony before our subcommittee indicated that oral statements by drug manufacturers' detail men, who contact physicians directly, are the most potent force in promoting the use of drugs. Mr. William Goodrich, FDA's Chief Counsel, feels that the FDA has authority over the claims made by detail men under the labeling provisions of the Food, Drug, and Cosmetic Act. The American Law Division of the Library of Congress has a different opinion which I shall insert at the appropriate place in the written proceedings of these hearings.[2]

While section 502 of the act (21 U.S.C. 352) gives the FDA authority over written advertisements, it is not clear whether or not FDA has authority over oral representations. In any case, it would be extremely difficult, if not impractical, to monitor what thousands of detail men say to physicians.

Hence, it is difficult to avoid the conclusion that the representations of the detail men, the most important source of information for the physician, are outside the practical application of our food and drug laws.

How, then, is the public to be protected?

Can salesmen, representing commercial drug interests, be expected to act in the interests of the public?

[1] Testimony for September 18, 19, and 25, 1968, appears in Competitive Problems in the Drug Industry, Part 9.

[2] See p. 3517, infra.

How can we insure that the information the physician receives on drugs via word of mouth conforms with the FDA's requirements on package inserts and printed advertisements of these same drugs?

These are some of the questions we hope to consider over the next several days.

Today, we shall direct our attention to the drug Indocin. On May 3, Mr. Henry W. Gadsden, president of Merck, testified as follows:

(Merck) seeks to make sure that the marketing profile of a drug corresponds in every respect to its medical profile. * * * It is Merck's policy to avoid the possibility of including any questionable statement or theme in any of our advertising or promotion. * * * Our internal procedures require that every piece of advertising and promotion must have the approval of a physician and a lawyer, who are responsible for its medical accuracy and conformity with the law. * * *

Testimony by the FDA indicated that these statements by the President of Merck were not in accord with reality. In fact, the FDA's Bureau of Medicine recommended prosecution of Merck for false and misleading advertising.

It was obvious that Merck's journal advertisement, submitted by the FDA as exhibits, made claims beyond those authorized in the package inserts.

In addition, the Merck Co., according to FDA's testimony on May 2, turned a "Dear Doctor" remedial letter into a promotional piece. FDA then directed Merck to send a second letter to correct the first. This kind of activity on the part of any drug company should not be tolerated by the FDA, and it is difficult, indeed, to conclude that Indocin's marketing profile, as Mr. Gadsden put it, corresponded in every respect with its medical profile.

What have the detail men been telling doctors about Indocin? I suspect that neither the FDA nor any of us here know. We do know, however, that Merck's promotional instructions to their detail men suggested uses not approved by the FDA and this is the subject of today's hearing.

On May 20, 1968, I sent the following letter to the Commissioner of the Food and Drug Administration:

I am enclosing a number of instruction bulletins on Indocin sent to Merck and Company's detail men, apparently by the district supervisor in one of the firm's sales regions.

Without attempting to interpret the law, it appears that these instructions seek to promote use of Indocin which you have not authorized.

It would be greatly appreciated if the relevant officials in your agency would examine these bulletins and send me their comments on the accuracy of the claims made and the effect on medical practice of the selling techniques recommended.

Your cooperation is greatly appreciated.

On June 17 I received an answer from the FDA, which I shall put into the record in its entirety at this point.

(The information referred to follows:)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
FOOD AND DRUG ADMINISTRATION,
*Washington, D.C., June 17, 1968.*

HON. GAYLORD NELSON,
*Chairman, Subcommittee on Monopoly, Select Committee on Small Business, U.S. Senate, Washington, D.C.*

DEAR SENATOR NELSON: This is in reply to your letter of May 20, 1968, enclosing a number of bulletins addressed to Western District Sales Associates of Merck Sharp and Dohme, Division of Merck and Company, Inc.

The Bulletins titled "Profit Improvement Promotional Program—'Indocin,'" are in memorandum form. Their form and contents would suggest that they are internal communications that are not intended to be distributed beyond the control of the firm.

These instructions to the detail force for increasing sales of Indocin recommend methods typical in the promotion of a variety of products with no public health implications. We regard the instructions as seriously misleading.

