Audiotape labeled:
*R.P. Ahlquist, intro J. Sutherland “Serendipity and Hypertension” Physiology Seminar 12/6/1976*

Transcribed by Renée Sharrock, January 2021

*NOTE: The speaker references the inclusion of slides in the presentation; however, it is not known the whereabouts of said slides. When additional information on places and names were confirmed by the transcriber, that information is enclosed in [brackets].*

Brief background info:

Raymond P. Ahlquist, PhD was internationally recognized as the originator of the alpha- and beta-receptor concept of the andrenergic system. His paper hypothesizing this theory, “A Study of the Adrenotropic Receptors” was published by the American Journal of Physiology in 1948 (153:586). His investigations led the way of the development of beta-blocking drugs used to treat blood pressure. In 1976 Ahlquist was honored with the Albert Lasker Clinical Medical Research Award and the Ciba Award for Hypertension Research.

For more information, please see the Raymond P. Ahlquist Collection finding aid.

*Note: tape begins during introduction of Raymond P. Ahlquist, PhD by James H.R. Sutherland, PhD*

Sutherland: … college added buildings to this campus, Ray was to get a new office built, and I would move into his old one with him leaving all his junk and papers for me to clean out. So for once in my life I get to follow him and I won’t leave much in the way of papers to clean up. He has told me he does not want the traditional introduction, but I thought for at least a few of you, you might want to know just a little bit about Ray so I will give you an abbreviated background. Ray comes from, actually he was born in Montana, but he spent most of his life, his formative years in Everett, Washington. He has his bachelors in pharmacy from the University of Washington School of Pharmacy where he graduated magna cum laude. I put that in that we will understand why he went from a lucrative profession in pharmacy into the study of pharmacology. Because he got his Masters in ‘37 in pharmacology and his PhD in 1940. Following his PhD he went to the South Dakota State College in Brookings, South Dakota where he was Assistant Professor in Pharmacology and pharmacognosy. He also was in experimental station there where he tried to raise and in fact successfully managed to raise a Chinese plant ephedra because all of our supplies of ephedra for the extraction of the medicine ephedrine had to come from China. And with this great triumph simultaneously one of the drug houses managed to come up with a synthesis, so that was one of his first successes in his career to be scooped. He came to the Medical College in 1944, as Assistant Professor of Pharmacology, quickly rose to Associate Professor in ’46, and
by ’47 was acting chairman. In ’48 he became chairman and professor of the department, which he stayed there until ’63 when he moved over to the dean of basic science office and research coordinator. Again, I came up behind him to clean up a lot of old papers. And then I moved out and turned the tables on him, and he came back in 1970 to take over the chairmanship again. Ray has belonged to a number of important societies and has held high office in quite a few of them. I think, if you wish to know, you could read his lengthy CV. He has performed on a variety of editorial boards, I’ll skip over those too. He was won several awards, some of them you have heard about, and participated in a variety of memorial lectures. All of this really started back in 1948 when he published his paper on the alpha beta receptors. I think it’s particularly appropriate that Ray is presenting this seminar today to this particular group because in 1948 he sent this paper to the *Journal of Pharmacology and Experimental Therapeutics* where it was promptly returned as an outright rejection because it was not appropriate to contradict the great doctor Cannon of Harvard [possibly Walter Bradford Cannon]. It was then passed on to the editor of the *American Journal of Physiology*, William F. Hamilton, who published it forthwith. So I think it’s appropriate that Ray will be talking to you today since it was a physiologist who recognized the importance of the work. As he told me, some time back, the paper then disappeared, nobody heard about it. I remember being invited back to my old home university Berkeley some ten years later to give a seminar in the Institute of Experimental Biology and I talked on the alpha and beta receptors of the autonomic nervous system and they all looked amazed and aghast and incredulous. They had not heard of it in ten years and didn’t even believe it then. But fortunately, it didn’t get lost forever and recently, as some of you may have seen in the paper, people are beginning to give credit to his contribution to this basic ...[inaudible]...I just passed three slides. This is all gonna work just fine...There, given credit to this, Ray recently won the Ciba Award for the contributions of the alpha-beta theory in the explanation of adrenergic antagonists. This also enabled the discovery of beta-blocking drugs which of course have become important in the treatment of hypertension. And then most recently the Lasker Award given for the alpha-beta concept which is led to most of the research in the clinical compounds in recent years. I hope that was a short enough introduction for you Ray.

Ahlquist: Thank you Jim. It’s a pleasure to follow you.

