Conference on the Role of the Renal Pressor System in Maintenance of Experimental Renal Hypertension

Led by Harry Goldblatt, M.D.

Dr. Goldblatt: I have the questions here in front of me and I shall read the first one, which I see is a loaded one, a prejudiced one, and certainly not formulated by me. It reads as follows: "Is a circulating hormone of renal origin clearly excluded [you see how loaded that is] as the cause of the chronic stage of renal hypertension? If yes, then what is the evidence, and if no, then what are the further studies to be done or repeated to settle this question?" Of course, my answer is simply that there probably is a circulating humoral substance involved in the chronic stage of hypertension, but perhaps Dr. Braun-Menéndez would like to answer this one.

Dr. Braun-Menéndez: I think that there is definite proof of the existence of some kind of humoral pressor substance in experimental hypertension. We have heard Dr. Skeggs today, who found increased concentrations of hypertensin in the blood in cases of experimental renal hypertension and of human hypertension, especially in the malignant form. With regard to the presence of renin, we can’t be so sure, but experiments done by Gollan, Richardson, and Goldblatt show that renin is present in the blood of dogs with chronic experimental renal hypertension. The question of the presence of renin in the blood in hypertension cannot be considered independently of the methods used for its detection. It may be present in very small amounts, our present methods being unable to determine precisely its concentration. For instance, there were no doubts about the presence of insulin in the blood, but only recently has it been detected. The same may be said about the presence of adrenalin. The methods we have used for detection of renin allowed us to detect the presence of renin in renal experimental hypertension of short duration and not in chronic long standing hypertension. The method used by Fasciolo and Taquinii, is probably more sensitive than ours, but I think not specific and quantitative enough. These authors were unable to find any difference in renin concentration in the blood of dogs with chronic experimental hypertension or in human hypertension as compared to normal. Using this method we were also unable to demonstrate an increase of renin in the blood of hypertensive rats, but again this doesn’t mean that such increase doesn’t exist.

Dr. Skeggs: I only have one comment which may be a little bit elementary, but I think it is well to bear in mind that the amount of metabolite found in the blood is a reflection of (a) the amount that is being produced and (b) the rate of utilization. It is possible that very small amounts are liberated and the transfers are very rapid so that its utilization is extremely rapid and little accumulates in the blood.

Dr. Wakerlin: I would only like to comment that Blackett and Pickering reported they could get an increase of blood pressure in rabbits by the intravenous infusion of homologous rabbit renin at such a rate that the increase in renin concentration in the plasma could not be detected even by the most delicate methods of assay. So, if there is no detectable difference with the present methods of assay, this does not prove that there may not be a small difference. I think that positive results are more important than negative results here as in other areas. The fact that it is possible even in dogs with 10 to 11 years of experimental renal hypertension to obtain an antihypertensive effect from antirenin produced by either active or passive immunization, must be explained by anyone who feels there is not a renin pathogenesis of
experimental renal hypertension. As I suggested, the renoprival people and supporters of renin might come together on the possibility that renin might have an intrarenal effect of decreasing the blood pressure regulating or depressing effect which the kidney appears to have.

DR. GOLDBLATT: Dr. Grollman, would you agree that there is such a hormone?

DR. GROLLMAN: Very definitely so! However, I cannot subscribe to the hypothesis just outlined, since it is not in accord with the observed facts, particularly as regards the latent period for the development of hypertension and the prompt response to renin.

DR. WAKERLIN: I have an answer, Dr. Goldblatt, in that acute experimental renal hypertension may be almost exclusively on the basis of increased secretion of renin and when you get into the chronic phase, which begins at the end of the third month, then this depressing effect may set in on a gradual basis. Of course, there is no proof of this, but I don’t think that the theoretical argument that you raised is more valid than the theoretical answer that I have given.

DR. GOLDBLATT: When you used the word depressant, Dr. Wakerlin, in what sense were you using it and what is this agent you are talking about? Is it an activity or a definite substance circulating in the blood, or is it present in the kidney? I would like to have Dr. Grollman also comment on that.

DR. WAKERLIN: It may be a substance which can be washed out of the kidney by the kind of experiment that Dr. Kolff carried out, for instance.