While there is considerable repetition (which in itself is a promotional tool) throughout the bulletins, the latter can be grouped for comparison into two time periods. For example, Indocin Bulletins 83, 84, 87, 88, 93 and 95 are dated between July 12 and August 4, 1965 (the period of introduction of the drug); and Indocin Bulletins 23, 66, 74, 80 and 85 are dated between April 5 and September 27, 1967.

The 1965 bulletins suggest generally to the detail men that they promote use of Indocin beyond approved indications, and play down side effects and other warnings present in the labeling. Some examples of passages from the bulletin are:

*Unwarranted Extension of Indications*

". . . when there is Heat . . . Redness . . . Swelling . . . and Pain in the muscles or joints . . . 'Indocin' is usually effective."

". . . treatment of the misery inflicted by arthritic diseases."

"Available to relieve pain, reduce fever tenderness and swelling, and increase joint mobility in patients with rheumatic disorders."

". . . *Just Plain* musculoskeletal *Aches and Stiffness* . . ."

In connection with the above, Bulletin 87 contains this admission:

"In fact, our guys are using a real expanded claim for 'Indocin' on inflammation. They are consistently telling their doctors that . . . [as above]"

*Deemphasis of Side Effects, etc.*

"Therapy with 'Indocin' is safer . . . a remarkable record of safety." ". . . Side effects . . . are usually minor and seldom constitute a problem. Usually they can be controlled by simple adjustment of dosage."

"With an extended margin of safety."

In relation to severity of side effects:

"Bothersome is probably as severe an adjective as we can use to describe these effects because in most patients they are tolerable, and transient."

The discussion of contraindications omits reference to the fact that Indocin is not recommended for use in children.

*Special Note*

Most reprehensible and significant in indicating the firm's disregard of the patient is the following passage:

". . . it is obvious that 'Indocin' will work in that whole host of rheumatic crocks and cruds which every General Practitioner, Internist, and Orthopedic Surgeon sees everyday in his practice."

As you know, there were a series of events that occurred between 1965 and 1967 which involved our dealing with the firm regarding their advertising and promotion of Indocin. Merck was cited in regard to Indocin advertising, conferences were held with the firm's management in 1966 and the Assistant General Counsel of the Department spoke publicly regarding the misleading nature of an Indocin advertisement appearing in the *Journal of the American Medical Association*, and elsewhere. With such notice, the firm did take action to correct its forms of promotion which are subject to our control.

Notwithstanding such notice, however, we find in 1967 Indocin bulletins:

The expansion of indications for open-ended uses, "Wherever there is pain, inflammation, and swelling in or around the joint with a resultant limitation of motion. . . ." [The remainder of this sentence mentions the approved indications but in context the listed indications are examples only and do not overcome the suggestion for expanded uses.]

The continued minimization of side effects and warnings, "Most of the adverse reactions which occur with 'Indocin' are common with any antirheumatic drug. They usually are transient, easily controlled, and often disappear on continued treatment." Also, "Gastric irritation can be minimized by giving the dose of 'Indocin' after meals."

While the foregoing comments are examples of things in the bulletins that have been given prominence by repetition or other emphasis, we believe that the

full misleading character of the promotional drive can be assessed only by considering the full text of the bulletins. The setting of substantial quotas and reports of sales suggest that the promotional scheme was successful. The extent to which the sales instructions were followed, or what extrapolation the Merck detail men may have given to the bulletin instructions, in their oral presentations is, of course, unknown to us. But we do know that "Indocin" has been promoted for conditions outside the approved labeling. We have no reason to doubt that the promotional instructions contributed to prescribing of the drug for unapproved uses.

We appreciate your making the bulletins available to us for examination.

Please let us know if we may be of further assistance.

Sincerely yours,

PAUL A. PUMPIAN,
*Director, Office of Legislative and Governmental Services.*

Senator NELSON. But let me quote a few passages from this letter:

The 1965 bulletins suggest generally to the detail men that they promote use of Indocin beyond approved indications, and play down side effects and other warnings present in the labeling. * * *

As you know, there was a series of events that occurred between 1965 and 1967 which involved our dealing with the firm regarding their advertising and promotion of Indocin. Merck was cited in regard to Indocin advertising, conferences were held with the firm's management in 1966 and the Assistant General Counsel of the Department spoke publicly regarding the misleading nature of an Indocin advertisement appearing in the Journal of the American Medical Association, and elsewhere. With such notice, the firm did take action to correct its forms of promotion which are subject to our control. Notwithstanding such notice, however, we find in 1967 Indocin bulletins: The expansion of indications for open-ended uses. * * * The continued minimization of side effects and warnings. * * *

The setting of substantial quotas and reports of sales suggest that the promotional scheme was successful. The extent to which the sales instructions were followed, or what extrapolation the Merck detail men may have given to the bulletin instructions, in their oral presentations, is, of course, unknown to us. But we do know that "Indocin" has been promoted for conditions outside the approved labeling. We have no reason to doubt that the promotional instructions contributed to prescribing of the drug for unapproved uses.