Once upon a time, in the land of Serendib there were three princes. There was a great famine and the princes set out to look for some hay. One prince while walking through a meadow fell down onto some stone and he found the great gem. Prince number two fell into a stream and when he came out of the stream, he had found a pearl of great price. The third prince found a pile of hay but when he jumped in it for joy, he found a beautiful maiden. That’s serendipity, meaning finding something of value when you’re looking for something else.

This just introduces what I’d like to talk about, the title of which is Serendipity and Hypertension, and it illustrates also how many things are found by serendipity. You look for one thing and find something else, maybe of even greater value.

This disorder of hypertension, just to start with, there are at least five curable kinds and one incurable, and this one we call essential hypertension. This is also called high blood pressure, and this is also one of the modern afflictions of man. Now the five curable ones, it’s easy enough to look at the patient and see what’s wrong and you can do something about it in most of them. But when you look at a patient with essential hypertension, you see, they have an elevated diastolic pressure and that’s the disease.
There’s nothing else you can look for. This again, just serves as an introduction to hypertension which we will drag in a little later.

In 1947 I was ordered by Dr. [Robert A.] Woodbury to find a cure for dysmenorrhea because we knew if we had a cure for dysmenorrhea we would become rich because there’s enough ladies with dysmenorrhea who would buy a magic potion that we really had something to look for. In casting about for how to treat dysmenorrhea, Dr. Woodbury first had to find the cause and he decided the cause was uterine hyperactivity. To begin the menstrual cycle, the uterus would contract so hard, the lady would have ischemic pain. If that was the cause, then obviously the treatment is to relax the uterus. So I had to look for something to relax the uterus. Now the only place I could figure to look would be through the autonomic nervous system and when you look at uteri in general because the myometrium is tremendously species dependent in its response, the only place to look would be at this ending here. To look for some androgenic drug, something related to epinephrine or norepinephrine to see if we could find something to relax the uterus. From the basis of this, I looked at five different compounds, all closely related to epinephrine, differing only in a couple of methyl groups scattered in different places. I came up with this marvelous theory that there must be two receptors to explain what I found. Instead of trying to tell you what I found, I’ll let this story develop as I go along. As Dr. Sutherland said, this was a marvelous paper. The real idea came to me one night as I was sitting on the throne in the bathroom and I decided, well, this is so marvelous I can turn it in to the pharmacology society and win the Abel Award [John J. Abel Award]. And I did, and I joined a large illustrious group of Abel Award losers. There’s probably many more of those than the winners. The worst part is I have never forgotten the winner of that year. Because the winner of that year, and that was back when radiation was just becoming popular, he had made an astounding discovery if you do whole body radiation, you find heparin in blood. This had been known, but nobody had had a good source to do whole body of radiation until shortly after the atomic bomb. And this man, fortunately stayed in relatively academic medicine. He’s chairman of surgery at Stanford [University]. So if you get sick and need surgery, don’t go to Stanford.

Now the place we’re going to start of this particular story today is at the adrenergic neuroeffector junction. This is the exact anatomical replication, as Dr. [Dale] Bockman [Professor and Chairman of Anatomy, MCG] can guarantee, of an adrenergic nerve end. In the nerve end is stored a chemical transmitter, noradrenaline. In the United States this is norepinephrine, but this is a slide from Japan, so it’s called noradrenaline. And the reaction releases adrenaline which comes out of the end and acts on this structure we call a receptor to bring about the typical response of this effector, depending on whether it’s smooth muscle, cardiac muscle, nerve, or gland.

This receptor is also sight of action of all drugs chemically related to adrenaline. Not only agonists such as isoprenaline or isoproterenol but the blocking agents and all the other drugs that I’m going to talk about, act through this receptor mechanism. Now this is what I had finally decided, was that there must be two receptors, and that’s why I colored it two colors. And I had to find names for the two receptors. It could have been “a” and “b”, could have been “1” and “2”, “x” and “y”, or anything else. But I chose alpha and beta, alpha standing for Ahlquist, who thought up the theory, and beta standing for Jim [James] Black, my co-winner of these awards, who discovered the beta-blocking agents. I just happened to be 12 years ahead of my time when I selected these two names.
The alpha receptor is defined as follows: to a pharmacologist, to have a receptor, you need two different drug responses. One, an agonist, something that makes it go, and you need a specific blocking agent, something that stops it. So, the specific agonist for the alpha receptor is a compound known as phenylephrine. If you buy at the drugstore, its neo-synephrine nose drops. And three typical responses is controlled by this receptor of nasal constriction. This is why you buy the phenylephrine nose drops to dry up your nose. The dryness is due to the contraction of the radial muscle of the iris and relaxation of the gut. There are many other responses, but these are three typical ones.

