Hypertensive Cardiovascular Disease Induced by Desoxycorticosterone in Hypophysectomized Rats Bearing Pituitary Autotransplants

By C. E. Hall, Ph.D., and O. Hall, M.Sc.

With the collaboration of E. G. Jennels, Ph.D.

The responsiveness of hypophysectomized female rats bearing pituitary autotransplants to chronic, low dosage treatment with desoxycorticosterone acetate was compared with that of intact females. Intact animals reacted rapidly, developed malignant hypertension, and died within 10 weeks. By contrast hypophysectomized autograft-bearing rats developed hypertension more slowly, and the majority of them were alive at 16 weeks when the experiment was concluded. At autopsy, as compared with intact animals which had died earlier from the sequelae of malignant hypertension, hypophysectomized animals were found to have far more severe periarteritis nodosa, but a lesser development of nephrosclerosis and an extremely low incidence of cardiac damage. Hypertensive cardiovascular disease occurred in these animals despite extreme atrophy of the thyroid and adrenal glands, of the ovaries and uteri, and cessation of somatic growth. Therefore, except for LH which such autografts are known to elaborate, or trace amounts of the other principals, none of the known regulatory hormones of the anterior pituitary singly or in combination is essential to this effect of DCA.

The ability of desoxycorticosterone to induce hypertensive cardiovascular disease, characterized by nephrosclerosis, myocarditis and periarteritis, is firmly established. Neither gonadectomy nor parathyroidectomy appreciably alters the response; adrenalectomy exerts little influence on the blood pressure, but increases the cardiovascular damage; thyroidectomy has been reported to prevent hypertension and to markedly inhibit nephrosclerosis and myocarditis, while actually augmenting periarteritis; and hypophysectomy allegedly prevents the development of hypertensive cardiovascular disease completely, or, if performed after the pathologic lesions have developed, causes them to regress. The diminished responsiveness to DCA after hypophysectomy can be somewhat overcome by daily implantations of fresh pituitary tissue or by simultaneous treatment with ACTH and STH. Such circumstances are said to cause nephrosclerosis, but very little myocarditis or periarteritis nodosa. The effect on blood pressure was not stated. The evidence thus suggests that the cardiovascular effects of DCA are modified by the concurrent level of endocrine activity, and dependent upon the presence of pituitary hormones.

It has been noted by ourselves and others that the blood pressure of hypertensive DCA-treated rats may suddenly and precipitously fall. The behavior suggests that the heart, usually found to be hypertrophic and often extensively damaged, failed to maintain output sufficient to sustain hypertension in the face of existing arterial resistance. Preliminary experiments revealed hypophysectomized animals to be particularly prone to behave in this fashion, suggesting that they might more easily develop and sustain hypertension if the treatment were not too rigorous, the heart given a chance to adapt gradually to the increasing load, and a special effort directed toward maintaining the animals in a satisfactory physiologic state. Induction of panhypopituitarism in animals which yet appear to be in a better physical condition than ordinary hypophysectomized animals, was achieved by ablating the pituitary and transplanting it beneath the renal capsule. From the Departments of Physiology and Anatomy, University of Texas Medical Branch, Galveston, Tex. Supported by a research grant (RG 4833) from the National Heart Institute, U. S. Public Health Service. Received for publication December 1, 1958.

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capsule. The reactivity to DCA treatment was then compared with that of intact animals.

METHODS

Thirty-six female rats of the Holtzman strain weighing 111 to 115 Gm. were utilized for the study. Twenty-two of these were hypophysectomized under ether anesthesia, and the intact pituitary gland transplanted under the left renal capsule as described by Everett.13 Eighteen were then assigned to group 1 and four to group 2. Group 3 consisted of 8 intact animals and group 4 of 6. All animals were then given Purina Laboratory Chow ad libitum, an aqueous solution containing 0.85 per cent NaCl and 5 per cent sucrose to drink, and individually caged in air-conditioned quarters. Five days later the right kidney was removed from all animals, and a 75 mg. pellet of DCA9 implanted subcutaneously into those of groups 1 and 3. Growth and arterial pressure were assessed at approximately weekly intervals. Blood pressures were measured in unanesthetized animals by means of a tail plethysmograph.14 The experiment was continued for 16 weeks and the survivors were then killed with ether. The viscera were examined for gross changes, and the sella turcica for hypophyseal remnants. The hearts, kidneys, adrenals, thyroids, ovaries, uteri, and selected vascular territories were fixed in neutral 3 per cent formalin for histologic examination. When fixed, the organs were removed, dissected free of extraneous tissue, blotted dry, and weighed accurately on a delicate torsion balance.

