Discussion of Reports on Renopralvial Hypertension

DR. GROLLMAN: The diversity of opinions expressed today is ample evidence of the apparent confusion in this field which you have already realized. Far be it for me to add to this confusion by describing some of my own experiments which are in obvious conflict with some you have already seen. Instead, I shall try to harmonize some of the views which have been expressed, because I personally feel that one can correlate the data which have been accumulated since Dr. Goldblatt stimulated investigation in this field 25 years ago. Such a correlation permits one to envisage much that is of great practical importance in managing this common disease. Much confusion has arisen from our failure to define what we mean by hypertension. Many of the “experts” who have written in this field deny that hypertension represents a disease at all. If that be true, we obviously are wasting time by trying to discover its pathogenesis. It seems to me that we must begin by defining just what we mean by hypertension. Personally, I feel that hypertension is a definite disease entity which is better designated as hypertensive cardiovascular disease. The word hypertension is too often used as a synonym for a rise in blood pressure. This is undesirable since a rise in blood pressure represents merely a change in one of the variables of the circulation. If you exercise, or are excited, your blood pressure rises acutely; you are not suffering from hypertensive disease. Hypertensive disease is not simply a rise in blood pressure. Many of the changes in blood pressure that have been shown today probably should not have been referred to as “hypertension” and do not contribute anything to the elucidation of this field, because all they represent are elevations in blood pressure. Hypertensive disease is a specific disorder which we can define hemodynamically, clinically, and pathologically.

The view that experimental hypertension has nothing to do with human hypertension is entirely unjustified. I think that they are entirely identical hemodynamically; their clinical course, in so far as we can relate the two, is similar; pathologically they are certainly similar. Accordingly, we are justified in applying our experimental results to clinical considerations.

Now, let us turn specifically to some of the points which have been raised this morning. There is no question that certain conditions, which we call hypertension, are induced by the elaboration by the kidney of a pressor agent. This has been demonstrated in acute glomerulonephritis, in infarction of the kidney, after tying a ureter, and in some atrophic kidneys. I don’t think that anyone will question that there is a pressor agent of some type which induces hypertension in these conditions. On the other hand, in most patients with hypertension no pressor agent can be demonstrated.

I have no patience with the view taken by so eminent a worker in this field as Dr. Pickering, who denies the very existence of hypertension as a disease and considers it an artifact. You may as well deny that diabetes is a disease, because it develops gradually and there is no sharp dividing line between the normal and the diabetic. It is generally accepted that so-called “essential” hypertension is an inheritable condition; it is initiated at the time of conception, before there is even a circulatory system. I agree entirely with Dr. Goldblatt’s conception that it is entirely renal in origin, and I believe that we can explain all true experimental as well as clinical hypertension on a renal basis, although I do not agree with his reasoning as to its pathogenesis. I do not think that a circulatory disturbance of the kidney must initiate the disease but rather that any defect in the function of
the organ often unrelated to its circulation is the cause of the disease.

In conclusion, may I make a plea that we not emulate the blind men describing the elephant. We have reached the point now, after 25 years of labor, where we can correlate many observations into a unified hypothesis, which not only clarifies an important clinical field, but also promises much for the future management of hypertensive disease in the human.

DR. HANDLER: Some years ago we wandered into the field of "experimental hypertension." At the time there was considerable controversy in the literature concerning the effect of the level of various nutrients on the blood pressure of humans with hypertensive disease and there was a not very extensive literature relating the effect of nutrition on animals with one or another form of experimental hypertension. We proceeded to feed rats diets made of purified nutrients which had been made available by the successes of the various drug houses in the vitamin business. We used rats in which hypertension was induced by placing a figure-eight ligature on one kidney and removing the other. It soon became apparent that almost anything we did to these animals reduced their blood pressures. The 3 principal techniques were severe restriction of sodium consumption, caloric restriction and very severe protein restriction. All effectively reduced blood pressure in such animals. We decided that we would follow the clue offered by the fact that protein restriction did effect a lowering of blood pressure, the notion being that if one could understand why protein restriction has some effect on the rat's blood pressure one might come a little closer to understanding the mechanism of the high blood pressure itself. Suffice it to say, after a long series of experiments, we satisfied ourselves that, in large measure, protein restriction is tantamount to a functional hypophysectomy in that the anterior pituitaries of severely protein restricted animals do not function. The various trophic hormones usually emanating from this organ are not released. I don't know if they are synthesized, but they certainly are not released in the severely protein restricted animal. Of these hormones, ACTH and growth hormone were effective in this situation. One could restore the high blood pressure in such animals by giving either ACTH or growth hormone. While pondering the significance of this phenomenon, we performed a rather simple experiment. ACTH was given to bilaterally nephrectomized rats. In modest dosage this elicited, in 2 to 4 hours, a marked rise in blood pressure which was sustained for a matter of 6 to 8 hours. The ACTH was given about 24 hours after the bilateral nephrectomy.

