"short-circuiting" surgery elsewhere with subsequent recurrence of symptoms with serious complications. Only the passage of time will prove if the present cures are permanent.

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SELF-SUSTAINED HYPERTENSION IN THE ALBINO RAT: A HYPOTHESIS TO EXPLAIN IT*

Sydney M. Friedman, M.D., Ph.D. and Constance L. Friedman, Ph.D.

Department of Anatomy, McGill University, Montreal, Que.

THE idea that the adrenal cortex is in some way involved in the pathogenesis of essential hypertension is not new. It has been entertained ever since Goldblatt first observed that some adrenal cortical tissue was necessary for the induction and maintenance of an elevated blood pressure following constriction of the renal artery.[1, 2] Subsequently, other workers demonstrated first, that adrenal cortical extract, and later that desoxycorticosterone, a synthetic adrenal cortical steroid, could replace the adrenal cortex in this function.[3, 4, 5] On the basis of this work it was postulated that the rôle of the adrenal was to sensitize the blood vessels or maintain them in such a state that they could react to circulating pressor material liberated from the kidney.

Doubt was cast on this purely secondary rôle for the adrenal cortex when several groups of workers observed that desoxycorticosterone acetate (D.C.A.) could elevate blood pressure not only in Addisonian patients[6, 7] but in normal man as well.[8] In addition, Selye and his co-workers, using large doses of D.C.A. together with saline as a substitute for drinking water, induced hypertension in a variety of animal species.[9, 10] This worker suggested that essential hypertension could result from an excess liberation of D.C.A.-like material by the adrenal cortex as a result of stress.[11] Thus, the adrenal was moved from a secondary position to one of possible primacy in the etiology of hypertensive disease in man, although there is only suggestive evidence of actual hypersecretion of the adrenal cortex in some cases of essential hypertension.[12]

Using sensitive functional tests we have been able to determine that small doses of D.C.A. suffice to elicit a hypertension in intact rats not otherwise sensitized.[13] This finding indicates that proof of adrenal cortical involvement in man need not necessarily rest upon the demonstration of grossly excessive amounts of circulating corticoids. Further, we observed that, as in man, the elevation in blood pressure antedated alterations in renal function, and that when eventually renal function became impaired, the evolution of changes followed a pattern similar to that observed in man. Salt, and specifically the sodium ion, intensified the process.[14]

Despite the lack of early renal functional change it was consistently noted that renal hypertrophy occurred immediately following D.C.A. treatment. Investigation of this point showed a positive correlation between renal mass and blood pressure, indicating that the kidneys were actually involved from the start of the process.[15] Renal function was thus maintained at apparently normal levels by a compensatory increase in renal mass. Eventually this compensation fails and the deterioration of renal function becomes evident.

Since D.C.A. impaired kidney function it might have been supposed that hypertension resulted from the liberation of a renal pressor agent by a damaged kidney. In several experiments in which both kidneys were removed from animals under D.C.A. treatment, however, blood pressure rose to new heights.[15] This suggested that the pressor action of D.C.A. was extra-renal and that involvement of the kidney was due to its opposition to this action.

In all of this work the effects of D.C.A. were observed to reverse rapidly if treatment was stopped. It seemed of interest to determine whether more intensive treatment might lead to an irreversible hypertension. The experiment here reported was designed to test this possibility. A self-sustained, permanent hypertension did result. This is of particular interest since it represents an endogenously maintained hypertensive state induced originally by a steroid closely resembling a natural secretion.

Experimental.—Thirty-six male albino rats of the Sherman strain, weighing approximately

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70 grams, were divided into three groups. Group 1 consisted of 11 animals serving as untreated controls, while the 11 animals of group 2 were subjected to a unilateral nephrectomy to serve as uninephrectomized controls. The 14 animals of group 3 were subjected to a unilateral nephrectomy following which they received D.C.A. pellets by subcutaneous implantation, one-third of a 75 mgm. Cortate pellet being implanted on the 4th, 8th, 12th, 16th, 21st and 25th days of the experiment.

The experiment was divided into 2 phases. In the first period D.C.A. was administered as described to the animals of group 3 together with 1% saline as drinking water. Saline was similarly substituted for the drinking water of the uninephrectomized control group 2 during this period. After 28 days of this active and intensive treatment, when the average blood pressure of the D.C.A. treated group was well elevated (Table I), treatment was discontinued. In order to stop treatment abruptly all implanted pellets were removed from the animals of group 3 while both groups 2 and 3 were returned to tap water. Five animals from each of the two control groups and 7 from the treated group were sacrificed at the end of this first period.