Results

For the first five weeks of the experiment there was no evidence of growth in the hypophysectomized animals. From then until the seventh week there occurred a sharp increase in body weight of both intact and hypophysectomized animals receiving steroid. The body weight of intact control animals increased in a regular fashion, and that of hypophysectomized control animals remained essentially unchanged throughout the experiment. The results are shown in figure 1.

Arterial pressure of control animals, either intact or hypophysectomized, showed no marked fluctuation during the period of study, although the average pressure was slightly lower in hypophysectomized rats. By the second week of treatment many DCA-treated animals tended to be of milder degree and slower progression than in intact animals, both hypophysectomized and intact, wore hypertensive, although somewhat higher levels were attained by the latter. Thereafter the pressure of intact animals increased progressively, whereas in hypophysectomized animals it behaved less regularly, showing a rather abrupt increase between the fourth and fifth and an equally abrupt decrease the fifth and sixth weeks. Early in the experiment, hypertension in hypophysectomized animals tended to be of milder degree and...
slower progression than in intact animals, although eventually many of the former developed the severest hypertension. Figure 2 summarizes the data.

Intact DCA-treated animals began to die after the fifth week of treatment and all, having developed arterial pressures in excess of 200 mm. Hg, were dead by the tenth week. Autopsy revealed them to have varying degrees of pneumonia, cardiovascular disease, and ascites. Hypophysectomized DCA-implanted animals tolerated the treatment much better. Two died from pneumonia and one from hypoglycemia during the first month of treatment, one from unknown causes in the twelfth week, one with advanced periarteritis and ascites in the thirteenth week, and another with severe periarteritis, edema, and ascites in the fifteenth week.

The experiment was terminated on the 112th day of steroid treatment. At autopsy it was found that 1 animal in group 1 had a detectable pituitary remnant and hence it was discarded from the series. Inspection revealed that the hearts and kidneys of group 1 (hypox + DCA) were larger than those of group 2 (hypox) although no gross lesions were evident. The hearts of group 1 animals were significantly larger than those from animals in either group 2 or 4 (control) when expressed proportionately to the body weight. Hypophysectomized animals receiving DCA (group 1) had larger kidneys than those which did not (group 2), but smaller than those of untreated controls (group 4). The adrenals, thyroids, ovaries, and uteri were equally atrophic in all hypophysectomized animals, whether or not they received steroid hormone. Unfortunately, none of the intact DCA-treated animals survived the duration of the experiment. However, the average weight of the hearts and kidneys of the 4 animals which lived the longest, until the tenth week, were even then much larger than those of hypox-DCA-treated animals, which survived a further six weeks.

Severe periarteritis of mesenteric, pancreatic, and splenic arteries was grossly visible in all but 2 of the surviving DCA-treated and autotransplant-bearing animals, 1 of the latter being that found to have a pituitary remnant in the sella. Histologic examination revealed the lesion to be present also in these. The typical gross appearance is shown in figure 3. The microscopic characteristics have frequently been described elsewhere and do not merit repetition.

Renal lesions, invisible in the gross, were quite distinct microscopically in all DCA-treated animals, but not in controls. These and cardiac lesions were arbitrarily graded in severity on a scale of 0 to + + + +. Kidney damage in the 4 animals of group 3 which survived for 10 weeks was severe. In any given section there were more damaged nephrons than otherwise. Sclerosis, fibrinoid necrosis, and hyalinization of arterioles and glomerular capillaries were common, and tubules in which the epithelium was affected by degenerative changes and the lumen greatly distended with hyaline casts were prevalent. In group 1 (hypox + DCA), since all animals were affected, the incidence of renal damage was as high as in group 3 (intact), but the proportion of affected nephrons in any given section was remarkably low. Similarly, the severity of the lesions was great in respect to the extent to which individual nephrons were affected, but slight in respect to the number involved. The glomeruli were appreciably enlarged, and often showed sclerosis or intracapillary glomerulonephritis; frank fibrinoid necrosis was not observed, and extracapillary glomerulonephritis with proliferation of capsular epithelium, so commonly seen in the intact DCA-treated animals, was rare in similarly treated hypophysectomized animals. Often there were small islands of damaged nephrons scattered sparsely among areas of essentially normal tissue. Inflammatory changes were exceedingly rare. A third of these animals had developed blood pressures in excess of 200 mm. Hg prior to death, but the degree of renal damage was slight in comparison to that in animals of group 1 which had shown similar pressures before death, six weeks earlier.

