Discussion of Reports on Neural Factors in Hypertension

DR. TOBIAN: I am pleased to hear some of the conclusions that were reached by Dr. Conway, in that his findings suggest that a change in the thickness of the wall of the arteriole by itself might significantly narrow the lumen. Such an increase of the wall thickness would increase the narrowing of the arteriolar lumen in response to a pressor agent, while the muscle fibers themselves are exhibiting the normal amount of shortening to this dose of pressor agent. Waterlogging of an arteriole could well produce this narrowing of the lumen as well as an apparent hyper-reactivity of arterioles to pressor agents. I am still a little troubled by one thing relating to the studies where you increased the blood pressure with renin and then found the same pressor response to adrenaline, as was seen in a rabbit with normal blood pressure. This comparison may be valid but, on the other hand, I suggest that it may not be. You might have some compensating errors. For instance, when you are giving some renin and the lumen size of the arterioles narrows, this narrowing itself might produce an apparent increased response to adrenaline even though the adrenaline is only causing its usual muscle shortening. This can be shown on geometric models of arterioles. On the other hand, the fact that the arterioles are already partially depolarized by renin might prevent the full range of depolarization by adrenaline. Hence you might have one factor compensating for the other and producing what seems to be normal responsiveness to adrenaline at various blood pressure levels. I think we should keep working toward other ways of attacking this problem in order to find out if an initial change in lumen size or wall thickness of arterioles produces an apparent rather than a real alteration in the reactivity of the arteriolar smooth muscle to adrenaline.

DR. LOUIS W. LEWIS: I would like to complement on Dr. Beck's very interesting paper. You can give enough of any agent, hexamethonium included, to eventually depress cardiac output. If there was no attempt made to stop exactly at the sympatholytic dosage of this drug it is possible that many times the required amount was given.

I would like to present direct evidence that in proper dosage there is a definite peripheral vasodilating effect of hexamethonium and would, furthermore, suggest that this is the principal mechanism by which the blood pressure is lowered. Figure 1 shows the sympathogalvanic reflex (SGR) tracings from 3 extremities and a digital plethysmographic tracing in the lowest channel. The SGR is a direct test of sympathetic activity in the intact, unoperated, unmedicated individual. If sympathetic activity is present, a biphasic curve is obtained in the tracing in response to a stimulus. If sympathetic activity is absent, any stimulus will fail to produce the typical response and a straight line results. At the beginning of the illustration sympathetic activity is present and the base line for the digital plethysmograph can be observed. Twenty-five milligrams of hexamethonium depressed but did not eliminate the SGR activity. There was some increase in amplitude of digital pulsation. Another 25 mg. of hexamethonium intravenously did sympathectomize this subject so no further drug was given. The plethysmograph showed a 100 per cent increase in digital pulsation. Thirty-five minutes later there was a slight return of sympathetic activity as the effect of the hexamethonium wore off, and about a 50 per cent decrease in digital pulsation is recorded. Dr. Beck might rightly argue that there is a "species difference" in our work. This study was done on man.

DR. BARKER: Dr. Stamler, will you continue with the discussion?

DR. STAMLER: I am particularly grateful
to Dr. Hoobler for this opportunity to speak, not because I have a great deal to contribute, but because, as one of the "younger generation" in hypertension research, I am most happy to pay tribute to Dr. Goldblatt personally. He has been an inspiration to all of us as a scientist, as a teacher, and as a person.

I would like to go back to where we started in this conference—to Dr. Goldblatt's "credo," that essential hypertension is of renal origin in its pathogenesis. Dr. Goldblatt was very forthright and definitive in reiterating this. Thus, he dealt squarely with the provocative and challenging problem of the much greater prevalence and incidence of hypertension in the Negro than in the white in the United States, a problem that is particularly intriguing to those of us studying the epidemiology of hypertension. He put forward his reasons for believing that, irrespective of the operation of any neurogenic mechanism such as psychological stress and tension, the inordinate extent and degree of hypertensive disease in Negroes is also an expression of a pathogenetic process having a renal mechanism. Without subscribing unequivocally to this concept, I want to state that all of us doing epidemiologic research need to address ourselves vigorously to the investigation of etiologic factors in the mode of life of Negroes possibly precipitating ultimate renal hypertension. It is clear from last night's proceedings that Dr. Moser, among others, is proceeding along such lines. In this connection it is perhaps worth stating that the whole problem of pyelonephritis and hypertension in Negroes and whites needs further work, as well as questions of possible renal damage resulting from nutritional aberrations and complications of pregnancy.

At the end of his presentation, Dr. Goldblatt spoke of a "fly in the ointment" of the nephrogenic theory of hypertension, the finding that in chronic renal hypertensive dogs
the ganglionic blocking agent pentolinium induces a fall in blood pressure. Is this observation a major road block in the path of acceptance of Dr. Goldblatt’s concept? I am wary of accepting such data as proof of excessive neurogenic arteriolar vasoconstriction in hypertension, and I am skeptical concerning this method for disproving the renohumoral pathogenesis of hypertension.

