

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:)

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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.^{8, 9, 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.

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NOTE.—Numbered footnotes at end of article, p. 3282.