Summary of the Symposion

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I am in a difficult position. Having "invented" beta receptors many years ago I have come here to hear them dissected very thoroughly.

Imagine how WILLIAM WITHERING would have felt if he were here trying to introduce digitalis as an effective drug. I think the arguments would have been the same as we have heard: it is good; it is not good; it is dangerous; it is not dangerous.

However, I think we have found out, yesterday and today, that propranolol (Dociton, Inderal) is a potent drug. It does block certain circulatory responses to adrenergic nerve stimulation, or to injected catecholamines. The blocking effect is confined to those responses we consider as being controlled by the beta adrenergic receptors. And obviously the effect on the heart has been the primary interest of this symposium.

Other studies, not all of them mentioned here, have shown that the effect of propranolol on the myometrium and bronchial smooth muscle is as it should be for a specific beta adrenergic blocking agent. However, as I stated in my introductory remarks, we should not be surprised that it has other effects. These have been demonstrated including a quindine-like action, monoamine oxidase inhibition and a local anesthetic action. And I would expect in months to come that other effects will be found. Although we attempt to classify drugs as simply as possible, all have effects other than those we classify them as having.

This has been a rather unique symposium in that we have had a pharmacological demonstration of beta adrenergic blockade in almost every species. For example, Dr. SHANKS, Dr. ROUSE and Prof. MEESMANN described the effect in cats and dogs. Dr. ROSEN and Dr. BüCHNER showed the effect in humans. This does demonstrate one drug at least that has the same effect in humans as it does in animals. I am sure everyone realizes that many drugs used today in man do not have the same actions in animals.

The clinical tests and trials that have been described show much more variation. However, as with all drug studies in humans, the personal opinions and viewpoints of the investigator strongly color drug response interpretation. It is difficult enough to make a personal interpretation of how a drug acts on a simple system such as the isolated of the rabbit. Pharmacologists can argue such a point for weeks and weeks. Then think of the complications that set in when two physicians try to see identical pictures in the same patient.

One of the questions that we can try to answer is – is propranolol effective in controlling angina pectoris? I remember that 15 years ago a drug known as khellin came out of Egypt. It had a dramatic, short life. It cured, treated and almost did away with angina pectoris. Today we seldom hear a single mention of this drug. Let us hope that propranolol does not depart like khellin.

The answer to the question, I think, has to be yes. We have a better pharmacodynamic basis for propranolol in so far as controlled clinical methods can be used. Dr. HAMER described most of the precautions that must
be taken to identify properly drug effect in a subjective disease such as angina. I find as a teacher that it is most difficult to describe to a student how he should objectively assess a subjective disorder in a patient. How can he know how much a patient hurts? He cannot objectively find this out; only the patient can tell him. This is why it is so difficult in clinical pharmacology to work with subjective disorders such as pain, insomnia or excitement.

Dr. Pritchard described a double blind study that showed propranolol to be effective in angina pectoris. He also described the main criteria for determining this effectiveness: reduction in number of attacks of angina, reduction in nitrite dosage, and increased exercise tolerance. Prof. Meesmann presented another aspect of the clinical studies of the drug. This is the selection of the patient to study; and this is probably the most difficult criterion. How do you know that the patient has angina pectoris. Perhaps it is just a muscle spasm in the shoulder. The patient cannot tell you; you have to make the decision. I think this probably explains much of the variation (in effectiveness) that has been found so far. A rigorous selection of patients, all of them really having angina pectoris, will probably not show as dramatic a result as a study using a less strict selection of patients.

I had intended to make some more extensive remarks about other things for which propranolol might be effective. But I think the roundtable has covered these quite thoroughly. Obviously any drug that reduces sympathetic drive by acting as a beta receptor blocking agent should in theory affect beneficially almost any type of tachycardia. However, I don’t believe that the evidence presented here has really answered this question as yet. I am sure that many more cases of tachycardia must be tested so that we may finally decide in which kind propranolol should be given, and in which kind it should not be given.

I think we can go away from here feeling that propranolol is an effective beta adrenergic blocking agent. In humans this effect results primarily in a negative chronotropic response under almost all conditions. This struck me as a uniform finding; none of the speakers said anything except that following propranolol the heart rate went down. I think it most unusual that no one said the rate went up, or if they did I did not hear it.

A decrease in force of myocardial contraction also occurs following propranolol. Whether this effect is good or bad I am not prepared to say. I can say that if you digitalize a normal heart, and to me this is the best positive inotropic effect known, this individual is severely handicapped; they cannot compensate for exercise. Therefore, I don’t know to interpret positive and negative inotropic effects other than simply as increased and decreased force of contraction.

The effects of propranolol on metabolic processes is species dependent. In attempting to prepare a review on this subject I have found that this is a field in which there is little agreement. Adrenalin seems to be the most potent adrenergic catecholamine in producing metabolic effects such as glycogenolysis and mobilization of free fatty acids. You will also find that these effects are blocked by alpha blocking agents, beta blocking agents, antihistamines and other drugs. So I think that at this moment we should not rely on blockade of adrenergic metabolic responses to explain any good effect of propranolol.