

laboratory findings to the patient in order to understand and treat the disease process.

For example, the sulfonylureas have been used clinically for about 20 years, yet a great deal of information regarding these compounds is still lacking. The metabolism of these compounds in patients and their precise mechanism of action are still very poorly known. These have been complicated problems and require additional studies in both animal systems as well as patients.

Scientists are very interested in coordinating such diverse efforts and studies. I feel that clinical research work in this area should be further nurtured, but that it must be balanced by a broad base in fundamental animal research as well.

And other aspects of the subject which you think might be helpful to the subcommittee.

I feel strongly that the time has come in terms of the oral hypoglycemic agents to restudy their effects in animals and patients. It is my feeling that since recent animal studies are proving of considerable interest in terms of the actions of these drugs on organs such as the heart, adrenal glands, and liver, it would be wise to restudy these compounds in animal systems during the time their clinical use is reevaluated in order to see whether we can gain an understanding of the mechanism of the cardiovascular deaths or even reproduce them in animals.

Here I note with particular interest two recent pieces of data in animals: One, the summary statement of the work of Wissler et al. which states that in rhesus monkey fed an average American diet for 74 weeks containing 20 milligrams per kilogram tolbutamide, there were present in the coronary arteries two times more frequent and three times more severe atheromatous changes than in the coronary arteries of control monkeys; two, the work of Hsu et al. from our Department of Pharmacology at Virginia which demonstrates that in heart, adrenal medulla, and other organs, sulfonylureas inhibited catecholamine release from the nerve endings of the autonomic nerves. Thus the function of the autonomic nervous system, which provides the involuntary control for many of the organs of the body, is significantly influenced by these drugs.

Therefore, I feel that it is time to caution physicians about the use of these drugs, and to restudy them in the clinical and basic laboratory much more extensively.

Mr. GORDON. Dr. Larner, thank you very much.

With respect to the Wissler study in rhesus monkeys, what conclusions can be drawn from this for humans?

Dr. LARNER. Well, I think, the obvious warning can be put on that these may be potentially harmful drugs, that they may affect selectively, the coronary arteries, that these changes in the artery, may lead to malfunction and difficulty in the heart.

I think the warning is obvious. I think that more studies need to be done, both of anatomical nature, and of a functional nature. These studies reported here were of an anatomical nature, in which the structural changes were pointed out. And I think they must also be accompanied by studies in which the function of the heart is also studied, so that we will have some more information.