The papers of both Dr. Kezdi and Dr. McCubbin are highly relevant with respect to this problem. Their work amply confirms the old observation of the exhaustion of the aorticecarotid buffering mechanism in the face of a persistent renohumoral pressor stimulus unleashed by the Goldblatt procedure. Research on experimental renal hypertension has always been confronted with a twofold problem, not only the nature of the pressor effect but also the mechanism whereby counter-pressor buffering reactions are overcome in the course of the genesis of elevated blood pressure. From Dr. McCubbin’s and Dr. Kezdi’s results it would appear that the carotid-aortic reflex is the principal depressor response, and this undergoes progressive physiologic exhaustion at the receptor level. The barostat of this reflex is gradually reset at a higher level, so that it continues to respond to fresh acute pressor stimuli, but becomes incapable of reacting to the sustained renohumoral pressor influence. Based on these findings, the debate as to whether in chronic renal hypertension a neurogenic pressor influence “takes over from” or “is superimposed on” the renohumoral mechanism seems to be of secondary importance. With respect to the “fly in the ointment,” the response to pentolinium, the ability of this ganglionic blocking agent to nullify normal sympathetic arteriolar vasoconstriction derived from the reset carotid-aortic reflexes, plus the venomotor and cardiogenic actions of this type of drug, would appear to be adequate to account for the observed profound depressor response in man and dog despite continued operation of the renohumoral pressor mechanism. Obviously, however, further work is necessary to demonstrate unequivocally that this is in fact the complex of reactions elicited.

This indication, that sympathetic arteriolar hyperactivity is not a decisive factor in the pathogenesis of early or late renal hypertension, receives further support from Dr. Conway’s findings suggesting that a structural change occurs in the arterial tree of renal hypertensive animals. Is this an edema of the arterial and arteriolar wall, a water-electrolyte shift, as suggested by Dr. Tobian? In any case, if such a change does occur, resulting in thickening of the vessel wall with consequent greater decrease in radius in response to a low order vasoconstrictor influence—and therefore with consequent greater pressor response—then all the more is it unnecessary to invoke a hypothetical, sympathetic, neurogenic hyperactivity as a decisive mechanism in sustained renal hypertension. Therefore, it would appear more appropriate to speak of “feathers in the cap” rather than “flies in the ointment” in evaluating the over-all results of this conference as they bear upon the validity of Dr. Goldblatt’s credo. Dr. Skegg’s demonstration of circulating hypertensin in the peripheral blood of hypertensive patients relatively large amounts in malignant hypertension, and smaller but apparently significant amounts in benign hypertension, is an additional “feather in the cap.” So is the cardinal achievement of the synthesis of hypertensin by Drs. Bumpus, Page and colleagues. So too is Dr. Wakerlin’s extensive documentation of the antihypertensive effect of immunization, active and passive, with antirenin.

Since so much of yesterday’s discussion pivoted around the renohumoral versus the renoprival theories, it is perhaps worth noting that there is a wide area of agreement in these seemingly disparate views: both adhere fundamentally to a renal theory of the pathogenesis of hypertension in contradistinction to any neurogenic concept.

Finally, one other general impression may be worthy of brief discussion. Throughout the 2 days of this conference, the discussion was focused on problems of the pathogenesis
of hypertension. It did not deal with problems of etiology, with factors initiating the train of events. The presentations by epidemiologists last evening were the exceptions, and clearly this work on etiologic factors is still in its stage of inception. If the renal theory is in fact receiving validation here, then research must face the cardinal question: What are the causes of the renal pathology, particularly arteriolar nephrosclerosis, which is the critical antecedent of hypertension? Along this line the whole problem of pyelonephritis may need re-exploration. This distinction between problems of pathogenesis and problems of etiology brings into sharpest focus, in my opinion, the meaning of adherence to the renal versus the neurogenic theory. Consider the problem of the possible role of psychological stresses in the etiology of hypertension. Research proceeding on the basis of the renal theory of pathogenesis must concern itself with the question of how stress-elicited cerebral nervous activity primarily induces altered renal function and structure, leading to hypertension. Based on the neurogenic theory of pathogenesis, on the other hand, the problem becomes one of how stress-elicited cerebral activity results in sympathetic hyperfunction and hypertension, with ultimate secondary renal alterations. These are 2 basically different possible sequences. Based on the accepted theory of pathogenesis, renal or neurogenic, fundamentally different research approaches must result.

With the evidence in support of the renal theory of pathogenesis becoming ever more convincing, the need for concerted work on the etiology and pathogenesis of renal arteriosclerosis becomes ever more compelling.

**Summary**

Dr. Tobian commented on the possibility of increased fluid content of arterioles as a cause of the altered vascular reactivity described by Dr. Conway. Dr. Lewis described the arterial vasodilation in the digit following ganglion blockade. Dr. Stamler reviewed the conference proceedings and attempted to interrelate the many reports presented. He concluded with a restatement of the central role of the kidney in the pathogenesis of human hypertension and emphasized the importance of determining whether neurogenic, inflammatory, or arteriosclerotic influences were the factors which initiated the renal lesion.

**REFERENCE**

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