The preclinical or animal work required of the drug developer is not specified in detail by the FDA and may vary within limits depending on the nature of the compound. The studies, however, must leave no "blind spots" in the animal pharmacology. It is generally accepted that the need of the manufacturer to intimately and thoroughly know his product and the responsibility of the FDA to protect the public from drug hazards is adequate proof that the manufacturer has done everything possible to provide, by animal studies, predictive information for use in human studies.

Regardless of the sophistication and exhaustiveness of animal studies, however, the definitive test of what the drug will do in the human is learned only by use in humans. The predicitive value of animal studies is less than absolutely established. Litchfield, in a retrospective study of six drugs evaluated in laboratory animals and man, found inconsistencies but concluded that some predictive value could be shown. Penylbutazone threshold difference between rabbit and man is more than forty fold. A compound shown by Brodie to anesthetize the rat satisfactorily so that infusion for 8 hours was followed by complete recovery in 10 minutes was, in a careful study in the first human subject, found to require 48 hours for recovery after a 10 minute infusion. Thus, there is inherent in the clinical testing to follow some usually small but inassessible hazard.

It is reassuring to remember, however, that the compound's activity is in the physical and chemical properties of its molecule. A clinical pharmacologist thoroughly familiar with the physical and chemical nature of the drug and with appreciation of the fact that the body's ability to dispose of a drug often depends on any enzyme system with broad or narrow substrate limits, will be prepared for dealing with blood levels that might result from the human's not possessing a polarizing enzyme with spectrum broad enough to include it. Clinical testing should either be done by an investigator trained in clincal knowledge of the new and potentally hazardous test material; or there should be extensive conferences between preclinical and clinical investigators and not just a mere presentation of the animal data reports with the assumption that they will be read and perceived.

It is our opinion that Phase I studies, in general, and, in particular, those involving a first human testing, do not give sufficient importance to either the choice of the investigator or the briefing of the investigator. This is particularly relevant for agents of an entirely new action category or having a new chemical configuration. There is the impression often that protocols are passed to any available clinical investigator to be carried out in a routine sterotype manner. A clinical investigator may thus be doing a job in which he feels competent from having performed perfunctorily in the same capacity for many years but with very little understanding of the role he is performing. FDA and pharmaceutical manufacturer's monitoring is provided but this evaluation may be too superficial and too remote to provide maximum safety. Less than ideal Phase I testing inevitably increases the risk for those volunteers used in Phase II (the first testing on selected sick patients). In a recent discussion of a new drug product, Dr. Gilgore of Pfizer Laboratories remarked that—

"For the early Phase II studies we want our investigators to be the most experienced available. Careful review of the literature and discussion with physicians at scientific meetings are important aspects in our investigator selection process. We selected four well-recognized experts in the field as our principal Phase II investigators. With these we discussed the experimental procedures to be followed and with collaboration of statisticians, designed the clinical protocol. . . . After pilot studies were completed we called our investigators together for a 'think tank' type of discussion at which their results were received."

In contrast the only mention of selection and briefing of Phase I investigators is that "two were selected."

In the present instance there is no reason to believe that the pharmaceutical firms failed to act in good faith or failed to discharge their responsibility to the general public to develop safe effective therapeutic agents. They contracted with approved clinical investigators to carry out approved research projects. However, there are some points for possible criticism, (1) There may have been a too superficial monitoring of the clinical work which they support, (2) They demonstrated some lack of discretion in selection of their Phase I investigator. Thus, there was a need to consider the number of projects to which the prospective investigator was already committed, (3) Their initial conference sessions may not have provided for adequate grounding of the investigator in all the significant basic properties of the test material, a particularly important point when the