COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

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HEARINGS

BEFORE THE

SUBCOMMITTEE ON MONOPOLY

OF THE

SELECT COMMITTEE ON SMALL BUSINESS

UNITED STATES SENATE

NINETIETH CONGRESS

SECOND SESSION

ON

PRESENT STATUS OF COMPETITION IN THE PHARMACEUTICAL INDUSTRY

PART 8

MAY 2, 3, AND SEPTEMBER 17, 1968

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COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

THURSDAY, MAY 2, 1968

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

The subcommittee met, pursuant to recess, at 10 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; Susan H. Hewman, research assistant; Elaine C. Dye, research assistant; and William B. Cherkasky, legislative director, staff of Senator Nelson.

Senator NELSON. We will open our hearings.

Our witness this morning is Dr. Robert S. McCleery, Acting Director of the Division of Medical Advertising of the Bureau of Medicine of the Food and Drug Administration, and Dr. Herbert Ley.

Doctors, we appreciate your coming over here today. Dr. McCleery, you may present your testimony as you see fit. I see you have appended biographical material of your distinguished background. That will be printed in full in the record at the beginning of your statement.

(The biographical material follows:)

BIOGRAPHICAL DATA OF ROBERT S. MCCLEERY, M.D.

1934: A.B. (Summa cum Laude)—Ohio State University.
1934: M.A. (with Highest Distinction)—Ohio State University.
1938: M.D. (with Honors)—Ohio State University.
1938–40: Interne and Assistant Resident—Jackson Memorial Hospital.
1940–42: Assist. Resident in Surgery—Univ. of Minnesota Hospital.
1942–45: U.S. Army Medical Corps.
1945–46: Resident in Surgery—University of Minnesota Hospital.
1946–48: Assistant Professor of Surgery—Ohio State University.
1948–52: Associate Professor of Surgery—Vanderbilt University, and Chief of Surgery, Thayer V.A. Hospital, Nashville, Tenn.
1952–56: Private Practice of Surgery—Great Falls, Montana.
1956–57: Carnegie Fellow, Institute for Advanced Study and Princeton Theological Seminary.
1957–60: Vice President and Medical Director—Burdick & Becker, Inc. (Medical Advertising), New York City.
1960–61: Associate Medical Director—Bristol Laboratories, New York City.
1961–62: Vice President and Medical Director—R. A. Becker, Inc. (Medical Advertising), New York City.
1962–63: Vice President and Medical Director—Sudler & Hennessey, Inc. (Medical Advertising), New York City.
1963– : Bureau of Medicine, Food and Drug Administration.

MEMBERSHIPS

1. Phi Beta Kappa.
2. Alpha Omega Alpha.
3. Sigma Xi.
4. Fellow, American College of Surgeons.
5. Diplomate, American Board of Surgery.
6. Society of University Surgeons.
7. Society for Vascular Surgery.
8. Association of Medical Directors.
9. American Medical Writers Association.

PUBLICATIONS

Research papers in the medical literature—22.

NOMINATION FOR DISTINGUISHED SERVICE AWARD

Name of Nominee: Robert S. McCleery, M.D.
Title of Present Position: Acting Director, Division of Medical Advertising, Office of Medical Support
Organization and Its Location: Bureau of Medicine, Food and Drug Administration, Arlington, Virginia.
Number of Years of Government Service: 12 years.
Number of Years of Service in DHEW/FDA: 5 years.
Previous Grade and Years in that Grade: GS–15 for 2 years.
Previous Grade and Years Held: GS–14 for 3 years.
Other Honors Received:
Phi Beta Kappa.
Alpha Omega Alpha.
Diplomate, American Board of Surgery.
Carnegie Fellow, Institute for Advanced Study and Princeton Theological Seminary.
FDA Award of Merit.
Citation: Dr. Robert S. McCleery is hereby awarded this Certificate for Distinguished Service. Dr. McCleery is the individual within the FDA most responsible for implementing the regulations insuring against faulty prescription drug advertising in the United States.

NARRATIVE STATEMENT

Education:
Ohio State University:
1930–34, A.B. (summa cum laude), Chemistry & Biology.
1934–34, M.A. (with highest distinction), Chemistry.
1934–38, M.D. (with honors).
Princeton: 1956–57, Carnegie Fellow, Institute for Advanced Study and Princeton Theological Seminary.
Honors Received:
Phi Beta Kappa: 1934.
Alpha Omega Alpha: 1938.
Diplomate, American Board of Surgery: 1947.
FDA Award of Merit: 1967.
Work Experience:
Jackson Memorial Hospital 1938–40, Miami, Florida—Intern and Assistant Resident in Surgery.
University of Minnesota Hospital, 1940–42, Minneapolis, Minnesota—Assistant Resident in Surgery.
U.S.A.M.C., 1942–45—Medical Officer.
University of Minnesota Hospital, 1945–46, Minneapolis, Minnesota—Resident in Surgery.
Ohio State University, 1946–48, Columbus, Ohio—Assistant Professor of Surgery.
Vanderbilt University, 1948–52, Nashville, Tennessee—Assistant Professor of Surgery.
Thayer VA Hospital, 1948–52, Nashville, Tennessee—Chief of Surgery.
Private practice of surgery, 1952–56, Great Falls, Montana.

Carnegie Fellow, Institute for Advanced Study and Princeton Theological Seminary, 1956–57, Princeton.
Burdick & Becker, Inc., 1957–60—Vice President and Medical Director of Medical Advertising Firm.
Bristol Laboratories, 1960–61—Associate Medical Director.
R. A. Becker, Inc., 1961–62—Vice President and Medical Director of Medical Advertising Firm.
Sudler & Hennessey, Inc., 1962–63—Vice President and Medical Director of Medical Advertising Firm.
Food and Drug Administration, Bureau of Medicine, 1963 to present, Washington, D.C., and Arlington, Va.—Medical Officer and Acting Director, Division of Medical Advertising.

Present Position: Administers and directs the activities of the Division of Medical Advertising, Office of Medical Support, Bureau of Medicine. Prepares or manages the preparation of advertising critiques involving complex medical features. Analyzes medical advertising and promotional labeling and makes final judgment from the Division's standpoint on the merit of cases to be forwarded for regulatory consideration. Verifies and independently searches the medical literature in relation to advertising and promotional labeling which are based on literature references. Evaluates the merit of cases in the regulatory stage and prepares comments for the assistance of General Counsel and other elements of the government as the cases proceed to completion. Develops policy and programs relating to the functions of the Division. Acts as the Agency's representative in seminars, etc. in presenting the knowledge of the Agency's responsibilities and functions for the education of the regulated industry.

Service or Achievement Which Merits Special Honor:

Dr. McCleery has not only competently performed all aspects of the duties required for the administration and direction of the Division of Medical Advertising, but through his most exceptional ability in dealing with complex medical issues in relation to advertising and his keen analytical ability, has contributed largely to the development of basic Agency principles on which advertising may be evaluated within the scope of the law and the regulations.

Dr. McCleery pioneered in bringing the first case under the advertising provisions of the Federal Food, Drug and Cosmetic Act to successful conclusion. In the Pree-MT case against Wallace Laboratories, which was initiated through critiques of journal advertising prepared by Dr. McCleery, the firm pleaded nolo contendere and was fined $1000 on each of two counts in a criminal information.

In the Peritrate-SA case, which was initiated by Dr. McCleery, and which involved a most exacting analysis of complex advertising copy, a shipment of the drug based on misbranding through advertising was seized in 1966.

Also, in 1966, the case against Serax was terminated through seizure of a shipment allegedly misbranded by advertising of the drug. Dr. McCleery's efforts in preparing the basis for seizure contributed largely in the successful completion of the case.

Dr. McCleery presented two other critiques in 1966 that resulted in seizures involving Lincoln and Lasix. Further, he sponsored action leading to the correction of many monographs in the Physicians' Desk Reference, the most important single reference book for physicians.

Dr. McCleery conceived a unique remedy for dealing with misbranding situations involving advertising or promotional labeling in the form of a "remedial letter." Early in 1967, Dr. McCleery's concept was reduced to practice. Sponsoring rapid action, Dr. McCleery presented a critique on initial advertisement for Ortho-Novum-SQ, the first advertisement for the product published after the drug was approved for marketing. Dr. McCleery's critique, charging that the ad failed to include a true statement of effectiveness of the product, resulted finally and rapidly in issuance of a "Dear Doctor" letter by the firm to other 200,000 practicing physicians in the United States.

Dr. McCleery had provided detailed guidance and counsel to the members of his staff in achieving greater effectiveness of the group in their development of critiques, searching the literature, analysis of advertising copy, etc. He has consulted in relationship to the evaluation of references, which entailed personal and independent study in many instances. For many months Dr. McCleery was the only medical officer exercising the duties of his unit. He has devoted many hours of overtime daily in keeping cur-

rent with the work of his Division. As a result of his personnel untiring efforts, the Division has not been in a backlog position on referred assignments.

The above summary of Dr. McCleery's accomplishments through 1966 was largely instrumental in his being granted the FDA Award of Merit in 1967.

Beginning early in 1967, his personal participation and direction of the Division of Medical Advertising led to even greater demonstration of his effectiveness in bringing advertising and promotions of prescription drugs into compliance with the requirements of the Act.

Evidence of his success in accomplishing the mission of his Division is represented specifically in the following examples. Following the introduction of the "remedial letter" concept which corrects faulty advertising of prescription drugs, the efforts of Dr. McCleery in the areas of preparation of critiques, in participating in meetings held between the Commissioner, FDA officials and representatives of drug firms and in the development of detailed drafts of "Dear Doctor" letters, have resulted in the issuance of 20 such letters by manufacturers to all practicing physicians in the United States.

Conservatively, a total of over 4 million remedial letters have been mailed to physicians as a result of action initiated by Dr. McCleery. Copies of the 20 letters are attached to show the nature and extent of the corrections involved.

While some of the "remedial letters" involve corrections of monographs in the Physicians' Desk Reference (a comprehensive reference book used by physicians), Dr. McCleery directed the activities of his group in analyzing monographs in the book and initiating various other actions leading to correction such as issuing letter and telephone calls to firms requesting correction, participating in conferences with firms on specific problems, etc.

During the period January 1, 1967 to date over 150 corrective actions have been initiated by Dr. McCleery. In addition to "Dear Doctor" remedial letters, there have been about 93 meetings with industry representatives, 35 requests made to firms for corrective actions, one seizure (Indoklon), four prosecutions, and support given in 33 cases. Approximately 245 monographs in the Physicians' Desk Reference, and 138 prescription drug advertisements were reviewed and assessed as forerunners to remedial consideration.

In the support of cases forwarded for prosecution consideration, Dr. McCleery personally participated in citation hearings as well as in one judicial proceeding. In the latter, Dr. McCleery's testimony was considered to be largely instrumental in the success of the Government in obtaining a nolo contendere plea from the defendant and a resultant fine.

In addition to matters involving regulatory attention, Dr. McCleery provided written advice in voluntarily submitted promotional materials or other inquiries in over 80 instances.

On May 23, 1967, proposed revisions in the advertising regulations were published in the *Federal Register*. Dr. McCleery's participation in providing the basis for policy and language of those proposed regulations was a contribution of paramount importance.

Dr. McCleery's contributions to the mission of the Agency and the Department have been broadly recognized in the public press. A selection of copies of accounts in the press are attached to show the public impact of the efforts of Dr. McCleery.

The Food and Drug Administration's responsibility in the area of prescription drug advertising is a recent one. Since the passage of these regulations in 1962, Dr. McCleery has been the individual most responsible for stimulating the efforts of the Bureau of Medicine in the implementation of these regulations.

Senator NELSON. I assume you have no objection to being interrupted by questions from time to time?

Dr. MCCLEERY. No, sir.

Senator NELSON. Please, go ahead, Doctor.

STATEMENT OF DR. ROBERT S. McCLEERY, ACTING DIRECTOR, DIVISION OF MEDICAL ADVERTISING, BUREAU OF MEDICINE, FOOD AND DRUG ADMINISTRATION; ACCOMPANIED BY DR. HERBERT L. LEY, DIRECTOR, BUREAU OF MEDICINE, FDA; AND WILLIAM W. GOODRICH, GENERAL COUNSEL, FDA

Dr. McCLEERY. Mr. Chairman, I appreciate this opportunity of appearing before you this morning to discuss our experience with the advertising of Indocin.

Shortly after Dr. Goddard became Commissioner of Food and Drugs, in early 1966, the agency's interests in prescription drug advertising were sharply accentuated. It was felt that manufacturers had had time enough to adjust to new requirements concerning advertising. Dr. Goddard spoke to the presidents of pharmaceutical firms, to their medical directors and to their advertising agencies to note what we regarded as a continuation of advertising abuses that had been so largely responsible for the enactment in 1962 of the Kefauver-Harris drug amendments and the promulgation in 1964 of the first advertising regulations.

Senator NELSON. Doctor, do you have any examples that you would like to give us of what you consider to be advertising abuses, in addition to those you have already mentioned?

Dr. McCLEERY. The case we are describing today is in our view a case typical of some of the major abuses. We could submit for the record the actions we have taken against drugs in the past in terms of the use of the sanctions for criminal prosecutions—the use of seizure of products for bad advertising and for a large number of "Dear Doctor" remedial letters which have been sent, roughly 20 in number.

Senator NELSON. I would like to have the examples you referred to.

Do I understand you to say that the case you are talking about today is quite typical of other instances that you have of the same kind of advertising abuses?

Dr. McCLEERY. Well, in some sense, yes, in that it contains a number of faults which are common to many other ads against which we have acted, and these were present during the introduction and the subsequent advertising of the drug under your interest here today.

Senator NELSON. The point I am interested in having clear for the record is whether or not this is an isolated case, or whether it is a general problem that you have to deal with.

Dr. LEY. Senator Nelson, may I suggest that we submit for the record the examples of what the FDA considered misleading advertising which were presented in October of 1966 by Mr. Goodrich, and secondly, a file of "Dear Doctor" letters stimulated by the FDA over the past year. I believe this will set the picture in proper perspective.

Senator NELSON. All right. If you would submit that for the record.

(The material to be furnished for inclusion in the record follows:)

THE STATE OF THE LAW AND COMPLIANCE*

(Address of William W. Goodrich, Assistant General Counsel, Department of Health, Education, and Welfare, Washington, D.C.)

Three years have passed since FDA first entered the world of prescription drug advertising.

We are more intrigued with what we see today, than we were by our first viewing. To borrow a quote: "We are reading more now and enjoying it less."

*Presented at "A Morning With FDA," Pharmaceutical Advertising Club, Roosevelt Hotel, New York City, Oct. 20, 1966.

And we are more convinced than ever that there is much room for needed improvement.

Getting to know you is a refreshing experience. It has been said of you that you have a unique ability to make a virtue out of a serious side effect.

The Kefauver investigations highlighted many excesses in drug promotion. But they suggested no remedies. The Executive Branch's first reaction was to strengthen the Federal Trade Commission Act. But the Congressional response was to require stronger control under the Federal Food, Drug, and Cosmetic Act. Instead of orders to cease and desist, new sanctions of seizure, injunction and criminal penalties were provided to do this job.

While the legislative developments were fast moving—and the legislative history is relatively thin—the message was loud and clear that there had to be some basic changes in this phase of drug promotion.

President Kennedy recommended—and the Congress enacted—provisions intended to "help assure the American people . . . that the promotional material [for Rx drugs] tells the full story . . . [the] possible bad effects as well as the good—and the whole truth about therapeutic usefulness."

This is the guideline that controls our operations.

The only concession made for the special needs of advertising was that the essential information might be presented "in brief summary". This requires the presentation of information in your ads which will fairly show the effectiveness of any drug, along with any side-effects, contraindications, precautions and warnings, in a form that is brief but neither false nor misleading. The central idea is to be sure that the message that comes through to the profession strikes a proper balance in telling what the drug is for, what the limitations are upon its usefulness, and what hazards may attend its use.

Lest there be any question as to precisely what is required—the law provides that every prescription drug advertisement and any other descriptive matter issued to promote sales shall contain a true statement of—

The formula;

The established name of the drug along with the trade name;

And "such other information in brief summary relating to side effects, contraindications and effectiveness as shall be required in regulations" issued by the Secretary.

Preclearance of ads is not required except in extraordinary circumstances. The Department was authorized to specify which promotional material is labeling (requiring full disclosure) and which is advertising (requiring the brief summary).

The regulations applicable to ad content were promptly issued—but only after a confrontation with both the pharmaceutical industry and the medical profession. Both professed to believe that advertising was not educational—that it served only a reminder role—and played no part in the physician's choice of drugs when be began to write on his prescription form.

We took the more realistic view that if advertising does not sell drugs it will not continue to run.

Therefore, the major issue requiring resolution was whether the regulatory controls would extend to the entire ad—or just to the little part that the advertiser might designate as the "brief summary."

Resolution of that issue was accomplished by final regulations, supplemented by a memorandum of understanding about their intent. The whole ad was controlled.

The regulations themselves are simple indeed. They were offered as the first step in public supervision of this very vital means of communication between the drug producer and the medical profession. The controls were not set in concrete; they can and will be improved as the need appears. To that end, we are announcing new proposals that would require that all new promotions—both advertising and labeling—to be submitted as soon as they are developed for use.

In essence, our current regulations require—insofar as the selling part of the ad is concerned—four things:

A fair summary of the effectiveness of the drug in the conditions for which it is offered, along with all of the side effects, contraindications, precautions, and warnings applicable both to the conditions for which the drug is advertised and for which it is commonly prescribed:

A fair balance in presenting the information on effectiveness and the related information on side effects, etc.;

A reasonably close association of the information on effectiveness and the information on side-effects, contraindications, etc., together with a discussion of the adverse data in the same degree of prominence that is achieved for the claims of effectiveness;

> And the use of only those promotional claims which have been approved in advance upon the clearance of the drug for the market as a "new drug" or as a certified antibiotic, or, for drugs that required no preclearance, claims of effectiveness that are generally recognized as true or which are supported by substantial evidence, consisting of adequate and well-controlled investigations or adequate clinical experience on the basis of which it can fairly and responsibly be concluded that the drug will have the effectiveness claimed.

This is not a very big order.

Simply stated, drugs may be promoted only on the basis of proven effectiveness.

The total advertising message must be fair and frank in discussing both the usefulness and the hazards that may attend the administration of the drug.

And the layout of the ad must deal fairly with the scientific data that underlies the message.

As Dr. Goddard said in his Chicago speech to the Midwest PA Club, we have difficulty in understanding how a group of creative people with the talents you so regularly display should have any difficulty at all in understanding the advertising restrictions of our regulations.

"Fair balance", "reasonably close association", and the "same relative degree of prominence" are words of ordinary English.

No more inflexible words were used because the Agency wanted to move with the drug industry and the creative people in correcting what was an indefensible state of drug promotion.

If these concepts in the present regulations seem perplexing—we offer the memoranda of understanding which passed between us and the industry back in October, 1963. And we offer also a statement we made public in 1964 calling attention to the most common failings in drug promotion. More recently, at the medical section meeting of the Pharmaceutical Manufacturers Association on March 30, 1966, we described in great detail the basic premises underlying our evaluation of advertising and promotional labeling.

Bearing in mind Ben Franklin's comment that "Laws too gentle are seldom obeyed; too severe, seldom executed", we are preparing to move the informal comments in the memo of understanding and in the policy announcement into the positive provisions of regulations. And we will continue to examine the performance of all advertisers under our rules, so that misunderstanding and noncompliance can be promptly corrected.

With this background as to the state of the law, let's turn to the state of compliance by examining a few cases of actual performance.

Remembering that "all things that hurt, instruct", I apologize in advance for any injured feelings that may flow from a critical examination of some examples of your most recent work.

We would like to view with you the ads for the "big eight"—all of the eight new 1965 model drugs that entered the list of the 200 most prescribed during the first years of their introduction.

They are:

Aventyl—Eli Lilly
C-Quens—Eli Lilly
Indocin—Merck Sharpe Dohme
Lincocin—Upjohn
Oracon—Mead Johnson
Pediamycin—Ross
Pre-Sate—Warner Chilcott
Tegopen—Bristol Laboratories

Without implying that there has been a complete medical work-up as to the validity of all of the advertised claims for these drugs, I can say that I asked our medical staff—including some of the physicians who were primarily responsible for the clearance of the drugs for market—to comment on some current ads for these important new offerings of the pharmaceutical industry.

Here are the results.

"No doubt, this ad will sell huge amounts of Aventyl. It is pretty, impressive, and seems to pack quite an emotional wallop. However, the term 'behavioral drift' doesn't appear to be more than a Madison Avenue description. It certainly is not a bona fide psychiatric diagnosis.

"It is, from the ad, difficult to tell in the first 4 pages, whether Aventyl is primarily an anti-depressant, primarily a tranquilizer or what.

* * * * * * *

"The first sentence under side effects in both the ad and the package insert states that 'No single side effect can be considered as occurring frequently * * *.'

This could lure the unsuspecting physician into not looking much further. While the incidence is mentioned later of the common side effects, it's a bit too late.

* * * * * * *

"All in all, the sins in this ad are those both of omission and commission. They include poor arithmetic, poor terminology, invention of psychiatric terms, and an overwhelming intent to 'snow' the practicing physician."

As the medical officer's comment shows, we share the responsibility for some of the defects in this ad, because we approved the package insert. That does not make the ad any better.

Aventyl was offered for a new psychiatric disorder, discovered right here on Madison Avenue. While this makes excellent ad copy, it does not promote the drug for the conditions for which it has been approved. Instead, it uses a new catch phrase to cover a host of "target" symptoms, so that the drug is indicated and prescribed for the ordinary frustrations of daily living to reach a much larger patient population than the scientific data will support.

C–Quens and Oracon were approved as new sequential oral contraceptives.

The central theme of the ad for Oracon is that is is safer than and superior to other oral contraceptives because it is so close to nature—that it is physiological, nautral, and normal.

These claims are unsupported by scientific facts. Thus far, there is no substantial evidence that any oral contraceptive is either more effective or safer than any other that has been approved for the market.

This ad also make a point that Oracon was "the first sequential oral contraceptive". It fails to inform the physician that it was approved only 13 days before C–Quens. The apparent purpose of the claim is to bolster the asserted, but unsupported, superiority.

The theme of the ad for C–Quens is directed to a single side effect of the oral contraceptives—weight gain.

The claim that women using sequential oral contraceptives experience less significant weight gain is ungrounded in scientific fact, and the ad is thus misleading in its major implication. Yet, it may serve its purpose of influencing the physician to shift a patient to this product on the basis of this illusory promise.

This ad, like the one for Oracon, claims "other advantages of therapy"—presumably less side effects, and this is bolstered by a claim that it contains "the smallest amount of hormone substance". The latter claim is literally false, and the claim of lower incidence of side effects has no scientific support.

The truth about the oral contraceptives is reported in an FDA publication, available from the Government Printing Office. It is that there is no adequate scientific data, at this time, proving these compounds unsafe for human use. There are nonetheless some very infrequent but serious side effects and some possible theoretic risks suggested by the experimental data. The physician must decide for his patient whether to accept the risk—small though it may be. And the Committee which advised us said: The physician "can do this wisely only when there is presented to him dispassionate scientific knowledge of the available data."

We leave with you the question whether these two ads present the physician with "dispassionate scientific knowledge".

Indocin has been marketed for slightly more than one year. Like most new drugs offered to replace established products, this one was offered as safer and more effective. As new experience with the drug has been gained, more side-effects have been noted and more warning information has been required. Only a few days ago, the sponsor mailed a new revised brochure to the profession, with new cautionary information in heavy print. Yet the current ad continues the headline "extends the margin of safety in long term management of arthritic disorders".

There is not yet enough experience to support the claim for greater long-term safety. To the contrary, the longer the drug is used the more side-effect information appears.

This ad quotes authoritative sources, without the full impact of the actual articles. And it uses one reference which is from a 2-inch abstract, apparently of a 1964 speech. This latter reference is used to support a claim for "ankylosing spondylitis", but the ad does not inform the reader that this same abstract also states "Excellent results have also been obtained in some cases of rheumatoid arthritis . . . there have been striking failures as well."

The claim for gout is not supported by the package insert or by the scientific data.

And, finally, the "Brief Summary" omits some very important warning information that is required in the package insert—and thus in the ad.

As a side-light on this drug, it was featured in the July issue of "Pageant" magazine 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 was user testimonials which, according to the article, were made available to the writers by the sponsor of the drug.

Lincocin is a new antibiotic entry among the 1965 models.

The ad to promote the drug is highly competitive in comparing the ease of use and the absence of some side effects expected from the established antibiotics. It is "practically painless on injection", unlike older intramuscular tetracyclines; it "does not share antigenicity with penicillin"; it has "no serious renal or neurologic abnormalities" and "no ototoxicity", unlike streptomycin or kanamycin.

Yet after such elaboration on what side effects the drug does not have, the ad obscures the most important information that the physician needs in using this drug—that hematologic toxicity can occur, and that the frequency of severe diarrhea is a unique feature of Lincocin therapy.

Pediamycin was another 1965 model antibiotic. It was featured as being especially safe for infants, but no substantial evidence existed to support the claim. And the range of its usefulness was exaggerated.

Tegopen was the final entry on the 1965 list of antibiotic drugs. The headline was "This is a new every-day penicillin for common bacterial respiratory infections".

Plainly this was to encourage indiscriminate and routine use of a drug that was approved for use primarily against penicillin resistant staph infections.

The brief summary failed to communicate the real message that it is important to identify the infectious organism and to shift to regular penicillin when the organism is later found to be senistive to penicillin G or V.

The artwork, layout, and design of the ad was to impress the reader with the frequency with which Tegopen can be used, and not to carry the real message which the approval of the drug intended.

Pre-Sate is a new drug for the treatment of an impossible condition to treat—overeating and overweight. It is, we believe, the consensus of medical opinion that there are no true anorexiants, and that dieting is the only answer to obesity.

This attractive ad is an admirable effort to crack this attractive market. While page 6 emphasizes the essential need for concurrent diet control, the total message is that Pre-Sate is a drug of superior efficacy in reducing body weight. Statistical data is offered to prove the superiority of this drug over its established competitors. Animal data are used to support the claim that the mechanism of its action has been established.

But the claims of superiority and that it acts on the human satiety center of the hypothalmus are not scientifically established.

It is generally assumed that the 1962 Amendment did not control "relative efficacy", but ads which make claims of that kind are subject to critical review and proof that the Company's claims of superior effectiveness are well founded.

This ad appeared about the time of the Peritrate seizure. We are pleased to note improvements in later presentations.

Advertising prescription drugs should be a very special operation—wholly unlike advertising the 1967 model automobiles or the tars and nicotine of cigarettes. It should be based on the scientific data that allowed the drug to enter the market—you need look and can look no further than the official brochure for the allowable claims and the required warnings. As tempted as you may be by a new piece of investigative work that may be whispered to you to mount a new campaign to capture an entire market, you must remember that the approved claims are the limits beyond which promotion cannot go.

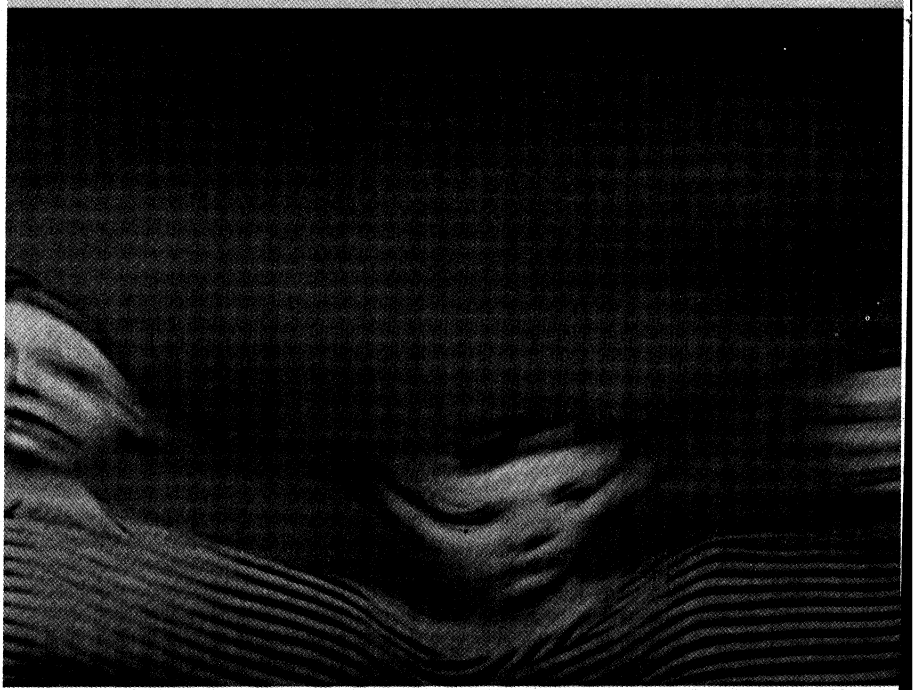
And in promoting newly developed and approved drugs, claims of greater safety and comparatively greater effectiveness can be made only on proven data—and then only with complete awareness that the limited experience with the drug accumulated during its investigational clinical practice; that clinical experience must be followed very closely and that ad campaigns will have to change as rapidly as clinical experience may require.

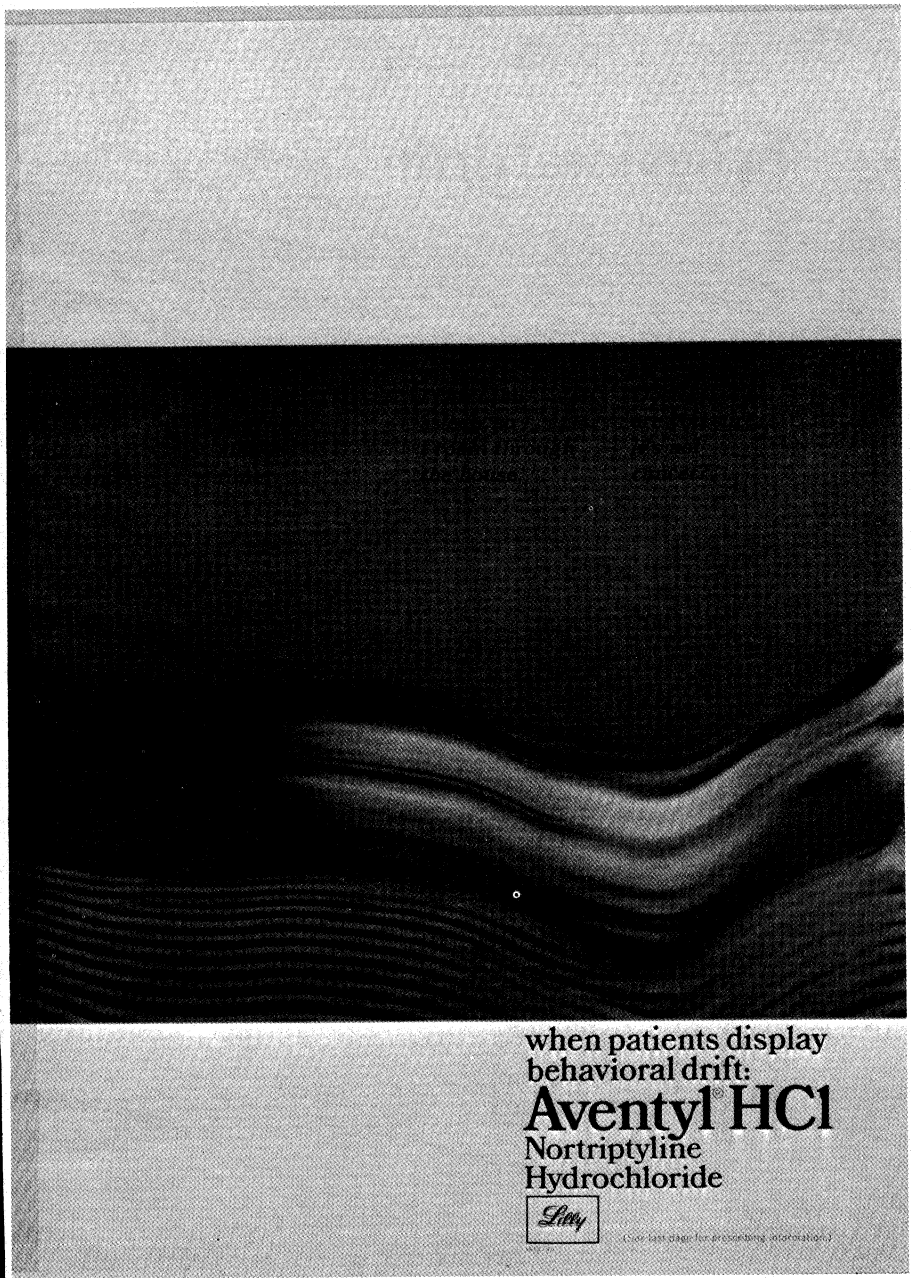
Please remember the thoughts that prescription drug advertising can go no further than the scientific support which sustains its approval for marketing; that you have an obligation in developing ad copy to tell the whole truth—good and bad; and that the entire advertising message must be designed around these basic ideas.

If the advertising copy for the "big eight" is typical of what is going on, Madison Avenue's new disease of "Behavioral Drift" is out of hand. Perhaps it can be cured by the placebo of talk, but more likely some stronger medicine will be necessary.

[From Journal of American Medical Association, Sept. 19, 1966, pp. 52–56]

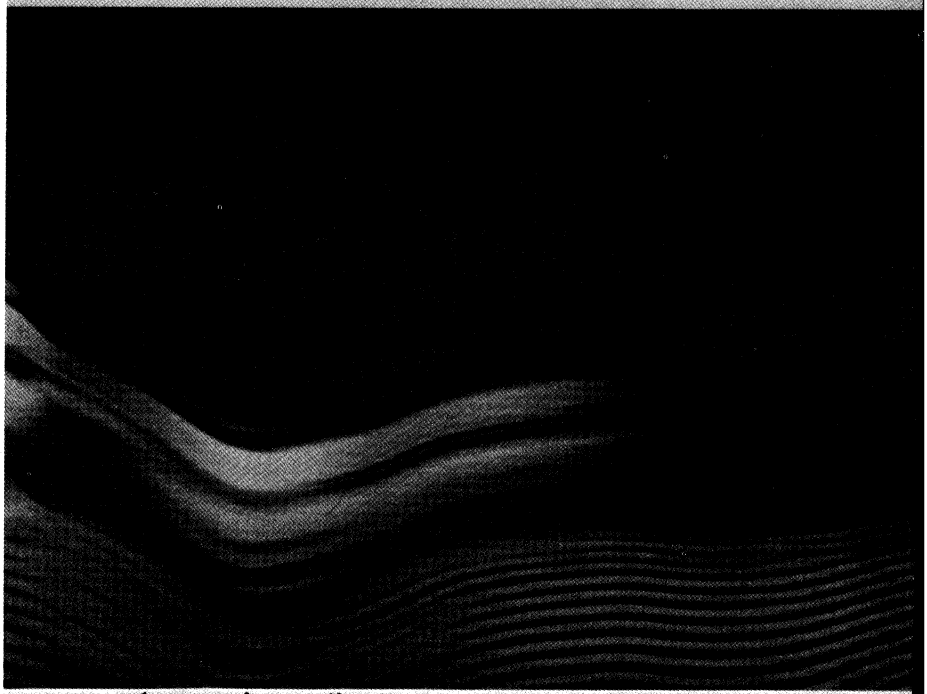
behavioral drift: the fluctuating symptoms of the patient's emotional problem ... Many emotional disorders are composed of a complex admixture of symptoms from both sides of the emotion spectrum. "Symptoms may change from time to time, waxing or waning under the complications of ever-changing situations of daily life... To the clinician this means that the same patient may present a varying constellation of complaints..."[1]




when patients display
behavioral drift:
Aventyl HCl
Nortriptyline
Hydrochloride
Lilly
(See last page for prescribing information)

behavioral drift:

When the true range of usefulness of Aventyl HCl was evaluated, common presenting complaints were used as a measure of therapeutic effectiveness. As the bar graph shows, regardless of the side of the norm from which these symptoms originated, Aventyl HCl produced a high degree of satisfactory response.



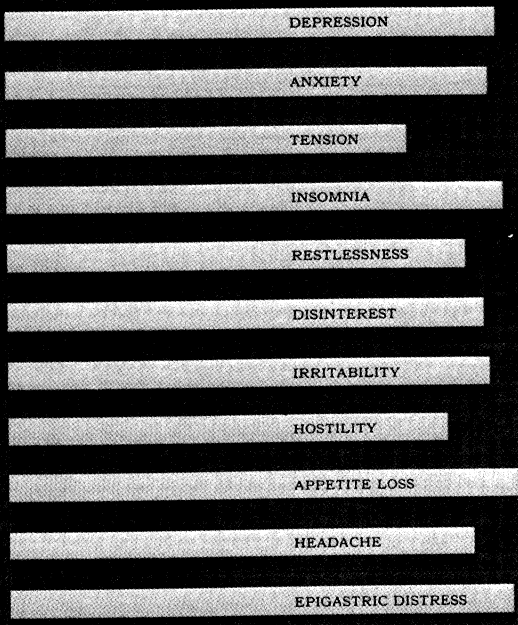
when patients display
behavioral drift:
Aventyl® HCl
Nortriptyline
Hydrochloride

Lilly

000796

Three years of clinical observation confirm effectiveness of Aventyl HCl in a variety of symptoms and emotional problems[2]

In 1,888 patients treated with Aventyl HCl, an over-all favorable response was seen in nearly 80 percent.[1]



A single-entity agent with biphasic antidepressant-antianxiety activity

(See next page for prescribing information.)

An immediate effect and a rapid over-all response

Prompt tranquilization occurs and provides evidence of initial improvement in some patients. In others, an immediate stimulatory effect is observed. Generally, a peak is rapidly reached and is soon followed by lasting over-all improvement.

Of those patients who responded to Aventyl HCl, 50 percent improved within one week, 79 percent by the second week, and 94 percent within one month.[2]

Well-tolerated therapy

Unwanted effects appear to be milder and less frequent than those produced by certain other antidepressants. Studies indicate Aventyl HCl has considerably less anticholinergic activity than certain of its predecessors.

In contrast to some tranquilizers, Aventyl HCl has not been reported to cause either habituation or withdrawal symptoms.

1. Cahn, R.: Guidelines for Undrecreasing Emotional Disorders, M. Times 97:982, 1969.
2. From data available through the Lilly Research Laboratories.

when patients display behavioral drift:

Aventyl® HCl

Nortriptyline Hydrochloride

Lilly

Additional information available to physicians upon request.
Eli Lilly and Company
Indianapolis, Indiana 46206

Actions and Indications: Aventyl HCl is a notably well-tolerated and effective agent for the treatment of mental depression, anxiety tension states, and psychosomatic disorders and for use as an adjunct to psychotherapy.

Contraindications: Concomitant use with a monoaminoxidase inhibitor is contraindicated, since potentiation of adverse effects can be serious—even fatal. The monoaminoxidase inhibitor should be discontinued for at least ten to twenty one days before treatment with Aventyl HCl is started.

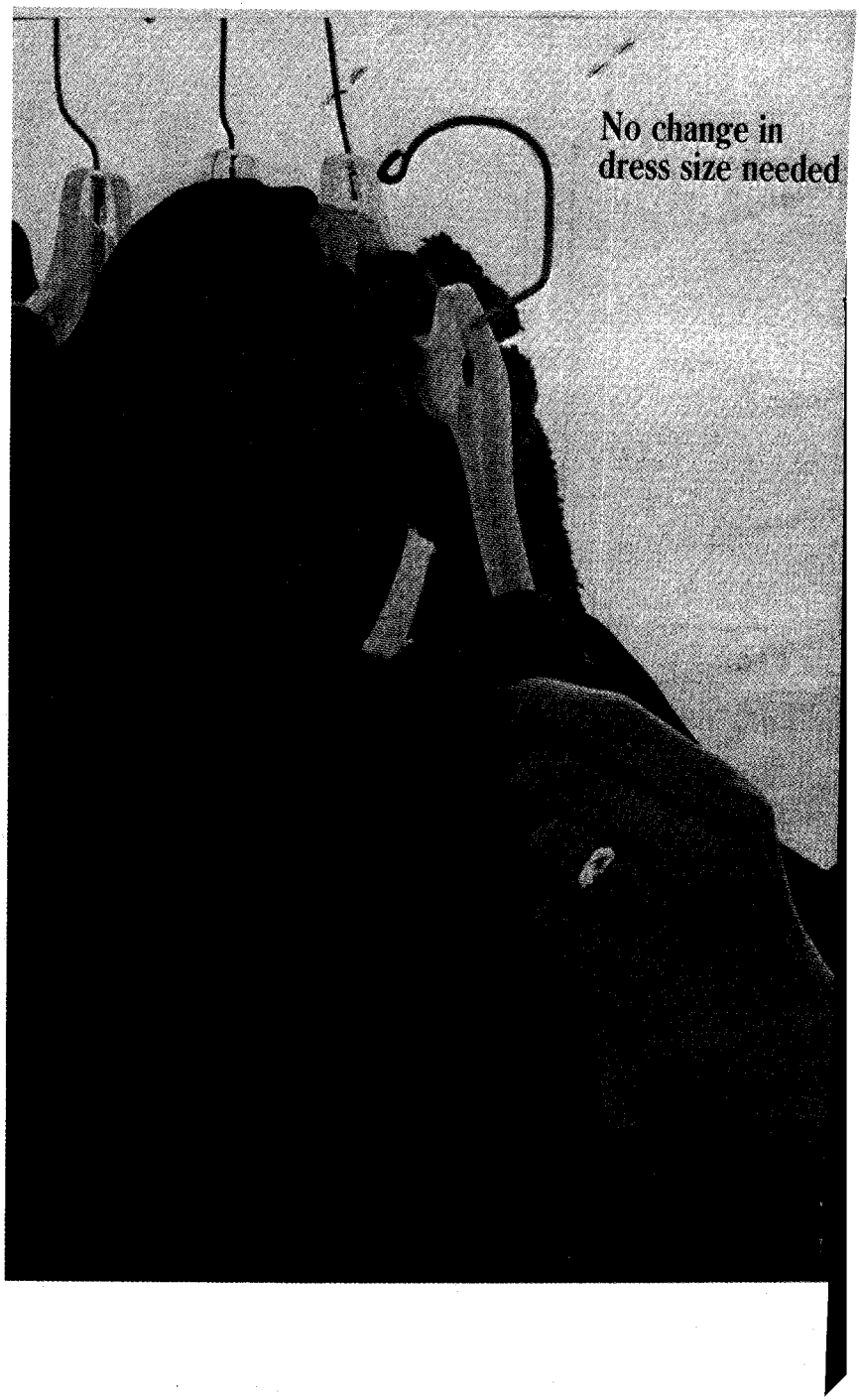
Warnings: Use in convulsive or hypotensive states should be closely followed. At present, data are insufficient to recommend use of Aventyl HCl during pregnancy. The possibility of a suicidal attempt in a depressed patient should always be considered. Although there have been no reports of bone marrow damage or other serious effects, careful observation of the patient and periodic laboratory studies are recommended as with all new medications.

Precautions: Because of its anticholinergic activity, Aventyl HCl should be used cautiously in patients with glaucoma or in those having a propensity for urinary retention. Care should be employed when Aventyl HCl is given in conjunction with sympathomimetic drugs. Its use in hypnonarcosis along with intravenous hexobarbital methamphetamine for severe anxiety has resulted in a higher than usual incidence of side effects. As with similar drugs, it is advisable to observe for epileptiform seizures during the initial phase of treatment.

Side-Effects: No single side-effect can be considered as occurring frequently, and most are mild and transitory. Dry mouth was noted in 26 percent of patients; drowsiness in 11 percent. The following were seen occasionally (in 6 to 10 percent): constipation, dizziness, tremulousness, confusional state, restlessness, weakness, and blurred vision. Side effects rarely noted (in 1 to 5 percent) were epigastric distress, sweating, peculiar taste, fatigue, weight gain, weight loss, insomnia, headache, paresthesia, nausea and vomiting, rash and itching, and delayed micturition. Miscellaneous side-effects were reported in less than 0.5 percent. There have been no reports of habituation or of withdrawal symptoms. No potentiation or increased incidence of side-effects was observed when Aventyl HCl was used together with tranquilizers, other antidepressants (except MAO inhibitors), oral stimulants, sedatives, hypnotic preparations, and standard drugs given for primary medical disorders.

Dosage: Most adults respond well to 25 mg. three times daily, but the dose should be adjusted to the needs of the patient. Usual dosage range (in divided doses):
Adults—20 to 100 mg. daily.
Children—10 to 75 mg. daily (1 to 2 mg. per Kg. of body weight).
(See package literature for complete dosage information.)

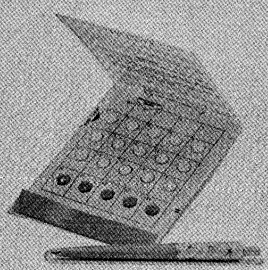
[From Medical Economics, Sept. 19, 1966, pp. 34–36]



with her sequential
oral contraceptive
Weight gain, a troublesome side-effect with combination agents, is not a major problem with C-Quens for possibly two reasons:
• C-Quens does not produce the state of pseudopregnancy observed with combination products.
• The progestational component of C-Quens does not exhibit the anabolic effects noted with some testosterone derivatives.
C-Quens®
Lilly
Sequential folder containing fifteen 80-mcg. tablets of mestranol plus five tablets each combining 80 mcg. mestranol and 2 mg. chlormadinone acetate.
60773

Other advantages of therapy with C-Quens

minimal spotting and breakthrough bleeding
low incidence of nausea
a menstrual cycle approaching the normal
the smallest amount of hormonal substance



Description: Each folder of C-Quens consists of fifteen tablets of an estrogen (mestranol, 80 mcg.) and five tablets containing the estrogen (mestranol, 80 mcg.) plus a progestational agent (chlormadinone acetate, 2 mg.).

Action: The mode of action of C-Quens is to suppress ovulation through inhibition of pituitary gonadotropins.

Indication: C-Quens is intended for use as an oral contraceptive.

Effectiveness: Both C-Quens and the combination products are considered to afford virtually 100 percent protection when taken as directed.

Contraindications: C-Quens is contraindicated in any patient with undiagnosed vaginal bleeding, known or suspected pelvic or breast malignancy, or a history of cerebrovascular accident. Until more information is available, pre-existing hepatic disease or prior thrombophlebitis or other thromboembolic phenomena should be considered contraindications to the use of C-Quens.

Warning: Discontinue medication pending examination if there is sudden, partial, or complete loss of vision or if there is a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Precautions: Like any new drug, C-Quens should be given with caution to patients with a previous history of drug, food, and contact allergies. Before C-Quens is used, a thorough physical examination should be given, with special attention to the breasts and pelvic organs. There is a possibility that the mestranol component may augment the growth rate of preexisting uterine fibroids.

Predisposition to excessive fluid retention may be aggravated by administration of female sex hormones. Caution should be exercised in patients with histories of renal or cardiac disease, asthma, epilepsy, or migraine. Elevated levels of protein-bound iodine in the serum should not be considered definitive unless therapy has been discontinued for sixty days.

Although no adverse effects on lactation have been observed, it is suggested that nursing be well established before therapy with C-Quens is instituted in the postpartum patient.

Patients with a history of psychic depression should be carefully observed during treatment with an oral contraceptive. It should be discontinued if the depression recurs to a serious degree.

If a patient has missed two consecutive menstrual periods while taking C-Quens, it is recommended that pregnancy be ruled out before the medication is continued. Administration should be discontinued pending examination of the patient if there is sudden onset of severe headache or dizziness when these have not occurred previously or if examination discloses defects in the visual fields.

Diabetic patients taking C-Quens should be closely followed for any decrease in glucose tolerance. In the presence of breakthrough bleeding, the possibility of noncontraceptive causes should be considered.

Until further long-term experience has been obtained, use for periods longer than twenty-two months is not recommended.

Side-Effects: Nausea may be noted occasionally during early treatment cycles, but it decreases rapidly in subsequent cycles. The incidence of breakthrough bleeding among patients who stated they had taken the medication according to directions was 1.9 percent of cycles; the incidence of spotting was also 1.9 percent.

The following symptoms were infrequent during administration of C-Quens, and their comparative incidence before and during treatment suggests that they were not related to the drug: premenstrual tension, premenstrual nervousness not associated with premenstrual tension, breast soreness, vomiting, abdominal fullness, abdominal pain, headache, acne, eclampsia, and swelling of the ankles.

Administration and Dosage: Initially, the medication should be started on Day 5 of a menstrual cycle (the first day of menstruation being counted as Day 1), whether or not menstruation has ceased. One white tablet (mestranol) is to be taken by mouth each day for fifteen days, the last one on Day 19 of the cycle. Beginning with Day 20, one peach tablet (mestranol plus chlormadinone acetate) should be taken by mouth each day for five days.

Menstruation usually begins within seven days after the last tablet was taken. Medication is then resumed on Day 5 as in the previous cycle. If the patient has not previously begun menstruation, tablets from a new folder are started on the eighth day after the last tablet from the old folder was taken.

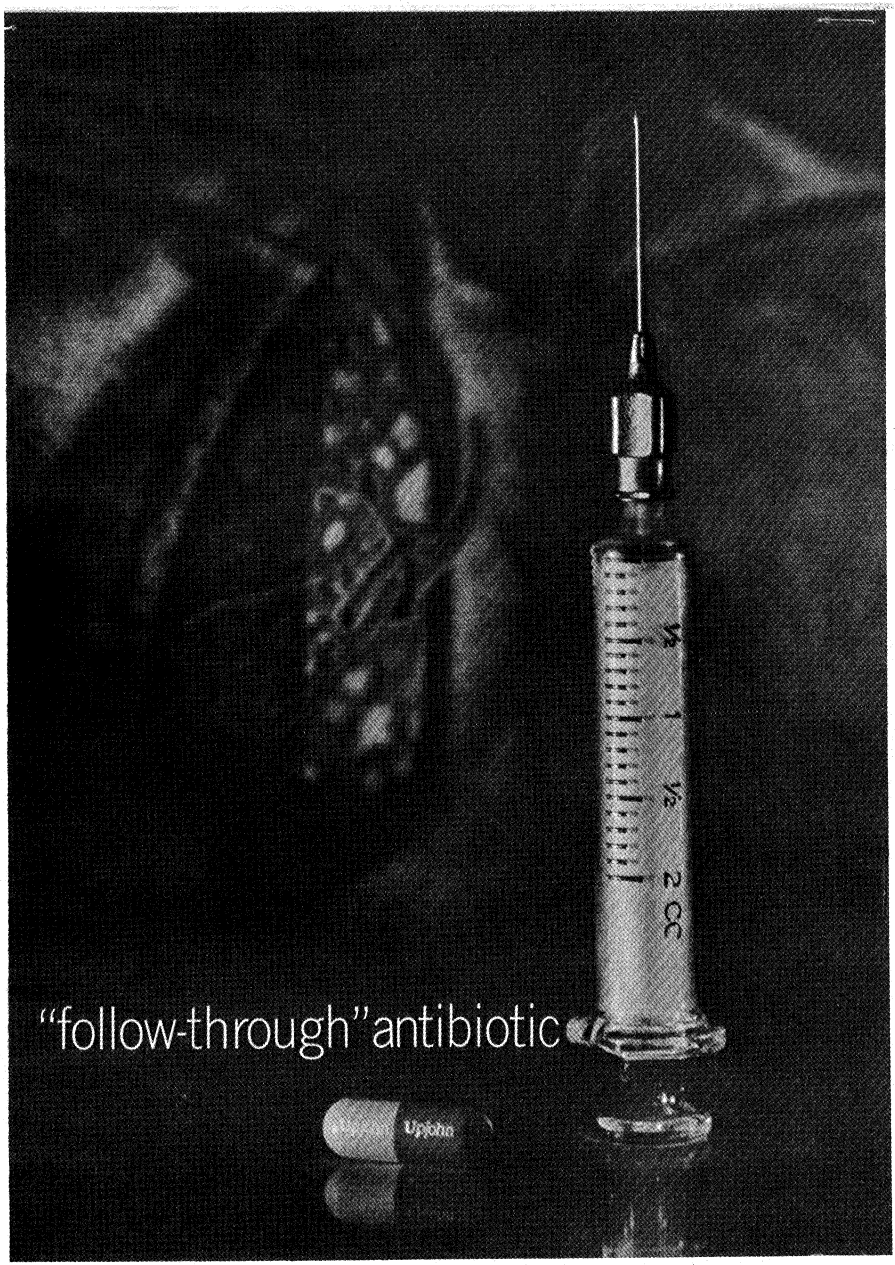
How Supplied: C-Quens is available in purse size folders containing fifteen mestranol tablets (white) and five tablets (peach) combining chlormadinone acetate and mestranol.

C-Quens® Lilly

Additional information available to physicians upon request. Eli Lilly and Company, Indianapolis, Indiana 46206.

601176

[From Journal of American Medical Association, Sept. 5, 1966, pp. 60–61]



in lower respiratory infections[1-7]

including pneumonia, bronchitis, and complications of influenza or common cold

caused by Staph-, Strep- and Pneumococci

practically painless on injection—therapy may be initiated parenterally and then followed through orally without switching antibiotic.

reactions rare, even for patients sensitive to penicillin—does not share antigenicity with the penicillin group of compounds.

no reports of serious renal or neurologic abnormalities; no ototoxicity.

no tooth discoloration to date: tests by 40 investigators involving 2,500 patients show no tooth discoloration with Lincocin.

References:

1. Holloway, W. J., and Scott, E. G.: Am. J. M. Sc. *249*:691 (June) 1965.
2. Duncan, I. B. R., and Jeans, B.: Canad. M.A.J. 93:685 (Sept. 25) 1965.
3. Kaplan, K.; Chew, W. H., and Weinstein, L.: Am. J. M. Sc. *250*:137 (Aug.) 1965.
4. Nunnery, A. W., and Riley, H. D.: Antimicrobial Agents and Chemotherapy-1964, Ann Arbor, Michigan, Am. Soc. Microbiol., p. 142.
5. Holloway, W. J.; Kahlbaugh, R. A., and Scott, E. G.: Antimicrobial Agents and Chemotherapy-1963, Ann Arbor, Michigan, Am. Soc. Microbiol., p. 200.
6. Walters, E. W.; Romansky, M. J., and Johnson, A. C.: *Ibid.*, p. 210.
7. Harnecker, J.; Contreras, J.; Gilabert, B., and Ubilla, V.: *Ibid.*, p. 204.

Lincocin®

(lincomycin hydrochloride monohydrate)

Contraindications: Patients previously found hypersensitive to drug; patients with known pre-existing monilial infections; and, until further clinical study is made, the newborn. **Precautions:** Use of antibiotics occasionally causes overgrowth of nonsusceptible organisms. If superinfections occur, take appropriate measures. An occasional patient has developed jaundice while receiving lincomycin, although this has not been definitely shown to be drug-related. Patients receiving treatment for longer than one or two weeks should have liver function tests. One case of irreversible toxicity to the hematopoietic system and only a few cases of neutropenia and/or leukopenia have been reported; however, it is recommended that blood counts be obtained early in course of therapy. Safety for use in pregnancy not yet established. Limited experience with 345 women receiving the drug during various stages of pregnancy revealed no ill effects on mother or fetus. Due to lack of adequate clinical data, use in patients with pre-existing kidney, liver, endocrine or metabolic diseases not recommended unless special clinical circumstances so indicate. Efficacy in rheumatic fever not established. **Side Effects:** Most frequent—loose stools or diarrhea. Cases of severe diarrhea causing drug discontinuance have been reported. Side effects of small proportion: nausea, vomiting, abdominal cramps or pain, skin rash, rectal irritation, vaginitis, urticaria and itching. A few cases of hypersensitivity reactions reported. If an allergic reaction occurs, discontinue drug. The usual agents for emergency treatment should be available. **Supplied:** 500 mg. capsules and pediatric capsules, 250 mg., in bottles of 24 and 100; 2 cc. disposable syringes; 2 cc. and 10 cc. vials—each cc. of sterile solution contains lincomycin hydrochloride monohydrate equiv. to lincomycin base, 300 mg.; also 9 mg. benzyl alcohol and water for injection, q.s.; Lincocin syrup equiv. to 250 mg. per 5 cc. lincomycin base in 60 cc. and pint bottles. Lincocin pediatric drops equiv. to 250 mg. per 5 cc. lincomycin base in 30 cc. bottles with dropper. **For more detailed prescribing information on this product, see the package circular or consult your Upjohn representative.** ©1966 by The Upjohn Company 366-6976-1

Upjohn

The Upjohn Company, Kalamazoo, Michigan

...physiologically

ORACON®

is so close to nature*

simulates a natural menstrual pattern

– produces a physiologically acceptable cycle

– simulates a normal endometrial response

– induces regular and predictable withdrawal bleeding

[From Journal of American Medical Association, Sept. 5, 1966, pp. 205-228]

Certainly
all oral contraceptives
are highly effective
and well tolerated
...yet ORACON®
16 White–Ethinyl Estradiol, 0.1 mg. Tablets; 5 Pink–Dimethisterone, 25 mg., and Ethinyl Estradiol, 0.1 mg. Tablets.
is unsurpassed...

...in patient benefits

ORACON®

affords few side effects*

month after month, women usually experience few side effects

- virtually eliminates amenorrhea
- dramatically low early-cycle breakthrough bleeding
- low incidence of weight gain
- significantly low incidence of monilial vaginitis

*For full documentation, please write to The Medical Department Mead Johnson Laboratories, Evansville, Indiana 47721, for the Physician's Brochure.

...so close to nature

ORACON®

16 White—Ethinyl Estradiol, 0.1 mg. Tablets; 5 Pink—Dimethisterone, 25 mg., and Ethinyl Estradiol, 0.1 mg. Tablets.

the first sequential oral contraceptive

Indication: To inhibit ovulation and provide an effective oral method of contraception.

Effectiveness: Oral contraceptives, including ORACON, are highly effective.

Contraindications: Because of estrogen content, ORACON is contraindicated in known or suspected malignancy of the breasts or reproductive tract, and in young women in whom epiphyseal closure is not complete. Do not use immediately postpartum in the nursing mother because of possible inhibition of lactation or estrogenic responses in the infant. Use is also contraindicated in presence of liver dysfunction or disease, and in patients with a history of thrombophlebitis, pulmonary embolism, or cerebral vascular accident.

Warnings: Use with caution in patients with cardiac or renal dysfunction. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a marked degree. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Precautions: Because of insufficient evidence concerning the possible effects of ORACON in patients with a history of metabolic disease or conditions which might be aggravated by possible estrogen-induced fluid retention (such as epilepsy, migraine, asthma, and cardiac or renal disease), ORACON should be used with care in such patients. Pre-existing uterine fibroids may increase in size while using this product. Any effect of prolonged use on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further studies. Discontinue before liver or endocrine function tests. Because of osteoblastic action of estrogens, carefully observe patients with metabolic bone disease or renal disease while on ORACON. Since safety in pregnancy is not proven, any patient missing 2 consecutive periods should have pregnancy ruled out before continuing the regimen. An estrogen-induced increase in cervical mucus is frequent; patients should be so advised. Continuous use for more than 18 months is not recommended at this time. Recurring breakthrough bleeding, particularly after the first few cycles, should be reported to the physician for further investigation. As a special precaution, another method of contraception should be used during the first 7 tablet days of the first cycle, or following discontinuance of ORACON for one or more months.

Side Effects: Few undesirable side effects occur with ORACON: Only 4.4% of patients discontinued medication because of side effects during clinical trials. As expected with estrogen therapy, nausea was the side effect reported most frequently. Nausea, when it occurs, is usually during the first cycle and is not severe. It may be alleviated with continued therapy or by administration at bedtime, with meals, or in divided doses. Other side effects reported during clinical studies included vomiting, abdominal cramps, bloating, anorexia, malaise, breakthrough bleeding, changes in amount and/or duration of menstrual flow, mucorrhea, and amenorrhea; headache, increased and decreased libido, weight gain or loss, nervousness, breast tenderness, dizziness, edema, diarrhea, drowsiness and premenstrual tension. Two cases of thrombophlebitis were reported during clinical trials; however, a cause-and-effect relationship has not been established.

Administration: Counting onset of menses as Day 1, the patient starts medication on Day 5 of the menstrual cycle and takes one white tablet daily from Day 5 through Day 20, then one pink tablet daily from Day 21 through Day 25. The patient should follow the dosage schedule strictly. If the regimen is interrupted, for the fullest possible protection the patient should consult her physician about the use of an additional contraceptive method for the rest of the cycle (also see Precautions). Menses usually begin 2 to 4 days after the last pink tablet has been taken. The patient starts her new cycle of medication on Day 5. If flow does not occur by the 7th day after taking the last pink tablet start the next full course of therapy on that day, thus allowing 6 days without drug. In case of breakthrough bleeding: if spotting, continue medication; if menstrual flow, discontinue medication and begin a new full course on Day 5; for recurring breakthrough bleeding or amenorrhea, see Precautions.

Availability: Available as 16 white and 5 pink tablets. Each white tablet contains 0.1 mg. ethinyl estradiol; each pink tablet contains 25 mg. dimethisterone plus 0.1 mg. ethinyl estradiol. Complete details on ORACON are available on request from Mead Johnson Laboratories, Evansville, Indiana 47721. 92666

Mead Johnson
LABORATORIES

Research for Life

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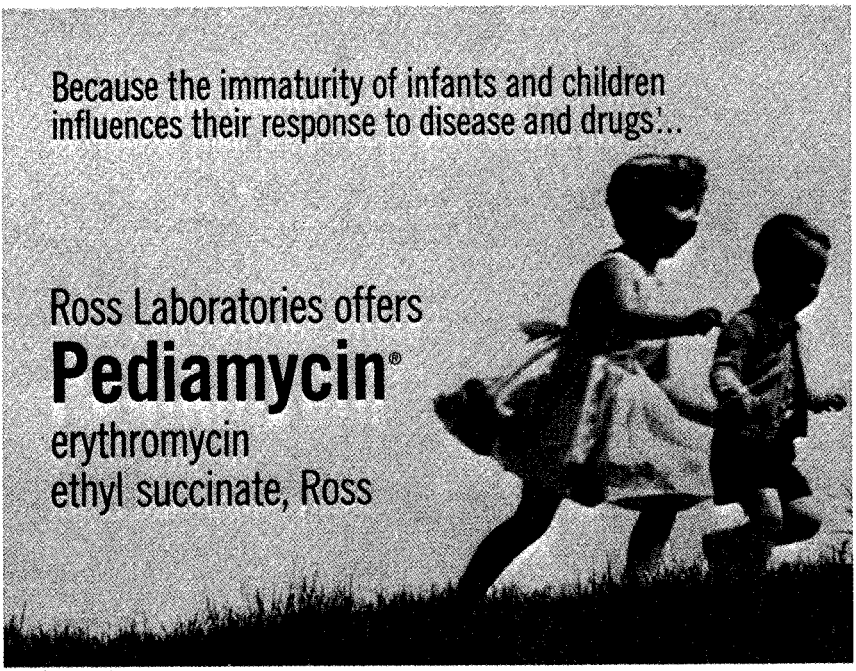
[From Medical World News, Feb. 12, 1965, pp. 42–43]



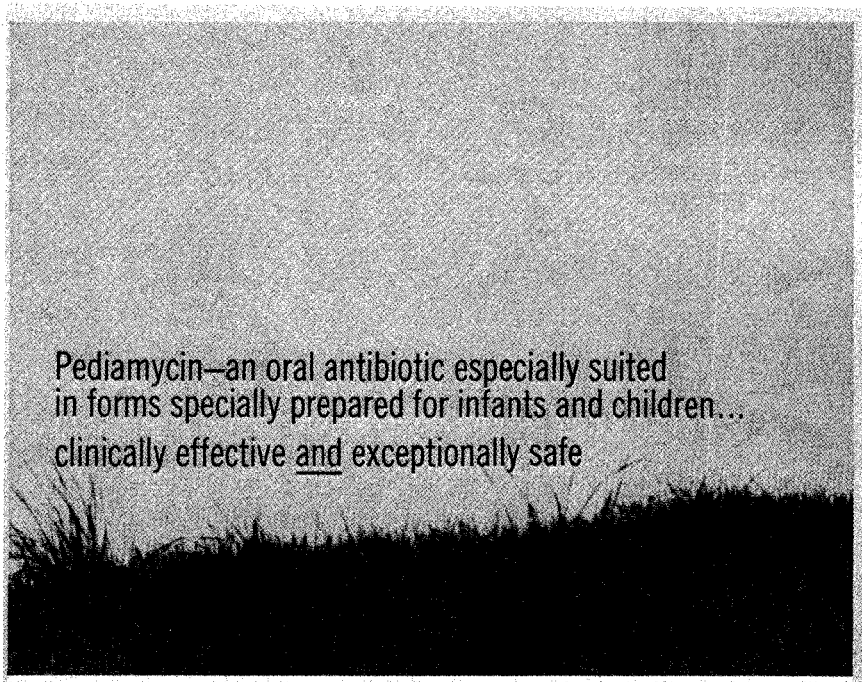
Pediamycin is effective in 86% of the common bacterial infections seen in infants and children. It is active against gram-positive cocci[2-5]; streptococci, including enterococci, pneumococci and most strains of staphylococci. It is also active against Hemophilus influenzae.[6,7] It has 4 to 16 times more activity against susceptible organisms than the tetracyclines and chloramphenicol.[8-13]

Pediamycin is especially useful in common infections of the ear, nose and throat, and in respiratory infections, including bronchitis, croup and pneumonia as well as in infections in other sites, caused by susceptible organisms.

Pediamycin has an exceptional record of safety. Erythromycin has been called "by far the least toxic of commonly used antibiotics,"[14] with "a minimum of side effects."[15] It has never been known to have an adverse effect on bone growth, to cause tooth staining or to damage the kidneys or impair the liver. Allergic reactions are extremely infrequent. Side effects such as diarrhea, nausea and vomiting, bacterial superinfections of the G.I. tract, moniliasis are rare and mild.

With Pediamycin the production of resistant organisms is low. Of 1017 strains of Staphylococcus aureus tested in vitro, 87 percent were sensitive.[16] In in vitro tests of hemolytic streptococci, all of 116 strains tested were sensitive.[17] In a clinical study, 20 percent of 218 strains of group A beta-hemolytic streptococci were resistant to tetracycline, none was resistant to erythromycin.[18]

Pediamycin is easy to administer. Its cherry flavor is liked by children. Pediamycin is provided as scored chewable tablets, suspension and drops, all forms which encourage cooperation in pediatric patients.



Supply: *For children:* **Pediamycin Chewable** tablet: scored, cherry flavored, 200 mg erythromycin activity. *For small children and infants:* **Pediamycin Suspension:** granules for oral suspension, 60 ml bottles, 200 mg erythromycin activity per teaspoonful (5 ml); full and half teaspoon measure enclosed in package. **Pediamycin Drops:** granules for oral suspension, 30 ml bottles, 100 mg erythromycin activity per dropperful (2.5 ml); calibrated dropper enclosed in package.
Dosage: The recommended dosage of erythromycin for infants and young children is 15 mg to 25 mg per pound of body weight per day in four to six divided doses. For larger children the adult dosage scale of 1 to 2 grams per day, depending upon the severity of the infection, is recommended. For unusually severe or critical conditions, larger doses may be considered.
Contraindications: Pediamycin is contraindicated for patients with a known sensitivity to erythromycin.
Precautions: Side effects are relatively rare. Should a patient show signs of sensitivity, appropriate countermeasures (e.g., administration of epinephrine, steroids, etc.) should be employed and the drug withdrawn.
References: **1.** Dunn, A. K., in Drugs of Choice 1964-1965, Modell, W., ed., St. Louis, The C. V. Mosby Co., 1964, p. 66. **2.** Cutting, W. C.: Handbook of Pharmacology, New York, Appleton-Century-Crofts, 1962, chap. 5. **3.** Keefer, C. S., in Drugs of Choice 1960-1961, Modell, W., ed., St. Louis, The C. V. Mosby Co., 1960, chap. 8. **4.** Kanter, A. E., Zummo, B. P., and Horwitz, C.: Obstet. Gynec. *6*:541, 1955. **5.** Welch, H.: Principles and Practice of Antibiotic Therapy, New York, Medical Encyclopedia, 1954, p. 171. **6.** Haight, T. H., and Finland, M.: Proc. Soc. Exp. Biol. Med. *81*:175, 1952. **7.** Sell, S. H. W., and Sanders, R. S., in Antimicrobial Agents and Chemotherapy—1963, Sylvester, J. C., ed., Ann Arbor, American Society for Microbiology, 1964, p. 756. **8.** Jones, W. F., Jr.; Feldman, H. A., and Finland, M.: Amer. J. Clin. Path. *27*:159, 1957. **9.** Jones, W. F., Jr., and Finland, M.: Amer. J. Med. Sci. *233*:312, 1957. **10.** Finland, M.: Med. Clin. N. Amer. *42*:1179, 1958. **11.** Perry, D. M., *et al.*: Antibiot. Med. *6*:347, 1959. **12.** Jones, W. F., Jr., and Finland, M.: New Eng. J. Med. *256*:115, 1957. **13.** Kirby, W. M. M.; Maple, F. M., and O'Leary, B.: Antibiot. Chemother. *3*:473, 1953. **14.** Herrell, W. E.: J.A.M.A. *168*:1875, 1958. **15.** Rubin, S. L.: Med. Times *89*:274, 1961. **16.** Koch, M. L.; Resnick, A., and Mach, R.: Antibiot. Chemother. *11*:284, 1961. **17.** Rantz, L. A., and Rantz, H. H.: Arch. Intern. Med. *110*:739, 1962. **18.** Kuharic, H. A.; Roberts, C. E., Jr., and Kirby, W. M. M.: J.A.M.A. *179*:1779, 1960.

