Conference on Electrolyte and Adrenal Factors in Human and Experimental Renal Hypertension

Led by David F. Bohr, M.D.

Dr. Bohr: I would like to hear first from Dr. Leonard about some work he has done with the artery strip. I have asked him to tell us also about a factor he has found in hypertensive plasma that differs from that in normal plasma.

Dr. Leonard: Last year I did some work on artery strips made by cutting rabbit carotid artery in the form of a helix. My viewpoint was somewhat different from Dr. Bohr's in that I was interested not only in the reactivity to a given stimulus but also in tone or baseline tension. I won't bore you with definitions of tone at the moment. In these experiments, then, tension rather than shortening was measured, the strip being suspended between a fixed point and a strain gage cantilever. In figure 1 is seen the response of this rabbit carotid artery strip to electric stimulation using a short train of AC current. These are photographs of a continuous experimental tracing. The distance from the bottom line to the top line is the same in each of these sets of tracings. At point zero the strip was stimulated electrically and you can see that a contractile response occurred. At A, the Krebs bicarbonate solution bathing the strip was changed to one containing no potassium, and the strip was again stimulated at the 20 minute point on the tracing. The magnitude of the tension response is somewhat increased over the control, but what I want to emphasize is that the time required for relaxation is increased. Indeed, by the end of 20 minutes you can see (C) that the tension of this strip is above the base line. The phenomenon is more marked after another stimulation, at the 40 minute point, and you can see that this strip shows no indication of dropping back to its original base line tension. This is in a solution containing no potassium. When the bath is replaced by a solution containing potassium, as was done at point F, the tension immediately, or quite rapidly, returns to the base line value. Electric stimulation is then followed by rapid and complete relaxation.

In figure 2 you see a similar phenomenon, this time produced not by a potassium-free bath but by a solution, added at A, which contains strophanthidin. As you probably know, it is now thought that cardiac glycosides cause a decrease in intracellular potassium. The preparations represented by these 2 figures have in common the fact that intracellular potassium is decreased. In both the base line does not return to normal. Indeed, at point C in the third tracing contracture occurs. One of the pretty things about this phenomenon is that it is quite reversible. At 45 minutes the strip was washed, the washing artifacts can be seen, and tension returned to normal. The post-strophanthidin response (60 minutes) resembles the control. It appears, then, that base line tension can be influenced by the level of intracellular potassium.

Dr. Bohr related epinephrine-responsive-ness to membrane potential and then pointed out that the membrane potential depends on the ratio of potassium concentration inside the cell to the potassium concentration in the extracellular fluid. The membrane potential depends on the log Kt/Km. This means that changes in intracellular potassium which may be very large in terms of the effect on the contractile properties of the actomyosin will produce very small changes in the membrane potential. Just to take an example, if you have a potassium concentration in the cell of 100 mEq per L. and a potassium concentration outside of 5 mEq per L. giving a ratio of 20,
the logarithm of the ratio is 1.30. If the potassium inside the cell goes from 100 to 110, the ratio increases from 20 to 22 and the logarithm is 1.32. The change in membrane potential accompanying this large change in potassium concentration will be very small. If increases in intracellular potassium have to do with changes in responsiveness or changes in base line tension, I do not think that this is mediated by the membrane potential.

Dr. Bohr: Say a few words about the factor in the plasma.

Dr. Leonard: Dr. Bohr gave me this time on the proviso that I would summarize the work that Dr. Steven Hajdu and I have been doing in the last year and a half. This has to do with the action of plasma on frog cardiac muscle. We have found that there is a system in plasma which has a rather striking effect on certain contractile properties of cardiac muscle. We selected a group of patients with severe essential hypertension with all the secondary changes in appropriate organs. When this group is compared with a group of normal persons, a striking difference in the amount of plasma activity is evident, with the severe essential hypertension group hav-
ing higher activity. Since September 1956 we have been trying to characterize this system. All we can state at the moment is that it contains at least 2 protein components. We feel that we cannot say anything about the biologic significance of this system until it is isolated and studied.

DR. BOHR: Would you say that there is a difference between hypertensive and normal plasma?

DR. LEONARD: We have found a difference.

DR. BOHR: I would like to ask Dr. Sturtevant to tell us about a new hypotensive steroid.

