the clinical program is developed and the clinical objectives—based on the pharmacological and toxicological data derived from animal studies—are established.

Clinical protocols are then prepared. These outline the broad design of the proposed clinical studies and convey the basic information on toxicology and pharmacology with which clinical investigators must be familiar in order to study the drug in man. In developing the protocols, we consult with clinical pharmacologists, biostatisticians, and selected investigators. In this process, we strive for the best possible study design, reconizing at the same time that the new drug can only be studied within the scope of presently available methodology as well as the availability of patients, volunteers, and clinical research facilities.

Once the clinical plan has been completed and submitted to the FDA, clinical studies are initiated in Phase I—which probes the basic pharmacology and metabolism of the drug in man. These studies are carried out only by expert clinical investigators in a few selected clinical laboratories, normally not more than five. These are almost always in university-affiliated medical centers and are carried out in carefully selected individuals.

If Phase I studies provide evidence of safety and pharmacological activity, the clinical program is expanded to include a half dozen or more expert investigators in the field of medicine where the drug promises to be useful (Phase II). An antihypertensive drug, for example, is taken to specialists in cardiology who have had experience in the investigation of such drugs.

By this time the appropriate dosage range for the drug is fairly well established, and the effects of the drug can be studied in various disease states where it is expected to have a beneficial effect. This additional experience, involving studies in depth, adds greater assurance of safety and efficacy and provides the basis for expansion of the studies into Phase III.

The final phase (III) provides still greater evidence of safety and therapeutic benefit which can then be well delineated in the clinical indications for use of the drug. These studies are carried out by carefully selected physicians experienced in the field of study concerned. These are selected by our medical staff based upon knowledge of their prior work in the field, their prior work for us, and in some instances on the recommendation of Phase I and II investigators. A primary purpose is to obtain a deeper insight into how the drug will respond in the hands of physicians generally.

During all three phases, the studies are well controlled. The more sophisticated and complex double-blind studies are undertaken particularly during the Phase III stage. These studies serve as much as possible to eliminate bias and the elusive clinical variables which are ever present. It must be recognized, however, that although data from such studies tend to appear more convincing, their validity may also be subject to question. In most fields of medicine, it has yet to be proved that *all* relevant factors have been accounted for in the control design, and thus we must avoid total reliance on what may be simply a tidier version of an imprecise appraisal of a drug.

The first and ultimate responsibility for drawing conclusions with regard to safety and efficacy of a drug lies within the medical staff and the research organization of the Conmpany sponsoring the studies. We do not and cannot delegate this repsonsibility to a third party.

Financial assistance in the form of grants-in-aid is given to the investigator to cover the expenses incurred in carrying out his research. For the most part a contractual relationship is established between the Company and the university or institution where the work is being carried out. Grants are made on a sound budgeting basis. Clinical research grants are never based on the condition that a certain number of case reports be submitted or that only positive data be provided. Our records clearly show that studies supported by grants frequently fail to support the objectives set forth in the clinical protocol, either because of a shortcoming in the drug itself or failure to anticipate one or more of the numerous variables which arise during the clinical study and result in negative data.

Most grants-in-aid cover the following costs: Laboratory, technical, clerical, hospital, and bed costs; supplies, mtaerials, and overhead. If there are indirect costs assigned to a project as part of the investigator's overall research budget, these too are covered. Should the investigator request that special studies be done—such as radioisotope work, or metabolic balance studies demanding the special facilities of metabolic ward—these are financed to cover all direct and indirect costs.

It is difficult to generalize about the costs of clinical research in the conduct of studies with new drugs. One cannot, for example, correlate the number of