DR. GOLDBLATT: Do you agree to that, Dr. Grollman?

DR. GROLLMAN: I consider the pressor response to be a consequence of the failure of the kidney to produce an essential agent in the absence of which hypertension ensues.

DR. GOLDBLATT: Do you think it all happens in the kidneys?

DR. GROLLMAN: No. I think it affects many tissues throughout the body. It is a systemic response.

DR. GOLDBLATT: What about the depressor effect presumably brought about in the kidney?

DR. GROLLMAN: I think it is produced by the kidney, but I would not designate it as a "depressor" because it does not lower the blood pressure in the normal organism. It is "essential" in the same sense that one could consider insulin as essential to prevent the appearance of acetone in the breath. Insulin doesn’t destroy acetone but in its absence acetone appears in the body.

DR. GOLDBLATT: The use of that word "depressor" in this connection certainly should be clarified.

DR. BRAUN-MENÉNDEZ: I agree with the wording of Dr. Grollman, something in the absence of which hypertension results, but that doesn’t mean, of course, that it should be a specific depressor substance.

DR. GROLLMAN: Since it does not lower the blood pressure in a normal animal it is obviously not "depressor."

DR. BRAUN-MENÉNDEZ: It may not be a substance at all, it may be some action of the kidney.

DR. GROLLMAN: Yes, that is certainly possible.

DR. GOLDBLATT: We welcome any questions from the group. Dr. Blaquier, do you have a comment to make on that?

DR. BLAQUIER: I would like to add that the difficulties of testing the amount of renin arise not only because of its small concentration, but also because of its quick action in transforming hypertensinogen into hypertensin. The hypertensinase present in the blood inactivates the hypertensin being formed. There are sensitive methods which can pick up the normal amount of renin present in the plasma of normal subjects. The main problem, I believe, does not arise because of the insensitivity of our methods, but because of the speed with which this substance is metabolized.

DR. BUMPUS: I would like to add one thing. A test for a substance such as angiotonin is not specific and one cannot say without a doubt that it is formed until we get an antiangiotonin. However, with renin this is
not true, for with antirenin you can without a doubt show its presence.

**Dr. Wakerlin:** I would like to add something to that, Mr. Chairman. About 12 years ago we attempted to produce an antiangiotonin or antihypertensin. The materials we had at that time, of course, were relatively crude and the amounts were not large. We did not succeed in producing an antihypertensin or antiangiotonin, but I think now that with the better methods, with the purified materials which I would hope could be obtained in quantities, it ought to be tried again. I might say that some 17 or 18 years ago our research group did produce an antivasopressin with the kind of vasopressin that was available at that time. This was the Parke-Davis material, Pitressin. It would seem to me that it might be well if this work were repeated with synthetic hypertensin now available. I would certainly think it possible, although the hypertensin molecule I think is smaller. Vasopressin has how many amino acids in it? 

**Dr. Bumpus:** Nine.

**Dr. Wakerlin:** Well, if you can get it with vasopressin having 9 amino acids, I think that it would be possible to get it with hypertensin II which has 8. We thought years ago that the reason we couldn't get an antihypertensin and we did get an antivasopressin was that the vasopressin molecule was larger.

**Dr. Goldblatt:** In our laboratory Dr. S. Deodhar, Dr. Erwin Haas and I have been working on this subject and recently Dr. Deodhar, by employing a hypertensin-albumin complex as the antigen, has succeeded in obtaining some evidence for the successful formation of antihypertensin (not hypertensinase) in the serum of an immunized rabbit. This work is still in the preliminary, unpublished stage.

**Dr. Surtshin:** I would like to ask Dr. Goldblatt to comment on his interpretation of the experiments of LeFebvre referred to in this morning's discussion period by Dr. Kolff in which kidneys from normal or renal hypertensive dogs were grafted into normal canine recipients.