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[From Journal of American Medical Association, Sept. 5, 1966]

JAMA VOL 197, NO 10 SEPTEMBER 5, 1966

THE JOURNAL of the American Medical Association

Harumi Tateishi International College of Surgeons, Chicago

A Japanese pioneer in the use of anesthesia in surgery was Seishu Hanaoka, who, 40 years before Long used ether, had removed breast cancers and kidney stones from sleeping patients. He dosed them with a narcotic compound of six plant extracts, including henbane and jimsonweed, members of the nightshade family; the method is reminiscent of much earlier attempts. This painting on silk, specially commissioned and presented to the International College of Surgeons, depicts a legend that grew around the surgeon's experiment. His elderly mother suggested that, as she expected to die shortly anyway, the proposed anesthetic be tried on her. But Hanaoka administered it to his wife for, as all three agreed, he could find another wife but he could never get another mother. The painting is reproduced here to help introduce a new regular JOURNAL feature, Anesthesia Problem of the Month (p 789).

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This is a new, everyday penicillin for common bacterial respiratory infections with extra therapeutic coverage at no extra cost.*

Clinical success. Tegopen (sodium cloxacillin monohydrate) assures you a high degree of clinical success against respiratory infections. A recent comprehensive analysis of office patients administered the drug proves the point: *96% of 259 bacterial respiratory infections treated were cured or improved.*[1]

***Kills common respiratory Gram-positive cocci.** In contrast to the penicillinase-limited Gram-positive spectrum of penicillins G and V, Tegopen (sodium cloxacillin monohydrate) destroys strep, pneumo and virtually all staphylococci.

Bactericidal in action. Tegopen (sodium cloxacillin monohydrate) is bactericidal, killing the offending organism. In contrast, erythromycin[2] and triacetyloleandomycin[3] are essentially bacteriostatic agents.

Minimal side effects. There is little likelihood of dose-related toxicity with Tegopen (sodium cloxacillin monohydrate).

Low in cost. Even with all of its extra advantages, Tegopen (sodium cloxacillin monohydrate) is priced comparably to penicillins G and V, and 33% less than either erythromycin or triacetyloleandomycin.

BRISTOL THERAPEUTIC SUMMARY: For complete information, consult Official Package Circular. *Indications:* Infections due to streptococci, pneumococci and staphylococci, particularly penicillin G-resistant strains of the latter. *Contraindications:* A history of severe allergic reactions to penicillins. *Precautions:* Typical penicillin-allergic reactions may occur, particularly in hypersensitive persons. Mycotic or bacterial infections may occur. Safety for use in pregnancy is not established. Assess renal, hematopoietic and hepatic function periodically during long-term therapy. *Adverse Reactions:* Nausea, epigastric discomfort, flatulence, diarrhea, eosinophilia, and allergic manifestations. Moderate SGOT elevations have been noted. *Usual Dosage:* Adults: 250 mg. *q. 6 h.* Children: 50 mg./Kg./day. Children weighing more than 20 Kg. should be given the adult dose. Treat beta-hemolytic streptococcal infections for at least 10 days. Administer 1 to 2 hours before meals.

References: 1. Data on file at Bristol Laboratories. 2. Geraci, J.E. (Panel Discussion, M. Finland, Moderator): Antibiot. Ann. 1958–59: 1051, 1959. 3. Thompson, W.T., Jr.: South. M. J. *56*:844 (Aug.) 1963.

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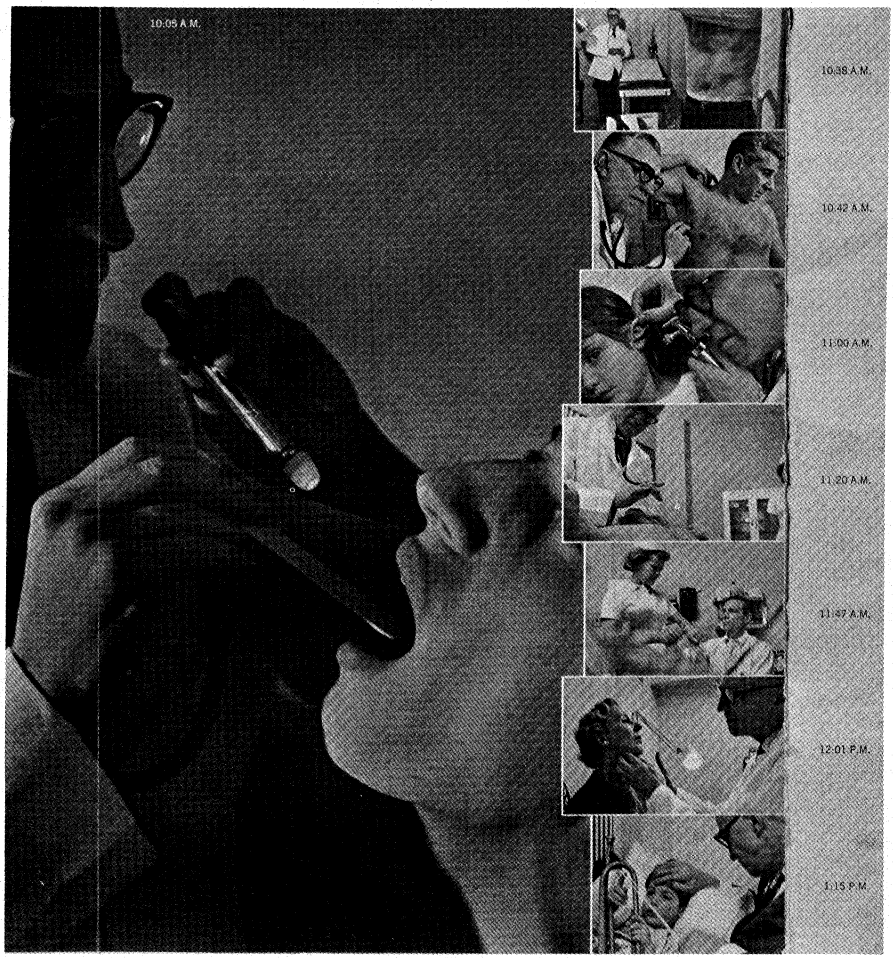
SODIUM CLOXACILLIN MONOHYDRATE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11:47 A.M.
12:01 P.M.
1:15 P.M.

10:38 A.M.

10:42 A.M.

11:00 A.M.

There is a new, everyday penicillin for common bacterial respiratory infections.

11:20 A.M.

An improvement over penicillin G and V, and the medium-spectrum antibiotics.

11:47 A.M.

Just lift the page at the left and read why.

12:01 P.M.

1:15 P.M.

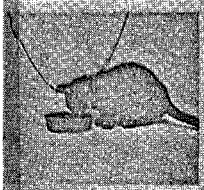
[From Journal of American Medical Association, Oct. 18, 1965, pp. 11–16]

presenting PRE-SATE®

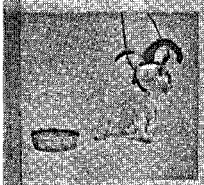
one of the most sophisticated comparative animal studies ever conducted with an appetite suppressant demonstrates[1,2]:

direct action on the satiety center[1,2]

SATIATED CAT NOT ELECTRICALLY STIMULATED DOES NOT EAT



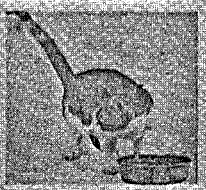
SATIATED CAT ELECTRICALLY STIMULATED EATS



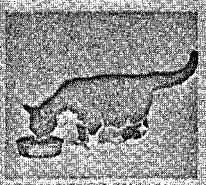
SATIATED PRE-SATE-TREATED CAT ELECTRICALLY STIMULATED DOES NOT EAT

far greater duration of anorexia than amphetamine[1,2]

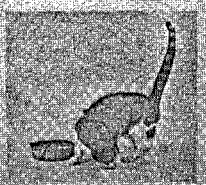
AFTER 2 HOURS STARVED AMPHETAMINE-TREATED CAT DOES NOT EAT



AFTER 2 HOURS STARVED PRE-SATE-TREATED CAT DOES NOT EAT

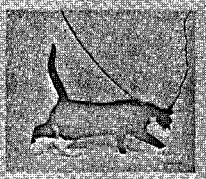


AFTER 6 HOURS AMPHETAMINE-TREATED CAT NOW EATS

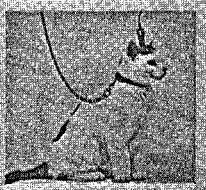


AFTER 6 HOURS PRE-SATE-TREATED CAT STILL DOES NOT EAT (up to 48 hours)

no CNS stimulation[1,2]

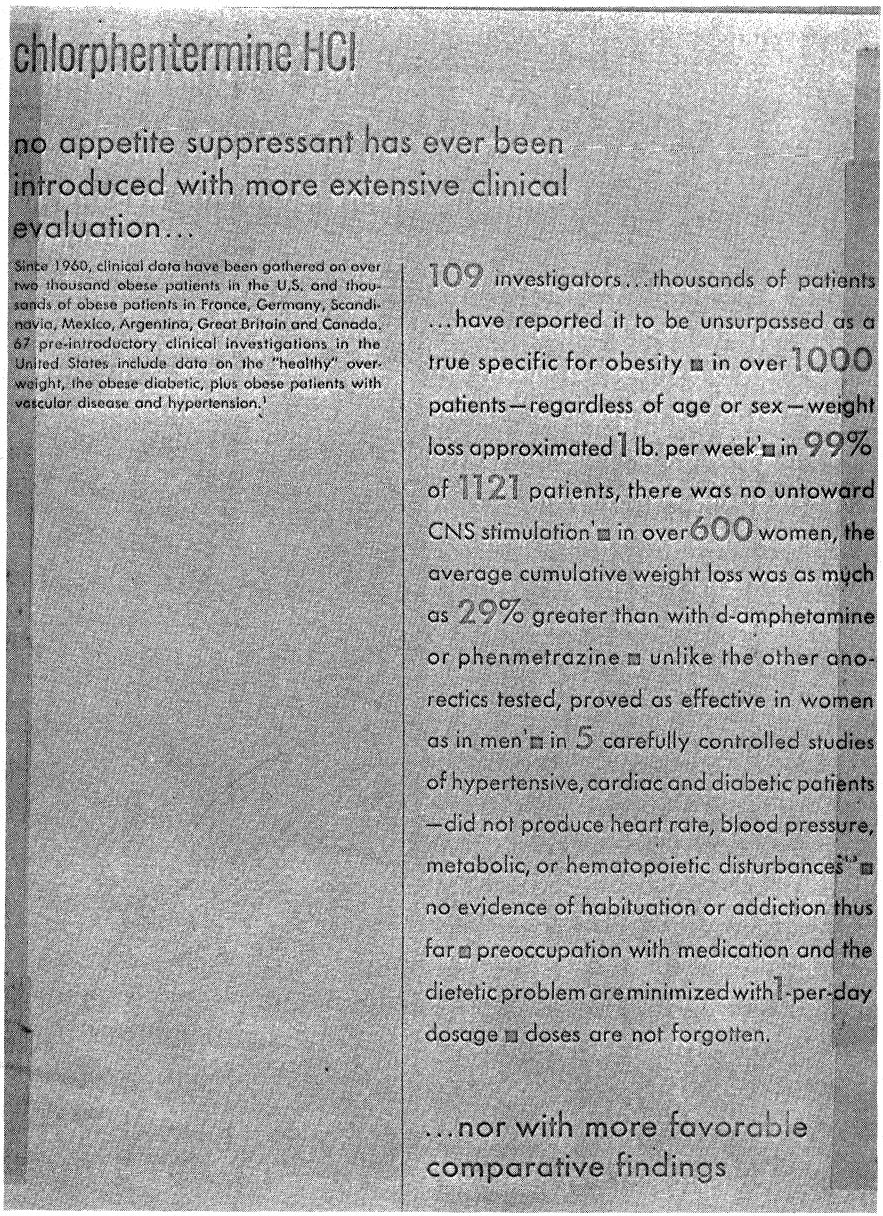


EXCESSIVE MOTOR ACTIVITY IN AMPHETAMINE-TREATED CAT



STABILITY AND NO UNUSUAL MOTOR ACTIVITY IN PRE-SATE-TREATED CAT

Two appetite centers have been identified in the hypothalamus. The lateral nucleus is associated with feeding response, the ventromedial nucleus with satiety. Pre-Sate (chlorphentermine HCl) produced electrical brain-wave patterns of satiety in cats, starved for 48 hours, similar to electrical patterns in nonstarved cats.


chlorphentermine HCl
no appetite suppressant has ever been introduced with more extensive clinical evaluation...
Since 1960, clinical data have been gathered on over two thousand obese patients in the U.S. and thousands of obese patients in France, Germany, Scandinavia, Mexico, Argentina, Great Britain and Canada. 67 pre-introductory clinical investigations in the United States include data on the "healthy" overweight, the obese diabetic, plus obese patients with vascular disease and hypertension.[1]
109 investigators...thousands of patients ...have reported it to be unsurpassed as a true specific for obesity ■ in over 1000 patients—regardless of age or sex—weight loss approximated 1 lb. per week[1] ■ in 99% of 1121 patients, there was no untoward CNS stimulation[1] ■ in over 600 women, the average cumulative weight loss was as much as 29% greater than with d-amphetamine or phenmetrazine ■ unlike the other anorectics tested, proved as effective in women as in men[1] ■ in 5 carefully controlled studies of hypertensive, cardiac and diabetic patients —did not produce heart rate, blood pressure, metabolic, or hematopoietic disturbances[1-5] ■ no evidence of habituation or addiction thus far ■ preoccupation with medication and the dietetic problem are minimized with 1-per-day dosage ■ doses are not forgotten.
...nor with more favorable comparative findings

1

steady weight loss, fewer patient "dropouts" than with phenmetrazine and d-amphetamine

In hundreds of patients, there was less discontinuance of program with Pre-Sate (chlorphentermine HCl) than with phenmetrazine or d-amphetamine.

Rate of discontinuation of program[1]

	Pre-Sate	phenmetrazine	d-amphetamine
Total patients	1121	203	124
Number dropouts	57	34	13

In 6 double-blind, comparative clinical studies,[1,3,4] employing a single daily dose of Pre-Sate (chlorphentermine HCl), patients lost weight steadily. In over 1000 patients—regardless of age or sex—weight loss approximated 1 lb. per week, even during the difficult fifth to tenth weeks of dieting.

More effective in women

Pre-Sate (chlorphentermine HCl) is equally potent within all age groups, and more effective in women than d-amphetamine or phenmetrazine.[1]

In over 600 women, the average cumulative weight loss in pounds per week was greater than with d-amphetamine or phenmetrazine[1]

age	under 21	21-30	31-45	46-60	over 60
medication					
Pre-Sate chlorphentermine HCl	1.04	1.07	0.98	0.98	0.96
placebo	.43	.41	.52	.45	.86
d-Amphetamine	.58	.32	.75	.79	1.03
phenmetrazine	.43	.89	.88	1.18	.50

new PRE-SATE®
chlorphentermine HCl

2

significantly fewer CNS side effects than with d-amphetamine[1,3,5,6] and phenmetrazine[1,4]

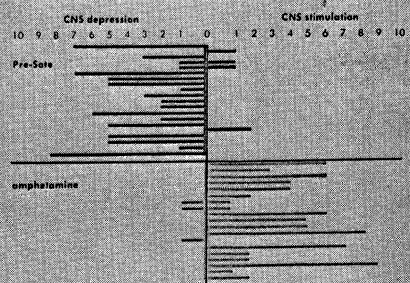
In contrast to phenmetrazine which produced a significant number of CNS side effects, Pre-Sate (chlorphentermine HCl) produced *no* CNS disturbances in a double-blind clinical test of 60 patients.[4]

Of 1,121 patients tested[1] with Pre-Sate (chlorphentermine HCl), 1,110 evidenced no untoward CNS stimulation.

In a double-blind, crossover study it was reported that "No evidence of central nervous system stimulation and no serious side effects developed during a four-week period on chlorphentermine [Pre-Sate]."[7]

In double-blind studies by 3 independent investigators Pre-Sate (chlorphentermine HCl) was found to have no untoward effect on fine coordinated movement, mental processes, or processes involving integration of special senses of sight or hearing with other centers of the central nervous system.[1,5] These clinical findings were corroborated in special laboratory studies employing critical "Flicker-Fusion Threshold Tests," one of the most reliable methods of measuring CNS effect of a drug.[1]

Critical flicker-fusion threshold tests[1]: Two anorectics



This test is chiefly an index of the subject's ability to discriminate between a steady beam of light and a rapidly flickering beam of light.

In contrast to the usual stimulatory effects of the amphetamines, numerous investigators have reported the lack of such untoward effects with chlorphentermine (Pre-Sate).[1,3,5,6]

3

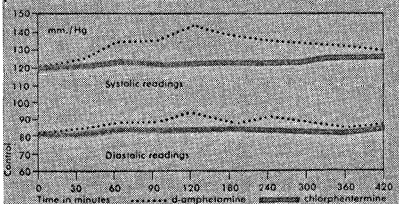
no adverse effect on the cardiovascular parameters[1,8]

In normotensive patients

In two independent studies in overweight subjects without cardiovascular disorders, Pre-Sate (chlorphentermine hydrochloride) had no biologically significant effect on blood pressure and pulse rate.[1]

A third study tested the safety of a greater-than-recommended dose (100 mg.). Daily administration of the drug in this dosage for *six months* caused no alteration in blood pressure, pulse or ECG.[1]

Blood pressure readings of normotensive obese patients after medication



In patients with hypertension

Hundreds of patients with cardiovascular disorders have received Pre-Sate (chlorphentermine hydrochloride), and no adverse effects on blood pressure, ECG or pulse rate have been evidenced. Most of the patients in this category had hypertension.[1] These findings indicate that the drug may prove useful in treating obesity complicated by mild to moderate cardiovascular disorders; however, until continuing studies are completed, caution should be employed in its use in patients with hypertension and acute coronary disease.

Compared to d-amphetamine in patients with cardiovascular disorders

Russek[8] contrasted the frequent (85.7%) cardiovascular side effects with d-amphetamine in one group of patients to the absence of such effects in 42 obese cardiac patients who were given Pre-Sate (chlorphentermine hydrochloride), daily for periods up to 27 weeks. All patients receiving the new drug had discontinued d-amphetamine either because of side effects or contraindications.

Side effects in patients with cardiovascular disorders*

	Pre-Sate	d-amphetamine
Cardiovascular disturbances	0	85.7%
CNS stimulation	2.9%	71.4%

*Adapted from Russek, H. I.: Am. J. M. Sc. 249:305, 1965.

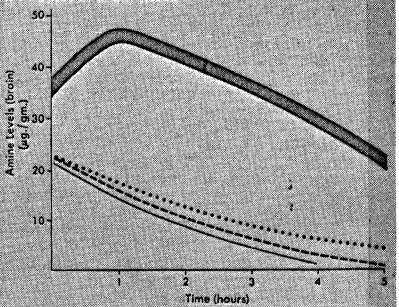
4

more prolonged anorexia than with phentermine, mephentermine, d-amphetamine[1,9,10]

Because of the introduction of a chlorine atom in the *para* position, Pre-Sate (chlorphentermine HCl) is qualitatively different in pharmacologic action from all

other anorectic agents . . . achieves higher brain concentrations and more prolonged effect than currently available anorectics.[1,9,10]

Persistence of chlorphentermine [Pre-Sate] in brain tissue[9]



Disappearance of amines from brains of mice after a single injection (15 mg./kg., i.v.).

Each point represents the average of values obtained in 3 experiments.

▬ = chlorphentermine
▪▪▪ = mephentermine
– – = phentermine
—— = d-amphetamine

Because Pre-Sate (chlorphentermine HCl) is an inherently long-acting molecule, appetite suppression is achieved with convenient one-per-day dosage.[1] Neither addiction nor habituation has occurred with Pre-Sate (chlorphentermine HCl) therapy.[1]

new
PRE-SATE®
chlorphentermine HCl

full day's anorexia with just one WC tablet

Convenient one-per-day dosage —after breakfast— minimizes preoccupation with medication and the dietetic problem. Doses are less likely to be forgotten.

Indications: Pre-Sate (chlorphentermine HCl), a sympathomimetic amine, is indicated for the treatment of obesity, and is distinguished by a selective pattern of pharmacologic action which makes it ideal for anorectic use. This pattern of activity differs qualitatively and quantitatively from amphetamine, whose indiscriminate effects at anorectic doses on the cardiovascular system and central nervous system are well known.

Advantages: The anorectic action of Pre-Sate (chlorphentermine HCl), mediated through the satiety center of the hypothalamus, reduces the desire for food and makes it easier to adhere to a program of caloric reduction. Equal to other drugs in anorectic effectiveness, Pre-Sate (chlorphentermine HCl) curbs appetite without the frequency and degree of CNS stimulation caused by other anorectic drugs. Unlike the anorectic agents to which it has been compared, this new drug is as effective in women as in men.

In extensive clinical trials, this drug produced no adverse effect on blood pressure, heart rate or blood sugar. No toxic reactions have been reported and prolonged testing with greater-than-recommended dosage did not produce any evidence of alteration in renal, hepatic, hematopoietic, or cardiovascular functions during or after completion of treatment. Basal metabolic rate and blood sugar were also unaltered by the drug. Such evidence indicated that Pre-Sate (chlorphentermine HCl) may prove to be especially useful in patients who cannot tolerate the CNS stimulatory or pressor effects of other anorectic agents.

Contraindications: Pre-Sate (chlorphentermine HCl) is contraindicated in patients who have glaucoma, or in patients who are receiving monamine oxidase inhibitors.

Precautions: As with all new drugs, physicians should be alert to the possibility of adverse reactions. The safety of Pre-Sate (chlorphentermine HCl) in human pregnancy has not yet been established. Its use in lactating women is not recommended. Although no toxic reactions have been observed with the use of Pre-Sate (chlorphentermine HCl), physicians should be alert to the rare individual who may be overly sensitive to the drug. While clinical studies have been completed in patients with diabetes and hypertension, until continuing clinical studies are completed, caution should be employed in its use in patients with thyrotoxicosis, hypertension and acute coronary disease.

Side effects: Side reactions rarely complicate Pre-Sate (chlorphentermine HCl) therapy and seldom require discontinuation of medication. Throughout clinical trials, Pre-Sate (chlorphentermine HCl), in recommended dosage, has manifested a comparatively low incidence of side effects. Complaints of mydriasis, nausea, constipation, dry mouth, and, rarely, difficulty in initiating micturition, have been reported.

Paradoxically, nervousness and insomnia, and drowsiness and sedation have been reported with almost equal incidence. Headache, urticaria, and dizziness have also been reported.

Dosage: The recommended adult daily dose of Pre-Sate (chlorphentermine HCl) is one tablet (65 mg. chlorphentermine base as the hydrochloride), taken after the morning meal.

How supplied: Pre-Sate (chlorphentermine HCl) is available in bottles of 100 tablets. Each tablet contains 65 mg. chlorphentermine base as the hydrochloride.

References: 1. Data on file in the Medical Department of Warner-Chilcott Laboratories. 2. Emele, J. F., Shanaman, J., and Warren, M. R.: Fed. Proc. 20:328, 1961. 3. Fineberg, S. K.: Am. J. Clin. Nutrition 11:509, 1962. 4. Rudolph, L. A., and MacLachlan, I.: Current Therap. Res. 4:629, 1962. 5. DiMascio, A., and Bute, D. H.: Clin. Pharmacol. & Therap. 5:174, 1964. 6. Levin, J.; Trafford, J. A. P.; Newland, P. M.; and Bishop, P. M. F.: Practitioner 191:65, 1963. 7. Lucey, C., and Haddon, D. R.: Ulster M. J. 31:181, 1962. 8. Russek, H. I.: Am. J. M. Sc. 249:305, 1965. 9. Dubnick, B.; Leeson, G. A.; Leverett, R.; Morgan, D. F., and Phillips, G. E.: J. Pharmacol. & Exper. Therap. 140:85, 1963. 10. Friedman, G.; Weingarten, L. A., and Janowitz, H. D.: Am. J. Clin. Nutrition 10:225, 1962.

WARNER-CHILCOTT

Warner-Chilcott, Morris Plains, N.J. Makers of Coly-Mycin Gelusil Peritrate Proloid Tedral

21 REMEDIAL ADVERTISING LETTERS ISSUED BETWEEN JANUARY 1967 AND APRIL 1968

Firm	Drug(s)	Date of letter
Ortho	Ortho-Novum	Feb. 1, 1967.
Wallace	Deprol and Miltown	March 1967.
Roche	Librium	Do.
Abbott	Enduron and Enduronyl	Apr. 13, 1967.
Pfizer	Renese, Renese-R, Rondomycin	May 22, 1967.
Geigy	Hygroton and Regroton	June 1967.
Mead Johnson	Oracon and Questran	June 30, 1967.
Flint	Choloxin	July 20, 1967.
Neisler	Diutensen-R	Aug. 11, 1967.
Astra	Cintanest	Aug. 23, 1967.
Squibb	Mysteclin-F	October 1967.
Organon	Cortropin Gel, Cortropin Zinc, Hexadrol, Hexadrol Phosphate	Oct. 27, 1967.
Lakeside	Norpramin	November 1967.
S. E. Massengill	Predsem, Salcort, Salcort-Delta	Nov. 1, 1967.
Upjohn	Medrol	Nov. 15, 1967.
Armour	H. P. Acthar Gel	Nov. 16, 1967.
PDR	H. P. Acthar Gel, Cortropin Gel, Cortropin-Zinc, Hexadrol, Hexadrol Phosphat7, Norpramin, Predsem, Salcort, Salcort-Delta.	Nov. 22, 1967.
Parke-Davis	Pontsel	Jan. 5, 1968.
Syntex	Norguen and Norinyl	Jan. 22, 1968.
G. D. Searle	Ovulen-21	Jan. 26, 1968.
Geigy	Persantine	Feb. 15, 1968.

RARITAN, N.J., *February 1, 1967.*

DEAR DOCTOR: The Food and Drug Administration has asked us to call your attention to the fact that a claim in our recent advertising of Ortho-Novum SQ* may be misleading.

In our introduction of this product to the medical profession we featured the theme, "The Most Effective Sequential", based on a comparison of pregnancy rates published in manufacturers' package inserts. The Food and Drug Administration has pointed out that such a comparison is invalid because there has been neither a direct comparative study of the efficacy of the three sequential oral contraceptives in the same population nor individual studies of the three products in population groups shown to be comparable. We are therefore discontinuing the promotional theme in question.

ORTHO PHARMACEUTICAL CORP.

CRANBURY, N.J.

DEAR DOCTOR: At the request of the Food and Drug Administration, we are calling your attention to one of our recent advertisements captioned, *"The published clinical studies indicate: 3 of 4 non-psychotic depressions respond to 'Deprol'."* The FDA considers that this advertising may have been misleading.

In the advertisement, we listed 21 studies comprising the total published 'Deprol' literature containing data on *non-psychotic* depressions. While the ad does not reflect the fact, data from these studies were *excluded* in whole or in part if—

(*a*) the diagnosis was not entirely clear;

(*b*) the recommended maximum dose of 6 "Deprol" tablets per day was exceeded;

(*c*) other psychotropic drugs or electroshock were part of therapy.

Moderate, marked, excellent, and complete responses were counted as favorable, while mild, fair, slight, and no responses were counted as unfavorable.

Using the above criteria, the final number of patients included was 323 selected from ten of the 21 listed studies. Nine of the ten studies were uncontrolled, and most patients in the ten studies concomitantly received informal or structured psychotherapy. The reported therapeutic results (ranging from 0% in a study with two non-psychotic depressed patients, through 64% in a study with 53 patients, to 90% in two studies with 38 and 41 such patients respectively) also include, to an undetermined degree, placebo responses and spontaneous remissions known to occur in the therapy of neurotic depression.

The factors noted above represent problems that exist in working with any literature and are present in some "Miltown" advertisements carrying the theme

*Trademark.

"one of a series". In order to avoid any misunderstanding, we have discontinued the use of these "Miltown" advertisements as well as the described "Deprol" advertisement.

Sincerely,

WALLACE PHARMACEUTICALS.

ROCHE LABORATORIES,
Nutley, N.J.,

DEAR DOCTOR: At the request of the Food and Drug Administration, we are extending the "brief summary" of prescribing information for Librium® (Chlordiazepoxide HC1) which appears in medical journal advertisements by adding several phrases and items from the unchanged official package circular.

The revised "brief summary" for medical journals is attached, indicating by capitalization the requested added material. Prescribing information in all Librium (chlordiazepoxide HC1) package circulars, direct mail information and brochures is complete and requires *no* change. The safety and effectiveness of the product are *not in question.*

In addition, in future medical journal advertisements for Libruim (chlordiazepoxide HC1) in geriatric patients, we are amplifying statements which have appeared concerning possible side effects and initial dosage:

The statement that "Side effects in most instances are mild in degree and readily reversible with reduction of dosage," will be extended by the observations made in our package circular which point out that drowsiness, ataxia and confusion have been reported in some patients, particularly the elderly and debilitated, occasionally at lower dosage ranges, and that in a few instances syncope has been reported.

Whereas in geriatrics, the *usual daily dosage* is 5 mg, two to four times daily, the *initial dosage* in elderly and debilitated patients should be limited to 10 mg or less per day, adjusting as needed and tolerated.

We hope the additional detail in medical journal advertising clarifies the use of the product in accordance with the enclosed package circular.

Sincerely,

ROBERT E. DIXON, M.D.
Director, Professional Services.

(NOTE.—This revised "brief summary" for use in future medical journal advertising contains additional phrases and items (printed in capital letters) from the official package circular which remains unchanged.)

BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR LIBRIUM® (CHLORDIAZEPOXIDE HC1)

Before prescribing, please consult complete product information, a summary of which follows:

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. AS WITH ALL CNS-ACTING DRUGS, CAUTION PATIENTS against hazardous occupations requiring complete mental alertness (*E.G.*, OPERATING MACHINERY, DRIVING). THOUGH PHYSICAL AND PSYCHOLOGICAL DEPENDENCE HAVE RARELY BEEN REPORTED ON RECOMMENDED DOSES, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefis be weighed against its possible hazards.

Precautions: In the elderly and debilitated, and in children over SIX, limit to smallest effective dosage (INITIALLY 10 MG OR LESS PER DAY) TO PRECLUDE ATAXIA OR OVERSEDATION, increasing gradually as needed and tolerated. NOT RECOMMENDED IN CHILDREN UNDER SIX. THOUGH GENERALLY NOT RECOMMENDED, IF COMBINATION THERAPY WITH OTHER PSYCHOTROPICS SEEMS INDICATED, CAREFULLY CONSIDER INDIVIDUAL PHARMACOLOGIC EFFECTS, PARTICULARLY IN USE OF POTENTIATING DRUGS SUCH AS MAO INHIBITORS AND PHENOTHIAZINES. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions, *E.G.*, EXCITEMENT STIMULATION AND ACUTE RAGE) have been reported in psychiatric patients and hyperative aggressive

children. Employ usual precautions in treatment of anxiety states with evidence of impeding depression; suicidal tendencies MAY BE PRESENT AND PROTECTIVE MEASURES NECESSARY. Variable effects on blood coagulations have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. IN A FEW INSTANCES syncope HAS BEEN REPORTED. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nauseau and constipation, extra-pyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reductions; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dysrasias (including agranulocytosis), jaundice and hepatic dysfunction HAVE BEEN REPORTED occasionally, making periodic blood counts and liver-function tests advisable during protracted therapy.

Usual Daily Dosage: Individualize for maximum beneficial effects. *Oral*—Adults: Mild and moderate anxiety and tension, 5 or 10 mg. t.i.d. or q.i.d.; severe states, 20 or 25 mg t.i.d. or q.i.d. Geriatric patients: 5 mg b.i.d. to q.i.d. (See Precautions.)

Supplied: Capsules, 5 mg, 10 mg and 25 mg—bottles of 50.

NORTH CHICAGO, ILL., *April 13, 1967.*

DEAR DOCTOR: The Food and Drug Administration has asked us to call your attention to a recent advertisement on Enduron® (methyclothiazide) and Enduronyl® (methyclothiazide and deserpidine). The advertisement, headlined "Thiazide-potassimum problems, doctor?" is regarded by the FDA as misleading.

The ad states that the advertised drugs provide "excellent sodium output with less potassium loss than either chlorothiazide or hydrochlorothiazide."

The consensus of expert medical opinion is that there is no significant difference in the amount of potassium loss caused by thiazide agents, including methyclothiazide (Enduron).

This ad suggests that any physician taking a patient off a thiazide-potassium combination may wish to consider Enduron as alternative therapy. It states that the product will "do an outstanding job for you, *without* routine potassium supplementation," and that it has "potassium-sparing characteristics." The FDA believes that these claims could lead to the erroneous conclusion that hypokalemia is less likely to occur, and consequently, that potassium supplementation is less often necessary with Enduron than with other thiazides.

In point of fact, the need to consider proper potassium supplementation, dietary or otherwise, is no less with Enduron or Enduronyl than with any other thiazide drug.

Because the ad's "brief summary" of warning information was considered inadequate, a new one is enclosed.[1] The information capitalized in the attached revised "brief summary" is not present in current ads, but will be incorporated into future ads for these products.

ABBOTT LABORATORIES.

FLINT LABORATORIES,
Morton Grove, Ill., July 20, 1967.

DEAR DOCTOR: The Food and Drug Administration has asked us to call your attention to the initial advertisements for Choloxin® (sodium dextrothyroxine), currently appearing in several journals, which are regarded by the FDA as misleading.

The headline, "A significant new advance in the management of hypercholesterolemia", does not include the qualification that Choloxin is indicated for the treatment of hypercholesterolemia in selected patients, i.e., euthyroid patients with no known evidence of organic heart disease. Also, the ad fails to stress that Choloxin is not intended to replace or to lessen the desirability of considering dietary regulation in the management of hypercholesterolemia.

The FDA points out that, while the ads emphasize that Choloxin effectively lowers blood cholesterol levels, they fail to emphasize that this effect has not been

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[1] Retained in committee files.

proven to alter the morbidity and mortality of atherosclerotic disease. The claim in the ads that Choloxin (sodium dextrothyroxine) is "significant in its accepted physiologic mode of action" is considered to oversimplify the extent of knowledge of its mode of action. Further, the reference to "over 6,000 patients treated in clinical studies" overstates pertinent clinical experience, since only 2,967 patients were in the diagnostic categories for which the drug is currently indicated.

The FDA also considers the summary of warning information in the ads to be incomplete. The enclosed "Brief Summary" contains information in capital letters that was not present in the current ads, but will be incorporated into future ads for Choloxin. We are discontinuing the ads in question. The safety and efficacy of Choloxin are not in question when used in accordance with the official package circular, which remains unchanged.

Sincerely,

THOMAS A. GARRETT,
Vice President, Medical Affairs.

(NOTE.—This revised "Brief Summary" for use in future medical journal advertising contains additional phrases and items (printed in capital letters) from the official package insert which remains unchanged.)

SUMMARY

THE USE OF CHOLOXIN® (SODIUM DEXTROTHYROXINE) DOES NOT REPLACE OR DIMINISH THE DESIRABILITY OF DIETARY MANAGEMENT OF HYPERCHOLESTEROLEMIA, THE INFLUENCE OF LOWERED SERUM CHOLESTEROL ON MORBIDITY AND MORTALITY OF ATHEROSCLEROTIC DISEASE CANNOT BE ASSESSED UNTIL LONG-TERM CLINICAL TRIALS HAVE BEEN COMPLETED.

INDICATIONS: THIS IS NOT AN INNOCUOUS DRUG. Strict Attention should be paid to the indications and contraindications. Indicated for treatment of hypercholesterolemia in euthyroid patients with no known evidence of organic heart disease. Also indicated for treatment of hypothyroidism in patients with cardiac disease who cannot tolerate other types of thyroid medication.

CONTRAINDICATIONS: (1) Known organic heart disease, INCLUDING ANGINA PECTORIS; HISTORY OF MYOCARDIAL INFARCTION; CARDIAC ARRHYTHMIA OR TACHYCARDIA, EITHER ACTIVE OR IN PATIENTS WITH DEMONSTRATED PROPENSITY FOR ARRHYTHMIAS; rheumatic heart disease; HISTORY OF CONGESTIVE HEART FAILURE; AND DECOMPENSATED OR BORDERLINE COMPENSATED CARDIAC STATUS. (2) Hypertensive states (OTHER THAN MILD, LABILE SYSTOLIC HYPERTENSION). (3) Advanced liver or kidney disease. (4) Pregnancy. (5) Nursing mothers. (6) History of iodism.

A *relative* contraindication is impaired liver or kidney function; WHEN EITHER OR BOTH ARE PRESENT, THE ADVANTAGES OF SODIUM DEXTROTHYROXINE THERAPY MUST BE WEIGHED AGAINST THE POSSIBILITY OF DELETERIOUS RESULTS.

WARNINGS: Because the effects of anticoagulants may be potentiated, REDUCE DOSAGE OF ANTICOAGULANTS BY ONE-THIRD ON INITIATION OF THERAPY and readjust as necessary ON THE BASIS OF WEEKLY TESTS OF PROTHROMBIN TIME. Concentration of Factors VII, VIII, IX, and platelet activity SHOULD ALSO BE MONITORED, since these factors may be decreased. CONSIDER WITHDRAWAL OF CHOLOXIN (SODIUM DEXTROTHYROXINE) 2 WEEKS BEFORE SURGERY IF USE OF ANTICOAGULANTS IS CONTEMPLATED.

Careful consideration of dosage schedule in hypothyroid patients WITH CARDIAC DISEASE is required, and the drug should be withdrawn or dosage reduced if AGGRAVATION OF ANGINA, INCREASED MYOCARDIAL ISCHEMIA, CARDIAC FAILURE, OR CLINICALLY SIGNIFICANT ARRHYTHMIA develops. HYPOTHYROID PATIENTS ARE MORE SENSITIVE THAN EUTHYROID PATIENTS, ESPECIALLY IF TREATED CONCOMITANTLY WITH OTHER THYROID PREPARATIONS; SPECIAL CONSIDERATION TO THE DOSAGE OF THE LATTER MUST BE GIVEN.

Thyroid preparations may enhance the effects of epinephrine injections, predisposing to arrhythmias OR CORONARY INSUFFICIENCY. DRUG WITHDRAWAL OR CAREFUL OBSERVATION OF PATIENTS RECEIVING SUCH INJECTIONS IS RECOMMENDED, ESPECIALLY BEFORE ELECTIVE SURGERY.

In diabetic patients, increased blood sugar levels may be observed, requiring upward adjustment of antidiabetic drug dosage, and SUBSEQUENT READJUSTMENT IF DEXTROTHYROXINE IS LATER WITHDRAWN.

USE IN WOMEN OF CHILDBEARING AGE: In women exercising birth control procedures, the drug should only be administered AFTER WEIGHING POSSIBLE RISK TO THE FETUS AGAINST POSSIBLE BENEFITS TO THE MOTHER, TERATOGENIC STUDIES IN TWO ANIMAL SPECIES HAVE BEEN NEGATIVE.

PRECAUTIONS: UNUSUALLY HIGH PBI VALUES ARE COMMON IN TREATED PATIENTS AND ARE NOT EVIDENCE OF HYPERMETABOLISM. IN CHILDREN, USE ONLY WHEN A SIGNIFICANT CHOLESTEROL LOWERING EFFECT IS OBSERVED. Withdrawal is indicated if iodism or new cardiac signs or symptoms develop.

ADVERSE REACTIONS: For the most part due to increased metabolism, AND THUS MORE COMMON IN THE HYPOTHYROID PATIENT, ESPECIALLY THE HYPOTHYROID CARDIAC. Cardiac changes have rarely been precipitated in non-cardiac patients. Angina pectoris (0.2% incidence), arrhythmia (0.5%), MYOCARDIAL ISCHEMIA (<0.1%), CARDIOMEGALY (<0.1%), FATAL AND NON-FATAL myocardial infarctions (<0.2%). Insomnia, nervousness, palpitations, tremors, WEIGHT LOSS, LID LAG, SWEATING, FLUSHING, HYPERTHERMIA, HAIR LOSS, CHANGES IN BOWEL HABITS, DIURESIS, AND MENSTRUAL IRREGULARITIES MAY ALSO BE RELATED TO THE MILD METABOLIC ACTION, A FEW PATIENTS DEVELOPED ITCHING AND SKIN RASHES, APPARENTLY FROM IODISM. DYSPEPSIA, NAUSEA AND VOMITING, AND CHANGES IN APPETITE OCCURRED IN LESS THAN 1%. HEADACHE, CHANGES IN LIBIDO, HOARSENESS, TINNITUS, DIZZINESS, PERIPHERAL EDEMA, MALAISE, TIREDNESS, VISUAL DISTURBANCES, PSYCHIC CHANGES, PARESTHESIA, MUCLE PAIN, AND BIZARRE COMPLAINTS WERE REPORTED IN LESS THAN 1% OF TREATED PATIENTS. GALLSTONES WERE NEWLY DISCOVERED IN 13 PATIENTS, AND CHOLESTATIC JAUNDICE IN ONE, ALTHOUGH RELATIONSHIP TO DRUG THERAPY WAS NOT ESTABLISHED. IN A TOTAL OF 19 PATIENTS, PRE-EXISTING PERIPHERAL VASCULAR DISEASE, EXOPHTHALMOS, RETINOPATHY, AND DISTURBED SENSORIUM CONTINUED TO WORSEN. CEREBROVASCULAR ACCIDENTS, THROMBOPHLEBITIS, AND G.I. HEMORRHAGES EACH OCCURRED IN LESS THAN 1% OF PATIENTS, BUT THERE APPEARS TO BE NO RELATIONSHIP TO DEXTROTHYROXINE THERAPY.

In the nearly 3,000 patients studied, the withdrawal rate was less than 3%.

PHARMACOLOGY: MOST EVIDENCE INDICATES THE MECHANISM OF ACTION IS TO STIMULATE THE LIVER TO INCREASE CATABOLISM OF CHOLESTEROL; SYNTHESIS OF CHOLESTEROL IS NOT INHIBITED, AND ABNORMAL METABOLIC END PRODUCTS DO NOT ACCUMULATE IN THE BLOOD.

DOSAGE RECOMMENDATIONS: Dosage should start at 1.0 or 2.0 mg daily to be increased monthly in 1.0 or 2.0 mg increments to a maximum of 6.0 to 8.0 mg daily if necessary for control of serum cholesterol in the adult. In hypothyroid patients, the more conservative dosage schedule should be observed. Pediatric dosage is 0.05 mg/kg daily, increased monthly in 0.05 mg/kg increments to 0.1 mg/kg or 4.0 mg daily if necessary for control.

SUPPLIED: 2.0 mg and 4.0 mg scored tablets in prescription bottles of 30.

MEAD JOHNSON LABORATORIES,
Evansville, Ind., June 30, 1967.

DEAR DOCTOR: The Food and Drug Administration has requested that we call your attention to current medical journal advertisements for Oracon and Questran which the FDA regards as misleading.

Oracon®

The ad claims that the drug provides ". . . oral contraception with effects which closely parallel those of the natural hormonal cycle" and also contains a related slogan implying such effects are "So Close to Nature." The FDA points out that not nearly all effects of oral contraceptives parallel those of the natural hormonal cycle and that some of the effects of these drugs are of profound or undetermined nature.

The ad emphasizes the low incidence of certain less serious side effects such as amenorrhea, breakthrough bleeding, weight gain, etc. However, it fails to give adequate emphasis to more serious known side effects—or adequate emphasis to the possible occurrence of thrombophlebitis, pulmonary embolism or cerebral vascular accident.

The FDA points out that the pregnancy rates claimed in the ad were incorrectly based on 1065 women instead of only 880, and that the ad improperly features a pregnancy rates of 0.2 per 100 women-years. While available data do not provide a reliable scientific basis for a statement of true pregnancy rates, experience reported to us shows that the unadjusted rate for all women who were given Oracon was 2.0 per 100 women-years. The rate of 0.2 used in the ad included only those patients who insisted that they had adhered to the regimen.

Questran®

The FDA considers the summary of warning information in the journal advertisement for Questran to be inadequate in that it did not contain any information on precautions and warnings. We have attached a revised "Brief Summary," which contains the omitted precautions and warning information in capital letters.

We are discontinuing the ads in question, and future advertising will incorporate the above corrections. The safety and effectiveness of Oracon and Questran are not in question when the drugs are used in accordance with the official package inserts.

Sincerely,

P. A. WALTER, M.D.,
Director, Medical Research Department.

(NOTE.—This revised "Brief Summary," for use in medical journal advertising, contains additional information, in capital letters, taken from the official package insert.)

BRIEF SUMMARY OF WARNING INFORMATION FOR QUESTRAN® (CHOLESTYRAMINE)

Indication—Questran relieves pruritus associated with partial biliary obstruction.

Contraindication—Patients with complete biliary obstruction.

Warning—ALWAYS ADMIX QUESTRAN WITH WATER OR OTHER FLUIDS BEFORE INGESTING. TO PREVENT DEFICIENCIES OF VITAMINS A, D AND K, SUPPLEMENT THE DIET, AND SEE PRECAUTIONS BELOW.

Usage in Pregnancy—THE SAFE USE OF QUESTRAN BY PREGNANT AND LACTATING WOMEN HAS NOT BEEN ESTABLISHED.

Precautions—WITH PROLONGED QUESTRAN ADMINISTRATION, GIVE VITAMINS A AND D DAILY. INCREASED BLEEDING TENDENCIES MAY DEVELOP. PROMPT RESPONSE TO PARENTERAL VITAMIN K_1 MAY BE ANTICIPATED. ADMINISTER CHLOROTHIAZIDE, PHENYLBUTAZONE OR WARFARIN ONE HOUR BEFORE QUESTRAN. AS A PRECAUTIONARY MEASURE, ADMINISTER ALL OTHER DRUGS 30 MINUTES TO 1 HOUR BEFORE QUESTRN. A THEORETICAL POSSIBILITY EXISTS THAT PROLONGED USE MAY LEAD TO DEVELOPMENT OF HYPERCHOLOREMIC ACIDOSIS. HERE IS NO ESTABLISHED RATIONALE FOR USE OF QUESTRAN IN THE RELIEF OF PRURITUS ASSOCIATED WITH OTHER DISEASE PROCESSES.

Adverse reactions

Gastrointestinal and Dermatological—Constipation, diarrhea, nausea, gastrointestinal distress, and vomiting have been reported by about 20% of patients using cholestrymine. Reported less frequently were ABDOMINAL PAIN AND DISTENTION, rash, irritation of the skin, tongue and perianal area.

Bleeding—In 1% of patients, increased bleeding tendencies occurred due to hypoprothrombinemia.

Steatorrhea—Steatorrhea occurred but rarely, and then on doses in excess of 24 grains per day.

Cholesterol—In patients with pruritus associated with partial biliary obstruction, serum cholesterol levels usually decreases during Questra therapy. (Clinical experience has not established the therapeutic use of Questran to reduce serum chlosterol.)

Biliary Calcification—Two possible instances have been observed, but a casual relationship has not been established.

ARDSLEY, N.Y.

DEAR DOCTOR: The Food and Drug Administration has asked us to call your attention to recent journal advertisements for our products (Hygroton® and Regroton®) which the FDA considers to be misleading.

Hygroton Advertisement

This ad is headlined, "Do your patients shell out too much for a diuretic?". It states that a published report on a new short-acting diuretic supports the claim that "If one considers maximum recommended doses for each product, tablet for tablet Hygroton was clearly superior. Two tablets of Hygroton were found to produce almost 40% more natruresis and 20% more weight loss than five tablets of the other diuretic."

The FDA points out that the studies were based on small numbers of patients (6 to 13), that the actual differences reported were clinically insignificant, and that the ad's claim for superiority was not supported by the data or by the authors' conclusions. Further, the report was not a direct comparative study of the two drugs, but rather a comparison of data obtained on the new diuretic with data obtained on Hygroton in a previous study.

In addition, the tablet-for-tablet comparison in the ad is not regarded as sound because single tablets of Hygroton and the other diuretic do not contain comparable therapeutic dosages.

Regroton Advertisement

This ad displays a single Regroton tablet in relation to two sets of five tablets representing drug regimens for treating hypertension. The ad states that "in moderate hypertension" Regroton was "better than reserpine + hydralazine + hydrocholorothiazide in 41 of 43 patients and better than reserpine + methyldopa + hydrochlorothiazide in 34 of 37 patients". These numbers, taken from a paper referenced in the ad, refer specifically to a comparison of average mean blood pressures after two years on Regroton with responses to prior therapy utilizing the other drug combinations.

The FDA points out that the differences observed in the blood pressure response to the various treatments were neither statistically nor clinically significant. Further, the study was not done on patients diagnosed as "moderate hypertension", and the authors did not state that the effect of Regroton on the patients' blood pressure was "better".

The FDA also considers the summary of prescribing information in each ad to be inadequate. Each enclosed "Brief Summary" contains information in capital letters that was not included in our current ads. We are discontinuing the ads in question and future advertising will incorporate the revised "Brief Summary". The safety and effectiveness of the products are not in question when used in accordance with the official package inserts.

GEIGY PHARMACEUTICALS.

(NOTE.—This revised "Brief Summary", for use in future medical journal advertising, contains additional words and phrases (printed in capital letters) taken from the official package insert.)

BRIEF SUMMARY OF HYGROTON®—BRAND OF CHLORTHALIDONE

Indications: Hypertension and many types of edema involving retention of salt and water.

Contraindications: Hypersensitivity and most cases of severe renal of hepatic disease.

Warning: With the administration of enteric-coated potassium supplements, WHICH SHOULD BE USED ONLY WHEN ADEQUATE DIETARY SUPPLEMENTATION IS NOT PRACTICAL; the possibility of small bowel lesions (OBSTRUCTION, HEMORRHAGE, AND PERFORATION) should be kept in mind. SURGERY FOR THESE LESIONS HAS FREQUENTLY BEEN REQUIRED AND DEATHS HAVE OCCURRED. DISCONTINUE ENTERIC-COATED POTASSIUM SUPPLEMENTS IMMEDIATELY IF OBDOMINAL PAIN, DISTENTION, NAUSEA, VOMITING, OR GASTROINTESTINAL BLEEDING OCCUR.

Use with caution in pregnant patients, since the drug may cross the placental barrier and adverse reactions which may occur in the adult (thrombocytopenia, hyperbilirubinemia, altered carbohydrate metabolism, etc.) are potential problems in the newborn.

Precautions: ANTIHYPERTENSIVE THERAPY WITH HYGROTON SHOULD ALWAYS BE INITIATED CAUTIOUSLY in postsympathectomy patients and IN PATIENTS RECEIVING GANGLIONIC BLOCKING AGENTS OR OTHER POTENT ANTIHYPERTENSIVE DRUGS, or curare. Reduce dosage of concomitant antihypertensive agents by at least one-half. Barbiturates, narcotics or alcohol may potentiate hypotension. BECAUSE OF THE POSSIBILITY OF PROGRESSION OF RENAL, DAMAGE, PERIODIC DETERMINATION OF THE BUN IS INDICATED. Discontinue if the BUN rises or liver dysfunction is aggravated. HEPATIC COMA MAY PRECIPITATED.

Electrolyte imbalance, SODIUM AND/OR potassium depletion may occur. IF POTASSIUM DEPLETION SHOULD OCCUR DURING THERAPY, HYGROTON SHOULD BE DISCONTINUED AND POTASSIUM SUPPLEMENTS GIVEN, PROVIDED THE PATIENT DOES NOT HAVE MARKED OLIGURIA.

Take special care in cirrhosis or severe ischemic heart disease and in patients receiving corticosteroids, ACTH, or digitalis. Salt restriction is not recommended.

Adverse Reactions: Nausea, gastric irritation, vomiting, anorexia, constipation and cramping, dizziness, weakness, restlessness, hyperglycemia, hyperuricemia, headache, muscle cramps, orthostatic hypotension, aplastic anemia, leukopenia, thrombocytopenia, agranulocytosis, impotence, dysuria, transient myopia, skin rashes, urticaria, purpura, necrotizing angiitis, ACUTE GOUT, AND PANCREATITIS WHEN epigastric pain or UNEXPLAINED G.I. symptoms DEVELOP after prolonged administration. Other reactions reported with this class of compounds include: jaundice, xanthopsia, paresthesia, and photosensitization.

Average Dosage: One tablet (100 mg.) with breakfast daily or every other day.

Availability: White, single-scored tablets of 100 mg. in bottles of 100 and 1000.

(NOTE.—This revised "Brief Summary", for use in future medical journal advertising, contains additional words and phrases (printed in capital letters) taken from the official package insert.)

BRIEF SUMMARY OF REGROTON®—CHLORTHALIDONE, 50 MG., RESERPINE U.S.P., 0.25 MG.

Indications: Hypertension.

Contraindications: History of mental depression, hypersensitivity, and most cases of severe renal or hepatic diseases.

Warning: With the administration of enteric-coated potassium supplements, WHICH SHOULD BE USED ONLY WHEN ADEQUATE DIETARY SUPPLEMENTATION IS NOT PRACTICAL, the possibility of small bowel lesions (OBSTRUCTION, HEMORRHAGE, AND PERFORATION) should be kept in mind. SURGERY, FOR THESE LESIONS HAS FREQUENTLY BEEN REQUIRED AND DEATHS HAVE OCCURRED.

DISCONTINUE COATED POTASSIUM-CONTAINING FORMULATIONS IMMEDIATELY IF ABDOMINAL PAIN, DISTENTION, NAUSEA, VOMITING, OR GASTROINTESTINAL BLEEDING OCCUR.

Use cautiously during pregnancy since adverse reactions (thrombocytopenia, hyperbilirubinemia, altered carbohydrate metabolism, etc.) are potential problems in the newborn.

Discontinue 2 weeks before general anesthesia, 1 week before electroshock therapy, and if depression or peptic ulcer occurs.

Precautions: ANTIHYPERTENSIVE THERAPY WITH REGROTON SHOULD ALWAYS BE INITIATED CAUTIOUSLY in postsympathectomy patients and IN PATIENTS RECEIVING GANGLIONIC BLOCKING AGENTS, OTHER POTENT ANTIHYPERTENSIVE DRUGS, or curare. Reduce dosage of concomitant antihypertensive agents by at least one-half.

BECAUSE OF THE POSSIBILITY OF PROGRESSION OF RENAL DAMAGE, PERIODIC KIDNEY FUNCTION TESTS ARE INDICATED. Discontinue if the BUN rises or liver dysfunction is aggravated, HEPATIC COMA MAY BE PRECIPITATED.

Electrolyte imbalance, SODIUM AND/OR potassium depletion may occur. IF POTASSIUM DEPLETION SHOULD OCCUR DURING THERAPY, REGROTON SHOULD BE DISCONTINUED AND POTASSIUM SUPPLEMENTS GIVEN, PROVIDED THE PATIENT DOES NOT HAVE MARKED OLIGURIA.

Take particular care in cirrhosis or severe ischemic heart disease and in patients receiving corticosteroids, ACTH, or digitalis. Salt restriction is not recommended. BILIARY COLIC MAY BE PRECIPITATED (IN PATIENTS

WITH GALLSTONES) AND BRONCHIAL ASTHMA MAY OCCUR IN SUSCEPTIBLE PATIENTS.

Adverse Reactions: The drug is generally well tolerated. The most frequent side effects are nausea, gastrict irritation, vomiting, diarrhea, constipation, muscle cramps, headache, dizziness and ACUTE GOUT. Other potential side effects include angina pectoris, anxiety, depression, bradycardia and ectopic cardiac rhythms (especially when used with digitalis), drowsiness, dull sensorium, hyperglycemia, hyperuricemia, lassitude, restlessness, transient myiopia, impotence or dysuria, orthostatic hypotension which may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics, leukopenia, aplastic anemia, skin rashes, THROMBOCYTOPENIA, AGRANULOCYTOSIS, nasal stuffiness, increased gastric secretions, nightmare, purpura, urticaria, ecchymosis, weakness, uveitis, optic atrophy and glaucoma, and PRURITUS, ERUPTIONS AND/OR FLUSHING OF THE SKIN, A REVERSIBLE PARALYSIS AGITANS-LIKE SYNDROME, INCREASED SUSCEPTIBILITY TO COLDS, DYSPNEA, weight gain, decreased libido, DRYNESS OF THE MOUTH, deafness, ANOREXIA, AND PANCREATITIS WHEN EPIGASTRIC PAIN OR UNEXPLAINED G.I. SYMPTOMS DEVELOP AFTER PROLONGED ADMINISTRATION. Jaundice, xanthopsia, PARESTHESIA, PHOTOSENSITIZATION and necrotizing angiitis ARE POSSIBLE.

Average Dosis: One tablet daily with breakfast.

Availability: Pink, single-scored tablets in bottles of 100 and 1000.

PFIZER LABORATORIES,
New York, N.Y., May 22, 1967.

DEAR DOCTOR: The Food and Drug Administration has requested that we call your attention to recent promotional messages for our products (Rondomycin, Renese, and Renese–R) which the FDA regards as potentially misleading.

Renese and Renese–R

The monograph in the 1967 *Physicians' Desk Reference* for Renese and Renese–R is considered inadequate in presenting information necessary for their safe and effective use. To provide you with the necessary additional information, we are enclosing a revised monograph for insertion into your *PDR*. The changes include additional warnings and precautions concerned with electrolyte imbalance, hepatic coma, maintenance dosage, and, in the case of Renese–R, the possibility of Parkinsonism and confusion.

Rondomycin

The FDA has also asked us to call to your attention certain features of our current advertising for the broad spectrum antibiotic, Rondomycin. The ad does not disclose that it is a member of the bacteriostatic tetracycline family and that administration for ten days is especially important in the treatment of Beta-hemolytic streptococcal infections. In referring to the "Protective dose (PD_{50}) tests," the ad did not specify that they were performed in mice utilizing laboratory strains of organisms injected intraperitoneally. While demonstrating the activity of Rondomycin against these test strains, the PD_{50} tests cannot be extrapolated directly to the clinical situation, in which sensitivity testing is recognized to be important for selection of the most appropriate antibiotic for a specific patient's infection.

In addition, the "Brief Summary" of warning information in the above ad, and also in the current journal ad for Renese–R, is considered inadequate. We are modifying the advertisements in question and future advertising will include the requested additional warning information.

Sincerely yours,

JOHN L. WATTERS, M.D.,
Medical Director.

NEW YORK, N.Y., *August 11, 1967.*

DEAR DOCTOR: The Food and Drug Administration has asked us to call your attention to a recent advertisement for Diutensen-R which the FDA regards as misleading.

The Food and Drug Administration regards the warning information in the ad to be so substantially deficient that the ad represents a potential danger to health. Therefore, we have rewritten our "Brief Summary", and the nature and extent of the changes are shown in capital letters in the attached revision. We

have discontinued the ad in question and all future ads will carry the new "Brief Summary".

The safety and efficacy of Diutensen-R are not in question when used in accordance with the prescribing information in the official package insert.

Sincerely,

NEISLER LABORATORIES.

(NOTE: This revised "Brief Summary," for use in future medical journal advertising, contains additional words and phrases (printed in capital letters) taken from the official package insert.)

BRIEF SUMMARY OF WARNING INFORMATION FOR DIUTENSEN-R

(For prescribing information, consult official package insert)

Indications: Hypertension.

Contraindications: SEVERE DEPRESSION and KNOWN HYPERTENSITIVITY TO reserpine, VERATRUM VIRIDE OR THIAZIDE COMPOUNDS.

WARNING: WITH THE ADMINISTRATION OF ENTERIC-COATED POTASSIUM SUPPLEMENTS, WHICH SHOULD BE USED ONLY WHEN ADEQNATE DIETARY SUPPLEMENTATION IS NOT PRACTICAL, THE POSSIBILITY OF SMALL BOWEL LESIONS CONSISTING OR STENOSIS WITH OR WITHOUT ULCERATION, AND CAUSING OBSTRUCTION, HEMMORRHAGE, AND PERFORATION, SHOULD BE KEPT IN MIND. SURGERY FOR THESE LESIONS HAS FREQUENTLY BEEN REQUIRED AND DEATHS HAVE OCCURRED. DISCONTINUE COATED POTASSIUM-CONTAINING FORMULATIONS IMMDIATELY IF ABDOMINAL PAIN, DISTENTION, NAUSEA, VOMITING, OR GASTROINTESTINAL BLEEDING OCCUR.

DISCONTINUE 2 WEEKS BEFORE GENERAL ANESTHESIA OR ELECTROSHOCK THERAPY, AND IF DEPRESSION OR PEPTIC ULCER OCCURS.

Precautions: ELECTROLYTE IMBALANCE, HYPOCHLOREMIC ALKALOSIS SODIUM AND/OR POTASSIUM DEPLETION MAY OCCUR. IF POTASSIUM DEPLETION SHOULD OCCUR DURING THERAPY, DIUTENSEN-R SHOULD BE DISCONTINUED AND POTASSIUM SUPPLEMENTS GIVEN, PROVIDED THE PATIENT DOES NOT HAVE MARKED OLIGURIA. HYPOCHLOREMIC ALKALOSIS MAY BE TREATED WITH AMMONIUM CHLORIDE IF NO LIVER DISEASE IS PRESENT.

PARTICULAR OBSERVANCE OF THE SERUM ELECTROLYTE BALANCE AND/OR POTASSIUM SUPPLEMENTATION IS NECESSARY IN PATIENTS RECEIVING HIGHER DOSAGE LEVELS, DIGITALIS, POTASSIUM DEPLETING CORTICOSTEROIDS, AND IN CIRRHOSIS ESPECIALLY WHEN THERE IS IMPENDING HEPATIC COMA.

IF PROGRESSIVE INCREASE IN SERUM NITROGEN (BUN, NPN, OR CREATININE) OCCURS, THERAPY SHOULD BS DISCONTINUED.

USE WITH CAUTION IN PATIENTS WITH A HISTORY OF PEPTIC ULCER, ULCERATIVE COLITIS, OR DEPRESSION.

DIUTENSEN-R MAY INCREASE THE POSSIBILITY OF DIGITALS INTOXICATION. Reduce dose or discontinue if myocardial irritability occurs (extrasystoles, bigeminy or AV block).

Adverse Reactions: Occasional urinary frequency, nocturia, nasal congestion, DRYNESS OF THE MOUTH, muscle cramps, skin rash, joint pains due to gout, nausea, VOMITING, and dizziness.

POTENTIAL SIDE EFFECTS INCLUDE HYPERGLYCEMIA, RISE IN SERUM URIC ACID, PURPURA, THROMBOCYTOPENIA, LEUKOPENIA, PARKINSONISM, BRADCARDIA AND EXCESSIVE HYPOTENSION WITH PROSTRATION. (TREAT BRADYCARDIA WITH ATROPINE AND HYPOTENSION WITH VASOPRESSORS.) DRUG SHOULD BE DISCONTINUED IF SUFFICIENT HYPERGLYCEMIA IS OBSERVED, OR IF PURPURA, THROMBOCYTOPENIA, OR LEUKOPENIA OCCUR.

Usual Dosage: One tablet twice daily at morning and evening meals. Daily dosage should not exceed 4 tablets.

WORCESTER, MASS., *August 23, 1967.*

DEAR DOCTOR: The Food and Drug Administration has asked us to call to your attention two of our recent mailing pieces for Citanest® which the FDA regards as so substantially misleading and lacking in adequate professional use information that in its view they represent potential hazards to health

These mailing pieces, identified as 118–67 and 119–67, should be discarded if still in your possession.

1. Intravenous regional anesthesia

Mailing piece 118–67 recommended the use of Citanest in intravenous regional anesthesia. The FDA regards use of this drug by that technique as experimental. The package insert for Citanest contains no information for its use in intravenous regional anesthesia and the drug has not been approved for use in that procedure.

2. Maximum single dosage

Mailing pieces 118–67 and 119–67 contained statements which implied that dosages of Citanest in excess of the maximum single dose (600 mg.) could be employed in clinical use. No such implication was intended by Astra, and Astra reaffirms that no more than 600 mg. of the drug should be used during any two-hour period.

Professional use information

Both booklets omitted essential and required professional use information. The attached page contains the warning, precautionary, and adverse reaction information which was omitted from the "full disclosure" sections of the booklets.

The safety and effectiveness of Citanest (prilocaine), when used in accordance with the conditions specified in the enclosed package insert, are not in question.

Sincerely yours,

ASTRA PHARMACEUTICAL PRODUCTS, INC.

ASTRA®

The following warning, precautionary, and adverse reaction information contained in the approved (November 18, 1965) Citanest labeling (identified "120" and "Issued October, 1965") is omitted from the product information text of Citanest® mailing pieces 118–67 and 119–67:

Warning: It should be remembered that all local anesthetics are potentially toxic drugs. Therefore, the minimum amount of local anesthetic agent necessary to produce adequate anesthesia and avoid toxic reactions should be used at all times. Moreover, as with other types of drugs, the use of local anesthetics such as Citanest (prilocaine) should be minimal during pregnancy. This, of course, does not exclude the use of local anesthetics at term for obstetrical analgesia. Citanest (prilocaine) has been used effectively for obstetrical analgesia with no adverse effects noted on the fetus, course of labor, or delivery.

Precautions: The peridural space can be approached from the thoracic, lumbar and sacral (caudal) regions. It must be kept in mind that these areas contain venous and arterial plexuses and lymph vessels. Further, the close proximity of these regions to the subarachnoid space constitutes an additional hazard of which the anesthesiologist must be constantly aware. Consequently, the technique of peridural anesthesia should be attempted only by skilled individuals. Close familiarity with, and readiness to make use of every known precautionary measure are mandatory. Further, in addition to the accepted procedure for locating the peridural space, a test dose of 5 cc should be administered at least 5 minutes prior to injecting the total required volume.

While desirable in most instances, the application of the test dose cannot be regarded as a completely effective safety measure. The judicious selection of needles of the proper length and bevel is also important; e.g., in the case of the sacral (caudal) approach, it is necessary that the sacral canal be penetrated for a distance of only 1½ to 2 inches. Since it is possible to puncture the dura by this approach, the use of excessively long needles is definitely precluded.

Local anesthetics react with certain metals and cause the release of their respective ions which, if injected, may cause severe local irritation. Adequate precaution should be taken to avoid this type of interaction.

Treatment:

1. In adverent subarachnoid injection:
   a) Resusciate with oxygen and control blood pressure with vasopressor agents.
   b) Aspirate spinal fluid until 50 cc is removed.

2. Barbiturates may be used prophylactically but offer only a small degree of protection against a lethal dose.

Side effects and their treatment:

1. Syncope—Stop injection, recumbent position with legs raised, oxygen, aromatic spirits of ammonia, cold compresses.
2. Hypotension—Stop injection, recumbent position with legs raised, assure adequate ventilation with oxygen. Support circulation with vasopressor if necessary.
3. Apnea—Stop injection, recumbent position, maintain patent airway, artificial respiration with oxygen.
4. Headache and/or backache—Bed rest, analgesic agents as needed. It should be remembered that these side effects most often accompany spinal anesthesia and Citanest (prilocaine) is not recommended for spinal use at this time.
5. Nausea and vomiting—Stop injection, maintain patent airway, prevent aspiration, anti-emetics as needed.

Methemoglobinemia: At a dose of 600 mg of Citanest (prilocaine), which is the maximum recommended dose for any anesthetic procedure, methemoglobin formation did occur but was less than 15% of total hemoglobin in all patients studied.

With respect to the clinical symptoms associated with methemoglobinemia, the following statement has been made in textbooks: In general, levels of less than 20 per cent methemoglobin are usually not associated with symptoms. At levels of 20 to 50 per cent fatigue, weakness, dyspnea, tachycardia, headaches, and dizziness may occur. In studies conducted to date no patient in whom the maximum recommended dose of 600 mg of Citanest (prilocaine) was used demonstrated a methemoglobin value in excess of 15% and no clinical symptoms have been observed. Moreover, in clinical studies involving approximately 9000 cases in which Citanest (prilocaine) has been used, only one patient who received a single injection of 900 mg has been reported to have exhibited clinical symptoms of lightheadedness and dizziness may have been related to methemoglobin value in excess of 20%.

Administration and Dosage: With the exception of therapeutic nerve blocks, 20–30 ml of Citanest (prilocaine) hydrochloride 1% or 2% and 15–20 ml of Citanest (prilocaine) hydrochloride 3% will usually produce adequate operative anesthesia.

The onset of anesthesia, the duration of anesthesia and the degree of muscular relaxation are proportional to the volume and concentration of local anesthetic used. Thus, an increase in volume and concentration of Citanest (prilocaine) will decrease the onset of anesthesia, prolong the duration of anesthesia, provide a greater degree of muscular relaxation and increase the segmental spread of anesthesia. It should be remembered, however, that increasing the volume and concentration of Citanest (prilocaine) may result in a more profound fall in blood pressure when used in peridural anesthesia. Although the incidence of side effects in clinical trials was quite low, caution should be exercised particularly when employing large volumes and concentrations of Citanest (prilocaine) since the incidence of side effects is directly proportional to the total dose of local anesthetic agent injected.