The reason I stress gut relaxation; this is a relaxing effect while most things are excitatory effects. And this is why I figured that Cannon couldn’t be right. So that thing about the gut was part of it. The other half of the alpha description is an alpha blocking agent and the one I’ve illustrated is phentolamine or regitine. This one specifically acting on the receptor competitively prevents phenylephrine from acting. And some thing happens is an old laboratory experiment known as epinephrine reversal. This consists normally when you give epinephrine to an anesthetized dog the blood pressure goes up. But if you give an alpha blocking agent and repeat the epinephrine then the blood pressure goes down. This was a mystery until the two receptor theory because all you have to do is show that epinephrine acts on both receptors, you shut off half its effect and you see the other half. You also get postural hypotension meaning, when you stand up, your blood runs to your feet. This compound cannot be used in hypertension because it does not innervate the heart. If you gave it to a patient, they would get postural hypotension but you would get reflex cardiac stimulation so great that the patient’s pressure might be down, but they couldn’t stand the cardiac effect. In miosis which is the opposite of mydriasis, this is because you paralyze the radial muscle and the sphincter of the muscle of the iris keeps working and causes the pupil to shut.

The beta receptor is defined as having an isoproterenol or isoproterenol as the specific agonist. And I should put in here parenthetically that phenylephrine does not act on this receptor. And isoproterenol does not act on the alpha receptor. So when you give isoproterenol you get the following sympathetic effects: increase in heart rate, sinus rate, increase in force of contraction, increase rate of impulse conduction through the heart, you get basal dilation in certain blood vessels, notably those nutrient vessels, the skeletal, muscle, and bronchial dilation, or relaxation of the smooth muscle of the bronchi. Now this illustrates again why the term sympathetic for excitatory or sympathitic for inhibitory doesn’t hold. Because the heart effects the all excitatory, the smooth muscle effect are inhibitory.

Now this much was known in 1948 and this is what I published. The two receptors, we knew the alpha agonist and blocking agent, we knew the beta agonist. There was no beta blocking agent known, but you could totally predict what it would be when it was found. Because it fit into this slot that appears in this manner. The first beta blocking agent found was a compound known as DCI, dichloroisoproterenol. And it was difficult to work with because it is what’s known as a partial agonist. First, it’s an agonist and then it turns into a blocking agent. So when you first gave DCI you got tachycardia, falling pressure, and bronchial dilation. Keep on giving it and that all turns around and then you get bradycardia, increase in total peripheral resistance, and bronchial constriction. So, this compound was difficult to work with. But it was the first beta-blocking agent and was recognized as such first by Neil Moran at Emory University, and a former trainee. You heard about our trainees from Dr. [Philip] Dow some time ago.
Robin Shanks was the first to give this drug in man in England. He worked for ICI [Imperial Chemical Industries].

So now this is the true beta blocking agent. I apologize for this slide, I lost the one that didn’t have the Japanese subtitles on it. This is propranolol, the only one available in the United States. This specifically blocks the beta receptor, so that the effects you get, you get bradycardia, you get removal of any increased force of contraction due to sympathetic activity, if it’s present. You get a slowing in conduction, you get an increase in total peripheral resistance, and you get bronchial constriction. Now in most patients, bronchial constriction is of no importance because the trachea bronchial tree, the whole is so vague you could shut it off by contracting all the muscles, and you could still breathe adequately. So this last one is of importance in patients with obstructive respiratory disease. In other words, if you have asthma, propranolol would make it worse.

Briefly, to show the structure of these. The top one is dichloroisoproterenol, DCI. If you look at the right hand, that is the isoproterenol side chain and isoproterenol has hydroxyl groups with those two chlorines are. So you make it into a blocking agent by removing the catechol hydroxyl group. Dr. [James] Black, needing a better compound because he had proposed its use in angina, first suggested pronethalol. You see the pronethalol, the two positions here where normally there’s hydroxyl would be closed off by adding another benzene ring to it. So the two compounds are identical except for these end positions. And this turned out to be a very good beta blocking agent. It had only one bad effect and this was discovered only after it had been tried in about 100 medical students. It’s a carcinogenic compound. So ICI, Imperial Chemical, apparently have a shelf that has nothing but beta blocking agents on it, so they reached up and got the next one which was propranolol. That’s the one at the top. You see it looks roughly like pronethalol. The difference is there’s an oxygen bridge that’s been put in between the ring and the isoproterenol side chain.