Myocarditis, granuloma formation, necrosis of arteriolar walls, and infiltration of the
TABLE 1.—Summary of Findings

<table>
<thead>
<tr>
<th>Data</th>
<th>Hypophysectomy and pituitary autotransplant</th>
<th>DCA Control</th>
<th>Intact DCA</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. animals</td>
<td>18</td>
<td>4</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Initial</td>
<td>11</td>
<td>4</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Organ weights (mg./100 Gm.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroids</td>
<td>5.2 ± 0.3*</td>
<td>5.4 ± 0.6</td>
<td>—</td>
<td>15.3 ± 0.9</td>
</tr>
<tr>
<td>Adrenals</td>
<td>6.6 ± 0.7</td>
<td>7.3 ± 0.9</td>
<td>41.3 ± 3.9†</td>
<td>32.6 ± 2.4</td>
</tr>
<tr>
<td>Ovaries</td>
<td>5.5 ± 0.4</td>
<td>5.9 ± 0.7</td>
<td>—</td>
<td>28.6 ± 1.3</td>
</tr>
<tr>
<td>Uterus</td>
<td>34.1 ± 1.4</td>
<td>32.3 ± 2.1</td>
<td>—</td>
<td>19.0 ± 12</td>
</tr>
<tr>
<td>Heart‡</td>
<td>461 ± 20</td>
<td>325 ± 11</td>
<td>502 ± 17</td>
<td>355 ± 15</td>
</tr>
<tr>
<td>Kidney</td>
<td>611 ± 15</td>
<td>513 ± 22</td>
<td>962 ± 38</td>
<td>828 ± 29</td>
</tr>
</tbody>
</table>

Lesions

<table>
<thead>
<tr>
<th></th>
<th>Hypophysectomy</th>
<th>DCA Control</th>
<th>Intact DCA</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periarteritis (% incidence)</td>
<td>100</td>
<td>0</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>Av. severity§</td>
<td>***</td>
<td>0</td>
<td>*</td>
<td>0</td>
</tr>
<tr>
<td>Nephrosclerosis (% incidence)</td>
<td>100</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Av. severity*</td>
<td>*</td>
<td>0</td>
<td>***</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac (% incidence)</td>
<td>17</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Av. severity*</td>
<td>*</td>
<td>0</td>
<td>***</td>
<td>0</td>
</tr>
</tbody>
</table>

*Mean ± S. E. of mean.
†Based on four longest survivors of group.
‡Ventricles only.
§Severity refers to amount of organ or tissue affected, not to severity of individual lesion.

myocardium by connective tissue, were evident to varying extent in the hearts of the 4 in group 3 that survived longest. In group 1, on the other hand, although cardiac hypertrophy was uniformly evident, frank lesions were encountered in only 2 out of the 11. In one of these there was slight subendothelial deposition of hyaline material and an incipient granuloma, and in the other connective tissue proliferation. No cause for the greater sensitivity of these 2 animals could be found in the course of their hypertension during life. Curiously, extensive cerebral hemorrhages, found at autopsy in many of the intact hypertensive animals, were never seen in hypophysectomized hypertensives. The data are summarized in table 1.

Histologically the pituitary autografts consisted of well preserved chromophobe cells with a few eosinophils. The tissue appeared to have regressed in volume, but was well vascularized. Renal lesions had no predilection for the vicinity of autografts. The characteristic histologic findings are presented in figures 3 to 6.

DISCUSSION

It is evident that mineralocorticoid hypertension can be produced in animals whose pituitary function is incapable of supporting either body growth or the integrity of...
the thyroids, adrenals, and gonads. The successful induction of cardiovascular lesions may be ascribed to the fact that in the present experiment treatment was continued for a much longer period than has been reported, and the general health of the animals was supported by pituitary autografts.