The second period was given over to observing whether the hypertension induced by the intensive treatment with D.C.A. would regress or persist. The surviving 6 animals in each of the two control groups, and the 7 animals from group 3, were studied during this period, which lasted eleven and one-half weeks. All animals received food and tap water *ad libitum* and were in no way disturbed except for the measurement of blood pressure which was carried out repeatedly during this period. After 80 days of observation, when it became clear that hypertension was persisting in 4 of the 7 animals of group 3, the experiment was terminated.

Observations. — First period. — The findings are presented in Table I. After 28 days of intensive D.C.A. treatment, the average indirect blood pressure reading in group 3 was 150 mm. Hg. as compared with 117 and 113 in the two control groups. This finding was substantiated by the significant increase in heart weight ob-

TABLE I.

FIRST PERIOD—28 DAYS

Group No.	*1*	*2*	*3*
Treatment	*Intact control*	*Uninephrectomized control—saline fed*	*Uninephrectomized D.C.A.—saline*
No. of animals	11	11	14
Blood pressure mm. Hg.—28th day	117 ± 8	113 ± 11	150 ± 21
Heart wt. mgm./100 cm.^{2}	188 ± 9 (5 rats)	188 ± 14 (5 rats)	216 ± 17 (7 rats)
Kidney wt. mgm./100 cm.^{2}	377 ± 46 (5 rats)	362 ± 45 (5 rats)	470 ± 15 (7 rats)

SECOND PERIOD—80 DAYS

Group No.	*1*	*2*	*3*
Treatment	*Intact control*	*Uninephrectomized control. Continued from first period.*	*Uninephrectomized D.C.A. stopped. Continued from first period.*
No. of animals	6	6	7
Blood pressure—average of 15 determinations	106 ± 8	106 ± 6	141 → 116 ± 15 (3 rats); 159 ± 18 (4 rats)
Heart wt. mgm./100 cm.^{2}	170 ± 13	183 ± 20	208 → 194 ± 7 (3 rats); 217 ± 16 (4 rats)
Kidney wt. mgm./100 cm.^{2}	416 ± 54	302 ± 17	362 → 341 ± 36 (3 rats); 376 ± 43 (4 rats)
Total wall/diameter as % vessels of 0-50 μ		64 ± 6	83 ± 5 / 84 ± 9
51-100 μ		62 ± 6	70 ± 9 / 81 ± 10
101-150 μ		56 ± 6	65 ± 12 / 69 ± 9

served in the animals sacrificed at this time. Evidence of interference with renal function was given by the significantly increased kidney weight.

Second period. — The findings are presented in Table I. After cessation of D.C.A. treatment the blood pressure of each animal was determined on 15 separate occasions. While the average pressure for group 3 remained consistently above the simultaneously determined control this was due to only 4 of the 7 animals whose pressure remained elevated throughout the remainder of the experiment. The pressure of the other 3 animals fell to normal levels within one week of cessation of treatment and remained within normal limits for the duration of the observed period. These findings are presented graphically in Fig. 1.

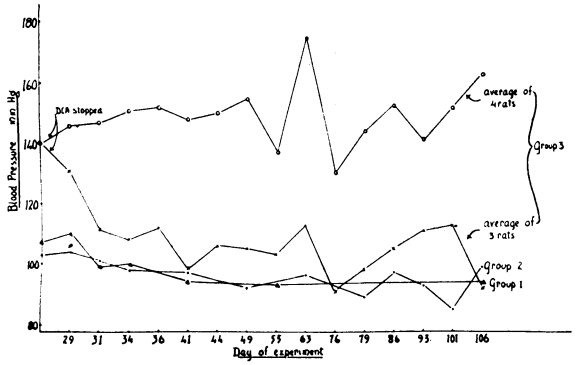

Fig. 1.—Average blood pressure values observed during the 80 day period following discontinuation of intensive D.C.A. treatment. Four of the seven treated animals remained "permanently" hypertensive.

The elevated blood pressure was reflected in an increased heart weight in only those animals of group 3 whose hypertension persisted. Renal involvement was indicated by an increase in the average kidney weight in group 3 compared with that of the uninephrectomized control group 2. This average increase in kidney weight was occasioned by increases in both the hypertensive and normotensive members of the group, but was somewhat greater in the 4 "permanently" hypertensive animals.

In agreement with the findings for kidney weight, pathological changes were observed in the kidneys of all animals in group 3, the difference between the hypertensive and normotensive members of the group being one of degree only. The most prominent change was a thickening of the arteriolar wall, apparently referable to medial hypertrophy. Both afferent and efferent arterioles were consistently involved, while vessels of larger calibre were less constantly affected. Eccentric thickenings of the wall were observed in many small arteries and what appeared to be necrosis of the media was observed in the pancreatic arteries of 2 of the "permanently" hypertensive animals.