We will hear now from the witness. Our witness this morning is Dr. Robert S. McCleery, Acting Deputy Director, Bureau of Medicine, Food and Drug Administration of the U.S. Department of Health, Education, and Welfare.

Dr. McClerry, we appreciate your appearance here this morning very much, and you may proceed to present your statement. I assume that you would have no objection to interruptions for questions from time to time.

Dr. McCLEERY. No, sir.

Senator NELSON. Please go ahead, Dr. McCleery.

## STATEMENT OF DR. ROBERT S. McCLEERY, ACTING DEPUTY DIRECTOR, BUREAU OF MEDICINE, FOOD AND DRUG ADMINISTRATION; ACCOMPANIED BY DR. B. HARVEY MINCHEW, ACTING DIRECTOR, BUREAU OF MEDICINE, FDA; HARRY CHADDUCK, DEPUTY DIRECTOR, DIVISION OF MEDICAL ADVERTISING, BUREAU OF MEDICINE, FDA; WILLIAM W. GOODRICH, GENERAL COUNSEL, FDA; AND MORTON M. SCHNEIDER, ASSISTANT DIRECTOR, OFFICE OF LEGISLATIVE AND GOVERNMENTAL SERVICES, FDA

Dr. McCLEERY. Mr. Chairman, on May 2, as you mentioned, I appeared before you at your request to discuss our experience with the

advertising of Indocin that had come to our attention. Later, you made available for our review and comment a number of sales bulletins on Indocin.

These bulletins appear to have been sent to Merck detail men by the district supervisor in one of the firm's sales regions. Their form and contents suggest that they are internal communications to the detailing force, not intended for distribution beyond control of the firm.

I would like to add here, Mr. Chairman, for the record, that the following comments are based on the assumption that these are indeed statements by responsible officials of the company, and all I have to say hereafter will be based on that assumption.

Senator NELSON. You are referring to the instructions?

Dr. MCCLERRY. Right.

Senator NELSON. Just so the record will be clear at this stage, a detail man sent the bulletins to us. At the top it says, "To all western district associates from H. Glassner," who is the district manager of that area, and it is these bulletins upon which we raise the questions——

Dr. MCCLEERY. Right.

Senator NELSON (continuing). With the FDA, and it is on these bulletins——

Dr. MCCLEERY. That we are making comments.

Senator NELSON (continuing). That you are making your comments.

Dr. MCCLEERY. Yes, sir; that is correct.

Before dealing with specific features of the instructions to Merck detail men, I should point out that the methods recommended in the bulletins for increasing sales of Indocin seem typical of methods used to promote a variety of products which ordinarily do not have such serious public health implications, as does a drug like Indocin.

And on the whole we regard these sales bulletins as seriously misleading.

Senator NELSON. Doctor, may I interrupt a moment?

If the detail man did, in fact, follow the instructions in the bulletins, he would be making some claims for this drug that were not approved by the FDA; is that correct?

Dr. MCCLEERY. I would say yes.

Senator NELSON. And if the doctor got his information and relied upon the detail man, he would then be using this drug for purposes not approved by the FDA; is that correct?

Dr. MCCLEERY. If he were not only influenced by some of the statements here, but derived a large part of his basis for judgment on the drug, that is why we are saying that they were misleading.

Senator NELSON. You say seriously misleading in your statement.

Dr. MCCLEERY. I did. The extent to which the sales instructions were followed or what extrapolation the Merck detail men may have given to the instructions in their oral presentations are unknown to us. As to the effect of the instructions on medical practice, there seems little reason to doubt that they would contribute to the prescribing of Indocin for unapproved uses.