**Dr. Goldblatt:** I prefer not to answer that question, because I have an innate, rather intense aversion for that kind of experiment, especially when it is used to answer a question about a chronic condition. I believe I should ask Dr. Kolff to clarify, or have someone else answer. I just cannot get myself to apply the results of acute experiments like that to the problem of the chronic phase of hypertension. Years ago, before we produced experimental renal hypertension, two other experimenters constricted the renal arteries of some animals, cats, I believe, and watched a kymographic tracing for the immediate effect on the blood pressure. They were pharmacologists, accustomed to plan acute experiments lasting only a few hours. Nothing happened, so they concluded that there was no effect on the blood pressure as a result of clamping the renal arteries. Had we been familiar with the results of these two experiments, before we began our study, we might not have had the courage to do what we did. Fortunately, we did not know it and, being pathologists, accustomed to wait a long time for our quarry, we designed a long lasting experiment for the investigation of a chronic condition such as essential human hypertension.

**Dr. Surtshin:** I still think that the Belgian experiment requires careful consideration.

**Dr. Goldblatt:** Would someone like to come forward and try to answer?

**Dr. Grollman:** I would say it is true that the kidneys were obviously not producing a pressor substance, and I think in that case the experiments are very valid. The only objection to it could be that the preparation per se is so poor that it might prevent that rise. This would be the type of objection that I think Dr. Goldblatt is referring to.

**Dr. Goldblatt:** There are times when certain experimental conditions imposed on an animal will result in complete suppression of the output of urine. Would you conclude from this that the kidney is not an excretory organ? That is the sort of reasoning of which
some investigators engaged in acute experiments have been guilty.

Dr. Wakerlin: I think too that the blood pressure regulation that Dr. Grollman talks about as coming from the kidney is in no way in contradiction with the strong possibility that the kidney also has, even at the same time, under certain circumstances, a positive pressor effect. I do not see any inconsistency in these two views. If we adopt one we do not necessarily have to reject the other.

Dr. Haas: This is in answer to the point raised by Dr. Surtshin. Variable amounts of renin can be released, apparently, from the grafted kidney, in the experiments carried out by Dr. Kolff and others, depending on the state of the grafted kidney. For example, the amount of renin which can be isolated from rabbit kidneys, in vitro, can vary almost twentyfold, depending on their history. From fresh kidney, about 0.3 unit of renin can be extracted per gram of tissue, while previous autolysis at body temperature, or repeated freezing and thawing can increase this value up to 12 units per Gm. This large amount of renin could be the cause of a considerable pressor activity, considering that 1 unit of renin induces a blood pressure elevation of 30 mm. Hg.

Dr. Helmer: We have a lot of evidence for a pressor agent in chronic hypertensive rats. Renal vein blood from hypertensive rats caused a sustained rise in pressure when injected intravenously into pithed cats that had been nephrectomized 18 to 24 hours previously. The renal vein blood from normotensive rats did not have this factor. This material could not be demonstrated in the peripheral blood of hypertensive rats. One objection could be made to these experiments. The 2 to 3 ml. of blood that had to be drawn might cause a release of renin. If such is the case, then renin is released from the hypertensive kidney more easily than from the normotensive one.

Dr. Tobian: What sort of hypertension did the rats have?

Dr. Helmer: They were Goldblatt-hypertensive rats.

Dr. Goldblatt: The second question overlaps the first. I shall read it to you so that you can think about it. It says, "What is the precise nature of the stimulus which liberates, acutely or chronically, a renal pressor substance when renal hypertension is initiated or maintained?" It is almost a reversal of the first question, an admission that there may be some such thing as a pressor substance, and the question is, what is the stimulus? In other words, this is where the experiment cited by Dr. Kolff comes in again. I would like to hear from Dr. Kolff on that.

Dr. Kolff: I believe the change from pulsatile to nonpulsatile perfusion of the kidneys under the most favorable conditions in an animal that is proved to be susceptible to renin production does not show any demonstrable difference. However, in such an animal there is a demonstrable output of renin if you reduce the total perfusion pressure or the total perfusion flow. On the other hand, Hawthorne performs more chronic experiments, producing nonpulsatile perfusion of the kidney by putting the clamp on the aorta above the kidney. Hypertension develops in these dogs. If he then takes these dogs, after a certain time, and makes an arteriovenous anastomosis between the femoral arteries and the femoral vein, then the hypertension that had previously developed disappears again when a pulsatile flow is restored to the kidneys of that animal. The only way I can reconcile these experiments is the way that has been suggested by Dr. Wakerlin just now, which is that the acute outpouring of renin is something entirely different from the constant outpouring of a very small amount of renin. I believe that this small amount of renin is probably being poured out by a nonpulsatile perfusion of the kidney not sufficient to cause a pressor response in itself, but sufficient to destroy the blood pressure reducing function of the kidney of which Dr. Grollman is the champion.