In an effort to assess the observed vascular change more objectively, renal arterial channels were measured in both the control and treated groups. Approximately 50 control vessels were measured and 50 each in the hypertensive and normotensive animals of group 3. As shown in Table I, the hypertrophy in the 3 non-hypertensive animals differed only slightly from that observed in the 4 rats with sustained hypertension.

The kidneys were singularly free of other changes except for various stages of sclerosis in some few of the glomeruli in group 3. It should be emphasized that in each section most glomeruli were entirely normal in appearance.

Pathological examination of the heart revealed little change except for the appearance of numerous small scars in the myocardium of that animal whose pressure had remained higher than any of the others throughout the experiment.

DISCUSSION

Some explanation must be sought for the fact that, after discontinuation of intensive D.C.A. treatment, a permanent, self-sustaining hypertension developed in some animals. Since D.C.A. can and does damage the kidney, it seems reasonable to consider first the possibility that this is a form of renal hypertension, the Goldblatt "clamps" here being applied chemically rather than mechanically. This explanation seems somewhat unlikely since vascular lesions only slightly different in degree were observed in both the hypertensive and non-hypertensive animals. Because this degree of difference may be crucial, however, the possibility cannot be completely ruled out.

While the arteriolar "clamp" idea seems rather remote, the fact that D.C.A. is known to damage the kidney suggests strongly that the hypertension may be related in some way to this organ. Previous experiments in which the blood pressure of D.C.A.-treated animals rose to new heights after nephrectomy suggested that the kidney normally antagonizes the pressor action of D.C.A.[15] This leads us to speculate whether the sustained hypertension here

reported resulted from an inability of the kidney to handle even endogenously produced D.C.A.-like adrenal cortical material as a result of the original overdosage and damage with D.C.A.

On the basis of this and previous work, we have formulated an hypothesis which reconciles, at least in part, essential hypertension, hormonal (adrenal) hypertension, chronic renal (Goldblatt) hypertension, and the present "self-sustaining" hypertension. It should be clearly understood that the hypothesis to be suggested makes no claim to explain all of hypertension. The manifold factors involved in the maintenance of blood pressure make it unlikely that one explanation suffices for all cases of clinical hypertension. Our suggestion does, however, offer a synthesizing explanation for certain observations.

whenever the balance between the production of an adrenal D.C.A.-like pressor material and its handling by the kidney is interfered with so that an accumulation of the pressor material results. Thus, chronic hypertension induced by constriction of the renal artery, in which the damaged kidney cannot properly cope with even normal amounts of the adrenal material, would share a common pathway with, for example, the hypertension of Cushing's syndrome, in which the normal kidney cannot cope with the excess amounts of pressor substance. This would explain the fall in pressure which occurs when the adrenal cortex is removed in an animal with constriction of the renal artery. It should be borne in mind that not all adrenal cortical tumours would be expected to produce the pressor material, so that those reported cases[17] in which removal of the tumour failed

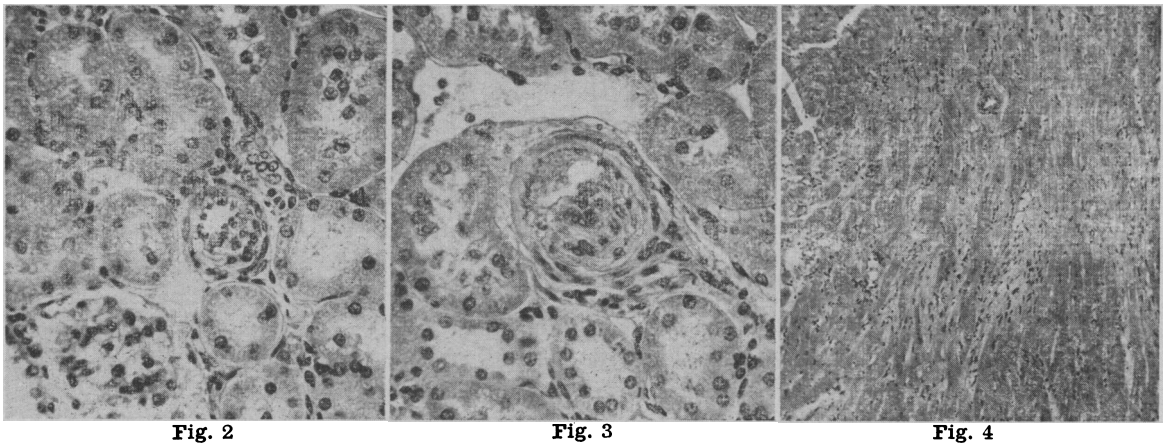

Fig. 2 Fig. 3 Fig. 4

Fig. 2.—Small artery from kidney of rat which did not maintain hypertension when treatment was stopped. Note the eccentric thickening of the wall. **Fig. 3.**—Small artery from kidney of rat with "self-sustained" hypertension. Note the eccentric thickening of the wall. Same magnification as Fig. 2. **Fig. 4.**—Myocardium of rat with "self-sustained" hypertension. Note the numerous small scars.