Mr. Chairman, we found that the bulletins could be grouped for comparative study into two time periods. Six bulletins, dated between July 12 and August 4, 1965, were representative of the group of instructions issued during the period of the introduction of Indocin to the marketplace. Six other bulletins, typical of the second group, were

dated between April 5 and September 27, 1967. This latter group was after we had had discussions with the company's top management about its promotional methods. There was, nevertheless, considerable repetition of the faulty sales concepts throughout the instructions for these two time periods.

In general, the 1965 bulletins, represented by bulletins that we selected out of the total that you submitted to us, bulletins Nos. 83, 84, 87, 88, 93, and 95 suggest to detail men that they promote the use of Indocin beyond approved indications, and play down side effects and other warning information present in the then approved Indocin labeling.

I offer now for the record a copy of the Indocin package labeling that was in effect at the time the 1965 instructional bulletins were sent out to Merck detail men.

Senator NELSON. That will be printed in the record at this point.

(The information referred to follows:)

A.H.F.S. Category: 92:00 Ph. 262301

# INDOCIN®

## (INDOMETHACIN)

INDOCIN* (indomethacin) is a new "anti-rheumatic" drug that has anti-inflammatory, analgesic, and antipyretic activity. It has a unique chemical structure which differentiates it from the salicylates, corticosteroids, phenylbutazone-like compounds, and colchicine. Unlike corticosteroids, it has no effect on pituitary or adrenal function.

INDOCIN is an effective anti-inflammatory agent that is suitable for long term as well as short term use in adult patients of all ages. It has been found effective to relieve pain; reduce fever, swelling, and tenderness; and increase mobility in patients with rheumatic disorders.

### INDICATIONS

INDOCIN has been found effective in the treatment of:

Rheumatoid arthritis
Rheumatoid (ankylosing) spondylitis
Degenerative joint disease (osteoarthritis) of the hip
Gout

In these conditions INDOCIN may often replace other commonly used agents such as corticosteroids, salicylates, phenylbutazone-like compounds, and colchicine.

*Rheumatoid Arthritis*

In many patients with chronic rheumatoid arthritis INDOCIN produces a significant decrease of pain and stiffness within 48 hours, while in other patients treatment must be continued longer before significant subjective relief or objective evidence of decreased joint swelling and tenderness occurs. Treatment with INDOCIN should be continued for at least a month before concluding that it has not produced significant benefit.

When a response to INDOCIN has been obtained, the daily salicylate requirements can usually be reduced and often stopped. Also, if patients have been receiving corticosteroids, the steroid dosage often can be gradually reduced by 25 to 50 per cent, and in some patients it can eventually be completely discontinued. In such instances the steroid dosage should be reduced slowly.

In acute rheumatoid arthritis, or in acute flares of chronic rheumatoid arthritis, INDOCIN will usually produce prompt improvement with relief of pain, tenderness, swelling and stiffness.

*Rheumatoid (Ankylosing) Spondylitis*

INDOCIN frequently produces marked relief of pain and improved motion of the spine within 3 to 10 days.

*Degenerative Joint Disease (Osteoarthritis) of the Hip*

INDOCIN has provided relief of pain and increased range of motion in patients with degenerative joint disease of the hip.

*Gout*

In acute attacks of gout the response to INDOCIN is usually rapid and often dramatic. Marked reduction of pain may be obtained within 2 to 4 hours. Tenderness and heat subside within 24 to 36 hours, and swelling decreases over a 3 to 5 day period.

During the interval phase of gouty arthritis, indomethacin together with adequate doses of a uricosuric agent may provide relief of pain and prevent the recurrence of acute attacks.

### CONTRAINDICATIONS

As with other anti-inflammatory agents, INDOCIN may mask the signs and symptoms of peptic ulcer. INDOCIN itself may cause peptic ulceration or irritation of the gastrointestinal tract. For these reasons it should not be given to patients with active peptic ulcer, gastritis, or ulcerative colitis, and should be used with caution if there is a history of these disorders. In 4 patients with regional enteritis treated for up to one month, and one patient treated for 6 months, INDOCIN was well tolerated. However, in view of the paucity of data, this drug should not be given to patients with regional enteritis until additional evidence of gastrointestinal tolerance is available.