Maximum recommended dosage: Normal Healthy Adults: No more than 600 mg of Citanest (prilocaine) hydrochloride should ever be administerd as a single injection, i.e., no more than 8 mg/kg or 4 mg/lb should be given as a single injection. The maximum total dose which may be administered over a period of several hours (e.g., for continuous peridural anesthesia) without side effects is not known as yet. Doses in excess of 2000 mg have been administered over a five-hour period with no toxic symptoms. However, until further data is available we would recommend that doses in excess of 600 mg not be administered at intervals of less than two hours so that one should not exceed a total dose of 1200 mg in a four-hour period.

Children: Experience in children under the age of ten (10) is limited. It is extremely difficult to recommend a maximum dose of any drug for children since this varies as a function of age and weight. With respect to Citanest (prilocaine) hydrochloride, 400 mg have been used without toxic effects in children of 10–15 years. However, for children of less than 10 years who have a normal lean body mass and normal body development, we recommend the use of one of the standard pediatric drug formulas (e.g., Clark's rule or Young's rule) to determine the maximum dose. For example, in a child of five years weighing 50 lbs., the dose of Citanest (prilocaine) hydrochloride should not exceed 150–200 mg

when calculated according to Clark's rule or Young's rule. In order to minimize the possibility of toxic reactions in children use of the 1% concentration of Citanest (prilocaine) hydrochloride is recommended.

Patients with Liver Disease and Debilitated Patients: The use of any general or local anesthetic agent is undesirable in patients with liver disease or severely debilitated patients. However, for emergency or definitive surgical procedures where a local anesthetic is required, care should be taken to use the lowest dose and concentration of Citanest (prilocaine) hydrochloride necessary to provide adequate anesthesia. It is extremely difficult to recommend a maximum safe dose of any drug for such patients, since this will depend on the degree of liver damage and degree of debilitation. For most anesthetic procedures, it is advisable to use the 1% concentration of Citanest (prilocaine) hydrochloride in order to obtain the minimum dose that will provide adequate anesthesia and thereby avoid possible toxic reactions in patients with liver disease or debilitated patients. In such patients it is probably not advisable to exceed a maximum dose of 400 mg.

DEAR DOCTOR: The Food and Drug Administration has asked us to call your attention to certain advertisements for Mysteclin–F products which the FDA regards as misleading. The main theme of the advertising, which we have stopped, suggests that "almost every candidate for broad-spectrum antibiotic therapy, is a candidate for Mysteclin–F."

We wish to emphasize that those patients selected for tetracycline therapy who are known to be particularly susceptible to candidal superinfection are the potential candidates for Mysteclin–F therapy.

The FDA points out that recent journal advertisements for these products suggested that candidal superinfection is a serious problem with the use of ampicillin. This was not supported by the reference used in the ads. Although the reference cited included the statement that candidal overgrowth may follow ampicillin therapy, the FDA has asked that we point out that the significance of this overgrowth has not been established.

Further, the same ads omitted important warning information relating to precautions and side effects. The nature and extent of the omission are capitalized in the enclosed "Brief Summary".

Sincerely,

SQUIBB.

(NOTE.—This revised "Brief Summary" for use in future medical journal advertising contains additional phrases and items (printed in capital letters) from the official package insert.)

Contraindications: History of hypersensitivity to either component.

Warning: If renal impairment exists, lower-than-usual doses are indicated to avoid systemic accumulation and possible liver toxicity; on prolonged use, tetracycline serum level determinations may be advisable. Photodynamic reactions, although rare with teracycline, may occur; if they occur, discontinue drug. Advise photosensitive patients to avoid direct sunlight.

Precautions: Watch for signs of secondary infection due to nonsusceptible organisms; discontinue drug and/or institute appropriate therapy if this occurs. SUPERINFECTION OF THE BOWEL BY STAPHYLOCOCCI MAY BE LIFE-THREATENING. Use of tetracycline, particularly long-term use, BUT ALSO IN USUAL SHORT TREATMENT COURSES, during the LATTER HALF OF GESTATION, NEONATAL PERIOD, AND EARLY CHILDHOOD tooth development may cause discoloration of teeth. TETRACYCLINE MAY FORM A STABLE CALCIUM COMPLEX IN BONE-FORMING TISSUE WITHOUT HARMFUL EFFECTS REPORTED THUS FAR. During long-term therapy, perform periodic renal, hepatic, and hematopoietic function studies. Increased intracranial pressure with bulging fontanels has been observed rarely in infants taking therapeutic doses of tetracycline. USE WITH CAUTION IN PERSONS WITH A HISTORY OF ALLERGY, ASTHMA, HAY FEVER, OR URTICARIA DUE TO GREATER POSSIBILITY OF SENSITIVITY REACTIONS. CROSS-SENSITIZATION WITH OTHER TETRACYCLINES IS COMMON. IN THE TREATMENT OF GONORRHEA, PATIENTS WITH A SUSPECTED LESION OF SYPHILIS SHOULD HAVE DARK-FIELD EXAMINATIONS BEFORE RECEIVING TETRACYCLINE AND MONTHLY SEROLOGIC TESTS FOR A MINIMUM OF THREE MONTHS.

Note: SOME STRAINS OF STAPHYLOCOCCI, STREPTOCOCCI, PNEUMOCOCCI, E. COLI, AND SHIGELLAE HAVE SHOWN RESISTANCE TO TETRACYCLINES. MICROORGANISMS THAT HAVE BECOME INSENSITIVE TO ONE TETRACYCLINE INVARIABLY EXHIBIT CROSS-RESISTANCE TO OTHER TETRACYCLINES, AND TETRACYCLINE RESISTANT GRAM NEGATIVE BACILLI MAY SHOW CROSS RESISTANCE TO CHLORAMPHENICOL. THEREFORE, INDICATED LABORATORY STUDIES, INCLUDING SENSITIVITY TESTS, SHOULD BE PERFORMED.

Side Effects: ANOREXIA, EPIGASTRIC DISTRESS, NAUSEA, VOMITING, BULKY LOOSE STOOLS, DIARRHEA, STOMATITIS, GLOSSITIS, ENTEROCOLITIS, PROCTITIS, PRUITUS ANI, BLACK HAIRY TONGUE, SORE THROAT, DYSPHAGIA, HOARSENESS, MACULOPAPULAR AND ERYTHEMATOUS RASHES, A RARE CASE OF EXFOLIATIVE DERMATITIS, rarely PHOTOSENSITIVITY, rarely ONYCHOLYSIS AND NAIL DISCOLORATION, DOSE-RELATED BUN RISE, URTICARIA, SERUM SICKNESS-LIKE REACTIONS, ANGIONEUROTIC EDEMA, ANAPHYLAXIS, BULGING FONTANELS IN INFANTS, DENTAL STAINING (see Precautions), TOOTH-ENAMEL HYPOPLASIA IN CHILDREN, ANEMIA, THROMBOCYTOPENIC PURPURA, NEUTROPEIA, EOSINOPHILIA, AND RARELY CHOLESTASIS ASSOCIATED WITH HIGH DOSAGE, URNARY NITROGEN LOSS WHICH MAY RESULT IN NEGATIVE NITROGEN BALANCE AND INCREASED SODIUM EXCRETION, DELAYED BLOOD COAGULATION, AND DEVELOPMENT OF PEPTIC ULCERS AND BLEEDING IN UREMIC PATIENTS. IF ALLERGIC REACTIONS OCCUR, OR IF AN INDIVIDUAL IDIOSYNCRASY APPEARS, TETRACYCLINE THERAPY SHOULD BE DISCONTINUED.

ORGANON, INC.,
West Orange, N.J., October 27, 1967.

DEAR DOCTOR: The Food and Drug Administration has requested that we call your attention to the monographs for Cortophin® Gel, Cortrophin® Zinc, Hexadrol® Phosphat Injection and Hexadrol® Tablets and Elixir in the current *Physicians Desk Reference.* The FDA considers these monographs to be incomplete in presenting necessary information for the safe and effective use of these drugs, and, therefore, potentially misleading.

To provide you with the necessary information, we enclose revised monographs for insertion in your *PDR.* The nature and extent of the additions and other revisions in the enclosed monographs are emphasized by the use of italics.

Sincerely yours,

JOSEPH D. CUONO, M.D.,
Director, Professional Services.

(NOTE.—Prescribing information for Cortrophin® Gel, Cortrophin® Zinc, Hexadrol® and Hexadrol® Phosphate Injection, which appears on pages *898–899* of your 1967 *PDR,* has been revised and is completely replaced by the following. The nature and extent of the additions and other revisions in the monographs are emphasized by use of italics.)

ORGANON, INC., WEST ORANGE, N.J.

PURIFIED CORTROPHIN® GEL

Repository Corticotropin Injection U.S.P.

Purified Cortrophin Gel is purified corticotropin (ACTH) in a sterile solution of gelatin for prolonged activity. It is supplied in two strengths: 40 U.S.P. Units and 80 U.S.P. Units per cc. Each cc. of each strength also contains 0.5% phenol (preservative), 15.0% gelatin, pil adjusted with IICI. This product requires fewer injections per day than aqueous corticotropin preparations to maintain adrenocorticotropic activity. It is solid at or below room temperature; before use, the gel should be liquefied by holding the vial under warm tap water. It should be injected subcutaneously or intramuscularly, never intravenously; a 20 or 21-gauge needle should be used. Injection sites should be alternated, and brief, firm pressure should be applied on the site after each injection.

Properities—This product offers prolonged ACTH activity. It stimulates the adrenals to an increased production of all the adrenocortical hormones. Three types of adrenal hormones are produced in this way: compound F-like hormones

(cortisone-like), which are the most abundant; desoxycorticosterone-like hormones; and the adrenal androgens. The production of compound F-like hormones is clinically the most significant, for these particular steroids are the ones that produce striking clinical response in so many diseases, and which enable the tissues and the body as a whole to meet serious stress. Adequate therapy usually produces the following desirable general changes: Temperature, if elevated, usually returns to normal within 6 to 18 hours. Pain is abolished within a short time and becomes an index of the reversibility of the disease under treatment. Patients develop a sense of well-being and of mental activity bordering on euphoria. Fibroblastic proliferation and inflammatory processes are blocked.

SPECIAL PRECAUTIONS WITH ADRENOCORTICOTROPIC THERAPY

This product functions by stimulating the production of steroid hormones by the adrenal cortices, and in this manner influences protein and carbohydrate metabolism, alters the metabolism of electrolytes with retention of sodium and excretion of potassium. In this same manner the steroid hormones of the adrenal cortices induce atrophy of the thymus and produce an increase in antihyaluronidase activity. Prolonged or excessive stimulation of the adrenals may produce undesirable effects, and for this reason each patient should be carefully observed to determine his response.

1. *Edema—With large doses or during prolonged use, sodium retention with intake, giving a diuretic, or by temporarily discontinuing therapy until diuresis results. If potassium deficiency with muscular weakness or edema occurs, supplemental potassium should be given: 1 Gm potassium citrate or chloride given orally three times a day.*

2. *Temperature and Infection—This product may mask signs of concomitant serious infections and therapy should be discontinued temporarily in order to permit diagnosis of the infection. Therapy may be resumed if warranted after specific therapy for the infection has been given.*

3. *Disturbed Psyche—If psychotic changes appear, these isolated cases should be treated by reducing or discontinuing dosage of corticotropin and the use of sedatives should begin.*

4. *Hyperglycemia and Glycosuria—Excessive dosage may increase the blood sugar and glycosuria may occur; this can be eliminated by reduction of dosage or cessation of therapy (see contraindications for diabetes below).*

5. *Hypertension—In certain individuals a marked increase in blood pressure may occur, and in these instances the dose should be reduced or eliminated.*

6. *Acne and Hirsutism—Prolonger therapy may cause overstimulation of androgenic hormone secretion which may induce these symptoms in some women; and these conditions may be controlled by suitable reduction in dosage. In severe cases, therapy may have to be discontinued.*

7. *Hypersensitivity—Susceptible individuals may become sensitized to traces of protein that accompany corticotropin so that subsequent injections given after intervals of several days may give rise to hypersensitivity phenomena. Therefore, patients who have previously been treated with corticotropin should be tested for sensitivity, and sensitive individuals should be desensitized before treatment is begun.*

Test of Adrenocortical Activity—One of the requisites to successful corticotropin therapy is a functioning adrenal cortex. The functional capacity of the adrenal conditions clinical response. A reduction in the number of circulating cosinophils is considered to reflect increased secretion of adrenal steroids and indicates a positive response to corticotropin. Normal subjects respond to the injection of adequate doses of ACTH with at least a 50 per cent fall in circulating cosinophils. The test (known as the Thorn test) is applied in the diagnosis of Addison's disease, as a test of adrenal reserve pre- and post-operatively, to determine the patient's ability to react to stress, and to differentiate between panhypopituitarism, functional hypopituitarism and Addison's disease. In hypopituitarism, where hypofunction lies in the hypophysis, reaction to the test is positive. In Addison's disease, where the deficiency resides in the adrenals, the response is negative.

Dosage Considerations—Because functional capacity of the adrenal varies with the patient, the dose must be individualized, the aim being to obtain a therapeutic effect with minimal dosage and minimal metabolic changes. *In severe cases, it may be advisable to initiate treatment with aqueous corticotropin (not*

the gel form) by the intravenous route, changing to this product for maintenance therapy.

Although the dosage must be individualized to the patient and the disturbance being treated, the initial dose requirements will probably be in the vicinity of 40 to 60 units of corticotropin per day. Ordinarily, where the preparation is to be used continuously, or for prolonged periods, the daily dose should not be over 20 units and usually less. It is preferable to maintain the dosage of ACTH at a level that will avoid undesirable side effects even though this dosage be insufficent to produce complete relief of the clinical disorder under treatment. Minimum dosage levels should be used in all cases of prolonged therapy. The amount required per day governs the frequency of injections; for example, if 60 units are required, the amount is given as two equally divided doses, if less than 40 units is required, the dose is administered as a single daily injection.

It is best to decrease the dosage as quickly as possible after the desired response is obtained. First, the dose is reduced to about three-fourths that needed initially; this is continued for about a week *to determine its adequacy. The dose is again reduced step-wise by one-fourth every 5 to 7 days until the lowest maintenance dose is established. After about a week, this dose is administered every other day. If improvement is maintained, then the interval is lengthened to every three days. The general principle is to give the smallest dose in the longest interval. If the dose needed for full relief produces significant side effects it should be reduced and the physician should content himself with less than full suppression of the disease being treated.*

CONTRAINDICATIONS

1. Tuberculosis—Active or latent tuberculosis is a definite contraindication for prolonged therapy.

2. Congestive Heart Failure and Hypertension—Corticotropin therapy, through its tendency to induce electrolyte and fluid retention, is undesirable for these conditions.

3. Psychotic and Psychopathic Personalities—Corticotropin therapy may precipitate undesired incidents, and hence persons with psychopathic personalities should usually not receive the drug until further studies have been made.

4. *Diabetes Mellitus—Corticotropin therapy may increase the blood sugar levels especially of controlled diabetics or latent diabetics so that glycosuria may result. This may be controlled by increasing the insulin dosage and adjustment of diet, and in most cases discontinuance of the corticotropin brings blood sugar levels and insulin requirements back to pretreatment values.*

5. Chronic Nephritis—It is essential that the patient be able to eliminate excess water which tends to be retained on corticotropin therapy, due to sodium retention. The inability of the nephrotic to eliminate excess fluid requires caution.

6. *Cushing's syndrome—This disease is due to excessive function of the adrenal cortex or to tumors, and corticotropin therapy is contraindicated.*

7. Addison's Disease—Corticotropin therapy is ineffective in the absence of adrenal tissue.

8. Thrombophlebitis—Since ACTH therapy tends to increase the thrombophilic tendency, patients, particularly those confined to bed or chair, should be watched for signs of phlebothrombosis, which should be treated with anticoagulant therapy before and during the ACTH therapy.

INDICATIONS

The following dosage recommendations for this product to be administered subcutaneously or intramuscularly are intended as suggestions for initial therapy, and thereafter the dosage must be adjusted to the individual needs of the patient.

Rheumatoid Arthritis—The initial dose is 60 units once a day; for severe cases, 30 to 40 units every 12 hours. If clinical response is not obtained after several days, increase dose to 80 units every 24 hours. After remission occurs, gradually reduce dose as described under Dosage Considerations.

Acute Rheumatic Fever—In young children 40 units per day as one injection; if acutely ill, 30 units every 12 hours. For older children, 60 units once a day. Full treatment for 4 days, then gradual tapering off and treatment discontinued.

Acute Lupus Erythematosus—The initial dose is 60 units every 24 hours. The patient should be maintained on the effective dose for 2 to 3 weeks at which time the dose should be reduced to the minimum maintenance level. These patients must be carefully observed for edema with cardiac and nephritic involvement. Low sodium diet and increased potassium intake is advisable.

Severe Hay Fever—40 to 60 units once a day. Treatment period averages 3 to 5 days with a gradual tapering off afterward.

Drug Sensitivities and Contact Dermatitis—A dosage of 80 units once a day for 2 days will usually control symptoms; dosage reduced gradually and then discontinued.

Urticaria—A dosage of 80 units once a day for 1 to 3 days, with gradual tapering off. Some cases may require maintenance of 10 to 40 units every 1 to 3 days.

Acute Inflammatory Diseases of the Eye—In ivitis, keralitis, uveitis, choroiditis, optic neuritis, sympathetic ophthalmia, acute secondary glaucoma, and conjunctivitis, 40 to 60 units are needed once a day until the eye lesion has fully healed. After gradual tapering off of dosage, treatment can be discontinued for most patients; in some who have had the disease for an extended period, maintenance therapy of 10 to 40 units once a day or every 2 to 3 days may be required. Attempts should be made periodically to discontinue treatment.

Acute Inflammatory Diseases of the Skin—In acute psoriasis, exfoliative dermatitis and severe pemphigus, from 40 to 60 units a day for a short period, with gradual tapering off. Most patients will require maintenance therapy of from 10 to 40 units once daily or every 2 to 3 days, unless the cause is known and eliminated.

Ulcerative Colitis—For less severe cases, 40 units once daily; for severe cases, 60 to 80 units daily until mucosa appears relatively normal. Maintenance dose of 10 to 40 units every 1 to 3 days may be required in chronic cases.

Acute Gouty Arthritis—Emergency treatment of 80 units per day. Less ill patients should receive 40 to 60 units once daily. Treatment is repeated until symptoms subside—usually after 1 to 3 injections. Other therapy for gout should be concurrently administered. ACT H therapy is usually not required

Congenital Idiopathic Hypoglycemia—20 to 40 units once a day for small children. Full treatment extends to at least 10 days after adequate control. Maintenance dose of 10 to 20 units every 1 to 3 days after patient is well under control.

Alcoholism (acute delirium tremens)—40 units twice a day until symptoms have disappeared (usually within 24–36 hours.) When symptoms are controlled, reduce dosage to 20 units twice a day for 2 to 3 days, then 20 units per day for 2 to 3 days; finally 20 units three times a week for 2 to 4 weeks. ACT H therapy is not recommended for Korsakoff's psychosis.

Packages—This product retains potency for at least three years. It should be kept in a refrigerator. Available in 5-cc vials, in two strengths: 40 U.S.P units and 80 U.S.P. units of purified corticotropin (ACTH) per cc. and in 1-cc ampuls containing 40 U.S.P. units.

CAUTION: Federal law prohibits dispensing without prescription.

CORTROPHIN"-ZINC"

Sterile Corticotropin Zinc Hydroxide Suspension U.S.P.

Composition—An aqueous suspension of purified corticotropin (ACTH) with alpha zinc hydroxide for repository action. It is available as 40 U.S.P. units of corticotropin 1<1 (1.0 mg. of zinc content per cc), which provides therapeutic ACTH activity for a period of from one to three days, depending upon individual patient requirements. Each cc also contains: 1.0% benzyl alcohol (preservative) and made isotonic with NaCl, pH adjusted with HCl and NaOH. This is a fine aqueoua suspension which flows readily through a 24–26 hypodermic needle. It should be given intramuscularly to avoid any possible local reaction.

Properties—This product supplies pituitary corticotropin in a form which provides sustained action of the hormone, causing the adrenal cortex to release its essential steroids in physiological proportions over a longer period of time than would be the case with corticotropin in equal amounts in other forms This period of activity ranges from 1 to 3 days depending upon the patient's requirements and upon the strength administered. The response is conditioned by the functional capacity of the adrenal cortex; a highly active gland would respond dramatically, while an inactive adrenal cortex would respond less, particularly at first. This response takes the form of an outpouring of three types of adrenal hormones: compound-F-like hormones which are the most abundant; desoxycorticosterone-like hormones; and the adrenal androgens. The production of compound-F-like hormones is clinically the most significant, for it is this aspect of therapy that promotes striking clinical response in so many diseases, and which enables the tissues and the body as a whole to meet serious stress.

Adequate therapy usually produces the following desirable general changes: Temperature, if elevated, usually returns to normal within 6 to 18 hours. Pain is abolished within a short time and becomes an index of the reversibility of the disease under treatment. Patients develop a sense of well-being and of mental activity bordering on euphoria. Fibroblastic proliferation and inflammatory processes are blocked.

Test of Adrenocortical Activity—One of the requisites to successful corticotropin therapy is a functioning adrenal cortex. The functional capacity of the adrenal conditions clinical response. A reduction in the number of circulating cosinophils is considered to reflect increased secretion of adrenal steriods and indicates a positive response to corticotropin. Normal subjects respond to an adequate dose with at least a 50 per cent fall in circulating cosinophils. This test (known as the Thorn test) is applied in the diagnosis of Addison's disease, as a test of adrenal reserve pre- and post-operatively, to determine the patient's ability to react to stress, and to differentiate between panhypopituitarism, functional hypopituitarism and Addison's disease, in hypopituitarism, where hypofunction lies in the hypophysis, reaction to the test is positive. In Addison's disease, where the deficiency resides in the adrenals, the response is negative.

Dosage Considerations—As with corticotropin in gelatin and aqueous corticotropin, the dosage must be individualized to the requirements of the particular patient and the disturbance being treated. Because of the enhanced and prolonged activity, fewer injections are required.

In general, it seems practical to gain initial control of symptoms with an injection of 40 U.S.P. units, (in more severe cases, 60 units) daily. Once symptoms have been controlled, the interval between injections should be increased to 48 hours and then to 72 hours. Thereafter, if symptoms are still controlled, the dose per injection should then be reduced. For maintenance therapy, 20 U.S.P. units (or even less) daily to twice weekly may suffice. The general principle is to give the smallest dose in the longest interval. If the dose needed for full relief produces significant side effects it should be reduced and the physician should content himself with less than full suppression of the disease being treated.

In the treatment of acute diseases, physicians who have had experience with corticotropin-in-gelatin preparations should consider the following dosage suggestions. In view of the fact that this product has an action which is prolonged for at least 24 hours, and in most cases for a longer period, and its activity is at least as great as that of the gel preparations, the initial dose should be the same as that employed per single dose of the gelatin preparation; however, this dose should be given only once in the 24-hour period, and seldom in more than 60 units. The interval between injections should be extended to 48 hours and to 72 hours as soon as expedient, and the dose per injection should then be reduced, as described in the foregoing paragraph.

When immediate therapeutic results are mandatory, as in acute status asthmaticus, it may be desirable for the physician to administer aqueous corticotropin initially by the intravenous route and at the same time to give the first dose of this product intramuscularly into the deltoid muscle. (This product must not be given intravenously.) *Once the initial control of the disease have been effected, the patient may be satisfactorily maintained intramuscularly.*

Withdrawal of therapy results temporarily in relative adrenocortical deficiency because the patient's own production of ACTH has been suppressed. Withdrawal should be gradual to prevent a rebound reaction of relative deficiency. It is noteworthy, however, that this period of inactivity is usually shorter than that following cortisone therapy.

INDICATIONS

The indications for this product are the same as those for other corticotropin preparations. In general the following dosage schedules have been employed successfully:

In dermotologic disorders (atopic dermatitis, schorrheic psoriasis, pemphigus vulgaris), dosage has been 40 units every two to four days. Maintenance treatment has in some cases been achieved with 40 units once a week.

In rheumatoid arthritis, dosage in general has been 40 to 60 units per day until control is achieved, then reduced to 20 to 40 units every other day for maintenance. It has been possible in some cases to reduce the dosage even further.

In drug sensitivities, dosage has been 20 to 40 units per day until symptoms are controlled. This dosage has also been employed in the treatment of poison ivy.

In acute lupus erythematosus, dosage has averaged 40 to 60 units or more per

day to gain control of the symptoms with maintenance treatment possible in some cases with 20 units every other day. However, many of these patients have relatively high dosage requirements, even during maintenance treatment, and in these cases the sustained action seems to be particularly beneficial to satisfactory control of the disease.

In bronchial asthma, including status asthmaticus, 60 units a day were required for control, and 40 units twice a week has in some instances provided successful maintenance.

In polyarteritis and periarteritis nodosa, the initial dosage suggested is 40 units per day, maintenance may be achieved with 40 units twice a week.

In pulmonary emphysema, initial dosage has been 60 units per day, reduced to 20 units per day or every other day for maintenance.

These dosages are, of course, only gauges for the physician to follow. As with other corticotropin preparations, either the gel-form or aqueous, the dosage must be adjusted to the needs of the particular patient being treated.

Contraindications—The use of corticotropin is contraindicated in Addison's disease. Tuberculosis, active, latent or questionably healed, herpes simplex of the eye, and acute psychoses are usually absolute contraindications. Peptic ulcer, psychotic tendencies, diverticulitis, fresh intestinal anastomoses, thromboembolic tendencies, local or systemic infections including fungal and exanthematous diseases, osteoporposis, renal insufficiency, congestive heart failure and pregnancy (except in severe disease) are relative contraindications.

This product should not be used in patients with a history of previous reactions to any form of corticotropin or who are known to be allergic to products of porcine origin.

Precautions and Side Effects—This product functions by stimulating the production of steroid hormones by the adrenal cortices, and in this manner *influences protein and carbohydrate metabolism. It also alters the metabolism of electrolytes with retention of sodium and excretion of potassium. Should sodium retention and edema occur this may be controlled by restricting sodium intake, giving a diuretic or by temporarily discontinuing therapy until diuresis occurs. If potassium deficiency with muscular weakness occurs supplemental potassium should be given: 1 Gm. potassium citrate or chloride orally three times a day. Periodic determinations of serum potassium during prolonged therapy is advised. In this same manner the steroid hormones of the adrenal cortices induce atrophy of the thymus and produce an increase in antihyaluronidase activity. Because the action of this product is enhanced and prolonged as compared with other corticotropin preparations, the possibility of overdosage symptoms must be borne in mind.*

Corticotropin will produce the same type of side effects as corticosteroids and these include: Cushing-like syndrome, purpura or petechiae, electrolyte imbalance, insomnia, osteoporosis, spontaneous fractures, peptic ulcer, euphoria, psychic disturbances, menstrual irregularities, weight changes, hyperglycemia, hypertension, edema, bloating or gastric distress, aseptic necrosis of the hip, protein depletion, pancreatitis, increased intracranial pressure, convulsions, and hirsutism. Vascular changes such as polyarteritis nodosa or an increased tendency for thrombophlebitis have been reported. The incidence, type and severity of untoward reactions is usually related to the size of the dose and duration of therapy. For example prolonged use of corticotropin may also cause growth suppression (reversible on withdrawal) in children, delayed wound healing, or posterior subcapsular cataracts in adults.

Susceptible individuals may become sensitized to traces of protein that accompany corticotropin so that subsequent injections given after intervals of several days may give rise to hypersensitivity phenomena ranging from mild urticaria to anaphylactic shock. The first sign of developing hypersensitivity may be localized itching or wheal formation at the injection site. This product should not be used in patients with a history of previous reactions to any form of corticotropin or who are known to be allergic to products of porcine origin.

It may be used as adjuvant therapy in certain infectious diseases providing such infections are adequately controlled by appropriate antibiotics or chemotherapeutic agents. *It must be remembered that the anti-inflammatory effects of corticotropin may mask signs of infection and such patients should be carefully observed.* While average doses will usually not increase insulin requirements in controlled diabetics, *when the drug is used in such patients, they should be observed closely for evidences of increased hyperglycemia or glycosuria. Periodic determinations of blood sugar during prolonged therapy is advised.*

Packages—This product should be refrigerated. Available in 5-cc vials containing 40 U.S.P. units of corticotropin (ACTH) per cc.

Caution: Federal law prohibits dispensing without prescription.

HEXADROL

Dexamethasone 'Organon'

Description and Action—Hexadrol (dexamethasone 'Organon') is an analogue of prednisolone. Its spectrum of anti-inflammatory activity is similar to other corticosteroids but it is clinically effective in much lower doses. Chemically it is 9-alpha-fluoro, 16-alpha-methyl prednisolone.

Indications—It may be used singly or as adjuvant therapy in a wide variety of clinical states known to be responsive to steroid therapy. Such conditions include rheumatic and other collagen diseases, hypersensitivity states, certain inflammatory eye diseases, blood dyscrasias, certain neoplastic diseases, and other miscellaneous disorders.

Contraindications—Tuberculosis, active, latent or questionably healed, herpes simplex of the eye and acute psychosis are usually absolute contraindications. Peptic ulcer, psychotic tendencies, diverticulitis, fresh intestinal anastomoses, thromboembolic tendencies, local or systemic infections including fungal and exanthematous diseases, osteoporosis, renal insufficiency are relative contraindications. Corticosteroids have produced teratogenic effects in animal fetuses and for this reason dexamethasone should not be used in pregnant women except in severe disease. In the event that corticosteroids must be used in pregnant women, newborn infants should be carefully observed for possible postnatal hypoadrenalism.

Precautions and Side Effects—All corticosteroids, including dexamethasone, produce the same type of side effects and these include: Cushing-like syndrome, purpura or petechiae, electrolyte imbalance, insomnia, osteoporosis, *spontaneous fractures*, negative nitrogen balance, peptic ulcer, euphoria, *psychic disturbances*, menstrual irregularities, weight changes, hyperglycemia, *hypertension*, edema, bloating or gastric distress, *aseptic necrosis of the hip or humerus*, and hirsutism. Vascular changes such as polyarteritis nodosa or an increased tendency for thrombophlebitis have been reported. Ulcerative esophagitis and acute pancreatitis have occurred during, and may be related to, corticosteroid therapy. Some corticosteroids such as the fluoro analogues of prednisolone appear to exert a relatively greater muscle wasting effect. The incidence, type and severity of untoward reactions is usually related to the size of the dose and duration of therapy. For example *prolonged use of corticosteroids may also cause growth suppression (reversible on withdrawal) in children, delayed wound healing, or posterior subcapsular cataracts in adults.* Because of the greatly enhanced anti-inflammatory activity of dexamethasone, lower doses can be used thus preventing or minimizing abnormal salt and water retention or potassium loss. *Periodic serum potassium determinations are advised during prolonged therapy.*

It may be used as adjuvant therapy in certain infectious diseases providing such infections are adequately controlled by appropriate antibiotics or chemotherapeutic agents. It must be remembered that the anti-inflammatory effects of corticosteroids may mask signs of infection and such patients should be carefully observed. While average doses will usually not increase insulin requirements in controlled diabetics, when the drug is used in such patients, they should be observed closely for evidences of increased hyperglycemia or glycosuria. Periodic determinations of blood sugar during prolonged therapy are advised.

It is safest to assume that prolonged therapy will result in depression of adrenocortical function. For this reason the drug should be withdrawn gradually when treatment is to be discontinued. *It may be advisable to administer ACT II during this period to hasten the return of normal function. Should the patient be subjected to surgery, severe trauma, or shock within one year following withdrawal it may be advisable to give a temporary course of corticosteroid therapy. Dexamethasone is not the drug of choice in adrenal insufficiency.*

Dosage—Rheumatoid Arthritis: It will effectively suppress the inflammatory reaction seen in rheumatic disorders generally within 24–48 hours. Improvement is characterized by relief of pain, decrease in redness, pain, swelling, stiffness and a sense of well-being. So predictable is the response of this disorder to steroid theraphy, assuming adequate dosage, that if no response is noted within seven days, the diagnosis should be questioned.

In general an initial daily dose of 1.5 to 3.0 mg. will produce a good clinical response although a few patients may require more. The effective minimal main-

tenance dose should then be determined for each patient and this will usually range between 0.75 and 1.5 mg. per day. Dosage titration is easily accomplished by decreasing the daily dose by 0.25 mg. or 0.375 mg. every three days or so. The use of a single daily dose may prove effective in certain patients and may be worthy of trial initially. However, if the response is not satisfactory the daily drug requirement should then be given in divided doses.

Because of the spontaneous remissions seen in this disease it may be advisable from time to time to discontinue therapy to evaluate this point, particularly in patients whose daily drug requirements are low. It should be emphasized that this agent is most effective when used in conjunction with other standard measures such as rest, physiotherapy, orthopedic correctons, etc.

Acute Rheumatic Fever—It can be expected to exert the same type and degree of beneficial effects noted with other corticosteroids in the treatment of this disease. Unlike earlier corticosteroids, it has the added advantage that salt and water retention are rarely observed, at least at the lower dosage levels. The true role of these agents in preventing valvular damage has yet to be determined. High doses are usually required to bring this disease under control and initially these may range from 7.5 to 10 mg. daily. As symptoms improve, dosage should be decreased gradually until a satisfactory maintenance level is reached.

Hypersensitivity States—Allergic diseases such as bronchial asthma, angioncurotic edema, allergic dermaloses, allergic purpura, certain drug reactions, transfusion reactions, etc. constitute another group of disorders responsive to corticosteroid thereapy. In general a single daily dose will usually provide adequate symptomatic control. Sufficiently high doses should be given initially to provide relief and these may range from 3.0 to 6.0 mg. per day. When long-term therapy is required, the effective minimal dose should be determined for each potient by gradually reducing dosage by 0.25 mg. to 0.375 mg. every second or third day.

For relatively minor conditions such as intractable hay fever or allergic rhinitis, the use of this agent may usually be discontinued after 10 to 14 days. Standard antiallergic therapy should be tried initially with corticosteroid supplementation only if required.

Inflammatory Eye Diseases—Ocular diseases which are known to respond to such therapy include: iritis, iridocyclitis, ureilis, choroiditis and choriorclinitis. In iritis or iridocyclitis topical treatment should be tried before restoring to systemic use. The drug is contraindicated in herpes simplex and herpes keralitis.

Beginning doses range from 3.0 to 6.0 mg. per day. When symptoms are satisfactorily controlled, dosage should be decreased by 0.50 to 0.75 mg. daily until a satisfactory maintenance dose is achieved. In acute or self-limited conditions. corticosteroids should be discontinued at the earliest possible moment.

Skin Disorders—Dermatitis of the atopic, contact, exfoliative, or drug reaction types respond rapidly and favorably, a single daily dose usually providing symptomatic relief. Skin diseases of a more serious impact such as pemphigus vulgaris and mycosis fungoides may also respond to corticosteroid therapy. The skin lesions associated with collaren diseases such as lupus entimatosus, scleroderma, and dermatomysitis do not require treatment but may respond favorably to courses of corticosteroid therapy being given for the underlying disease. Dosage requirements for these various skin disorders should be based on the degree of involvement and severity of the underlying disease. Minor afflictions require therapy for a few days or weeks at most while the more serious ones may demand continuous treatment. In general initial doses range from 3.0 to 6.0 mg. per day with gradual reductions down to a satisfactory maintenance level. Higher daily drug requirements should be given in divided doses.

Dosage recommendations for the treatment of pemphigus, scleroderma, and mycosis fungoides vary considerably and the interested physician is advised to consult the latest literature for suggested therapeutic regimens.

Adrenogenital Syndrome—It will effectively suppress adrenocortical hypersecretion with prompt decreases in urinary 17-ketosteroid levels. Optimal maintenance doses must be determined for each individual as reflected by continuation of normal urinary 17-ketosteroid levels. A dose of 0.75 to 1.5 mg. daily will usually provide the desired effect.

Bursitis—Soft tissue inflammations such as bursitis, synovitis, and lenosynovitis will respond favorably to corticosteroids. Initial daily doses of 1.5 to 3.0 mg. will provide a rather prompt and satisfactory result and short courses of therapy usually suffice. The majority of patients will respond satisfactorily to a single daily dose.

Miscellaneous Diseases—The anti-inflammatory corticosteroids may provide a measure of relief in certain other diseases such as: pulmonary fibrosis, pulmonary emphysema, lupus erythematosus, nephrosis, ulcerative colitis, idiopathic thrombocytopenic purpura, and may provide a temporary palliative effect in lymphatic leukemia and lymphomas. It is contraindicated in metastatic carcinoma.

Dosage requirements for the above indications must be individualized since most of these diseases have a serious, if not greater prognosis, and vigorous therepy may be justified. The use of high doses will increase the incidence of undesirable side effects. If the risk is accepted, the patient must be carefully observed for their occurrence and treated accordingly.

As with all potent drugs the dosage of corticosteroids should be individualized. *The best dose is the smallest dose which will produce adequate but not necessarily complete relief of symptoms. Higher doses or prolonged periods of thereapy tend to produce an increased incidence of side effects and this risk must be balanced against anticipated benefits in every instances. Where large doses are required the patient should be carefully watched for the appearance of the classical signs of overdosage when it may become necessary to decrease the dose or stop therapy.*

Corticosteroids are usually given in divided doses. Clinical studies, however, have convincingly demonstrated that a single daily dose is effective for the majority of patients suffering from hypersensitivity states, demratoses, barsitis or other mild connective tissue diseases, etc. While the response has been less striking in rheumatoid arthritis the incidence of effective control is sufficiently high to make this regimen worthy of trial. Single doses are best given in the morning unless clinical reasons dictate an evening dose.

It is advisable, when discontinuing corticosteroid therapy, to reduce dosage gradually and not abruptly. The administration of ACT II during the withdrawal period may help to accelerate the return of normal adrenocortical function.

Patients currently being treated with other corticosteriods may be transferred conveniently to this agent using the following dosage equivalents:

0.75 dexamethasone equivalent to:
- 25 mg. cortisone.
- 20 mg. hydrocortisone
- 5 mg. prednisone or prednisolone.
- 4 mg. methylprednisolone
- 4 mg. triamcinolone.

Caution: Federal law prohibits dispensing without prescription.

Supplied:
- 0.50 mg. tablets (yellow, scored), bottles of 30 and 500.
- 0.75 mg. tablets (white, scored), bottles of 100 and 500.
- 1.5 mg. tablets (peach, scored), bottles of 50.
- 0.50 mg./5 ml. elixir (alcohol 5%), bottles of 120 ml.

HEXADROL® PHOSPHATE INJECTION

(Dexamethasone Sodium Phosphate, N.F.)

Description—Hexadrol phosphate injection (dexamethasone sodium phosphate N.F.) is a water-soluble inorganic ester of dexamethasone which produces a rapid response even when injected intramuscularly. Chemically it is 9-alpha-fluoro, 16-alpha-methyl prednisolone 21-phosphate.

Each cubic centimeter contains:

Dexamethasone sodium phosphate, N.F.	4.0 mg.
Sodium Bisulphite U.S.P.	3.5 mg.
Sodium Citrate U.S.P.	10.0 mg.
Sodium Chloride U.S.P.	3.2 mg.
Disodium ethylene diamine tetra-acetate	0.1 mg.
Methylparaben U.S.P.	0.85 mg.
Propylparaben U.S.P.	0.15 mg.
Sodium hydroxide U.S.P. q.s.	to pH 7.7.
Water for Injection U.S.P. q.s.	1.0 cc.

Action and Uses—Dexamethasone sodium phosphate N.F. exhibits the intrinsic properties and hormonal effects of the parent substance and other corticosteroids. When administered intravenously, intramuscularly, intrasynovially or locally it

is an effective anti-inflammatory and anti-allergic agent. Because it is highly soluble, speed of absorption following intramuscular injection is almost as rapid as that following intravenous injection.

Since this product is intended for emergency, short-term or local therapy the pronounced hormonal effects associated with long-term therapy usually will not be seen. It is important, however, to watch for any untoward effect when administering a potent agent such as this. Local injections of therapeutic doses into joints or soft tissues are usually well-tolerated and significant systemic hormonal effects are unlikely if injections are few in number or are given at infrequent intervals.

When this product is given intravenously or intramuscularly it is useful in the following conditions:

1. Hypersensitivity reactions such as:
   (a) Anaphylactic reactions
   (b) Drug reactions
   (c) Status asthmaticus
   (d) Transfusion reactions
   (e) Severe urticaria
   (f) Laryngeal edema
   (g) Acute dermatosea
   (h) Severe reaction to insect bites
2. Acute or relative adrenal insufficiency:
   (a) Medical
   (b) Surgical
   (c) Iatrogenic
3. Shock not responding to conventional therapy.
4. Overwhelming infactions with severe toxicity.
5. To initiate therapy in:
   (a) Acute rheumatic fever
   (b) Acute disseminated lupus erythematosus.
   (c) Acute gout

In treating anaphylactic shock or other severe allergic reactions nonepinephrine or epinephrine should be used initially together with other accepted procedures. This may be followed by the parenteral administration of this corticoid to provide a more prolonged effect.

Patients who have received prolonged corticoid therapy may develop a state of relative adrenal insufficiency which may persist for a year or more following cessation of therapy. If such patients suffer sudden stress such as trauma, shock, surgery, overwhelming sepsis etc., reinstitution of corticoid therapy during this period may be indicated. This product may be employed for emergency use in these patients. However, because dexamethasone sodium phosphate N.F. lacks significant mineralocorticoid activity supplemental therapy with salt and a salt-retaining steroid such as desoxycorticosterone is required when it is used for the treatment of adrenal insufficiency. Because of the supplemental therapy required, dexamethasone is not the drug of choice in the treatment of adrenal insufficiency.

It may prove lifesaving in critically ill patients suffering from severe overwhelming infections for which specific antibiotic therapy is available. It may permit survival until the antibiotic has had time to take effect. Since corticoids mask the classical signs of infection their use in such cases must be undertaken with the greatest caution. Bacteriological studies and adequate antibiotic therapy must be started before the first dose of this corticoid and its use should be discontinued as soon as possible and at least 3 days before antibiotic therapy is stopped.

Surgical infections requiring corrective surgery should be performed as soon as possible. Clinical improvement following steroid therapy is not an indication to postpone surgery. Increased doses of antibiotic may be indicated while the steroid is being given.

When given intrasynovially or locally into soft tissue sites this product may provide relief of symptoms in:

(a) Rheumatoid arthritis.
(b) Acute gouty arthritis.
(c) Traumatic arthritis.
(d) Osteoarthritis.
(e) Bursitis.
(f) Fibrositis.
(g) Strains and sprains.
(h) Ganglia.

(i) Tendinitis.
(j) Localized myositis
(k) Heloma.

Contraindications—Tuberculosis, active, latent or questionably healed, herpes simplex of the eye and acute psychosis are usually absolute contraindications. Infectious arthritis is also an absolute contraindication to intra-articular injection. Peptic ulcer, psychotic tendencies, diverticulitis, fresh intestinal anastomoses, thromboembolic tendencies, local or systemic infections including fungal and exanthematous diseases, osteoporosis, renal insufficiency are relative contraindications. Corticosteroids have produced teratogenic effects in animal fetuses and for this reason dexamethasone should not be used in pregnant women except in severe disease. In the event that corticosteroids must be used in pregnant women newborn infants should be carefully observed for possible postnatal hypoadrenalism.

Precautions and Side Effects—Hexadrol phosphate injection (dexamethasone sodium phosphate N.F.) is usually given for short periods of time and the known signs of corticoid overdosage are rarely seen. The appearance and nature of untoward effects depends largely on dosage, duration of treatment, and route of administration. *Faintness, weakness, nausea, dyspnea, weight gain, increased appetite and mental stimulation have been reported as immediate or short-term side effects following its parenteral use.* Untoward systemic hormonal effects from the intrasynovial or soft tissue injection of this agent are not anticipated when injections are few in number or are given at infrequent intervals.

All corticosteroids, including dexamethasone, produce the same type of side effects and these include: Cushing-like syndrome, purpura or petechiae, electrolyte imbalance, insomnia, osteoporosis, spontaneous fractures, negative nitrogen balance, peptic ulcer, euphoria, psychic disturbances, menstrual irregularities, weight changes, hyperglycemia, hypertension, edema, bloating or gastric distress, aseptic necrosis of the hip, and hirsutism. Vascular changes such as polyarteritis nodosa or an increased tendency for thrombophlebitis have been reported. Ulcerative esophagitis and acute pancreatitis have occurred during, and may be related to, corticosteroid therapy. *Some corticosteroids such as the fluoro analogues of prednisolone appear to exert a relatively greater muscle wasting effect.* The incidence, type and severity of untoward reactions is usually related to the size of the dose and duration of therapy. For example, prolonged use of corticosteroids may also cause growth suppression (reversible on withdrawal) in children, delayed wound healing, or posterior subcapsular cataracts in adults. Because of the greatly enhanced anti-inflammatory activity of dexamethasone, lower doses can be used thus preventing or minimizing abnormal salt and water retention or potassium loss, Periodic serum potassium determinations are advised during prolonged therapy

It may be used as adjuvant therapy in certain infectious diseases providing such infections are adequately controlled by appropriate antibiotics or chemotherapeutic agents. It must be remembered that the anti-inflammatory effects of corticosteroids may mask signs of infection and such patients should be carefully observed. While average doses will usually not increase insulin requirements in controlled diabetics, when the drug is used in such patients, they should be observed closely for evidences of increased hyperglycemia or glycosuria. Periodic determinations of blood sugar during prolonged therapy are advised.

Post-injection flare-up of joint pain may sometimes be seen following intra-articular injection. Instability of a joint following repeated intra-articular injections is a rare occurrence.

It is safest to assume that prolonged therapy will result in depression of adrenocortical function. For this reason the drug should be withdrawn gradually when treatment is to be discontinued. It may be advisable to administer ACTH during this period to hasten the return of normal function. Should the patient be subjected to surgery, severe trauma, or shock within one year following withdrawal it may be advisable to give a temporary course of corticosteroid therapy. If this product is employed, supplementary salt and/or desoxycorticosterone should be used. Because of supplemental therapy required, dexamethasone is not the drug of choice in adrenal insufficiency.

Dosage—The dose for intramuscular or intravenous administration varies from 4 to 20 mg, depending on the nature and severity of the disease being treated. *Intravenous doses exceeding 8 mg. (2cc) should be given slowly over a period of one minute. The initial dose may be repeated as necessary until the desired response is noted but the daily dose, with few exceptions, need not exceed 80 mg.*

Maintenance doses average 2 to 4 mg. daily. After achieving satisfactory control the patient should be switched to oral therapy as soon as feasible.

The dose for intrasynovial administration is usually 4 mg. for large joints and 0.8 to 1 mg. for small joints. For soft tissue and bursal injections a dose of 2 to 4 mg. is recommended. Ganglia require a dose of 1 to 2 mg. A dose of 0.4 to 1 mg is used for injection into tendon sheaths and helomata. Injections into inter-vertebral joints should not be attempted at any time and hip joint injection cannot be recommended as an office procedure.

Intrasynovial and soft tissue injections should be employed only when affected areas are limited to 1 or 2 sites. It should be remembered that corticoids provide palliation only and that other conventional or curative methods of therapy should be employed when indicated.

Supplied—5-cc (4 mg/cc) multiple dose vial; 1-cc (4 mg/cc) vial, box of 25.

LAKESIDE LABORATORIES,
Milwaukee, Wis., November 1967.

DEAR DOCTOR: The Food and Drug Administration have requested that we call your attention to the monograph for Norpramin (desipramine hydrochloride) in the 1967 *PDR*: page 687, white section. The FDA consider this monograph incomplete (in relation to the official labeling, the package insert), and therefore potentially misleading as prescribing information to allow safe and effective use of the drug.

To provide you with the necessary adequate reference, we enclose a revised monograph for 1967 Physicians' Desk Reference in which the changes have been emphasized by italics. Please insert this revision opposite page 687.

Sincerely yours,

WILLIAM C. JANSSEN, M.D.

(Insert opposite p. 687—*PDR*, 1967 edition)

(NOTE.—Prescribing information for Norpramin which appears in the 1967 edition of PDR has been revised. The following is the new monograph and completely replaces the old one. Changes are emphasized by means of italics.)

NORPRAMIN

(Desipramine hydrochloride)

Composition: Norpramin (desipramine hydrochloride) (10, 11-dihydro-5-(3-methylaminopropyl)-5H-dibenz [b, f] azepine hydrochloride), available in two dosage sizes: 25 mg. tablet, round, sugar coated, yellow; 50 mg. tablet, round, sugar coated, light green.

Action and Indications: Norpramin (desipramine hydrochloride) is a primary active metabolite of imipramine. It differs from earlier antidepressants in its rapid onset of action. Approximately 60 to 70% of patients with neurotic or psychotic depressions will respond satisfactorily. More than half will begin to improve in 2–5 days, others within a wek. Usually, patients not responding within one week are less likely to improve. Norpramin is useful in the treatment of neurotic and psychotic depressive reactions, and in manic depressive or involutional psychotic reactions. It may be used as co-therapy with tranquilizers in the treatment of markedly agitated forms of repressions.

Contraindications: (1) Norpramin should not be given in conjunction with or within two weeks of treatment with a monoamine oxidase inhibitor. (2) Because of its physiologic effects (both anticholinergic and epinephrine potentiating), it is contraindicated in patients with glaucoma, urethral or ureteral spasm and recent myocardial infarction. (3) *The presence of severe coronary heart disease with EKG abnormalities indicating a progressive disability and symptoms of heart failure due to this disability is likewise a contraindication.* (4) Active epilepsy as it lowers the threshold for epileptiform seizures.

Warnings (Relative Contraindications): Palpitations, due to tachycardia, have been observed with desipramine hydrochloride therapy. Desipramine hydrochloride should be given therefore to patients with a history of paroxysmal tachycardia only with awareness that palpitations may be induced. In some such patients, the myocardium may not be in condition to tolerate well the increased work and decreased perfusion incident to such paroxysms.

In two instances transient jaundice, probably analogous to that seen previously with chlorpromazine and (infrequently) with imipramine, has been noted; liver function studies in suspect cases, prior to and during prolonged desipramine hydrochloride therapy are thus advised.

In patients suspected of having glaucoma or urinary or gastric retention, the anticholinergic nature of the drug may be deleterious.

Patients receiving thyroid hormone, or sympathomimetic drugs may experience potentiation of the effects of these drugs, resulting in behavioral and/or cardiovascular toxicity. Patients receiving desipramine hydrochloride and anticholinergic drugs simultaneously are known to experience enhanced atropine-like side effects.

Animal teratology studies have proved negative. *However, the drug is new and there is little clinical information about its use during pregnancy. Consideration of the possible risks relative to benefits should guide the decision to use Norpramin (desipramine hydrochloride) in women who are pregnant or who may be anticipated to become so.*

Precautions: (1) Norpramin treatment should not be substituted for hospitalization or restraint if the risk of homicide or suicide is considered grave. (2) In patients with manic depressive illness, Norpramin may induce a hypomanic state after the depressive phase terminates. (3) *As with any drug, death may ensue from the suicidal ingestion of large doses of desipramine hydrochloride.* (4) Discontinue therapy prior to elective surgery. (5) Use with caution in patients receiving sympathomimetic drugs or thyroid hormone as potentiation of the action of these drugs may occur. (6) *Reduce dosage, or alter treatment, if serious adverse effects occur.*

Adverse Effects: Undesired side effects in the desipramine hydrochloride treated patients were usually well tolerated; *only occasionally did therapy have to be discontinued because of them. The side effects of desipramine hydrochloride were considered to be similar to those of imipramine; in general, these can be expected in about one of four patients.*

The following side effects have been encountered: dry mouth, constipation, dizziness, palpitation, delayed urination, agitation and stimulation (*"jumpiness", "nervousness", "anxiety", "insomnia"*), bad taste, sensory illusion, tinnitus, sweating, drowsiness, headache, hypotension (orthostatic), flushing, nausea, cramps, weakness, blurred vision and mydriasis, rash, *tremor*, allergy (general), altered liver function, ataxia and extrapyramidal signs, agranulocytosis.

Additional side effects more recently reported include: seizures, eosinophilia, confusional states with hallucinations, purpura, photosensitivity, galactorrhea, gynecomastia, and impotence. Side effects which could occur (analogy to related drugs) include weight gain, hearburn, anorexia, and hand and arm parasthesias.

Dosage and Administration: Optimal results are obtained at about 150 mg./day. Dosage over 200–225 mg./day increases incidence of side effects. Norpramin may be administered as follows: two tablets (50 mg.) t.i.d. (150 mg./day). Partial response may be expected within 2–5 days; optimal response within 2–3 weeks. After optimal results are achieved a maintenance dose . . . 50–100 mg./day . . . should be sought.

An alternate method of giving Norpramin (desipramine hydrochloride) which may, however, delay the rapid onset of therapeutic respones is: One tablet (25 mg.) three or four times a day= 75 or 100 mg. with a 25 mg. increment every few days, if needed, to a maximum dose of 200 mg. per day.

Overdosage: (1) Prevention: Keep out of reach of children. (2) Treatment: Gastric lavage, catharsis. For coma and circulatory collapse: adequate fluids, oxygen, assisted respiration, assisted cardiac impulse. Do not hesitate to digitalize. Use sympathomimetic drugs with caution. For seizures: parenteral barbiturates or diphenylhydantoin (note: diphenylhydantoin, though having an antiarrhythmic effect, has not been fully defined in respect of its effect on the heart or its rhythm.)

Blood dialysis is of little avail; continuous gastric lavage has been advocated on the basis of desipramine resecretion in gastric juice.

Supplied: Norpramin (desipramine hydrochloride) tablets of 25 mg., in bottles of 50, 500, and 1000; and tablets of 50 mg., in bottles of 30, 250, and 1000.

THE S. E. MASSENGILL CO.,
Bristol, Tenn., November 1, 1967.

DEAR DOCTOR: The Food and Drug Administration has requested that we call your attention to the monographs for our products, Predsem, Salcort and Salcort-Delta, in the current (1967) *Physicians' Desk Reference.* The FDA considers these monographs to be incomplete in presenting the necessary information for the safe and effective use of these drugs and therefore potentially misleading.

To provide you with the necessary information, we enclose revised monographs for insertion at page 812 of your current (1967) PDR. The nature and extent of the additions and other revisions in the enclosed monographs are emphasized by use of italics.

Sincerely,

ROBERT P. EWING,
Vice President, Marketing.

PROFESSIONAL PRODUCTS INFORMATION (P. 812)

PREDSEM

Composition: Each multiple-compressed white tablet contains:

Prednisone	5.0 mg.
Calcium pantothenate	10 mg.
Aluminum hydroxide gel, dried	0.2 Gm.
Magnesium trisilicate	0.1 Gm.

Prescribing information for Predsem which appears on page 812 of the 1967 PHYSICIAN'S DESK REFERENCE has been revised and is completely replaced by the following. The nature and extent of the additions and other revisions in the monograph are emphasized by use of italics.

Action and uses: For the treatment of the acute phase of rheumatoid arthritis and related diesases. Also of value in other conditions in which corticosteroid theraphy is indicated. Antacids are incorporated to reduce gastric distress caused by hyperacidity in relation to steroid therapy.

Contraindications: Tuberculosis (active or latent), chronic nephritis, acute psychosis, Cushing's syndrome, peptic ulcer and in patients prone to thrombophlebitis. *Herpes simplex of the eye is usually an absolute contraindication. The appearance of ocular herpes simplex in patients receiving adrenocortical steroids systemically, or locally in the eye for other conditions, has been reported. If this occurs, Predsem Tablet should be discontinued unless the need for them is greater than the risk to the function of the eye.*

Relative Contraindications: As in the case of other powerful therapeutic agents, the physician must weigh the advantages of treatment with prednisone against the possible harmful effects. In congestive heart failure, hypertension, diabetes, frank osteoporosis associated with senility or with rheumatoid arthritis, renal insufficiency, history of peptic ulcer and mental diesase. Predsem must be administered with caution.

In patients with diabetes millitus being treated for a concurrent disease amenable to therapy with Predsem Tablets, the hyperglycemia may be aggravated; therefore, the diabetic status must be followed and regulated with great care. Usually it is possible to control the diabetes by increasing the insulin dosage.

While euphoria is the usual psychic reaction to large doses of prednisone, occassionally pronounced psychic derangements may appear. Early symptoms include insomnia, swings in mood and increased psychomotor activity.

Precautions: Corticosteroids should be used with caution in congestive heart failure, diabetes, renal insufficiency, history of peptic ulcer and mental disease. Predsem can mask infections by interfering with elevation of temperature, etc. If there is any question, drug should be temporarily discontinued until accurate diagnosis is made. May be reinstituted as soon as adequate measures have been taken to treat the infection.

Special Precautions: Furthermore, because edema and weight gain from prednisone are extremely infrequent, the physician must be especially on his guard to detect less conspicuous side effects.

Management of Patient During Stress: Prednisone in large doses may produce adrenal atrophy. The physician should assume the continued therapy with prednisone, similar to theraphy with cortisone and hydrocortisones, will result in some depression of adrenocortical function. It may be advisable to institute rest periods and to stimulate adrenocortical function by the use of ACTH. If, after long-term therapy, the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly. However, a potentially critical degree of adrenal insufficiency may still persist, and for at least six months hydrocortisone in increased dosage proportionately much larger than the previously used prednisone should be administered if the patient is subjected to shock or significant stress such as surgery or trauma. Also, if a patient is subject to unusual stress, during prednisone therapy it should be continued usually in markedly increased dosage at least for the duration of the stress and immediately following it.

Supervision of Patient Following Prednisone Therapy: Continued supervision of the patient after discontinuation of prednisone is essential because there may be a reappearance of severe manifestations of the disease for which the patient was treated.

Clinical Effects: In rheumatoid arthritis initial benefit from prednisone has usually been seen in a day or two, diminution in subjective distress occurring promptly. The appetite improves rapidly, energy reappears, and a feeling of well-being develops. Objective conditions, such as joint involvements and pain on motion, recede gradually. The extent of return to normal is limited by the degree of irreversible pathological changes present.

Elevated sedimentation rates are decreased usually with a drop to or near normal. Low hematocrit and hemoglobin values tend to increase when prednisone is administered.

Discontinuance of therapy usually results in a return of symptoms in a few days.

Dosage and Administration: The suggested suppressive dosage for severe rheumatoid arthritis is 30 mg. (six 5 mg. tablets) per day. In less severe cases, 20 mg. (four 5 mg. tablets) per day will generally suffice. The suppressive dosage should be continued until a good response is noted. This will usually be three or four days, but this dosage may, if necessary, be continued for as long as seven days. If no response is noted within seven days, consideration should be given to the question of whether or not the disease under treatment is true rheumatoid arthritis.

Maintenance: Gradual reduction in dosage every 5 to 6 days by steps of 5 mg. (5 to 20 mg. daily provides adequate maintenance therapy for many patients).

How Supplied: In bottles of 30, 100 and 1,000 multiple-compressed monogrammed white tablets.

SALCORT

Composition: Each pink tablet contains:

Cortisone acetate	2.5	mg.
Sodium salicylate	0.3	Gm.
Aluminum hydroxide gel, dried	0.12	Gm.
Calcium ascorbate (equivalent to 50 mg. ascorbic acid)	60	mg.
Calcium carbonate	60	mg.

Prescribing information for Salcort which appears on page 812 of the 1967 PHYSICIANS' DESK REFERENCE has been revised and is completely replaced by the following. The nature and extent of the additions and other revisions in the monograph are emphasized by use of italics.

Action and Uses: Salcort is indicated in common rhetumatic disorders and as a means of adjusting corticosteroid dosages in treating chronic cases of rheufatic disease. The complementary corticosteroid-salicylate supplemented with vitamin C provides effective corticosteroid therapy for a wid range of common rheumatic disorders with minimum risk of undesirable side effects. Salcort is of particular value for patients not responding to salicylates alone and with those in whom a larger does of corticosteroid is neither necessary nor advisable.

Administration and Dosage: Maintenance dosage may require from 6 to 8 tablets to as little as 3 or 4 tablets daily, depending on severity of symptoms. Acute stages may require a high dosage of 4 tablets four times daily for two or three days, or until the acute episode subsides.

Contraindications: Tuberculosis (active or latent), chronic nephritis, acute psychosis, Cushing's syndrome, peptic ulcer and in patients prone to thrombophlebitis.

Relative Contraindications: In congestive heart failure, hypertension, diabetes, frank, osteoporosis associated with senility or with rheumatoid arthritis, and mental disease other than acute psychosis, Salcort must be administered with caution.

Precautions: Coreticosteroids should be used with caution in congestive heart failure, diabetes, renal insufficiency, history of peptic ulcer and mental disease. Salcort will mask infections by interfering with elevation of temperature, etc. If there is any question, drug should be temporarily discontinued until accurate diagnosis is made. May be reinstituted as soon as adequate measures have been taken to treat the infection.

Cortisone is a potent hormonal substance. Although the greater anti-rheumatic action of cortisone is not accompanied by an increased tendency to produce undesired hormonal effects, patients receiving it should be observed for the possible development of any signs of such excessive hormonal manifestation.

Daily weighing of the patient and, as indicated, measurement of fluid intake and output should be alone to detect early evidence of fluid retention. Restriction of the daily sodium intake to 2 Gm. or less may prevent or correct fluid retention. If salt and water retention occur, sodium intake should be further restricted and the dosage of cortisone reducod or discontinued.

In the presence of hypopotassemia, as detected by blood potassium determinations, characteristic changes in the electrocardiogram, and muscular weakness, the dietary potassium intake should be supplemented with 2 to 4 Gm. of potassium chloride daily and the dosage of cortisone reduced or discontinued.

Hyperglycemia and glycosuria may occur in nondiabetic individuals receiving cortisone. In patients with diabetes mellitus, the insulin requirements are increased.

While euphoria is the usual psychic reaction to cortisone, occasionally pronounced psychic derangements may appear. Early symptoms include marked insomnia, swings in mood and increased psychomotor activity.

Since the use of cortisone tends to depress the normal pituitary-adrenocortical mechanism, the patient should be carefully supervised not only during but following therapy, and treatment should be discontinued gradually. The occurrence of any unexpected stress, such as surgery, severe infections, or accidental trauma, during or for at least a year following treatment, is an indication for vigorous adrenocortical supportive therapy with cortisone acetate, or whole adrenocortical extracts. Dosage and duration of such therapy is governed by the severity of the stress and the patient's clinical status.

How Supplied: In bottles of 100 pink monogrammed tablets.

Literature Available: On request.

SACORT-DELTA

Composition: Each multiple-compressed yellow tablet contains:

Prednisone	1.0	mg.
Potassium salicylate	0.3	Gm.
Calcium pantothenate	5.0	mg.
Calcium ascorbate (equivalent to 25 mg. absorbic acid)	30	mg.
Aluminum hydroxide gel, dried	0.12	Gm.
Calcium carbonate	60	mg.

Prescribing information for Salcort-Delta which appears on page 812 of the 1967 PHYSICIANS' DESK REFERENCE has been revised and is completely replaced by the following. The nature and extent of the additions and other revisions in the monograph are emphasized by use of italics.

Action and Uses: For the treatment of the subacute, severe phase of rheumatoid arthritis and related disease. Salcort-Delta provides a prednisone dosage which is relatively high but may be adjusted to "long-term" therapy. In the subacute phase, the prednisone-salicylate combination is more effective than either agent when used alone. Salcort-Delta includes antacids to guard against gastric distress related to corticosteroid therapy.

Contraindications: Because of their prednisone content, Tablets Salcort-Delta are contraindicated in tuberculosis (active or latent), chronic nephritis, acute psychosis, Cushing's syndrome, active peptic ulcer, and in patients prone to thrombophlebitis. Salcort-Delta will mask infections by interfering with the

elevation of temperature, etc. If there is any question, the drug should be temporarily discontinued until an accurate diagnosis is made. It may be reinstated as soon as adequate measures have been taken to treat the infection.

Herpes simplex of the eye is usually an absolute contraindication. The appearance of ocular herpes simplex in patients receiving adrenocortical steroids systemically, or locally in the eye for other conditions, has been reported. If this occurs, Salcort-Delta Tablets should be discontinued unless the need for them is greater than the risk to the function of the eye.

Relative Contraindications: As in the case of other powerful therapeutic agents, the physician must weigh the advantages of treatment with prednisone against the possible harmful effects. In congestive heart failure, hypertension, diabetes, frank ostcoporosis associated with senility or with rheumatoid arthritis, renal insufficiency, history of peptic ulcer and mental disease, Salcort-Delta must be administered with caution.

In a patient with diabetes mellitus being treated for a concurrent disease amenable to therapy with Salcort-Delta Tablets, the hyperglycemia may be aggravated; therefore, the diabetic status must be followed and regulated with great care. Usually it is possible to control the diabetes by increasing the insulin dosage.

While euphoria is the usual psychic reaction to large doses of prednisone, occasionally pronounced psychic derangements may appear. Early symptoms include insomnia, swings in mood and increased psychomotor activity.

Precautions: Since edema and weight gain due to prednisone are infrequent, the physician must be especially watchful for the development of less conspicuous side effects. The use of prednisone tends to depress the normal pituitary—adrenocortical mechanism and the patient should be carefully supervised, not only during, but following therapy. The dosage should be reduced very gradually, but even then a potentially critical degree of adrenocortical insufficiency may persist asymptomatically for some time. Therefore, if the patient is subjected to stress, such as surgery or trauma within at least six months after therapy has been terminated, steroid therapy should be reinstituted. Furthermore, if a patient is subjected to unusual stress while receiving Salcort-Delta Tablets, steroid therapy should be continued for the duration of the stress and immediately following it. In both instances, proportionately much larger dosages of prednisone, cortisone, or hydrocortisone than that of the previously used Salcort-Delta should be used during the stress. As the prednisone, cortisone, or hydrocortisone is being discontinued, Salcort-Delta may be resumed in the former dosage.

After discontinuation of Salcort-Delta Tablets, continued supervision of the patient is essential, because there may be sudden reappearance of the disease for which the patient was treated.

In administering Salcort-Delta Tablets the possibility of the occurrence of the side effects of salicylates should be borne in mind. Any form of salicylates should be administered with caution to patients with hypoprothrombinemia and bleeding or with asthma and other allergic conditions.

Administration and Dosage: Can be started at 12 tablets daily in divided doses and dose diminished as symptoms subside.

How Supplied: In bottles of 100 multiple compressed, monogrammed yellow tablets.

THE UPJOHN CO.,
Kalamazoo, Mich., November 15, 1967.

DEAR DOCTOR: The Food and Drug Administration has asked us to call your attention to certain promotional messages for Medrol Tablets which the FDA regards as misleading.

Some journal advertisements have recommended use of Medrol 16 mg. Tablets by an alternate day dose regimen. Although reports of this usage have appeared in the literature, the FDA points out that information currently available and submitted by us to them is not adequate to justify this regimen as advertised. Consequently, we are ceasing all reference to alternate day therapy in our promotion of the product.

The monograph for Medrol Tablets in the 1967 *Physicians' Desk Reference* is considered by the FDA to be inadequate in presenting information for the safe and effective use of the product. To provide you with the necessary information, we enclose a revised monograph for insertion at page 1143 of your current (1967) *PDR.*

Sincerely yours,

FENIMORE T. JOHNSON, M.D.

(NOTE.—Prescribing information for Medrol (methylprednisolone) Tablets which appears on pages 1143–1144 of your 1967 *PDR* has been revised and is completely replaced by the following.)

MEDROL TABLETS

(Methylprednisolone)

Composition: Each tablet contains methylprednisolone 16 mg., 4 mg. or 2 mg.

Action and Uses: Medrol is indicated in conditions known to be responsive to corticoid therapy, including: (1) collagen diseases, (2) allergic diseases, (3) certain dermatological conditions, (4) acute ocular inflammatory disease, (5) certain leukemias and lymphatic neoplastic diseases, (6) ulcerative colitis, nephrosis and as adjunctive therapy in pulmonary and meningeal tuberculosis.

Administration and Dosage: The average total daily doses recommended should be given in four equally divided dosages and should be individualized according to the severity, duration and patient's response. The average daily dosage of Medrol is approximately two-thirds (0.7) the required daily dosage of prednisolone. Initial suppressive dosages should be continued for 3 to 7 days during which time satisfactory clinical response is usually obtained. Should there be no satisfactory response within 7 days, re-evaluation of the case to confirm the original diagnosis is indicated.

Reduction of dosage to maintenance levels should be accomplished slowly in decrements of not more than 2 mg. at intervals of 7 days when the initial daily dosage is 15 mg. or more. (See table below)

Adjustment of the dose level is indicated from time to time in concert with fluctuations in the disease activity and patient response. Experience has indicated that long-term benefits are greater when steroid maintenance is accomplished at the lowest possible dose level. Dose levels for protracted use of methylprednisolone should be in the range of 1.5 to 2.0 mg. daily for children and adolescents, 4 to 5 mg. daily for young women, 3 to 4 mg. daily for postmenopausal women, and 5 to 7 mg. daily for men. IMPORTANT—In the management of patients with chronic disease such as rheumatoid arthritis, methylprednisolone should be regarded as a valuable adjunct to be used in conjunction with but not as replacement for standard therapeutic measures.

Diuresis and increased excretion of sodium have occurred following administration of Medrol to adrenalectomized animals, normal human subjects and patients with cardiac edema or cirrhosis of the liver with ascites. These findings have suggested the value of this agent as adjunct to therapy of these and other forms of edema. Medrol has been reported to potentiate the actions of mercurial and carbonic anhydrase inhibiting diuretic agents and the restore response to diuretics in patients with resistant cardiac edema.

The use of corticoids in tuberculosis, while usually contraindicated, may be life saving when given with adequate and effective dosage of antituberculosis agents to patients with fulminating pulmonary tuberculosis or meningeal tuberculosis. Rapid improvement with defervescence, weight gain and clearing of pulmonary lesions have been reported.