This seemed a rather significant observation. These were animals without kidneys and the hypertension so induced must relate to the fact that there were no kidneys present: renoprival hypertension, if you will. To explain it, we cannot draw on the renin mechanism or any other mechanism which implies a positive role of the kidney under such circumstances. However, we thought there were many clues in the literature. Among these was the fact, to be discussed later, that in the dog if one clamps the artery leading to one kidney, one obtains reasonably high blood pressure which then subsides. To obtain satisfactory chronic hypertension one must remove the other kidney, implying a protective influence of some sort by the kidney whose circulation has not been altered. This kidney therefore does something useful for the animal in this regard. There had also begun to appear the body of literature to which several references have been made by Dr. Grollman and Dr. Kolff, implying that there is something that can be called renoprival hypertension, a phenomenon which relates to the lack of functional kidney tissue rather than to the presence of abnormal renal tissue. This led us to the old and naive notion that there may be something in normal urine which, under proper circumstances, would elicit a pressor response. The proper circumstance would be an animal lacking use-
ful functioning renal tissue and so unable to excrete this material.

In defining the disease situation with which he was concerned, Dr. Goldblatt insisted that there must be no impairment of excretory function. However, we decided to modify this definition to say that there would be no impairment of excretion of the usual quantitatively major components of urine. He has told us today that one must exclude Diodrast excretion from this definition. Surely, since normal kidneys are not normally required to excrete Diodrast, the definition remains unaffected. But this observation does imply something wrong with the excretory machinery of human hypertensive patients. Thus we considered the possibility that there might be some hitherto unrecognized material which might result in a rise in blood pressure when there is failure to excrete it. We conducted some experiments which I now regret, since if we had not done them, I would not have to stand here at this moment.

We proceeded to inject concentrations of normal human urine into rats prepared by 2 different procedures. The one used most frequently was the bilaterally nephrectomized rat. In our earliest experiments, and in experiments sporadically conducted over the last 4 to 5 years, this has worked. Such injections have elicited sustained rises in the systolic blood pressure of the bilaterally nephrectomized rat. We attempted to isolate and identify this material on those occasions when this assay technic worked. It didn’t always work. We were able to locate the active material in a rather ill-defined mucoprotein fraction of normal human urine. Of the various experiments performed to establish the physiologic significance of this material, assuming it to be real, the most impressive was the fact that this activity seemed to disappear from the urine of 2 dogs with clamps on both renal arteries and from the urine of rats which were rendered hypertensive by our usual technic.\(^6\) We have pursued these observations sporadically for several reasons. One of them is that my graduate students and postdoctorate fellows always seem to want to work with enzymes and do not want to play with this problem. And they are wise. The second reason is that this assay is utterly inconsistent in our hands. The folks in our laboratory keep pressing me to seek another assay but I insist that if this assay does not work then we have no phenomenon, and we have nothing to look for. This is the situation in which we now find ourselves.

Some years ago our chairman, Dr. Davenport, had the courage to write a paper which I recall was entitled “In Memoriam, the Carbonic Anhydrase Theory of Gastric Aeidity.” He wrote it prematurely, because it turned out that he didn’t have to write it at all since he was right in the first place, but it was the true measure of his scientific integrity. Well, I don’t think I lack the courage to write another “In Memoriam,” but at the moment I am rather ambivalent about all this. We have seen the phenomenon work so many times that I am convinced there must be some real basis for it, but in pushing it further we have had a dreadful lack of success. There the matter must rest at the moment. We will keep trying.