The possible role of the autografts in making this response possible warrants speculation. Such grafts are known to secrete LTH, but at present there is no evidence that appreciable amounts of any other anterior pituitary hormone are elaborated. The moderate increase in weight of DCA-treated hypophysectomized rats, that began on the fifth week of treatment, seems to be attributable to steroid-induced salt and water retention rather than growth, inasmuch as it occurred also in the DCA-treated intact animals, but not in control hypophysectomized animals. Atrophy of the adrenals, gonads, and thyroids in all the hypophysectomized autograft-bearing animals appeared to be complete. Nonetheless, the data do not permit exclusion of the possibility that trace amounts of anterior lobe hormones, of either known or unknown nature, may have been secreted by the autografts. It has been reported that pituitary autografts exert effects on the pelage of hypophysectomized animals. In our experience, hypophysectomized animals bearing them are also more active and have better muscle tone than those which do not. Possibly arteriolar tone is also better, thus facilitating the development of hypertension.

In an antecedent experiment the left kidney bearing the autograft was removed instead of the right at the time of nephrectomy, thus effecting complete hypophysectomy. Half of the 8 animals bearing a 75 mg. DCA pellet survived for two months. All of these had hypertension and 2 of them had severe periarteritis. This leads us to believe that pituitary hormones are not essential to the development of DCA hypertension. However, it is our belief that hypophysectomized animals bearing autografts are materially healthier than those not bearing them, and that in them both survival and responsiveness to DCA are materially improved. The rapid evolution and malignant course of hypertension in the intact DCA-treated rat contrasts markedly with the slower onset and more benign characteristics of hypertensive disease induced by the steroid in the hypophysectomized animal. Consonant with this difference in reactivity was the finding that, whereas the former commonly developed extracapillary glomerulonephritis with formation of epithelial crescents, in the latter the intracapillary form of glomerulonephritis was characteristic.

The absence or virtual absence of cerebral and cardiac vascular lesions, and the milder extent of renal lesions in the presence of the severest periarteritis in mesenteric, splenic, and pancreatic arterioles is curious. By minimizing the involvement of the vessels supplying vital organs the animals were permitted to survive long enough to develop the severest lesions in less critical vessels. On the whole, the distribution and characteristics of the pathologic changes were more reminiscent of that which is said to occur in the DCA-treated thyroidectomized rat. In fact, the severe periarteritis in both instances may simply be due to the loss of adrenal glucocorticoids, which normally exert a suppressive effect on this particular lesion.

It has been clearly established that the vascular lesions produced by DCA treatment are dependent upon the presence of elevated blood pressure. A ligature placed about the mesenteric arterioles prevents the occurrence of periarteritis distal thereto, although the proximal portions are still affected, and similarly a ligature applied to the carotid arteries completely prevents the customary cerebral vascular lesions. Since many of the hypophysectomized DCA-treated rats had the severest hypertension, and yet the affection of the various vascular territories was markedly different from that found in the intact animals, two possibilities suggest themselves. Either the various vascular beds were exposed to different pressures in the hypophysectomized animals, or the alteration in the pattern of the lesions was due to the slow
onset and progress of hypertension, and the altered reactivity of the different territories as a consequence of changes in endocrine balance. The latter seems more plausible.

Production of hypertensive cardiovascular disease by DCA in hypophysectomized animals appears to require a longer period of treatment than has been attempted hitherto. Further, we believe small dosages of hormone to be preferable to large, since the adaptability of hypophysectomized animals is impaired, and in our hands they have not well tolerated the toxic effects of high dosages. Experiments are in progress that are designed to elucidate the conditions under which desoxycorticosterone most effectively produces hypertensive cardiovascular disease in animals completely deprived of pituitary tissue.

SUMMARY

Immature hypophysectomized animals bearing pituitary autotransplants beneath the renal capsule ceased to grow, and developed extreme involution of the thyroids, adrenals, and gonads. When sensitized to DCA by uninephrectomy and NaCl, they readily developed hypertension and hypertensive cardiovascular disease. However, as compared with intact animals, hypertension began later, progressed more slowly, and was better tolerated. Hypophysectomized animals survived treatment for a much longer period than the intact, and were found at autopsy to have a more severe periarteritis of the pancreatic, splenic, and mesenteric vessels, but a lesser degree of renal, cardiac, and cerebral arteriolosclerosis. Thus the ability of DCA to produce hypertension and arteriopathy does not require the presence of significant quantities of thyrotrophin, adrenocorticotropic, somatotrophin or the gonadotrophins, with the possible exception of LTH.

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