numerous other instances could be cited. One wag suggested a second way to classify tests: "Drug trials can be divided into two groups: fraud and gross fraud."

DRUG PROMOTION

I am a specialist in rheumatic diseases, and through my career I have watched the development of a series of new drugs for the treatment of rheumatoid arthritis. I, and many other rheumatologists, have considerable doubt that any drug is really effective in arresting the course of rheumatoid arthritis, so surely our first concern should be *primum non nocere:* first not to injure the patient. Often it seems, however, that for the long-suffering arthritic the purported cure is worse that the disease.

Early in my career, corticosteroids were being widely acclaimed. Unfortunately, they cause a variety of severe and even fatal side reactions including psychoses, peptic ulcers, osteoporosis, fractures, cataracts, diabetes, and so forth. Another great hope was phenylbutazone, which was moderately effective, but which unfortunately caused peptic ulcers, and even worse caused severe depression of the bone marrow and occasionally resulted in leukemia. Next was chloroquine, which was relatively weak, but seemed almost free of side effects.

Unfortunately, after a few years of therapy, some patients became totally blind. Then came indomethacin, another rather weak drug, which had numerous serious side effects. More recently dimethylsulfoxide (DMSO) was proposed as a panacea. This drug probably has no effect at all, but acts as a classical counter irritant. When rubbed on the skin, it causes redness, scaling, burning, and pain—the skin hurts so badly that the patient forgets his arthritis. Some patients developed ocular changes, and a few died of shock after receiving DMSO; human use of the drug is now prohibited. Today, we are beginning the era of the immunosuppressives, which can cause total depression of the blood-forming elements in the bone marrow. These are the most dangerous agents ever used in treating rheumatoid arthritis, and we can only wait to see what will result.

THE INDOMETHACIN STORY

Indomethacin is a good example of how a drug is tested and promoted. The drug was developed at the research laboratories of Merck, Sharpe and Dohme, and the basic studies represented careful pharmaceutical research. By 1964, extensive clinical testing of the drug was underway. The only requirement of present U.S. law is that a drug be safe and effective as labeled. Advertising is legally defined as labeling. By June 1965, the FDA felt that the drug met these requirements and that it was relatively safe if used as labeled, so they allowed the drug to be marketed.

Merck immediately embarked on an ambitious advertising campaign. By early 1966, most medical journals contained eight-page color advertisements with headlines stating that indomethacin was "the most promising antirheumatic agent that has been made available for clinical investigation since the introduction of cortisone." Many physicians might misinterpret this statement as meaning the drug could be used in any rheumatic disease. In fact, it has been tested and approved in only four specific diseases. The advertisements also stated in large type that the drug "extends the margin of safety in long-term management of arthritic disorders." Again, this implied that the drug was safer than other drugs and it could be used in any form of arthritis. Unfortunately, it did not specify what indomethacin was safer than.

The advertisements also contained four testimonial statements by eminent pratitioners, two of which stated indomethacin was "the drug of choice," implying this drug in comparisons had been found more effective than other drugs when in fact such comparisons had not been made. One physician claimed that he had found the drug "extremely helpful in over 500 patients." Later, FDA officials indicated Merck's own records revealed the physician had never treated anywhere near 500 patients. The claim was also made that the drug did not increase susceptibility to infection. They omitted mentioning that these claims were based on experiments in a few rats with a system involving bacterial endotoxins, evidence which certainly could not be projected to claim that all infections in human beings would behave in a similar fashion. In fact, the drug increases human susceptibility to infection. Further, the advertisements stated periodic blood counts were not necessary, implying that the drug did not depress the bone marrow: the drug is known to cause total fatal marrow depression.