DR. STURTEVANT: Since it is well-known that desoxycorticosterone is capable of inducing a self-sustaining hypertension in the rat (metacorticoid hypertension) we have been investigating the ability of synthetic steroids to reverse this hypertension in the hope that eventually some such steroid might induce a self-sustaining normotension. A compound of recent interest to us was SC-6584 (17α propyl-4, 5 3-dihydro-19-nortestosterone) synthesized by Dr. F. B. Colton and L. M. Nysted, which was found to be hypotensive in acute experiments on metacorticoid, perinephritic, and "adrenal-regeneration" hypertensive rats.

The results of chronic administration of SC-6584 on the blood pressure of metacorticoid rats are depicted in figure 3. The upper curve represents the controls, which were sacrificed at the end of the treatment period. The lower curve represents the treated group, half of which were sacrificed with the controls. Similar results were obtained when the experiment was repeated with chronic perinephritic hypertensive rats (fig. 4).

The interaction of SC-6584 with DCA was studied in the next experiment. Group A served as untreated control rats, group B received a 20 mg. DCA pellet only, group C, 44 daily injections of SC-6584, and group D, a DCA pellet plus SC-6584 injections. The measurements of fluid and sodium intake, output of water, sodium, and potassium and the urinary sodium:potassium ratio all showed the same general trend as exemplified in figure 5 for sodium excretion. The action of SC-6584 was opposite that of DCA in both the DCA and the non-DCA treated groups. SC-6584 has been found to be essentially devoid of any other kind of steroid property in standard tests run by our division. The single exception is barbiturate potentiation; however, the substance has no anesthetic action by itself and is nontoxic in large doses.

In the investigation of some 2 dozen derivatives of SC-6584 (20 mg. per Kg. subcutaneously) for their acute hypotensive potencies in the metacorticoid rat, we uncovered homolog specificity that may be of some interest (fig. 6). In the 4, 5-dihydro series, the activity of the propyl SC-6584, was shared by the methyl, but not by the ethyl homolog. In fact, the ethyl compound was still inactive at...
doses up to 60 mg. per Kg. It is interesting to compare this situation with that found in the 4, 5-dehydro series, where the methyl was inactive and the ethyl and propyl were active.

In summary, SC-6584 is a nontoxic steroid with a hypotensive action separable from other steroid actions and with an effect on water and electrolyte metabolism opposite to that of DCA.

Dr. Bohr: Although Dr. Sturtevant does not consider it as such, this could be used as strong evidence for the involvement of the adrenal glands in hypertension. Let’s hear from Dr. Fregly who can discourage such a concept.

Dr. Fregly: There is almost complete agreement that adrenalectomy of renal hypertensive animals and man is followed by reduction of blood pressure toward normal levels. There is further agreement that replacement of the adrenocortical hormones in adrenalectomized-hypertensive animals or man returns the blood pressure to hypertensive levels. This would seem to indicate that adrenalectomy does not “cure” hypertension but that algebraic summation of the effect of adrenalectomy added to the effects of hypertension produces a reduction in blood pressure. This makes it difficult to evaluate the role of the adrenal cortex in the maintenance of hypertension. Whether pressure is maintained by a substance or substances elaborated in excess by it, or whether this fall in blood pressure following adrenalectomy really results from indirect changes accompanying ablation of the adrenal glands is not yet completely settled.

I therefore tried to study the role of the adrenal in the development of renal hypertension. I wished to determine whether it was possible to produce hypertension in adrenalectomized rats by latex encapsulation of both kidneys. Both male and female rats of the Sprague-Dawley strain were used. Fifty-four female rats were adrenalectomized and their kidneys were encapsulated in a single-stage operation. Twenty-five other female rats were adrenalectomized to serve as controls. Eighteen male rats were used and the procedure varied somewhat; these were adrenalectomized first and 2 weeks later their kidneys were encapsulated. Thirteen other male rats were adrenalectomized to serve as controls. The results are shown in figure 7. In both male and female adrenalectomized-encapsulated rats the blood pressure rose to a high level which was maintained. The control adrenalectomized rats did not show a significant elevation in pressure. When parts A and B of this figure are compared, it will be observed that the time course of the elevation of pressure and the maximal elevation obtained are similar for adrenalectomized-encapsulated rats and encapsulated rats with intact adrenal glands.
**Question:** What are these rats being treated with, Dr. Fregly?