Dr. Wakerlin: I think we can certainly say that renal ischemia has been proved by a number of investigative groups not to be necessary for the hypertensive effect of the
kidney following bilateral renal artery constriction. I think it has been proved, within the limits of at least a 5 per cent reduction, that reduced renal blood flow is not primary for the release of the renal pressor substance, or whatever the mechanism is for the production of experimental renal hypertension. Yet one still sees in the literature "renal ischemic hypertension."

**Dr. Goldblatt**: Well, I think that once you grant that there is such a thing as ischemia you have to grant that there are various grades of it so that even the slightest reduction in the renal blood flow can still be considered ischemia. Call it by another name, if you like, so long as you define it and say that there is a reduction in blood supply to the functioning components of the kidney. Dr. Homer Smith, who is not a champion of the primary renal origin of hypertension, nonetheless has made the unequivocal statement to me that, so far as he and his group are concerned, they have found something wrong with the function of the kidney even in the early stage of essential hypertension. How early this means I cannot tell you at this moment, but the following is an extract quoted from his communication to me: "In early hypertensive disease $T_m$ appears to be significantly depressed, indicating impairment of tubular function. The renal plasma flow is decreased, increasing the filtration fraction. But the filtration rate may remain within the normal range until $T_m$ is substantially reduced. With a normal filtration rate there would, of course, be no nitrogen retention. If there is 'renal impairment' beyond the decrease in $T_m$ and the increase in filtration fraction in early hypertension, we cannot as yet define it."

**Dr. Wakerlin**: As Dr. Kolff said, the conclusion of Dr. Hawthorne and his group is that the initiating stimulus is a reduction in the arterial volume pulse of the kidney, not any change in the pulse pressure, but in the volume pulse or palpable pulse in the kidney.

**Dr. Goldblatt**: I wish Dr. Page were here to comment on this matter.

**Dr. Wakerlin**: I don’t think it could possibly be due to the pulse pressure because of the experiment Dr. Page himself did, in which he placed a silk bag around the kidney and obtained hypertension. The effect in this procedure would be to increase the pulse pressure.

**Dr. Surtshin**: Did Dr. Smith imply that an early depression of the tubular maximum for Diodrast was followed by restoration of $T_m$ to normal in the presence of maintained hypertension?

**Dr. Goldblatt**: I regret that I am not in a position to quote Dr. Homer Smith about the later stage of established hypertension and, as I said, I am not exactly sure what he means by early hypertensive disease, but my own interpretation of the statement I have quoted is that $T_m$ would remain depressed, as in the early stage of hypertension, and gradually become more impaired.

**Dr. Rodbard**: In some earlier work in which we applied an acute intracranial compression, an acute hypertension resulted, initiated by the stimulation of an intracranial blood pressure receptor. The mechanism appears to operate by means of changes in the intramural pressure, i.e., the effective intra-arterial pressure. At the moment of compression, the intra-arterial pressure remained unchanged; however, presumptive receptors inside the blood vessel wall would respond as if the blood pressure had fallen. The hypertensive response is then initiated to counterbalance the apparent, but unreal, intra-arterial pressure fall.