Reproduction studies in mice, rats, and rabbits showed no effect on fetal development or the reproductive cycle, although in rats there was some decrease in fetal viability. Studies in mice demonstrated that INDOCIN crosses the placental barrier. Since the effects of INDOCIN on the human fetus cannot be predicted with certainty from animal studies, the safety for use in pregnant patients has not been established.

Since the experience with INDOCIN in children is limited, it is recommended that this drug should not be administered to pediatric age groups until the indications for use and dosage have been established.

*Registered trademark of Merck & Co., INC.

INDOCIN®
(Indomethacin)

**WARNING**

Patients who suffer from dizziness, lightheadedness, or feelings of detachment on INDOCIN should be cautioned against operating motor vehicles or other machinery, climbing ladders, etc., if these symptoms are present.

INDOCIN should be used with caution in patients with psychiatric disturbances, epilepsy, or parkinsonism, since it may, in some instances, aggravate these conditions.

**PRECAUTIONS AND ADVERSE REACTIONS**

The most frequent adverse reactions associated with INDOCIN are headache, dizziness, lightheadedness, and gastrointestinal disturbances such as nausea, anorexia, vomiting, epigastric distress, abdominal pain or diarrhea. The central nervous system effects are often transient and frequently disappear with continued treatment or with a reduction of dosage. The severity of these effects may, on occasion, require stopping therapy.

The gastrointestinal effects may be minimized by giving the drug immediately after meals or with food.

Studies in normal subjects with radioactive chromate-tagged red blood cells indicate that large doses of indomethacin (50 mg. four times a day) produce less fecal blood loss than average doses of aspirin (600 mg. four times a day). Notwithstanding, INDOCIN may cause single or multiple ulceration of the stomach, duodenum, or small intestine. There have been reports of severe bleeding and of perforation with a few fatalities. Patients may also develop gastrointestinal bleeding with no obvious ulcer formation. If gastrointestinal bleeding occurs, INDOCIN should be discontinued. In many patients with peptic ulceration a history of a previous ulcer was present or they were on concomitant steroids, salicylates, or phenylbutazone. The possible potentiation of the ulcerogenic effect of these drugs cannot be ruled out at present. In some patients there was no history of a previous ulcer and other drugs were not being given. As a result of obvious or occult gastrointestinal bleeding some patients may manifest anemia. For this reason periodic hemoglobin determinations are recommended.

Rare reports where it is not known whether the effects can be attributed to the drug include bleeding from the sigmoid colon, either from a diverticulum or without a known previous pathologic condition, and perforation of pre-existing sigmoid lesions (diverticulum, carcinoma). In other rare cases a diagnosis of gastritis has been made while INDOCIN was being given. One patient developed ulcerative colitis and another regional ileitis while receiving INDOCIN. When INDOCIN was given to patients with pre-existing ulcerative colitis, there was an increase in abdominal pain.

Other adverse effects that have been infrequently reported include drowsiness, tinnitus, mental confusion, depression and other psychic disturbances, blurred vision, stomatitis, pruritus, urticaria, angioneurotic edema, skin rashes, and edema.

Extensive laboratory examinations have been made during treatment with INDOCIN. A slight, usually transient, increase in BUN has been reported in some patients. Although two investigators have reported apparent changes in renal function, the reliability of the techniques used was uncertain. The preponderance of evidence indicates that INDOCIN does not have an adverse effect on renal function. Nevertheless, renal function should be checked periodically in patients on long-term therapy. Patients with pre-existing renal disease have received INDOCIN without difficulty.

A few cases of leukopenia have been reported in patients with rheumatoid arthritis; leukopenia is not uncommon in this disease.

Transient elevations in alkaline phosphatase, cephalin-cholesterol flocculation, and thymol turbidity tests have been observed in some patients and, rarely, elevations of SGOT values. The relationship of these changes to the drug, if any, has not been established.

Unlike steroids, INDOCIN has not been associated with an increased incidence of infections.

As with any new drug, patients should be followed carefully to detect unusual manifestations of drug sensitivity.

**DOSAGE AND ADMINISTRATION**

INDOCIN is available as 25 mg. and 50 mg. capsules for oral use.

In chronic disorders treatment should be started with a dosage of 25 mg. two or three times a day. Starting therapy with low doses, with gradual increases when necessary, will produce maximum benefit and minimize adverse reactions. Always give INDOCIN with food or immediately after meals to reduce gastric irritation.