I put in one other beta blocker which is alprenolol used widely in Sweden just to show that by putting in substitutions at this point, you can make any sort of a beta blocking agent you want. In England and in other parts of Europe there are 11 other compounds in clinical use. In the United States there is only one.

Now Dr. Black’s contribution to this whole story is that he invented a disease for the beta blocking agent. I can remember giving a lecture entitled “Drug Looking for a Disease”. We had beta blocking agents, but what good were they? So, he decided if angina is due to excessive cardiac activity due to exercise, if you fix it so the heart doesn’t know the patient is exercising, it won’t hurt. So, he suggested doing a denervation with a beta blocking agent, and if you denervated the heart, do a sympathetic denervation, you could exercise but the heart wouldn’t know you’ve done anything, so you could exercise more.

Now when you give a beta blocking agent to a human, these are some of the effects you get. You get a decrease in the chronotropic and inotropic responses to exercise, emotions, and drugs, such as isoprenaline and adrenaline. You do basically a sympathectomy of the heart. This is of importance because beta blockers have been used in many, many disorders. And in many of the older studies, nobody bothered to prove if you have beta blockade. So today if you do experiments in humans, and you want to make sure they have beta blockade, then you either have to see if you block isoprenaline which is very easy to do or block the response to exercise. Which is to have the patient do a standard two-step
procedure, measure heart rate increase, then give them a drug, and have them repeat the two-step procedure. And unless you can demonstrate cardiac blockade, then you can’t say that your action is due to beta blockade. There is also decrease in conduction rate. In other words, the PR interval is prolonged. There is a decrease in cardiac output. There is a decrease in adrenergic basal dilation. Now this you don’t usually see unless there’s peripheral vascular disease. And there’s a decrease in bronchial dilation.

There are the clinical uses based on cardiac sympathectomy. And this slide has been arranged for Japanese consumption again because in Japan angina pectoris is a disease they don’t know about. They don’t call it that. They call it coronary insufficiency, painful coronary insufficiency, but not angina. Because today angina is a little different disorder that I might get around to talk about. But in the first three - angina pectoris, coronary insufficiency, obstructed cardiomyopathy - the objective is all the same, is to prevent the heart from responding to exercise. Because in obstructed cardiomyopathy, the faster the heart goes, the cardiac output goes down rather than up. So the first thing you try to do is a cardiac sympathectomy. It has been found that in most tachyarrhythmias, the most fast arrhythmias, regardless of the cause, there is a sympathetic component. So regardless of what makes the heart go fast, beta blockade will probably slow it down. And clinically, a slow heart is better than a fast heart. It’s more efficient. And many symptoms of anxiety are effectively treated. And this is based on shutting off the hyperdynamic cardiovascular response to the CNS [central nervous system] problem of anxiety. It is the hyperdynamic peripheral response that seems to act as a feedback to the burning.

Some other uses based on some other beta blocking effect. Again, certain types of tachyarrhythmia such as atrial tachycardia, atrial fibrillation, and atrial flutter can be treated with beta blockade because of decreasing the conduction rate. In other words, increase heart block. The decrease in cardiac output is useful in treatment of hypertension, which we’ll come to later. Here are some things whose mechanism is uncertain, but still useful. It’s very good in essential tremor. This is not the tremor of Parkinson’s, but a peripheral type of tremor. In the action of propranolol is local because if you have a patient who’s shaking in both hands, and you inject the drug arterially in one hand and the one hand stops shaking, the other one doesn’t. So, it is a peripheral effect.

In migraines it turns out to be fine. This was another use discovered by serendipity. Patients who had angina and migraine, after you put them on propranolol they had neither angina nor migraine. So just tried in just migraine and it works just as well as any other treatment. Nobody else knows how these treatments work, so you don’t have to explain the thing. And then there are those who say it works in schizophrenia, but I don’t understand what they’re talking about. I don’t know how you judge whether schizophrenic is better or worse. But these psychiatrists think it works fine.

Now here’s where the serendipity comes from. I started out looking for a cure for dysmenorrhea. But what I found was a good teaching aid. And medical students since 1948 have had this beat into their heads. Not only at this school, but most other schools today.