**Dr. Fregly:** These rats are on Purina diet, with a choice between water and 0.9 per cent sodium chloride solution as drinking fluids.

In an experiment such as this it is extremely important to determine whether or not the animals are completely adrenalectomized, that is, whether there is any accessory adrenal tissue present. To assess completeness of adrenalectomy I have (a) subjected all rats to cold air (5 C.) to test their ability to maintain body temperature, (b) measured their growth rates, (c) measured fluid intakes when the animals were given choice between water and 0.9 per cent sodium chloride solution to drink, and (d) autopsied all rats to determine whether adrenal tissues were present. Adrenalectomized-encapsulated rats cooled approximately twice as fast as normal or encapsulated rats. Growth rates of adrenalectomized-encapsulated rats were similar to those of adrenalectomized rats and both of these groups grew more slowly than either normal or encapsulated rats. The amount of 0.9 per cent sodium chloride solution ingested by adrenalectomized-encapsulated rats was similar to that by adrenalectomized rats; however, water intake of adrenalectomized-encapsulated rats was 2 to 3 times greater than that of adrenalectomized rats. Autopsies revealed no adrenal tissue in either adrenalectomized group. The heart weight to body weight ratio of adrenalectomized-encapsulated rats was similar to that of encapsulated rats. Both these groups had significantly larger heart weights than either normal or adrenalectomized rats.

In conclusion, I feel that adrenalectomy was complete and that hypertension can be induced in adrenalectomized rats. It is also true that bilateral adrenalectomy of established hypertensive rats will reduce the elevated blood pressure. Future experiments must elucidate whether the role of the adrenal cortex in the maintenance of renal hypertension is a direct or an indirect one.

**Dr. Bohr:** Now let us look at some of the conference questions. The first one is:

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**Fig. 7.** Average weekly blood pressure measurements of adrenalectomized, kidney-encapsulated female (black square) and male (black circle) rats. Operation at zero time for the females, single stage adrenalectomy and encapsulation; for the males, encapsulation 2 weeks after adrenalectomy. B. Average weekly blood pressure measurements of normal rats (open circles) and rats with kidneys encapsulated and adrenals intact (black circles). (Reprinted from Am. J. Physiol. 191: 542, 1957.)

"What is the role of the adrenal hormones in various forms of hypertension?" Dr. Dus-tan has already evaluated various possibilities. This diagram indicates possible relations between the kidney and the adrenal cortex in the production of hypertension:

1. Kidney → adrenal → hypertension
2. Adrenal → kidney → hypertension
3. Kidney → hypertension
Adrenal → hypertension
4. Other

The panelists have heard the evidence and each will vote for his choice with a one sentence summary supporting his decision. Let's start with Dr. Skelton.

**Dr. Skelton:** I'll take number 2, but I shall reserve my reasons for doing so until later.
Dr. Bohr: Dr. Findley?

Dr. Findley: Well, I vote for number 1. No very good reason except that I am struck with the fact that the kidney mass has to be reduced, apparently, before any of these glandular tricks will work.

Dr. Bohr: Dr. Tobian?

Dr. Tobian: Is this in all types of hypertension or in adrenal hypertension?

Dr. Bohr: This is all types of hypertension.

Dr. Tobian: Well, I vote for 2 and 3 both.

Dr. Bohr: Dr. Dustan? (Dr. Dustan has really already voted, but she may vote again.)

Dr. Dustan: I cannot do anything but accept them all.

Dr. Bohr: Fine. Dr. Weller?

Dr. Weller: Well, it is a terrible question. I think that number 3 is probably the best choice that I can make, although I agree with Dr. Findley that number 1 is probably more attractive if we are talking about human essential hypertension.

Dr. Morita: I think that I would also vote for number 1, especially as it applies to humans.