Adverse Reactions: Adverse reactions associated with use of corticosteroids, including Medrol (methylprednisolone), include electrolyte imbalance, osteoporsis which is reversible only with difficulty, spontaneous fractures, aseptic necrosis of the hip, activation and complication of peptic ulcer including perforation and hemorrhage, hyperglycemia, glycosuria, hypertension, neverousness, acne, hirsutism, rounded facies, cutaneous striac, amenorrhea, cervicothoracic hump, acute pancreatitis, necrotizing angiitis, thinning of scalp hair, petechiae and purpura, posterior subcapsular cataracts occasionally requiring extraction, myopathy, growth retadiation in children, relative adrenocortical insufficiency (particularly in times of stress due to trauma, surgery or severe illness), protein catabolism with negative nitrogen balance, weakness, aggravation or masking of infection, increased intracranial or intraocular pressure., thromboembolism ulcerative esophagitis, psychic disturbances, abnormal euphoria, insomnia, headache, vertigo, facial flushing, sweating, and abnormal fat deposits.

When adverse reactions occur, they are usually reversible and disappear when the hormone is discontinued.

Precautions: Medrol (methylprednisolone) should be given only with full knowledge of the characteristic activity of, and the varied responses to, adrenocortial hormones.

Diabetes mellitus, hypertension and congestive heart failure may be aggravated by the administration of corticoids. However, concomitant administration of Medrol with diuretics may be beneficial in patients with cardiac edema. Negative nitrogen balance may occur with protracted maintenance therapy. Measures to counteract persistent nitrogen loss include a high protein intake and the administration, when indicated, of a suitable anabolic agent. Likewise, ecchymotic manifestations have occasionally been reported. If such reactions are serious or distressing to the patient, reduction in dosage or discontinuance of methylprednisolone therapy may be indicated.

While current investigations indicate that muscle weakness in patients receiving corticoids may occur in the presence of normal or low potassium levels and may be due to a disturbance in muscle metabolism, data indicate that the incidence of this complication is low with Medrol. This effect should be kept in mind and periodic serum potassium determinations perfounded in patients on prolonged therapy. In some instances, steroid-induced myopathy has actually improved when patients have been transferred to a predoisteroid such as Medrol from flourinated steroids containing the 9-alpha-fluoro configuration.

Because Medrol manifests little sodium retaining activity, the usual sign of cortosone or hydrocortisone overdosage (i.e., increase in body weight due to fluid retention) is not a reliable index of overdosage. Hence, recommended dose levels should not be exceeded, and all patients should be under close medical supervision. All precautions pertinent to the use of prednisolone apply.

While corticoids may be considered as effective therapy in polyarteritis nodosa, current data indicates that such therapy may have an undesirable effect and may cause lesions characteristic of the disease. Likewise, data indicates that the use of corticoids may in some instances induce acute pancreatitis. The development of posterior subcapsular cataracts has been associated with prolonged, high dosage corticoid therapy. To minimize this effect, doses should be kept as low as possible when administered for prolonged periods.

Retardation of linear growth has been noted in children receiving corticoids for 6 months or longer. With methylprednisolone this has been noted with doses of 5 mg. per square meter of body surface per day or greater. Retardation is usually proportional to dose and following cessation of therapy, the growth rate may be accelerated. The growth of children receiving prolonged therapy should be observed carefully. If growth has been retarded, the dose should be reduced sufficiently to permit recovery before epiphyseal closure.

Continued supervision of the patient after cessation of Medrol (methylprednisolone) therapy is essential, since there may be a sudden reappearance of severe manifestations of the disease for which the patient was treated.

Warning: Because of its inhibitory effect on fibroplasia, methylprednisolone may mask the signs of infection and enhance dissemination of the infecting organism. Hence, all patients receiving methylprednisolone should be watched for evidence of intercurrent infection. Should infection occur, it must be brought under control by use of appropriate antibacterial measures, or administration of methylprednisolone should be discontinued.

Since methylprednisolone suppresses endogenous adrenocortical activity, it is highly important that the patient receiving methlyprednisolone be under careful observation not only during the course of treatment but for some time after treatment is terminated. Adequate adrenocortical supportive therapy with cortisone or hydrocortisone, and including ACTH, must be employed promptly if the patient is subjected to any unusual stress such as surgery, trauma, or severe infection.

Tuberculosis: Use of corticoid therapy as an adjunct in pulmonary or meningeal tuberculosis must be based on careful assessment of all factors. Such therapy should not be instituted unless the tubercle bacilli are shown to be sensitive to the antituberculosis agent. Use of adequate and effective antituberculosis therapy currently with corticoid therapy is mandatory. When the tuberculous condition is complicated by fungal infections, corticoid therapy in constraindicated. "Rebound" fever, joint pains and temporary deterioration of pulmonary lesions as indicated by x-ray may follow certicoid withdrawal. Hypersensitivity to the antituberculosis agent may be unmasked by withdrawal of corticoid.

Hematological Disorders: Therapy with methylprednisolone has been effective in producing remissions with certain types of leukemia, in producing symptomatic improvement of patients with other lymphomatous diseases and in thrombocytopenia and hemolytict anemia. As a general rule, the therapy with corticosteroids produces remissions more frequently in acute lymphatic leukemia

than in other types of leukemia and remission occurs more frequently in children than in adults.

The sodium retaining properties of cortisone and hydrocortisone prevented the use of these agents in large doses. However, since Mdtol (methylprednisolone) demonstrates a lesser propensity for salt retention, the administration of massive doses of this compound may be less likely to be associated with troublesome fluid retention. It has been found that large doses of corticoids may be effective in producing remissions in some patients with acute granulocytic, acute monocytic, and chronic lymphocytic leukemia. Such therapy has been particularly helpful in controlling thrombocytopenia and hemolytic anemia associated with chronic lymphatic leukemia and other chronic lymphomas.

Dosage—Dosage varies with the individual patient and the condition being treated and ranges from 1 to 2 tablets (16 mg. size) 1 to 3 times daily. In some cases, doses of the order of 300 mg. daily have been employed. Following symptomatic control of production of a remission, the daily dose should be reduced by decrement to maintenance level or discontinuation.

LUPUS ERYTHEMATOSUS: Large doses of cortocoids may be necessary to control the manifestations of acute systemic lupus erythematosus. When a rapid onset of action is desired, Solu-Medrol (methylprednisolone sodium succinate) may be injected intravenously for the first two or three doses. When therapy is initiated orally, daily doses as high as 32 to 96 mg. (two 16 mg. tablets 1 to 3 times daily) may be necessary to control symptoms. After symptoms have been controlled, the daily dose should be reduced by decerments to a maintenance dose of 8 to 20 mg. daily.

CONTRAINDICATIONS: Medrol, like other corticoids, is usually contraindicated in patients with latent, questionably healed or active tuberculosis. However, Medrol administered with antituberculosis agents may be life saving in certain cases. Absolute contraindications to corticoid therapy include herpes simplex keratitis and acute psychoses. Relative contraindications include: peptic ulcer.

HOW SUPPLIED: White, scored 16 mg. tablets in bottles of 50. White, scored 4 mg. tablets in bottles of 30, 100 and 500. Pink cross-scored 2 mg. tablets in bottles of 30 and 100. Medrol Dosepak—21 four mg. tablets with patient instructions for 6 days of countdown therapy.

(Shown in Product Identification Section.)

MEDROL® (METHYLPREDNISOLONE): ADMINISTRATION AND DOSAGE TABLE

Disease	Initial daily dose	Daily maintenance dose
Rheumatoid arthritis:		
Severe	12 to 16 mg	6 to 12 mg.
Moderate	6 to 8 mg	2 to 6 mg.
Children	6 to 10 mg	2 to 8 mg.
Lupus erythematosus	20 to 96 mg	8 to 20 mg.
Allergic diseases	12 to 40 mg	4 to 16 mg.
Ocular inflammatory diseases	12 to 40 mg	2 to 12 mg.
Adrenogenital syndrome		4 to 12 mg.
Ulcerative colitis	16 to 60 mg	
Nephrosis	20 to 60 mg. (for 10 to 14 days until diuresis occurs).	12 to 40 mg. (3 consecutive days of each week for 6 to 12 months).
Refractory congestive heart failure	16 to 24 mg. (concurrently with other accepted therapy).	4 to 12 mg.
Tuberculosis: Pulmonary and meningeal (concurrently with antituberculous agents).	16 mg. for 10 to 12 weeks	Reduce by decrements in a period of 2 to 7 weeks.
	or	
	48 mg. for 14 days	Reduce by decrements over 2-week period.

ARMOUR PHARMACEUTICAL CO.,
Chicago, Ill., November 16, 1967.

DEAR DOCTOR: The Food and Drug Administration has requested that we call your attention to the monograph for H.P.*ACTHAR® GEL in the current (1967) *Physician's Desk Reference.* The FDA considers this monograph to be incomplete in presenting necessary information for the safe and effective use of this drug and, therefore, potentially misleading.

To provide you with the necessary information, we enclose a revised monograph for insertion at page 527 in your 1967 *PDR*. The nature and extent of the additions of previously omitted information are indicated by the use of italics.

Sincerely yours,

J. A. HUBATA, M.D.,
Medical Director.

(NOTE.—Prescribing information for H.P.* ACTHAR® GEL which appears on Pages 527 and 528 of the 1967 *PDR* has been revised and is completely replaced by the following. The nature and extent of the additions of previously omitted information are indicated by the use of italics.)

ARMOUR PHARMACEUTICAL COMPANY

CHICAGO, ILL.

H. P.* ACTHAR® GEL

(Repository Corticotropin injection)

Highly Purified

AND

ACTHAR®

(Corticotropin injection)

Description: H.P.* ACTHAR GEL (Repository Corticotropin Injection) is a Highly Purified preparation of CORTICOTROPIN in gelatin which has both rapid onset and prolonged action. One injection may have 24- to 72-hour effectiveness. The high degree of purity also allows its administration by intravenous infusion. Each milliliter contains the labeled activity of Corticotropin U.S.P., 16% Gelatin, 0.5% Phenol, not more than 0.1% Cysteine (added) and Water for Injection, q.s. ACTHAR (Corticotripin Injection) is sterile powered lyophilized ACTH which in the dry form is stable at room temperature. Each vial contains the labeled activity of Corticotropin U.S.P. and approximately 9 milligrams of hydrolyzed Gelatin.

Actions: ACTHAR (Corticotropin Injection) is the Armour Pharmaceutical Company brand of ACTH (Corticotropin). ACTH is the anterior pituitary hormone which stimulates the functioning adrenal cortex to produce and secrete all of its steroids, which number over 30. In contrast, corticosteroids may depress adrenal cortical function and produce adrenal atrophy. The fact that ACTH acts directly on the adrenal cortex provides a rationale for use of ACTH in treatment of the adrenal insufficiency produced by cortisone, hydrocortisone, prednisone and prednisolone.

Indications: Allergic Diseases—Angioneurotic Edema, Asthma, Drug Reactions, Hay Fever, Serum Sickness. *Note:* Epinephrine is the drug of choice for acute allergic reactions, corticotropin or steroid therapy being adjunctive. *Collagen Diseases*—Acute Rheumatic Fever; Arthritis, Rheumatoid; Bursitis; Lupus Erythematosus; Periarteritis Nodosa; Psoriatic Arthritis; Scleroderma; Spondylitis, Rheumatoid; Still's Disease; Tenosynovitis. *Dermatologic Diseases*—Anogenital Pruritus, Atopic Dermatitis, Dermatitis Venenata, Dermatitis Medicamentosa, Exfoliative Dermatitis, Dermatomyositis, Pemphigus, Psoriasis, Urticaria. *Endocrine Diseases*—Panhypopituitarism. *Eye Diseases*—Choroiditis; Conjunctivitis; Glaucoma, Acute Secondary; Iritis; Keratitis; Optic Neuritis; Sympathethic Ophthalmia; Uveitis. *Hemolytic Diseases*—Acquired Hemolytic Jaundice. *Other Uses*—ACTHAR (Corticotropin) preparations have also been used in numerous other disease states such as: Agranulocytosis; Aplastic Anemia; Bell's Palsy; Beryllium Poisoning; Burns; Erythema Nodosum; Erythroblastosis Fetalis; Fibrositis; Gout; Guillain-Barre Syndrome; Heat Sickness; Hepatic Coma; Hodgkin's Disease; Hypoglycemia, Idiopyathic; Infections, Acute Overwhelming (e.g., Peritonitis, Meningitis); Insect Bites; Leukemias, Acute and Chronic Lymphatic; Loeffler's Syndrome; Myositis; Nephrotic Syndrome; Neuritis; Orchitis; Rhinitis; Sarcoidosis; Shoulder-Hand Syndrome; Snake Bite; Sprue Syndrome; Stevens-Johnson Syndrome; Thyroiditis; Ulcerative Colitis.

Contraindications: "Absolute Contraindications": Tuberculosis (active, healed or questionably healed), ocular herpes simplex, and acute psychosis are usually absolute contraindications to corticotropin therapy. Corticotropin is of no value in patients with Addison's Disease or after adrenalectomy since its action depends on the integrity of the adrenal cortex.

"Relative Contraindications": (1) Relative contraindications are Cushing's Disease, congestive heart failure, diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, thromboembolic tendencies, osteoporosis, diabetes mellitus, psychotic tendencies and acute or chronic infections (especially varicella or vaccinia) as well as other exanthematous and fungal diseases. (2) Pregnancy is a relative contraindication to corticotropin therapy, particularly during the first trimester, because fetal abnormalities have been observed in experimental animals. (3) If corticotropin is used in the above conditions, the risks should be weighed against the possible benefits.

Warning: Skin testing should be considered prior to treatment of patients with known or suspected sensitivities to corticotropin (which is a polypeptide) or porcine proteins. It is recommended that all patients be observed for a period of at least 15 minutes following administration of corticotropin. Epinephrine 1 : 1000 for emergency treatment should be available.

Precautions: (1) Corticotropin should be given only with full knowledge of the characteristic activity of, and the varied responses to, this preparation. (2) Average and large doses of corticotropin can cause elevation of blood pressure, salt and water retention, and increased potassium and calcium excretion. *The hypertension may be transitory during a period of electrolyte and water retention. Observe blood pressure responses until the maintenance dose is established.* Dietary salt restriction and potassium supplementation may be necessary. *If this does not control fluid retention, decrease the dose, omit a few injections until diuresis occurs, administer a diuretic, or consider discontinuation of therapy. Daily weights should be charted as a guide to abnormal weight gains.* Muscle weakness, fatigue or paresthesias may be a reflection of potassium deficiency, but are seldom observed if a potassium supplement is added to the diet. *EKG's or serum potassium levels are recommended guides if ACTH or corticoids are administered at high dosage levels for prolonged periods. If necessary, decrease the dosage or temporarily interrupt treatment and resume at a later date on a high potassium regimen.* (3) *Corticotropin may mask the signs of infection and enhance dissemination of the infecting organism. Hence all patients receiving corticotropin should be watched for evidence of intercurrent infection.* Chest x-rays should be done at regular intervals during prolonged therapy. *Should infection occur, initiate vigorous, appropriate anti-infective therapy. Abrupt cessation of corticotropin should be avoided if possible because of the danger of superimposing adrenocortical insufficiency on the infectious process.* (4) Since spontaneous remission of some diseases, such as rheumatoid arthritis, may occur during pregnancy, every effort should be made to avoid hormone treatment in pregnancy. (5) To avoid relative pituitary hypofunction, corticotropin therapy should be terminated gradually, particularly when patients are receiving large doses or have undergone prolonged treatment. Furthermore, if such patients are subjected to undue stress, such as surgery or trauma, while being treated or within one year after treatment has been terminated, hormone therapy should be augmented or reinstated and continued for the duration of the stress period and immediately following it. It is preferable to use corticotropin and/or cortisone or hydrocortisone in the immediate preoperative and postoperative periods. (6) Continued supervision of the patient after cessation of corticotropin is essential, since there may be a sudden reappearance of severe manifestations of the disease for which the patient was treated. (7) *Long-term corticotropin therapy may be accompanied by gastric hyperacidity and/or peptic ulcer. It is recommended, therefore, that patients with a history of peptic ulcer be placed on an ulcer regimen (including administration of an antacid) as a prophylactic measure.* Peptic ulcer patients complaining of gastric distress should be the subjects of appropriate x-ray examinations of the gastrointestinal tract. (8) Corticotropin may aggravate diabetes mellitus so that higher insulin dosage may become necessary or manifestations of latent diabetes mellitus may be precipitated. *Frequent urine sugar determinations and two hour postprandial blood sugar determinations are recommended during the period of dosage adjustment.* (9) Phychotic changes may be observed. *If exaggerated euphoria, nervousness, pronounced insomnia or depression occur, reduce or discontinue therapy and administer sedatives as indicated.*

Adverse Reactions: Adverse reactions, when they occur, are usually reversible and disappear when corticotropin is discontinued. Abscess, sterile. *Activation and complication of peptic ulcer (including perforation and hemorrhage).* Aggravation or masking of infection. Alteration of Glucose Metabolism, with aggravation of diabetes mellitus, including hyperglycemia and glycosuria. Aseptic Necrosis of Hip and Humerus. Convulsions. Cushing's Syndrome (including moon facies, supraclavicular fat pads, hirsutism, striae, and acne). Electrolyte imbalance. Facial Erythema. Headache. Increased Blood Pressure. Increased Intracranial Pressure with Papilledema (pseudo-tumor cerebri). Increased Intraocular Tension. Insomnia. Menstrual Irregularities. Myopathy. Necrotizing Angiitis. Osteoporosis (reversible only with difficulty). *Pancreatitis.* Petechiae and Purpura. Posterior Subcapsular Cataracts (occasionally requiring extraction). Postinjection Flare. Protein Catabolism (with negative nitrogen balance). Psychic Disturbances (especially abnormal euphoria). Spontaneous Fractures. Suppression of Growth in Children. Sweating. Thromboembolism. Ulcerative Esophagitis. Vertigo. Weakness.

Dosage and Administration: Directions for Use of ACTHAR (Corticotropin) Preparations—Clinical response is the criterion of adequate dosage. Unusual laboratory studies are not necessary. Because the adrenals vary in their sensitivity to stimulation by ACTH there can be no specific, uniform dose effective for all individuals. The aim is to obtain a therapeutic effect with minimal dosage and with minimal or no metabolic alterations. A clinical response is secured within 2 weeks in the majority of conditions. *Once the disease is under control, decrease the total daily dose as rapidly as possible consistent with maintaining a remission—thus try to reduce the total dose to about 75% of that needed initially. If adequate, this dosage is continued for 3–7 days before making a further similar reduction. When the lowest daily maintenance dose is thus established, attempts should be made at lengthening the interval between doses. If symptoms are not suppressed after dosage reduction, return to the previous effective schedule. If the nature of the disease requires maintenance therapy, aim to employ the smallest effective dose with the longest possible interval between injections. If the doses needed for full relief produce significant "side effects", reduce the dose and be satisfied with less than full suppression of disease under management.*

Administration and Dosages of H.P. ACTHAR GEL (Repository Corticotropin Injection) and ACTHAR (Corticotropin Injection): Either H.P. ACTHAR GEL (Repository Corticotropin Injection) or ACTHAR (Corticotropin Injection) may be given subcutaneously, intramuscularly, or as an intravenous infusion. Since ACTHAR (Corticotropin Injection) is a lyophilized preparation, it must be reconstituted before administration by dissolving in a convenient amount of Water for Injecton or Sodium Chloride Injection in such a manner that an individual dose will be contained in 1–2 cc. of solution. Like all aqueous solutions of ACTH, ACTHAR (Corticotropin Injection) is usually given every 8–12 hours. When reconstituted, the solution should be refrigerated. *SUBCUTANEOUS OR INTRAMUSCULAR TREATMENT OF SPECIFIC DISEASES—Note:* The dosages expressed are for H.P. ACTHAR GEL (Repository Corticotropin Injection) only. For ACTHAR (Corticotropin Injection) give the same total daily dose stated for H.P. ACTHAR GEL (Depository Corticotropin Injection) but give this in 3 divided doses every 8 hours initially. Tapering and maintenance regimens should be carefully observed.

For children under 40 lbs. in weight, reduce by one-third the dose recommended below. The dosages stated below for specific diseases are suggestive only and not absolute. *ADRENAL INSUFFICIENCY—secondary to pituitary deficiency or to corticoid-induced adrenal atrophy. As a rule, 100 Units daily for 3 days will reactivate the corticoid-suppresed adrenal and 40 Units twice a week or 100 Units weekly will prevent adrenal atrophy induced by the administration of corticosteroids. ALCOHOLISM and D.T.'S—40–60 Units once daily; recovery usually within 36 hours. Injections may be continued 3 times a week for several weeks. ANGIONEUROTIC EDEMA—60–80 Units once daily or 40–50 Units b.i.d. if severe; maintenance treatment not required if cause removed. ANOGENITAL PRURITIS—60–80 Units once daily or 40–50 Units b.i.d. if severe. ARTHRITIS, RHEUMATOID including SPONDYLITIS, STILL'S DISEASE and PSORIATIC—60–80 Units once daily; 40–50 Units b.i.d. for severe cases. Maintenance therapy usually required. ASTHMA—60–80 Units daily or 40–50 Units b.i.d.; maintenance treatment may be necessary. BURNS—60–80 Units daily or 40–50 Units b.i.d. if severe; give for 5–10 days reducing dosage as patient's condition improves. BURSITIS—60–80 Units daily; results in hours especially in acute cases. COLITIS. Ulcerative—60–80 Units daily or 40–50 Units b.i.d. for severe*

cases; continue until mucosa appears relatively normal. The most dramatic results are seen in the acute cases. DERMATITIS, CONTACT, DRUG, ETC.—60–80 Units daily or 40–50 b.i.d. if severe; maintenance treatment not required if cause removed. DERMATOMYOSITIS—60–80 Units daily; 40–50 Units b.i.d. if severe; maintenance treatment usually required. EXFOLIATIVE DERMATITIS—60–80 Units daily or 40–50 Units b.i.d. if severe; continue for 2 weeks after skin is essentially normal; maintenance usually not required if cause determined. EYE DISEASES: CHOROIDITIS, CONJUNCTIVITIS; ACUTE SECONDARY GLAUCOMA, IRITIS, KERATITIS, SYMPATHETIC OPTHALMIA, OPTIC NEURITIS—60–80 Units once daily or 40–50 Units b.i.d. for severe cases; continue treatment until lesion healed. GOUT—60–80 Units once daily or 40–50 Units b.i.d. if severe; result usually in 1–3 injections. Concurrent colchicine therapy advised. GUILLAIN-BARRE SYNDROME—60–80 Units daily or 40–50 Units b.i.d. if severe. HAY FEVER—60–80 Units once daily or 40–50 Units b.i.d. if severe; periodic injections advisable during pollen season. HYPOGLYCEMIA, Congental Idiopathic—40–60 Units daily; small amounts may be required to maintain control. JAUNDICE, Hemolytic Acquired—40–60 Units daily until blood picture normal; maintenance treatment unless cause removed. LUPUS ERYTHEMATOSUS—40–80 Units b.i.d. and continue for several weeks after adequate remission; maintenance treatment usually required. NEPHROTIC SYNDROME—For patients weighing 50-100 lbs., 60 Units once daily; 100 lbs. or over, 80 Units daily. Initial dose is continued 10-12 days and then abruptly stopped to allow for spontaneous diuresis; diuresis may occur before 10 days. If edema disturbing, stop treatment diuresis may occur. If diuresis inadequate, repeat after 5 days. Patients are kept on usual nepbrotic regimens during therapy. PANHYPOPITUITARISM—20–40 Units daily; maintenance therapy indicated with smaller doses and lengthened intervals between doses. PEMPHIGUS—60–80 Units daily or 40–60 Units b.i.d. if necessary. Continue treatment for 10–14 days after old lesions heal and new lesions cease to appear. Most cases require maintenance therapy. PENICILLIN REACTIONS—See Dermatitis (Contact and Drug). PERIARTERITIS NODOSA—60–80 Units daily or 40–50 Units b.i.d. if necessary; maintenance treatment usually necessary. POISON IVY—See Dermatitis (Contact and Drug). PSORIASIS—60–80 Units daily or 40–50 Units b.i.d. until skin lesions essentially gone; maintenance therapy generally required. RADIATION SICKNESS—20–60 Units daily; symptoms usually controlled within few days. RHEUMATIC FEVER—60–80 Units daily or 40–50 Units b.i.d. if acutely ill. Continue for 2–3 weeks before tapering dose. Do not discontinue until clinical and laboratory signs of disease disappear, usually a total period of 6–8 weeks. Cardiac decompensation is not a contraindication—diuretics may be used. SARCOIDOSIS—40–80 Units daily; improvement usually within 5-7 days; maintenance therapy may be necessary. SERUM SICKNESS—40–80 Units once daily; if severe, 40–50 Units b.i.d. TENOSYNOVITIS—40–80 Units daily or 40–50 Units b.i.d. if severe; results usually within 24–36 hours. THYROIDITIS—80 Units daily for 3 days followed by 60 Units for 2 days, 40 Units for 2 days, 20 Units for 2 days, and 10 Units for 3 days. URTICARIA—60–80 Units daily or 40–50 Units b.i.d. if severe; maintenance therapy not required in cases with known etiology. ACTHAR (Corticotropin) preparations have also been used in a number of other diseases; Agranulocytosis (especially drug-induced), Aplastic Anemia, Bell's Palsy, Beryllium Poisoning, Erythema Nodosum, Erthroblastosis Fetalis, Fibrositis, Hepatic Coma, Heat Sickness, Hodgkin's Disease, Infections (acute overwhelming as Peritonitis, Meningitis, etc.), Insect Bites, Leukemia (acute and chronic lymphatic), Loeffler's Syndrome, Myositis, Neuritis, Orchitis, Rhinitis, Scleroderma, Shoulder-Hand Syndrome, Snake Bite, Sprue Syndrome, Stevens-Johnson Syndrome.

INTRAVENOUS USE: This method of administration may be used where a rapid response is desired, in patients refactory to intramuscular ACTH, for reactivation of adrenals suppressed by cortisone, hydrocortisone, prednisone, prednisolone, etc., and for diagnosis. The recommended dose is 10–25 Units of ACTHAR (Corticotropin Injection) or 40 to 80 Units of H.P. ACTHAR GEL (Repository Corticotropin Injection) in 500 cc. of 5% glucose in water given as a continuous intravenous infusion over an eight hour period, once daily. *For children under 6 years, reduce the dosage to 50% of the adult dose recommended for the ACTHAR (Corticotropin Injection) preparation being used.* There is no long-acting effect when H.P. ACTHAR GEL (Repository Corticotropin Injection) is used intravenously. *Patients known to be highly sensitive to proteins should be carefully evaluated even though the slowness of infusion and the normal blocking effect of ACTH in hypersensitivities would appear to offset reactions. Patients*

should be watched closely for the first 30 minutes; epinephrine should be available. Tapering can be started much sooner than when ACTH is given intramuscular or subcutaneously because with continuous intravenous infusion, clinical results are obtained more rapidly. After obtaining a remission by the intravenous route, further therapy, if necessary, is usually given subcutaneously or intramuscularly in the form of H.P. ACTHAR GEL (Repository Corticotropin Injection) which because of its repository properties fewer injections are required. *LABORATORY TESTS OF ADRENAL CORTICAL FUNCTION: (1) The Four Hour or Thorn Test—An eosinophil count is made in the fasting state and immediately thereafter 25 Units of ACTHAR (Corticotropin Injection) are injected intramuscularly. Another eosinophil count is made 4 hours later. Breakfast may be given following the first eosinophil count but lunch should be withheld until after the second. A fall in eosinophils of 50% or more below the pre-injection level indicates a satisfactory adrenal cortical response. (2) The 8 Hour I.V. Test—25 Units of ACTHAR (Corticotropin Injection) in 500 cc. of 5% dextrose are infused over an 8 hour period. Eosinophils are counted at 0 and 8 hours; a fall of 50% or more is indicative of a responsive adrenal.*

PACKAGE FORMS: H.P. ACTHAR GEL (Repository Corticotropin Injection) is supplied in 5 milliliter multiple-dose vials in strengths of 40 and 80 U.S.P. Units (I.U.) per milliliter; 1 milliliter vials containing 40 and 80 U.S.P. Units (I.U.) per milliliter; and 1 milliliter B–D disposable syringes containing 40 U.S.P. Units (I.U.) per milliliter. ACTHAR (Corticotropin Injection) is supplied as a lyophilized powder in vials containing 25 and 40 U.S.P. Units (I.U.) per vial.

PHYSICIANS' DESK REFERENCE,
Oradell, N.J.

DEAR SIR: The Food and Drug Administration has requested that we call your attention to the monographs for the following products in the current (1967) Physicians' Desk Reference:

	Page
HP Acthar Gel	527
Cortrophin Gel	898
Cortrophin-Zinc	898
Hexadrol	899
Hexadrol Phosphate Injection	899
Norpramin	687
Predsem	812
Salcort	812
Salcort-Delta	812

The FDA considers these monographs to be incomplete in presenting the necessary information for the safe and effective use of these drugs and therefore potentially misleading.

To provide you with the necessary information, we enclose revised monographs for insertion in your 1967 PDR at the pages indicated at the top of each sheet.[1] The nature and extent of the additions and other revisions in the enclosed monographs are emphasized by the use of italics.

Sincerely,

ALBERT B. MILLER,
General Manager.

PARKE, DAVIS & Co.,
Detroit, Mich., January 15, 1968.

DEAR DOCTOR: The Food and Drug Administration has asked us to call your attention to our recent Ponstel® (mefenamic acid) journal advertisement and certain promotional mailing and detailing pieces which the Food and Drug Administration regards as misleading.

The introductory campaign featured results from non-blind clinical trials using only a single 500 mg. dose for several types of pain. The Food and Drug Administration points out that Ponstel has also been studied in several double-blind clinical trials in which the drug was compared to aspirin and other non-narcotic analgesics. These trials demonstrated that Ponstel was essentially equal

[1] Retained in committee files.

to the comparison drug and better than placebo. However, in certain individual trials aspirin was found better than Ponstel and the latter could not be distinguished from placebo; in some trials pain relief with placebo was obtained in as high as 40% of the patients. In other trials the results with Ponstel were better than those with aspirin or placebo.

The Food and Drug Administration considers that the introductory campaign failed to give adequate prominence to the fact that Ponstel is indicated for short-term administration not exceeding one week of therapy. Also, in a promotional brochure, results were reported from a double-blind effectiveness comparison with codeine and placebo, which represented that Ponstel was equal in effectiveness to 25 mg. of codeine. However, the dosage of Ponstel employed in this study was at a level which is still in the investigational phase.

We are discontinuing the advertising campaign in question.

Sincerely,

J. E. GAJEWSKI, M.D.

SYNTEX,
January 22, 1968.

DEAR DOCTOR: The Food and Drug Administration has asked us to call your attention to the fact that certain statements in recent advertising for our oral contraceptives, Norquen® and Norinyl®-1, may be misleading.

In the Norquen advertisement, the paragraph headed "Low incidence of side effects" emphasizes the low incidence of certain less serious side effects such as spotting, break-through bleeding, nausea, vomiting and other gastrointestinal disturbances, but fails to give adequate emphasis to the more serious known side effects such as cholestatic jaundice, rise in blood pressure in susceptible individuals, and mental depression which also occur in low incidence. Further, although a cause and effect relationship has neither been established nor disproved, the advertisement does not give adequate emphasis to the possible occurrence of thrombophlebitis, pulmonary embolism, and neuro-ocular lesions which have been observed in users of oral contraceptives.

The advertisements for both Norquen and Norinyl-1 state that "careful observation and caution are required for patients with symptoms or history of . . . cerebrovascular accident, psychic depression. . . ." The ads should have been more specific in stating:

> "Oral contraceptives should be used with caution in patients with a history of cerebrovascular accident and should be discontinued if there is a sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia, or migraine, or if examination reveals papilledema or retinal vascular lesions, since these may be symptoms of cerebrovascular accident."

The advertisements disclose that careful observation and caution are required for patients with symptoms or history of psychic depression but do not specifically state that oral contraceptives should be discontinued if psychic depression recurs to a serious degree. Also, the ads fail to disclose that a decrease in glucose tolerance has been observed in a small percentage of patients on oral contraceptives.

We are modifying all future advertising to reflect these changes.

Sincerely,

BEN Z. TABER, M.D.,
Medical Director.

G. D. SEARLE & Co.,
Chicago, Ill., January 26, 1968.

DEAR DOCTOR: In June 1967, the Food and Drug Administration and all manufacturers of oral contraceptives agreed on certain changes in the uniform portions of the labeling for all oral contraceptive products. These changes were to be included in all advertisements after October 1, 1967.

The FDA has asked us to call your attention to recent journal advertisements for Ovulen®-21, which departed from the new uniform labeling in several respects.

The original uniform labeling stated,

> "The following occurrences have been observed in users of oral contraceptives. A cause and effect relationship has not been established:
>
> "Thrombophletbitis
> Pulmonary embolism
> Neuro-ocular lesions."

Because that labeling did not accurately represent the present status of opinion concerning the possible danger of side effects, the warning statement was changed to read: "A cause and effect relationship has been *neither established nor disproved.*" [Italic supplied.] The FDA regards the advertisements as potentially misleading because they omitted this important change which emphasizes the possibility of these serious hazards.

Further, the advertisements failed to include the following side effects which, although causation has not been established, have been reported in users of oral contraceptives: an ovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, backache, nervousness, dizziness, fatigue, headache, hirsutism.

We have modified our current advertising to reflect these changes.

Sincerely,

HERBERT HELLING,
Food and Drug Administration Affairs.

ARDSLEY, N.Y., *February 15, 1968.*

DEAR DOCTOR: In our promotion of Persantine® (brand of dipyridamole) for long-term therapy in anginal patients, we sent a letter to physicians stating that "Several studies document the effectiveness of Persantine in extending walking distance and general increasing exercise tolerance." Enclosed with the letter was a reprint of a study in the *Journal of Chronic Diseases* of March 1967 to support the claims for effectiveness.

The Food and Drug Administration has asked us to inform you that the claims for effectiveness of Persantine, and many other drugs marketed prior to 1962, have been neither approved nor disapproved by the Agency. The FDA is proceeding on the basis that the Drug Amendments of 1962 require the Agency to evaluate the effectiveness of such drugs, and this is currently being done with the assistance of the drug efficacy panels of the National Academy of Sciences/National Research Council.

The FDA regards the promotional letter as potentially misleading because it presented only favorable information regarding the drug's effectiveness when there is a substantial body of opinion that does not suport the claimed effectiveness of the product. For example, the AMA Council on Drugs (in *New Drugs* 1967) has stated that double-blind studies comparing dipyridamole with a placebo have shown equivocal results and that the drug has not been convincingly shown to be effective in the long-term treatment of angina pectoris.

Recently, in the *JAMA* issue of September 11, 1967, a paper by Sbar and Schlant disclosed results of a six-month double-blind study. The authors concluded that "The study failed to detect a statistically significant difference between the improvement in patients receiving dipyridamole and the improvement in patients receiving a placebo."

Our future promotion will express the range of expert medical opinion on the effectiveness of Persantine when any segment of that opinion is referenced.

GEIGY PHARMACEUTICALS.

Dr. MCCLEERY. Also along the way of developing public awareness of the type of expectations which the FDA considered the law to require, the Commissioner of Food and Drugs had appeared before the Fountain Subcommittee of the House Committee on Government Operations, and had reviewed for them our programs in this important area of our public responsibilities.

In short, and in many ways, we felt that the industry's attention had been brought emphatically to promotion excesses in specific and in many ways.

As far as our experience with the problem represented by the drug under discussion today is concerned, we felt that there were three approaches to the promotion of this new product by Merck & Co., all of which had elements with which we disagreed—one of which was mentioned yesterday by Dr. Jennings, in his testimony, in the use of a "Dear Doctor" letter sent by the company, accompanying with it the

revision of the package insert, which was the occasion for the letter. We took exception to the promotional style of that letter, and that represented one episode in the history of this drug.

There was a second episode which I would like to speak about next, which was in regard to an article in the Pageant magazine—and a third, which I want to cover last, the advertising campaign used by Merck & Co. in reference to the subject drug for the medical profession in journals that go only to doctors.

Now, in June 1966, the director of public relations for Merck & Co., Mr. John Fletcher, wrote to Theodore O. Cron, our Assistant Commissioner for Education, enclosing a print of an article that was about to appear in the July 1966 issue of Pageant magazine.

Senator NELSON. Do you have a copy of that Pageant magazine article?

Dr. MCCLEERY. Yes, sir, we will submit one for the record.

Senator NELSON. Would you submit that for the record?

Dr. MCCLEERY. Yes, sir.

(The article referred to, for inclusion in the record, follows:)

[From Pageant Magazine, July 1966]

INDOCIN

A special report on a remarkable new drug that relieves the pain of arthritis, bursitis, gout, trick knee, tennis elbow, and sprains

(By Phyllis and Robert P. Goldman)

Two months ago a Miami housewife, aged 29, hobbled off the tennis court with a sharp, knife-like pain in her knee. She went home and lay down. But within five hours the knee was tender, inflamed, and stiff.

The housewife, Mrs. R. L., called her doctor, who, after examining the knee, declared, "Let's try something new, something that many of my patients are beginning to call a miracle drug."

Mrs. R. L. took the drug, and the most incredible thing happened. Within 36 hours she was no longer limping in pain. The knee swelling and stiffness began to subside. She found that she could walk almost normally. In a week the pain and inflammation had become simply a memory.

A Cleveland grandmother, Mrs. C. M., suffered for ten years from excruciating arthritis of the hip. Almost every available drug was tried, but not one provided sustained relief. She felt she would be condemned to a life of semi-invalidism.

Four months ago her doctor decided to try a "new drug that is producing dramatic results" in a number of joint pain and inflammatory conditions.

Mrs. C. M. took the drug, and within two weeks she was up and around—walking pretty much as though she had never suffered from arthritis of the hip. She's been comfortable and active ever since.

"I can't believe it," she declares. "This medicine is marvelous. I would call it a miracle."

Miracle or not, tens of thousands of patients throughout the United States and Europe, with a broad variety of physical ailments, are beginning to swear by the drug that is proving to have remarkable effects—in some cases within 36 to 72 hours.

The drug, largely unheralded and unpublicized until now, is called Indocin (indomethacin is its chemical name). Perhaps its most extraordinary quality is that it can relieve pain and inflammation caused by rheumatoid arthritis, gout, bursitis, arthritis of the hip, trick knee (usually the result of injured tendons and cartilage), "tennis elbow," and a host of other less common disorders characterized by pain and swelling in and around the joints.

Indocin is encouraging news if only because a estimated 12 million Americans suffer from arthritis and related joint disorders, and a good many of them—perhaps two million—cannot tolerate previously developed drugs, or such drugs have had little if any beneficial effect.

Actually, it is among many of these patients that Indocin is beginning to score its most impressive victories. These are individuals who have been "put on" almost every available drug—without lasting benefit.

Indocin, however, provides such dramatic relief for some of these patients—and so quickly—that many of them are moved to sit down and write about their experiences with the drug to its producer, Merck Sharp & Dohme of West Point, Pennsylvania.

The following are some samples of these letters to the pharmaceutical firm:

From Kansas City, Missouri: "I have had rheumatoid arthritis for 12 years. And I have taken many different medications. But for the first time—with Indocin—I'm free of pain. I'm no longer ornery. My wife says she's glad to have the old me back again. . . ."

From Minneapolis: "Because of bursitis I had to give up golf two years ago. But with your wonderful medicine I'm in good enough shape now to play golf once again. . . ."

From Detroit: "For five years the pain of my arthritis of the hip was unbearable. Now, with this drug of yours, I feel like a new person. Your Indocin is the best present anyone could have given me. . . ."

And from San Diego: "This is the first 'love letter' that I have ever written to a corporation. . . . After a very short period of taking Indocin. I can walk again without a cane. . . . I pray that you will realize fully the rewards that your splendid discovery so richly merits. . . ."

The "splendid discovery" actually took place several years ago at Merck Sharp & Dohme. Research workers there came upon a synthetic compound that had some surprising effects in animals. Not only could it reduce pain and inflammation but, given together with older pain killers, Indocin was found to reduce the need for these latter drugs.

This particular capability of Indocin is especially important. For in study after study, it has been found that if Indocin is given along with the corticosteroids (a commonly used "family" of anti-inflammation drugs), the need for these steroids gradually diminishes. This, in turn, can be invaluable, because very often when steroids are given for prolonged periods the side effects are worse than the disease itself.

Steroids are known to produce changes in body fluid balance and can cause weight gain, stomach upset, changes in contour of the face, and they are suspected of having adverse effects on vision.

The "steroid reduction" value of Indocin has been commented upon in scientific papers by a number of medical researchers. But one group from the University of Buffalo School of Medicine summed up the entire subject after studying more than 200 patients who were taking Indocin. The Buffalo group declared:

"At present 65.7 per cent of the patients have been improved for periods of six to 14 months. There has been a gradual decrease in the inflammatory indices, improvement in joint mobility and function. . . .

One of the most interesting facets of indomethacin administration has been the ability to gradually reduce the amount of steroid therapy in patients who had been using these hormones for periods of three to eight years. . . .

"This effect is very gradual and sometimes difficult to ascertain but does occur in the majority of patients under prior steroid therapy. . . ."

The same effect has been noted—along with Indocin's other values—at other leading medical centers located at the University of Colorado, the University of Southern California, the University of Washington, and elsewhere throughout the nation.

Despite Indocin's dramatic effects in some cases and its increasing acceptance by even some of the most skeptical medical practitioners, a few facts should be borne in mind—facts that are indispensible to understanding the role of any drug—new or old.

All prescription drugs, Indocin included, have side effects—that is, they produce negative reactions, reactions that make the patient either mildly annoyed and anxious or profoundly distressed physically or mentally.

All prescription drugs, Indocin included, work for some patients and not for others. No drug is a universal cure-all. In arthritis and related joint diseases, the actual causes are not known—and therefore there are at present no available drug "cures." At best, the drug provides relief from the symptoms.

However, Indocin is a "new" drug—that is, it was approved for prescription use in 1965. Therefore, it has been subjected to extremely rigorous tests—tests that were not required of certain of the older anti-inflammatory drugs.

Within the past four years the Federal Food and Drug Administration, which is charged with approving—or disapproving—new prescription drug applications, has tightened the requirements leading to a new prescription drug being permitted on the market. Indocin has passed these new, much tougher standards.

Despite this, Indocin *does* have side effects—at least for some patients. And some patients get little if any therapeutic effect from the drug.

Here, in brief, is a rundown on the "minus" side of the Indocin ledger: Somewhere between ten and 25 per cent of the patients experience side effects. Some of these are mild, some are severe. Some patients experience headache, nausea, dizziness, and a few have intestinal bleeding. However, it is estimated that these effects are mild much of the time. Only an estimated ten to 15 per cent of the patients must give up the drug because of negative effects.

Says the Council on Drugs of the American Medical Association in a report not yet published: "With prolonged administration, ten per cent to 15 per cent of the patients who responded initially must stop taking indomethacin because of its untoward effects. . . ."

However, also within the AMA report, the following appears: "Indomethacin has been particularly useful in the treatment of . . . osteoarthritis of hip joint, a condition that is resistant to all other anti-inflammatory agents. . . .

"Indomethacin produces anti-inflammatory effects in patients with gout. . . . It has produced relief in acute attacks within 48 hours.

"Because it lacks the untoward effects of colchicine [another anti-gout drug], some clinicians consider it to be the drug of choice for these attacks. . . ."

One of the most striking talents of Indocin lies in its ability to go to work quickly on the painful joint. Animal and human tests have shown that once Indocin is given, it reaches peak levels in the blood in just 30 minutes to two hours.

Thus, certain patients have begun to note relief from joint aches in two, three, six, or ten hours. One bursitis patient, for example, a 35-year-old executive from Hartsdale, New York, told his family doctor that once he took Indocin, "My shoulder began to feel better in just two or three hours. On just two Indocin capsules per day, I can feel pretty comfortable during an acute bursitis attack."

A random sampling of a half-dozen doctors in various medical centers around the country produced the following assessments of Indocin:

1. When the drug works in a patient, the results are very dramatic. Relief comes quickly and may last for long periods.

2. In some patients, however, there are no beneficial effects at first. The drug must be continued for some weeks before it does any good at all.

3. Patients on Indocin should be watched very carefully for side effects. It has been reported that, following Indocin administration, some individuals have developed ulcers. However, it cannot be stated categorically that the drug had anything to do with the onset of this stomach ailment.

4. Somewhere around 75 to 80 per cent of all patients tolerate the drug well—and *most* of these patients experience real relief from symptoms.

5. Apparently, results are most remarkable among patients with arthritis of the hip, but many other patients with joint ailments do get dramatic relief in comparatively short periods.

Actually, the first human trials with Indocin started in November 1961. Since that time, more than 5,000 patients have been involved in worldwide studies of Indocin. Prior to the "patient-testing stage" more than 100,000 animal experiments were conducted by Merck to establish that the drug was potent and had worthwhile effects.

In those animal studies it was found that if researchers injected animals with a drug that itself could cause considerable inflamation, Indocin could reverse the inflammatory effects.

As is the case of so many other drugs, the exact mode of action of Indocin is not known. The same holds true for aspirin—the most widely used of all medications—and for penicillin—the miracle drug that has saved more lives than perhaps any other drug in the history of man. Doctors know that aspirin and penicillin work but are not exactly sure how they work. This is true, too, of Indocin.

Once it was established that Indocin could reduce inflammation, further tests indicated that its site of action must be within the inflamed joint itself. In addition, tests showed that its anti-pain capabilities at least equaled those of aspirin (which also is widely prescribed for arthritis) and in some instances exceeded the results aspirin could produce.

Interestingly, Indocin not only reaches peak levels in the blood quickly but it is eliminated from the body quickly, too. This is a distinct advantage, because pharmacologists (specialists interested in the chemistry of new drugs) are convinced that drugs that are quickly eliminated usually have a greater built-in safety factor. The feeling is that the quicker the drug gets in and then out of the body, the safer it is likely to be.

Studies show that Indocin may be eliminated entirely within 48 hours, which, as prescription drugs go, is extremely quick. There are, for example, some drugs on the market that remain in the body for several days, or even weeks, after initial administration.

During the clinical trials of Indocin the majority of patients treated were suffering from chronic joint disorders and related rheumatic diseases that had a "history" of at least five years' duration. Most of the patients selected for treatment had failed to get relief or had experienced serious side effects from other available drugs.

Thus, from the outset, Indocin was designed as a sort of "trouble-shooter" drug that could help patients who might not have gained beneficial effects from any other medication. There are, as a result, countless cases in the Merck files that show that Indocin works where no other drug has.

Whenever a new drug is introduced, doctors wonder whether it will have major effects on the body's vital systems. Indocin's record in this regard is good. Studies show that it has no significant effect on weight, pulse rate, or blood pressure. Nor does it upset the body's glandular system or its blood-clotting mechanisms.

Indocin's history is a fascinating story in itself. Research at Merck into Indocin-type compounds started about a decade ago, but Merck's interest in the entire subject of pain and inflammation goes back at least 30 years.

In 1933 Dr. R. E. Gruber, a Merck vice-president, agreed to a request made by the Johns Hopkins School of Medicine, Baltimore, to develop a process for producing adrenal cortex hormones for the relatively few sufferers of Addison's disease and other adrenal disorders.

Merck did this, and the spark of interest was rekindled during World War II when the company was asked to help Dr. Edward C. Kendall in research on adrenal hormones. Merck was told that this research "would be in the national interest."

It seems that during the war American intelligence had heard rumors that Germany was buying adrenal gland extract from Argentine slaughterhouses and giving it to Luftwaffe pilots in the hope that the extract would enable the pilots to fly at altitudes of 40,000 feet or more.

Obviously, the United States military wanted to know if adrenal extract conferred any such capability upon airmen. (It didn't.) Dr. Kendall went to work with a young Merck chemist, Dr. Lewis H. Sarett, who, in 1944, just before turning 27, developed the first synthesis of compound E. This development, in turn, paved the way for the discovery that compound E had therapeutic effects. The compound then became known as cortisone.

After the war cortisone and its later modifications came into wide use for arthritis and other inflammatory ailments, but gradually it was discovered that cortisone produced a great many undesirable side effects.

Thus, from the early 1950s until the present, researchers have been hard at work trying to develop anti-inflammation drugs that work but do not produce cortisone-like side effects.

In 1953 a Merck research group, led by Dr. Sarett, began to wonder if they could develop a drug that was nonhormonal in nature, and thus unlike cortisone, but a drug that would provide the same benefits as cortisone.

In their search they worked on compounds at first thought to be valuable against certain emotional disorders. But the compounds later proved to be of very limited value in mental disease. One of the compounds screened, however, did have some positive effects on inflammation, and this in turn led to the synthesis of still another chemical. In March 1964 this chemical, indomethacin, became, in the words of one well-known scientist, "the most promising drug since cortisone."

After considerable testing, the drug was approved for prescription use in June 1965. Merck has deliberately avoided publicity for the drug for several reasons.

Since the FDA's new tough line on all new drugs, pharmaceutical companies are becoming reluctant to blow their horns about any new compound. And more

important, Indocin is designed to relieve symptoms of chronic disorders—illnesses that come and go or come and stay for years on end.

The company has been under standably reluctant to sound the trumpets about Indocin until it had at least a year's experience with the drug on the prescription market. Now, with patients receiving lasting benefit from Indocin, Merck feels it can begin to bring some aspects of the story of the drug to the public. The drug is proving itself to even the most conservative physicians and laboratory scientists.

Of course, each day the line of grateful Indocin patients becomes longer and longer. The drug does not have to prove itself to these people. It already has been a "lifesaver" to thousands.

There is, for example, the 62-year-old New York City carpenter who could not work for nine years. His hands were so crippled by arthritis that he could not hold his tools. After five weeks on Indocin his hands improved markedly.

"I can hold a hammer again, and what's more, I can drive a nail—pretty straight, too," he says.

Within a few months this man expects to be back at work. Indocin will have returned him to a reasonable level of personal dignity—not to mention to a reasonable level of income.

But perhaps the most extraordinary Indocin success story of all involves a 68-year-old Connecticut woman who has been a virtual invalid for the past eight years. Her arthritis was so bad that years ago she gave up going to the corner grocer for the absolute kitchen necessities.

"After I began to take Indocin," she relates, "I noticed that I felt better. It was only a couple of days or so that I'd been taking the drug, but I began to feel better. After a few weeks I felt that I could actually take a little walk—perhaps down to the front of the house and back."

Last week she walked about 60 yards to the corner grocer. When she left, still somewhat unsure of herself, though not in great pain, she was sobbing just a little bit. But it was a joyous cry.

Dr. McCLEERY. The story, written by two science writers, in the July issue featured Indocin by name in the title of the article, and said it was useful 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 support for these claims was largely lay testimonials some of which, according to the article and the firm, were made available to the writers by the sponsor of the drug.

Mr. Fletcher said that the firm was in no way responsibile for the article, that the authors had heard of stories about the drug from a variety of sources and wanted to do an article about it, and that the firm had simply responded to this inquiry from responsible science writers. Mr. Fletcher said the article was in no way promotional and wanted to so assure the agency.

The drug, of course, had not been approved for use for the above-mentioned conditions for which it was claimed to be effective in the Pageant article. We knew also that a popular article of this sort is apt to create a demand for the drug by the patients who read it.

Senator NELSON. As I understand from your testimony at the top of page 2, this article for Pageant magazine was submitted to the FDA prior to publication?

Dr. McCLEERY. Yes, sir.

Senator NELSON. So there wouldn't be any question about what was in the article, and FDA could, at least, express their disagreement with claims made for the drug to Pageant magazine if they desired.

Dr. McCLEERY. That is right. I believe that the time interval from the submission of the letter, which was to Mr. Cron—that at that time we would have to assume that the article was already in press, although not yet mailed in the July issue. And again, it was, without any question in our minds, an article actually written by the authors

who were independent, I guess well known, science writers in their field. So it was their article in substance, and not that of Merck & Co., so far as we know.

Senator NELSON. But they had advance copies of it.

Dr. MCCLEERY. Yes.

My office, the Division of Medical Advertising in the Bureau of Medicine, was asked to review the article for possible violation of the law, and to review also the advertising of this drug in medical journals to determine if the drug was being promoted to the medical profession on the basis of unapproved claims?

Our concern was that if the firm would make these data on unauthorized uses available to a free-lance team of writers, it might not be scrupulous in its advertising to the medical profession.

I would like to leave this now and go to the performance of the company——

Mr. GORDON. What did your Division do about this article?

Dr. MCCLEERY. We responded to the internal inquiry from the office of Mr. Cron and gave our view of what the article in fact was, and we wrote a report of the deficiencies which we thought the Pageant article contained and what our opinion was of whether or not the law might be considered to have been violated by Merck & Co. as a consequence of this article.

Mr. GORDON. And what was your opinion about that? Did you think the law had been violated?

Dr. MCCLEERY. Yes. Our opinion in the Division of Medical Advertising—which I would like to ask Mr. Goodrich to follow up on—our opinion of whether the law in fact had been violated, I have some apology for. But we thought that the law had been violated because the article, in the form it took, could be considered to have been caused to be issued by the company because of the turning over of documents to the writers which were built into the article and which would have come from no other source. And for this reason, the promotion of unauthorized, unapproved uses, which could be a consequence of the article, we thought should be laid to the door of the company.

Senator NELSON. Well, now, this article was published in the July 1966 issue of Pageant.

Dr. MCCLEERY. Yes, sir.

Senator NELSON. I notice that in a letter dated March 8 of this year, 1968, you concur in the recommendation for prosecution of the company.

Dr. MCCLEERY. That is true.

Senator NELSON. And that on March 11, 1968, Dr. Ley stated, "The Bureau of Medicine recommends that prosecution of the firm be instituted subject to approval by the Attorney General." What is the status of that recommendation now?

Dr. MCCLEERY. I think Mr. Goodrich can speak better to that.

Mr. GOODRICH. The case is in my office.

Senator NELSON. But the recommendation has not left your office.

Mr. GOODRICH. It has not.

Senator NELSON. Is it correct that the prosecution involved not only the Pageant article, but also some other advertising materials?

Mr. GOODRICH. Yes, sir.

Senator NELSON. There are several documents here as well as letters by Dr. Weinstein, Dr. Ley, Dr. McCleery, and others; and since they explain this situation in some detail, and specify the kinds of violations that the FDA believes do occur, and give examples of them, I would ask that they be printed in the record at the appropriate place.[1]

Dr. MCCLEERY. I would like to turn now to the third element of the promotional campaign with which we had to deal, and that concerns the medical journal advertising to the medical profession by Merck Sharp & Dohme.

We have already supplied for the record copies of two major kinds of ads [2] which have been used by the company, one characterized by a submission which you have in your hands dated July 18, and which is identical in content to the issues of the same ad in July 4 and August 15, 1966, issues of the Journal of the American Medical Association. There is a second ad, with some minor changes, which you also have a copy of, and bears a handwritten inscription called the "The" Ad, which was published in November 1966, and I want to make comments on both ads.

Mr. GORDON. Which ones are these?

Dr. MCCLEERY. The first ad, you have a copy of the JAMA dated July 18, 1966. We happened to act in our memos on an issue dated July 4. All of these ads are identical. They are just prints of the same ad in different issues. The one you have at hand is marked with the hand inscription "A." The "A" ad is July 18, 1966. As I go along, we will deal with the features which are common to the second ad, marked November 1966, in the American Journal of Medicine.

Senator NELSON. Are you referring now to the AMA Journal?

Dr. MCCLEERY. Right.

Senator NELSON. In looking at the ad, it shows a radiograph of a left foot and says, "Indomethacin is a drug of choice in acute gout." Is that correct?

Dr. MCCLEERY. Are you reading correctly?

Senator NELSON. "Indocin is a drug of choice in acute gout."

Dr. MCCLEERY. I just wonder what your question is.

Senator NELSON. Is it a drug of choice, do you know?

Dr. MCCLEERY. One of the reasons we have submitted both this ad and the ad of November is because the author said "the drug of choice." You will note in the JAMA ad there is a bracket around the "a" which the company at this time inserted in place of the author's own statement that it was the drug of choice.

Senator NELSON. Who inserted the "a"?

Dr. MCCLEERY. The company and its advertising agency. We have assumed this was in a mood of good instinct and caution that the company changed the author's quote from the word "the" which is correct, and which is in the view of many a far less defensible statement concerning the value of the drug. The complexities of what the statement says with the word "a" in instead of "the" is the problem. In any event, in answer to your question, in my opinion, and in the opinion of many who are expert in this field which I am not, indomethacin is a good drug for the treatment of acute gout—it had not reached the level of "the drug of choice" for acute gout.

[1] See documents and letters beginning at p. 3246, infra.
[2] See supplemental information beginning at p. 3221, infra.

Senator NELSON. It had reached the level of the drug of choice?

Dr. MCCLEERY. That it had reached the level of "the drug of choice" at that time I think hardly anyone would accept—perhaps the authors would, but most would not agree that even today it is the drug of choice.

Senator NELSON. They would not agree today that it is the drug of choice.

Dr. MCCLEERY. I believe not. That it is a good drug, yes. But there is no evidence that exists on any scientific basis of comparative studies with Indocin and other drugs used in the treatment of gout. The kinds of studies that would be required to make an acceptable statement that this is the drug of choice have not yet been done.

Senator NELSON. The phrase "the drug of choice" are words of art, aren't they, in the medical profession? That is, they have a special meaning. When you say "the drug of choice," those are words of art in medical language, are they not?

Dr. MCCLEERY. I would be more inclined to say that the company's use of the word "a" puts it into more the realm of art and not of science.

Senator NELSON. I was using a legal phrase. I meant to say the phrase has a special meaning to the medical profession if you say a drug is "the drug of choice," does it not?

Dr. MCCLEERY. I would say that the phrase "the drug of choice" should be based on science, and not on art.

Senator NELSON. I am confusing you. I am using a legal phrase, so we will just skip that. The phrase "the drug of choice" has a special meaning in medical language.

Dr. MCCLEERY. Yes.

Senator NELSON. That is what words of art mean in legal phraseology. And what is the meaning of that phrase "the drug of choice" in medicine?

Dr. MCCLEERY. If one takes at face value the claim, and believes that the person making such a statement is to be believed, it is the highest accolade that one can give a drug in competition with other drugs used for the same treatment—that is the best drug, and it is the drug that should be chosen for the treatment of most cases—should be tried first if one is choosing from a number of drugs.

Senator NELSON. That is my point. If you say "the drug of choice" you mean that it is the first drug recommended to be tried, based upon all the scientific evidence that is available as of that time; is that correct?

Dr. MCCLEERY. Yes.

Senator NELSON. I had to read it twice before I saw the "a" in parenthesis. If you glance at this as I do you see "indomethacin, drug of choice for acute gout." This is this kind of very clever advertising which, it seems to me, can be very misleading. Isn't it easy enough to read something like that ad and not notice the little "a" in parenthesis. You simply see "drug of choice," and interpret it to mean automatically, as medical people would, that this must be the drug of choice?

Dr. MCCLEERY. You put me in the difficult position of defending the company, Senator, and I do not welcome it. But I must say that in our discussions with the members of the firm, they affirmed, and I for one believe, that their reason for putting in the word "a" was

that they were queasy about claiming it was "the" drug of choice, and this, in their mind, was to weaken the impact of the claim, and I believe they were telling the truth.

Senator NELSON. It is weaker than "the drug of choice." But why use the phrase "drug of choice" which are words of art to the medical profession unless you are trying to give the impression to somebody who glances at it that it is the drug of choice? I read all kinds of these ads. If you sit and analyze them long enough, carefully enough, you can end up defending them. But that is not the way people read ads.

Dr. MCCLEERY. No, sir; but I think there is more of interest on this point than we have gotten to, and I direct your attention to the use of "a" in two other places in the same ad. If you start on your left, I believe you will see another quotation from the paper by the same authors in reference to rheumatoid arthritis. At that point you will see the use of the word "a" in brackets again inserted into the quote. The article actually said at that point this is "the first noncorticosteroid drug" to do what follows. And the company again removed the words "the first" and inserted in caution and I would say good instincts, regardless of other attributes of the ad, the word "a." You will find it again in the third panel, in a quote from, not a paper, but remarks at a symposium sponsored by Merck & Co., by a Dr. Englund of Phoenix, Ariz., where his quote is changed to include the word "a" in the body of it. Do you see that?

Senator NELSON. I see it. And if I understand what drug of choice means, I am impressed by the fact that every time the company can use the phrase "drug of choice" it is there. Why don't they say a useful drug?

What would FDA say if under the reproduction of this radiograph of the foot it said "indomethacin is a", and then in capital letters "drug of choice," and then back to lower case, "in acute gout."

Dr. MCCLEERY. We would have said it is very little worse than we thought it was in its present form.

Senator NELSON. You would say it was very little what?

Dr. MCCLEERY. Very little worse. I say it is bad the way it is. What you suggest would make it very little worse. It is bad enough.

Senator NELSON. These are words of art in the medical profession, so every time the words can be fitted in, the phrase "drug of choice," which captures any medical person's eye, the phrase is used. Then to technically clear themselves they add a little "a" with a bracket around it.

Dr. MCCLEERY. Yes, sir. We felt it was wrong, and the use of the word "a" in the insertion did not relieve them of the fault. We charged the ad as misleading in its JAMA form. I would only like to point out to you that you also have an ad which we labeled the "The" ad, which is a November 1966 issue. There the ad that you see appears in all of its glory with the quotes intact, so that the word "the" is in all of the places where the word "a" is here. And these are the two ads that I want to discuss in detail this morning.

Senator NELSON. All right. Thank you.

These ads will be put in the record in the appropriate place.

Are you going to get to the October 24 issue of Modern Medicine, which carried almost the same ad as the Journal of the American Medical Association, again where they say it is the drug of choice?

Dr. MCCLEERY. Yes, sir. The reason we submitted that little magazine,

in its October issue is to show the breadth of the November 1966 campaign containing the word "the" in place of "a," and you have copies of the October 26, I believe, issues of Modern Medicine, you also have copies of the November 1966 issues of the American Journal of Medicine, and Arthritis and Rheumatism magazine, all of which are the same. They are just prints of the same ad in different journals.

Senator NELSON. Did the package insert at any time include the same phrasing, "the drug of choice"?

Dr. MCCLEERY. No, sir; it did not.

Senator NELSON. And the FDA did approve the package insert? So at the same time that the package insert is making a lesser claim, using different language, the company is running advertisements in the Journal of the American Medical Association and other medical magazines claiming that Indocin was the drug of choice in gout; is that correct?

Dr. MCCLEERY. Correct.

Senator NELSON. So there was no question that the company knew what the viewpoint of FDA was as to the requirements for the package insert at the time they were running these ads in the medical journals.

Dr. MCCLEERY. I should say not.

The so-called A ads that we have been discussing appears as identical advertisements in the Journal of the American Medical Association in many issues, but also in issues of July 4 and August 15. And these were found to be featuring under the major headline the theme that the drug "extends the margin of safety in the long-term management of arthritic disorders." At the same time——

Senator NELSON. Where are you, Doctor?

Dr. MCCLEERY. The middle of page 3.

Senator NELSON. Please proceed.

Dr. MCCLEERY. At the same time, the Office of Marketed Drugs, under Dr. Jennings, who appeared yesterday, was negotiating with Merck for changes in the package labeling to emphasize newly recognized hazards that had emerged during the first year of clinical experience since original approval of the drug.

The JAMA ads in July 4 and August 15, 1966, issues were analyzed and found to be defective, in our opinion, in several respects. I am going to mention only a few of them. I would not want you to believe we have exhausted our objections by what I point out today.

Senator NELSON. This is now in what edition of JAMA?

Dr. MCCLEERY. The July 18 issue that you have in front of you.

Senator NELSON. That is the one you are going to discuss now?

Dr. MCCLEERY. Yes, sir. I would like first to mention generally the major defects of the ad in our view, and then will be more specific regarding the details of our objections to certain of the features of this and of a later ad which appeared among others in the November 1966 issue of the American Journal of Medicine.

The basic theme of greater long-term safety in the ads was not supported by the clinical experience.

Mr. GORDON. You say "greater"?

Dr. MCCLEERY. It is a kind of advertising technique which has a great deal of value because it says "greater" but does not specify greater than what, and goes in the advertising world under the delight-

ful phrase called a "dangling comparative." And this is represented well by this headline.

Senator NELSON. You are referring to the headline that reads "extends the margin of safety in long-term management of arthritic disorders"?

Dr. MCCLEERY. Yes.

This implies that the drug, as a theme of advertising, has greater long-term safety than something else, or in effect, in our view, everything else.

To the contrary, in our experience the longer the drug had been on the market, the more serious adverse experience information had been reported to us.

Now, the ad, as you have seen, and talked about, used four blocks of depictions of X-rays that were accurate representations of the four indications for the drug. And they quoted underneath these depictions, and in support, presumably, if the ad were a good ad—in support of the headline claim. And they quoted apparently authoritative sources, but without the full impact of the limited experience contained in the actual articles they were quoting. And the ad features, for example, one reference which on checking proved to be only a 2- or 3-inch abstract of a 1964 speech. That is the one on the second block by Dr. Rothermich.

The ad quoted the author's opinion that "results have been uniformly excellent or good." Dr. Rothermich's same abstract, although brief, also included his view that while "excellent results have also been obtained in some cases of rheumatoid arthritis, there have been striking failures as well." So it is perhaps not surprising that while the advertising included this author's favorable remark regarding his experience with spondylitis, which they did, they then turned to another author, namely Hart and Boardman for a more favorable quote concerning the possible value of the drug on rheumatoid arthritis, and did not reflect Dr. Rothermich's view on rheumatoid arthritis in the ad. We consider this as not quite cricket, at least.

It offered the drug for "arthritic disorders," rather then solely for the specific four conditions for which it has been approved.

This is a small point, and one of the kind of things we have been accused of "nit-picking" about. All we would have asked here was they merely put in the word "certain," to show the reader when he was getting a quick view of what the drug was for, that this was not for all arthritic disorders, but at least only for certain of them. And then he would look more carefully as to what he expected the drug to be indicated for.

Senator NELSON. Did the company object to the insertion of the word "certain"?

Dr. MCCLEERY. Well, we met them somewhat later than this time. Whereas I am not sure whether they objected or not, there was a marked change in their advertising subsequent to our meeting, so that this became an issue of no importance, because all of these claims disappeared subsequently.

The ad goes on in a major way to characterize the drug as nonsteroid, which of course it is, but failed to disclose in this connection that whereas it was not a corticosteroid, which is a class of drugs also used for the treatment of these conditions, and for which there are major side-effect concerns already well established in the minds of

the profession—so they failed to disclose in this connection that Indocin has some of the major side effects of these steroids themselves—for example, an ulcer-producing effect.

The ad goes on to claim that the drug extended the margin of long-term safety without any evidence in our view to support the claim, and it quoted from isolated pieces of literature to support this—one an excerpt from a symposium sponsored by the company—and to claim that the drug was "the drug of choice" in gout and in osteo-arthritis of the hip, neither of which claims had been approved for inclusion in the package labeling of the drug.

It also quoted from two leading English authorities to the effect that the drug was useful in most cases of rheumatoid arthritis, when these authors had used the tablet and not the marketed capsule, and when their actual opinion, known to Merck, was that the drug was useful in only selected cases of rheumatoid arthritis.

It 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 3 years, when Merck's own records would have told them this was not true.

And finally, in the "brief summary" of information on side effects and contraindications, some of the major warning information was left out, such as the fact that indomethacin itself had caused ulcers of the stomach and so on, and that the drug should not be administered to children.

Now, how they did this is a very interesting operation——

Senator NELSON. Which ads were they? In which ads were the two warnings left out?

Dr. MCCLEERY. They were left out in both of the ads. Most of these features that I have been discussing are common to the July ads and the November ads, Senator. You see at the bottom of the page of the ad that you have in front of you what we call "the brief summary," and it contains information from the package insert that summarizes the warning information on the product. We say that, in practical fact, they had left out significant warnings which they are required to include in that brief summary of warning information.

Because it is a very subtle, but very important, advertising kind of language—I would like to point out why we say this.

Senator NELSON. You are saying that in no place in the fine print of this ad do they include the warnings that indomthacin may cause ulcers, and that the drug should not be administered to children.

Dr. MCCLEERY. Yes, sir.

Senator NELSON. And that was well known at that time, was it not?

Dr. MCCLEERY. Yes. But the issue is much more subtle, because there are references to both of these subjects in the ad which we have found fault with, and I would like to stress this kind of advertising technique which appears to fulfill the requirements of law, but in our view does not, because it is a very common practice, one which we are trying to fight. It is often called nit-picking by our opponents, as a way to denigrate the significance of changes in words, which we think is very important.

Senator NELSON. I have not read all the fine print. Are you saying that in this JAMA ad of July 18, 1966, somewhere in the fine print, there is the warning that it should not be used for children?

Dr. McCLEERY. I am saying that in our view it is not, although the subject is discussed. I would like, if I can go on just for a moment, to point your attention to the way that the ad differs from the package insert in these respects.

We believe that these that follow exemplify what might be called the euphemistic style of revealing warning information. The ad's "brief summary" translated the package insert's warning "Indocin itself may cause peptic ulceration * * *" into the area of causal doubt in this manner: "Ulceration of the stomach, duodenum, or small intestine have been reported. * * *"

Senator NELSON. I do not see that in the ad. Is that the July 18 ad?