In the course of doing all this, we have developed a profound distrust of one’s ability to measure, with reasonable confidence, the systolic blood pressure of the rat. Our expanding scientific apparatus industry provides more gadgets annually, but with each of them it seems possible to determine that a rat’s blood pressure is almost any value you want it to be. We have had to insist upon a double blind arrangement with the people making these measurements to insure that these emotional problems are avoided. With most apparatus used for this purpose there is a very elegant device that permits determination of the endpoint quite precisely but does not establish exactly what the blood pressure was at that endpoint, largely because of the inadequacy of the pressure cuff arrangement. We have devised a simple little gadget which permits one to place a cuff on the rat and at least obtain reproducible relative data on that animal, independent of the operator (fig. 1).
Finally I would like to take exception to a remark of Dr. Grollman. I admit that the term "hypertension" is loosely used, but the semantic problem should be placed back on the clinician and pathologist. If they mean "hypertensive cardiovascular disease" let them say so, or devise a new term. "Hyper-ventilation" and "hyperacidity" are physiologic facts, whether they be pathognomonic of a specific disease is another matter. So also is "hypertension" a physiologic measurable entity, not a disease, and we are justified in employing this term simply to indicate a blood pressure in excess of whatever values are considered to be normal in a given patient or animal.

DR. RODBARD: I would like to say something about a possible relation between renopriv al hypertension and renal hypertension. About 20 years ago Dr. Katz and I were engaged in a series of studies on the hypertension which follows unilateral renal artery constriction. Removal of the clamped kidney led to a fall in blood pressure in a few hours. By contrast, when we removed both kidneys in such a dog, the blood pressure persisted at high levels until the animal died in uremia several days later. This was, and can still
be, interpreted as follows: The ischemic kidney produces and secretes a pressor material which manifests itself in an elevated blood pressure. This circulating pressor material is eliminated by the normal kidney. The hypertension therefore is a resultant of the secretion of pressor materials by the ischemic kidney, minus the activity of the normal kidney which neutralizes the circulating pressor substance. We also demonstrated that the normal kidney destroys the pressor agent by means of a metabolic, rather than an excretory, function. This was shown in experiments in which the ureter of the normal kidney was grafted into the vena cava, so that the renal excretory products were returned to the circulation. When the ischemic kidney, the source of the pressor material, is then removed, the blood pressure falls to normal within a few hours, just as if a normal kidney were present. A metabolic function of the normal kidney is therefore responsible for reduction of the blood pressure to normal.

Perhaps this concept may also fit with the data on renoprival hypertension. The basic question, it seems to me, is that having to do with the source of the pressor material in this form of hypertension. It has been reported that grafting of a normal kidney into an animal with renoprival hypertension brings about a rapid fall in blood pressure. This is the same pattern noted previously; that a normal kidney removes from the circulation certain pressor materials.

We are rather fixed in our notions that pressor materials must somehow arise in the kidney. Perhaps pressor material originating in nonrenal sources as well, in the intestines as peptisensin, or the arterial breakdown of proteins in the arterial wall to peptipressor material as discussed by Dr. Braun-Menéndez, may account for hypertension. This production of pressor materials is apparently not as active as that in the kidney, but given a sufficiently long period of time, animals kept alive without kidneys may accumulate enough of such pressor materials to become hypertensive. It is therefore not necessary to consider renoprival hypertension as due to the lack of an antihypertensive material which is normally supplied to the body by the normal kidney. Instead, hypertension may result because no kidney is available to destroy pressor materials of extrarenal origin. The fact that the pressure falls rapidly when the animal's blood is perfused through a grafted kidney would seem to support such a concept.

**SUMMARY**

It was pointed out that some of the confusion in this field resulted from failure to define the term "hypertension." A simple rise in blood pressure was not hypertensive disease and should not be referred to as "hypertension" according to Dr. Grollman.

It was stated that all hypertension is renal in origin, but due to a defect in the function rather than in the circulation of the kidney (Dr. Grollman). In both renal and renoprival hypertension there is lack of the normal renal protective mechanism, i.e., the kidneys fail to excrete some pressor substance (Dr. Handler). This protective action of the kidneys may be metabolic rather than excretory, and both renal and renoprival hypertension may be due to the lack of renal catabolism of pressor materials which may be of extrarenal as well as of renal origin (Dr. Rodbard and others).

**REFERENCES**

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