We may implicate a similar mechanism in the kidney. Let us assume that in the renal arterial system there are similar receptors. When the renal arteries are sufficiently distended, receptors would be in an inactive state. However, when the pressure inside the renal arteries falls, as it does with the application of a Goldblatt clamp, by an increase in intrarenal tissue pressure as in hydronephrosis, by extrarenal support as by the Page perinephritis technic, or in the raised intrarenal pressure of polycystic kidneys—in all of these the relative intrarenal tissue pressure increases. A reduced tension in the renal
receptors of the renal arteriole walls would result, just as if the blood pressure had fallen. Under these circumstances the elaboration of pressor material from the intrarenal arterioles would be initiated to increase the renal perfusion. This mechanism would act effectively to return the intrarenal arteries to their proper state of distention. Such a mechanism would fit with some of the discussion by Dr. Kolff this morning. Dr. Howard G. Swann$^{10}$ of Galveston has compressed kidneys and shown that after an hour or so, pressor material begins to enter the circulation.

Such a baroreceptor concept may help clarify some of the thinking on the problem. If this mechanistic approach is further supported, it would no longer be necessary to focus attention on the excretory function of the kidney. Instead, we could look more effectively for a relatively simple pressure-sensitive mechanism which would respond to the tension in the wall of the renal arterioles.

**Dr. Findley:** What happened to the word tachyphylaxis? Has that ceased to be a problem?

**Dr. Goldblatt:** I wish I could show you illustrations of an experiment which Dr. Haas and I did a number of years ago. If you read about tachyphylaxis I think you will find that renin tachyphylaxis, or the failure of the pressor mechanism to respond to repeated injections of the same dose of the same substance (renin), results only when every injection after the first is given before the blood pressure has returned to the original level. When we made repeated injections of 2 units of renin in the unanesthetized dog and waited 1 hour between successive injections, the blood pressure went up exactly the same amount after every injection. Our experiment lasted about 8 hours, I believe.$^{11}$

Under those conditions, at least, there is no tachyphylaxis; but when you do not wait long enough between injections there appears to be what is called tachyphylaxis. We presume that in these circumstances the vessels are still in a state of constriction as a response to the previous dose and the response is less. If that is tachyphylaxis, then there is such a process.

**Dr. Helmer:** Dr. Goldblatt, we did even better than you. We got a resident to stay up all night to do the same experiment that you did. He injected a cat every hour and didn't get any tachyphylaxis at all.

**Dr. Wakerlin:** One of my graduate students (Mr. Leonard Graham) solved this problem so that he got his sleep and also his injections of renin in sufficient quantity in a given period of time. He did it by injecting antirenin intravenously into each nephrectomized assay dog after the peak of the blood pressure increase from renin. With amounts of antirenin, sufficient to neutralize the renin injected, he has been able to delay the onset of tachyphylaxis and to carry out large numbers of renin determinations in a single dog.$^{12}$

**Dr. Goldblatt:** The question then is, what is tachyphylaxis?

**Dr. McCubbin:** We do find tachyphylaxis with the renin preparations that we use. One thing that might account for some of the confusion is that these quite crude preparations may well contain some of the depressor extract that Dr. Grollman is so interested in; it might block the response to renin and angiotonin. With these preparations response to both renin and angiotonin disappeared after tachyphylaxis, while response to noradrenal and other drugs was unaffected. I would also like to suggest that with the pure preparation we might get an entirely different effect.

**Dr. Goldblatt:** Did you wait until the blood pressure had returned to normal each time?

**Dr. McCubbin:** Yes.

**Dr. Schwarz:** The rise Dr. Goldblatt gets with a certain dose of renin depends on the blood pressure of that dog or the state of constriction of the vessels, is that correct? If you do not wait long enough the rise will be smaller with the same dose. We do not observe that with angiotonin and we all assume the action of renin is due to the formation of angiotonin. How do you explain this?

**Dr. Goldblatt:** Well, of course, in the
case of the renin there is a time factor involved. As you know, renin continues to circulate and to act for a considerable length of time, by producing angiotonin; while angiotonin gives almost an immediate response and the return to the original level is prompt. I think the differences may lie there, if that is what you are after. I am not too clear about the significance of your question.

Dr. Schwarz: I am saying that the same amount of angiotonin is formed from the same dose of renin regardless of blood pressure and that the response to an injected dose of angiotonin can be superimposed onto infused angiotonin without being reduced.

Dr. Goldblatt: You are relating angiotonin to renin tachyphylaxis. I am not aware that there is such a thing as angiotonin tachyphylaxis.