Dr. McCLEERY. Yes, under the "Precautions." "Ulceration of the stomach, duodenum, or small intestine have been reported."

Senator NELSON. Is this under the warning section in the package insert?

Dr. McCLEERY. It is under the contraindications section—but it is in the ad's precaution section. Under the contraindications section in the package insert is the statement that I read first, which is a plain statement which carries the idea that the company has agreed with the Bureau of Medicine to say "Indocin itself may cause peptic ulceration." We are saying that in no way is that statement in the package insert properly reported to the physician in the ad by the statement "Ulceration has been reported." This is a style of statement about side effects that is traditional in ads over the years. It only means that many side effects are reported to be associated with the use of a drug, which may be by chance, and to say merely that it has "been reported" in no way suggests that it is "caused by" the drug in question. On the other hand, the package insert is very clear.

Senator NELSON. Where does this precaution appear in the package insert?

Dr. McCLEERY. Under the contraindications section. It is a piece of information under the contraindications section.

Senator NELSON. It does not appear under the warning section?

Dr. McCLEERY. I cannot tell you whether it also appears in the warning section. But it does appear in the package insert in the contraindications section.

Senator NELSON. There is also a warning section in the package insert, isn't there?

Dr. McCLEERY. Yes.

Senator NELSON. Those warnings do not appear in the warning section of the package insert?

Dr. McCLEERY. I frankly cannot tell you. I do not know that well enough by heart.

Senator NELSON. I wish you to submit for the record the package insert that was being used by the company at that time. I would like to have that in the record at this stage of the testimony.

(The information to be furnished for the record follows:)

DIRECTION CIRCULAR

INDOCIN®
(INDOMETHACIN)

MERCK SHARP & DOHME

MERCK SHARP & DOHME
Division of Merck & Co., Inc.
West Point, Pennsylvania

A.H.F.S. Category: 92:00

Ph. 262401 Effective May 1965 Printed in U.S.A.

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.

*Registered trademark of Merck & Co., Inc.

INDOCIN®
(Indomethacin)

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 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,

INDOCIN®
(Indomethacin)

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.

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

INDOCIN®
(indomethacin)

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, stoma-

titis, 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.

INDOCIN®
(Indomethacin)

DOSAGE AND ADMINISTRATION

INDOCIN is available as 25 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 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*

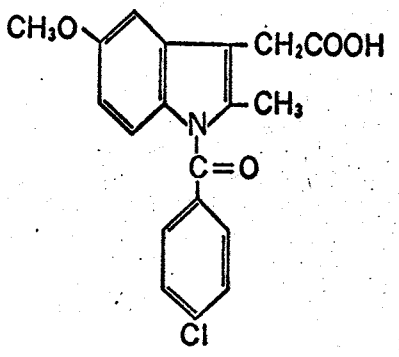
To control acute attacks: 50 mg. three times a day until all signs and symptoms subside. Definite relief of pain has been reported within 2 to 4 hours. Tenderness and heat usually subside in 24 to 36 hours, and swelling gradually disappears in 3 to 5 days.

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

INDOCIN®
(Indomethacin)

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.

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. Therat, guinea pig, monkey, and man eliminate it by both routes. In man, about two-thirds of the drug is excreted in the urine.

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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.

REFERENCES

Bilka, P. J., Wollheim, F., and Williams, R. C., Jr.: Indomethacin: A New Antirheumatic Agent, Minnesota Med. *47:* 777, July 1964.

Boland, E. W.: Nonspecific Anti-Inflammatory Agents. Some Notes on Their Practical Application, Especially in Rheumatic Disorders, California Med. *100:* 145, March 1964.

Catoggio, P. M , et al.: Indomethacin in Rheumatoid Arthritis: Properties, Side-Effects, Arthritis & Rheumatism *7:* 300, June 1964 (in Soc. Proc.).

Clark, G M.: Indomethacin in Rheumatoid Arthritis, Arthritis & Rheumatism *7:* 300, June 1964 (in Soc Proc.).

Datey, K. K., and Pandya, V. N.: The Value of Indomethacin in Rheumatoid Arthritis, J. Indian M. A. *42:* 166, Feb. 16, 1964.

Harman, R. E., Meisinger, M. A. P., Davis, G. E., and Kuehl, F. A., Jr.: The Metabolites of Indomethacin, a New Anti-Inflammatory Drug, J. Pharmacol. & Exper. Therap. *143:* 215, Feb. 1964.

Hart, F. D., and Boardman, P. L.: Indomethacin: A New Non-Steroid Anti-Inflammatory Agent, Brit. M J. *2:* 965, Oct. 19, 1963.

Hart, F. D., and Boardman, P. L.: Current Therapeutics: Indomethacin, Practitioner *192:* 828, June 1964.

Hucker, H. B., Zacchei, A. G., and Cox, S. V.: Studies on the Physiological Disposition of Indomethacin, Fed. Proc. *22:* 544, March-April 1963.

Katz, A. M., Pearson, C. M. and Kennedy, J. M.: The Anti-rheumatic Effects of Indomethacin in Rheumatoid Arthritis and Other Rheumatic Diseases, Arthritis & Rheumatism *6:* 281, June 1963 (in Soc. Proc.).

Katz, A. M., Pearson, C. M., and Kennedy, J. M.: A Clinical Trial of Indomethacin in Rheumatoid Arthritis, Clin. Pharmacol. & Therap. *6:* 25, Jan.-Feb. 1965.

Kelly, M.: Indomethacin: An Antirheumatic Drug, Lancet *2:* 474, Aug. 29, 1964 (in Letters to the Editor).

Kelly, M.: Indomethacin, Remarkable Antirheumatic Drug, M. J. Australia *2:* 541, Oct. 3, 1964.

Lövgren, O., and Allander, E.: Side-Effects of Indomethacin, Brit. M. J. *1:* 118, Jan. 11, 1964 (in Correspondence).

Norcross, B. M.: Treatment of Connective Tissue Diseases with a New Non-Steroidal Compound (Indomethacin) Arthritis & Rheumatism *6:* 290, June 1963 (in Soc. Proc.).

Paul, W. D.: Indomethacin: A New Anti-Inflammatory Agent, Arthritis & Rheumatism Foundation Med. Information Bull., Vol. 4, March 1963.

Percy, J. S., Stephenson, P., and Thompson, M.: Indomethacin in the Treatment of Rheumatic Diseases, Ann. Rheumat. Dis. *23:* 220, May 1964.

Rothermich, N. O.: Indomethacin: A New Pharmacologic Approach to the Management of Rheumatoid Disease, Arthritis & Rheumatism *6:* 295, June 1963 (in Soc. Proc.).

Rothermich, N. O.: Clinical Experiences with Indomethacin in Rheumatic Diseases, Arthritis & Rheumatism *7:* 340, June 1964 (in Soc. Proc.); Some Pharmacologic Effects of Indomethacin, ibid.

Smyth, C. J., Amoroso, C., and Velayos, E.: Objective Evaluation of Indomethacin in Rheumatoid Arthritis, Arthritis & Rheumatism *7:* 345, June 1964 (in Soc. Proc.).

Smyth, C. J., and Godfrey, R.: The Treatment of Rheumatoid Spondylitis with Indomethacin, Arthritis & Rheumatism *7:* 345, June 1964 (in Soc. Proc.).

Smyth, C. J., Velayos, E. E., and Amoroso, C.: A Method for Measuring Swelling of Hands and Feet: Part II. Influence of New Anti-Inflammatory Drug, Indomethacin, in Acute Gout, Acta rheumat. scandinav. *9:* 306, 1963.

Smyth, C. J., Velayos, E. E., and Amoroso, C.: Indomethacin in Acute Gout Using a New Method of Evaluating Joint Inflammation, Arthritis & Rheumatism *6:* 299, June 1963 (in Soc. Proc.).

Sunshine, A., Laska, E., Meisner, M., and Morgan, S.: Analgesic Studies of Indomethacin as Analyzed by Computer Techniques, Clin. Pharmacol. & Therap. *5:* 609, Nov.-Dec. 1964.

Wanka, J., and Dixon, A. St. J.: Treatment of Osteo-Arthritis of the Hip with Indomethacin: A Controlled Clinical Trial, Ann. Rheumat. Dis. *23:* 288, July 1964.

Wanka, J., Jones, L. I., Wood, P. H. N., and Dixon, A. St. J.: Indomethacin in Rheumatic Diseases: A Controlled Clinical Trial, Ann. Rheumat. Dis. *23:* 218, May 1964.

Winter, C. A., Risley, E. A., and Nuss, G. W.: Anti-Inflammatory and Antipyretic Activities of Indomethacin, 1-(*p*-Chlorobenzoyl)-5-Methoxy-2-Methylindole-3-Acetic Acid, Fed. Proc. *22:* 543, March-April 1963; J. Pharmacol. & Exper. Therap. *141:* 369, September 1963.

European Rheumatology, 1963: The Fifth European Congress on Rheumatic Diseases, Canad. J. A. J. *89:* 781 Oct. 12, 1963.

Senator NELSON. Now, is there any place in this ad where the warning or precautions is made that it is not to be used in the treatment of children?

Dr. MCCLEERY. Yes.

Senator NELSON. Where is that?

Dr. MCCLEERY. The statement in the package insert is the one that was under considerable discussion yesterday, but includes among other verbiage the statement that the drug should not be administered to children. Those words are contained in the original package insert for the drug, under the contraindications section.

Senator NELSON. Are those the exact words? What are the exact words in the package insert?

Dr. MCCLEERY. That the drug shall not be administered to children. That is in the contraindications section.

Senator NELSON. And is some reference made to that under contraindications in this ad?

Dr. MCCLEERY. Yes. In the ad it is transformed into another style of transmitting information, and in the ad you will find near the bottom of the contraindications section the statement "safety in pregnancy and pediatric age groups has not been established." That is the only reference to children in the ad.

Senator NELSON. So instead of saying it should not be administered to children, as it says in the package insert, as required by the FDA, in the ad it says "safety in pregnancy and in pediatric age groups has not been established."

Dr. MCCLEERY. That is right.

Senator NELSON. You consider that to be a much weaker cautionary statement.

Dr. MCCLEERY. Yes, I do. I consider it is not the same information. Deficiencies in the ads were publicly noted in a speech before the Pharmaceutical Advertising Club in New York, on October 20, 1966, by our General Counsel, Mr. Goodrich. The firm quickly protested, and shortly thereafter on November 11, 1966, a sort of "Armistice Day," the firm's principal officers met with Dr. Goddard and his staff to go over the problem. The problem took into account all of the elements of the advertising that we have discussed.

At that meeting, the firm reported that on hearing Mr. Goodrich's comments in New York concerning Indocin advertising, that it had immediately ordered that ad discontinued, and was taking a close look at all of its promotional efforts.

Later on, not too much later, its physician and counsel responsible in the area of advertising came down to go over some ads for other products, that Merck makes and advertises, with us. And I must say in defense of the company that from that point in time on, they have behaved in a very exemplary way. We have watched their advertising on Indocin carefully subsequent to this point. We have watched their advertising on a number of their products for tranquilizers and antidepressants. We have seen them introduce two major new products subsequent to the meeting in Dr. Goddard's office, and we could find no serious objection to those. And so I am glad to say this concerning the performance of Merck & Co. And I regret I cannot say it very broadly concerning a number of other companies with which we have dealt.

Senator NELSON. I am glad to hear that the Merck Co. is now cooperating in their advertising. But something puzzles me about it. This is from a letter of March 8, 1968, signed by you. Maybe you will want to look at it. But quoting from your letter, it says "Attitude of the firm. The poor attitude of Merck regarding the advertising regulations has persisted since their promulgation. This is clearly shown in the following pages from Attorney Colburn's letter." And then there are some quotes. Then you say, "In effect, Merck challenges all of the principles of fair balance provided in the existing regulations, and even challenges the Government's authority in respect to requiring ingredient information in advertisements except as specified in section 502(n)," and so forth and so on.

How does this letter dated March 8 conform to your present statement that they are cooperating in every way?

Dr. McCLEERY. It does seem contradictory, doesn't it?

Senator NELSON. A little bit.

Dr. McCLEERY. I hope that is not a letter, because I do not like to write letters.

Senator NELSON. I will show it to you.

Dr. McCLEERY. I am well aware of it, Senator. It is an internal memo.

Senator NELSON. Yes.

Dr. McCLEERY. What I said before——

Senator NELSON. Is the attitude internally different from what it is externally?

Dr. McCLEERY. No. I hope without looking at it I won't contradict what I said in that memo at least. What I said was, Senator, what Merck has done in reference to conforming to the law and the regulations—you did not ask, and I did not feel it necessary to say, what I think they think, why they are doing it, or what they think of our view of the law on proper advertising. So there is no contradiction.

Senator NELSON. I see. What you are saying is that they have made some changes in their advertising policy of which you approve, but they sharply contest FDA's position of authority to regulate and so forth.

Dr. McCLEERY. Right. I did not feel compelled, knowing that Merck would testify tomorrow, to say they disagreed, feeling they would probably get around to that themselves tomorrow.

Senator NELSON. All right. I think the two fit together.

Dr. McCLEERY. Thank you.

Soon after this episode, Merck began to show significant improvements in its advertising practices for prescription drugs but not before it ran, I would say inadvertently, because it is hard to stop a hard-running advertising campaign—in the November 1966 issue of the American Journal of Medicine, another ad which contained most of the faults of the original July ad, plus some additional new faults.

I will expand on this.

It represents a very serious kind of advertising practice that I would like for you to understand, and to be aware of what kind of bases we are criticizing ads on, for your own purposes.

You have heard me refer to the articles used in the July JAMA ad, by two Englishmen, Hart and Boardman in the 1963 issue of the British Medical Journal. While the authors had in fact published the

report quoted in the Merck ad, we felt that Merck had no right to adopt the quotation in their 1966 advertising. The quotation from an article by Hart and Boardman in the BMJ, October 18, 1963, was used under the ad's caption "Rheumatoid Arthritis," and the quote that the company chose and chose to adopt as their own, was "The first noncorticosteroid agent which produced a predictable and measurable reduction in joint swelling in most cases of active rheumatoid arthritis."

Senator NELSON. That is a quote from the British Medical Journal from an article by Hart and Boardman.

Dr. MCCLEERY. Yes, sir. Our comments with reference to this 1963 quotation are that, first, it does not represent a true statement of the effectiveness of the advertised product, Indocin. And in this regard, the company, we feel, is responsible for choosing and using an author's view; that it becomes in this effect their own, that they are responsible.

Senator NELSON. What you are saying is that they quoted Hart and Boardman accurately, but Hart and Boardman were incorrect?

Dr. MCCLEERY. I do not think I will get around to my view on that if I can avoid it. I am saying that they quoted the article correctly. Whether it represented a correct view of the drug, other than in the mind of the authors, is a responsibility, I say, that the company has to assume—that when they choose a view expressed by an author in the scientific literature, that they have to stand on whether or not that represents a general view that is accepted widely by the medical profession at the time that they use it in an ad—that they must assume responsibility for making that view their own view.

Senator NELSON. All right.

Dr. MCCLEERY. Now, the approved package insert for the product does not contain the promissory concept represented by "most cases" or "predictable," which were the views of Hart and Boardman.

Senator NELSON. Will you explain that. You are referring back to the quote from Hart and Boardman?

Dr. MCCLEERY. Yes, sir; all of this will be in reference to that one quote—all that follows.

Senator NELSON. And you are saying that——

Dr. MCCLEERY. That the approved package insert reflecting the agreed-upon view of the drug between the Government and the company does not contain the concepts of the features of the drug expressed by Hart and Boardman in their view—that the company thereby chose an opinion of someone else which was not, and has not, been approved for representing the drug in the package insert.

Senator NELSON. Are you saying that if the company requested to use the words "most cases," and "predictable" in the package insert, you would not have approved that language in the product package insert as of that date?

Dr. MCCLEERY. That is not my responsibility, nor do I have enough information to make that judgment. I am saying that the package insert of record at the time the ad was printed did not contain these concepts, these promises. The companies are obligated in our view by the law, and the regulations written on it, to describe a drug, their drug, not beyond the terms included and approved in the official labeling for the drug. This is a baseline for the judgment of advertising,

and it is a baseline we are trying to establish in the mind of the industry. It should be their benchmark in keeping their claims within the approved concepts concerning the nature and effectiveness of the drug. It is the official document, negotiated for all drugs of this type, the so-called package insert.

Senator NELSON. Do I understand you correctly that they may use words in ads that are not in the package insert, but they may not make claims for the drug's performance that extend beyond the authorized claims that they are able to make in the package insert?

Dr. MCCLEERY. Right; we are saying if this kind of information appears in the scientific literature, or as a result of research, the company has a very good legal method to begin to use this in advertising. They should gather together this kind of information and submit it to the Food and Drug Administration as a supplement to their New Drug Application, have this evidence judged and agreed on between the manufacturer and the agency, and get it into the package insert, and then they may indeed use it in their advertising. But the way not to do it is through the route of advertising.

Senator NELSON. If this is correct, what you are saying is that you have the legal authority to prohibit them from putting in an ad a claim for the drug that extends beyond the approved claims made for it in the package insert?

Dr. MCCLEERY. Yes, sir. I believe that is true.

Senator NELSON. I am not familiar with your authority on that. Is there any question about the law on that?

Dr. MCCLEERY. May I ask you to ask Mr. Goodrich?

Mr. GOODRICH. No, no question on that, Senator.

Senator NELSON. What are the penalties for violation of the law on that point?

Mr. GOODRICH. The same penalties for shipping any other misbranded drug, which is a maximum of a thousand dollars, and in the case of an individual up to a year in jail. But the regulations, the authority to specify what should be in the ad, is granted to us by the Kefauver-Harris amendments, and our regulations provide, acquiesced in by the industry, that in advertising drugs that had been cleared through the new drug procedures, the only permissible claims were those that had been approved.

Here the point is that the claim that this product is effective in most cases and gives predictable results were not approved. We went over yesterday, in connection with Dr. Hodges' statement, the points made at the time of approval, in which the limits of the claims were spelled out. The record yesterday will show that the breadth of this claim was not permitted.

Senator NELSON. Well, I would assume that anybody reading the package insert, and reading the ad could easily see that the ad is making a claim beyond what is authorized in the package insert.

Mr. GOODRICH. We think so. That is the simplicity of our regulatory scheme—to have the approved label as an identifiable, usable benchmark for all promotional efforts—advertising or direct mailing.

Senator NELSON. Do you have the authority to require that an ad be submitted for approval in advance of publication?

Mr. GOODRICH. In extraordinary circumstances, yes.

Senator NELSON. What are those circumstances?

Mr. GOODRICH. Where the product has a possibility of serious adverse effects or of causing fatalities. This was one of the issues that was in dispute when the Kefauver-Harris drug amendments were passed. There was a strong feeling on the part of the industry that we should not have routine preclearance. Of course we did not want that. But we said it would be necessary in some circumstances to have advance preclearance. As the regulations worked out, a provision was inserted to require preclearance when a newly discovered serious hazard or fatality came about, and we have a mechanism through which the company itself, on being notified by us of this new hazard and requirement of preclearance, can submit a program for their advertising that will assure prompt transmission of this important information to the profession through the company's promotional efforts.

Senator NELSON. You referred to a new drug?

Mr. GOODRICH. Any prescription drug, Senator, whether it be a new drug, or certified antibiotic, or even a prescription drug that has been on the market for a long time, and is under the grandfather protection for effectiveness. If we should learn that even an old drug suddenly had been discovered as a causative factor in serious adverse experience or fatalities, we have the authority to require preclearance of ads and to make sure the profession is notified through all mechanisms of this new hazard.

Senator NELSON. Supposing it is a new or an old drug and it is on the market; it is a very toxic drug, has dramatic side effects, such as this one or chloramphenicol, or any one of many, many more, and the company continues to put in its advertisements, such as this one, claims that extend beyond what is authorized in the package insert—do you have the authority, when that happens, to say, "From now on we will insist on preapproval of the ad"?

Mr. GOODRICH. Yes.

Senator NELSON. Have you ever exercised that authority?

Mr. GOODRICH. We have not. In this case, as Dr. McCleery's statement shows, we met with the firm on November 11, 1966, which was less than a month after we challenged this ad, this promotional practice, publicly, and the firm immediately developed a program to change its advertising practice. It was not necessary for us to require a preclearance. We have the authority to do so.

Senator NELSON. If I understand your testimony and other previous testimony before the committee, there have been a number of cases where the advertising for a drug has made a claim beyond the claims approved for the package insert; is that correct?

Mr. GOODRICH. Yes. And our reaction to those ads has been prompt and decisive in calling the company in, Dr. Goddard himself meeting with the companies to go over the defects, and to make sure that the company does and will immediately communicate with the profession to call attention to these defects. There have been, I believe, 21 or 22 letters in the last year and a half involving these advertising practices. We will put those into the record for you, so that you can see both the details of the advertising abuses that called for the letters, and the mechanisms that we used to require the companies to communicate this information to the profession.

Senator NELSON. What puzzles me a little bit is that this has been the law since 1963, has it not?

Mr. GOODRICH. The law was passed in 1963. It required that before we could do anything on advertising, we had to promulgate the regulations. We set to work promptly at that. We promulgated the regulations effective in 1964—after confrontation with the industry. The regulations became effective at that time. The original enforcement actions were—some were taken, but it was not until Dr. Goddard became Commissioner that this program was sharply stepped up, and I believe since certainly March of 1966—he came in February or March—I forget which—but soon after he came, it became one of his most—one of his highest priority programs. It has been a high-priority program since.

Senator NELSON. So the regulations were promulgated about 4 years ago.

Mr. GOODRICH. Yes, sir. As a matter of fact, we now have under consideration—we have had over about the past year—an improvement in those regulations in terms of making them much more specific. This improvement will be carried out very shortly. But meanwhile, we think the regulations are entirely adequate to deal with the major problems of advertising. We are revising them simply to be more specific and to avoid any contention on the part of the pharmaceutical industry that they did not understand what was required, or what our attitude towards specific kinds of advertising practices were.

Senator NELSON. Have there been any cases where the penalties under the law were levied against any of the companies?

Mr. GOODRICH. Yes. There has been one prosecution involving a product called Pree MT. There have been a number of others under discussion back and forth with the Department of Justice. Several of them are in controversy.

Senator NELSON. Do I understand you to say the penalty is a thousands dollars?

Mr. GOODRICH. Yes, sir—for each shipment of the drug. So there is a possibility of a substantial penalty.

Senator NELSON. We are talking about advertising in a journal now.

Mr. GOODRICH. Yes. But the offense is in terms of an interstate shipment of a supply of the drug.

Senator NELSON. The liability under the law is what?

Mr. GOODRICH. The introduction into interstate commerce of a misbranded drug, and the drug is misbranded because its advertising failed to comply with the regulations.

Senator NELSON. And what is the effective date from which you start measuring the penalty—the date of the publication of the ad?

Mr. GOODRICH. Yes—the ad must be related to a shipment made after the date the ad appeared.

Senator NELSON. And then the penalty is based upon the number of shipments, not the quantity?

Mr. GOODRICH. Yes, sir.

Senator NELSON. So if an ad were run on April 1 that violated the regulation by making claims that were not approved in the package insert, and one shipment of drugs was made after that, the maximum penalty would be a thousand dollars, is that correct?

Mr. GOODRICH. Yes, sir. Regardless of the size.

Senator NELSON. Do I understand you to say that in the last year and a half there have been 22 "Dear Doctor" letters sent out?

Mr. GOODRICH. I do not have the exact count. That is very close to it. We will supply the exact count.

Dr. MCCLEERY. There have been I think 21 in just a little over 12 months.

Mr. GOODRICH. Right.

Senator NELSON. Were all these "Dear Doctor" letters based upon violations of what we are talking about here, a claim in an ad in excess of what was approved for the package insert?

Mr. GOODRICH. Not all of them. Most of them were, but there were a few instances in which the promotion in Physicians' Desk Reference was not up to date and current. I believe there were about four or five in that category. And the rest of them were concerned with journal advertising.

Senator NELSON. It seems to me from the cases I have seen, like the one today—would appear fairly clear violations of that—they clearly made claims beyond what was authorized in the package insert. How do you expect them to really conform if you are not tough about it?

Mr. GOODRICH. Well, I would rather—if you will permit me—not discuss the case that is going on.

Senator NELSON. I do not refer to any particular case.

Mr. GOODRICH. We feel we have been, and Dr. Goddard feels, I am sure, we have been quite strict with them in requiring the mailing out these "Dear Doctor" letters.

Senator NELSON. That is after the fact.

Mr. GOODRICH. And it is the only way that we can effectively correct that false message. The ad, after the fact, requires a communication to the profession, to make sure that it is understood that FDA regards the ad as misleading, and has requested the company to communicate with the profession, to tell what is wrong with the ad. This has been the pattern of the "Dear Doctor" letters. We think as of now it has been an effective mechanism for communicating with the profession about proper advertising, and we hope that it has brought about improvement, industry wide, in terms of the quality of the advertising messages.

Senator NELSON. Well, as to the question of its effectiveness, you were here yesterday at the hearing when we discussed the "Dear Doctor" letter that was sent out by Merck and which ended up being a promotional plug for the drug. The FDA subsequently had to get them to send another "Dear Doctor" letter to supplement the first one. But, in the second one you did not require that they say this is being sent because the first one was misleading.

Mr. GOODRICH. The first one was sent without our approval, and the second one did not refer to the fact that Food and Drug had required it. It was stated to you, and I can assure you it is true, that a great many "Dear Doctor" letters have been sent since that time, and they have uniformly referred to the fact that the Food and Drug Administration requested that they be mailed. Just the point you made yesterday—which we ourselves recognized early in this—the importance of including in the message the statement that this was an action precipitated by Food and Drug. There was of course much argument about that at all stages. But it has been a uniform requirement, I am sure, for a year now.

Senator NELSON. But you would agree, would you not, that one of these long closely typed "Dear Doctor" letters coming to a busy doctor is a whole lot less effective than a series of Roentgrams demonstrating how effectively this drug cures the patient's problem? So you end up with an after-the-fact situation where the doctor has been misled by the ad, and then you require that a letter be sent afterward which probably is not going to be read. As a matter of fact, since I have been conducting these hearings, many doctors, and good ones, have told me that the first thing they do with any of this material is throw it in the waste basket—they do not have time to read it all.

Mr. GOODRICH. We have, as you know, made sure these "Dear Doctor" letters are sent first-class mail, that they are sent in a distinctive type of envelope—the letters themselves, I am sure you will read them, are devised to put across the essence of the complaint about the advertising, and the details are put on the next page. We think those letters are effective as a means of communication.

Senator NELSON. They are not effective with the doctors who tell me they do not read them, any more than they are with the doctors who tell me they do not read the package insert.

If you are really going to make this work, why don't you do a couple of more things. One of them is, when they violate our regulations in an ad—this is a nice, beautiful, big color ad that I have here—why don't you just tell them you are going to send the "Dear Doctor" letter, and you are going to enclose a copy of the ad, because this is the ad that has been impressing the doctors; and, in addition, you are going to have the firm say "We have been required to correct this ad. This ad is inaccurate, and here is why."

No. 2—if you are really going to be effective, why don't you just tell the firm, "we are going to review for the next year all of your ads." I think they would shape up pretty fast. But if all you have is a little thousand dollars penalty here and there, and a little discussion here and there, you will have 22 "Dear Doctor" letters in the next 6 months, and have another 22 in the following 6 months. In the meantime doctors are being misled in a very important matter involving the health of their patients. And you have the power to do this. I do not know why you do not say, "You clearly violated advertising regulations, and for 1 year you must submit to us all ad copy in advance of publication." I think you would find that you would not have to send many "Dear Doctor" letters after that. They would take the package insert and use it as a basis for their ads.

Mr. GOODRICH. I think it is equally effective for the Commissioner to have the president of the firm come in and go over the faults in the ads, what was wrong with them, and then to require the company to mail out a first-class mailing to every physician in the United States, telling what was wrong with the ad.

Now, this is the mechanism that has been adopted. We think it is effective. We have seen in the case of Merck Sharp & Dohme, that after the meeting between the Commissioner and the president of that firm there was a significant improvement. We have seen this same pattern with most of the other companies that have been involved in "Dear Doctor" letters. But there have been some that have had more than one "Dear Doctor" letter. We are constantly working on this. Dr. McCleery has a relatively small staff. But I am sure Dr. Ley will agree this is a

top priority item in the Bureau of Medicine. We understand its importance in having drugs prescribed. As Dr. Jennings testified yesterday, the promotion of this drug was in part responsible for its tremendous use. It was launched with a message with which we cannot agree. So we adopted in March or June of 1966, a program of monitoring the initial promotion for every new drug approved to make sure the drug was launched on the right foot, and promoted to the profession for the conditions for which we had actually approved it.

Senator NELSON. Are you saying that you preexamine the advertising for all new drugs?

Mr. GOODRICH. We require them to submit, as soon as the first promotion is run—we do not require it to be submitted before it is run—submit that to us. Dr. McCleery's office processes that. If it is not in accordance with the conditions for which the drug has been approved, we then take action to be sure that it is.

Now, trying to preclear the ads at what you call the viewing board stage—this is just not a practical thing that we have felt we could do so far. We are calling for the ads to be submitted as soon as they are first placed. We are exercising care to make sure they are promptly reviewed.

Senator NELSON. Well, I do not know what the problem would be in preclearing all ads. I assume it would be massive. I am not talking about that. An ordinary layman such as myself can look at the ad promoting Indocin for gout, and knowing what I do about it, see the misleading point there, when they use the phrase "drug of choice." I know why they did it. I know why their highly paid advertising experts sat all day long figuring out the best phrase they could use to convince the doctors to prescribe their product.

The company knows that. So I do not know why you should not say to the company, "This is an overt, gross violation, and you know it, and you are the one company that is going to spend the next year submitting your ads for preclearance from us." I think if you did that once or twice, you would end up with very, very few "Dear Doctor" letters, and then you would not be permitting the misleading of the medical profession by ads such as this one.

My question is, Why don't you really get tough with these firms?

Mr. GOODRICH. I think we have been as tough as possible within the limits of our people. This is a good suggestion. But if spending time to preclear all the advertising——

Senator NELSON. Just a minute. I have never said that. I have suggested that you notify the industry that in clear cases of ads where the claims for a drug go beyond the package insert, the FDA will preclear the ads of this particular firm for the next 6 months or the next year. Then you are not going to have very many violations to bother with; that is my point. And if you told them also that they are going to have to send the ad to all doctors and tell the medical profession in the "Dear Doctor" letter, "We misled you in that ad; we made claims not permitted in the package insert and the FDA has told us to send you this ad and correct the ad," in my judgment you would not have much problem with this any more. The medical profession would no longer be subjected to misleading ads of the sort that caused Dr. Goddard to say of chloramphenicol, "I am at my wits end as to how to effectively warn the profession." I know why. Because the industry

runs ads like this. If I were a practitioner out in the country someplace, with a patient, and saw an ad like this showing feet and hips and hands, and stating that Indocin "extends the margin of safety," I would be impressed, too. After all, this is the Journal of the AMA—I am shocked that they would even run it. But here it is. I am a doctor. And I have high respect for the JAMA. They would not permit cheating in their advertising—I know that. And this distinguished company would not try to mislead me. So I prescribe it. And that is why the testimony was yesterday that this drug is being widely misused.

All I am saying is, for heaven's sakes why don't you do something instead of all this fluff-fluff we get all the time that goes on and on. It is a simple answer. You have the authority. Tell them to stop it "or we are going to review all your ads." And I predict you will be able to come back in 6 months and say "Senator, we have no trouble with advertising any more."

Mr. GOODRICH. Our answer is on that that we did tell Merck Sharp & Dohme, quite bluntly and quite pointedly, that the ad was bad, they stopped running it within 2 weeks after we told them, they destroyed, according to their statement, $73,000 worth of comparable promotional material. They have been, according to the statement from Dr. McCleery made here, better since that experience. And he has in fact been over some ads with them to—brand new products, to show that we did get the messages across to this company. We think we have gotten it across to others. But your suggestion is a good suggestion, and we will certainly consider it.

Senator NELSON. Well, if I am around here for that long, the next time I find an ad that extends the claims beyond what is allowed in the package insert, I am going to invite you back, and we will talk about it again, and find out whether you are still satisfied with the methods you are using. I am not saying you have not improved them a lot.

Mr. GOODRICH. And I am not saying that the present method, Senator, is a hundred percent or the best one available. But it was one that was within our capability, it was one that has been carried out, I believe, with effectiveness.

Senator NELSON. Well, as you say, I think Dr. Goddard has done a magnificent job. I just think it is nonsense to permit this to go on, and you have been pretty soft on the industry. They know what they are doing. They are fooling the public—particularly the doctors. And it ought to stop. A great industry like this should not be overpromoting drugs for nonindicated cases. It is as simple as all that. Now, as long as they can get by with it, and make money, I guess this is what happens. I am not saying that it is a criminal offense. We had the same thing with the auto industry. As long as they could give us cheap tires that would not even hold the car, they did so. But, then we passed a law telling them to stop it. That does not mean the automobile industry is not a great industry—it is. But putting on cheap tires saved them $400 or $500 million a year, so they did it. And, it took Congress to do something about it. And the industry, or if necessary, the Congress ought to do something about this, because it has gone too far.

Mr. GOODRICH. We think Congress did do something about it. And in dealing with patients taking drugs, we expect a higher responsibility even than the automobile manufacturers.

Senator NELSON. Well, I think if you told those who drafted the Kefauver-Harris law, passed in 1963, that we would still have this kind of advertising going on in 1968, they would tell you that the will of Congress has not quite been complied with. Correction of such ought to happen sooner than 5 or 6 years.

Mr. GOODRICH. And I would agree with them.

Senator NELSON. We will take a 5-minute recess at this time.

(At this point in the hearing a short recess was taken.)

Senator NELSON. Let us resume, gentlemen.

Doctor, the minority counsel has a couple of questions.

Mr. GROSSMAN. Mr. Goodrich, I want to get a clear idea of this preclearance authority which you presently have—I think we just sort of skimmed over the fact that you do have some preclearance authority. Where and when does it apply, and when have you used it?

Mr. GOODRICH. It applies in the language that Congress adopted—except in extraordinary circumstances there shall be no requirement of preclearance of ads—section 502(n), Federal Food, Drug, and Cosmetic Act.

The implementing regulations say that when the Department learns of a newly discovered serious hazard that has not been widely disseminated, not widely known to the medical profession, it can require the preclearance of ads. It specifies there that upon being notified of the necessity for preclearance, the company can develop a plan, develop and present a plan to us which will assure that promptly their ads will cover this new hazard in which case preclearance would not be required.

There have been no instances so far in which preclearance has been required.

Mr. GROSSMAN. Required.

Mr. GOODRICH. Under those regulations.

Mr. GROSSMAN. That there have been no instances?

Mr. GOODRICH. Right.

Mr. GROSSMAN. You have never sought to implement this, because you never thought there was anything serious enough. Is that what we are to interpret?

Mr. GOODRICH. Haven't thought there was anything in terms of fatalities or serious side effects that was not promptly reflected in the ads.

Mr. GROSSMAN. Now——

Mr. GOODRICH. We have not run on to such a case.

Mr. GROSSMAN. How many deaths do you need before something becomes serious enough? What is your criterion here? I do not understand when you are going to use the preclearance authority.

Mr. GOODRICH. We are going to use it when a newly developed, newly discovered hazard is learned by us, and the company fails to immediately provide for including this information in its promotional program. Our experience has been that this newly discovered information is processed through our supplementary review, and is promptly put into the promotion.

Mr. GROSSMAN. What I am trying to say is—you talked about reacting to this, having meetings with companies about actions that they have taken, following up—everything is reacting or following up. I want to know, in other words, in what circumstances you feel you should act, and not react.

Mr. GOODRICH. Well, I think we have been doing most of the acting to initiate these meetings. I am sure we have.

Mr. GROSSMAN. I think that the companies have done some things that have forced you to react to them. What—I am trying to say—in other words, as far as we are concerned, this section 502(n) is really worthless—it has never been used, and you do not think there have ever been indications that the——

Mr. GOODRICH. I do not think that is so at all. This preclearance proviso in the section, which Congress told us not to routinely preclear ads——

Mr. GROSSMAN. I did not say you should routinely preclear. In other words, there is authority for you here to use preclearance, as I understand it, in hazardous situations. Now, I want to know what you consider hazardous. Obviously this was not a hazardous situation. Chloramphenicol—has there been anything you can think of that might be hazardous? In other words, how many deaths do you require?

Mr. GOODRICH. This was a serious situation, and we did get the company in within 2 weeks after the ad, and required the "Dear Doctor" letter shortly thereafter.

Mr. GROSSMAN. Do you require preclearance on all their advertising now?

Mr. GOODRICH. No. But they have been over—after we first had our discussion about this, their lawyer and their physician in this area came down to Washington, and went over a series of their ads with us, to make sure that they did fully understand what we intended, and their performance and behavior since that time has been improved.

Mr. GROSSMAN. Dr. McCleery, do you have anyone in your division who is assigned to decide when a drug is hazardous, and should become part of the section 502(n) proceedings?

Dr. MCCLEERY. No, I have no one specifically assigned. The information of the kind that you are talking about would be developed principally in the area of the Office of Marketed Drugs. If they, in their work in surveillance of the reports of new adverse reactions of drugs on the market, would find an instance of this kind that they felt was not generally known—that the profession had not been prominently and widely informed, then at that point we would be able to enter in and to act as agents of this particular requirement of the law. We would not develop the information.

Mr. GROSSMAN. Is it fair to say that the committee could interpret that since 1964, since section 502(n) went into effect, there have been no cases of hazardous drugs which would qualify for preclearance? There have not been any?

Dr. MCCLEERY. The paragraph in the regulations which give form to this section of the law that Mr. Goodrich talks about, is paragraph 1.105(j), and we have not as an agency invoked the provisions of that paragraph of the regulations.

We have, on the other hand, precleared many ads.

Mr. GROSSMAN. I am just thinking back to what Mr. Goodrich was discussing before—there are a lot of questions on which Congress has gone far enough. I just wonder whether 502(n) does not give us authority; and whether authority that you have could be used and has not been used.

In other words, it is one thing to say that the Congress should legislate. But when it has legislated, and there is a broad discretion that has not been enforced, it is not our job.

Dr. McCLEERY. I do not think I could agree with you that it has not been enforced.

Mr. GROSSMAN. Section 502(n).

Dr. McCLEERY. 502(n) is the broad language, and includes as one of its parts the exclusion that except in extraordinary circumstances we should not require a company to preclear its ads, as a part of that section of the Kefauver-Harris amendment.

Mr. GROSSMAN. I will not pursue this.

I wonder if you can answer as to when you think an extraordinary situation exists?

Dr. McCLEERY. I believe that paragraph 1.105(j) is the paragraph of detail in the regulations which gives form to one view of "extraordinary circumstances." In the negotiations with the industry in 1963, at the time the regulations were being proposed to the industry, this was a prominent feature of difficulty in the industry's acceptance of the original regulations written on the basis of the amendment to the act. That the paragraph exists at all, I think, has had an effect which has been salutary in causing companies to be aware of the need to move more quickly, than they might otherwise, to get new warnings into advertising.

Mr. GROSSMAN. I would question whether they would act because of their fear of your implementation of it. We have not seen very many examples of it.

Senator NELSON. Mr. Goodrich, so that I have this clear in my own mind—we have referred several times to your authority to preclear ad copy and I think, in that context, you have always referred to new drugs.

Mr. GOODRICH. If so, I misspoke myself. The advertising provisions apply to all prescriptions.

Senator NELSON. That was my impression. So if a drug is on the market, no matter how long it has been there, and the company at some stage makes claims that extend beyond the authorized package insert claims, you do have authority in that case to preclear a future ad or ads.

Mr. GOODRICH. Yes—and even with drugs on which we have no approved package insert—that is the drugs on the market since 1938, without new drug clearance. If there should be discovered some new hazard about such a drug, it would be possible to preclear, and to require preclearance of the ad. Only, I believe, 2 years ago we reclassified a drug on the market in 1936 as a new drug, because of a newly discovered hazard in it, and did take regulatory action. It was not advertised broadly, so it was not necessary to preclear advertising. But we did require its reclearance through the new drug procedure. It was a product called Dipyrone, discovered to have some blood hazards.

Senator NELSON. You referred to drugs marketed before 1938. Do you approve a package insert from them?

Mr. GOODRICH. No; they are totally exempt from preclearance. They are required to have a package insert with full disclosure information in it. But we do no preclear it.

Senator NELSON. You do not preclear the package insert?

Mr. GOODRICH. We do not. The law exempted—just drew a line—products on the market June 1938 and before. So long as they have the same claim they are not subject to new drug preclearance.

Senator NELSON. Have the same what?

Mr. GOODRICH. Same claims in use as in 1938.

Senator NELSON. Supposing you found out that these claims were not justified. Do you have any authority to require that changes be made?

Mr. GOODRICH. Yes. We would have the authority to proceed through the courts to charge them to be—as being misbranded, and then for us to bear the burden of proving the claims false rather than the burden under the new drug provisions being on the company to prove the drug's effectiveness. That is just a difference in the burden there.

Senator NELSON. Do you know what percentage of the prescription drugs in the marketplace are exempt from your authority to regulate?

Mr. GOODRICH. No; we do not have any reliable figures on that. We are pretty sure that a great majority of the drugs now in use are drugs that have entered the market since the enactment of the new drug law in 1938. There would be a number of oldtimers, of course, that were on the market in 1938, that are still around—phenobarbitol, thyroid, a lot of others. But the great majority of drugs, I think I am correct in saying, now in use are drugs that have been developed between 1938 and the present time. This is why we regard as quite important, our contract arrangement with the National Academy of Sciences, to review the claims of effectiveness for these drugs marketed between 1938 and 1962, enabling us to bring to bear the new requirements of effectiveness on those products. Congress' solution to this in 1962, rather than exempting all those premarketed drugs completely, was to give us the right to, through administrative action—to go back and review the claims, product by product, and to be sure that they were effective as claimed.

Senator NELSON. That authority extends just on drugs marketed from 1938 to 1962?

Mr. GOODRICH. Yes, sir.

Senator NELSON. And you are in the process of reviewing them now?

Mr. GOODRICH. Yes, sir. The contract has been virtually completed, I think. We are getting the reports now, and we have begun to implement the reports by requiring changes in the labeling and packaging.

Senator NELSON. Once the review has been done, do you then, under the law, have the authority to control the package insert?

Mr. GOODRICH. Yes, sir. But we have a dispute with the drug industry about the extent of our authority. But we think we have enough authority to carry this forward.

Senator NELSON. Go ahead, Doctor.

Where were you?

Dr. MCCLEERY. I would like to pick up in the middle of page 8, paragraph c.

We believe that the quotation that we have been talking about misleads in that it is obsolete when used in the ad in 1966, in that it fails to take into account more recent, more scientific, but less salubrious opinions of the same authors available to the firm in medical literature published about a year prior to the ad. The company was aware of the more recent literature, and the facts are that—(1) in 1965 the

same authors published the results of a much better controlled and double-blind study on a larger population than the 1963 paper—here 26 patients crossed over on both indomethacin, and the competitive product, phenylbutazone.

(2) This was a study of the response to the marketed capsules within the limits of approved dosage, the authors ended the paper with a note of thanks to company personnel "for generous supplies of indomethacin," it was published in the same journal as the first article (British Medical Journal, 2: 1281, Nov. 27, 1965), and was available well before the ad was created and published.

(3) The overall patient response greatly favored the competitive product to an extent that was statistically highly significant, for example, when the 2-month blind trial was over "* * * 15 patients preferred phenylbutazone, 10 found them to be equally effective, and one preferred indomethacin."

(4) The authors' conclusions re Indocin were strikingly different (the key words "predictable" and "in most cases" no longer were included) after this study, that is, "* * * the first nonsteroid to produce a measurable reduction in joint size in selected cases of active rheumatoid arthritis."

Now, the phrase "the first nonsteroid" is common to both articles. It should be noted that the authors' retention and the company's use of the phrase "the first" is in my view highly questionable.

Within the authors' own results in the 1965 article, they included the observation that reduction in joint size occurred not only in patients on indomethacin, but also on phenylbutazone as well, and that taking into account both the number of patients improved, and the extent of reduction, differences between the two drugs were not statistically significant. And yet the authors were still using the phrase "the first nonsteroid," and so on.

It is difficult for me to see any validity or significance to the claim "the first" especially when the authors failed to find such difference in the reduction that they did find—to find any statistically significant difference between the amount of reduction.

Mr. Chairman, since your committee may wish to consider the Hart and Boardman papers in some detail, I have made copies of both papers available to you and for the record, and I have gone into some detail on this point, because it typifies several advertising practices which we regard as seriously misleading.

Senator NELSON. We will print those in the record. If I understand you correctly, what you have said is that the company quoted from an early study by these two doctors.

Dr. MCCLEERY. That study being of less quality than the later.

Senator NELSON. And was the second study which modified the position taken in the first study published and available at the time they ran the questionable ad?

Dr. MCCLEERY. Yes, and known to the company long before that, because they were in contact with the authors of the study and supplied the drug to the authors, so that they were well aware of the study going on.

Senator NELSON. So here you say there is a clear-cut case where they knew a subsequent study modified the original one; yet, they continued to use in their advertising a quote from the original study.

Dr. McCLEERY. Right. And which quote was not the opinion of the author at the time that the ad was created?

Senator NELSON. Yes.

Dr. McCLEERY. You might wonder, as we did, why the company might choose—if they chose, it may be a matter of inattention to the literature—but whether they chose to use the '63 paper and ignore the '65, I do not know. But I think I would like to offer you evidence from the second paper—just a few brief recountings of the results reported by the authors in the second paper which may suggest why the second paper was undesirable as a form of promotion. And I would like to read a few excerpts from the Hart and Boardman paper of 1965.

Senator NELSON. You say the company was aware of the second paper?

Dr. McCLEERY. I cannot say that. I can only assume that if they were not, that it was a matter of inattention which I would not find excusable.

Senator NELSON. Since it was a trial run on their own drug.

Dr. McCLEERY. And it was published in the same journal, and was in print available well before they created the ad, and since they were clearly aware of the research of Hart and Boardman, having been in contact with them from the days of the IND.

I would like to read some of the comparative results which this ad did not point to—which a doctor might see if he read the 1965 article.

The following from the article, not used by the company in its promotion, are some of the results found by the same authors.

As far as subjective signs are concerned, when they asked the patients at the end of the trial which one was found by the patients to be more satisfactory, "15 patients preferred phenylbutazone, 10 found them to be equally effective, and one preferred indomethacin. This difference is statistically significant with a 'p' value less than 0.001."

They go on at much greater length and deal with the question of pain as recorded by them for each patient during the month on each drug. And they found that the "improvement in pain"—that five on phenylbutazone, but only two on indomethacin found their pain relief better, and that 19 found no difference.

As far as "joint stiffness" was concerned, assuming a 25-percent difference to be significant, five were less stiff during phenylbutazone, and only one less stiff on indomethacin—20 patients found no detectable difference.

As far as the very commonly used parameter of judgment, "early morning stiffness," for drugs in this category, they found that in the first month on phenylbutazone seven patients were improved, and on indomethacin only three improved. In the second month, on indomethacin improvement occurred in three patients, and on phenylbutazone four improved.

As far as "grip strength" was concerned, I won't review the comments in detail, but there was no real difference between the two drugs on that parameter.

As far as the objective "change in joint size," which is a common feature of the 1966 ad, and is related to the authors' comment about the "first nonsteroid" to produce reduction in joint size, these are the actual figures given by the authors in their paper, which precede their conclusions. So they say—assuming a change of three ring sizes

in joint size to be significant, there was no difference in 17 patients, five were better on indomethacin, but also four were better on phenylbutazone. And they go on to conclude that this difference between the drugs' effect is not statistically significant. But it is significant that the number of patients showing reduction in their joint size was almost equal between the two drugs, and that there also was a positive effect for phenylbutazone noted in the same study that showed a positive effect on some cases with indomethacin.

Senator NELSON. That is from the second study.

Dr. MCCLEERY. Yes, sir. Whether these results have any connection with its lack of desirability, or are related to the company's decision not to use it as a source of reference, I do not know. But those are the authors' conclusions in the second paper.

Now, there are several other claims made in the JAMA ad to which we objected in detail in our internal memos. For example, one of the most serious of all was this matter of a drug of choice, to which I referred. Whereas in the earlier ads the company did change these quotes to tone them down by inserting the bracketed letter "a," the last ad in the series, later, in November, quoted it unadorned, unchanged, as "the drug of choice."

I might say in passing also that the Hart and Boardman article used in regard to the treatment of gout, which is the most right block of the ad, was based entirely on the indomethacin formulation that was not marketed, the tablets. Furthermore, the dosages used by the authors, which gave the results that led to "the drug of choice" opinion, were far in excess of the upper approved safe limit when the drug was marketed in this country in capsule form. Outside of all these features I would have to agree that the use of the quote is proper.

Now, Congress has already recognized that it is dangerous to promote a new drug with inadequately based claims for greater safety and comparatively greater effectiveness than established competitive products. Safe promotion can be based only on adequate clinical data, and then only with a complete awareness that the limited experience with the new drug as it enters the market, accumulated during its investigational state, may change rapidly and significantly when the drug is released for general use by physicians at large. Also experience will dictate changes from time to time as you have seen in the testimony yesterday, and for as long as the drug is marketed, very possibly.

Indomethacin was recognized from the first as a drug with significant capacity for adverse effects. We believe its 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 as to the margin of its safety.

Mr. Chairman, this emphasizes, for us at least, the need for our continued special attention to the advertising of newly released drugs as they enter the marketplace, as well as that for older prescription drugs, to help provide assurance—and, I might add, I would like to insert the word "help" for the record here as a qualifier, which we so often insist that our opponents in advertising use—so with your permission, and with some seriousness, may I request that you insert the word "help" after the word "to"—to help provide assurance that they are fairly presented to the medical profession under the approved conditions of marketing. Further it demonstrates a need for constant sur-

veillance, both by us and by the manufacturer, of clinical experience to keep advertising messages in step with the realities for safe and effective prescribing of new drugs as more experience is developed during their marketing history.

Thank you. I will be glad to answer any questions.

(The complete prepared statement and supplemental information submitted by Dr. McCleery follows:)

STATEMENT OF DR. ROBERT S. MCCLEERY, ACTING DIRECTOR, DIVISION OF MEDICAL ADVERTISING, BUREAU OF MEDICINE, FOOD AND DRUG ADMINISTRATION, U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Mr. Chairman, I appreciate this opportunity of appearing before you this morning to discuss our experience with the advertising of Indocin. For the sake of brevity, and with your permission, I will submit for the record a statement of my educational and professional background.

Shortly after Dr. Goddard became Commissioner of Food and Drugs, in early 1966, the Agency's interests in prescription drug advertising were sharply accentuated. It was felt that manufacturers had had time enough to adjust to new requirements concerning advertising. Dr. Goddard spoke to the presidents of pharmaceutical firms, to their medical directors and to their advertising agencies to note what we regarded as a continuation of advertising abuses that had been so largely responsible for the enactment in 1962 of the Kefauver-Harris Drug Amendments and the promulgation in 1964 of the first advertising regulations.

The Fountain Subcommittee, House Committee on Government Operations, had reviewed with the Commissioner our programs in this important area of our public responsibilities. In short, industry's attention was brought emphatically to promotion excesses in many ways.

In June 1966, the Director of Public Relations for Merck & Co., Mr. John E. Fletcher, wrote to Theodore O. Cron, our Assistant Commissioner for Education, enclosing a print of an article that was about to appear in the July 1966 issue of *Pageant* magazine.

The story featured Indocin as useful 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 support for these claims was largely lay testimonials some of which, according to the article and the firm, were made available to the writers by the sponsor of the drug.

Mr. Fletcher said that the firm was in no way responsible for the article, that the authors had heard of stories about the drug from a variety of sources and wanted to do an article about it, and that the firm had simply responded to this inquiry from responsible science writers. Mr. Fletcher said the article was in no way promotional and wanted to so assure the Agency.

The drug, of course, had not been approved for use for the above-mentioned conditions for which it was claimed to be effective in the *Pageant* article. We knew also that a popular article of this sort is apt to create a demand for the drug by the patients who read it. My office, the Division of Medical Advertising in the Bureau of Medicine, was asked to review the article for possible violation of the law, and to review also the advertising of this drug in medical journals to determine if the drug was being promoted to the medical profession on the basis of unapproved claims.

Our concern was that if the firm would make these data on unauthorized uses available to a free-lance team of writers, it might not be scrupulous in its advertising to the medical profession.

Identical advertisements which appeared in the *Journal of the American Medical Association* issues of July 4, 1966 and August 15, 1966, were found to be featuring the theme that the drug "extends the margin of safety in the long-term management of arthritic disorders." At the same time, the Office of Marketed Drugs was negotiating with Merck for changes in the labeling to emphasize the newly recognized hazards that had emerged during the first year of clinical experience since original approval of the drug.

The *JAMA* ads in July 4 and August 15, 1966 issues were analyzed and found to be defective, in our opinion, in several respects. I will first mention generally the major defects of this ad and then will be more specific regarding the details of our objections to certain of the features of this and of a later ad which appeared in November 1966. The basic theme of greater long-term safety in the ads was not supported by the clinical experience. To the contrary, the longer

the drug had been on the market, the more serious adverse experience information was reported.

The ad quoted apparently-authoritative sources without the full impact of the limited experience contained in the actual articles. And it featured, for example, one reference which on checking proved to be only a 2-inch abstract of a 1964 speech. The ad quoted the author's opinion that ". . . results have been uniformly excellent or good in ankylosing spondylitis." The same abstract also included the author's view that, while "Excellent results have also been obtained in some cases of rheumatoid arthritis . . . there have been striking failures as well." It is, perhaps, not surprising that, while the advertiser included this author's favorable remark regarding his experience with spondylitis, the ad turned to another author for a more favorable quote concerning the possible value of the drug on rheumatoid arthritis.

It offered the drug for "arthritis disorders," rather than solely for the four conditions for which it had been approved.

It characterized the drug as non-steroid—which of course it is—but failed to disclose in this connection that it had some of the major side effects of the steroids, e.g., an ulcerogenic effect.

It claimed that the drug extended the margin of long-term safety, without any evidence to support the claim—it quoted from isolated pieces of literature—one an excerpt from a symposium sponsored by the company—to claim that the drug was the drug of choice in gout and osteoarthritis of the hip, neither of which claims had been approved.

It quoted from two leading English authorities to the effect that the drug was useful in most cases of rheumatoid arthritis, when these authors had used the tablet and not the marketed capsule, and when their actual opinion, known to Merck, was that the drug was useful in only selected cases of rheumatoid arthritis.

It featured the claim of one of the participants in a Merck-sponsored 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.

And finally in the "Brief Summary" of information on side effects and contraindications some of the major warning information was left out—such as the fact that indomethacin itself had caused ulcers, and that the drug should not be administered to children.

This exemplifies what may be called the euphemistic style of revealing warning information. The ad's "Brief Summary" translated the package insert's warning, "INDOCIN itself may cause peptic ulceration . . ." into the area of causal doubt in this manner: "Ulceration of the stomach, duodenum, or small intestine have been reported . . ." Further, the package insert's directness, regarding administration of the drug to children, became the "Brief Summary's" statement that "Safety in pregnancy and pediatric age groups has not been established."

Deficiencies in the ad were publicly noted in a speech before the Pharmaceutical Advertising Club in New York on October 20, 1966, by our General Counsel, Mr. Goodrich.

The firm protested and shortly thereafter, on November 11, 1966, a sort of armistice day, the firm's principal officers met with Dr. Goddard and his staff to go over the problem.

The firm reported that it had immediately ordered the ad discontinued after the October meeting and was taking a close look at all of its promotional efforts. Later, its physician and counsel responsible in the area of advertising came down to go over some ads for other products with us.

Soon after this episode, Merck began to show significant improvements in its advertising practices for prescription drugs but not before it ran, in the November 1966 issue of the *American Journal of Medicine*, another ad which contained most of the faults of the original ad, plus some additional new faults.

I will expand on this. While the authors, in 1963, had published the report quoted, we felt that Merck had no right to adopt the quotation in their 1966 advertising.

The quotation from an article by Hart and Boardman (Hart, F.D. and Boardman, P.L.: *British Medical Journal*, 2:965, October 18, 1963) and used under the ad caption "rheumatoid arthritis," namely, ". . . the first non-corticosteroid agent which produced a predictable and measurable reduction in joint swelling in most cases of active rheumatoid arthritis."

Our comments in reference to the quotation are that it:

a. Does not represent a true statement of effectiveness of the advertised product, "Indocin:"

(1) The approved package insert for the product does not contain the promissory concepts represented by "most cases" and "predictable."
represented by the words "the first." That the firm had previous knowledge of

(2) The approved package insert provides no basis for the comparative claim represented by the words "the first." That the firm had previous knowledeg of the impropriety of the claim is evidenced by that in an earlier, similarly-appearing ad the company more cautiously excluded this phrase from the quoted clause and substituted "a" for "the first."

b. Misleads by its use out of the article's context in such a way as to present an unfair and distorted view of the drug's identity, safety and effectiveness:

(1) The authors had not used the marketed "Indocin" capsules, but instead employed an experimental tableted formulation.

(2) The authors had only 15 pertinent patients from which the represented conclusion was drawn. The reader would have been forewarned, and not overly impressed, if he had known the generalization "in most cases" rested not on a large experience from which a generalization might not be misleading, but on only a favorable result in 8 out of 15 patients.

(3) An unknown and unspecified proportion of the above results were obtained by dosages well over the 200 mg. upper limit of approved dosage, e.g., 300 mg. per day. The physician reader could not know from the ad that he could not necessarily expect similar results by employing dosages approved as safe in the drug's package insert.

c. Misleads in that it is obsolete and fails to take into account more recent, more scientific, and less salubrious opinions of the same authors available to the firm in medical literature published about one year prior to the ad. The company was aware of the more recent literature and the facts are that:

(1) In 1965, the same authors published the results of a much better controlled and double-blind study on a larger population (26 patients crossed-over on both indomethacin and the competitive product, phenylbutazone).

(2) This was a study of the response to the marketed capsules within the limits of approved dosage, the authors ended the paper with a note of thanks to company personnel "for generous supplies of indomethacin," it was published in the same journal as the first article (*British Medical Journal*, 2:1281, November 27, 1965), and was available well before the ad was created and published.

(3) The overall patient response greatly favored the competitive product to an extent that was statistically highly significant, e.g., when the two months blind trial was over ". . . 15 patients preferred phenylbutazone, 10 found them to be equally effective, and one preferred indomethacin."

(4) The authors' conclusions re Indocin were strikingly different (the key words "predictable" and "in most cases" no longer were included) after this study, i.e., ". . . the first non-steroid to produce a measurable reduction in joint size in selected cases of active rheumatoid arthritis."

(5) It should be noted that the authors' retention and the company's use of the phrase "the first" is highly questionable.

(a) Within the authors' results in the later article they included the observation that reduction in joint size occurred not only in patients on indomethacin, but on phenylbutazone as well, and that, taking into account both the number of patients improved and the measured extent of reduction, differences were not statistically significant.

Mr. Chairman, since your Committee may wish to consider the Hart and Boardman papers in some detail, I would like to make copies of both papers available for the record. I have gone into some detail on this point because it typifies several advertising practices which we regard as seriously misleading.

Congress already has recognized that it is dangerous to promote a new drug with inadequately-based claims for greater safety and comparatively greater effectiveness than established products. Safe promotion can be based only on adequate clinical data—and then only with a complete awareness that the limited experience with the new drug, accumulated during its investigational state, may change rapidly and significantly when the drug is released for general use by physicians. Also, experience will dictate changes from time-to-time as long as the drug is marketed.

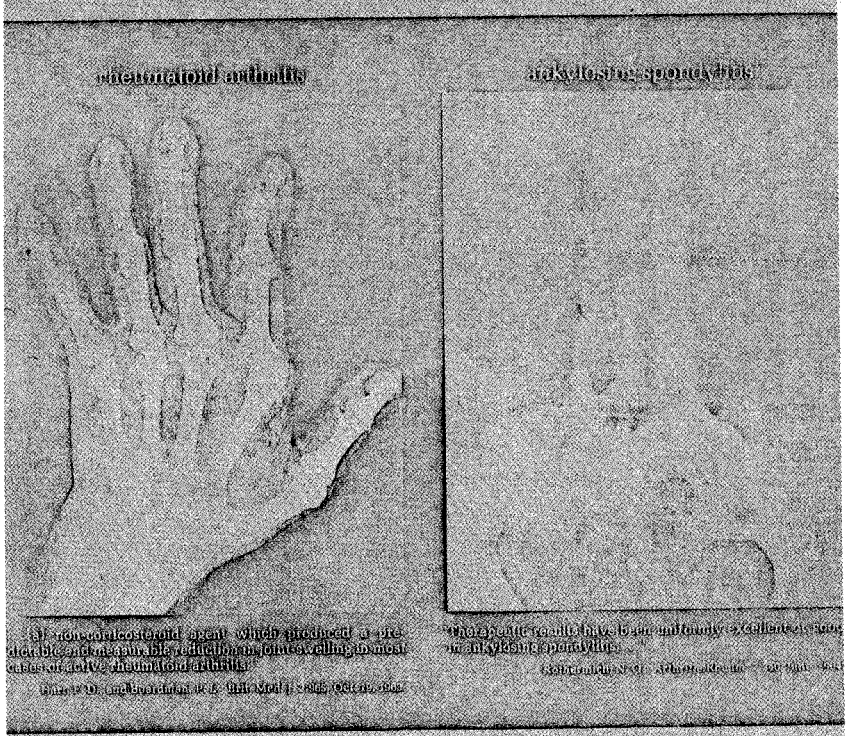
Indomethacin was recognized from the first as a drug with a significant capacity for adverse effects. We believe its promotion over the first year of its approved marketing improperly presented the drug to the medical profession—both as to the range of its effectiveness and as to the margin of its safety.

Mr. Chairman, this emphasizes the need for our continued special attention to the advertising of newly-released drugs, as well as older drugs, to provide assurance that they are fairly presented to the medical profession under the approved conditions of marketing. Further it demonstrates a need for constant surveillance, by both the manufacturer and the FDA, of clinical experience, to keep advertising messages in step with the realities for safe and effective prescribing of new drugs as more experience is developed during their marketing history.

Thank you for your attention. I will gladly answer any questions you may have.

[From the Journal of the American Association, Vol. 197, No. 3. July 18, 1966]

extends the margin of safety in long-term management of arthritic disorders



Indications: Chronic and acute rheumatoid arthritis, ankylosing spondylitis, degenerative joint disease (osteoarthritis) of the hip, and gout.

Contraindications: Active peptic ulcer, gastritis, regional enteritis, or ulcerative colitis. Safety in pregnancy and in pediatric age groups has not yet been established.

Precautions: Ulceration of the stomach, duodenum, or small intestine has been reported and, in a few instances, severe bleeding with perforation and death. Gastrointestinal bleeding with no obvious ulcer formation has also been noted; INDOCIN should be discontinued if G.I. bleeding occurs. As a result of G.I. bleeding, some patients may manifest anemia, and for this reason periodic hemoglobin determinations are recommended. Use cautiously in patients with history of ulcer, gastritis, ulcerative colitis, and regional enteritis.

Adverse Reactions: Most commonly, headache, dizziness, lightheadedness, G.I. disturbances such as nausea, anorexia, vomiting, epigastric distress, abdominal pain, diarrhea. The C.N.S. effects are often transient and frequently disappear with continued treatment or reduced dosage. G.I. effects may be minimized by giving the drug with food or immediately after meals. The severity of these effects may occasionally require cessation of therapy. Infrequently observed side effects may include drowsiness, tinnitus, mental confusion, depression and other psychic disturbances,

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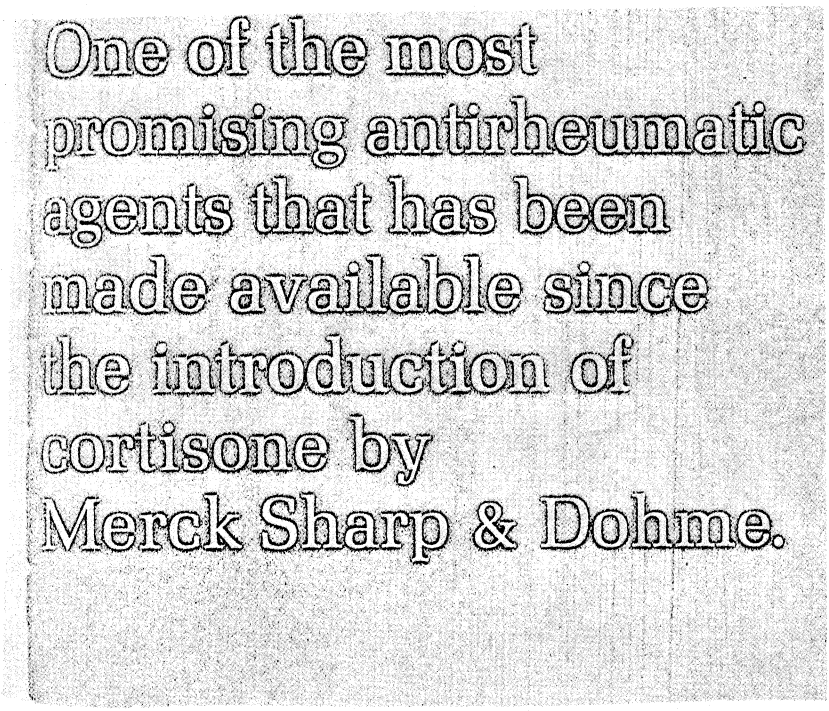
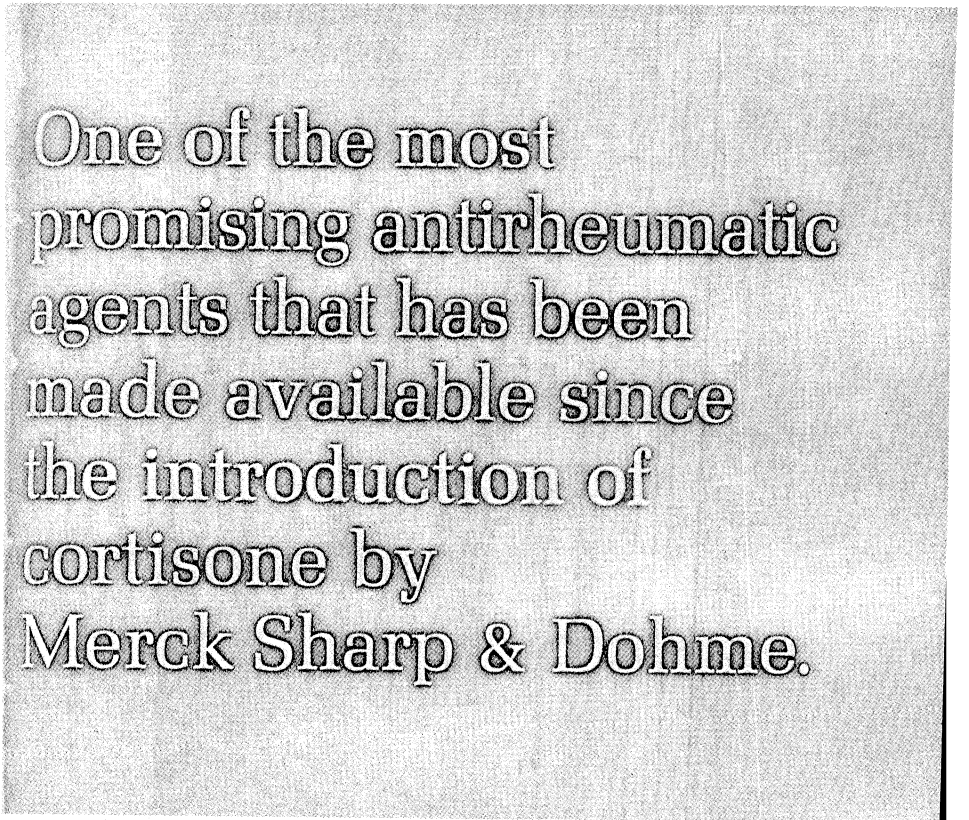
INDOCIN®
INDOMETHACIN
ANTI-INFLAMMATORY
ANTIPYRETIC · ANALGESIC
a new, highly effective nonsteroid anti-inflammatory agent
degenerative joint disease
(osteoarthritis) of the hip


One of the most
promising antirheumatic
agents that has been
made available since
the introduction of
cortisone by
Merck Sharp & Dohme.

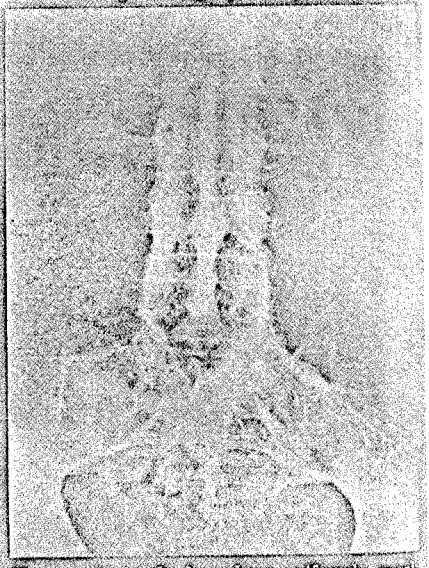
[From the American Journal of Medicine, November 1966]



extends the margin of safety in long-term management of arthritic disorders

rheumatoid arthritis

ankylosing spondylitis



"... the first non-corticosteroid agent which produced appreciable and measurable reduction in joint swelling in most cases of active rheumatoid arthritis."