(Considerable investigation has been carried out concerning the "renal pressor mechanism". The present hypothesis does not discount the importance of this work nor does it deny the possibility that such a mechanism is operative in certain cases, particularly in the acute early stage and in those cases where compression of the kidney or its blood supply is demonstrable and removal is followed by a return to normal pressure. Since increases in neither renin nor hypertensin have been demonstrated in essential hypertension, however, it seems to be a generally held opinion[16] that the renal pressor mechanism is not responsible for chronic hypertension.)

As extended, our hypothesis states simply that hypertension may be expected to arise

to alleviate the hypertension would not invalidate the hypothesis.

The observation of Pickering[18] that removal of a constricted kidney late in the course of renal hypertension is not followed by a reduction in pressure would thus be explained on the basis of the pressor material being adrenal in origin rather than renal. On the other hand, Byrom and Dodson's observation,[19] which formerly seemed to conflict with that of Pickering, is similarly understandable. These workers found that if, in the late phase of renal hypertension, the constriction was removed, blood pressure fell. By the present hypothesis, removal of the constriction at any stage might be expected to improve the renal handling of the adrenal pressor agent, either partially or com-

pletely, depending on the amount of residual damage. Similarly, pathological involvements of the kidney will be accompanied by hypertension only in those cases where the specific mechanism for handling the pressor material is affected.

Examination of the evidence with regard to renal hypertension has led Grollman to discount the primacy of a renal pressor mechanism and recently, with Muirhead and Vanatta[20] to state that "the kidney normally, in addition to its excretory function, also exerts a function which is concerned in the maintenance of normal blood pressure levels. Hypertension of renal origin according to this view is not due to the liberation of a pressor agent, but results from a failure of this activity of the kidney". The present hypothesis satisfies the arguments of this investigator but substitutes for the broadly phrased renal deficiency an already circulating adrenal pressor material.

A similar examination of the evidence has led Braun-Menendez *et al.*[21] to state recently

> "Renal mass (or renal function) is normally conditioned by the concentration in the blood of a substance X. An increase in X determines an increase in renal mass (or function) while the opposite follows when X diminishes. On the other hand if X increases and there exists any impediment to the kidney increasing its function in order to maintain the hypothetical principle at a normal level, arterial hypertension results."

This statement was based on an exhaustive investigation of factors determining renal hypertrophy as well as on careful work with parabiotic animals which clearly indicated that normal renal tissue opposes renal hypertension. They also observed that nephrectomized animals become hypertensive. In our previous experiments, we have found that a linear relationship exists between blood pressure and renal mass in D.C.A.-treated animals and that the accumulation of D.C.A. by overdosage results in hypertension. Accordingly, the present hypothesis would substitute "adrenal cortical pressor material" for "substance X" in the statement by Braun-Menendez *et al.*

Examination of the problem of essential hypertension from the renal functional standpoint led Smith, Goldring and Chasis[22] to conclude that it was illogical to suppose that the kidney was the source of pressor material which caused arterial constriction in the kidney and at the same time that the constriction caused the appearance of the pressor agent. The present hypothesis removes this difficulty by offering a pressor material produced extra-renally. Selye's[10] view that overproduction of the adrenal cortex occurs in stress and may lead to hypertension fits the hypothesis in that it is one of the two ways in which hypertension can be caused.

In the present state of knowledge, when it is not even certain that essential hypertension in one disease, it is footling to attempt to postulate an all-embracing theory. Our suggestion does, however, attempt to reconcile certain observations. It is submitted at the present time as a partial correlation of some of the voluminous data which have accumulated as a direct outcome of Goldblatt's initial demonstration of the central position of the kidney in the genesis of hypertension.

SUMMARY

1. After discontinuation of intensive treatment with D.C.A. and saline 4 out of 7 animals maintained a "self-sustaining" hypertension. This hypertension persisted until the experiment was terminated 80 days later.

2. A hypothesis to reconcile various observations in experimental and clinical hypertension is presented. This hypothesis suggests that the maintenance of normal pressure depends, in many cases, on a correct balance between the production of a pressor material from the adrenal cortex and its handling by the kidney.

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