Dr. Braun-Menéndez: I think the phenomenon of tachyphylaxis occurs when the substance is still in circulation and acting. If the substance rapidly disappears, as in the case of hypertensin or angiotonin, then you do not have tachyphylaxis. If you inject angiotonin at the height of the blood pressure response then you don't get a similar rise because the receptors are already occupied by the substance, but if you allow the blood pressure to come down and the substance to disappear from the blood and the receptors, you get exactly the same response. One unit of renin takes about ½ hour at least to disappear from the blood; if you give 2 units it would take longer. If you wait long enough before you inject renin again the animal is in the same condition as he was before; no renin circulating in the blood, no hypertensin being formed, no vasoconstriction, and you don't get tachyphylaxis.

Dr. Bumpus: I would like to add one thing to this. When crude angiotonin is infused over a long period of time the response goes down. However, pure angiotonin can be infused all day in an animal and the response will not go down. This could possibly indicate that what you are doing with renin, when allowing the pressure to return to normal each time before the repeating injection, is to allow the animal to rid itself of all metabolites of angiotonin. It may be these metabolites that are causing the decrease in the response each time. By allowing the body to rid itself each time of possible metabolites after injection of renin the receptors could not be tied up. This may be an explanation for the two existing opinions on renin tachyphylaxis.

Dr. Goldblatt: The panel agrees that we ought to go on to question no. 3, which is an important one. "How long after unilateral renal ischemia in man or animal can removal of the offending kidney result in unequivocal and permanent cure of the hypertension?" Would someone like to take that from here?

Dr. Wakerlin: I think you ought to answer it, Mr. Chairman; you answered it partly in your paper this morning.

Dr. Goldblatt: Well, Dr. Wakerlin, just a few months back I would not have had as much to say as I have today. Of course, I can tell many stories about the disappearance of hypertension as a result of the removal of a diseased kidney, when the other kidney was normal. I have in mind a little girl, 12½ years old, with a blood pressure of 260/160, which was called juvenile essential hypertension. She had one small kidney almost functionless and a contralateral kidney with excretory function within normal limits. The small kidney was removed and it was the seat of pyelonephritis and vascular disease. I saw her 1½ years later and her blood pressure was 110/65. This was 18 years ago. She married, has had 3 children, and 3 husbands, a pretty normal young woman, as you see. Now, as a result of the publications of Dr. Homer Smith of New York University, and of Dr. Thompson of the Mayo Clinic, we know about several hundred authenticated cases of patients with clinical essential hypertension, but with unilateral renal disease (usually pyelonephritis or vascular disease) whose blood pressure has remained normal from at least 1 to 18 years after the removal of the diseased kidney. I do not see how we can get away from the fact that something coming from the diseased kidney, which brings about the elevated blood...
Dr. Grollman: In my own experience I would say that it is a relatively infrequent occurrence. I have been interested in and have followed some of these patients, including the one from Dallas that you mentioned. The condition should be considered particularly in thrombosis or infarction of the kidney, the ones that have shown the most favorable response. If followed for any length of time, many of the other patients subjected to nephrectomy have manifested a return of their blood pressure to its formerly high levels, or have suffered an exacerbation of their disease with death following unilateral nephrectomy. These failures obviously are not reported in the literature which gives the reader a false notion of the true state of affairs.

Dr. Goldblatt: Dr. Homer Smith has gone into this matter with great care, reserve and restraint, yet he has come to the unequivocal conclusion that there has been a cure of the hypertension in 149 of 575 patients whose cases have been reported in the literature, that is 26 per cent, and Dr. Thompson of the Mayo Clinic in a large group of cases with unilateral atrophic kidneys, found that 50 per cent had been cured. I agree with you that the condition of unilateral renal disease is a comparatively infrequent phenomenon in human beings with essential hypertension, but that does not matter. Granted that you may find unilateral renal disease of one type or another in only one in every 500 patients with so-called essential hypertension, we are interested in the basic phenomenon involved in the development of the hypertension and the basic phenomenon, I believe, is the disturbance of the intrarenal hemodynamics, which is probably similar to that produced by constriction of the main renal artery in an animal.