*Dosage Recommendations for:*

1. *Rheumatoid arthritis and rheumatoid (ankylosing) spondylitis*

*Initial dosage:* 25 mg. two or three times a day. If the response is not adequate, increase the daily dosage by 25 mg. at about *weekly* intervals until a satisfactory response is obtained or a dosage of 150 to 200 mg. a day is reached. If a satisfactory response is

## INDOCIN®
(Indomethacin)

not obtained with 200 mg. a day, larger doses probably will not be effective.

If adverse reactions develop as the dosage is increased, decrease to a tolerated level and maintain at that dosage for 3 to 4 weeks. If an adequate response has not then been obtained, gradually increase the daily dosage by 25 mg. at about weekly intervals to 150 to 200 mg. a day.

For patients with *acute* rheumatoid arthritis or with *acute flares* of chronic rheumatoid arthritis, increase the dosage *daily* by 25 mg. until a satisfactory response is obtained or a total daily dosage of 150 to 200 mg. is reached. If adverse effects develop as the dosage is increased, it should be reduced to a tolerated level for 2 or 3 days and then gradually increased by 25 mg. every few days as tolerated. After the acute phase is under control, it is often possible to reduce the daily dosage of INDOCIN gradually to 75 to 100 mg.

*Reduction of steroid dosage:* Use of INDOCIN often will permit a gradual reduction of steroid dosage by 25 to 50 per cent. In some patients steroids can be slowly discontinued over a period of several weeks or months. The usual precautions should be observed in withdrawing steroids.

2. *Degenerative Joint Disease (Osteoarthritis) of the Hip*

*Initial dosage:* 25 mg. two or three times a day. If the response is not adequate, increase the daily dosage by 25 mg. at about *weekly* intervals until a satisfactory response is obtained or a dosage of 150 to 200 mg. a day is reached. If a satisfactory response is not obtained with 200 mg. a day, larger doses will probably not be effective.

If adverse reactions develop as the dosage is increased, decrease to a tolerated level and maintain at that dosage for 3 to 4 weeks. If an adequate response has not then been obtained, gradually increase the daily dosage by 25 mg. at about weekly intervals to 150 to 200 mg. a day.

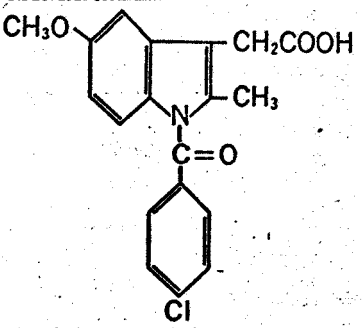
3. *Gout*

*To control acute attacks:* 50 mg. three times a day until all signs and symptoms subside. Definite relief of pain has been reported within 2 to 4 hours. Tenderness and heat usually subside in 24 to 36 hours, and swelling gradually disappears in 3 to 5 days.

*To prevent acute attacks:* During the interval phase of gouty arthritis the dosage may be reduced to as little as 25 mg. twice a day, given with an adequate dose of a uricosuric agent such as probenecid.

### CHEMISTRY AND PHARMACOLOGY

The chemical name for indomethacin is 1-(*p*-chlorobenzoyl) -5-methoxy -2-methylindole-3-acetic acid. It has the following structural formula:




*Anti-Inflammatory Action*

In laboratory animals, INDOCIN is a potent anti-inflammatory compound. Results of granuloma inhibition tests in rats receiving the compound either orally or by local application indicated activity about 85 times that of phenylbutazone. Given orally, the compound was about 4 times as active as hydrocortisone. When given in effective doses to intact rats, indomethacin, unlike anti-inflammatory steroids, did not affect the size of the adrenals or thymus, or retard gain in body weight. Its anti-inflammatory activity does not depend upon activation of the adrenals, since it was fully active in adrenalectomized rats.

The anti-inflammatory activity of INDOCIN was also demonstrated by its ability to inhibit edema formation induced by subplantar injection of carrageenin in rats. By this test, the relative potency of indomethacin was: 30 times aspirin, 20 times phenylbutazone, and 2 times hydrocortisone. INDOCIN does not possess antihistaminic or antiserotonin activity, since it did not affect edema induced by injection of egg white, serotonin, or yeast. Combinations of indomethacin and a steroid were more effective than comparable doses of either drug alone in inhibiting granuloma growth or edema formation.

