The direct promotion of the drug to physicians seemed even more distorted than the advertising. One regional sales manager instructed detail men under his supervision: "It is obvious that Indocin will work in that whole host of crocks and cruds which every general practitioner . . . sees everyday in his practice." (The drug is too toxic for routine use in minor complaints, and the "crocks and cruds" indicates considerable contempt for the public.) Further, the salesmen were told to play down side effects.

### A SEMANTIC PROBLEM

In the summer of 1966, officials of the FDA demanded that Merck drastically alter its advertising. Officials felt that the advertising did not contain sufficient information on toxicity and overstated the usefulness of the drug, particularly in implying that it could be safely used in any form of rheumatic disease or arthritis. Merck complied for a brief period, but in November 1966 the firm began an even more objectionable campaign, resulting in a second crackdown, and a request by the FDA to the Justice Department that the company be criminally prosecuted for the November advertisements. At the Senate hearings on indomethacin, the president of Merck and Company pleaded:

"Language is not a perfect method of communication, and it may well be that words and phrases that we used in the belief that they mean one thing may have been interpreted by some physicians to mean something else. Such are the complexities of semantics."

This company's advertising converted the legally approved labeling of "Indocin itself may cause peptic ulceration . . ." unto "Ulceration of the stomach . . . has been reported." The difference is hardly semantic, since the second statement implies doubt as to causality, while the first does not. Even worse "semantic" difficulties were arising over the use of the drug in children.

In late 1964, the FDA had recommended to Merck that the prescribing directions for the drug state that this drug should not be used in children. No experiences in children had accumulated and children often react differently to drugs than do adults. Unfortunately, in the prescribing directions issued with the drug, this warning was altered to read "not recommended for use in children," rather than an absolute prohibition. In the fine print in the advertising, this was further changed to "Safety in pediatric age groups . . . has not been established," implying that the drug was safe in children, but little experience had accumulated as yet.

This language was, indeed, not a perfect method of communication, and physicians did use the drug in children. By July 15, 1966, the FDA had learned of sudden deaths due to overwhelming infection in several children receiving indomethacin. The officials requested that Merck immediately warn all American physicians by letter against the use of this drug in children. In addition, the FDA required that the labeling include additional warnings, contraindications, and clear indications of adverse reaction and precautions.

By November 1966, the Canadian Food and Drug Directorate became increasingly concerned about deaths in children. Rather than rely on the company to warn physicians, the Directorate sent letters directly to every Canadian physician, stating:

"Several deaths have been reported in children with severe forms of rheumatoid arthritis, dermatomyositis, and rheumatic fever who were receiving indomethacin. Some of these children succumbed to an intercurrent infection, the severity of which may have gone unrecognized during treatment. The exact relationship to indomethacin was difficult to determine in these reports. However we recommend that indomethacin should not be used in children until the results of further studies become available."

### A PILL PER ILL

In early 1967, further disquieting news appeared. Previous evidence of the effectiveness of indomethacin had been based almost solely on testimonials by physicians and much of this information had never been fully published in reputable scientific journals. In early 1967, for independent, careful, double-blind trials were published in leading medical journals. In these trials two groups were used, one receiving indomethacin and another receiving some contrast medication (either a standard drug such as aspirin or an inert dummy). Neither the physician nor the patients knew which capsules were active. All four of these independent scientific trials (none of which relied on art or clinical opinion) failed to show that indomethacin had any more potency than simple aspirin.