Experimental Vascular Lesions in Desoxycorticosterone Hypertension in Rats

Hideo Ueda, M.D., Hiroko Nishimura, M.D., and Hisakazu Yasuda, M.D.

Renal and vascular lesions of rats elicited by DCA and 1% saline for drink were studied periodically for 7 weeks. An attempt was made to clarify the relationship between vascular lesions and the elevation of blood pressure.

Acute necrotizing vascular damage appeared in bursts at 2 to 3 weeks after the DCA treatment was begun and its evolution diminished thereafter. Interstitial cells and fibers proliferated in the areas involved, replaced them and accumulated in parallel with time. Moreover in the kidney lesions extended with destruction of the glomeruli and tubules secondary to vascular damage.

Necrotizing vascular damage evolved when blood pressure was elevating rapidly. However, it diminished when hypertension became established. This means that the sustained high blood pressure is not an only determining factor.

It has been generally recognized that desoxycorticosterone acetate (DCA) causes necrotizing arteritis and arteriolitis, nephrosclerotic lesions and periarteritis nodosa as well as a persistent elevation in blood pressure in rats which are 'sensitized' by an excessive intake of sodium chloride and uninephrectomy.11-15 Although a sustained elevation of blood pressure, altered vascular permeability, and disturbed electrolyte equilibrium in the peripheral vascular bed are considered to be of fundamental importance in the pathogenesis of these renal and vascular lesions, the exact mechanism of their development and progress has remained obscure.

The purpose of the present study is to detect the evolution of these vascular lesions and follow their progress in relation to the elevation of blood pressure in uninephrectomized rats which were given daily injections of DCA and 1% NaCl solution for drinking fluid by examining their pathological changes periodically.
MATERIALS AND METHODS

Sixty-eight Wistar female albino rats, weighing 150 to 160 Gm., were divided into 2 groups. They were fed Oriental Laboratory chow. Group 1 consisted of 30 untreated animals which were given tap water to drink ad libitum and served as controls. Group 2 was 38 animals, unilaterally nephrectomized and maintained on 1% NaCl solution as a substitute for water. Starting on the 7th postoperative day the animals of group 2 were treated with subcutaneous injection of 1 mg./day of an aqueous DCA suspension. Body weight was measured regularly twice a week and blood pressure of unanesthetized rats was determined at least once a week by the microphonic tail method\(^6\),\(^7\) after warming at 45°C for 5 min. Several rats were individually housed in metabolism cages and daily excretion of urinary proteins was measured by Tsuchiya’s method.

Three to 6 rats from the DCA-treated group were exsanguinated by the tube inserted into the carotid artery at the end of the 1st, 2nd, 3rd, 4th, 5th, 6th and 7th week of the treatment. At the end of the 1st, 3rd, 5th and 7th week of the experiment 6 to 8 control rats were killed. Plasma total protein and blood urea nitrogen were measured by refractometer and U-Ni-GRAPH (Warner-Chilcott), respectively. An estimate was made of gross lesions in autopsies of all animals. Heart, kidney, liver, brain and other main organs were removed, dissected free of extraneous tissues, weighed fresh and fixed in neutral 8% formalin. Tissues were stained for microscopic study with hematoxyline and eosin, Mallory’s azan and periodic acid fuchsina (PAS). Weigert’s elastic tissue stain and silver impregnation by Bielschawsky Pap’s method were also employed.

Based on the duration of the treatment the animals were assigned to 3 groups as: (1) early period (rats killed at the 1st, 2nd and 3rd week), (2) middle period

| Table I. Severity of Necrotic and Proliferative Changes Graded from 0 to 3+ |
|-------------------------------|-----------------|-----------------|
| Necrotic Changes               | Proliferative Changes |
| 0                             | no significant change | no significant change |
| 1+                            | glomeruli: degenerative changes of cells of capillary loops and Bowman’s capsules; thickening of basement membrane | changes between 1+ and 3+ |
|                               | small arteries and arterioles: degenerative changes of vessel walls; low and homogenous in staining of media; occasional cellular and/or fibrous proliferation | 1) glomeruli and tubules: hyaline-thrombi in capillary loops; obliteration of capillary spaces and tubules with hyaline casts; degeneration of glomerular and tubular epithelium, advanced |
|                               | 2) small arteries and arterioles: extensive fibrinoid, necrotic changes of vascular walls and occasionally in perivascular tissue | 2) small arteries and arterioles: onion-like proliferation of perivascular collagen fibers; more or less fibrous thickening with narrowing of the lumen |
|                               | 3) myocardium: foci of fibrinoid necrosis | 3) myocardium: scar formation |
|                               | changes between 1+ and 3+ | 4) periarteritis nodosa |
(those of the 4th and 5th week), and (3) late period (those of the 6th and 7th week), and compared the physiological and morphological findings with one another. The severity of lesions in the organs and tissues examined was graded from 0 to 3 plus based on findings described in Table I. The representative severity of each group was expressed by dividing the total severity by the number of rats.