Dr. Bohr: You have heard the jury's verdict, and the answer is that we do not know the sequence of events. There obviously is some involvement of the adrenal gland and without belaboring its possible role, which was so adroitly evaluated by Dr. Dustan this morning, I should like to describe the simplest of possibilities in relation to the second question posed to this conference: "What is the effect of vascular reactivity and sodium distribution between cells and extracellular space on the final mechanism in all forms of hypertension?" We might break this down and ask first: "Is vascular reactivity altered in hypertension?" Then the second part of the question would be: "Is there an altered electrolyte distribution in hypertension?" A simple mechanism for hypertension can be described if we are willing to concede that both of these questions have affirmative answers. Assuming that the primary determinants of vascular tone are the neurogenic-adrenergic influence and circulating epinephrine, and that the shift in cell membrane electrolyte gradients occurring in hypertension significantly increases the response of vascular smooth muscle to these stimuli, the whole problem of the mechanism of hypertension would be resolved, at least superficially. Let's look at the question of vascular reactivity. Is it really altered in hypertension? What evidence is there for altered vascular reactivity in hypertension? Would one of the panel care to tackle this question?

Dr. Tobian: Well, I'd like to make a few comments. A lot of people have made studies suggesting that vascular reactivity is altered. If you study the circulation in the forearm of nail bed you can show that it takes a smaller amount of adrenaline in a hypertensive patient to cause a given decrease in blood flow. This has been interpreted as a greatly heightened reactivity. I think we will have to admit that it takes less adrenaline to cause a given degree of reduction of flow in hypertensive individuals, but I do not think this necessarily means that the individual muscle fiber is hyper-reactive, and this is really the basic question. These studies are always comparing normotensive and hypertensive persons, and the initial size of the lumen of the arterioles is not the same to begin with. The hypertensive individual always has a narrower arteriolar lumen than does the normotensive, otherwise he would not be hypertensive. Since arteries in different conditions are being compared, the fact that it takes less adrenaline to get the same degree of constriction really has not satisfactorily proved that the fiber is actually more sensitive to adrenaline. It may be, but I do not think that it has been proved by the 3 or 4 studies of this general type. It can be shown geometrically that waterlogging of arterioles, hypertrophy of arterioles or some initially increased shortening of arteriolar smooth muscle can produce an apparent or artificial induction of hyper-reactiveness when the actual muscle fiber has normal reponsiveness. Moreover, as the arterioles become narrower the apparent viscosity of the blood increases, producing a greater resistance to flow. This factor could possibly give the picture of hyper-reactivity of the hy-
pertensive arteriole even if the actual smooth muscle fibers were normally reactive.

Dr. Bohr: We are not starting then from a common baseline. To get around this problem we have used strips from normotensive and hypertensive rat aortas in this type of study. Both renoprival hypertensive rats and renal ischemic hypertensive rats have been used. We were discouraged to find that the responses to epinephrine of these isolated aortic strips from the hypertensive rat were not as great as those from the normal rat.

Dr. Leonard: I am delighted to hear about these results. I am not surprised that in experimental hypertension in which, according to Dr. Tobian's studies, the concentration of sodium in the arterial walls is increased, you find reactivity decreased. I have always been rather attracted, perhaps more than Dr. Tobian himself, by his ingenious suggestion that in experimental hypertension the arterial lumen might be narrowed, at least in part, by encroachment of edematous walls. It is possible that the reactivity of such vessels to certain stimuli is actually decreased in vivo.

Dr. Tobian: I am not unattracted to this waterlogging hypothesis. Dr. Redleaf and I have studied the reactivity of spirals of rat aorta in various types of experimental hypertension and have found no evidence of hyperreactivity to norepinephrine in any spirals from hypertensive rats.

Dr. Bohr: Thank you. I think it is important to emphasize that these are large artery studies and there are differences in responsiveness between the aorta and the vessels that determine vascular resistance. For instance, the aortic strip will not respond to vasopressin in concentrations which cause a marked increase in vascular resistance.

Dr. Helmer: Why use epinephrine when apparently the catechol amines have nothing to do with essential hypertension—they have to do with pheochromocytoma? I do not think that epinephrine sensitivity is important in essential hypertension.

Dr. Bohr: The question of the agent we use certainly is pertinent, because I am sure that the reactivity would vary with different stimuli. However, whether the animal is normotensive or hypertensive, his vessels are being subjected to norepinephrine. This is a physiologic stimulus.