On the basis of this, Dr. Black found the treatment for angina. And a fellow named [B.N.C.] Prichard in 1964 noted that in his patients with angina and hypertension, when you treated them with propranolol, both the angina and the hypertension went away. So you see, it’s kind of double serendipity here that ends up with probably the single best drug ever discovered for the treatment of hypertension. It has been
used in essential hypertension in Europe and every other place else in the world except the United States since 1965.

In 1976 the FDA finally approved it for use for hypertension in the United States. But the FDA went even further. They said how it worked. And this is most unusual. Everybody agrees that its mechanism in hypertension is based on beta blockade. There’s no question about this. But the argument is about these other three things. Now I vote, as you can see by the underline, for the decrease of cardiac output. You don’t need any other explanation. There are some people who believe that there must be a central action involved. But you can show that all beta blocking agents work in hypertension but not all of them can get into the CNS, therefore it can’t be all central effect. And then there’s the one about decrease in plasma renin activity and this is where most of the argument comes right now. And a fellow I always end up arguing with is a guy from New York named John Laragh, who always shows up at my seminars to tell me I’m wrong.

The thing you can prove if you give isoproterenol, plasma renin activity increases. And you can prevent this with beta blockade. The part I don’t agree with is the increase in plasma renin activity has anything to do with hypertension. So that, we keep fighting about this.

But as I said, there is good evidence that in at least 60% of essential hypertension, propranolol is the single best drug to give. You don’t have to give anything else, only propranolol. In fact, it is so good, that I think the tendency now is to classify hypertension into two categories – those that you can treat instantly with propranolol, a beta blocking, and all the others. I think this is the explanation. Because there’s no reason why essential hypertension should just be one disorder, one disease.

Now how to you use propranolol? First thing you have to select your patient, because if you select the wrong patient, you could get into great trouble. You don’t give it to patients who have congestive heart failure, because it in itself produces congestive heart failure. But a patient adequately controlled with digitalis, I mean if their congestive failure is controlled with digitalis, propranolol can be given. Don’t give it to a patient who has untreated congestive failure. You have to be careful in obstructed lung disease, this includes asthma, emphysema, and other conditions, because this drug, number one, it may bring on the asthma, if your bronchial tube is just not quite big enough. And if you are treating a patient with isoproterenol for asthma, the propranolol will shut off your treatment. It shouldn’t be used in heart block, because this is one of the effects of propranolol. It can produce heart block on its own.

It should not be used in preinfarction angina. This is an angina usually associated with hypertension and atherosclerosis which isn’t treated with beta blockade. And there are certain types of peripheral vascular disease in which you have to be careful, notably Raynaud’s phenomenon, the increase in total peripheral resistance would make it bad.

Now just to review, so we all know what we’re talking about, let’s talk about postural hypotension. This you can see is the human in the recumbent position, and they have a blood pressure of 120 over 80 and a heart rate of 72. And when we stand up, the reflexes squeeze down in the legs and other places and the blood pressure changes a little bit, 125 over 78 and a little increase in heart rate, but the patient is in good activity. But if the reflexes fail, this is the way they look when they stand up. As you will see, all the blood ran to their feet, and their pressure is 60 over 40 and the heart rate is 150. And this patient then
will, as you can see by looking at the eye, she’s unconscious and they’ll fall on their face, and their pressure will normalize. They’ll get up and fall on their face again.

Now all of the other antihypertensive drugs act by producing controlled postural hypotension, such as guanethidine and methyldopa, and so on. They fix it so that when the patient is erect, they have some lack of postural reflex. But with propranolol, there is no postural hypotension and therefore it works 24 hours a day. Other patients who are on methyldopa or on guanethidine, their anti-hypertensive therapy is only working while they are standing up. The minute they go to bed, they’re hypertensive again, but not with propranolol; it works 24 hours a day. You can get by with only two doses per day, morning and night. And in the treatment of hypertension, in otherwise healthy individual, this probably one of the most important considerations. Because for most, hypertension is asymptomatic. The patient will say, “Why do I have to take this tablet? It’s easy enough for me to forget, I won’t take it in the middle of the day because it’s too much trouble.” So, anything you can do to help the patient comply is very useful.

And with propranolol only two doses are necessary and with some of the newer ones that have a longer half-life known as atenolol, you can get by with one dose per day. This is in hypertension, not in angina. In angina, you have to give the dose three to six times per day.