Ehrs, R. D., and Bjordman, R. L.: Bull. Med. J. 2486: (Oct. 6) 1968.

"Therapeutic results have been uniformly excellent or good in ankylosing spondylitis."

Rothermich, N. O.: Arthritis Rheum. 7:810 (Dec.) 1964.

Indications: Chronic and acute rheumatoid arthritis, rheumatoid (ankylosing) spondylitis, degenerative joint disease (osteoarthritis) of the hip, and gout.

Contraindications: Active peptic ulcer, gastritis, regional enteritis, or ulcerative colitis. Safety in pregnancy has not been established. Not recommended for pediatric age groups.

Warning: Patients who experience dizziness, lightheadedness, or feelings of detachment on INDOCIN should be cautioned against operating motor vehicles, machinery, climbing ladders, etc. Use cautiously in patients with psychiatric disturbances, epilepsy, or parkinsonism.

Precautions and Adverse Reactions: Most commonly, headache, dizziness, lightheadedness, G.I. disturbances. The C.N.S. effects are often transient and frequently disappear with continued treatment or reduced dosage. The severity of these effects may occasionally require cessation of therapy. G.I. effects may be minimized by giving the drug with food or with antacids or immediately after meals. Ulceration of the stomach, duodenum, or small intestine has been reported and, in a few instances, severe bleeding with perforation and death. Gastrointestinal bleeding with no obvious ulcer formation has also been noted; INDOCIN should be discontinued if G.I. bleeding occurs. As a result of G.I. bleeding, some patients may manifest anemia, and for this reason periodic hemoglobin determinations are recommended. Rare reports of effects not definitely known to be attributable to INDOCIN include bleeding from the sigmoid colon (either from a diverticulum or without a known previous pathologic condition), perforation of preexisting sigmoid lesions (diverticulum

INDOCIN®

ANTI-INFLAMMATORY · ANTIPYRETIC · ANALGESIC

INDOMETHACIN

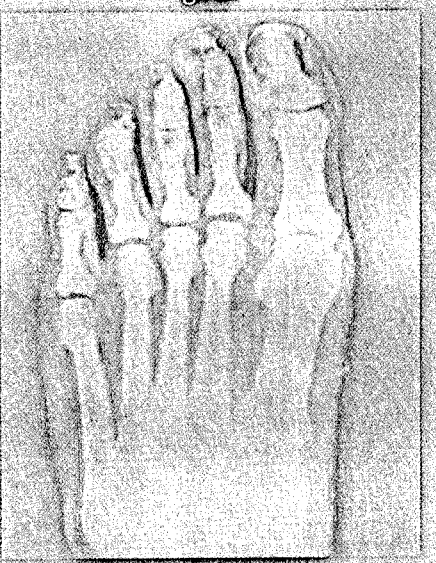
a new, highly effective nonsteroid anti-inflammatory agent

degenerative joint disease (osteoarthritis) of the hip

"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 the drug of choice. One of these is osteoarthritis of the hip."

Zvaifler, N. J., in Non-steroidal Anti-inflammatory Drug Therapy in Rheumatic Disease. New York, Excerpta Medica Foundation, 1965, p. 27

gout



"Indomethacin is the drug of choice in acute gout...."[1]

[1] Hart, F. D., and Boardman, P. L.: Brit. Med. J. 2:965, Oct. 10, 1959

carcinoma), and hematuria. In other rare cases, a diagnosis of gastritis has been made while the drug was being given. One patient developed ulcerative colitis, and another, regional ileitis, while receiving INDOCIN; when the drug was given to patients with preexisting ulcerative colitis, there was an increase in abdominal pain. Infrequently observed side effects may include drowsiness, tinnitus, mental confusion, depression and other psychic disturbances, blurred vision, stomatitis, pruritus, edema, and hypersensitivity reactions. Slight BUN elevation, usually transient, has been seen in some patients, although the preponderance of evidence indicates that INDOCIN does not adversely affect renal function, even in patients with preexisting renal disease. Nevertheless, renal function should be checked periodically in patients on long-term therapy. Leukopenia has been seen in a few patients. 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. As with any new drug, patients should be followed carefully to detect unusual manifestations of drug sensitivity.

Before prescribing or administering, read product circular with package or available on request.

MSD **MERCK SHARP & DOHME** Division of Merck & Co., Inc., West Point, Pa.

where today's theory is tomorrow's therapy

[From British Medical Journal, Oct. 19, 1963, pp. 965–970]

INDOMETHACIN: A NEW NON-STEROID ANTI-INFLAMMATORY AGENT

(By F. Dudley Hart, M.D., F.R.C.P., and P. L. Boardman, M.B., M.R.C.P.)

The measurement of joint-swelling in the human subject is not easy, but in the assessment of drugs purporting to have an anti-inflammatory effect in conditions characterized by the presence of chronic inflammatory swelling, such as rheumatoid arthritis, some clinical measure is essential. We have found that the only practical and reliable measurement which can be done repeatedly and reasonably quickly in the wards is finger-swelling measured by jewellers' rings (Hart and Clark, 1951). All patients with active rheumatoid arthritis entering our wards have finger-swelling measured in this way twice weekly by the same clinician at approximately the same time of day as a routine measure. Also, the patient's own assessment of pain, stiffness, the number of analgesic tablets taken daily, the time taken to limber-up in the morning, and the clinician's assessment of grip strength, joint tenderness, and sedimentation rate are done routinely on all patients as measures of progress irrespective of the treatment given throughout their stay in hospital.

Measurable reduction of joint-swelling occurs regularly and demonstrably with steroid therapy, but not with salicylates, phenacetin, paracetamol, or the pyrazoles (phenylbutazone or oxyphenbutazone) as measured by this method; and since the early use of the corticosteroids and corticotrophin no other therapeutic substances of the many we have tried have produced a measurable reduction in swelling of the interphalangeal joints. It was therefore a pleasant surprise when we found that in indomethacin (MK 615) we had the first non-corticosteroid agent which produced a predictable and measurable reduction in joint-swelling in most cases of active rheumatoid arthritis.

CHEMISTRY

Indomethacin is a non-steroid anti-inflammatory and antipyretic agent. Its activity does not depend upon pituitary-adrenal stimulation and it is fully active in adrenalectomized animals. Chemically it is 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindol-3-acetic acid, having the empirical formula of $C_{19}H_{16}NO_4Cl$ and a molecular weight of 357.8. It is relatively insoluble in water but soluble in the common organic solvents. It is rapidly cleared from the plasma, having a half-life of 0.3–4 hours in various species. From 46 to 63% of an intravenous dose of indomethacin-2-C^{14} is rapidly exreted in bile of dogs, guinea-pigs, and monkeys (Hucker, Zacchei, and Cox, 1963). Its anti-inflammatory activity can be demonstrated in rats by the cotton-pellet granuloma-inhibition test and by inhibiting oedema on subplantar injection of irritant agents. Granuloma inhibition can be observed by oral administration or by local application to the cotton pellet in the same animal. After oral administration to rats the drug appears to be well absorbed and gives an estimated plasma half-life of about 21 hours; about 90% of the drug in plasma is bound to the non-diffusable constituents. Excretion in rats is largely through the kidney, little being found in the faeces. That rat and the dog apparently tolerate the drug less well than does man or monkey.

Antipyretic activity has been demonstrated by inhibiting the fever produced by injection of *Escherichia coli* endotoxin in both rats and rabbits. Analgesic effects could not be demonstrated in mouse or rat by current methods. Toxic effects in rat, dog, and monkey consist largely of gastrointestinal irritation, monkeys tolerating larger doses of the drug than rat or dog. Judged by the work on animals, gastro-intestinal toxicity seemed to be the only effect likely to occur in man, but early clinical trials in the United States of America indicated that it was usually well tolerated by the human digestive tract (R. Hodgkinson, personal communication, 1963).

MATERIAL AND METHOD

Indomethacin has been used in the treatment of a group of patients in whom a clinical response might be anticipated from administration of a compound with anti-inflammatory, antipyretic, and possible analgesic properties (see Table I).

TABLE I.—OVERALL CLINICAL RESPONSE IN 99 PATIENTS TREATED WITH INDOMETHACIN

Disease	Number of patients	Clinical improvement	No clinical improvement	Inconclusive
Gout	15	13	1	1
Ankylosing spondylitis	14	11	0	3
Rheumatoid arthritis:				
Measurable soft-tissue swelling	15	8	3	4
No measurable soft-tissue swelling	37	14	14	9
Osteoarthritis	7	6	1	0
Miscellaneous	11	6	5	0
Total	99	58	24	17

At the beginning of the trial patients were started blind on either the drug or placebo. It was soon apparent that on the high initial dose of 300 mg. daily by mouth patients developed marked symptomatic improvement or side-effects, and, with few exceptions, were able to differentiate the true tablet from placebo. It was felt that a comparison against placebo would therefore provide less information than against other potentially anti-inflammatory agents such as phenylbutazone or the corticosteroids. In the absence of side-effects patients received a minimum of 14 days' therapy, and some have been on treatment for up to one year.

Indomethacin was used for the treatment of acute gout, ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis.

Gout

Fifteen patients (14 male, 1 female) with gout received indomethacin for the acute attack. It was given orally in high initial dosage and gradually reduced as symptoms and signs improved. The first four subjects received indomethacin 400–500 mg. in the first 24 hours, dosage then being reduced by 100 mg. every second day. This dose was found to require modification because side-effects occurred not infreqently and most acute attacks responded satisfactorily to a smaller amount of the drug. Subsequently 200–300 mg. was given in the first 24 hours in divided dosage, and this was gradually reduced to 100–150 mg. daily for five days, or longer if symptoms persisted. Patients were not given a maintenance dose between attacks. Plasma uric-acid estimations were performed during and after the acute attack, but these revealed no significant changes. Patients were asked to record their impression of the effect on the acute attack, the rate at which relief ensued, the extent of relief, the occurrence of side-effects, and the presence or absence of symptomatic rebound on cessation of therapy. An attempt was made to compare the response with that previously obtained from phenylbutazone, oxyphenbutazone, or colchicine.

Ankylosing Spondylitis

Fourteen patients with ankylosing spondylitis were treated with indomethacin. These patients had all suffered from the disease for at least two years and six had a history longer than 10 years. All had characteristic *x*-ray changes. All experienced considerable pain and had taken different analgesics for a long time. Ten of these patients received indomethacin 300 mg. daily in divided doses for 14 days and four received 200 mg. daily. When a steady baseline was obtained this was changed blind to placebo and rebound noted. Some patients received the placebo first. They were asked to assess their symptoms during this time and to compare the relief obtained from indomethacin with that previously obtained from phenylbutazone.

Osteoarthritis

Seven patients with osteoarthritis were treated with indomethacin: three of them had involvement of the hips, one severe disease in the knees, and three involvement of the cervical spine. They received indomethacin 150–300 mg. daily in divided doses for 14 days. They were asked to note any change in symptoms while on the drug and to compare this with the effect of phenylbutazone taken immediately before. Withdrawal symptoms on cessation of therapy were also noted.

Rheumatoid Arthritis

Patients with rheumatoid arthritis were treated with indomethacin and assessed not only on their symptomatic response but also by reduction of joint-

swelling. This group of 52 patients was divided into those exhibiting measurable inflammatory features (15) and those with less active but painful disease (37). Initially, 300 mg. was given daily in divided dosage, but subsequently 50–150 mg. daily was found to produce similar change with a lower incidence of side-effects.

The patients with inflammatory features all suffered from classical rheumatoid arthritis, 7 out of 11 having positive sheep-cell-agglutination titres ranging from 1 : 32 to 1 : 512. The method of assessment varied according to whether the patient was seen regularly as an out-patient or was admitted to hospital. In-patients were assessed by their own daily record of pain, stiffness, and morning limbering-up time. Twice weekly the size of proximal interphalangeal joints was measured by standard jewellers' rings by one observer at the same time of day. Joint tenderness over proximal interphalangeal and metacarpophalangeal joints was recorded, as was the strength of grip, using a soft cuff inflated to a pressure of 30 mm. of mercury. A Westergren erythrocyte sedimenation rate (E.S.R.) was estimated each week. In addition, four in-patients with swollen knees were assessed by daily clinical examination. Out-patients were seen weekly and the severity of symptoms was recorded, as was their range of activity. Their disease was also assessed by joint size, tenderness, and grip strength. Anti-inflammatory effect was assessed by weekly change in swelling of the proximal interphalangeal joints.

No change in the basic rest-exercise therapy was made during the trial. The patient was started on an identical placebo and observed until a steady baseline assessment was obtained; the genuine tablet was then substituted and when the new baseline was established indomethacin was withdrawn and identical placebo restarted. In assessment of the patient's condition not only an improvement on introduction of the drug was required but also deterioration when the drug was withdrawn before the clinical response was considered positive. In addition to patients with rheumatoid arthritis and inflammatory disease, 37 without measurable soft-tissue swelling were treated with indomethacin and the same parameters assessed. These patients had classical rheumatoid arthritis and the sheep-cell-agglutination titre was positive (1 : 32 to 1 : 2,048) in 22. Eight were in-patients and 29 out-patients.

Miscellaneous

Eleven patients with miscellaneous disorders were treated with indomethacin to assess its influence on fever, as in glandular fever and Reiter's disease, and pain from noninflammatory lesions such as bony metastases.

RESULTS

Gout

Of 15 patents with gout, 11 noted a dramatic and rapid response with full symptomatic relief, two noted a moderate analgesic response without complete alteration of symptoms, one patient noted no effect, and one developed immediate side-effects. The following case histories demonstrate the rapid response that may occur.

Case 1.—A man aged 52, who was diagnosed as having gout in 1956 and had acute episodes several times each year, developed an acute attack in May, 1963. Indomethacin 100 mg. t.d.s. was started. After 100 mg. he noted a dramatic improvement, and within 24 hours pain and inflammatory features had settled completely. Colchicine had produced relief in previous attacks only after several days and diarrhea had always followed. Phenylbutazone 500 mg. in 24 hours had produced some improvement, but with this drug full symptomatic control occurred only after four days or more. The patient felt indomethacin was quicker and more effective. Not all patients noted such benefit (see Case 6).

Case 2.—A man aged 62, who had suffered from gout since 1941, developed an acute attack involving the right carpus, the right elbow, and the left hand. After indomethacin 100 mg. he noted complete relief within four hours and was able to sleep the following night. The attack had previously been treated for four days with colchicine and phenylbutazone with little effect, and he had been kept awake at night by the pain.

Case 6.—A man aged 64 developed acute gout. Indomethacin 100 mg. t.d.s. resulted in mild symptomatic relief, but the joint remained painful and inflamed, and after 48 hours he developed acute gout in another joint. There were no side-effects. This may represent a failure of response, or it may that indomethacin absorption from the gastro-intestinal tract was impaired. Response in previous attacks to phenylbutazone had been entirely satisfactory.

Case 8.—A man aged 34 was admitted for observation after a hand injury sustained in a road accident. The next day he developed acute gout in the right ankle. Colchicine 8 mg. in divided dosage in 48 hours had no therapeutic effect and diarrhoea ensued. Indomethacin 100 mg. was given and definite relief was noted within an hour. After a further 100 mg. he was able to walk a few steps and the signs of acute inflammation were reduced. He was maintained on 300 mg. daily for five days, in which time the acute attack completely subsided. After 48 hours he developed a feeling of muzziness and headache, but this cleared on chlorpheniramine ("piriton") 4 mg. q.d.s. and on reduction of the dose to 200 mg. daily.

Case 9.—A man aged 50, in whom gout was diagnosed in 1956, noted no relief and no side-effects on indomethacin 100 mg. t.d.s., but obtained relief within 24 hours form 4 mg. of colchicine in divided dosage. He was the only patient who obtained no relief whatsoever from indomethacin. There seemed some doubt on his history that he took sufficient dosage to obtain therapeutic effect, for he was against taking any new drug when his old favourite, colchicine, was available.

In Table II a comparison is made between phenylbutazone and indomethacin in the seven patients who had received both drugs for the acute attack. It was suspected that Case 7 did not take the indomethacin.

TABLE II.—COMPARISON OF EFFECT OF INDOMETHACIN AND PHENYLBUTAZONE IN TREATMENT OF THE ACUTE ATTACK OF GOUT

Case No.	Indomethacin		Phenylbutazone		Preference
	Speed of action	Degree of relief	Speed of action	Degree of relief	
1	24 hours	Full	4 days	Full	Indomethacin.
2	4 hours	do	do	Nil	Do.
3	2 hours	do	do	do	Do.
4	24 hours	do	12 hours	Full	Phenylbutazone.
5	2 hours	do	24 hours	do	Indomethacin.
6	24 hours	Partial	do	do	Phenylbutazone.
7	do	Nil	do	do	Do.

Note: The speed of action is the time between the initial dose and the onset of symptomatic relief. The degree of relief was assessed when the maximal clinical improvement had occurred. Patient 7 is suspected of not taking indomethacin.

Ankylosing Spondylitis

Of the 14 patients with ankylosing spondylitis who were treated with indomethacin, nine noted marked relief from pain and thought indomethacin 100 mg. was more effective than phenylbutazone 100 mg., one had moderate relief of symptoms and considered 100 mg. of indomethacin equal in effect to 100 mg. of phenylbutazone, and one noted mild improvement, less than that obtained from phenylbutazone. Except for three patients with early side-effects necessitating withdrawal of treatment, all noted deterioration on blind introduction of placebo. Three patients had side-effects which prevented assessment. The following are examples of case histories of patients who benefited from indomethacin.

A Scotsman aged 48, with ankylosing spondylitis since 1945, was experiencing severe pain in the lower back and between the shoulders. Previous therapy included phenylbutazone 300 mg. daily, which resulted in mild symptomatic relief but was associated with the development of dyspepsia. On his own initiative he started taking compound tablets of codeine in large quantities, and, although this was hard to assess, he probably took 25 tablets daily. After some weeks he was admitted as an emergency to hospital unrousable and cyanosed from excess medication. He started on indomethacin 100 mg. t.d.s., and this was increased to 100 mg. q.d.s. This dose controlled his pain to an extent that enabled him to stop taking any other treatment. On stopping indomethacin he deteriorated to his previous state.

A man aged 38, who was diagnosed in 1952 as having ankylosing spondylitis, had episodes of severe low-back pain lasting from 10 to 21 days, with full remission of symptoms between attacks. On starting phenylbutazone 100 mg. b.d. he had partial relief of symptoms after three days. Any increase in dosage produced a rash. Indomethacin 100 mg. b.d. controlled symptoms completely within 48 hours.

A woman aged 27, with ankylosing spondylitis and peripheral joint involvement, was maintained on 12 units of corticotrophin daily. Indomethacin 100 mg.

t.d.s. produced a marked improvement in pain and corticotrophin was reduced by 5 units a day. Within two days she developed a severe headache; indomethacin was withdrawn and symptomatic deterioration ensued. Corticotrophin was increased to the original dose level and symptoms improved only slightly; a further temporary increase of 5 units a day was required before her clinical condition was adequately controlled. Subsequently she was found to have a good clinical response to indomethacin 50 mg. once or twice a day, dizziness on 50 mg. t.d.s., and headache on 100 mg. t.d.s.

Osteoarthritis

Six of seven patients with osteoarthritis noted symptomatic relief. Four out of five in whom a direct comparison was made preferred indomethacin to phenylbutazone. One patient noted no change in symptoms.

Rheumatoid Arthritis

Eleven patients with rheumatoid arthritis with measurable inflammatory features were assessed. Eight were out-patients and three were in-patients. In addition, four in-patients with swelling of the knees were included, making a total of 15 patients with active inflammatory disease (Table III). Of these 15 patients, eight showed clinical improvement with reduction in joint-swelling and two were inconclusive in that no rebound occurred on cessation of therapy. The following are examples of patients who improved clinically and noted reduction of joint-swelling.

A woman aged 58, with rheumatoid arthritis of two years' duration (Fig. 1), was severely incapacitated by pain, and the knees in particular had deteriorated to such an extent that she spent much time in bed and did not go out of doors. She was maintained on prednisone 20 mg. a day and aspirin 60 gr. (4 g.) a day. Indomethacin 300 mg. a day produced a marked clinical improvement and reduction in ring size. When she was changed blind to placebo she deteriorated to such an extent that the house-physician, who did not know of the alteration, ultimately used pethidine for analgesia. On reintroduction of indomethacin she improved once more, and after five weeks was discharged greatly improved and able to take short walks. She has been on indomethacin for a year with sustained improvement and with no side-effects. She had previously had a partial gastrectomy for duodenial ulceration and was able to tolerate indomethacin satisfactorily. Butazolidin had been ineffective in dosage of 300 mg. a day.

A 38-year-old woman developed rheumatoid arthritis at the age of 36. Neither paracetamol nor aspirin produced significant symptomatic improvement. Indomethacin 100 mg. b.d. gave her a feeling of drunkenness after 24 hours, but this disappeared on 50 mg. t.d.s. Placebo was introduced blind and assessment showed deterioration; improvement occurred on reintroduction of indomethacin.

TABLE III.—EFFECT OF INDOMETHACIN COMPARED WITH THAT OF PHENYLBUTAZONE IN ANKYLOSING SPONDYLITIS AND RHEUMATOID ARTHRITIS

Disease	Number of patients	Better than Phenylbutazone	Equivalent to Phenylbutazone	Less effective than Phenylbutazone	Inconclusive
Ankylosing spondylitis	14	9	1	1	3
Rheumatoid arthritis:					
With measurable soft-tissue swelling	15	8		3	4
With no measurable soft-tissue swelling	37	9	4	15	9

Five patients failed to show reduction in ring sizes on indomethacin. In two the explanation was probably that treatment was given for too short a time to cause much change, as it had to be stopped after a few days because of side-effects. Two patients probably did not respond because there was inadequate initial acute oedema to show measurable change. The fifth patient responded to corticosteroids but not to indomethacin.

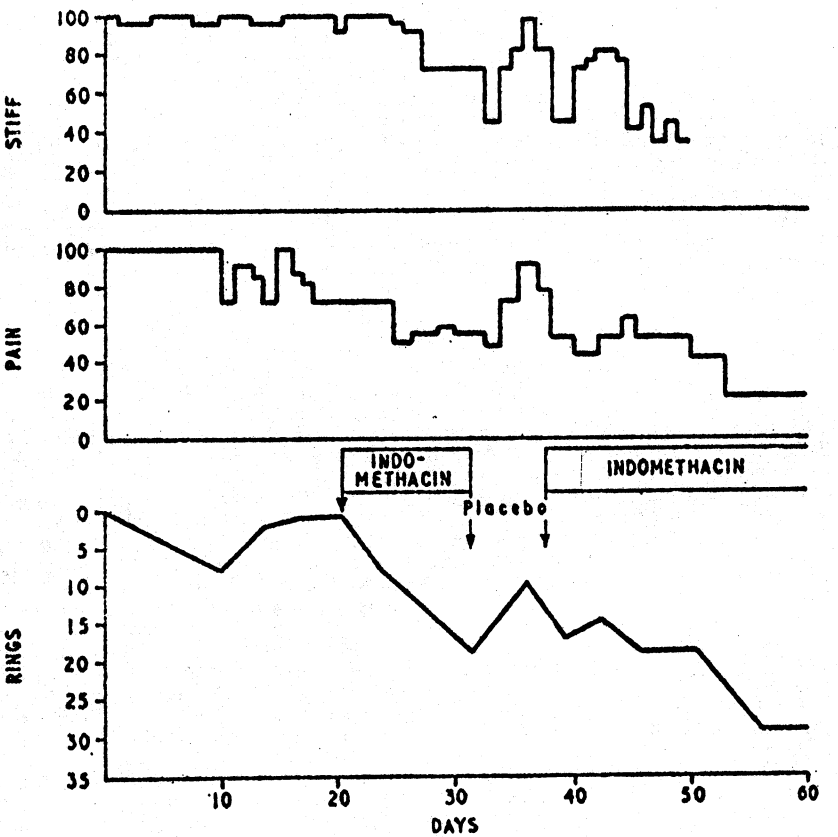


FIG. 1.—Chart of woman aged 58 treated with indomethacin for rheumatoid arthritis of two years' duration.

A man aged 61 developed acute rheumatoid arthritis over a period of nine months and required admission to hospital. As can be seen in Fig. 2, his condition was not improved by salicylates. Indomethacin was introduced without any pronounced effect and he was changed to corticotrophin. This resulted in clinical improvement and marked loss of inflammatory swelling.

In this case the rheumatoid disease was very active and a dosage of 60 units of corticotrophin was required initially to control the condition. In five cases where both drugs were used corticotrophin proved a much more effective anti-inflammatory agent than the new one.

Of 37 patients with rheumatoid arthritis without measurable inflammatory features, 14 noted a beneficial effect, 14 noted no effect, and in 9 the result was inconclusive. Of the 14 patients who noted a good effect 9 preferred indomethacin (100 mg.) to phenylbutazone (100 mg.), four noted a moderate improvement, equivalent to that obtained from phenylbutazone, and one noted mild symptomatic relief only. Of the 14 patients who noted no improvement on indomethacin, six benefited from phenylbutazone, while seven noted no effect; one had not received phenylbutazone. Indomethacin was inconclusive in a further nine patients, eight of whom experienced side-effects and one developed an influenza-like illness and stopped taking the tablets. Six of these patients found phenylbutazone to be of value, two noted no effect, and one had never taken phenylbutazone.

SIDE-EFFECTS

Side-effects were frequent with indomethacin on a dosage of 300 mg. daily, occurring in 26 of 50 patients. Reactions at this dose level usually accurred 48 to 96 hours after starting treatment. Seven patients who experienced side-effects on 200–300 mg. a day were found to be symptom-free on a smaller dose more gradually introduced.

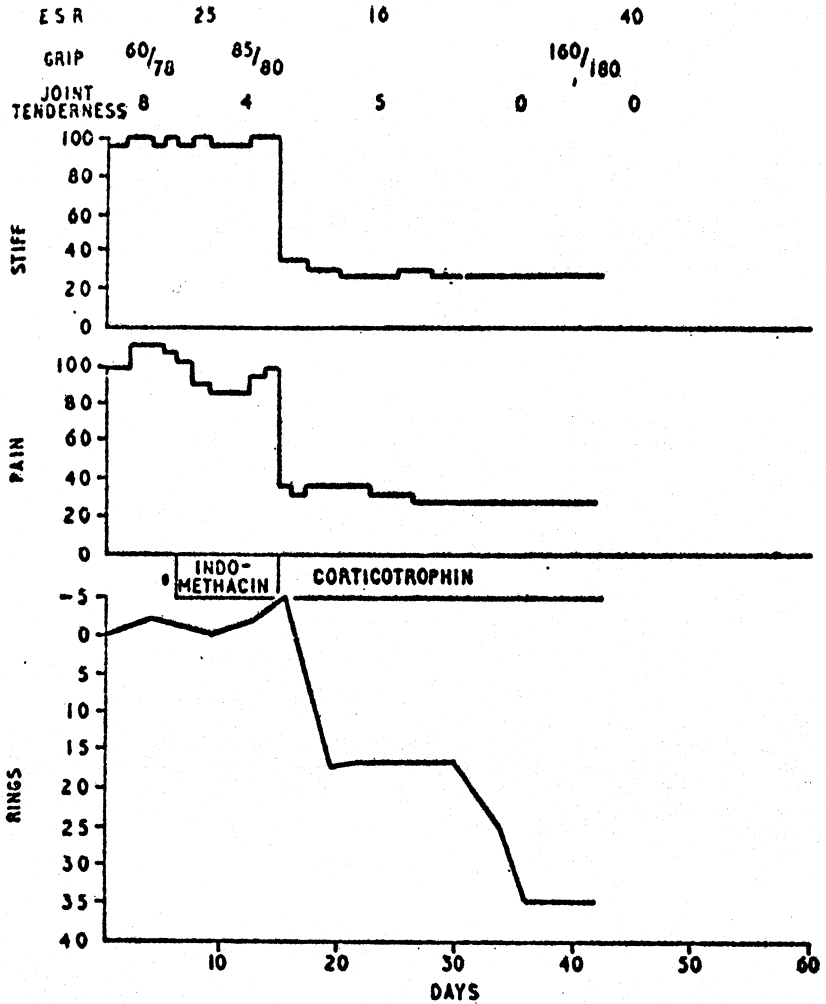


FIG. 2.—Chart of man aged 61 treated with indomethacin for acute rheumatoid arthritis with little effect.

Gout

Of 15 patients who received indomethacin for the acute attack of gout, three experienced side-effects. One developed a headache after 48 hours on 300 mg. daily, which cleared on 200 mg. a day and was relieved by an antihistaminic preparation. Another patient noted mild headache and giddiness on 400 mg.

daily after 48 hours. Only one patient had a severe but transient reaction. This woman, aged 23, had hyperuricaemia, a family history of gout, and congenital hypoplastic kidneys, and was subject to acute gout. Her blood urea was 52 mg./100 ml. and uric acid 13.2 mg./100 ml. She took indomethacin 100 mg. for an acute attack of gout and within 10 minutes became drowsy, was unable to focus on any object, and later developed a severe throbbing headache. Symptoms improved after four hours, but the headache remained for 24 hours. Several cups of coffee reduced her drowsiness. The reaction was thought to be too rapid in onset to be accounted for by high blood levels of indomethacin due to impaired renal function. This was an abnormal incident, no similar reaction being observed in any other patient.

Rheumatoid Arthritis

Of the 52 patients with rheumatoid arthritis who received indomethacin 31 noted side-effects. The age of these patients varied from 20 to 56. Symptoms developed within two to three days in 16. They occurred within six hours of the first dose in 10, and in five reactions were delayed until after six days. Patients usually experienced several side-effects at the same time. Of 37 patients with relatively inactive rheumatoid arthritis, 28 experienced side-effects, while only 3 of the 15 patients with measurable inflammatory disease were affected.

Headache occurred in 14 of 31 patients. This was characteristically a generalized throbbing in the head and ears; one was severe, eight were moderate, and five mild.

Giddiness was present 12 patients. This was a sensation of unsteadiness without vertigo. It interfered with gait and driving a car. Three were mild, eight moderate, and one was severe.

Faintness, coupled with a sense of impending loss of consciousness, was experienced by two patients. This symptom occurred only when other side-effects were pronounced. In no case, however, was there loss of consciousness.

Muzziness and mental change: two patients noted muzziness with inability to concentrate or think out intellectual problems, two felt emotionally detached, and four said they felt drunk.

Nausea and vomitting: nine patients experienced anorexia and nausea, two of whom vomited.

Diarrhoea: four patients experienced diarrhoea. This was usually associated with nausea or vomiting.

Dyspepsia: four patients experienced dyspepsia, which was severe and necessitated cessation of treatment: one had no previous gastro-intestinal history, two were intolerant of phenylbutazone, and one, who had both a hiatus herina and gall-stones, developed dyspepsia with soluble aspirin, paracetamol, and placebo tablets identical in appearance to indomethacin. Two patients developed dyspepsia within two days of starting the drug and the other two first noted symptoms after seven days' therapy.

Drowsiness: two patients developed drowsiness within one hour of the first dose. If they sat down they fell asleep. This symptom occurred only after the more severe reactions and was improved by taking coffee. Blurred vision was noted by these patients.

Side-effects usually cleared within 24 hours of cessation of treatment, but occasionally lasted for two to three days. Five patients were given anithistamines, chlorpheniramine 4 mg. q.d.s., and four noted improvement in the headache but not in gastro-intestinal symptoms.

The effect of a lower dose on side-effects has been studied in seven patients intolerant of high dosage. Of three patients who experienced side-effects on 300 mg. a day, two were symptom-free on 200 mg. and one on 150 mg. a day. Three patients with side-effects on 200 mg. daily were able to tolerate 150 mg. a day, and one of these who suffered side-effects on 100 mg. b.d. was found to become symptom-free on 50 mg. q.d.s. One patient, intolerant of 100 mg. a day, was maintained satisfactorily on 50 mg. a day.

Anklosing Spondylitis and Osteoarthritis

Six of the fourteen patients with anklosing spondylitis developed side-effects; four were taking 300 mg. a day, one of whom later had no symptoms on 200 mg. a day; one was on 200 mg. a day; and one on 100 mg. a day, experienced a mild headache.

Of seven osteoarthritic patients treated none noted side-effects.

PATTERNS OF SIDE-EFFECTS

Of 88 patients with disorders of the locomotor system treated with indomethacin, 40 (45.4%) suffered side-effects. These effects were commoner in patients with rheumatoid arthritis (59.6%) than with gout (20%). Side-effects included headache, giddiness, faintness, muzziness, mental change, anorexia, nausea and vomiting, dyspepsia, diarrhoea, drowsiness, and blurred vision. More than one symptom occurred in all patients. Headache was improved by antihistamines, and drowsiness by coffee. Seven patients with rheumatoid arthritis and one with ankylosing spondylitis who had side-effects on relatively high initial dosage were found to be symptom-free on a lower dose more gradually introduced. It is probable, therefore, that with a starting dose of indomethacin 50 mg. daily and gradual increase by 50 mg. every third day to a maximum of 200 mg., the incidence of side-effects may be much lower than this figure. A dosage of 300–500 mg. daily may occasionally be used, but side-effects are likely to be frequent. There was no evidence of toxic effect on the blood, liver, or kidneys.

Side-effects occurred in four patterns: (1) Within a few hours the patient experienced severe symptoms independent of the dose. (2) Side-effects developed most often between 48 and 72 hours and were reduced by adjusting the dose. This appars to be a cumillative effect. (3) A small number of patients developed symptoms after seven days, as in two of the four cases of dyspepsia. (4) Some patients experienced muzzy feelings and mild headache about two hours after each dose, which wore off after an hour and did not progress. This occurred only with the 100-mg. tablet, never the 50 mg.

DISCUSSION

It is clear that in indomethacin we have an agent that will reduce swelling and also relieve pain. As an anti-inflammatory agent it is less effective than the corticosteroids and corticothrophin, but it is the only non-steroid agent we have used to date which has produced measurable reduction in finger-swelling in active rheumatoid arthritis. In this disorder those cases with measurable inflammatory swelling did appreciably better and had fewer side-effects than those with less inflammatory change. In two cases the dose of corticosteroids previously needed to control symptoms was gradually reduced under cover of the new drug, but in 12 others it proved ineffective. The response in acute gout is, in our opinion, better than with any other therapeutic agents at present available, for its action is more rapid than is that of phenylbutazone and the patient is less subject to rebound attacks than with corticotrophia. The definite relief of pain in the few cases of osteoarthritis assessed makes it seem likly that the drug has analgesic properties independent of its anti-inflammatory ones, and its use in a few febrile cases demonstrated that it is also an effective antipyretic: in one case of glandular fever treated with indomethacin there was rapid improvement in symptoms and signs, with relapse as soon as it was discontinued.

As regards toxicity, it is clear that our initial dosage was too high and we now seldom use 100-mg. tablets, but favour 50 mg. one to four times daily. On this lower dosage side-effects are much less troublesome and the headache and muzziness which are the commonest complaints often pass off on continuation of low-dosage therapy. Many patients intolerant of other drugs because of gastrointestinal side-effects are tolerant of indomethacin, which in our hands has proved relatively non-toxic in this respect to man, unlike the results in experimental animals. Time will show if there are any other side-effects, but at present no changes in blood counts or liver- or renal-function tests have been noted, nor were skin reactions seen. We have not used it in children or in pregnant women. On present evidence we consider that indomethacin, in spite of its tendency to cause headaches and dizzy feelings, has a definite part to play in the treatment of the chronic rheumatic disorders, and we regard it as the drug of choice in acute gout. In ankylosing spondylitis, osteoarthritis, and active rheumatoid arthritis it has also much to offer.

SUMMARY AND CONCLUSIONS

Indomethacin (1-*p*-chlorobenzoyl)-5-methoxy-2-methylindol-3-acetic acid) has proved to have anti-inflammatory and pain-relieving effects in gout and rheumatoid arthritis. It has also proved effective in the treatment of ankylosing spondylitis and osteoarthritis. As a dosage about 200 mg. a day headaches and dizziness were frequent, occurring in over 50% of those treated. At a daily dosage of 50–200 mg. side-effects occurred in 43%.

Dyspepsia has been rare—in 4 out of 99 patients. Also rare were faintness (2), drowsiness (2), and feelings of drunkenness (4). Intolerance or resistance to the drug has not been observed in up to one year of continuous treatment.

Indomethacin is the drug of choice in acute gout, where relief is obtained more rapidly than with phenylbutazone. It is useful also in ankylosing spondylitis, in osteoarthritis, and in cases of rheumatoid arthritis with inflammatory features and swelling of joints.

Although more time is needed before the true incidence of toxic effects can be evaluated, indomethacin appears to be a useful addition to the treatment of these rheumatic disorders.

ADDENDUM

We have now followed up 123 patients for periods of up to one year; other workers have reported dyspepsia and occasional gastrointestinal haemorrhage as complications of indomethacin therapy. In our experience to date, only 4 out of 123 patients have experienced dyspepsia and none has had clinically detectable haemorrhage. Three of these four patients have suffered dyspepsia on phenylbutazone.

One patient who noted an initial symptomatic improvement on indomethacin has found that the symptoms have gradually returned in spite of continued treatment. This was thought to be due to the possible development of tolerance.

Three out of 123 patients developed skin lesions; one of these suffered from disseminated lupus erythematosus. The rash was irritating and consisted of discrete red macules and papules on the limbs. It disappeared completely within 48 hours of stopping the drug.

In one patient a reduction of the drug from 350 to 150 mg. a day resulted in the rash resolving.

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References

Hart, F. D., and Clark, C. J. M. (1951). *Lancet*, 1, 775.
Hucker, H. B., Zacchei, A. G., and Cox, S. V. (1963). *Fed. Proc.*, 22, 544.

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INDOMETHACIN AND PHENYLBUTAZONE: A COMPARISON

(By F. Dudley Hart,* M.D., F.R.C.P., and P. L. Boardman,* M.R.C.P.)

Early papers on indomethacin reported promising results from its use as a non-specific anti-inflammatory agent in the treatment of the chronic rheumatic disorders (Paul and Strottman, 1963; Ballabio *et al.*, 1963), with dramatic results in gout (Smyth *et al.*, 1963). A controlled clinical trial demonstrated significant preference for indomethacin against placebo in rheumatoid arthritis (Dixon *et al.*, 1963). Measurable reduction of joint swelling as a result of treatment with indomethacin was reported in active rheumatoid arthristis (Hart and Boardman, 1964). There was no significant difference between indomethacin and phenylbutazone (Percy *et al.*, 1963)—in this trial the treatment period on each drug was one week and the indomethacin used was in tablet form, which, for various reasons, has been replaced by a gelatin-coated capsule.

This paper reports the results of a double-blind trial in which the effect of phenylbutazone is compared with that of indomethacin capsules, each drug being given for one month to patients with active rheumatoid arthritis. A brief account is also given of the results obtaind from the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis with indomethacin during a period of two and a half years.

I. DOUBLE-BLIND TRIAL

All 26 patients who took part in the double-blind trial of indomethacin and phenylbutazone had classical rheumatoid arthritis or definite rheumatoid arthritis as defined by a Committee of the American Rheumatism Association (1959).

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The diagnosis of the classical form of the disease is applied to those patients in whom 7 out of the 11 criteria listed by the A.R.A. are present. A diagnosis of "definite" requires the presence of five of the criteria. Phenylbutazone, 100 mg. three times a day, was given to 13 patients in the first months, and indomethacin, 25 mg. three times a day, to 13, therapy being changed to the other agent at the end of the month. To provide double-blind conditions they received active indomethacin and dummy phenylbutazone in one month, and in the other active phenylbutazone and dummy indomethacin. The group who started on indomethacin had a mean age of 47.6 years; five were males and eight females. The mean duration of disease was 6.7 years. The patients who received phenylbutazone in the first month had a mean age of 48.8 years, an average length of history of 6.2 years, and there were four males and nine females. There were six patients with classical and seven with definite rheumatoid arthritis in each group. These patients were assessed by their own daily record of pain, stiffness, and loosening-up time, and the measurement of joint tenderness, joint swelling, and grip strength at each visit (Hart and Boardman, 1963). All were attending the out-patient clinic at monthly intervals. They were assessed at the start of treatment and at the end of each trial period of 28 days. Their personal opinion as to the more satisfactory treatment period was recorded at the end of the trial.

RESULTS

When asked at the end of the trial, before the identification of the specific treatment periods, which month was the more satisfactory, 15 patients preferred phenylbutazone, 10 found them to be equally effective, and one preferred indomethacin. This difference is statistically significant ($P<0.001$).

A comparison of the pain record of each patient in the month on phenylbutazone with that of those on indomethacin revealed that this parameter improved selectively in five in phenylbutazone and in two on indomethacin, 19 finding no difference. A clinically significant alteration of pain was taken to be 25% or more in the month. Likewise, assuming a 25% difference to be significant, five were less stiff during phenylbutazone therapy and one on indomethacin, 20 finding no detectable difference. There is obviously no significant difference in these symptoms between the two groups.

An alteration in the duration of early-morning stiffness was assumed to be of clinical significance if it exceeded 30 minutes. In the first month, on phenylbutazone, there was improvement in the loosening-up time in seven patients and deterioration in one, five being unchanged. On indomethacin there was improvement in three, deterioration in four, and no change in six. These changes are not statistically significant ($X^2=1.4$; $n=1$; $0.3>P>0.2$). In the second month, on indomethacin, improvement occurred in three patients, and this parameter worsened in two, eight exhibiting no change. On phenylbutazone there was no change in six, four improved, and three deteriorated.

A difference in grip strength of 50 mm. of mercury was assumed to be clinically significant. In the first month, on phenylbutazone, none improved, five deteriorated, and eight remained unchanged. On indomethacin three improved, one deteriorated, and there was no chance in nine. There was no statistically significant difference between the groups ($^2X=1.5$; $n=1$; $0.3>P>0.2$). In the second month, on indomethacin, 11 patients remained unchanged, one improving, and one deteriorating. In comparison, on phenylbutazone, there was no change in 10 patients, improvment occurring in three. There was obviously no significant difference.

As 17 of the 26 patients had no tender joints at any time during the trial this was an unsatisfactory parameter.

Assuming a change of three ring sizes in joint size to be significant, there was no difference in 17 patients, five were better on indomethacin, and four on phenylbutazone. The improvement in joint size, in the first month, in the patients on phenylbutazone, was by four rings. On indomethacin the improvement was by 35 rings. This difference is not statistically significant ($t=1$; $n=24$; $0.2>P>0.1$). In the second month indomethacin was associated with an improvement of 21 ring sizes, compared with 17 on phenylbutazone.

II. LONG-TERM STUDIES

Ninety-seven out-patients and 21 in-patients with classical or definite rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis were treated with indomethacin. In some cases it was possible to compare results with those previously obtained with pyrazole derivatives.

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Rheumatoid Arthritis

Ninety-seven out-patients an 21 in-patients with classical to definite rheumatoid arthritis (American Rheumatism Association Committee, 1959) were followed up for two and a half years. Ninety were females and 28 males. Their average age was 53.3 years, and the mean duration of rheumatoid arthritis was 8.1 years. The sheep-cell-agglutination titre was positive in 85 patients.

The in-patients were assessed by their own daily record of pain, stiffness, and the duration of early-morning stiffness, together with twice-weekly estimations of grip strength, joint tenderness, and joint size (Hart and Boardman, 1963). Identical placebo was administerd to conceal the exact time of the start and the withdrawal of indomethacin by blind substitution. The E.S.R. was measured weekly. Four grades of response were recognized in the out-patients with rheumatoid arthritis, according to the criteria of therapeutic response defined by the American Rheumatism Association Committee (Steinbrocker *et al.*, 1949, recorded in this paper as good, fair, poor, or nil; the E.S.R. was excluded from this assessment. In all patients in whom treatment had included a pyrazole derivative indomethacin was compared with phenylbutazone or oxyphenbutazone, their relative effectiveness being recorded at arbitrary maintenance dosage. This was 300 mg. daily for the pyrazoles, 200 mg. daily for indomethacin tablets, and 75 mg. daily for the capsule preparation. The prolonged effect of indomethacin was checked by the observation of rebound deterioration on withdrawal of the drug.

Osteoarthritis

With one exception the 52 patients with osteoarthritis were treated in the out-patient clinic. They included 35 females and 17 males with an average age of 61.2 years and a mean duration of symptoms of 4.5 years. A good response was one with 85% control of symptoms as assessed by the sufferer, the residual pain constituting minor discomfort only and not interfering with daily activity. A fair response was one in which there was therapeutically useful improvement but not to the extent of removing all serious discomfort. A poor response was one in which there was some slight symptomatic improvement, insufficient to be of therapeutic value.

Ankylosing Spondylitis

There were 26 males and six females in the group of 32 patients with ankylosing spondylitis, the average age being 37.6 years and the mean duration of disease 13.4 years.

RESULTS

Rheumatoid Arthritis In-patients

Pain and stiffness were reduced in 15 of the 21 in-patients, there being no change in five and side-effects in one. Early-morning stiffness improved in eight, remained static in six, and was too short initially for assessment in six; in one patient side-effects prevented assessment.

Grip strength improved by more than 50 mm. of mercury in seven patients. It improved slightly in one patient, remained unchanged in six, and was an unsatisfactory parameter in seven—in five as a result of side-effects, and in two because of lack of involvement of the hands. Joint tenderness improved in five patients, was unchanged in two, and side-effects interfered in five; in nine there were no tender joints.

Compared with the baseline, there was reduction of joint size on indomethacin of 79 ring sizes in seven patients, while three deteriorated by 11 ring sizes. There was no change in five. Assessment was unsatisfactory in six because of side-effects and lack of involvement of the hands.

There was no significant change in the E.S.R. in response to the administration of indomethacin.

Of the 21 in-patients 19 had previously received a pyrazole derivative. The preference was for indomethacin in six, and for phenylbutazone or oxyphenbutazone in four; nine patients were unable to detect significant difference.

Rheumatoid Arthritis Out-patients

In the 97 out-patients the response to indomethacin was good in 28, fair in 21, poor in 10, and nil in 38 patients. A comparison with a pyrazole derivative was possible in 80 patients. Indomethacin was preferred by 30, a pyrazole derivative by 19, and they were found to be equally effective in 31 patients.

Ankylosing Spondylitis

The response to indomethacin in the 32 patients with ankylosing spondylitis was good in 16, fair in six, poor in one, and nil in nine. In 19 patients the treatment of choice was indomethacin, and in nine it was phenylbutazone or oxyphenbutazone; four patients considered them to be of equal value.

Osteoarthritis

The response to indomethacin in the 52 patients with osteoarthritis was good in 30, fair in four, poor in seven, and nil in 11. It was possible to compare indomethacin with the pyrazoles in 39 patients. Indomethacin was the drug of choice in 15 and phenylbutazone or oxyphenbutazone in 13; 11 found them equally satisfactory.

SIDE-EFFECTS

Side-effects occurred in 104 of the 202 patients treated with indomethacin (51.48%); this consisted of 67 out of 101 (66.3%) on indomethacin tablets, and 37 out of 101 on capsules (36.6%).

The following complaints were noted, the incidence being recorded in brackets: headache (46), giddiness (25), dyspepsia (16), muzziness (16), nausea (12), vomiting (5), rash (4), diarrhea (4), felt odd (2), sleepy (2), heavy legs (2), drunk (1), faint (1), mouth ulceration (1), unpleasant taste (1), depression (1), lassitude and nightmares (1), swollen tongue (1), costive (1), and shakiness (1).

In 88 patients side-effects occurred within seven days of starting indomethacin, in nine patients within seven to 14 days, and in two patients between 14 and 21 days. Side-effects occurred after three weeks in five patients only.

Dyspepsia occurred in 16 of the 202 patients (7.92%). In contrast, of the 170 patients who received a pyrazole agent 40 had dyspepsia (23.5%). In no patient was there overt evidence of gastro-intestinal haemorrhage, and none developed perforation. One patient with rheumatoid arthritis and one with osteoarthritis of the hip had slow gastro-intestinal blood loss, the administration of indomethacin being associated with a fall in the haemoglobin by 20–40% within a month.

Barium studies were available for 16 patients, all of whom had dyspepsia on phenylbutazone or oxyphenbutazone and eight on indomethacin. A duodenal ulcer was detected in seven patients, all intolerant of pyrazoles; indomethacin was tolerated by four of these patients and caused dyspepsia in three; these seven have received 995 patient days of treatment with indomethacin to date. In five patients with demonstrable gastric ulcers—one with a hiatus hernia also—all intolerant of phenylbutazone, indomethacin was associated with dyspepsia in one, being well tolerated in four patients; this group has received 571 patient days of treatment to date without serious gastro-intestinal complications. In three patients no abnormality was detected on barium-meal examination. All three were intolerant of phenylbutazone; indomethacin was associated with dyspepsia in two patients, and in one may have been the cause of anaemia by slow continuous blood loss. One patient, with both a hiatus hernia and gall-stones, suffered from dyspepsia on indomethacin, phenylbutazone, salicylates, and placebo.

DISCUSSION

It is increasingly apparent that the therapeutic effect of indomethacin has many similarities to that of phenylbutazone, irrespective of the mode of action. Though painful symptoms are relieved by phenylbutazone, the action being remarkably even throughout the 24 hours, reduction of joint swelling occurs in only occasional cases of rheumatoid arthritis. The regular, predictable reduction of joint size with the corticosteroids, offset by the untoward affects of prolonged therapy, suggested that the advent of a new non-steroid preparation with this property would be a considerable advance. Of the many preparations tried in the last 17 years at the Westminster Hospital (F.D.H.) indomethacin has been the first non-steroid drug to produce a measurable reduction in joint size in selected cases of active rheumatoid arthritis. The spectrum of side-effects on indomethacin overlaps phenylbutazone slightly with respect to the gastro-intestinal tract but is otherwise quite different. It is possible that the response to indomethacin is not as consistent as that obtained from phenylbutazone over the 24 hours; in this series the overall response was slightly less than 60%.

The double-blind trial confirmed that, under defined conditions, there was no significant difference between indomethacin, 75 mg. daily, and phenylbutazone, 300 mg. daily, in the relief of pain and stiffness in rheumatoid arthritis. Though the alteration of joint size on the two drugs was not statistically significant, the

trend in each group suggested that this parameter improved specifically on indomethacin. The magnitude of the response obtained depends not only on the anti-inflammatory effect of the administered drug but also on the amount of soft-tissue inflammatory swelling present that is potentially capable of exhibiting reduction of size. It is unlikely that optimal conditions existed in these patients, for reduction of joint size; they were selected from the regular attenders at the out-patient clinic and had disease of moderately long duration. That indomethacin was associated with reduction of joint size, as compared with the baseline, was demonstrated in the patients admitted to hospital.

Indomethacin was initially available in the form of tablets. These proved to be unsatisfactory and gelatin-coated capsules were substituted. The patients in the long-term studies received both preparations. These results are not given separately, except for side-effects, because the capsule is the only preparation available; a comparison of the two preparations revealed that the only difference of statistical significance was the incidence of side-effects.

The most consistently satisfactory results from indomethacin were obtained in patients suffering from ankylosing spondylitis (68.7%) and osteoarthritis (65.3%). Results for gout are reported separately (Boardman and Hart, 1965). Excellent results did occur in rheumatoid arthritis, in particular in patients with active disease, but there were also some dramatic failures, and overall benefit was obtained in only 50.5%.

Side-effects were a more frequent cause of therapeutic failure than inadequate drug potency. The change from the tablet to the capsule preparation was associated with a reduction in frequency from 66.3% to 36.6%, together with a decrease in the severity of untoward reactions. The most common pattern of side-effects consisted in headache, giddiness, muzziness, and nausea. These were transient, dependent on dosage, and occurred within the first few days of starting treatment.

Dyspepsia was relatively rare during indomethacin administration. Smyth *et al.* (1964), in a study of 63 patients with rheumatoid arthritis during an 18-month period, found one who developed peptic ulceration on indomethacin and one on placebo. Catoggio *et al.* (1964) had two cases of duodenal ulceration in a group of 33 patients. Clark (1964), in a study of 100 patients with rheumatoid arthritis, encountered peptic ulceration in 10, nine of whom also received corticosteroids; there were three instances of perforation and one of hemorrhage. Bilka *et al.* (1964) reported one patient, out of a total of 61, who developed a small gastric ulcer after 12 weeks of indomethacin therapy. Haemorrhage and perforation do not appear to be serious risks as judged on the figures of this series, in contrast to the findings of Lövgren and Allander (1964). Unlike their six patients with a history of gastric or duodenal ulceration treated in hospital, in our series four of seven patients with duodenal ulceration and four of five with gastric ulcers tolerated indomethacin well, the total period of therapy being 1,566 days. Nevertheless, with certain exceptions, dyspepsia occurring on indomethacin was considered an absolute indication for cessation of therapy. In our series antacids were not used for symptomatic control. Lövgren and Allander (1964) treated their patients in hospital with anticholinergics and antacid agents; it is possible that some of their problems arose as a result of the masking effect of these symptomatic remedies on what should be considered a warning symptom.

The dose probably suitable for most patients is 25 mg. three times a day, administered after food. It is suggested that to overcome the frequent early side-effects the dose should be increased slowly during the first week, from an initial 25 mg. daily. Dyspepsia due to indomethacin is an indication for the withdrawal of therapy.

During the two and a half years that indomethacin has been available to us it is of relevance to note that only three patients with rheumatoid arthritis have been started on long-term corticosteroid therapy or A.C.T.H. The fact that a non-steroid anti-inflammatory agent is now available may well make a profound difference to the present use of corticosteroids in this condition.

SUMMARY

A double-blind cross-over trial was carried out to compare indomethacin, 75 mg. daily, with phenylbutazone, 300 mg. daily, each being given for a period of 28 days to patients with active rheumatoid arthritis. No significant differences were found between the two groups in the relief of symptoms, but the results

obtained were indicative of greater reduction of early-morning stiffness on phenylbutazone and of joint swelling on indomethacin. The personal preference, expressed at the end of the trial, was in favour of phenylbutazone.

In a mixed group of patients treated over two and a half years indomethacin was effective in improving the symptoms of osteoarthritis (65.3%) and of ankylosing spondylitis (68.7%). In rheumatoid arthritis failures were more frequent, a satisfactory response being recorded in 50.5% of cases.

Side-effects on indomethacin capsules, at an average maintenance dose of 75 mg. daily, occurred in 36.6% of patients in the mixed group. The common side-effects were headache, giddiness, muzziness, nausea, and vomiting. Dyspepsia was not a major problem, occurring in 7.92% of patients; it was only rarely dose-dependent and occurred at any time during long-term administration in contrast to the other side-effects, which were dependent on dose and developed almost always within the first 14 days of treatment.

ADDENDUM

Since the completion of this study, one patient on indomethacin, 200 mg. daily, and prednisolone, 8 mg. daily, with a history of duodenal ulceration, present 20 years earlier, developed dyspepsia after six months on indomethacin. This was followed by a haematemesis which required blood transfusion. In many of the cases of haematemesis reported this combination of drugs was used.

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References

American Rheumatism Association Committee (1959). *Ann. rheum. Dis.*, 18, 49.
Ballabio, C. B., Cirla, E., Girardi, G., Caruso, I., and Colombia, B. (1963). *Rheumatismo*, 15, 487.
Bilka, P. J., Wollheim, F., and Williams, R. C., jun. (1964). *Minn. Med.*, 47, 777.
Boardman, P. L., and Hart, F. Dudley (1965). *Practitioner*, 194, 560.
Catoggio, P. M., Centurion, A., Alberti, H., Roldan, H., and Canepa, L., (1964). *Arthr. and Rheum.*, 7, 300.
Clark, G. M. (1964), Ibid., 7, 300.
Dixon, A. St. J., Jones, L., Wanka, J., and Wood, P. (1963). *Abstracts of Communications*, Fifth European Congress on Rheumatic Diseases, p. 174.
Hart, F. Dudley, and Boardman, P. L. (1963). *Brit. med. F.*, 2, 965.
——— (1964). *Practitioner*, 192, 828.
Lövgren, O., and Allander, E. (1964). *Brit. med. F.*, 1, 118.
Paul, W. D., and Strottman, M. P. (1963). *Arthritis and Rheumatism Foundation (Iowa) Medical Information Bulletin*, 4 (3), 1.
Percy, J., Stephenson, P., and Thompson, M. (1963). *Abstracts of Communications*, Fifth European Congress on Rheumatic Diseases, p. 176.
Smyth, C. J., Valayos, E. E., and Amoroso, C. (1963). *Arth. and Rheum.*, 6, 299.
——— Amoroso, C., and Valayos, E. (1964). Ibid., 7, 345.
Steinbrocker, O., Traeger, C. H., and Batterman, R. C. (1949). *F. Amer. med. Ass.*, 140, 659.

Senator NELSON. This is probably a question for Mr. Goodrich.

As you know, all of these drugs are handled and promoted by detail men. What legal control, if any, do you have over the information presented by detail men to the physician?

Mr. GOODRICH. Basically our control would be over the detailing pieces—the written, printed and graphic materials that the company develops to be used as detailing pieces. As we move into some of the drugs, particularly Vibramycin which is coming up later, a detailing piece is one of the major pieces there we will be going over with you.

In addition to that, the regulations require that all promotions, whether it be advertising, direct mailings, promotional material left by the detail man, must all conform to the approved labeling, and must all present the full disclosure of both the good and the bad about the drug.

Now, in terms of what the detail man says in the doctor's office, legally we could do something about that. But as a practical matter, we have no means of regulating that unless the doctor who is detailed tells us what happened and is willing to be a witness.

You will remember that in the hearings on Chloromycetin before the Kefauver committee, there was one instance in which one of our own men, one of our own physicians who was in private practice, was detailed by the company for Chloromycetin, and we did communicate with the company immediately about that improper detailing, and they represented that they had corrected it.

But we have no program of monitoring what the detail men say.

Now, we do have physicians attending meetings, and observing exhibits around the meetings, who hear the detailing of a public nature. In those instances, any time an oral advertising claim is made which exceeds the permissible bounds of the approved labeling, this results in the product being misbranded for failure to bear adequate directions for use.

Senator NELSON. If my recollection is correct, those who have commented on this question before the committee felt that the detail man is frequently quite effective in influencing physicians' prescribing habits. I am wondering how you, the FDA, can control the advertising that goes to the doctor and be effective yourself if one large aspect of the promotion of the drug, that is, the detail man, is not effectively controlled?

Mr. GOODRICH. This is certainly a problem, Senator. But if we can be successful, as we hope we are, moving in this direction, in providing assurance that publications such as Physicians' Desk Reference, which is on the doctor's desk, all the advertisements in the journals, the mailing pieces that go out, fairly comply with the requirements of the law, either by providing full disclosure in case of mailing pieces and adequate brief summary in case of journal advertising, that the physician who is detailed certainly has a place to turn where he can be adequately and completely informed about the drug, to have a basis on which he can make a comparison with the detail man's claim.

Another point is that PDR is a limited volume, as we all know, and this is one of the reasons we are advocating the bill you yourself introduced, to have a reliable compendium which will provide every doctor's office on his desk complete, reliable, adequate information on drug prescribing.

Senator NELSON. Do you evaluate and pre-evaluate the literature that the detail man is permitted to give to a doctor?

Mr. GOODRICH. We do not. We certainly have the right to, and do, look at a good deal of this, that is promotional material. The companies are required to submit with their records and reports the promotional material that is being used—not every piece, because they are quite voluminous. But any piece that—any promotional piece that is different in any significant way from one that has already been submitted is required to be submitted.

That does not mean that Dr. Ley's group adequately reads all that material, because its volume, even in terms of not being complete—not being the complete outpouring of promotion—the volume that we receive, only part of the total, is still quite large, and more than we can handle with our present people.

Senator NELSON. Do they hand out this type of promotional piece and so forth, like the JAMA ads?

Mr. GOODRICH. Sure. The same kind. You will see in the ads you have before you some of them run several pages—it is not unusual to see an elaborate ad running several pages, that is suitable for reprinting, either for direct distribution or handout by the detail man. The companies also use attractive visual aid type of promotional material to make their detailing more effective. And they use a great many other promotional techniques. I am constantly amazed at the creativity of the people on Madison Avenue who think up these ideas. But they certainly have a lot of ways of getting the message across. It could not be better stated than you did, that the problem of competing with a message such as the ad you have in front of you is a difficult problem.

Senator NELSON. In the event that some promotional material being handed to the doctor by the detail man exceeds the claims in the package insert, do you have the authority to make them correct it?

Mr. GOODRICH. Yes, sir.

Senator NELSON. Do you ever do that?

Mr. GOODRICH. Oh, yes.

Senator NELSON. You say the material is very massive. You do not review it all—or do you?

Mr. GOODRICH. We just physically cannot review it all. I would certainly recommend a substantial increase in the amount of effort we have on this. But Dr. Ley is the one who has to put the medical resources into it, and I believe the judgment has been made by him and by Dr. Goddard that we are at the level of maximum now that we can put into it—although it could stand some more help.

Senator NELSON. Do you require the detail man to submit any piece of literature, the contents of which you regulate, like the package insert, to the doctor on each occasion that he is detailing the drug?

Mr. GOODRICH. Only in the sense that every piece of written material, written, printed, or graphic material that he leaves or shows to the doctor in the course of his detail, is required to have a full disclosure of the effectiveness, side effects, contraindications, warnings, precautions, and so forth, applicable to insure safe, effective use of the drug by that physician—every piece of it.

Senator NELSON. That is the requirement as to advertising.

Mr. GOODRICH. The advertisement requirements differ only in the sense that a brief summary of information related to side effects and contraindications is permitted in general advertising. In direct mailing pieces and other labeling material the discussion must be in greater depth and detail.

Senator NELSON. Well, is it in as much detail as the package insert?

Mr. GOODRICH. Not completely, but it has to be substantially the same—not in the same words, not in the same unattractive form as that you see in the package insert. But the message has to be substantially the same. That is, all of the side effect, precaution, warning, contraindication ideas that are presented in the package insert, must be presented in the mailing piece.

Senator NELSON. And you do review that?

Mr. GOODRICH. To the extent of the facilities available for surveillance, yes.

Senator NELSON. Do you ever find any of this literature that does not comply with your requirements.?

Mr. GOODRICH. Yes, we do. And we find that some of it does not comply for many different reasons. We have had instances in which the company claimed that a paragraph was left out inadvertently. It is entirely possible that might have been so. There have been other instances in which the writeup was shortened unduly. There have been instances such as with the Merck Sharp & Dohme here this morning, in which a message that we thought was quite clear, that the drug did cause ulcers, is translated into a lesser language that ulcers have occurred. We find all types of this. The surveillance over prescription drug promotion is a full-time job for an active person—for several active persons who have a great interest in this problem.

Senator NELSON. Dr. Ley?

Dr. LEY. The material which will be presented in subsequent hearings will give the concrete example of a preclearance operation of a promotional ground for the detail man's use in the physician's office. I think this review will answer many of the questions that you are directing at us today as a concrete example.

Senator NELSON. We will leave the rest of the questions on the detail men until subsequent hearings.

Mr. GORDON. As I understand it, then, FDA really does not know what the detail man is saying about Indocin; am I correct?

Senator NELSON. Or any other drug.

Mr. GOODRICH. We know what his company tells him to say. Now, we do not know what he says when he goes to Dr. X's private office and talks with him about the drug. The only way we could know about it is if the doctor tells us. This is a delicate part of surveillance in which we have no mechanism of carrying it forth, except as the doctors tell us.

Mr. GORDON. I believe we have had testimony in the past that the oral presentation is probably the most important presentation of all to the doctor; that the doctor very seldom, if ever, reads the promotional material, printed material, that is left with him; that he relies to a large extent or mostly on the oral presentation.

Now, you will also recall that in the *Love* v. *Wolf* case, the court held that the activities of the detail men in the case of Chloromycetin washed out the warnings in the printed material. Do you recall that?

Mr. GOODRICH. Yes.

Mr. GORDON. Even if you had adequate staff, and you were to revise your regulations, would this be enough to protect the public?

Mr. GOODRICH. Well, I know that certainly the drug companies feel that detailing is an effective means of promotion. But I could not accept the idea that the tremendous amount of money and effort and the elaborate outlays of printed material have no impact on the prescriber. I think myself that an ad, such as the one you have before you, has a tremendous impact on the doctors prescribing.

Mr. GORDON. I do not say it would not be helpful in protecting the public. But would other measures be necessary. Would this alone be enough?

Mr. GOODRICH. I do not know what you are suggesting, Mr. Gordon. It certainly would be fine with us if doctors who considered the detailing they got was wrong would communicate with us, we would be much interested in that. We would be prepared to take action if we found violations. But that is the only mechanism we have for getting at that, beyond assuring everyone that all the printed material,

all the graphic material, does make a full breast of the whole thing.

Mr. GORDON. But that is a big problem, isn't it?

Mr. GOODRICH. It is one problem, of course.

Mr. GROSSMAN. Mr. Goodrich, on this same point, I assume, then, that you believe physicians read these drug ads in the professional journals. I was just wondering—you said you assumed they had a major impact on doctors. Do we have any evidence—have we had any survey, anything that shows what doctors actually read in this area, and what they believe—or how they are influenced?

Mr. GOODRICH. Dr. McCleery says he has a survey. I base my statement on a quotation from an advertising man himself who made it over in Baltimore at a meeting soon after the law was passed, that we could be sure that if advertisements do not sell drugs, they will not continue to run. And for that reason, I am convinced that they do play a major role.

Mr. GROSSMAN. Has there been any study or survey on this, Dr. McCleery?

Dr. MCCLEERY. Yes, there have been several, and several published. I brought one along today in case we were asked. I think it will reinforce Mr. Goodrich's point concerning the isolated effect of journal advertising alone. By saying that, I would not like to imply that I do not feel there is a general agreement amongst all sides of our dispute, on industry's and our side, that the activities of the detail men constitute the most effective element of all elements of promotion, and as such is a very great and, as Mr. Goodrich says, an uncovered area of our responsibility. But in terms of the evidence that a printed ad is effective in leading to a change in prescribing habits, I will make available copies for the record—from our library. In 1966, we received one of these studies conducted under the sponsorship of Modern Medicine magazine, and conducted by an expert polling outfit, the Politz outfit. What they set out to do, using all of the skills of isolating an area so as to measure effect—and, without going into all the details as to why, it seems that they succeeded. What they did was to take old drugs, eight old drugs—the name of this publication is "The Important Thousand"—done as a Modern Medicine Politz study on advertising effectiveness. We will make copies of it available, but the conclusions are very revealing, I think.

The magazine was interested in determining, for understandable reasons, was what it would be possible to learn—about the effects of ads for some selected drugs, that were not being actively detailed, and had not been for some time, and for which there were no mail campaigns going on, and which had not been going on for some time. They set up a control study to determine the effect of eight ads for eight products, and that is what the basis of this study was.

Now, among the effects and the results they found was that the "belief in excellence" of a product was increased 18 percent by the very simple one or two page black and white or color ads used in this study; and that, as to that most important parameter of effectiveness, the increase in that "intent to prescribe" was of the order of 21 percent. All this from a very small ad, for only six consecutive issues in the Modern Medicine magazine, and in no other journals.

There are numbers of studies like this which show that even the effect of journal advertising alone is quite substantial in leading physicians to change their prescribing habits.

I might point out, in contrast to this very simple, limited advertising on one and two pages for old drugs, that the Merck introductory ad for Indocin in the JAMA (of which you have a copy) in November 1965, was a 10-page, very impressive, four-color ad. It ran for 6 months, approximately. The impact of this kind of ad, in this and many journals, I believe would be likely to be substantially greater than the 21 percent results from these rather limited ads.

Senator NELSON. What study was that?

Dr. MCCLEERY. It was an Alfred Politz study for Modern Medicine magazine.

Senator NELSON. Is additional discussion of that going to be presented?

Dr. MCCLEERY. I intend, if you wish it, to give you a copy of the entire study.

Senator NELSON. Yes. Do you intend to discuss it further at a future hearing?

Dr. LEY. If the Senator wishes, we may.

Senator NELSON. I would like to see a copy of it, and then appropriate parts of it might be printed in the record. But we ought to have a chance, as Mr. Goodrich says, to evaluate it.

I want to thank all three of you very much. You have made a most valuable contribution to the hearings. We appreciate your taking the time to come here and present this testimony.

(The information submitted by Senator Nelson follows:)

MERCK SHARP & DOHME,
West Point, Pennsylvania,
July 14, 1966.

H. I. WEINSTEIN, M.D.
Director, Division of Medical Review.
ACTING CHIEF,
Medical Advertising Branch/DMR.

Indocin (indomethacin)—Misbranding under 502(n).

I. "Indocin" article in July 1966 issue of *Pageant* magazine by Phyllis and Robert P. Goldman.

II. 3-page ad in the July 4, 1966 *Journal of the American Medical Association.*

III. Recommendation.

I. PAGEANT ARTICLE, TITLED "INDOCIN"

A. The subject article has come to our attention most prominently in connection with information accompanying a letter of June 21, 1966 from Mr. John E. Fletcher (Merck) to Mr. Cron. This was called to our attention by Mr. Goodrich, who also asked us to check Indocin's medical journal ads. Mr. Fletcher attached a copy of his note of June 17, 1966 to members of the Merck management admitting that the firm cooperated with the Goldmans in making information available for the article, but disclaiming any responsibility of Merck in the matter on the grounds that the article was not "promoted" or "sponsored" by the firm.

B. Thus, the question whether FDA has jurisdiction over the article must be settled before proceeding to deal with the question of whether its contents misbrand the drug.