Dr. Stampler: Two questions, Dr. Goldblatt: First, what is the interpretation of those cases of essential hypertension in which demonstrable obliterative vascular disease has presumably not been noted, e.g., in the biopsy studies by Smithwick and Castleman and in the autopsy studies by E. T. Bell. Second,
to shift from the problems of pathogenesis of the pressor response, which has been the focus thus far today, to problems of etiology of the presumed underlying pathologic process, what is responsible for the obliterator arteriolar vascular disease?

Dr. Goldblatt: Because I have to close this discussion in a few minutes, and because I am in a position to answer your questions, I am going to take the prerogative of the Chairman to try it. So far as Castleman and Smithwick are concerned, you must realize that a minute piece of tissue from the cortex alone cannot possibly give a reliable estimate of the hemodynamic state of the entire kidney. It tells you absolutely nothing; in other words, about the larger blood vessels in the kidney, or outside of it, and, insofar as pyelonephritis is concerned, it is the larger intrarenal vessels which most frequently show the obliterator fibroelastosis, not the small ones, which occur in the periphery of the cortex. To me it was therefore gratifying that Castleman and Smithwick found as much vascular disease as they reported. Bell, of course, found it in 100 per cent of the cases, but at autopsy, and he regards the vascular disease as secondary to the hypertension. There are many things involved in the consideration of this topic which cannot be covered at this time. The other part of your question referred to the etiology of the vascular disease. Well, those of you who have read my reviews on the subject of hypertension know that I, too, consider the etiology and pathogenesis of the vascular disease of prime importance. That is still problem number one, to which I cannot give the answer at present.

**Summary**

The hypothetical presence of increased circulating renin or hypertensin in chronic renal hypertension was debated; eventually it was agreed that methods were too insensitive for accurate assay. Pressor amounts of infused renin could not be detected by some methods of bioassay (Dr. Wakerlin). Hypertensinase activity in blood may destroy the end product before the assay can be performed (Dr. Blaquier). Perhaps rapid tissue removal from circulating blood may account for the inadequacy of the results (Dr. Skeggs). Previous experiments to detect these substances in circulating hypertensive blood have been indecisive (Dr. Braun-Menéndez) or only weakly positive (Drs. Goldblatt and Skeggs) and the clear-cut depressor effects of antirenin might act on a hypothetical nonpressor action of renin (Dr. Wakerlin). Dr. Helmer commented on the sustained pressor substance found in renal vein blood of hypertensive rats. Dr. Grollman believed chronic renal hypertension to be due to interference with an essential function of the kidney which in the normal animal prevents the blood pressure from rising. The failure of the blood pressure to rise when the kidneys from renal hypertensive dogs were perfused in situ by normotensive recipients was again discussed by Drs. Surtshin, Goldblatt and Grollman, and the possible fallacies involved in reasoning from such acute experiments were brought out.

The nature of the stimulus to renin release was discussed again by Dr. Kolff. Non pulsatile flow was probably not a requirement (Dr. Kolff), nor was renal ischemia (Dr. Wakerlin), but some alteration in renal function seemed to be necessary (Dr. Goldblatt). Dr. Wakerlin and Dr. Rodbard advocated, respectively, the view that the primary stimulus might be the volume pulse or the transmural pressure in the renal arterial bed.

An objection to renin as the cause of chronic hypertension based on tachyphylaxis experiments was raised by Dr. Findley. Dr. Goldblatt denied the presence of true tachyphylaxis and was supported by Drs. Helmer and Wakerlin. Dr. McCubbin suggested it might occur only with cruder preparations of renin, and Dr. Braun-Menéndez theorized that receptor sites might be occupied for a time after restoration of normal blood pressure, thus giving rise to a transient tachyphylaxis. Dr. Bumpus supported this explanation by reporting that a pressor response to crude angiotonin can sometimes not be maintained,
while the response to pure angiotonin is persistent.

Considerable discussion ensued between Drs. Goldblatt and Grollman concerning the mechanism of blood pressure reduction by removal of a single ischemic kidney. The human renal biopsy and autopsy studies suggesting the primacy of renal arteriolosclerosis in human hypertension were reviewed by Dr. Goldblatt.

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