established for rheumatoid arthritis, which presents the largest potential market for indomethacin, Indocin).

Perhaps an answer can be found in Dr. Hurwitz's memorandum of August 25, 1967, in which he stated that: "At the present time, then, it would seem wise to consider Indocin as probably effective in rheumatoid arthritis pending further studies in this area." The word "probably" should be emphasized.

How can we reconcile the FDA medical officers' opinion that there is a "paucity of controlled studies" and that the drug is "probably effective" with the statutory requirement of substantial evidence of efficacy?

How can we reconcile the requirement of "substantial evidence" of safety with the opinion of an FDA medical officer that "* * * Indocin has shown a similar propensity to cause a wide variety of serious and sometimes fatal reactions, and its clinical usefulness has been limited by its toxicity."

The American Medical Association's New Drugs, 1967 edition, states that:

"Central nervous system effects (headaches, usually severe in the morning; vertigo; light headedness; mental confusion) occur during the early weeks of therapy in about 20% to 30% of patients taking indomethacin. Drowsiness, convulsions, depression and psychic disturbances such as depersonalization have also been reported. * * * Indomethacin should be regarded as being potentially ulcerogenic. It may produce single (or) multiple ulceration of the esophagus, stomach duodenum or small intestine. Cases of perforation and hemorrhage, a few of them fatal, have been reported."

I am inserting at this point a summary of side effects reported by Merck's investigators.

(The summary follows:)

SIDE EFFECTS—INDOCIN

"The patient complains of a distressing lightheadness, a feeling of being in outer space, a feeling of the head being foggy and a feeling of difficulty in concentration or in cerebration. There may or may not be an associated violent headache and in a few cases, the headache was so violent that it was predominant or alone. In a few instances, these symptoms have been so severe as to be totally incapaciting and even prostrating" (Oct. 9, 1962).

Dr. NORMAN O. ROTHERMICH,
Columbus Medical Center, Research Foundation, Inc., Columbus, Ohio.

"The greatest deterrent to increasing dosage to an effective level is the appearance of cerebral toxicity. This manifests itself clinically in excruciatingly severe headaches, dizziness, lightheadedness, disturbances of sensorium, a feeling that the head is floating away or even separating from the body and feelings of detachment from reality" (June 12, 1963).

Dr. NORMAN O. ROTHERMICH.

"As higher dosage levels are approached, it is to be expected that the incidents of cerebral toxicity goes up proportionately and this, in my opinion, represents a not insignificant disadvantage to the drug for it reduces the number of arthritics who can be benefited by the drug. . . . on the other hand some patients have developed disabling cerebral toxicity . . . on comparatively low dosages" (Oct. 12, 1963).

Dr. NORMAN O. ROTHERMICH.

"I am sorry to report but I am sure you should know, that we saw rather severe dermatitis in one patient after taking four tablets (100 mg) of MK-615 over a 24 hour period. We sincerely hope we will have better results to report in the future" (Apr. 24, 1962).

Dr. H. M. MARGOLIS,
Pittsburgh, Pa.

"We had 31 patients who started the (short term) double-blind study. . . . 13% had side effects requiring stopping medication." "In our work with Indocin we have found that heachache while not an infrequent side effect, has not been particularly difficult to control, responding either to antihistamines or to reduc-