*Antipyretic Activity*

INDOCIN is an antipyretic in laboratory animals. In rabbits it was about 20 times as potent as phenylbutazone and 10 times as potent as aminopyrine. Its duration of action was much longer than that of aminopyrine and comparable to that of phenylbutazone. In rats indomethacin appeared to be about 10 times as potent as phenylbutazone.

The antipyretic activity of INDOCIN has been confirmed clinically by observations in patients with Hodgkin's disease, acute rheumatic fever, and a variety of other acute febrile conditions.

*Analgesic Activity*

Laboratory tests designed to detect mild analgesic activity indicate that indomethacin is more potent than aspirin or aminopyrine.

INDOCIN®
(Indomethacin)

Ph. 262301

*Absorption and Excretion*

INDOCIN is well absorbed after oral administration in all animals, including man. In dogs, monkeys, rats, and man, peak plasma levels after an oral dose occur within 0.5 to 2 hours. The drug present in the plasma of dog and man is virtually all unchanged indomethacin, but a metabolite (probably the glucuronide conjugate) may be present for the first half hour after intravenous injection in the guinea pig.

The route of excretion is related to the species of animal and is independent of the route of administration or size of dose. Nearly all the compound could be recovered in urine and feces. The rabbit eliminates indomethacin almost entirely in the urine, while the dog excretes nearly all the compound in the feces. The rat, guinea pig, monkey, and man eliminate it by both routes. In man, about two-thirds of the drug is excreted in the urine.

In rabbits, rats, guinea pigs, and monkeys, some indomethacin is metabolized by deacylation or demethylation and the metabolites are excreted in the urine as such or as the glucuronide conjugate. In man, however, no evidence of molecular breakdown has been observed, and virtually all of the material excreted in the urine is indomethacin glucuronide.

## AVAILABILITY

No. 3316—INDOCIN capsules, 25 mg. each, are opaque blue and white, imprinted with an MSD trademark and potency, and are supplied in bottles of 100.

No. 3317—INDOCIN capsules, 50 mg. each, are opaque blue and white, imprinted with an MSD trademark and potency, and are supplied in bottles of 100.

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Merck Sharp & Dohme
Division of Merck & Co., Inc.
West Point, Pa.

Effective May 1965

Printed in U.S.A.

Dr. McCLEERY. The approved package labeling—package insert—includes the allowable claims and the required precautionary and warning information which is to be included in advertisements and promotional labeling of a prescription drug like Indocin.

As you will see, the Indocin package insert limits the use of this drug to four indications: (*a*) rheumatoid arthritis, (*b*) rheumatoid (ankylosing) spondylitis, (*c*) degenerative joint disease (osteoarthritis) of the hip, and (*d*) gout. This labeling indicates that Indocin will relieve pain, reduce fever, swelling and tenderness, and increase mobility in patients with rheumatic disorders. Indocin is a potent drug and, as the package insert shows, it has many side effects, contraindications, precautions, and warnings that must be heeded for its safe and effective use. For these, and other, reasons, it was not approved for use in all rheumatic disorders, but only for those rheumatic disorders I have named.

The Indocin Bulletin No. 83, dated July 12, 1965, is typical of the group of instructions sent out during that time period. So that your committee may consider the bulletins as a group, I am including copies of the group as exhibit B for the record. These were sent out to Merck detail men.

Senator NELSON. They will be printed in the record at this point.

(The information referred to follows:)

BULLETIN NO. 83, JULY 12, 1965

To: All Associates Western District.
From: H. Glassner.
Subject: 'Indocin.'

One of the reasons a real Senior Salesman like John Brekke consistently writes over $300,000 a year is that the physicians in his territory believe him.

Physicians believe John because he tells them a concise, clear story that meets their needs, their wants, their desires, or allays their anxieties. Here is John Brekke's story on 'Indocin'. I'll bet he leads them with this.

"Doctor, I'm certain that in your busy practice no day passes without several patients seeking your help from the misery inflected by painful, reddened, swollen, feverish joints—the classic signs of inflammation.

It is true that short term therapy with 'Decadron' has offered dramatic relief to many of these patients.

However, today, with 'Indocin', a new compound which is not a steriod—you can offer these patients new hope, new vistas of relief from their pain and an extended margin of safety.