Dr. Skeggs: Yes, but I understand that you were using epinephrine.

Dr. Bohr: We were. Epinephrine does the same thing as norepinephrine to the rabbit artery strip.

Dr. Skeggs: Are we then to understand that in the paper presented earlier concerning contraction of the muscle strip, that norepinephrine would give exactly the same picture?

Dr. Bohr: I did not use norepinephrine in that study, but norepinephrine gives a response of the artery strip which we have not seen to be different from that given by epinephrine.

Dr. Skeggs: I protest this extrapolation from one compound to another. I do not know how you can be sure until you have done the experiment with both compounds.

Dr. Bohr: We have used both compounds on the strip, but not in this study. I would like to point out, however, that we are using concentrations of epinephrine that are in the circulating blood and therefore the vessels are subjected to this concentration of epinephrine physiologically, so the responsiveness to epinephrine itself is pertinent in these electrolyte studies.

Dr. Skeggs: I would like to go along with Dr. Helmer. It seems to me that since hypertension, or angiotonin, has been indicated in hypertension, that would have been the substance to use.

Dr. Bohr: I hope Dr. Helmer will do that; we have not been able to get the strip to respond without developing tachyphylaxis to angiotonin.

Dr. Helmer: To some rabbit aortic strips angiotonin can be added for 10 to 12 hours without tachyphylaxis. One strip may be practically insensitive to angiotonin, yet very sensitive to epinephrine and vice versa.

Dr. Bohr: There are consistent differences between the rat aortic strip and the rabbit
strip which will support this thesis. Let us have one more question on reactivity.

**Dr. Sancetta:** Is it wise to give so much emphasis to an aortic strip which physiologically, possibly biologically, certainly neurogenically, differs so totally, both in the normal and the abnormal response, from the arteriolar bed?

**Dr. Bohr:** I would certainly welcome any experience which anyone here has had comparing responsiveness of an isolated perfused system from normotensive and hypertensive animals. Do we have any such offerings?

**Dr. Tobian:** Dr. Duff in England has recently published some, but he has the old problem that the normotensive and hypertensive do not start from the same place, so they cannot be compared—it is a tough situation experimentally.

**Dr. Bohr:** As soon as we get arteriolar strips working, we can answer Dr. Sancetta’s question. Time is such that we had better get on to say a word about the interesting problem in the kidney. The kidney’s handling of electrolytes in hypertension differs from normal. Dr. Hollander, would you care to tell us a thing or two about this?

**Dr. Hollander:** I’d like to add some of our observations to some of the findings that were presented this morning on the excretion of sodium and water in hypertensive individuals. First, we would like to confirm the observation that hypertensive individuals, including those with renal hypertension, have an increased capacity to excrete sodium. Additional studies carried out on hypertensive individuals following treatment also suggest that the excretion of sodium following an infusion of hypertonic saline is to a large degree dependent upon the arterial pressure. Associated with reduction in arterial pressure, sodium excretion following the saline load is reduced to or towards normal. This reduction in sodium excretion produced by antihypertensive treatment may occur without a significant change in the control sodium excretion which remains abnormally elevated, or in the glomerular filtration rate and renal plasma flow.

Likewise, we have studied the renal responses to intravenous hypertonic saline in splanchneectomized and adrenalectomized hypertensive individuals and find that they also have an increased capacity to excrete sodium. These observations suggest that the hyperexcretion of sodium by hypertensive subjects does not necessarily depend upon an overactive sympathetic nervous system or adrenal gland.

Hypertensive individuals not only have a disturbance in sodium excretion, but also in water excretion. Subjects with essential or renal hypertension, during an infusion of 5 per cent glucose in water at a rate of about 12 ml. per minute, have a water diuresis which is significantly less than that found in normotensive individuals. This impairment in water excretion likewise is corrected by antihypertensive treatment. It therefore appears that disturbances of electrolyte and water metabolism in arterial hypertension may result from, and not necessarily cause, an elevated blood pressure.