Even taking Merck's admission and disclaimers into account, we believe that the *Pageant* article is subject to section 502(n) of the Act and that Merck is a responsible party for causing issuance of the article:

1. While section 502(n) excludes labeling defined by regulation 1.105(1), it includes all advertisements *and other descriptive printed matter* that is not determined to be labeling.

We believe that the Pageant article should be regarded as "other descriptive printed matter" that is not labeling.

2. Section 502(n) of the Act does not require material subject to the Act to be "promoted" or "sponsored" by a prescription drug manufacturer, packer or

distributor. It requires only that such material be issued *or caused to be issued* by the manufacturer, etc.

We think it is clear from the dictionary meanings of "cause" that Merck caused the *Pageant* article to be issued. For example, a pertinent meaning is that "cause applies to any event, circumstance, or condition or any combinaation of these that brings about or helps brings about a result."

There are several statements in the article that could not possibly have been made unless the information had been furnished by Merck; thus, it is apparent that the firm can be considered to have caused the article to be issued.

Additionally, the article itself contains direct confirmation of Merck's participation in causing the article to be issued. For example, on page 8, the authors state:

> "... many of them [patients] are moved to sit down and write about their experiences with the drug to its producer, Merck, Sharp and Dohme of West Point, Pennsylvania."
>
> "The following are some samples of these letters to the pharmaceutical firms: . . ."

C. In our opinion, the *Pageant* article by Phyllis and Robert P. Goldman misbrands Indocin, a prescription drug, under section 502(n) of the Act.

Having "caused" the article to be issued, Merck then had the obligation to insist that it meet the requirements of section 502(n). Merck did not meet this obligation. For example, the article fails to contain a true statement of information in brief summary relating to side effects, contraindications and effectiveness as required by section 502(n)(3) and regulations 1.105(e) and 1.105(f)(1).

We believe that a most serious aspect of this misbranding situation is the flagrant appearance of claims in the article that go far beyond the indications for use approved in the package insert. For example, use of 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" has not been approved in labeling for the drug. To demonstrate Merck's direct responsibility in causing such unapproved claims to be published in the offending article, the following sample of a letter furnished to the writers by Merck is quoted:

> "From Minneapolis: 'Because of bursitis I had to give up golf two years ago. But with your wonderful medicine I'm in good enough shape now to play golf once again . . .'"

II. THREE-PAGE AD IN THE JULY 4, 1966, JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

A. *Promotional Copy* (re effectiveness)

1. The headline, "extends the margin of safety in long-term management of arthritic disorders," is misleading since:

a. It implies that sufficient experience has been obtained to establish Indocin's long-term safety. This is neither the case, nor does the approved package insert (FPL) contain such an affirmation.

b. It contains an implication that Indocin is safer than all other effective anti-arthritic agents for long-term therapy. This is neither proved, nor does the FPL contain such an affirmation.

c. The claim, ". . . of arthritic disorders," is too broad. It extends the FPL indications by implication to other arthritic disorders which have not been approved for inclusion in the FPL. At least it should be modified by a word such as certain."

2. The use of the quote from the Hart and Boardman article (attachment #1), under the caption "rheumatiod arthritics," is misleading since:

a. It is taken out of the context of the article which reveals that the very impressive phrase, ". . . in most cases of active rheumatoid arthritis," refers to the small number of 8 out of a total of 15 cases.

b. It fails to reveal that dosages far in excess of those approved in the FPL were employed (see pages 966 and 968), at least in the early phases of therapy; e.g., 200–300 mg./day versus the FPL's upper initiating limit of 75 mg./day.

c. It fails to reveal, for fair balance, that approximately 60% of the patients with rheumatoid arthritis got side effects, and that all of these got more than one side effect (pp. 969–970).

d. The duration of therapy (p. 966) in these patients was far too short to support the layout's implication that this paper supports the headline's claim of long-term safety.

3. The use of the quote from the Rothermich reference (attachment #2), under the caption "ankylosing spondylitis," is potentially misleading:

a. The quote seems to come from a scientific article. This is not the case—it is from a 2-inch abstract apparently of a talk presented at the "American Rheumatism Association" meeting in 1964.

b. The quote is accurate, but it is surprising that the company used this abstract as a reference when almost certainly the full details have been published as a regular article later in 1964 or early in 1965. (We have not yet located this article.)

c. The use of the abstract is also potentially misleading since long-term results (re the headline's claim for safety) and dosages were not included. Therefore, dosages that produced these results may well have been in excess of FPL limits.

d. For fair balance, against the quote of good results described in the Hart article above, the company could have included Rothermich's results in rheumatoid arthritis. In this same abstract, he stated that although "Excellent results have also been obtained in some cases of rheumatoid arthritis . . . there have been striking failures as well . . ."

4. The use of the quote from Englund, under the caption "degenerative joint disease (osteoarthritis) of the hip," is at least potentially misleading:

a. It gives the appearance of being from an article in a symposium-book. Such are not widely distributed, nor easily available.

b. It was not available in BuMed Library. Dr. Standard of DSB/DMR made a trip to the NIH Library, which had a copy.

c. There was no reference to Dr. Englund's work on page 27, as cited.

d. There was no reference to an article by him in the symposium, either in the index or table of contents.

e. We did locate a physician by that name, in the AMA directory, practicing in Phoenix, Arizona.

f. We will search further to try to find the quote. It could be seriously misleading if Dr. Englund did not, as seems likely, have all "500 patients on indomethacin *for about three years*" (italic added).

5. The use of the quote from the same Hart and Boardman article (attachment #1), under the caption "gout," is misleading and shows a serious lack of "fair balance."

a. The quote from a seemingly authoritative source from a leading foreign medical journal implies that this opinion must have been based on a large experience (unspecified in quote), and that it was consistent with the general experience of experts using the drug according to the FPL.

b. It was not:

(1) The implied claim that indomethacin is the drug of choice in acute gout is not supported by the FPL.

(2) A reasonable source of early consensus on a relatively new drug, about which "drug of choice" claims are being made, is the view of the AMA Council on Drugs. Its view is expressed in *New Drugs* (1966)—"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."

If the company wanted properly to use the authors opinion, it should have included the dosage they used and the number treated. Even then, "fair balance" would still require inclusion of an authoritative opposite or consensus view if such existed.

(3) The experience was not large—the authors report on a study of only 15 cases treated for relatively short periods (see pages 966 and 967).

(4) The "good" results, that led the authors to make the quoted statement, were based on dosages far in excess of permitted (150 mg./day) upper FPL dosage limits—they administered 200–500 mg./day for several days (see pages 966 and 967).

(5) Their opinion was not based on a well-controlled experience. In only 7 patients were any direct comparisons made, and that only to one drug, phenylbutazone (see Table II, page 967). Even here, 3 patients out of 7 preferred phenylbutazone to Indocin.

c. It is very misleading that the company should employ this quote to imply it represents an accepted view of Indocin's effectiveness compared to all other drugs, especially when they know it is based on a very limited (15 patients) and uncontrolled experience—and when the results achieved are based on dosages far

in excess of approved dosages. Both of these important and material factors are concealed from the reader of the ad.

B. *Re: the "Brief Summary"*

The following important warning ideas in the FPL are omitted from the ad's "brief summary":

1. "As with other anti-inflammatory agents, Indocin may mask the signs and symptoms of peptic ulcer." (see Contraindications)
2. "Indocin itself *may cause* peptic ulceration . . ." (see Contraindications)
3. ". . . Indocin *may cause* [single or multiple] ulceration of the stomach, duodenum, or small intestine." (see Precautions and Adverse Reactions)
4. "The possible potentiation of the ulcerogenic effect of these drugs [steroids, salicylates or phenylbutazone] cannot be ruled out at present." (see Precautions and Adverse Reactions)
5. A summary of the following cautionary information (see Precautions and Adverse Reactions):

"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."

III. RECOMMENDATION

Seizure, with or without such injunctive measures as may be feasible.

When Mr. Goodrich called, he asked that we expedite our review of the ad and article while they are still current. He felt that the two items might be joined in one regulatory action. For this reason, they are both included in this one memo.

R. S. MCCLEERY, M.D.

MERCK SHARP & DOHME,
West Point, Pa., September 22, 1966.

Hon. L. H. FOUNTAIN,
Chairman, Intergovernmental Relations Subcommittee, Committee on Government Operations, House of Representatives, Washington, D.C.

DEAR MR. FOUNTAIN: This is in reply to your letter of September 7, 1966, enclosing an ad from the August 15, 1966, issue of the Journal of the American Medical Association for Indocin (indomethacin, Merck).

This advertisement and the labeling of the drug have been undergoing review by this agency. In our opinion, the ad is inconsistent with the prescription drug advertising provisions of the law. Further, we regard the quotes from the medical literature used in this ad as not being in conformity with the guidelines described in my statement to your Subcommittee on May 25, 1966.

We are proceeding to take corrective action in this matter.

Sincerely yours,

JAMES L. GODDARD, M.D.,
Commissioner of Food and Drugs.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
October 31, 1966.

FRED BARTENSTEIN, Jr.,
Administrative Vice President,
Merck & Co., Inc.,
Rahway, N.J.

DEAR FRED: This acknowledges your letter of October 26, 1966, about my speech at the PAC in New York City, October 20.

My points were based on a medical evaluation of your Indocin ad. Our Philadelphia District has been instructed to issue citation to your firm. This involves both the Pageant article and the ad. You will, of course, have the opportunity to make your points in response to the citation.

We feel that the effectiveness of the drug and its safety in use have been misstated. The things I pointed out involved the approved brochure (before the recent revision) and the ad which is still running. We do not agree that the "profile" of "Indocin" remains the same today as it appeared when the new drug application was approved.

The revised mailing piece is also under review. It was not approved by us in the form in which it issued. Our impression is that it is more a promotional piece than a warning letter. As to the gout claims, our position is as stated in New Drugs (1966). As to the omitted warning information, please compare the approved brochure with the advertisement.

Very truly yours,

WILLIAM W. GOODRICH,
Assistant General Counsel, Food and Drug Division.

[U.S. Government Memorandum]

NOVEMBER 2, 1966.

To: Herbert L. Ley, Jr., M.D., Director, Bureau of Medicine. Through: H. I. Weinstein, M.D., Acting Associate Director for Medical Review.
From: Acting Director, Division of Medical Advertising/OMR.
Subject: Misleading promotional labeling piece under guise of apparent "Dear Doctor" letter re Indocin.

By first class mail, a letter (copy attached) was sent 10/4/66 by the firm in an envelope flagged for the physician's attention by a beguiling euphemism, "Safety," in very large red letters.

It contained the attached new FPL submitted, under 130.9 (presumably "justified" because it only added warning ideas), by 9/2/66 Company letter to Dr. John Jennings. Whether this was a legitimate act is open to serious question since revision of the FPL was under serious dispute in several details at the last meeting of BuMed and Company personnel on 7/15/66.

The 9/2/66 letter (copy attached) affirmed the intent to put the FPL into use O/A October 31, 1966, without awaiting approval as would be necessary if it were a suplemental NDA submitted under regulation 130.4—this is spite of the fact the 9/2 letter was really a "negotiating" communication turning down a number of specific requests made at the same 7/15/66 meeting.

The above must also be viewed from the perspective that the Company therein rather imperiously turned down at least two important requests for "warnings" by BuMed—see paragraphs "2)" and "3)" of the letter's page 2. Their unwillingness to state, *"NOT FOR USE IN CHILDREN,"* appears irresponsible in the face of their knowledge of deaths in children—deaths not prevented by the old FPL language they even here aver to be adequate.

Further, they jumped the implied 10/31/66 "use" date by putting the FPL into use via the 10/4/66 letter to the medical profession.

Misleading features of subject "October, 1966" letter: 1. The first sentence sets the tone of the letter as blatantly promotional. It is both out of place and a non-sequitur, since experience in 98 of the 99 countries is largly if not solely beside the point. This is especialy improper because of the tie-in to the second sentence's idea that presumably only this massive "global" experience with circa 150 million patient days therapy resulted in the few and new additional warning idea "reflected in the revisions . . ." in the included FPL.

2. The Company's decision to highlight "one change in particular," namely the "potential of masking . . . ," must be judged against the following:

a. It represents a unilateral act of rejection of a BuMed proposal to warn of the "Possible activation of latent infection." (See 9/2/66 letter, page 3.)

b. The above "change" constitutes a minimized alert to a standard idea, which, while important, has competed successfully in the Company's "mind" against the prominent inclusion of the following *new* FPL contraindications and side effect ideas:

(1) Contraindicated in aspirin-sensitive asthmatics and during lactation.
(2) Convulsion, depersonalization.
(3) Jaundice, hepatitis.
(4) Angiitis, elevated blood pressure.
(5) Acute respiratory distress.
(6) Agranulocytosis.
(7) Hyperglycemia.

3. It subtly promotes use of the drug more widely than the FPL permits:

a. Re: end of first sentence, ". . . in the treatment of *arthritic* disorders . . . ."—and the end of the last sentence, ". . . next to aspirin, the most frequently prescribed *antirheumatic drug* . . . ." (underscoring added);

(1) Although the "descriptive" first paragraphs of the old and new FPL begin with the latter phrase (notably it is in quotes, "antirheumatic"), and end with "rheumatic disorders," this information refers only to the "generic" capacity of the drug and is clearly not an approved broad indication for such "generic" use of Indocin.

(2) The forced association in the physician's mind with aspirin and its use in rheumatic fever, acute rheumatic arthritis and "carditis," etc., is at least potentially misleading.

Recommend: Prompt and vigorous regulatory action, with serious consideration being given to the advisability of a forced "remedial" letter designed to correct the above misconceptions.

R. S. McCLEERY, M.D.

[U.S. Government Memorandum]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
FOOD AND DRUG ADMINISTRATION,
November 4, 1966.

To: Herbert L. Ley, Jr., M.D., Director, Bureau of Medicine.
Through: John J. Jennings, M.D., Acting Associate Director/ODS.
From: Marvin Seife, M.D., Acting Deputy Director/DSR.
Subject: Indocin (indocmethacin)—NDA 16-059

A revised indomethacin package insert, #6176404, dated August, 1966, submitted on September 2, 1966, contained most of the changes suggested by the Bureau of Medicine at a meeting with M.S.D. on July 15, 1966. Nevertheless, aditional revision of the proposed insert is considered mandatory.

A. A drug warning statement must appear at the beginning of the insert as follows:

IMPORTANT WARNING

"Indocin, brand of indomethacin, cannot be considered a simple analgesic and should never be administered casually. Each patient should be carefully evaluated before treatment is started and should remain constantly under the close supervision of the physician. The drug should not be used in children because safe conditions for use have not been established and severe reactions, including fatalities, have been reported."

B. The following misleading words, phrases and unsupported material should be deleted from the package insert introductory section, (paragraphs one and two).

1. Paragraph one, sentence one—omit the word "antirheumatic".
2. Paragraph one, sentence three—eliminate the entire sentence—("Unlike corticosteroids, it has no effect on pituitary or adrenal function.")
3. Paragraph two, sentence one—omit the phrase "of all ages".
4. Paragraph two, sentence two—omit the phrase "in patients with rheumatic disorders".

C. Indications:

1. The first sentence should be changed from "INDOCIN (indomethacin) has been effective in the treatment of:" to "INDOCIN (indomethacin) has been found effective in the symptomatic treatment of".
2. Eliminate the sentence following the listing of the indications: ("In these conditions indomethacin may often replace other commonly used agents such as corticosteroids, salicylates, phenylbutazone—like compounds, and colchicine.")
3. Rheumatoid Arthritis Section: Eliminate the last sentence of paragraph one—("Treatment should be continued for at least a month before concluding that it has not produced significant benefit")—unless M.S.D. can substantiate the recommendation contained therein.

D. Contraindications:

1. Eliminate sentences four and five from paragraph one.
2. The third sentence of paragraph one should be changed from "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." to "For these reasons it should not be given to patients with active peptic ulcer, gastritis, regional enteritis, or ulcerative colitis, and should be used with caution if there is a history of these disorders."

3. The last paragraph of this section must be eliminated in favor of a straightforward statement such as—"This drug should not be used in children because safe indications for use have not been established and severe reactions, including fatalities, have been reported."

E. Dosage and Administration:

1. Paragraph three of this section must be eliminated in favor of a straightforward statement such as—"This drug should not be used in children because safe indications for use have not been established and severe reactions, including fatalities, have been reported."

The issuance of an Indocin (indomethacin) DRUG WARNING letter to the medical profession is necessary in view of the aforementioned package insert additions and changes, the extensive use of this drug, and the possibility of severe and fatal reactions.

[U.S. Government Memorandum]

JUNE 16, 1967.

To: R. S. McCleery, M.D., Acting Director, Division of Medical Advertising/OMR.

From: D. C. Hurwitz, M.D., Office of Drug Surveillance.

Subject: Survey of NDA Data by Dr. D. W. Englund.

I have reviewed the Indocin studies conducted by Dr. D. W. Englund contained in Volumes 4, 11, 53 and 76 of the Indocin file. The specific material reviewed consists of two copies of a speech presented before the Merck Research Institute at West Point, Pennsylvania on February 11, 1965, one letter to Merck Sharp and Dohme describing the results of clinical studies, and clinical data on 172 patients.

Dr. Englund has apparently had extensive clinical experience with Indocin, and he discussed in his speech at West Point his experiences with 550 patients using Indomethacin. At the time of this speech, Dr. Englund had been studying Indocin for two years and 50% of his total patient group had been taking the drug for eighteen months or more. Diagnostic categories included rheumatoid arthritis, rheumatoid spondylitis, psoriatic arthritis, gout, scleroderma, lupus, osteoarthritis and primary fibrositis. The author claimed good results in all groups. The largest single diagnostic category was rheumatoid arthritis in which 426 patients were treated with the drug and 362 or 85% showed "definite benefit and clinical improvement." Of 32 patients with rehumatoid spondylitis, 30 showed definite clinical improvement. The percentage improvement varies from group to group but in general the majority of patients were significantly improved.

The only data available to support Dr. Englund's contentions is contained in Volume 11 in which the raw data for 172 patients is assembled. There seems to be a representative cross section of the diseases that he has treated. The treatment period varied from one to "over forty-eight" weeks with the largest number of patients (70) having undergone treatment for 13–24 weeks. Only 22 patients received the drug for longer than 48 weeks at the time the data was compiled—March 13, 1964. Forty patients remained unreported because the investigator did not feel that they had been on the medication for sufficient time to enable evaluation.

As with most of the other Indocin studies the data consists of a clinical evaluation sheet on which various parameters are observed and an overall response to Indocin therapy graded none, poor, fair, good or excellent. In common with the other studies of this type carried out by the company, this clinical trial is completely uncontrolled and lacks the usual elements contained in a well-designed study: a placebo controlled group, random patient selection, regulation of dosage and length of administration of drug, as well as adequate and carefully designed response criteria. The study therefore has testimonial value only and in no way can be construed to show any objective evidence of efficacy of the drug in question. Unfortunately, the author's all-to-obvious bias has undoubtedly played a large role in his evaluation of the efficacy of Indocin.

In conclusion, then, one can regard this study as having only testimonial value in determining the efficacy of Indocin. While such a study has some value for preliminary use in determining whether it is worthwhile to further investigate a compound, it certainly has no definitive value in determining efficacy in this group of diseases since they do not lend themselves to easy clinical evaluation. I am able to find data for only 172 of Dr. Englund's 550 patients; it is impossible to tell at this time whether the rest of the data was submitted in another volume

and has been overlooked or whether it was never submitted to Merck Sharp and Dohme.

JULY 19, 1967.

HOWARD I. WEINSTEIN, M.D.,
Acting Associate Director for Medical Review, Med.

R. S. MCCLEERY, M.D.,
Acting Director Division of Medical Advertising, OMR.

126–350 B—Indocin (indomethacin)—
Alleged Misbranding through Advertising—
S & R Philadelphia District, January 26, 1967
and I–AR DCG to Med 2/1/67.

SUMMARY STATEMENT

We have reviewed Philadelphia District's S & R dated January 26, 1967 and its attachments, as well as the written response by Attorney Coburn, representing Merck, to charges set forth in Notice of Hearing dated November 23, 1966. In summary, we do not believe that the firm has presented adequate defense in relation to the charges. Taking into account the shipment date (11/7/66) of sample 126–350 B; the fact that the 9/26/66 *JAMA* ad contained changes in the "Brief Summary" that affect the 1.105(f)(1) charges which stemmed from the July 4, 1966 *JAMA* ad (which was the initial basis for our critique of July 14, 1966); more recent information suggesting new or revised charges; etc., we have re-evaluated the situation and conclude that the case should proceed in relation to Indocin advertising. However, the situation now indicates that the FDA should consider dropping the basis for the Notice of Hearing of November 23, 1966, i.e., the Indocin ad in the *JAMA* issue of September 26, 1966, but retaining the sample (126–350 B) as a basis for certain charges in relation to a more suitable Indocin ad.

RECOMMENDATIONS

It is recommended that the case be redeveloped in three categories as discussed below and that a new citation be instituted, because it will be noted that the advertisement under this proposal that caused the misbranding is not the same as the one on which the initial citation was based, because the more recent ad is more closely dated in reference to the collected sample, and because the charges have been considerably expanded primarily due to more extensive violative features. Specifically, we recommend that advertisement for Indocin in *The American Journal of Medicine*—November, 1966 be alleged as misbranding the November 7, 1966 shipment of Indocin represented by sample 126–350 B. The package insert accompanying this sample is "Effective: August 1966" and identified in Collection Report of November 18, 1966.

JANUARY 26, 1967.

SUMMARY AND RECOMMENDATION

Sample number, 126–350 B; Product, Indocin Capsules, 25 Mg.; Date shipped (on or about), 11–7–66; Carrier, Parcel Post; Seizure, None.

CITATION ISSUED TO

Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pennsylvania 19486

LEGAL STATUS

The firm, Merck Sharp & Dohme Division, is a wholly owned subsidiary of Merck & Co., Inc., a New Jersey corporation with principal place of business at Rahway, New Jersey.

The officers are as follows: Stuart T. Henshall, President; John J. Horan, Executive Vice President, Marketing; Frederick K. Heath, Vice President, Professional Communications; John L. Huck, Jr., Vice President, Market Planning; Eugene L. Kuryloski, Vice President, Sales.

ALLEGED VIOLATIONS

Misbranded by failure of medical journal advertisement sponsored by the manufacturer to fairly show the effectiveness of the drug in conditions for which it is recommended in the advertisement and failure to achieve fair balance in its presentation.

Misbranded by failure of medical journal advertisement sponsored by the manufacturer to contain a true statement in brief summary relating to side effects, contraindications and effectiveness.

WITNESSES FOR INSPECTIONAL AND ANALYTICAL FINDINGS

Sample Collection: Inspector William M. Troetel (P), 126-350 B, November 18, 1966, DOC. 126-351 B. October 28, 1966.

Analytical: Analyst John L. Mietz (P), 126-350 B, DOC. 126-351 B November 23, 1966.

RECOMMENDATION

Prosecution of: Merck Sharp & Dohme, Division of Merck & Co., Inc. (126-350 B)

REASONS FOR RECOMMENDATIONS

Summary and Findings

The product, Indocin (Indomethacin), is a newly developed nonsteroid drug which was first marketed following the approval of NDA June 10, 1965. The medical journal advertisement for the product appearing in the September 26, 1966 issue of the *JAMA*, is one of the earliest ads for the product. Sample 126-350 B represents a shipment made on November 7, 1966, 11 days after the publication date of the journal. The product was shipped from the firm's West Point, Pennsylvania warehouse to The Drug House, Inc., Trenton, New Jersey, for distribution to retail pharmacists in central New Jersey.

The advertisement was critically reviewed by several members of the Bureau of Medicine and citation issued to the firm for various types of shortcomings:

(1) The copy for the ad, particularly the headlines employed, utilized broad and unwarranted statements such as "extends the margin of safety in long-term management of arthritic disorders."

(2) Unwarranted and misleading representations concerning quotations from articles describing clinical studies and failure to quote the unpleasing data from the same articles.

(3) Lack of fair balance in omitting pertinent information on contraindications.

The firm was cited to a hearing scheduled to be held at Philadelphia District on December 6, 1966. At the request of the respondent firm the hearing was rescheduled for December 14, 1966.

History of Firm

About 10 years ago, Merck & Co. acquired Sharp & Dohme and incorporated this drug manufacturing firm as a corporate division presently doing business as Merck Sharp & Dohme. Corporate offices are maintained in the manufacturing facility located at Sunneytown Pike, West Point, Pennsylvania. According to our most recent inspections, this firm manufacturers and markets an estimated $130 million annually in prescription drugs for human use. A review of available files shows no record of formal regulatory action instituted against the West Point firm. A check of New York District records may disclose regulatory actions involving the parent corporation, Merck & Co. Our records indicate the firm has been involved in the recalls enumerated below:

(1) 10-5-64—Sulfasuxidine, 0.5 Gm.—Carton mixup.

(2) 10-30-64—Cortone Acetate, 0.5%—Carton mixup.

(3) 1-14-65—Alflorone Acetate, 0.1%—Below potency.

(4) 2-9-65—Hydropres Tablets, 25 Mg.—Tablet mixup.

(5) 4-15-65—Cortisone Acetate Ophthalmic, 2.5%—Carton mixup.

(6) 5-20-65—Emulsion Mephyton, 10 Mg. and 50 Mg.—Emulsion breakdown.

(7) 9-22-65—Cathomycin Capsules, 250 Mg.—Penicillin cross-contamination.

(8) 9-22-65—Cathomycin Lyovac, 500 Mg. Vials—Penicillin cross-contamination.

(9) 110-10-65—DMSO (in all combinations, concentrations, and package sizes)—All current IND's terminated.

(10) 12-19-65—Decadron, 0.1% and Decadron-N—Lacks pharmaceutical elegance.

(11) 2-14-66—MK-665—Firm's IND terminated.

(12) 5-20-66—Cremomycin. 8 oz.—Lack of expiration date.

(13) 7-18-66—Tyroderm, 0.5 Mg/gm.—Declared potency.

(14) 11-3-66—Humorsol, 0.25% and 0.125%—Increased incidence of eye irritations.

In addition to the above, the firm recalled eight drug products which had been distributed to outside clinical investigators whose eligibility to handle investigational drugs was terminated. Investigations are presently continuing on the firm's handling of DMSO and MK-665 with view to ascertaining whether or not there is adequate evidence to sustain criminal action concerning the firm's handling of these investigational drugs. With the exception of the Humorsol recall, all of the recalls are considered "closed" from the standpoint of adequate accounting for the returned merchandise.

RESPONSIBILITY FOR ALLEGED VIOLATIONS

Our investigations of the promotional practices of the larger pharmaceutical firms indicate the planning, drafting and approval of medical journal advertising involve essentially an institutional decision on the part of the firm. In addition, outside advertising agencies are generally involved. In the instant case we do not believe we have evidence to fix any individual responsibility for the placing of this ad beyond the responsibility normally carried by corporate officers. For this reason, we have not recommended the naming of individual defendants.

INTERSTATE RECORDS AND LABELING

The records covering this shipment consist of invoice issued by Merck Sharp & Dolme and identified by both dealer's statement and affidavit of the consignee firm. In addition, we have established distribution of the medical journal and prescribing of the product through affidavit of Mischa F. Grossman, M.D., Cherry Hill Hospital, Cherry Hill, New Jersey, whose affidavit states that he has received the September 26, 1966 issue of *JAMA* which bears an advertisement for Indocin, and that in the regular course of his practice he has prescribed Indocin for some of his patients.

RESPONDENTS' VIEWS PRESENTED AT HEARING

At the hearing held on December 14, 1966, the firm was represented by house counsel Robert L. Banse and retained counsel Hayward H. Coburn of Drinker Biddle & Heath, Philadelphia, Pennsylvania. At the hearing the firm indicated that it would challenge the validity of regulations, disagree with our conclusions and question the wisdom of recommending prosecution for this type of violation. The respondents stressed, however, that the firm's actual response would be in the form of a detailed written response and asked that our evaluation be based on the written record. They did submit a tabulation (Exhibit A) but indicated this would be resubmitted with their written response. During the hearing X asked to be provided with a copy of Dr. England's article in the *Excerpta Medica Foundation* because our medical officers had been unable to locate this publication. They promised to furnish me a copy, but stressed again this would be done apart from their response in that our Charge Sheet had contained no allegations concerning this publication. At the insistence of the respondents for adequate time to prepare their response, they were granted until January 10, 1967 to present this material.

The firm's response to the charges is set forth in considerable detail in Exhibit B and will not be repeated here because the response, itself, should be studied in view of this proposed action. Briefly, the firm challenges our legal position concerning our jurisdiction over false and misleading statements in the body of the advertisement. The firm disagrees with our conclusions concerning use of terms such as "extends the margin of safety in long-term management of arthritic disorders." The firm sets forth its disagreement with each of the interpretations we have alleged in the Charge Sheet. The firm contends that the quotations from the articles cited below the illustrations in the advertisement fairly represent the views of the author. The firm takes issue with our views on listing of contraindications in the brief summary and claims its condensation is both fair and accurate. The firm's views are supported with a tabulation comparing information alleged to be omitted with information actually presented in the advertisement.

The firm also advances the view that even if it were in error the circumstances do not merit institution of criminal action. It recites the history of its dealings with General Counsel William W. Goodrich, Commissioner James L. Goddard

and representatives of the Bureau of Medicine. The firm takes the position that since it has made forthright correction of the alleged violations prosecution should not ensue. Attached to the firm's response is a copy of the advertisement for the November 14, 1966 issue of *JAMA* which it contends fully meets the requirements of Section 502(n).

DISTRICT'S CONCLUSIONS

In reviewing the firm's position in response to the hearing we find we cannot agree with most of the firm's contentions. With regard to the jurisdictional question concerning false and misleading claims in the body of the advertisement, we understand this was one of the issues presented by the industry during its initial request for a hearing on the proposed regulations. Thereafter, in the ensuing dialogue the industry withdrew its objections in light of the exchange of memoranda of understanding. Although we do not have a record of these events at the District, we understand that Merck Sharp & Dohme was a party to these proceedings and its attack upon the validity of the regulation is somewhat belated.

We believe the misrepresentations concerning the comparative safety of Indocin are serious in nature, particularly in light of the continued receipt of medical data indicating this product must be prescribed with caution. The manner in which the clinical studies were quoted is also of serious consequence, particularly when viewed from the standpoint that few physicians have available to them the original articles to compare for a more complete evaluation of the product. In this connection, we wish to point out that one of the articles (the *Excerpta Medica Foundation* booklet) could not be located in our rather extensive medical library.

The firm's comment concerning references in the brief summary to ulceration of the stomach, duodenum, or small intestine, may have some merit. If this recommendation is approved, I believe it would be well to delete reference to them lest we become involved in unnecessarily complex semantics in presentation of our case.

Although the firm presents persuasive arguments for mitigating circumstances tending to establish that need for prosecution no longer exists, we do not agree with the firm's position. As one of the leaders of the pharmaceutical industry, the firm had available to it the best brains and talent in the medical advertising field, yet it chose to utilize advertising tactics that should have been abandoned upon passage of the Kefauver-Harris Amendment of 1962. The contention that mitigating circumstances can exist appears to be of little consequence when we consider there exists no adequate method to correct the improper advertising once it has been printed and disseminated to prescribing physicians.

SPECIAL REVIEW REQUESTED

In separate communication of January 10, 1967 (Exhibit C), Mr. Coburn transmitted a copy of the *Excerpta Medica Foundation* publication entitled "NONSTEROIDAL ANTI-INFLAMMATORY DRUG THERAPY IN RHEUMATIC DISEASE" (Exhibit D). Attached with the Summary and Recommendation is the single copy of this publication which the Bureau of Medicine requested for review. Upon review of this material they may consider inclusion of additional charges. If they do, we recommend no additional citation issue because the charges would be included within the general scope of the first portion of our Charge Sheet enclosed with the Notice of Hearing.

IRWIN B. BERCH,
Director, Philadelphia District.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
FOOD AND DRUG ADMINISTRATION,
Philadelphia Pa., January 3, 1968.

MERCK SHARP & DOHME,
Division of Merck & Co., Inc.,
West Point, Pa:

Investigation by this Administration indicates your responsibility for violation of the Federal Food, Drug, and Cosmetic Act, as described in the attached Charge Sheet, with respect to the following:

Consignment of an article labeled in part: (btl) "100 *** CAPSULES INDOCIN (INDOMETHACIN) *** 25 mg. Merck Sharp & Dohme West Point, Pa. Division

of Merck & Co., Inc. CAUTION: Federal law *** H3088" shipped by you on or about November 7, 1966 to The Drug House Inc., 1880 Princeton Avenue, Trenton, New Jersey.

An informal hearing will be held on Monday, January 15, 1968 at 10:00 (EST) in Room 1204 U.S. Customhouse, 2d and Chestnut Streets, Philadelphia, Pennsylvania, to give you an opportunity to present your views in the matter. The enclosed INFORMATION SHEET explains the purpose and nature of the hearing, and how you may reply. If no response is received on or before the date set, our decision on whether to refer the matter to the Department of Justice for prosecution will be based on the evidence at hand.

By direction of the Secretary of the Department of Health, Education, and Welfare.

IRWIN B. BERCH,
Director, Philadelphia District.

PROHIBITED ACT

Section 301(a) of the Federal Food, Drug, and Cosmetic Act. The introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded.

CHARGES

A. The journal advertisement for Indocin appearing in the November 1966 issue of the *American Journal of Medicine* causes the drug to be misbranded under section 502(n) of the Act in that said ad does not fairly show the effectiveness of the drug in the conditions for which it is recommended in the advertisement and fails to achieve fair balance in its presentation as required by regulation 1.105(e) in that:

1. The headline "Extends the margin of safety in the long-term management of arthritic disorders" misleadingly implies that Indocin is safer than all other effective anti-arthritic agents for long-term therapy. Furthermore, the unqualified phrase "arthritic disorders" misleadingly extends by implication the indications for use in the labeling accepted as part of the new drug application.

2. The quotation ". . . the first non-corticosteroid agent which produced a predictable and measurable reduction in joint-swelling in most cases of active rheumatoid arthritis" from an article by Hart and Boardman (Hart, F. D. and Boardman, P. L.: *British Medical Journal*, 2:965, October 19, 1963) under the ad caption "rheumatoid arthritis" does not represent a true statement of effectiveness for Indocin and presents a distorted view of the drug's effectiveness. In addition, the use of this quotation, along with the reference to the October 19, 1963 article by Hart and Boardman is further misleading in that the quotation and reference is obsolete since it fails to take into account a more recent and more scientific article by the same authors.

3. The quotation "Indomethacin is the drug of choice in acute gout. . ." attributed to Hart and Boardman (Hart, F. D. and Boardman, P. L.: *British Medical Journal*, 2:965, October 19, 1963) appearing under the caption "Gout" misleadingly implies that the author's opinion was based upon a large experience and that it was consistent with the general experience of experts using the drug according to the approved labeling. Furthermore, the claim "the drug of choice" for this new drug, is not supported by the NDA and is contrary to all expert opinion.

4. The quotation "I have had some 500 patients on Indomethacin now for about 3 years. I find it an extremely helpful drug. I think there are certain areas where it will be without question the drug of choice. One of these is osteoarthritis of the hip" attributed to Englund (Englund, D. W. in *Non-Steroidal Anti-Inflammatory Drug Therapy in Rheumatic Disease*, New York Excerpta Medica Foundation, 1965, page 27) appearing under the caption "degenerative joint disease (osteoarthritis) of the hip" is misleading in that the statement "I have had some 500 patients on Indomethacin now for about 3 years . . ." when considered in relation to the headline claim, "extends the margin of safety in the long-term management of arthritic disorders" misleading gives the reader the impression of powerful support through massive research experience of 3-years-long administration to 500 patients on a new drug, when in fact, the statement is an "off the cuff" remark at a symposium supported by a grant from Merck, Sharp & Dohme.

In addition, the advertisement fails to achieve fair balance in that the advertisement failed to give the reader a more properly balanced view of this new drug by not including the summary view, expressed by the moderator at the end of the symposium, that Indocin's use ". . . warrants a lot more study and observation. Its long-term effect in rheumatoid arthritis is still unknown. . . ."

B. The article is misbranded within the meaning of 502(n) in that the journal advertising failed to present information concerning those side effects and contraindications that are pertinent with respect to the uses recommended or suggested in the advertisement as required by regulation 1.105(f)(1) in that the following important information has been omitted:

1. The warning that "as with other anti-inflammatory agents, Indocin may mask the signs and symptoms of peptic ulcer."

2. The warning that "indomethacin itself may cause peptic ulceration or irritation of the gastrointestinal tract."

3. The contraindication that "indomethacin is contraindicated in asprin-sensitive asthmatics."

4. The precaution that "indomethacin should be used with caution if there is a history of ulcer, gastritis, regional ileitis, or ulcerative colitis, because of its potential for causing gastrointestinal bleeding."

5. The precaution that "It [indomethacin] may cause simple or multiple ulceration of the stomach, duodenum, or small intestine."

6. The precaution that "a possible potentiation of the ulcerogenic effect of these drugs cannot be ruled out at present."

7. The side effect information concerning "ulceration of the esophagus, convulsions, nausea, anorexia, vomiting, epigastric distress, abdominal pain, diarrhea, gastritis, jaundice, hepatitis, elevation of blood pressure, hematuria, angioneurotic edema, angiitis, rashes, loss of hair, acute respiratory distress including dyspnea and asthma, purpura, thrombocytopenia, agranulocytosis hearing disturbances, orbital or pariorbital pain, vaginal bleeding, hyperglycemia, and glycesuria."

C. The article is misbranded within the meaning of 502(n) in that the journal advertisement does not prominently display the name of at least one specific dosage form and quantitative ingredient information in direct conjunction with such display as required by regulation 1.105(d)(2).

FEBRUARY 14, 1968.

From: R110.
To: R100—Mr. Barnard.
Subject: 126–350B Indocin—Merck Sharp & Dohme.

SUMMARY

Attached is Philadelphia District's S&R of 2–6–68, renewing their recommendation of prosecution in this advertising case.

Merck's response to the Notice of Hearing is a written response by the Law firm of Drinker Biddle & Reath. The response presents legal, administrative and medical arguments against forwarding.

This matter was the subject of a conference between BRC, Med & GC last October. (See Memo of Conf. 10–16–67, cy. attached.)

Your guidance in this matter will be appreciated.

Bureau of Medicine has not reviewed the Merck's response to this most recent citation.

D. W. JOHNSON.

PHILADELPHIA DISTRICT,
February 6, 1968.

SUMMARY AND RECOMMENDATION

SUPPLEMENTAL

Sample number, 126–350 B; product, Indocin Capsules, 25 Mg.;
Date shipped (On or about), 11–7–66; Carrier, Parcel Post; Seizure, None.
(This hearing involved additional citation on the sample which was the subject of Summary and Recommendation submitted on January 26, 1967.)

This hearing was held to afford the respondent an opportunity to present his views on additional advertisement appearing in *American Journal of Medicine*, November 1966.

The position of the firm with respect to the charges remains essentially the same. Our review of the written summation does not change any of our views as set forth in the January 26, 1967 Summary and Recommendation. Accordingly, we renew our recommendation for prosecution of Merck Sharp and Dohme, Division of Merck & Co., Inc., on this number.

IRWIN B. BERCH,
Director, Philadelphia District.

FOOD AND DRUG ADMINISTRATION,
Philadelphia District, February 6, 1968.

RECORD OF HEARING

Sample number and product: 126–350 B, Indocin Capsules, 25 Mg.
Firm cited [additional citation]: Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pennsylvania 19486.
Date of Hearing: February 6, 1968.
Where Held: Philadelphia District—FDA.
Present: Mr. Hayward H. Coburn, Attorney-at-Law, Drinker Biddle & Reath, Philadelphia, Pennsylvania 19107. Mr. Irwin B. Berch, Director, Philadelphia District.

This hearing was originally scheduled for January 15, 1968 and was rescheduled at the request of the respondent. Mr. Coburn presented an up-to-date Legal Status Sheet and acknowledged that the shipment was made as alleged and that the advertisement in question did appear as set forth in the Charge Sheet.

Mr. Coburn stated that the firm's response would be the written response presented to me at the hearing. This is an 18-page statement to which are attached Exhibits A–1, A–2, B, C, D, E, and F. I asked Mr. Coburn whether or not the firm had made any changes in its promotional or advertising practices since the receipt of the current citation. He stated the firm's revisions are reflected in the mailing to physicians (Exhibit E) and the revised advertisement (Exhibit F) which appeared following the earlier citation. He added that, in common with other newly-introduced drugs, additional data accumulated from human experience serve to identify other possible human reactions. He assured me these were being regularly incorporated in the revised labeling which the firm submits in accordance with the new drug regulations.

The respondent did not remain for the dictation of this hearing record.

IRWIN B. BERCH,
Director, Philadelphia District.

MERCK SHARP & DOHME,
West Point, Pa., March 8, 1968.

DIRECTOR
Bureau of Medicine
ACTING DIRECTOR
Division of Medical Advertising/OMS

We concur in the prosecution recommendation of Philadelphia District in its S & R dated February 6, 1968, and we recommend that the subject number not be placed in permanent abeyance unless such action is advocated in an opinion from General Counsel. We think that there is a valid basis for prosecution on the issues. Further, the attitude of the firm, as reflected in the letter response to the Notice of Hearing dated January 3, 1968, is poor to the extent of inviting prosecution notwithstanding its *pro forma* conclusion that prosecution should no follow.

Our comments will be directed to the written response dated February 6, 1968 and prepared by H. H. Coburn, attorney for Merck on the staff of Drinker, Biddle and Reath. Our purpose will be to show: (a) the poor attitude of the firm, (b) the inadequacy of the response, and (c) to point up tryable issues that we believe exist on the basis of the clear language of the statute, and apart from the regulations. Our comments are not intended to be all-inclusive.

A. Attitude of the Firm

The poor attitude of Merck regarding the advertising regulations has persisted since their promulgation. This is clearly shown in the following passage from attorney Coburn's letter:

> "Regulations 1.105(a)–(e) to the extent they purport to regulate or specify the contents or form of an advertisement for a prescription drug in other respect [except as provided in the statutory langugae of section 502(n)] are, we submit, unauthorized by law and do not constitute an independent basis for determination of whether or not a violation of Section 502(n) has occurred."

In effect, Merck challenges all of the principles of fair balance provided in the existing regulations, and even challenges the Government's authority in respect to requiring ingredient information in advertisements except as specified in 502(n).

We believe that Merck's challenges present a basis for trying the validity of the promulgated-regulations 1.105(a) through (e). Because revisions of the regulations are in process, however, the time may not be advantageous to the Government to proceed toward a Federal Court determination of the validity of the existing regulations, particularly 1.105(e). We are omitting, for the present, comments in rebuttal of Merck's position in respect to the charges on the promotional copy of the ad. We have to say, however, that the Merck position in respect to each of the charges against the promotional message is, in our view, extremely weak should such issues come to trial. We would anticipate reframing charges in relation to the promotional message within the statutory language.

B. Examples of Issues Available Under Section 502(n) Relating to Omissions

1. The statute provides that the advertisement alleged to misbrand the sample must include a true statement of information in brief summary relating to side effects and contraindications.

(a) A charge was that the ad omitted the warning (side effect) information that "As with other anti-inflammatory agents, INDOCIN may mask the signs and symtoms of peptic ulcer."

The respondent implies evasively and erroneously that the contraindication in the ad applying to "active peptic ulcer" satisfied the test of a true statement in relation to the quoted side effect.

The issue is whether that side effect information is in brief summary or otherwise in the ad. We contend that it is not.

(b) A charge was that the ad omitted the warning (side effect) information that "indomethacin itself may cause peptic ulceration or irritation of the gastrointestinal tract."

The respondent claims that the information "is clearly set forth in the advertisement." The claim is untrue.

The issue is whether any information in the ad meets the tests of a true statement with respect to the quoted side effect. We contend that it does not.

A charge was that the ad omitted the precaution (relative contraindication) that "a possible potentiation of the ulcerogenic effect of these drugs [steroids, salicylates, phenylbutazone] cannot be ruled out at present."

The respondent does not deny the omission but uses somewhat unintelligible language to reconcile the omission by stating that the omission "strengthened the specific warning against *any* use of INDOCIN in the presence of the conditions stated, with or without other agents."

The issue is whether the quoted precaution is omitted from the ad. We contend that it is.

(d) A charge was that the ad omitted side effect information concerning a list of specific side effects which included, among others:

> (1) nausea, anorexia, vomiting, epigastrict distress, abdominal pain, diarrhea, gastritis; and
>
> (2) angioneurotic edema, rashes, acute respiratory distress, purpura, thrombocytopenia.

The respondent does not deny the specific omissions but attempts to reconcile the omissions by stating that the side effects (1) were included under the "general side effect of 'G.I. disturbances'" and that the side effects (2) were included under the "general side effect of 'hypersensitivity reactions.'"

The issue is whether the general headings used by the respondent represent a true statement of information regarding the specifically named side effects.

We contend that the test of a true statement has not been met through use of general headings.

2. A charge was that the ad misbranded the sample under 502(n) because it did not prominently display the name of at least one specific dosage form and quantitative ingredient information in direct conjunction with such display as required by regulation 1.105(d)(2).

The respondent attempts to defend the charge (1) by making a general denial of the validity of the regulation and (2) by implying irrationally that regulation 1.105(d)(2) is dependent on 1.105(d)(1). The fact is that 1.105(d)(2) is an independent regulation, as a careful reading will disclose.

Consistent with not proceeding toward Federal Court determination of the validity of existing advertising regulations now under revision, we do not believe that regulation 1.105(d)(2) is needed as a basis for continuing the essential element of this charge.

Section 502(n)(2) provides the basis for requiring "the formula showing quantitatively each ingredient of such drug to the extent required for labels under section 502(e)."

Possibly due to ignorance, the respondent appears to take comfort in relying on section 502(n)(2) as a basis for omitting quantitative ingredient information from the ad. He even goes so far as to recite the language of 502(e) to require "the label to bear . . . in case it is fabricated from two or more ingredients, the name and quantity of each active ingredient."

The fact is that Indocin Capsules, 25 mg., are fabricated from 2 or more ingredients; this means that the quantity of indomethacin (the active ingredient) in the capsule must be declared on the label and in the advertisement.

The issue here is so clear cut that it needs no further comment.

C. COMMENTS ON CERTAIN FEATURES OF THE RESPONDENTS LETTER OF FEBRUARY 6, 1968

1. The respondent claims that the contraindication that "indomethacin is contraindicated in aspirin-sensitive asthmatics" was included in labeling for the first time in a package circular put into general use on October 31, 1966. It claims, therefore, that it was not possible to make the change in this advertisement on such short notice. In this connection, the respondent states in paragraph 7 on page 13 of its letter, in relation to a separate charge of omitting a large number of specific side effects from the ad, that such side effects were only included in the labeling at the same time as the foregoing contraindication.

The respondent also claims that the period of 90 days (suggested as a guide by Dr. McCleery on January 23, 1968) for conforming promotional labeling and advertising to package labeling had not expired when the ad appeared.

It can be shown that the respondent is in error in respect to the claims regarding the timing involved.

2. Section D of the respondent's letter deals primarily with matters such as meetings between the Agency and Merck management; current more careful handling of clearances within the firm; voluntary destruction of substantial quantities of promotional material, presumably also violative; a prior citation; the fact that a prosecution would be punitive [which is admitted], etc.

We believe that such information as that presented by the respondent to show good behavior would be properly the subject of an inquiry from a probation officer. Such information is often useful in determining the amount of fine, etc. This was the case when Wallace Laboratories was prosecuted in re Pree-MT; in that case Wallace not only had undertaken massive corrective action but also took Pree-MT off the market.

We believe that the prosecution action taken against Wallace should be taken into account in determining whether Merck should be prosecuted in relation to this sample.

R. S. MCCLEERY, M.D.

MARCH 11, 1968.

DIRECTOR, BUREAU OF REGULATORY COMPLIANCE.
DIRECTOR, BUREAU OF MEDICINE.

The Bureau of Medicine recommends that prosecution of the firm be instituted, subject to approval by General Counsel. As you may note from the attached memorandum of March 8, 1968, subject as above, from the Division of Medical

Advertising to the Bureau Director, specific comments are provided in response to the communication from the firm on February 6, 1968. We will be pleased to discuss the matter with you and the General Counsel at any time.

HERBERT L. LEY, Jr., M.D.

Senator NELSON. Dr. Norman Rothermich, who conducted a trial with Indocin, has just returned from Europe. He has requested the opportunity to present a statement to the committee.

We will recess until 1:30.

(Whereupon, at 12:35 p.m., the subcommittee was recessed, to reconvene at 1:30 p.m., on the same day.)

AFTERNOON SESSION

Senator NELSON. Dr. Rothermich, I apologize for being late, but I was tied up and, until this moment, I could not get here.

The committee is pleased to have you appear before us today. We are well aware of your distinguished professional credentials. Did you submit a biographical sketch with your statement?

STATEMENT OF DR. NORMAN O. ROTHERMICH, CLINICAL PROFESSOR OF MEDICINE, OHIO STATE UNIVERSITY; SENIOR PHYSICIAN, COLUMBUS MEDICAL CENTER; MEDICAL DIRECTOR, COLUMBUS MEDICAL CENTER RESEARCH FOUNDATION, COLUMBUS, OHIO

Dr. ROTHERMICH. No; I did not, Senator.

Senator NELSON. Would you wish for the record to simply give your professional credentials and background?

Dr. ROTHERMICH. Either that, or I can save time by sending you it in writing——

Senator NELSON. If you would prefer to do that for purposes of accuracy, we would be glad to print prior to your statement your biographical and professional background.

Dr. ROTHERMICH. I will send you a complete biography.

Senator NELSON. Thank you, Doctor.

(A subsequent biographical sketch was received and follows:)

BIOGRAPHY OF NORMAN O. ROTHERMICH, M.D.

Born: October 9, 1912; St. Louis, Mo.

St. Louis University: B.S. 1934; M.D. 1936 (also special postgraduate student in biochemistry under Dr. E. A. Doisy, 1933–36).

1936 to 1940: Internship at St. Louis City Hospital; residency at Robert Koch Hospital in St. Louis and at Ohio State University and Columbus State Hospital.

1941: Appointed Chief of Arthritis Clinic at Ohio State University Hospital.

1942 to 1946: Military service; Army Medical Corps, Southwest Pacific Theater (special certificate, Army School of Roentgenology).

1946: Certified, American Board of Internal Medicine.

1950: Fellow, American College of Physicians.

1947 to 1959: Founder and Director, Division of Rheumatic Diseases at Ohio State University Colloge of Medicine.

1947: Post graduate study in Rheumatology at The Mayo Clinic.

1948 to 1950: American College of Physicians postgraduate courses in Internal Medicine at the Universities of Michigan, Pennsylvania, Northwestern, Harvard and Duke University.

1941 to Present: Faculty, Ohio State University College of Medicine, Full Professor of Clinical Medicine 1960.

1957: President, Columbus Academy of Medicine.

1955: Founder and Director of The Columbus Medical Center Clinic and Research Foundation.
1952: Founder and Director of the Arthritis Foundation, Central Ohio Chapter.
Author of more than forty publications in endocrinology and rheumatology, complete bibliography upon request.
Member, American Rheumatism Association and six other national medical scientific organizations.

Senator NELSON. If there is any part that you wish to extemporize on or summarize, you may do so. In any event, your full statement will be printed in the record.

Dr. ROTHERMICH. Thank you.

First, Senator Nelson, I would like to express my gratitude for your accommodating me. I know this is at some trouble. I am appreciative of it.

Senator NELSON. We are glad to do so.

Dr. ROTHERMICH. I did not have an opportunity to see the testimony of Dr. O'Brien and Dr. Mainland until, I think, Monday night. So this has been prepared since that time. I have reviewed it once and corrected it, but it is not as detailed as I would like it to be. However, I am satisfied that it carries my position and I think it will help to clarify it and I would like to read it.

Senator NELSON. Because you wrote it so hurriedly, if there is something you recollect subsequently that you would like to add to your statement, send it to the committee and we will include it with your statement.[1]

Dr. ROTHERMICH. Thank you, sir.

I would like to say at the start that in requesting the privilege of making this statement for the hearing records, it is not my wish to subject you to a medical backyard brawl. I would like to make clear that I carry no ill will nor any personal animosity toward Dr. Mainland or Dr. O'Brien, who appeared before you last week. My work on indomethacin needs no defense or apology, and I assume that my reports in the medical literature are not on trial. I do believe that Dr. O'Brien made some unwarranted statements which, though assuredly unintentional, cast reflection on my professional integrity and competency. I should like to reply to those statements and perhaps offer additional comments which may help to clarify for you some points, both in my reports and elsewhere, which apparently have not been entirely understood.

Without intending any impertinence, I feel compelled also to offer a mild demurrer that the committee did not find it appropriate or desirable to invite me to appear before it, despite the acknowledged major influence of my reports in the Journal of the American Medical Association.

I am not a statistician and know little of the ways of such, but, as I will try to illustrate later on, it would seem that, contrary to a rather generally held impression, statistics is not an exact science. Furthermore, I am not a laboratory or test tube doctor, although I have a degree of experience with laboratory and animal experimentation. I am generally regarded, and consider myself to be, a clinical rheumatologist, engaged primarily in the medical examination and treatment of people. I am a full professor of clinical medicine at Ohio State

[1] See supplemental statement beginning at p. 3276, infra.

University College of Medicine on a part-time basis, and for this I receive a small annual salary. The major part of my time is engaged in private medical practice in a group association with other internists. All income derived from the application of my medical knowledge is received by me as a percentage from my share of the partnership receipts.

A large proportion of my private patients suffer from various rheumatic diseases, and I am particularly interested in the problem of rheumatoid arthritis, which in my opinion is one of the most devastating, persistent, and painful diseases which affect mankind. Rheumatoid arthritis is a major producer of disability, striking characteristically in the most productive years. The degree of this disability has not been entirely recognized by business and industry, for reasons not clear to me. Rheumatoid arthritis is not one of the so-called glamour diseases and has not received the attention it deserves from the public nor, I am afraid, from some segments of the medical profession, and in certain aspects it might be said to have an "untouchable" status. Patients with rheumatoid arthritis seem to sense this general attitude and feel almost apologetic or embarrassed at having their disease. The disability aspect is all too apparent, and the patient makes every effort to adjust to and compensate for disability. However, the constant and relentless nature of the pain and suffering are little appreciated and not well understood.

Now, I would like the opportunity to reply to certain of Dr. O'Brien's statements which I thought were unwarranted. On page 4528, he refers to my publication in the Journal of the American Medical Association, volume 195, page 1102, May 1966 (although he fails to refer to the equally important paper published 1 month prior in the Journal of the American Medical Association, February 14, 1966, page 531). He states that the study is highly biased, but I must insist it was done without bias and with complete objectivity. He makes objection to my statement "placebo was introduced whenever the patient seemed to be established and well controlled on indomethacin therapy."

Mr. GORDON. Doctor, may I interrupt you for a moment?

My feeling when I heard Dr. O'Brien testify was that when he used the word "bias," he used the word "bias" from a statistical point of view. I do not know, but it certainly did not seem to me that he used it in an ad hominem sense.

Senator NELSON. I do believe that he did not intend to say that you, yourself, were biased. I think that is correct.

Dr. ROTHERMICH. I think he should have made that clear in his statement. He should have said it was statistically biased, because he refers later to a statistical bias, so I assume this statement that "it was biased" meant that it was personally biased.

Senator NELSON. I do not have the understanding that he intended that, and I do not think he would intend to imply that you were personally biased. I think he was talking about statistics and I think that you may have interpreted it in a way he did not intend.

Dr. ROTHERMICH. Basing this exception on the fact that the disease is "cyclical," he introduces a non sequitur in his reasoning when he states that "since the disease is cyclical, introducing a placebo when a patient was doing well would probably be followed by a relapse."

There is just no connection between those two phrases. If the disease is cyclical, it would be difficult if not impossible to have a patient established and well controlled on indomethacin or any other therapy.

On the contrary, if any disease is under good control by an effective therapy, the introduction of a placebo would probably result in a relapse. Parallel examples of this could be demonstrated by the introduction of placebo in patients with congestive heart failure who are well controlled on digitalis therapy, patients with diabetes who are well controlled on insulin therapy, and patients with thyroid deficiency who are well controlled on thyroid therapy. Clinicians know that in such instances severe relapse would consistently follow each placebo trial. Applying the term "cyclical" to rheumatoid arthritis would suggest a lack of actual clinical experience with the disease. It is true that the disease is characterized in some degree by exacerbations and remissions, but these are highly capricious, both in onset and duration, and do not have any rhythmic circular aspects as suggested by the word "cyclical." A patient with rheumatoid arthritis may have an exacerbation with continuing activity of the disease for a year or two or more, and then he may suddenly develop a remission, that is, disease inactivity, for a variable period lasting a month, several months, or in a rare case, permanently. Exacerbations are much more protracted and tenacious, and remissions are usually brief and seldom total. Furthermore, even if the disease were cyclical, the introduction of a placebo would certainly not "probably be followed by a relapse." The introduction of a placebo relapse when the disease was apparently well controlled by a certain drug is evidence itself that the drug was actually controlling the disease, and this is reinforced when relapse is precipitated on more than one occasion by the repeated introduction of placebo.

Mr. GORDON. Doctor, I have here an article from Clinical Pharmacology and Therapeutics, by Drs. Albert M. Katz, Carl M. Pearson, and Joseph N. Kennedy.[1] I should like to read something from it:

> All eight subjects who received the drug (with benefit) followed by placebo experienced severe exacerbations within 24 hours of the change. One patient had a severe exacerbation lasting four days, after he was symptomatically the same as when taking indomethacin. Once again, he was given the drug, but derived no further benefit. The experience in this case cast some doubt upon the validity of accepting an exacerbation which occurs after a drug has been discontinued or replaced by a placebo as proof of the drug's efficacy.

Would you comment on that?

Dr. ROTHERMICH. I would agree that one case does not prove anything.

Mr. GORDON. He talks about eight subjects.

Dr. ROTHERMICH. He only mentions the one case, though, as an exception to that.

Mr. GORDON. Yes, and his conclusion is that the experience in this case casts some doubt upon the validity of accepting an exacerbation which occurs after a drug has been discontinued or replaced by a placebo as proof of the drug's efficacy.

Dr. ROTHERMICH. Do you not yourself think that one case out of eight is rather a weak statement?

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[1] See p. 3277, infra.

Mr. GORDON. I am not a doctor. I am just giving you the conclusions reached by a team of doctors.

Dr. ROTHERMICH. I am asking you as a layman, not a doctor. One case in eight. Do you think that proves anything at all, really?

Mr. GORDON. You do not agree with these people?

Dr. ROTHERMICH. I think it has no significance at all.

Mr. GORDON. There is no significance?

Dr. ROTHERMICH. One out of eight, no.

On page 4528, Dr. O'Brien states that "a study of this type was designed in such a way that the bias is in favor of the drug." This is a highly arbitrary statement, but Dr. O'Brien proceeds to use this as a false premise for further condemning my report. As a matter of fact, the study was not designed in such a way that the bias was in favor of the drug, and I have done other studies in exactly the same manner before and since Indocin, and my conclusions were discouraging and unfavorable to the drug under study.

Mr. GORDON. Have these been published?

Dr. ROTHERMICH. No, sir.

Mr. GORDON. Have these been given to the FDA?

Dr. ROTHERMICH. Yes, sir.

Mr. GORDON. Yesterday?

Dr. ROTHERMICH. No, I said yes, sir.

Mr. GORDON. Could you supply them to us for the record?

Dr. ROTHERMICH. I think the FDA has all the material I have given them.

Mr. GORDON. I have looked through the files and I have not seen the studies.

Dr. ROTHERMICH. This is not related to Indocin. This is other drugs.

Mr. GORDON. Oh, you said before and since——

Dr. ROTHERMICH. Yes, I have done this same kind of study on other drugs and they did not come out at all.

Mr. GORDON. I see.

Dr. ROTHERMICH. On page 4529, Dr. O'Brien states that my study, as submitted to the FDA, differs drastically from the manuscript that was published in the Journal of the American Medical Association. This would imply that something about this condemns my report. I would like to say that much of this was due to the fact that the editor considered my manuscript entirely too long and felt that he could not devote that much space to it. We had considerable correspondence, between the editor and myself, but I agreed only to delete the word "blind" because of differences with the statistician-reviewer of the journal. It was the opinion of the latter that the blind and double-blind trial could not be done with Indocin, only because of my thoroughly honest statement that "occasionally patients would suspect the placebo substitution by a change in side effects;" and, in reference to and in deference to the statistician-reviewer, I made the further statement in the journal that "for this reason, from the statistician's viewpoint, the placebo trials in this report (and probably in most clinical drug reports) cannot be considered as true 'blind studies'." My article goes on further to elucidate this point, and I should like to quote the sentences which follow immediately after that:

> Usually there was enough delay in this awareness (of a change in side effects) to permit the therapeutic assessment. Furthermore, the appearances of side effects are often capricious and inconsistent, thus further limiting the patient's ability to detect placebo.

I went on to state:

> The placebo substitutions were made in 86 of the patients, and in 70 of these there was a decisive clinical relapse on placebo. This clinical relapse was verified on repeated placebo trials in 55 patients.

In my opinion, these are well controlled observations, despite the fact that some statisticians would deny the validity of "single-blind" trials.

I believe it should be emphasized right at this point that, if the statistician reviewing my manuscript for the Journal of the American Medical Association was of the opinion that the appearance of side effects from indomethacin invalidated any single- or double-blind trials, logic and consistency would demand that he deny the validity of the double-blind trials carried out by Dr. Mainland and his group, and other double-blind trials. Apparently, what is one statistician's meat is another statistician's poison. There is not consistency.

When Dr. O'Brien implied that it was demeaning of me and my report that it was published in "modified form," he is not being entirely fair to this committee. The fact is that medical journal editors are generally assuming more and more of an authoritarian position and demanding modification of practically every article or report submitted to them. These modifications are based on recommendations from editorial boards and reviewers who no doubt are themselves quite human and fallible. And I might add at this point that Dr. O'Brien admitted in his own testimony last week that the article he submitted to Clinical Pharmacology and Therapeutics, to Dr. Modell and three reviewers, was found to contain errors. It was sent back to him, and he had to revise and modify those, so his report was also published in a modified form.

Because of the increasing influence of the statistician in medical reporting, the double-blind trial has been given a position of infallibility which is not entirely justified. For example, does Dr. O'Brien realize that patients will sometimes break open a capsule and taste the drugs to see if there is a difference? If they are taking a capsule one week and getting another one next week and getting a different effect, they may break open the capsule to see if there is a difference. These are difficult things to control when you are dealing with human beings. When you are dealing with animals, it is different. Even though the capsules may look identical, does he realize that some patients will reduce the dose or discontinue the drug if it is giving adverse reactions, but without informing the investigator? I think this is true especially if the work is being done in a large impersonal institutional clinic rather than the atmosphere of close rapport of the personal patient-physician relationship.

This frailty of the double-blind trial is further illustrated in the report of Dr. Mainland for the Cooperating Clinics Committee of the American Rheumatism Association. I should like to add here for the benefit of the committee that this impressive and high-sounding title gives this committee and its work an aura of authority and Olympian omniscience which its own members would be the first to deny categorically and emphatically.

In the first place, with reference to Dr. Mainland's work, it is an extremely attractive hypothesis that a lumping together of observations by a number of different clinics would, because of increasing size

of the sample, increase the statistical validity. The weakness of this is the known remarkable variation between one observer and another. We in our own group, and there are three of us engaged in rheumatology in our group—have tested this repeatedly; and although we have tried on many occasions to standardize our observations and have seen patients jointly and in conference, we still find a distressing degree of variation between the three of us who work so closely and harmoniously as a unit. To have 11 different observers from 11 widely scattered clinics making observations which are then stated to be of an identical character seems hazardous at least. There were a number of exclusions in the ARA–CCC study which would certainly weaken the trial's validity.

For example, the patients were to be "out-patients or domiciliary hospital patients," but it does not say how much of each sample comprised the total. Certainly a rheumatoid arthritic in a domiciliary hospital environment is much more likely to have a quiescent disease than one in an outpatient environment. The exclusion of all patients who have had antirheumatic therapy would effectively eliminate all cases of even moderate severity. So you would have to assume that most of the cases in that study were cases of mild degree.

Senator NELSON. I have a question in reference to your sentence that a rheumatoid arthritic in a domiciliary hospital environment is much more likely to have a quiescent disease than one in an outpatient environment. In setting up a double-blind test, or any kind of study, if those making the study were comparing the person in a domiciliary facility versus one who is outside of it, it would be a fault in the study immediately, would it not?

Dr. ROTHERMICH. Oh, yes.

Senator NELSON. In other words, do you not, in setting up studies, compare age groups and try to get them as comparable as possible?

Dr. ROTHERMICH. Yes, and this factor, Senator Nelson, of putting an arthritic at rest, not necessarily bed rest, but outside of an environment that is distressing to him, putting him away in a domiciliary hospital environment, you see, is much more likely to allow his disease to become quiescent. So they should have said "we have x number of patients who are hospital domiciliary type and we have x number of patients who are outpatients," and given the result of those studies in the given categories.

Senator NELSON. In other words, you would compare domiciliary patients versus other domiciliary patients and the outpatients versus other outpatients?

Dr. ROTHERMICH. Yes. I would like to add the point, too, that this study was being done by 11 different centers, and they have, I think, 110 total patients. I think half or more of the centers had less than 10 patients in their study group, and some of them as few as four patients. Now, Dr. O'Brien made the statement before this committee at another point that some of the reports in the literature were only of 10 patients or so and any work on such a small number—I cannot think of his exact words, but the substance of it was that it was meaningless, or had no validity.

Now, he was referring to other types of work. But I would point out to you, Senator Nelson, that the components of this combined study, you see, had less than 10 patients in many of their centers.

Now, I would like to emphasize that not only do they have less than 10 in many of these, but their duration of therapy was only for a few weeks—3 months, which in my opinion is much too short a time to evaluate any drug. This is what I will try to emphasize later on.

They allowed an unlimited consumption of aspirin in both the placebo and the treated patient. So they have no idea of how many aspirin tablets were taken by either group. Now, it is entirely conceivable that a patient may have been on the active drug and taking two aspirin tablets a day, or four aspirin tablets a day, and when placed on placebo, because of an increase of symptoms, he may have increased his aspirin consumption to 12 or 16 a day, but they do not know this.

Senator NELSON. There is no way to be sure about it, is what you are saying?

Dr. ROTHERMICH. They kept no records of it.

Senator NELSON. Oh, I see.

Dr. ROTHERMICH. I would like to emphasize, too, Senator Nelson, that I am not saying that this is not a worthwhile trial. I do not mean that at all. I think this kind of trial should be done. But I think it is wrong to assume that this particular type of study is the only study that should be done, and I think it is wrong to assume that this type of study has no flaws. It has many flaws, because we are dealing with human beings. When you can take mice and rats and put them in cages and keep them under fixed control, then you can have the ideal, well controlled study. But when you are dealing with human beings, this is something else again.

Senator NELSON. This has always been my view. I have always said politics would be a wonderful thing if you did not have to deal with human beings.

Dr. ROTHERMICH. Yes.

I did think it was rather significant that Dr. Mainland himself testified that if he were treating rheumatoid arthritis—although he disclaimed that he was treating any patients—he would select indomethacin for a cautious trial in those patients who have failed to respond to basic therapy, including salicylates, despite the fact that his report indicated negative results.

In this context, for the information of this committee, I would like to quote from my article in the JAMA in the section under comments:

> However, it should not be inferred that indomethacin 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, et cetera, et cetera.

It would seem that Dr. Mainland and I have identical views on the clinical usefulness of indomethacin.

In my early studies, I was repeatedly admonished by my preceptors that it was unhealthy for medicine generally and unwise for the investigator to rush into publication with short-term observations. For this reason, I went to great pains to delay my report in the Journal of the American Medical Association until I had accumulated more than three and one-half years of intensive experience with this drug. I subjected the drug to the most thorough and penetrating clinical scrutiny.

Every possible means was taken to determine the true action of this drug and to avoid bias on the part of myself or the patient.

Dr. O'Brien suggests that my patients were badly neglected and that I had lost interest in them until I suddenly presented them with a wonder drug. All of my patients with rheumatoid arthritis continually receive the most personalized attention from me, regardless of what drugs or therapies I have been or am employing. No change whatsoever was made in our approach or routine management. As I have previously stated, most of these patients have at various times been subjected to one or another type of clinical experimentation. In accordance with my own scruples and ethics, and with the law, I did explain to each patient that he was undertaking a new experiment, and often this was done in the presence of a spouse or a near relative, and the patient was then required to sign an appropriate release form.

Dr. O'Brien would lead you to think that some poor miserable arthritic had staggered into my examining room, discouraged and depressed by my indifference to his disease activity, and that I suddenly burst into the examining room, wildly elated and exclaiming to the patient that I had found a wonder drug and that the patient was about to be miraculously cured. Such an ugly implication is dangerous at worst and naive at best.

The fact is that our whole setup was geared to achieve the greatest objectivity in our evaluation of this drug. Of course, as stated previously, I informed the patient fully that an experimental drug trial was to be initiated, but that no patient should feel in any way coerced into joining in this trial, because I think that a patient must give informed consent. I think if there was any bias in our study, it was as a result of this informed consent of the patient, which tended to eliminate the timid and the weak of heart, but this is now required by law and a necessary part of any drug trial.