But the most important is this no stress reaction. Let me just describe the experiment how this was demonstrated. In Glasgow, Scotland, which is an industrial area, they wanted to test this drug in industrial stress. So, the investigator devised a test where the subject, while their pressure and heart rate were being recorded, were asked to select metal balls and put them in five proper holes and each size differed by one millimeter over the next size. And they were checked to see that they sorted these exactly right. At the same time, they had earphones on, and through the earphones, they had a jazz band, a steam engine and a few other things playing. On top of that they had a light that turned on and off. And they weren’t allowed to stop whether the light was on or off. They didn’t know when the light was going to be on. You do this to any human, and the blood pressure goes straight up and the heart rate goes straight up. You do it to a hypertensive, and the heart rate goes up higher and the blood pressure goes up higher. But when you have the patient on propranolol, nothing happened. There is no change in heart rate, there is no change in blood pressure. And this is probably the biggest advantage of propranolol as an anti-hypertensive.

In conclusion, let me give you a couple of pearls about how to use it. Number one, the only dangerous dose is the first one. Only the first dose is dangerous because you’re giving an unknown amount of block in the face of unknown amount of sympathetic activity. So, if you can get by the first does, you’re alright. So, the usual treatment is to start with 10 milligrams four times a day or 20 milligrams four times per day. But once you have an idea of what the response is and you get no effect on the blood pressure, you can keep doubling the dose every two weeks. The maximum dose isn’t known. In one study in Scotland, they set 960 milligrams as the daily upper limit, before you start adding other drugs. Because there is no toxic effect that appears with a big dose that won’t appear with the first dose, with the exception of a very rare occasional skin rash such as you can get with almost any known drug.

In Japan when we went around giving our pitch for propranolol, sponsored by ICI Japan, we said that the dose was 960 milligrams per day, and the Japanese were horrified, not because they thought that was a big dose, but because the Japanese FDA allows them to have only 10 milligram tablets. So, they asked,
“How do you give 960 milligrams per day if you only have 10 milligram tablets?” I answered, “You have to give a lot of tablets.” So, it worked fine.

I have put this in here just to illustrate a couple of totally irrelevant points. In the study of beta blockers, these two things in the middle, ISA intrinsic sympathomimetic action and MSA membrane stabilizing action are always carefully studied with each compound. It turns out however, these are totally irrelevant clinically. First, there is no way you can give a dose big enough of any one of them that has this local anesthetic effect. There is no way you a dose big enough to do this in a human. Oh, I suppose you could, if you injected about 500 milligrams intravenously, but the intravenous dose is 5 milligrams. So, this column is irrelevant. The intrinsic sympathomimetic action which was best illustrated by DCI, meaning it is a partial agonist, this is also clinically irrelevant. It was thought for example a compound that had it, like alprenolol, it would be easier to use because it wouldn’t slow down the heart. But when you use it clinically, it doesn’t make any difference. In the plasma renin activity, you can disregard that. I used to use that as an argument that if you looked through the literature, you could find people who say it either increases or decreases or has no effect on it. The problem is that everybody uses a different method. And the real secret to having plasma renin mean anything is to treat the patient properly. You have to increase it by controlling the salt intake, the water intake, and giving diuretics. If you just take patients and take their blood and measure plasma renin activity, it doesn’t correlate with anything.

And in the other column was some of the compounds show selective activity for one beta receptor or the other. And the only one in which this seemed to have any clinical effect was practotol. That’s third from the bottom. You’ll note that most of them act on all beta receptors. Timolol acts a little on the heart, practotol a little, and atenolol. Practotol did seem to be useful in acting mainly on the heart. This was demonstrated in patients having angina and asthma. Because if you had one that was selected for the heart, it would not act on the bronchial fluid muscles. And practotol seemed to do this. You could use this as a beta blocker and not interfere with respiration. Unfortunately, it turned out that about 15% of all patients on practotol after about 25 months developed such nice things as sclerosing peritonitis and sclerosing otitis media so this compound is no longer available. But no other beta blocking agent has shown this terrible effect of these sclerosing disorders.

So in conclusion when we say that if you set out looking for something and find something else, don’t worry about it. Because what you do find is the valuable thing and what you don’t find, well you wouldn’t know what it was anyway. And the only bad thing this presentation has illustrated is that it took 29 years from the theory until this drug was accepted in the treatment of hypertension. And the way that the FDA is going, the next drug will probably take 39 years. It becomes longer and longer because more and more tests are required. And the single reason why this happens is that the FDA does not believe that there has ever been any valid clinical studies done anywhere except in the United States. Thank you.