**Dr. Bohr:** A vote for a mechanical pressure factor rather than an electrolyte metabolism factor as being primary?

**Dr. Hollander:** Correct. I’d like to mention some further observations on electrolyte and water metabolism which might be of help in clarifying the role of the adrenal cortex in arterial hypertension. We have compared exchangeable body sodium (Na), potassium (K) space, and extracellular fluid volume (S35O4 space) in a group of 80 subjects with and without hypertension. These were found to be perfectly normal in essential hypertension and in renal hypertension caused by bilateral kidney disease. These observations are in contrast with those in hypertension associated with clinical overactivity of the adrenal cortex or the administration of steroids, in which body potassium is low while body sodium and extracellular fluid volume are normal or elevated. In keeping with Dr. Conn’s observations after surgery, we have found that the correction by diet of the electrolyte disturbances in primary hyperaldosteronism prior to surgery is not neces-
sarily accompanied by a reduction in the blood pressure.\textsuperscript{20}

Dr. Bohr: Dr. Weller has a few sentences concerning the relationship of the increased pressure to the rejection of sodium by the renal tubule.

Dr. Weller: I just want to mention that Selkurt in 1951,\textsuperscript{21} using a perfused dog kidney preparation, showed that a reduction in the mean renal arterial pressure, without a change in para-aminophippurate or creatinine clearance, caused a reduction in sodium excretion and urine volume. An increase in pressure resulted in an increase in sodium excretion and urine volume. Here again it appears that the arterial pressure itself is the controlling factor in the excretion of sodium.

Dr. Sampstein: Dr. Weller has shown that the hypertensive patient exhibits an increased excretion of sodium under load. Others have shown that hypertensive animals seem to have excessively high sodium in the body. The reconciliation of these findings raises an interesting point.

It is too often forgotten that the kidney is not only an excretory organ but also a regulatory one which serves to control not only the volume but, more importantly, the composition of the body fluids. When it is shown that a hypertensive kidney excretes sodium in excess of the normal, one is compelled to ask at once: How does this excretory abnormality affect the internal environment? Clearly, if water is excreted with the sodium so that the urine sodium concentration is the same as that which exists in the plasma, the hypertensive kidney has produced a change in the volume but not in the sodium concentration of the extracellular fluid. In the same sense, a kidney which eliminates a strong sodium solution leaves behind in the body a weak one, just as a kidney which excretes a weak salt solution leaves behind a strong one.

A few years ago, like many others, I was attracted by the idea that many forms of hypertension had in common an ionic abnormality, particularly an increase in the concentration of sodium in the body fluids.

In experiments on the excretion of sodium and water in rats loaded with hypotonic, isotonic and hypertonic saline solutions, we first found that the pattern of sodium excretion in the hypertensive rat did not differ significantly from that displayed by the normal rat,\textsuperscript{22} but upon closer examination it developed that the hypertensive animals invariably excreted water at a greater rate than the controls. The urine of the hypertensive animal when hypotonically loaded was more hypotonic than that of the normals. The hypertensive’s urine was slightly hypotonic in animals isotonically loaded and it was less hypertonic than the control urine in hypertonically loaded rats. In every case the solution left in the animal was more concentrated with respect to sodium in the hypertensive than in the normotensive animal. Thus there is a defect in the regulation of sodium concentration in the hypertensive animal even though this defect is not revealed or may even be wrongly described by measuring the urinary excretion of sodium alone.

I would like to urge that when sodium excretion is discussed it should always be discussed in relation to water excretion. By so doing the functional activity of the kidney in controlling the composition of the body fluids can be placed in evidence.

Dr. Bohr: Dr. Skelton, let’s hear about your adrenal regeneration hypertension.

Dr. Skelton: I wanted to hear the opinion of the panel regarding the pathogenesis of hypertension before I said anything about my views on the genesis of that form of experimental hypertension which has interested me for the last couple of years—“adrenal-regeneration hypertension”\textsuperscript{23} —and about which Dr. Findley talked this morning. I have collaborated with Dr. Findley in those dog experiments which were done to see whether we could produce a significant degree of hypertension in this species by the procedure of unilateral nephrectomy, unilateral adrenalectomy and contralateral adrenal enucleation. In the rat the hypertension develops as the adrenal cortex regenerates, hence the name. Up to the present time we have studied 9 puppies and 7 adult dogs. In the puppies,
uniformly, there was either no adrenal regeneration, or such a small amount that it was insignificant, and no hypertension. In the adult dogs, the adrenals from 5 of the 7 animals have been studied and in all cases where hypertension was present there was significant regeneration of the adrenal cortex. However, the degree of regeneration was in no way comparable to that which occurs in the adult dogs, the adrenals from 5 of the 7 hypertensives were present there was significantly, a failure of regeneration of the adrenal cortex. Hence, I think that our failure thus far to obtain as severe a type of hypertension in the dog as in the rat may be the result of inadequate adrenal regeneration. Nevertheless, the fact that some elevation of blood pressure did occur in this species under these conditions seems to me to be a significant observation.