Under such circumstances, the subjective response of the patient, in my opinion, is about equally divided between some 20 percent on the one hand who want very much to have a good result and therefore get an unrealistic benefit from the drug, and about 20 percent on the other end of the spectrum who, because of their great fear of the nature of experimentation, would like to have the drug discontinued as soon as possible and tend to report minor or imagined ill-effects, or even tend to minimize possible good effects. Only long-term trial with these patients can effectively bring their results into true perspective. Achieving this true perspective can be greatly aided and solidified by the liberal use of placebos, both single-blind and double-blind, as well as by the gradual but systematic reduction or withdrawal of other effective therapies, most notably the corticosteroids, or cortisone.

Likewise, evaluation of side effects of a drug can only be determined in patients on the basis of long-term observation. These side effects must be carefully appraised, keeping in mind at all times the safety of the patient, but weighing and balancing out as far as possible the need for truth and knowledge about the nature of the drug under investigation. In my opinion, it is wrong to suddenly thrust at a patient a double-blind study without some prior preliminary trial of the drug. Such an early double-blind trial is bound to have the built-in problem of the patient's first experiences with the good and

bad effects of a drug, and these will undoubtedly color his own responses to the investigator's questionnaire. In my opinion, such a study is far more valuable if the patient is allowed to be on the drug for a sufficient time to familiarize himself with it and to become casual and unconcerned, and then the application of either single-blind or double-blind studies will have much greater validity.

Finally, I would like to add here—and I do not want Dr. O'Brien to take any offense at this statement, but I must say it—that many rheumatologists would disagree vigorously with his seemingly cavalier statement that no therapy influences the course of the disease. Furthermore, such a statement could have an extremely demoralizing effect on hundreds of thousands of rheumatoid arthritics throughout this country and the world.

The evaluation of rheumatoid arthritis is extremely difficult in all its aspects. Even the diagnosis is often a tenuous one. Our methods of measuring good effects and bad effects leaves much to be desired, and I am sure Dr. Mainland would be the first to agree; in fact, I think he has already reported elsewhere this general opinion about evaluating therapy in rheumatoid arthritis. Parenthetically, I can say that we sat on a panel discussion with several noted rheumatologists in Japan—Dr. Joseph Hollander from Philadelphia and Dr. William Kuzell from San Francisco. This was organized by the Japanese as a panel for evaluating therapy in rheumatoid arthritis. Dr. Kuzell was asked his opinion, and he said the best way to measure it was to say to the patient: How do you feel?

Dr. Hollander went to the trouble of describing a palpometer, which is a mechanical device for squeezing on a patient's joint to see at what point it would cause pain. Now, one of the criteria that the Mainland group used was tenderness of a joint. Now, this is tenderness in San Francisco and in New York and in Miami and so on, and each examiner is squeezing that joint. You cannot make me believe that the one in Miami knows how hard the one in New York is squeezing a joint, too, so that there can be real objective comparison of tenderness.

If Dr. Hollander feels the need to develop a palpometer, I think you can readily appreciate that determining with any exactitude the tenderness of a joint is a very difficult thing.

We have great difficulty in knowing truly how much, if any, influence we have produced on any given disease, and this is about equally true of rheumatoid arthritis, or perhaps a little more so. One could probably say that insulin has no influence on the basic course of diabetes, and there would be a certain amount of truth in this. But no one would say, do not give the diabetic insulin.

How can we say that a patient who has active inflammatory disease in his joints has not had his basic disease altered when the inflammation has been reduced or eliminated by certain types of therapy?

Dr. O'Brien even referred to cortisone as having a powerful antiarthritis effect. Now, "antiarthritis" means that it acts against inflammation within the joint. If he thinks that cortisone can abolish the inflammation in the joint, he must concede that this has to have some basic influence on the course of the disease.

Even if the eventual outcome of the disease has not been influenced, we still cannot say that it has not been retarded, or its harmful effects minimized or reduced. I think that today you do not see the extremely

severe, advanced crippling of the arthritic that we used to see 20 years ago, I think this is eloquent testimony itself that our therapies are effective in at least partially influencing the course of the disease. We have patients under our care whose disease we regard as static, but whenever we attempt to reduce or withdraw certain therapies, the disease process flares up and accelerates intensively. No single therapy benefits every patient with rheumatoid arthritis, not even aspirin, and, yes, not even corticosteroids. Certainly it has never been suggested, hinted, or implied that indomethacin benefits every case of rheumatoid arthritis.

Senator NELSON. Are there any statistics as to longevity of rheumatoid arthritics now vis-a-vis 20 years ago?

Dr. ROTHERMICH. I do not believe so. I think that this is a very difficult thing, because of its long term nature.

Senator NELSON. No statistics?

Dr. ROTHERMICH. Yes, it is very difficult, because patients with rheumatoid arthritis do tend to live an awfully long time; in fact, you might say in some cases too long because of their prolonged suffering. But—to compare longevity—I do not think this has been done.

Finally, the members of this subcommittee should know that eminent, highly competent, and highly respected rheumatologists from all over the world have reported favorably on their results with indomethacin in rheumatoid arthritis and have indicated the important adjunctive place of this drug in its overall management. Numerous congresses on rheumatic diseases have been conducted in various parts of the world, and these eminent rheumatologists (who are held in highest esteem and often closely affiliated with the American Rheumatism Association) in paper after paper have reported favorable results in what they consider to be controlled trials of the drug for extended periods of time.

Most rheumatologists would be dismayed (and large numbers of patients with rheumatoid arthritis would be bitterly disappointed) if they were to be deprived of the clinical and therapeutic benefits of indomethacin on the basis of a few brief-trial negative reports.

I wish to thank you, Senator Nelson, and all of the members of the subcommittee for the opportunity of presenting this statement and having it included in the hearing records.

If I can be of any further assistance or service to the subcommittee, I shall be glad to cooperate as fully as possible.

Senator NELSON. Doctor, we were very pleased to have you come to present your informed viewpoint based upon your long experience.

Mr. GORDON. Dr. Rothermich, I have several letters here written by you to the Merck Co. which were secured from the files of the Food and Drug Administration. I would like to read one of them. This is from you to Merck Co. It says:

> Few improvements were noted in the peripheral arthritis group at dosage levels of 150 mg daily. Most of the peripheral arthritics are now being carried on a daily dose of 300 mg daily, but a significant number were benefited to a striking degree to 200 mg daily. 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, feeling of detachment from reality. The higher the dose, the more severe the symptoms.

Here you say that most of your patients—these are your words—most—are being carried on dosage of 300 mg. On the other hand, the upper limit of approved dosage is 200 mg. Now, it seems to me that no doctor could repeat your experiences.

In other words, what I am questioning is can your studies be used as proof of efficacy for this drug?

Dr. ROTHERMICH. What is the date of that letter, sir?

Mr. GORDON. Your letter is dated June 12, 1963.

Dr. ROTHERMICH. This is the point I have made in my report to the JAMA. On long-term trials, we came to realize that patients experienced cerebral side effects worst when they suddenly had the drug thrust on them in high dosage, and we realized that there were certain times of day when they were more likely to have cerebral side effects than others. We also came to realize that if we began at a very low dose and built it up, they were far less likely to have any significant cerebral side effects.

Mr. GORDON. But you still cannot go over 200 mg. now. That is the approved dosage. You cannot go above that, but you went beyond it in your trial. You went up to 300 mg. and 400 mg., too.

My point is this: The studies that you made cannot be used as proof of efficacy of that drug, because nobody can duplicate that dosage today.

Dr. ROTHERMICH. No, I said that in my report to the Journal of the American Medical Association, too.

Mr. GORDON. Yes, I know that.

Dr. ROTHERMICH. That the dosage I used should not be used clinically and therefore physicians could not expect as high a degree of improvement as I had reported—this is stated in that article.

Mr. GORDON. I have it right here.

Dr. ROTHERMICH. You will see it right in the first part, if the synopsis, right at the bottom, that they should not use this high a dosage, that if they used it in smaller dosage and gradually increased it to tolerance, they would then begin to get effects which were not discernible at the early stages. This was proven repeatedly to us by patients, both on single-blind and on what we call double-blind study, although the statistician for the JAMA refused to allow us to use that term. We felt it was inadequate. But we did feel, as we developed greater experience with the drug, we came to realize that there was a significant number of patients who were getting benefit from indomethacin.

Now, what we were trying to show in our studies, and this was for the benefit of the profession, we felt obligated to report to them as fully as possible. We were trying to show what the maximum dosages were and what would happen if those maximum dosages were exceeded. We put six patients in the hospital, at the university, and subjected them to enormous single-dose trials, as much as 350 milligrams in one dose in the morning, and we made intensive studies on them throughout the day, using all kinds of parameters of study, because we felt we had to know what happened to a human with increasing dosage and where therapy was jeopardized by toxic effects.

Now, we were impressed early in our studies by the cerebral side effects, and I emphasized this: that since then we have learned that we can mitigate or minimize by certain techniques of therapy, by

always giving the drug on a full stomach or with milk at bedtime, as we had recommended in the JAMA report; that we avoid a morning dose; and that we avoid having the patient take it in association with caffeine ingestion, because we feel this aggravates the tendency for the cerebral side effects.

We also did learn that there is a certain idiosyncratic reaction, that some patients are exquisitely sensitive to this. I had one patient develop this in very bad form on 25 mg., whereas many patients can take much more and get no side effects.

Did I answer your question?

Mr. GORDON. Not exactly.

Dr. ROTHERMICH. Well, what do you want me to say?

Mr. GORDON. You are aware that 200 mg. is the maximum dosage approved by the FDA? That we can agree on.

Dr. ROTHERMICH. Yes.

Mr. GORDON. You also stated that most of your patients were on 300 mg., which was above the Food and Drug Administration limit, and that it cannot be duplicated today.

Then I asked you whether this could be used as proof of efficacy, given the present limitation by the Food and Drug Administration on dosage. I do not think I got a clear answer from you.

Dr. ROTHERMICH. I thought I answered quite clearly. I said that we got a remarkably high percentage of good and excellent results, but that in many of these cases the dose was at levels in excess of what should be used in general practice, and that physicians could not expect a comparable high percentage of good effects because they would necessarily have to use smaller doses.

Mr. GORDON. Let me read another excerpt from one of your letters. This is a letter from you to Merck & Co., dated October 12, 1963, in which you state:

> Indocin has an excellent beneficial effect in some cases of peripheral rheumatoid arthritis but only a good effect in a large percentage and there is a complete failure or ineffectiveness in a distressingly high percentage of such cases.

Does that add to what you said before?

Dr. ROTHERMICH. No, I think it simply amplifies it. I think, yes, I would say today that indomethacin will prove of significant clinical—because of the statistician, I have to avoid the word "significant"—that it will prove to be of appreciable clinical benefit, worthwhile for the physician to give his patient, in something over 50 percent of the patients—about 50 or 55 to 60 percent, in that area, on the limited dosages we have.

Mr. GORDON. This is Indocin as against nothing. How about Indocin as against aspirin?

Dr. ROTHERMICH. Now, I think this brings out a point that I appreciate. Many physicians around the land have a sort of all-or-none attitude toward treatment of rheumatoid arthritis. They give the patient this drug and if it is not beneficial, they stop it, and then they give him that drug. We do not believe in this, and I have said in other papers that combinations of therapy are vastly important in rheumatoid arthritis—that aspirin will contribute, let us say, 10- to 15-percent benefit; Indocin may add another 20-percent benefit; small doses of a corticosteroid may add another 30-percent benefit. Even giving paren-

teral injections of gold may add another. So that the cumulative benefit from small amounts of all of these drugs will give the patient a 70- or 80-percent total benefit.

Do you see? Did I answer that?

Mr. GORDON. Yes.

Mr. Chairman, I ask that this correspondence as well as Part 2 of Dr. Rothermich's article which appeared in the March 28, 1966 issue of JAMA be placed in the record right after the testimony of Dr. Rothermich. The chart appearing on page 126 of the 1966 JAMA article indicates that most of the patients were on daily doses well above the permitted level.[1]

Dr. ROTHERMICH. Senator Nelson, I am not objecting that it be put in there, but I believe that the date should certainly be emphasized; 1963 was a long time ago.

Senator NELSON. I don't know if it is particularly relevant at this stage, because that was before we had much clinical experience with it, right?

Dr. ROTHERMICH. Right.

Mr. GROSSMAN. Doctor, I would like to ask you one question. On page 6 of your testimony, concerning your report in modified form, you say, in the first full paragraph:

> The fact is that Medical Journal editors are generally assuming more and more of an authoritarian position and demanding modification of practically every article or report submitted to them. These modifications are based on recommendations from editorial boards and reviewers who, no doubt, are themselves quite human and fallible.

How do you see your role? You talked before about doing things for the benefit of the profession. What do you see as your role in seeing to it that, for example, reports are not published in modified form? If they say they are only going to publish it in a modified form, why would you not say, then, do not publish it if you are going to leave out significant aspects of it? Do you not have some responsibility there?

Dr. ROTHERMICH. This is a question that I find difficult to answer. I cannot quite agree with the increasing authoritarian position assumed by medical journal editors, and I find that at times they are extremely arbitrary. But, you see, they have total power of veto; and if you want to get some information to the profession, you may find it necessary to modify to some extent.

Now, if you feel it is going to be modified substantially, then I think you are honorbound not to agree to its publication, But when I agreed to the publication by striking out the word "blind," I did go to great lengths to explain in the article for the benefit of the statistician-reviewer, that I was doing this, so I felt that my position was tenable.

Does that answer your question?

Mr. GROSSMAN. I think so. As far as you are concerned, there is no control over the various journals to see that this is not done, except for the particular physician who writes the article. Otherwise, nobody checks to see what he leaves out or what he does not?

Dr. ROTHERMICH. No, I think when the article is submitted to the medical journal, the editor submits it to several different reviewers. These reviewers may be all academicians, for example, who are not patient oriented and know little or nothing about the practice of

[1] See information beginning at p. 3282, infra.

medicine. They may be laboratory-oriented physicians or they may be statisticians.

I once submitted to the editor of Arthritis and Rheumatism an article dealing with my extensive study of the incidence and prevalence of rheumatoid arthritis in criminal and insane populations. We examined 20,000 insane and 4,400 criminals in the Ohio penitentiary to determine if they had rheumatoid arthritis. I submitted this and was told that this was referred to some prison psychiatrist, and he took exception to certain parts of it and wanted to have these deleted. I refused, and the article was not published.

The editor subsequently apologized to me and said that he was bound to follow the reports of his reviewers and his editorial board. He subsequently agreed that he would publish it as a brief report without any editorial changing of it. I had to condense it, then, so that it would fit in length with the qualifications of "brief reports."

Mr. GROSSMAN. My point is only this: It seems there should be two responsibilities. One rests with the individual author of the piece, to make sure that his piece is honorable, that it goes to the points, and does not leave anything out; and secondly, that these medical journal editors, whoever they are—I happen to know that we are giving them, if they are nonprofit organizations certain tax advantages and other advantages—these editors should at least own up to these things and make sure we are getting the full story.

Dr. ROTHERMICH. I am sure that these medical journal editors are highly conscientious men, and they strongly believe, some of them, for example, in the infallability of the double-blind study, which I have today tried to show you is not infallible.

Mr. GROSSMAN. Then we are wholly dependent on the individual author's integrity. It comes to a point where he says, I will not let you print my material.

Dr. ROTHERMICH. Yes. Then he might just as well go hide in a closet.

Mr. GROSSMAN. He may have to.

Dr. ROTHERMICH. You see, this is the problem now.

Mr. GROSSMAN. Thank you.

Senator NELSON. Thank you, Dr. Rothermich, for coming in today. We appreciate having you here.

Dr. ROTHERMICH. Thank you.

(A supplemental statement was subsequently submitted by Dr. Rothermich and follows:)

SUPPLEMENT TO STATEMENT OF NORMAN O. ROTHERMICH, M.D.

Finally, I should leave with the committe a clear-cut, concise statement of my present views and attitudes regarding indomethacin, and to emphasize the objectivity of this (as not something suddenly thought up for the benefit of this committee), I will simply quote from the invitational lecture which I gave before 1,200 Yugoslavian doctors at their Symposium on Rheumatic Diseases in Ljubljana, Yugoslavia on Friday, April 26, 1968.

"*Conclusions.*—After six and one-half years of clinical experiences, I continue to regard indomethacin as a valuable adjunct to the treatment of rheumatoid arthritis. It may be considered as a treatment of choice in ankylosing spondylitis, chronic gouty polyarthritis and psoriatic arthritis and may be beneficial in some other miscellaneous rheumatic diseases, such as osteoarthritis (especially of the hip) and in some cases of fibrositis. Cerebral and gastric side effects are certainly not uncommon, but with prophylactic attention to dosage and method of administration and with reasonable vigilance on the part of both the physician

and patient, these should not prove harmful or a deterrent to clinical trial with the drug. As with all drugs, certain peculiar idiosyncratic effects may be expected, but only rarely. No one should make the mistake of thinking that indomethacin is the final word or the cureall for rheumatoid arthritis, but to many of these unfortunate patients it is a godsend and the physician should be prepared to offer such patients this possible benefit. At the same time, he should certainly not ignore the basic fundamental approach to the treatment of rheumatoid arthritis with increased rest, physical therapy, aspirin or other salicylates and attention to any other diseases and malfunctions in the body which may be contributing to or worsening the arthritis."

Lastly, I should also offer to Senator Nelson and the subcommittee my own recommendations regarding the development of a new drug in the field of rheumatic diseases, as follows:

1. Thorough and intensive basic pharmacologic studies in animals and preliminary trials in paid human volunteers.

2. Cautious initiation of therapeutic trials in patients by one or a few experienced clinical rheumatologists, beginning with very low doses and gradually increasing to therapeutic levels.

3. After achieving a satisfactory baseline, the rheumatologist should then introduce single-blind trials with placebos and also initiate attempts at reducing other therapies or eliminate them entirely, if possible.

4. If the drug seems promising from these preliminary investigations (which should last from six months to a year), then controlled double-blind cross-over trials should be initiated by those already studying the drug and also by other qualified groups who may be interested.

5. If these studies continue to indicate promise of therapeutic effectiveness of the drug, then it should be given to a large number of rheumatologists for controlled therapeutic trials over a prolonged period. Again at least six months to a year.

6. If at the end of these studies the drug shows continued therapeutic effectiveness and the side-effects can be considered reasonably acceptable and not unduly hazardous to the patient, the drug can then be released for sale and general prescription by the medical profession.

It is my opinion that the public is well protected by the surveillance presently exercised by the Federal Food and Drug Administration in the development of clinical drug trials. It is not within my province to make any comment regarding drug advertising.

(The supplemental information submitted by Mr. Gordon follows:)

[From Clinical Pharmacology and Therapeutics, vol. 6, No. 1, June 5, 1964, pp. 25–30]

A CLINICAL TRIAL OF INDOMETHACIN IN RHEUMATOID ARTHRITIS*

(Indomethacin, a new nonsteroidal compound, was tested as an antirheumatic drug in 97 patients. Beneficial effects were recorded as excellent in 6, good in 23, and fair in 12. The drug was discontinued in 60 patients, and 6 others were lost to follow-up. The most common reason for discontinuation of the drug was gastrointestinal effects.[1] Peptic ulcer developed in 6 patients.)

(By Albert M. Katz, M.D., Carl M. Pearson, M.D., and Joseph M. Kennedy, M.D., Los Angeles, Calif., Division of Rheumatology, Department of Medicine, U.C.L.A. School of the Health Sciences, and the Wadsworth Hospital, Veterans' Administration Center.)

Indomethacin (Indocin) is a nonsteroidal compound, 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid, which possesses significant antipyretic properties and analgesic effects in animals.[11] Toxicologic studies in animals showed effects which were similar to those demonstrated by many other anti-inflammatory agents. These included fluid retention, gastric irritation, and ulcerative lesions of the gastrointestinal tract.[3 5 10]

Since indomethacin is active when given orally, and because it possessed certain potentially advantageous clinical properties, its value as an antirheumatic agent was tested in man.

*Received for publication, June 5, 1964.

NOTE.—Numbered footnotes at end of article, p. 3282.

TESTING PROCEDURES

The majority of patients included in this series had one of the rheumatic diseases, in most cases rheumatoid arthritis. Criteria for admission included:

1. Continuing difficulty with current regimen of treatment or the need for large doses of corticosteroids.
2. The ability of the patient to return frequently to the clinic, at least 2 consecutive weeks originally.
3. Freedom from significant complicating disease.
4. A reasonable measure of reliability of the patient's observations of his symptoms.
5. Stage III of ARA classification (although a few stages II or IV are included)[8] if rheumatoid arthritis was present.

The patients were first examined weekly, then biweekly, and later monthly. Evaluation was made of the amount of pain, tenderness, effusion, range of motion of the joints or other structures involved, general well-being, the presence or absence of fever, and possible side effects.

Almost all patients were on other medications at the time indomethacin was first administered. Medications were continued at the same dose level so as not to influence the evaluation of the effect of the indomethacin. In some cases, however, the dose of other drugs, such as cortisone, was reduced when the indomethacin was found to be of benefit. Some patients were evaluated in a study in which they received either indomethacin or an identically appearing placebo. After one week on one treatment, the drug was changed without the patient's knowledge to the opposite substance.

The dosage of indomethacin ranged from 100 mg. to 400 mg. daily, given in the form of 25 or 50 mg. coated tablets in the most convenient divided dose schedule for the patient. Four hundred milligrams was given as 100 mg. four times each day, 300 mg. as 100 mg. three times daily, etc. In the beginning, patients were instructed to take the medication with meals but, as gastrointestinal side effects became evident, they were instructed to take it after meals. Antacids were used prophylactically in a number of subjects in the later phases of the study. Periodic laboratory examinations, which included complete blood count, erythrocytic sedimentation rate, urinalysis, stool guaiac, serum bilirubin, alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), and serum uric acid, were performed. Other examinations were made as indicated.

The test drug was immediately discontinued if any potentially serious complications developed, or if annoying side effects became more incapacitating than the disease under treatment. If no benefit was noted after a suitable period of time, usually about 2 weeks, the trial was concluded. Each patient was seen by one of the three authors. Every patient started on the drug is included in this report; 97 in all, 52 females and 45 males. Age ranges from 10 to 81, with the majority between 30 and 50.

RESULTS

The effects of indomethacin on clinical signs and symptoms were rated by comparison with the therapeutic regimen of aspirin that nearly all of the patients had been receiving immediately prior to the trial. The major benefit was a decrease in joint and muscular pain and stiffness. A significant number of patients also experienced a marked decrease in the duration and intensity of morning gel, or the elimination of it altogether. The response was considered *fair* if it was judged to be as effective as a therapeutic amount of aspirin, *good* if it greatly surpassed aspirin, and *excellent* if it completely relieved symptoms. The advantageous clinical effects noted in 41 patients who tolerated the drug for a period of 3 months or more are noted in Table I. Borderline cases were always listed in the less favorable category. Among the 97 subjects to whom indomethacin was administered, 41 were benefitted, the drug was discontinued for one reason or another in 50 patients, and 6 were lost to follow-up.

TABLE I.—DEGREE OF BENEFICIAL EFFECTS IN 41 PATIENTS TREATED WITH INDOMETHACIN

Disease	Excellent	Good	Fair
Rheumatoid arthritis (71)	3	14	10
Rheumatoid spondylitis (6)		1	2
Reiter's syndrome (4)		3	
Gout, chronic (5)		1	
Osteoarthritis (4)	1	2	
Acute gout (1)	1		
Psoriatic arthritis (1)		1	
Causalgia (1)		1	
Erythema nodosum (1)	1		
Scleroderma (2)			
Adiposa dolorosa (1)			
Total (97)	6	23	12

Note: Figures in parentheses total treated in each category.

In 71 patients with rheumatoid arthritis, improvement was excellent in 3, good in 14, and fair in 10. Ten of the 37 subjects with rheumatoid arthritis who stopped taking the drug had noted improvement. This response was not graded, however, because of the short duration of drug administration in most of these patients. Excellent results also were noted in one patient with erythema nodosum, one with acute gout, and one with both osteoarthritis and rheumatoid arthritis. If there were beneficial effects, they were almost always noted within the first 24 to 48 hours, usually after the first or second dose of indomethacin.

The 41 patients who responded favorably have been treated from 3 to 12 months. The dose has ranged from 100 mg. to 400 mg. dailiy, and for the most part the beneficial effect does not seem to be dose-related. Rarely have we noted greater improvement when the dose was increased in a patient who had not responded to a lower dose.

Indomethacin was evaluated in 17 patients, of whom 12 were started on the drug and 5 on placebo. After one week, the drug and placebo were exchanged without the patient's knowledge. Six of the 17 patients were clinically unaffected by either agent, although 2 stated that they were "benefited" at a time they were taking the placebo. Three of the 5 patients receiving placebo followed by drug benefited from the change. All 8 subjects who received the drug (with benefit) followed by placebo experienced severe exacerbations within 24 hours of the change. One patient had a severe exacerbation lasting 4 days, after which he was symptomatically the same as when taking indomethacin. Once again he was given the drug, but derived no further benefit. The experience in this case casts some doubt upon the validity of accepting an exacerbation which occurs after a drug has been discontinued or replaced by a placebo as proof of the drug's efficacy.

Six patients out of 8 had exacerbations of symptoms on a trial discontinuation of the drug. In most cases the exacerbation that followed substitution of the placebo for the drug exceeded in severity the clinical state prior to indomethacin treatment. In 5 of the 44 cases the indomethacin appeared to become less effective with the passing months. This, of course, may have been the result of altered activity of the disease.

Two patients were unable to take the medication during the day because of lightheadedness, but were able to sleep uninterrupted and had no morning gel when taking indomethacin before sleep only. Both had previously awakened frequently to "loosen up" and had considerable morning stiffness and pain. One patient with psoriasis and arthritis had a remission of the dermatitis coincident with that of the arthritis and an exacerbation of both when placebo was substituted. In most cases existing effusions did not change perceptibly. The erythrocytic sedimentation rate was unaltered despite clinical improvement.

ADVERSE EFFECTS

There were substantial adverse reactions in the study. Thirty-seven of the 97 patients (37 percent) found it necessary to discontinue the medication after a short period because of adverse effects (Table II). Thirteen patients experienced neither benefit nor side effects, despite a stepwise increase in dose to 400 mg. daily. Six patients did not return.

TABLE II.—SIGNIFICANT ADVERSE EFFECTS FROM INDOMETHACIN IN 97 TREATED PATIENTS

Disease	Number treated	Headache	Peptic ulcer	Other gastrointestinal symptoms	Lightheadedness and dizziness	Mixed symptoms	Other [1]	Total	Percent
Rheumatoid arthritis	71	5	6	6	8	4	3	32	45
Rheumatoid spondylitis	6	1						1	
Reiter's syndrome	4	1						1	
Osteoarthritis	4				1			1	
Scleroderma	2	1						1	
Adiposa dolorosa	1			1				1	
Total		8	6	7	9	4	3	37	

[1] 1 each: ankle edema, abnormality of glucose tolerance, and urticaria.

The major reasons for discontinuation of indomethacin were, in order of frequency, gastrointestinal symptoms, lightheadedness, giddiness, headache, and psychic changes (Table II). In almost all cases the adverse effects were evident within hours or a few days. Occasionally, gastrointestinal symptoms did not develop for a week.

Nine patients had to stop taking the drug because of lightheadedness, giddiness, loss of equilibrium, inability to concentrate, and dissociation of mind and body. No neurological signs were evident, although a majority of the patients had discontinued the drug before they were examined again. One subject had a syncopal attack and fell, sustaining minor injuries. Four patients who were still taking indomethacin had similar symptoms which, however, were mild and transient.

Seven patients had bothersome gastrointestinal complaints which necessitated discontinuation of the drug, and another 5 had transitory symptoms but were able to continue with the medication as the symptoms lessened. The symptoms included epigastric burning, nausea and vomiting, diarrhea, and melena. Peptic ulcer developed in 6 of the 97 patients (6 per cent). In each case the drug was stopped immediately. Three of these patients were also taking small doses of prednisone (5 to 10 mg. daily), but each had been on a corticosteroid preparation continuously for several months at least, often in the higher dosage range, without epigastric distress. In one patient, a 60-year-old woman with advanced active grade IV rheumatoid disease, who was on prednisone 7.5 mg. per day and indomethacin 250 mg. per day, a prepyloric ulcer perforated into the lesser omental sac 4 months after treatment with indomethacin, with only 4 or 5 days of mild epigastric symptoms.

Four of the 6 patients who developed ulcer did so very rapidly after receiving indomethacin. Epigastric distress usually began after the first two or three doses. In one patient, a prepyloric ulcer was demonstrated 48 hours after the start of treatment and 24 hours after the onset of symptoms. Only 1 of the 6 patients had a prior history of ulcer, which was known to have healed. Antacids were not given routinely since this was not part of our protocol in the early phases of study. Antacids, however, were used in most of the patients late in the study.

Headache developed in 13 patients, 8 severe enough to discontinue the drug. There was no apparent pattern as to location, although the bifrontal type was the most common. Both steady and throbbing headaches were encountered. Although most patients with headaches had an accentuation of symptoms shortly after each dose, 2 reported partial relief of their headaches after each dose of medication and an accentuation of headache proportional to the length of time between medication. Three subjects were given ergotamine tartrate with caffeine without relief of headache.

Urticaria developed in one patient on two separate occasions following ingestion of indomethacin. However, she had had urticaria once previously without known

cause. A patient with rheumatoid arthritis had ankle edema on two separate trials of indomethacin.

LABORATORY FINDINGS

Almost all patients had a large number of laboratory examinations before treatment was begun. There was the expected high percentage of moderate anemia and elevated erythrocyte sedimentation rates. Other pretreatment laboratory abnormalities included moderately increased Bromsulphalein retention in 5 patients with rheumatoid arthritis, elevated SGOT levels (3 patients), elevated serum alkaline phosphatase (1 patient), and elevated serum uric acid (4 patients). A not unexpectedly high percentage of patients with reversed albumin/globulin ratio was also found.

Complete blood count, urinalysis, and erythrocytic sedimentation rate were all performed routinely and repeatedly in follow-up. With two exceptions, no pattern of change was noted that could not be attributed to chance or spontaneous variation in disease activity. Other laboratory examinations performed randomly in the follow-up period, which showed no abnormalities, were: serum creatinine (19 determinations), serum uric acid (23 determinations), albumin/globulin ratio (21 determinations), serum bilirubin (17 determinations), cephalin flocculation (18 determinations), and thymol turbidity (22 determinations). Five of 51 patients had guaiac-positive stools. Of these, 2 had melena without radiologically demonstrable cause and 3 had peptic ulcer.

One subject with diabetes mellitus noted increased glycosuria after starting indomethacin. The patient was then studied on a constant dosage of aspirin, with and without indomethacin. While on indomethacin, the glucose tolerance curve appeared to be more abnormal; on 200 mg. of indomethacin daily, there was 0.5 per cent to 2.0 per cent glycosuria, whereas it was negative to 0.5 per cent before medication.

Other abnormalities were noted in 2 patients with rheumatoid arthritis while on treatment, but neither had control determinations for the specific abnormality. One had a serum SGOT of 106 and a serum pyruvic oxaloacetic transaminase (SGPT) of 123 after 2 weeks of treatment. Two weeks after discontinuation of the drug, the SGOT was 37 and SGPT was 46. Indomethacin was then administered for 5 days, after which the SGOT was 53 and the SGPT 56. The patient had no clinical signs that could be related to the changes and had symptomatic relief of the arthritis. The second patient was found to have a serum alkaline phosphatase of 25 King-Armstrong units (normal 2.9) 3 weeks after starting indomethacin. Bilirubin and transaminase were normal. The drug was discontinued and over the next 6 weeks the alkaline phosphatase slowly fell to normal.

DISCUSSION

The discovery of a new class of compounds with antirheumatic effects is a significant advance. Indomethacin is not related chemically to the salicylates, pyrazalones, or corticosteroids, and yet in many respects it seems to operate like them. The way in which indomethacin induces symptomatic relief is unclear. The compound possesses antipyretic, analgesic, and perhaps "anti-inflammatory" effects, although specific histologic evidence on the latter point is so far lacking in man. The dramatic effect of indomethacin in cases of acute gout[3 7] suggests actions resembling those of the corticosteroids. In the rheumatic diseases indomethacin is, in some respects, nonspecific in its action, since symptomatic relief is obtained in a variety of conditions; rheumatoid arthritis, gout, Reiter's disease, ankylosing spondylitis, osteoarthritis of the hip, and other conditions.[1 4 5 6 9 10]

So far, it has not been possible for us to select the patients who will respond to indomethacin. Our observations seem to indicate that indomethacin does not specifically alter the basic rheumatoid process or that of other diseases which have been treated. Synovial effusions have generally persisted, and the sedimentation rate and titer of rheumatoid factor have not decreased significantly. Where these have improved, in a few cases, the change probably was a result of the natural course of the underlying disease.

The incidence of adverse effects from indomethacin is unfortunately high. Annoying headache and gastrointestinal irritation come soon after the drug has been given. We have found no satisfactory way of overcoming them. The more serious problem of peptic ulcer aligns indomethacin with other established antirheumatic agents. Most of the ulcers in our series were noted in the latter

months of the study; hence, we were not as cautious with the use of prophylactic antacids or other measures as we otherwise might have been. Early in the series we carefully checked stools for blood with no positive results. It should be emphasized that this study was conducted completely with the use of a now obsolete compressed tablet which was subsequently shown to have a variable dissolution rate and erratic absorption.[2,5,10] When a new formulation of indomethacin was used, and a smaller daily dose employed, the incidence of toxic and adverse effects was said to have been reduced.[9]

The discovery of a new type of antirheumatic agent is notable. However, indomethacin is by no means the ideal agent because of the large number of patients who do not respond favorably and because of large number of adverse effects which it induces. It is hoped that related substances may prove to be effective antirheumatic agents and free of serious adverse effects.

SUMMARY

Indomethacin, a new nonsteroidal compound, was tested in 97 patients. Results were excellent in 6, good in 23, and fair in 12. The drug was discontinued in 50 patients, and 6 others were lost to followup. The most common reason for discontinuation of the drug was gastrointestinal side effects, which includes 6 cases of peptic ulcer. Although the ratio of adverse to beneficial effects is high, the significant and symptomatic relief which many rheumatoid and other rheumatic patients experience suggests the possibility that a related drug may be found with a more acceptable therapeutic ratio than that of indomethacin.

This study was supported by a grant from Merck Sharp & Dohme, Inc.

References

1. Boland, E. W.: Non-specific anti-inflammatory agents, California Med. 100: 145–155, 1964.
2. Cantwell, N. H. R.: Personal communication.
3. Hart, F. D., and Boardman, P. L.: Indomethacin: A new non-steroid anti-inflammatory agent, Brit. M. J. 2: 965–970, 1963.
4. Norcross, B. M.: Treatment of connective tissue diseases with a new non-steroid compound (indomethacin), Arth. — Rheumat. 6: 290 (abst.), 1963.
5. Percy, J. S., Stephenson, P., and Thompson, M.: Indomethacin in the treatment of rheumatic diseases, Ann. Rheumat. Dis. 23: 226–231,1964.
6. Rothermich, N. O.: Indomethacin: A new pharmacologic approach to the management of rheumatoid disease, Arth. & Rheumat. 6: 295 (abst.), 1963.
7. Smyth, C. J., Valayos, E. E., and Amorosco, C.: Indomethacin in acute gout using a new method of evaluating joint inflammation, Arth. & Rheumat. 6: 299 (abst.), 1963.
8. Steinbrocker, O., Trager, C. H., and Batterman, R. C.: Therapeutic criteria in rheumatoid arthritis, J.A.M.A. 140: 659–662, 1949.
9. Wanka, J., and Dixon, A. St. J.: Treatment of osteoarthritis of the hip with indomethacin: A controlled clinical trial, Ann. Rheumat. Dis. 23: 288–94, 1964.
10. Wanka, J., Jones, L. I., Wood, P. H. N., and Dixon, A. St. J.: Indomethacin in rheumatic diseases: A controlled clinical trial, Ann. Rheumat. Dis. 23: 218–225, 1964.
11. Winter, C. A., Risley, E. A., and Nuss, G. W.: Anti-inflammatory and antipyretic activities of indomethacin, 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole acetic acid, J. Pharmacol. & Exper. Therap. 141: 369–376, 1963.

THE COLUMBUS MEDICAL CENTER,
Columbus, Ohio, June 12, 1963.

NELSON H. REAVEY CANTWELL, M.D., Ph. D.,
Merck Sharp & Dohme Research Laboratories,
Division of Merck & Co., Inc.,
West Point, Penn.

DEAR DR. CANTWELL: Our interest in the therapeutic effects of Indomethacin has been centered largely on Rheumatoid Arthritis, both peripheral and spinal. In reviewing and analyzing our data, I have come to the conclusion that 61 patients have had sufficient trial to be included in our study. Of these, 49 were of the peripheral and 12 of the spinal variety. A good (decisively beneficial) effect was

obtained in 45 (in all of the spinal) and only a fair (indecisive) effect was obtained in 10. No benefit was noted in 6.

The duration of treatment was sufficiently long to permit good clinical observation, being between 12 and 18 months in at least 22 of the patients. As you know, placebos were used, both in single and double blind and 128 relapses were produced by substituting placebo.

As regards dosage, the spondylitics uniformly required less than the peripherals and the daily dose for them varied from as low as 50 mg. to 200 mg. with an average of about 125. In the peripheral arthritis, the average therapeutic dosage level was about 200 to 250 mg. daily. However, in many cases, the dose was taken up to 300 and higher and at least 6 patients received 400 mg. daily for at least one week. Few improvements were noted in the peripheral arthritis group at dosage levels of 150 mg. daily. Most of the peripheral arthritics are now being carried on a daily dose of 300 mg. daily but a significant number are benefitted to a striking degree on 200 mg. daily.

The greatest deterrent to increasing dosage to an effective level is the appearance of cerebral toxicity. This manifests itself clinically in excruciating 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.

The higher the dose, the more severe the symptoms but there was some variation in individual susceptibility. A few individuals experienced considerable toxicity at levels of 100 mg. daily whereas, a goodly number could take 300 mg. a day without any adverse symptoms. However, the usual appearance of symptoms was at the range of about 200 to 225 mg. although cerebral toxicity occurred in over half of our patients, that is 31 out of 61. In 80% of these, the toxicity could be adequately ameliorated or abolished by reduction in dosage. We did not run a specific questionnaire regarding an antecedent history of migraine but a prominent history of headache was present in only about 8 to 10.

I trust the above will provide you with the information you desire. If however you desire additional information, please let me know.

Yours truly,

NORMAN O. ROTHERMICH, M.D.

COLUMBUS MEDICAL CENTER RESEARCH FOUNDATION, INC.,
Columbus, Ohio, July 3, 1963.

NELSON H. REAVEY CANTWELL, M.D., Ph. D.,
Merck Sharp & Dohme Research Laboratories,
Division of Merck & Co., Inc.,
West Point, Pa.

DEAR NELSON: Enclosed is the Indomethacin questionnaire which you asked me to fill out from our work. As you know, we have interested ourselves almost exclusively in the benficial effect of Indomethacin on rheumatoid arthritis and have used it only sporadically and in a random way on other rheumatic disorders. We have chosen to exclude the latter groups since they have not been formally organized and analyzed.

From the nature of the questionnaire, you must understand that all of our patients have been treated for a greater or less period of time with 150 mg. or less and hence are included on the questionnaire but in a significant number of these, the dose was raised to a much higher level to achieve a satisfactory result. Consequently, the number listed under unimproved should not be looked upon as the total number of Indomethacin failures. Furthermore, the number experiencing headache is given as that number which occurred at the dosage range of 150 mg. or less. As you know, we had a considerably higher incidence of cerebral toxicity at higher dosage levels. These data are well explained in my previous report to you several weeks ago. The one case of bleeding was probably from a diverticulum and not ulcer and furthermore is not included among those who experienced gastrointestinal symptoms since his only symptom was that of weakness and faintness.

We are in the process of trying to develop satisfactory control techniques for determinations of Indomethacin blood levels. I don't see how you can possibly refute the finding of a zero blood level in every instance where blood was drawn 24 hours after the preceding dose. We hope to resolve this question.

As you know, we are also keenly interested in whatever effects, if any, Indomethacin may have on tryptophane and serotonin metabolism and how this may relate to the disease of rheumatoid arthritis.

Best wishes always.

Sincerely yours,

NORMAN O. ROTHERMICH, M.D.

INDOMETHACIN QUESTIONNAIRE, JUNE 19, 1963

Name of Investigator: Norman O. Rothermich, M.D.

1. How many patients have been treated with 150 mg. or less?	60
a. Number who experienced relief of pain?	40
b. Number who experienced relief of swelling & inflammation?	40
c. Number who had definite over-all improvement?	40
d. Number unimproved?	20
2. How many of the above patients experienced headache?	15
3. Of those who had headaches	
a. how many had to discontinue the drug because of it?	8
b. how many became tolerant of the headache and continued on the drug?	3
c. how many had relief of their headache at a lower dosage?	4
4. How many of the patients experienced gastrointestinal symptoms (abdominal distress, nausea, vomiting, etc.)?	3
a. How many had to discontinue the drug because of these symptoms?	0
b. How many developed a definite ulcer or bleeding?	1
5. How many of your treated patients have	
a. chronic rheumatoid arthritis?	48
spondylitis?	12
b. Arthritis or inflammatory disorders other than chronic rheumatoid arthritis?	---
6. Does acute inflammatory disease respond better than chronic disease?	No

NORMAN O. ROTHERMICH, M.D.

COLUMBUS MEDICAL CENTER RESEARCH FOUNDATION, INC.,
Columbus, Ohio, October 9, 1962.

NELSON H. REAVEY CANTWELL, M.D., Ph. D.,
Merck Sharp & Dohme Research Laboratories,
Division of Merck & Co., Inc., West Point, Pa.

DEAR NELSON: A special report to you is in order regarding the appearance of an adverse effect of the new drug, MK–615, now under investigation. This effect is an entirely symptomatic one and as yet not measurable by any objective methods. The patient complains of a distressing lightheadedness, a feeling of "the head 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 incapacitating and even prostrating.

The physical findings at this time are not remarkable. The ocular fundi are negative and there is no papilledema. The neurologic examination is likwise negative in all other respects. In a few instances, the electroencephalogram has shown no decisive or characteristic changes. Other laboratory studies are not changed significantly during these episodes. The spinal fluid has not been studied.

In general, this adverse effect appears to be a dosage related phenomenon and in most cases, does not appear until 250 mg. daily has been reached. However, there is a considerable variation in individual susceptibility to this effect. Some patients have been on 300 mg. or more daily for some time without any adverse effects. Some patients have felt this effect at dosages as low as 150 mg. daily. It is definitely reproducible in the same patient at approximately the same dosage levels. There appear to be no residuals from this adverse effect. Symptoms disappear usually within 24 to 48 hours after discontinuing the drug. The antirheumatic effects of the drug are not reduced by this effect. As a matter of fact, the antirheumatic effect may be very striking at these higher dosage levels. In some severe arthritics, it has been impossible to control the arthritis without producing these adverse effects. As of this date, 16 patients have had toxic effects out of a total of 49 patients receiving the drug. No other ill-effects of the drug have been noted.

Yours truly,

NORMAN O. ROTHERMICH, M.D.

THE COLUMBUS MEDICAL CENTER,
Columbus, Ohio, October 12, 1963.

NELSON H. REAVEY CANTWELL, M.D., Ph. D.,
Merck Sharp & Dohme Research Laboratories,
Division of Merck & Co., Inc., West Point, Pa.

DEAR DR. CANTWELL: The results of our experiences with the capsular form of 'Indocin' are contained in detail on the enclosed summary tables.

There can be no doubt that 'Indocin' does have clinically observable antirheumatic effect. This effect is uniformly consistent at comparatively low dosage levels in the rheumatoid spondylitic. It is in this particular disease that phenylbutazone and derivatives have been particularly effective but it would appear that 'Indocin' is equally effective at a slightly lower dosage level and, of course, without any of the life-threatening adverse effects which so often complicate therapy with the former compounds. In other words, it is my belief that in rheumatoid spondylitis, 'Indocin' can do as much for the patient as phenylbutazone but do it with comparative safety.

In the peripheral rheumatoid arthritis, there is considerable variation from one patient to the next and sometimes in the same patient from one time to another in the ability of 'Indocin' to exert a consistently and significantly beneficial effect. There is no doubt that higher dosage levels are required than in the case of the rheumatoid spondylitic. As higher dosage levels are approached, it is to be expected that the incidence 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 and also reduces the degree of benefit in a given arthritic because it necessarily puts a ceiling on maximum maintenance dosage. This is particularly frustrating because I am personally convinced that this cerebral toxicity does not threaten the life of the patient nor does it leave any permanent residuals. In fact, there is usually prompt subsidence of the cerebral toxic symptoms within comparatively few hours (usually 12 to 24) after the drug has been discontinued. Most of the time, the drug can be resumed at a lower dosage level without a recurrence of the cerebral toxicity. It is quite apparent from the chart that we have been able to carry some patients on a comparatively high maintenance dose and, of course, this implies that these patients did not have enough cerebral toxicity for them to wish to be taken off the drug or have it reduced in dosage.

On the other hand, some patients have developed disabling cerebral toxicity usually in the form of severe vertigo, lightheadedness or violent headaches on comparatively low doses. One patient tried on three separate occasions to take a 25 mg. capsule but just on the one dose developed such a violent headache that he could not continue it. On the other hand, another patient had been on 50 mg. and h.s. for at least a year when his vertigo and lightheadedness had increased to a disabling degree and required him to discontinue the drug temporarily. One other patient developed a violent toxic reaction after only one week of therapy and had to be confined to bed, more or less continuously, for four or five days. One patient while on a ladder working became dizzy and fell off suffering a fractured arm. Another busy executive became so dizzy and lightheaded that he feared crossing the street against all traffic.

It would seem worthwhile to list the various manifestations which I have chosen to lump together under the designation of cerebral toxicity:

1. Headache.
2. Vertigo (usually not true room-spinning).
3. Lightheadedness.
4. Feelings of fogginess in the head.
5. Sometimes difficulty in concentration.
6. Occasional feelings of unreality.
7. Marked stimulation with resultant insomnia. Very similar in designation to caffeine effect.
8. In higher doses, some ataxia and even personality change, more toward a paranoid state, were observed.

It is my belief that the capsule is superior to the tablet only in that it permits for a more consistently reliable rapidity of absorption whereas the tablet form varied greatly in its rate and degree of absorption. However, it cannot be said that the capsule has reduced the incidence of cerebral toxicity.

At the same time, "Indocin" is notably free of other toxic effects. A few patients complain of some stomach pain but these were rarely consistent and reproducible. There were no deleterious effects on the formed elements in the peripheral blood including the red and white corpuscles and platelets. There were no alterations of

any of the chemical elements of the blood. Notably, we could not find any consistent elevation of the BUN. All liver function studies remained normal during therapy and there were no evidences of any ill-effects on the kidneys or lower urinary drainage structures. No cardiovascular effects could be detected. The drug did not have any reproducible effect on the Latex Fixation Test nor was there any significant effect on the Sedimentation Rate regardless of the clinical response. No effects on the skin were observed and there were no changes in the lower bowel or the bowel habits. The drug had no apparent effects on appetite or on muscle strength.

In summary, "Indochin" would appear to be an excellent therapeutic vehicle for treating rheumatoid spondylitis. In the very few cases where it was tried, it seemed to have a beneficial effect on acute attacks of gout. It did not seem to influence materially cases of generalized chronic fibrositis or acute localized periarticular fibrositis nor did it have any beneficial effect on back problems, especially posterior cervical fibrositis. In one case of chronic gouty arthritis, it has proved to be dramatically but consistently beneficial to a very high degree over a period of nearly two years. "Indochin" has an "excellent" beneficial effect in some cases of peripheral rheumatoid arthritis but only a "good" effect in a larger percentage and there is complete failure or ineffectiveness in a distressingly high percentage of such cases. In most of these latter cases, it was our feeling that the failure was due largely to the inability to break through the therapeutic ceiling maintained by the cerebral toxicity.

I hope the enclosed summarized data will be helpful to you.†

Cordially yours,

NORMAN O. ROTHERMICH, M.D.

[From Journal of the American Medical Association, vol. 195, No. 13, Mar. 28, 1966, pp. 124–128]

AN EXTENDED STUDY OF INDOMETHACIN*

II. CLINICAL THERAPY

(By Norman O. Rothermich, M.D.)

A new antirheumatic drug, indomethacin, was evaluated over a long period of observation (42 months maximum). Clinically satisfactory results listed as both good and excellent were obtained in a high percentage of patients with ankylosing spondylitis, gouty polyarthritis, psoriatic arthritis, and other miscellaneous benign (nonfatal) rheumatic diseases. In rheumatoid arthritis, indomethacin produced good and excellent results in a lesser, though appreciable, percentage of cases and may be regarded as another valuable drug to be added to the overall program of therapy in this notably difficult disease. As indicated in the previous report, the experimental nature of this study required that in some cases the dosages be increased to and beyond tolerance. Therefore, therapy in private practice may not yield as high a percentage of favorable results as indicated in this report.

The present treatment of rheumatoid arthritis still leaves much to be desired. Virtually all therapeutic agents which are believed to have beneficial effect in this disease have limitations on their utility and efficacy because of harmful side effects, usually dose-related. The development of an antirheumatic agent with little or no clinical hazards would be very desirable. In a previous publication,[1] it was reported that indomethacin was not hazardous, except for the possibility of gastric-ulcer formation.

Previous reports have indicated that indomethacin produces significant benefit in certain rheumatic diseases.[2,3,4,5] These reports were based largely on com-

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†Retained in committee files.

*From the Department of Medicine, Ohio State University Hospital, and the Columbus Medical Center Research Foundation, Columbus, Ohio. Reprint requests to 1211 Dublin Rd., Columbus, Ohio 43212.

[1] Rothermich, N.O.: A Report of 42 Months Experience With Indomethacin: I. Clinical Pharmacology, *JAMA*, to be published.

[2] Norcross, B. M.: Treatment of Connective Tissue Disease With a New Nonsteroidal Compound (Indomethacin), *Arthritis Rheum* 6:290 (June) 1963.

[3] Smyth, C. J.; Valayos, E. E.; and Amoroso, C.: Indomethacin in Acute Gout Using a New Method of Evaluating Joint Inflamation, *Arthritis Rheum* 6:299 (June) 1963.

[4] Rothermich, N. O.: Indomethacin: A New Pharmacologic Approach to the Management of Rheumatic Disease, *Arthritis Rheum* 6:295 (June) 1963.

[5] Hart, F. D., and Boardman, P. L.: Indomethacin: A New Nonsteroid Anti-inflammatory Agent, *Brit Med J* 2:965–970 (Oct 19) 1963.

paratively short-term observations. The present report will describe clinical experiences with indomethacin which began in November 1961. Our attention was given mainly to its effects on patients with rheumatoid arthritis, but other rheumatic diseases were also treated. Because this was the first trial of indomethacin in the human, small amounts were given initially and effective dosages were not reached until late January 1962. For this reason, the present report deals with experiences during a 42-month period from Feb. 1, 1962, to Aug. 1, 1965.

Materials and Methods

The treatment sample comprised 216 patients and 234 patient-trials. This does not include 23 patients on whom therapy was begun but for one reason or another became "dropouts." These will be discussed later. It is noteworthy that 26 patients have been on continuous therapy for 30 months or more, the longest being 42 months. In the treatment sample, there were 147 females and 69 males, and all were adults with the exception of three children ages 9, 11, and 13 years. There were 117 patients with probable, definite, and classical rheumatoid arthritis as defined by the Committee on Diagnostic Criteria of the American Rheumatism Association (ARA); all cases of "possible" rheumatoid arthritis were listed under nonspecific polyarthritis. There were 22 cases of ankylosing spondylitis and 14 cases of chronic gouty polyarthritis (ie, the chronic polyarthritis having characteristics similar to rheumatoid arthritis, but associated with a negative latex titer and a high serum uric acid level and occurring in an indivdual who has been diagnosed as having gout). In addition, there were 15 cases of osteoarthritis, 29 cases of fibrositis, and 19 cases of other miscellaneous rheumatic diseases as follow: 10 "possible" rheumatoid, 3 juvenile rheumatoid, 2 psoriatic arthritis, and 1 each of Reiter's disease, pseudogout, villonodular synovitis, and Tietze syndrome.

In the initial trials, patients were selected with moderately severe rheumatoid arthritis which was fairly well controlled with the standard basic program of therapy consisting of increased rest, physical therapy, salicylates, and sedation, as well as small doses of corticosteroids and sometimes gold or phenylbutazone therapy or both. The first step was to discontinue administration of all therapeutic agents except salicylates and corticosteroids, or as many as possible consistent with the patient's continued good management and control of the disease process. Indomethacin therapy was initiated in small doses and gradually increased according to the patient's ability to tolerate higher levels. At the same time, a gradual reduction of corticosteroid therapy was begun. If and when corticosteroid therapy could be discontinued entirely, gradual reduction of salicylate therapy was attempted. In some cases all therapeutic agents were withdrawn and control of the disease was continued at the same level on indomethacin alone. (Withdrawal of salicylates was for experimental purposes and is not to be construed as recommended clinical procedure.)

The evaluation of clinical results was based on those factors described in a previous report.[6] Greatest emphasis was placed on the patient's own gradation of his disease from 0 (no symptoms or disability) to 4+ (severe pain, morning stiffness, and total disability) based on his past experience with his disease. In addition, a separate evaluation of disease activity and disability was made by the physician. It is believed that accuracy and objectivity of such gradations can be greatly enhanced and made more secure by liberal use of placebo substitution and by quantitation of the steroid and aspirin requirements of the individual. When used by a clinician interested in the management of rheumatoid arthritis, these criteria can often be as accurate and precise as the many criteria which have more formalized physical and arithmetical indices.

The well-recognized decisively beneficial effects of corticosteroids (and to a much lesser degree of aspirin) provide an excellent base for reference in therapy of rheumatic diseases. Any new agent therefore must be able to reduce materially or eliminate the need for corticosteroids in an appreciable number of cases. After such elimination, therapy may be further evaluated by the ability to reduce the dose of or discontinue salicylate therapy. These have been important criteria in our evaluation of a favorable response to indomethacin. In all cases listed as having had an excellent response to indomethacin, either of these two or the clear-cut, unequivocal placebo relapses have been a required criterion.

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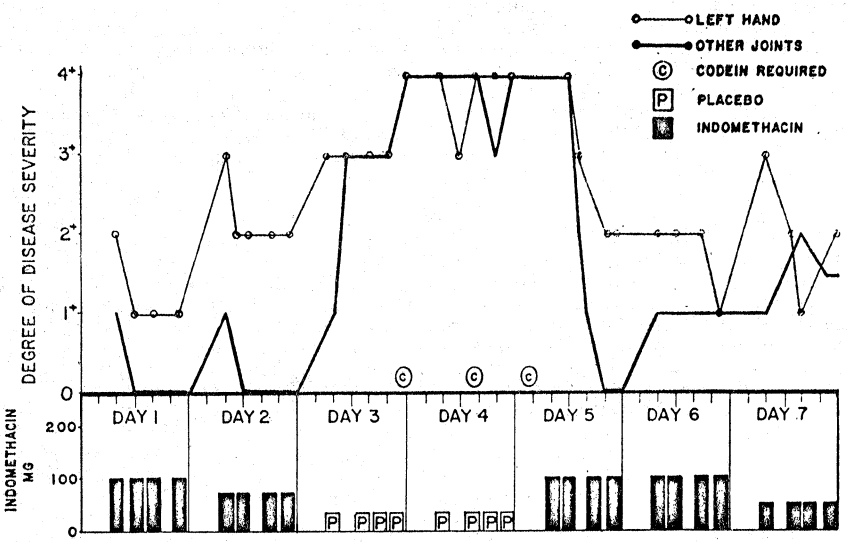
[6] Rothermich, N. O.: Clinical Experiences With Indomethacin in Rheumatic Diseases, *Proceedings of the Eighth Congress of the Japan Rheumatism Association, Okayama, Japan,* 1964, pp. 159–163.

In "fresh" cases of rheumatoid arthritis where corticosteroid therpay had not been previously used, a patient was rated as having good or excellent response to indomethacin if evidences of active synovitis, the jelling phenomenon, and painful disability, as indicated by the patient's symptoms and the physician's observations, receded under active drug therapy and promptly exacerbated when placebo was substituted. In some patients, the placebo trials were made several or more times in order to establish with certainty the relapsing character of the disease under placebo influence. In cases other than rheumatoid arthritis, such as spondylitis, psoriatic arthritis, and chronic gouty polyarthritis, therapeutic evaluation was based on control of disease activity on indomethacin alone, with relapses precipitated by placebo substitution. Occasionally, patients would suspect placebo substitution by a change in side effects. For this reason from the statistician's viewpoint, the placebo trials in this report (and probably in most clinical drug reports) cannot be considered as true "blind" studies. Usually there was enough delay in this awareness to permit the therapeutic assessment. Furthermore, the appearance of side effects is often capricious and inconsistent, thus further limiting the patient's ability to detect placebo. In some of these cases, adequate control had previously been achieved by the use of phenylbutazone, and effectiveness of indomethacin could be measured by its ability to replace such therapy.

Placebo substitutions were made in 86 of the patients. In 70 of these, there was decisive clinical relapse on placebo; this was verified on repeated trials in 55 patients. In most instances, placebo was introduced whenever a patient seemed to be established and well-controlled on indomethacin therapy. In addition, at times when an adverse reaction appeared, a placebo was substituted to determine if the adverse reaction was actually due to indomethacin or some other cause. Occasionally, in a patient whose therapeutic response to indomethacin could not be determined with any reasonable accuracy or whose disease continued to progress even though he was on other antirheumatic medications as well, a placebo was administered to observe if actual worsening of disease occurred while administration of other medications was continued in exactly the same dosage. In 21 instances, neither the patient nor the physician was informed of the placebo substitution, and in one such case a striking effect was observed and charted (Fig 1).

FIGURE 1



1. Placebo trial on a 40-year-old woman with severe psoriatic arthritis. Note profound relapse on receiving placebo and partial loss of disease control on day 7 with reduction in dosage.

Results

The therapeutic results in rheumatoid arthritis are shown in Table 1. The good and excellent results combined totaled 88 out of 117 (75%). The patients are categorized according to the diagnostic criteria of the ARA into classical, definite, and probable. It is noteworthy that in the classical group, which is notoriously resistant to treatment, the percentage of favorable results was surprisingly high (65%). As might be expected, this was appreciably lower than the 82% in the combined groups categorized as "definite" and "probable." The dosage range was approximately the same in the three different groups; in all patients where no side effects were encountered, the vast majority received a maintenance dose between 100 and 200 mg. In the 88 patients who obtained a good or excellent result, 69 had been receiving a maintenance dosage of corticosteroids at the time indomethacin therapy was begun, and 44 of these were able to reduce the corticosteroid dosage by 25% or more categorized as follows: 3 patients, a dose reduction of 25%; 8 patients, 33⅓%; 10 patients, 50%; 4 patients, 75%; and 19 patients, 100% (discontinued).

TABLE 1.—RESULTS IN 117 PATIENTS WITH RHEUMATOID ARTHRITIS

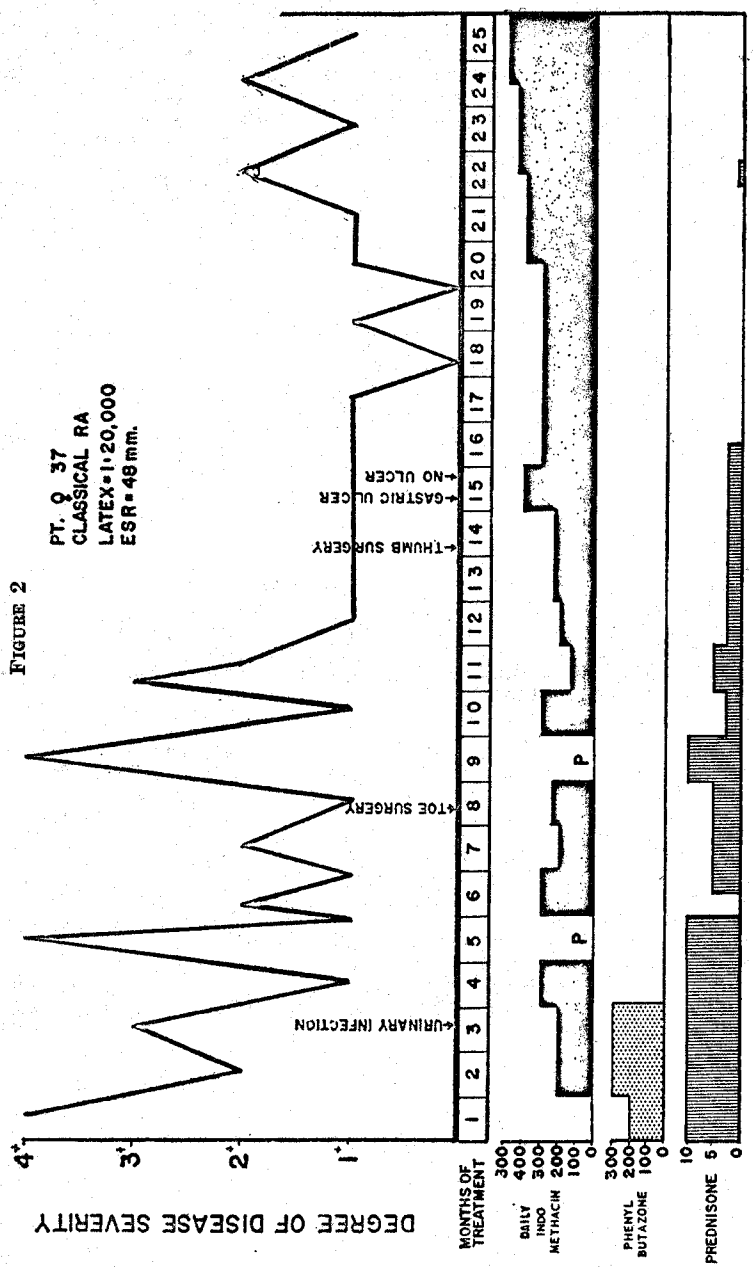
Diagnosis	Number of patients	Results		
		Excellent	Good	Poor[1]
Classical	55	18	19	18
Definite	35	14	14	7
Probable	27	16	7	4
Total	117	48	40	29

[1] Equivocal or no benefit.

In ten patients with rheumatoid arthritis, administration of the drug had been discontinued for one reason or another for an appreciable period of time. A second and clinically distinct trial of indomethacin therapy was made in these patients. The results were the same in both trials in six of the patients, but in two, the first trial obtained a good result and the second a poor result, whereas in two others the exact opposite held true.

Illustrative case reports

CASE 1.—A 37-year-old white woman has had classical rheumatoid arthritis for eight years in an extremely active, progressively disabling form. Several years ago, on large doses of aspirin, she developed a huge gastric ulcer. On a trial of gold therapy, there was mild improvement but toxicity developed. On corticosteroid therapy, there was definite improvement, but this therapy was withdrawn for obscure reasons and she had a severe relapse. Chloroquine phosphate produced severe toxicity and phenylbutazone aggravated the ulcer. When first brought into this study in December 1962, the patient was a stage IV, class IV, with total disability, and the arthritis was in a very active, destructive phase. Treated with small doses of corticosteroid, enteric-coated aspirin, and cautious doses of phenylbutazone, the arthritis was somewhat controlled. Indomethacin therapy was begun and with gradually increasing doses, the arthritis became fairly stable and of questionable activity despite reduction and eventual elimination of all other medications, including salicylates (Fig. 2). After 14 months of indomethacin therapy, the ulcer was reactivated but it healed on treatment while the drug therapy was continued. The patient is now up and about, takes care of her entire household, and occasionally even goes to dances. The total duration of indomethacin therapy was 25 months and the patient had received no other medication for the last ten months.



2. Disease activity in patient with classical rheumatoid arthritis. Note elimination of all therapy except indomethacin with continued reasonably good control of disease, and the gastric ulcer appearing and healing on continued high-dosage indomethacin therapy.

In the benign rheumatic diseases other than rheumatoid arthritis, the results are even more encouraging as indicated in Table 2, and the average effective maintenance dose was lower, being only 100 mg. or less in 72% of the cases. Out of 22 cases of spondylitis, there were only three treatment failures, and three such failures were also seen in 14 cases of chronic gouty polyarthritis. In the cases of osteoarthritis, the results were not quite so spectacular, with a good or excellent result in ten out of 15 cases. In the cases of fibrositis, the results were even less favorable, but still impressive with a good or excellent result in 55%. There was a high percentage of benefit in the miscellaneous group of disorders which comprised for the most part those cases with chronic polyarthritis of an indeterminate nature which would otherwise have qualified as "possible rheumatoid arthritis," according to the ARA classification. Also in this miscellaneous group and deserving of special mention are two cases of severe psoriatic arthritis (ie, cases having the clinical characteristics of rheumatoid arthritis and active psoriasis but with a negative latex titer) in which there was a dramatically beneficial effect on the arthritis, but no effect whatever on the psoriasis.

TABLE 2.—RESULTS IN 99 PATIENTS WITH MISCELLANEOUS RHEUMATIC CONDITIONS

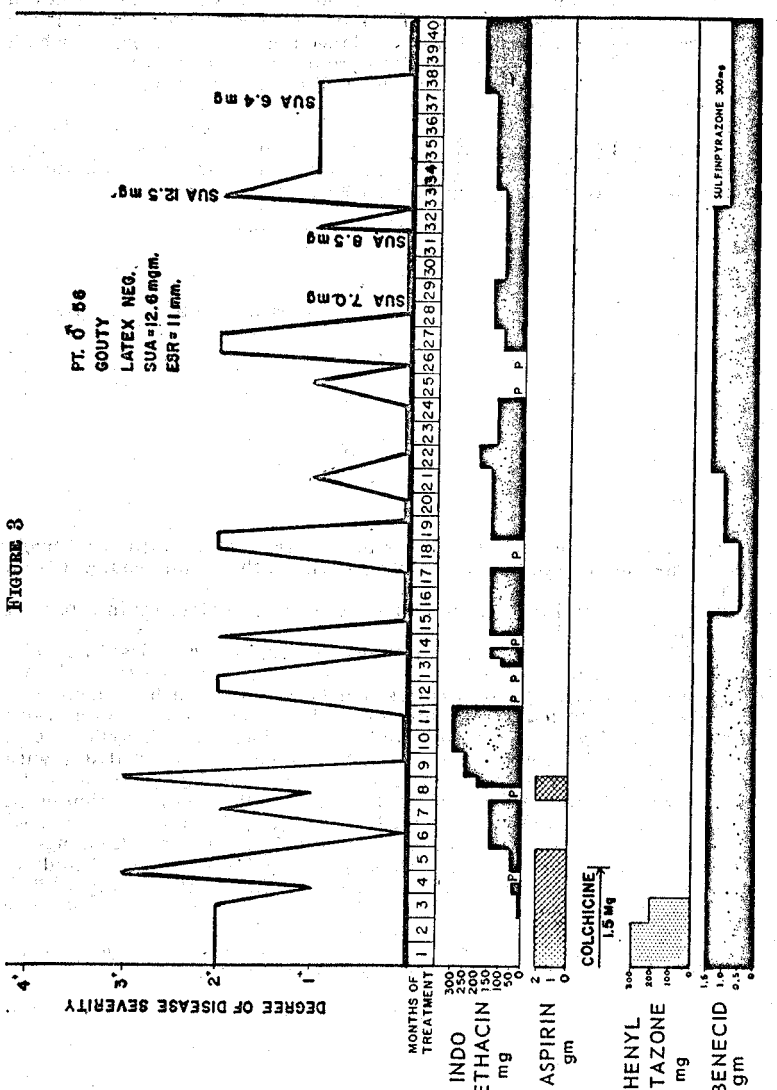
Diagnosis	Number of patients	Results		
		Excellent	Good	Poor [1]
Rheumatoid spondylitis	22	15	4	3
Gouty arthritis	14	10	1	3
Fibrositis	29	12	4	13
Osteoarthritis	15	4	6	5
Miscellaneous	19	10	4	5
Total	99	51	19	29

[1] Equivocal or no benefit.

In eight patients, a repeat clinically distinctive trial of therapy was made and the result was the same in five cases, while in three, the results changed from poor to good.

The following case is an illustration of indomethacin effectiveness in a patient with nonrheumatoid arthritis.

CASE 2.—A 56-year-old white man developed a very severe, disabling polyarthritis five years previously. He was in continuous pain, unable to work and having extreme early-morning stiffness. He had been known to have gout, and serum uric acid determinations were quite high (10–12 mg/100 cc). As a result of treatment with salicylates, corticosteroids, colchicine, and phenylbutazone, there was considerable improvement in his arthritis but he was still left with occasional joint pain and tenderness and some early-morning stiffness. Indomethacin therapy was begun in January 1962 and gradually administration of all other antirheumatic drugs was discontinued (Fig. 3). In later months, relapse occurred apparently associated with failure of the uricosuric drug. A change in the uricosuric drug again brought the serum uric acid level to normal and remission was again achieved with administration of indomethacin alone. The patient is well with no indications of rheumatic disease, although relapses occur whenever he is given placebo. The total duration of indomethacin therapy was 42 months, and the patient has received no other medication except probenecid and then sulfinpyrazone (Anturane) for the past 38 months.



3. Disease activity in patient with chronic gouty polyarthritis. Before indomethacin therapy, phenylbutazone, colchicine, and aspirin were given with only fair disease control. Note the prompt relapses with each placebo trial. SUA = serum uric acid.