More than 300 clinicians both here and abroad have concluded that when there is heat—redness—swelling—and pain in the muscle or joints—'Indocin' is usually effective.

'Indocin' is indomethacin—a modification of the naturally occurring amino acid tryptophan. 'Indocin' is chemically unique. 'Indocin' is not an aminopyrine derivative like phenylbutazone nor is 'Indocin' a steroid.

'Indocin' relieves stiffness, reduces swelling, alleviates tenderness, decreases fever, and above all soothes pain.

The advantages of 'Indocin' are these:

1. Therapy with 'Indocin' is safer. Clinical investigation in thousands of advanced cases has shown 'Indocin' to have a remarkable record of safety.

2. Therapy with 'Indocin' is rapid in onset of action. In many cases—particularly in acute flare ups of gouty arthritis—relief of pain is evident in 2–4 hours.

Usually on therapy with 'Indocin' tenderness and heat subside in 24–48 hours and swelling is reduced in 3–10 days depending upon the severity of the condition being treated.

3. Furthermore, unlike steroids, tolerance to 'Idocin' has not been reported.

4. The dosage schedule with 'Indocin' is simple and uncomplicated. Usual-

ly 1–25mg capsule of 'Indocin' 2–3 times a day taken with meals—does the job.

If necessary 1 capsule per day may be added at weekly intervals up to a maximum dose of 8 capsules per day.

In acute gout, where speed of relief is urgent, 2 capsules of 'Indocin' t.i.d. may be given until the flare up is controlled.

5. Unlike toxic aminopyrine derivatives or steroids, the side effects of therapy with 'Indocin' are usually minor and seldom constitute a problem. Usually they can be controlled by simple adjustment of dosage.

Like all new agents today therapy with 'Indocin' is contraindicated in pregnancy. Other than that the only contraindications to therapy with 'Indocin' are ulcerative colitis, active peptic ulcer and gastritis. These are not unusual since as you know doctor, even aspirin causes some gastric complaints.

The other side effects are not serious. Some patients on therapy with 'Indocin' may experience headache, dizziness, or lightheadedness, and even some minor G.I. disturbances. This effect can be minimized by giving 'Indocin' with meals. Headaches usually disappear after the patient has had a cup of coffee.

Doctor, clearly 'Indocin' represents a giant step forward in the safe and effective treatment of the misery inflicted by arthritic diseases. I'm certain you have in your practice ten or more patients who right now—today—would welcome the dramatic relief 'Indocin' can afford.

Would you like some starter doses of 'Indocine' for those patients whom you want to start on 'Indocin' therapy today? 'Indocin' is now stocked at the pharmacies in this area. You may prefer to call your prescriptions in right now rather than bother or have the patient come in."

There's a detail that clearly should convince the physician that

Whenever the problem is oppressive joint pain associated with heat, redness, tenderness and swelling.

When the muscles around an inflamed joint are in spasm causing a limitation in motion.

Whether the tentative diagnosis is osteoarthritis of the hip, gout, rheumatoid arthiritis, rheumatoid spondylitis, or just plain muscoskeletal aches and stiffness.

For short term use in acute conditions or long term use in chronic diseases.

'Indocin' will afford relief to three out of four patients effectively—with an extended margin of safety—with fewer tables—at less cost—with less doseage adjustment—and therefore fewer problems for both the physician and his patient than any other currently available product.

Unless you've got a better story put together I would suggest you consider using this one. It will sell 'Indocin'.

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BULLETIN No. 84, JULY 14, 1965

To: All Sales Associates in the Western District.
From: H. Glassner.
Subject: 'Indocin.'

Top salesmen reach peak sales ability by training their instincts to think of advantages and benefits. Such men react naturally, instantaneously, and instinctively with maximum selling power to the physicians needs, desires, wants, or fears. Some trainers call this the "hot button approach".

You call on a busy physician. He is thinking about his patients' problems. Only when you give him a glimpse of some advantage he does not now enjoy will he listen.

Charlie Mitchell has done just that with his approach on 'Indocin'. With many years of experience on a regular territory and now with over eighteen months of experience in a specialist-hospital territory Charlie has learned the need for personalizing each presentation. Here are three attention getting hot button individualized approaches he is planning to use.

For the G.P.

Doctor, you do agree that in the treatment of chronic rheumatoid diseases—aspirin is too weak for optimal effect.