In No. 563 of WHO's Technical Report Series, "Guidelines for Evaluation of Drugs for Use in Man," it is stated that preclinical "pharmacodynamic studies should be designed to demonstrate the expected therapeutic effect of the drug and, wherever practicable, its mechanism." In many cases it is difficult, if not impossible, to comply with that request, especially with respect to the mechanism of action of many of the drugs in use, often for a long time, for which we do not know precisely how and where they act. Furthermore, problems may arise in planning experimental studies to show probable therapeutic effect because such experimental models either do not exist or are inadequate and do not allow us to draw conclusions about what may happen in man. Of course, each new chemical entity will be studied by appropriate in-vitro methods as well as in acute experiments in animals, to establish its pharmacodynamic profile. However, the pharmacological features of a new chemical give only limited information about its therapeutic usefulness. Despite the fact that the species of man does not differ fundamentally from various animal species with respect to pharmacodynamic responses, and that, consequently, human pharmacology resembles animal pharmacology, the therapeutic potential of a new substance cannot simply be derived from the pharmacodynamic effects demonstrable in acute studies. A blood-pressure lowering substance is not necessarily an antihypertensive, an anti-inflammatory drug not an antirheumatic, and a reserpine antagonist may not have antidepressant activities. Hence, acute pharmacodynamic results may be useful indicators for further, more detailed investigations, but may also be misleading with respect to therapeutic efficacy.

The discrepancy between the pharmacodynamic profile of a new chemical substance and its possible application as a therapeutic
demonstrates the dilemma which the pharmacologist who works in an industrial laboratory has to face continuously. On the one hand, he has to avoid being overenthusiastic about interesting pharmacological findings which may be of little--if any--therapeutic significance; on the other hand, the possibility of overlooking a special activity of a new substance is a permanent threat. Can this situation of uncertainty be reduced by guidelines? How could guidelines contribute to a better and more competent experimental evaluation and assessment of the pharmacodynamics of a new drug and of their significance for the treatment of diseases?

ARE PRECLINICAL GUIDELINES OF USE IN ESTABLISHING THE PHARMACODYNAMIC PROFILE?

For the study of the acute effects of a new chemical substance, no guidelines can be given; the experience, skill, and good luck of the pharmacologist or biologist who studies the substance determines whether all its activities will be revealed. It may well be that the main activity is missed because no studies in that direction have been undertaken, but once a drug has been found to cause an effect which promises a possible therapeutic application, investigations should be as comprehensive as possible. This means that attempts should be made to obtain a complete pharmacodynamic profile which includes all effects that the drug may produce, the positive and the negative ones, the desired and the undesired. As an example, the fate of the sulfonylurea derivative carbutamide should be quoted. Originally given into clinical trial on the basis of its antibacterial action, it was not before the completion of quite extensive clinical trials in various types of bacterial infections that its antidiabetic activity was discovered on the basis of severe hypoglycaemic responses, including shock. This effect could have been observed easily in experimental animals if the drug had been studied in that direction. Similarly, a pyrazolopyrimidine derivative, allopurinol, which was characterized as a weak coronary dilator was found somewhat later, in some other drug research laboratory, to be the powerful inhibitor of xanthinooxydase. It is not surprising that the effect on the enzyme involved in uric acid formation was overlooked when the cardiovascular actions of the substance were studied. A last example is praziquantel, the potent anthelmintic and schistosomicide, which was originally conceived as a psychotropic drug and was only found to have antiparasitic action in a routine screening to which each newly synthesized chemical was submitted.

It is obvious that a complete screening for all the pharmacodynamic effects will be feasible for no new chemical substance, but for drugs which will be submitted to clinical trials an extensive experimental study has to be undertaken. This includes not only the acute studies necessary to establish a complete profile, but also investigations which contribute to the understanding of the mechanism of action.