One of our projects has centered around whether or not adrenal-regeneration hypertension will persist after the regenerated adrenal has been removed. In a preliminary experiment done some time ago, 3 of 22 animals developed persistent hypertension. In this last series 17 of 19 animals which survived for 5 weeks following the removal of the regenerated gland had persistent hypertension. Of course, this is only if the animals were allowed to continue drinking sodium chloride. Thus, the reason I chose mechanism no. 2 was that from my studies on adrenal-regeneration hypertension, the working hypothesis has been developed that the regenerating adrenal produces an elevation of blood pressure as a result of some abnormality of steroid production. This then acts on the kidney to produce lesions of some type, either morphologic or chemical, leading to the liberation of a pressor principle or exciting some renal mechanism which ultimately produces a sustained type of hypertension which no longer is dependent upon the adrenal cortex.

Dr. Bohr: Dr. Dustan has a closing thought.

Dr. Dustan: The subjects of this discussion have ranged widely around the central topic of "the role of adrenal steroids and electrolytes in renal hypertension." From this one might get the idea that we are more interested in isolated facts than in the synthesis of facts. We are not that irresponsible. To take a specific point: we have talked much about the roles of sodium and potassium in the genesis of experimental and clinical hypertensive disease, but we cannot define these roles because we cannot measure intracellular electrolyte composition. Here, as always, our results are only as good as our methods and our understanding of the actual participation of sodium and potassium in hypertension must await the development of better methods.

SUMMARY

In addition to reviewing evidence bearing on the broad relationship of adrenal and electrolyte changes to the pathogenesis of hypertension, this conference considered more specifically the changes in vascular reactivity and electrolyte excretion in hypertension.

Supporting the theory of an adrenal mechanism in hypertension was evidence that the development of adrenal-regeneration hypertension in different species may bear a direct relationship to the degree of adrenal regeneration (Dr. Skelton), and that a steroid having electrolyte action opposite to that of desoxycorticosterone is hypotensive in action both in DCA and renal ischemic hypertension, but not in normotensive animals (Dr. Sturtevant). On the other hand, it was observed that adrenalectomy does not alter the development of hypertension produced by kidney encapsulation in the rat (Dr. Fregly).

Although it is probable that constrictor agents cause a greater increment in vascular resistance in hypertension than in normotension, the interpretation of this relationship in terms of responsiveness of vascular smooth muscle is fraught with difficulties: 1. The base line of vascular resistance in hypertension is different from that in normotension, and it is possible that the increment in resistance for a given amount of smooth muscle shortening is greater in the constricted than in the normal vessel (Dr. Tobian). 2. It is possible that the increase in resistance in hypertension is due to the encroachment of the edematous blood vessel wall into the lumen.
without an increase in tone of vascular smooth muscle (Dr. Tobian). 3. The responsiveness to epinephrine of aortic strips from hypertensive animals is less than (Dr. Bohr) or no greater than (Dr. Tobian) that from the normal animal. The pertinence of the aortic strip studies was questioned, both because the aorta differs in function (Dr. Sancetta) and responsiveness (Dr. Bohr) from the arteriole and because epinephrine was used in these studies (Dr. Skeggs). The problem of tachyphylaxis of the isolated artery strip in response to angiotonin may not yet be resolved (Drs. Bohr and Helmer).

In hypertension there is an increase in sodium excretion by the kidney which is accentuated by the administration of a sodium chloride load. This abnormality reflects an impairment of the tubular reabsorption of sodium which is related to an impaired reabsorption of water (Dr. Sapirstein) and is a direct function of the arterial blood pressure (Drs. Hollander and Weller).

REFERENCES