RESULTS

Changes in Body Weight (Fig. 1)

The control animals showed a physiological increase of body weight and general conditions remained good throughout the experiment. In the DCA-treated rats polyuria developed within a few days after the treatment was begun and persisted throughout. Between 2 and 4 weeks, 13 of 35 rats lost 6 to 12% and 11 lost 1 to 5% of body weight while the rest continued to increase. The animals which lost 1 to 5% returned to the original level after approximately 1 week, but those which lost 6 to 12% failed to regain or even continued to decrease because of difficulty in eating and became emaciated and lethargic, or contrarily harsh and irritable. Transitory edema also developed with daily fluctuation of body weight from 30 to 60 Gm. in the late period.

Changes in Blood Pressure (Fig. 2)

The mean blood pressure of the control rats showed 93.0 mm.Hg with a range of 80 to 123 mm.Hg. In the DCA-treated rats systolic blood pressure started to elevate at the end of the 1st week, rose rapidly during the 2nd and 3rd week (early period), and reached the values of 171.0±11.2 mm.Hg. At the 4th and 5th week (middle period) it rose more gradually. After the 6th

![Fig. 1. Body weight of the DCA-treated rats as expressed in percentage of the initial weight.](image-url)
week (late period) systolic blood pressure, averaging 200.0 mm.Hg, was sustained in some cases while further elevation or a slight drop was observed in others.

Changes in Urinary Protein Excretion, Plasma Total Protein, Blood Urea Nitrogen, and Organ Weight (Table II, III)

Urinary protein excretion of the DCA-treated group was $24.7 \pm 7.9$ mg./day at the 2nd week which was approximately 3 times of the control value and increased further at the 5th and 6th week. The levels of plasma total protein and blood urea nitrogen of the DCA-treated rats did not differ significantly from those of the control group except one case whose blood urea nitrogen was 43 mg./100 ml. at the 5th week. The heart weight of the DCA-treated rats increased progressively after the 2nd week in parallel with the elevation of blood pressure.

Gross Findings

The heart and kidney were enlarged and occasionally mottled with petechiae in the early period in the DCA-treated group. Among 29 cases killed in the middle and late periods, 11 showed white patchy lesions on the surface of the heart mainly localized in the right ventricle. The kidney changed in color from red brown to pale gray with small, scattered grayish white spots in 20 cases. Ten demonstrated small brownish white nodules near the attachment of the small bowels or along the mesenteric arteries. The brain was swollen and edematous in the late period though no gross cerebral or subarachnoid hemorrhage was observed. Subcutaneous tissue edema, ascites, hydrothorax and hydropericardium were present in 9 of 10 rats killed in the late period.
Table II. Changes in Blood Urea Nitrogen, Plasma Total Protein, Urinary Protein Excretion and Severity of Lesions Shown in the DCA-Treated Rats

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Blood urea nitrogen (mg./100 ml.)</th>
<th>Plasma total protein (Gm./100 ml.)</th>
<th>Excretion of urinary proteins (mg./day)</th>
<th>Incidence of lesions (%)</th>
<th>Severity of lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>DCA-treated</td>
<td>Control</td>
<td>DCA-treated</td>
<td>Control</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>21.0±1.0</td>
<td>15.2±0.7</td>
<td>5.6±0.3</td>
<td>6.3±0.3</td>
<td>7.0±2.1</td>
</tr>
<tr>
<td>Early</td>
<td>period 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>22.3±1.5</td>
<td>22.2±3.7</td>
<td>6.0±0.04</td>
<td>5.7±0.5</td>
<td>5.4±1.0</td>
</tr>
<tr>
<td>Middle</td>
<td>period 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>19.5±2.5</td>
<td>20.5±0.4</td>
<td>6.5±0.3</td>
<td>6.5±0.4</td>
<td>7.7±2.5</td>
</tr>
<tr>
<td>Late</td>
<td>period 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>22.7±1.0</td>
<td>15.8±1.9</td>
<td>6.6±0.2</td>
<td>5.6±0.1</td>
<td>9.1±2.0</td>
</tr>
<tr>
<td>7</td>
<td>23.7±0.6</td>
<td>15.8±1.9</td>
<td>6.6±0.2</td>
<td>5.6±0.1</td>
<td>9.1±2.0</td>
</tr>
</tbody>
</table>

* Results are expressed as mean values with standard errors.
Table III. Changes in Organ Weight of the DCA-Treated Rats

(Gm./100 Gm. of Body Weight**)

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Kidney</th>
<th>Heart</th>
<th>Brain</th>
<th>Lungs</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>DCA-treated</td>
<td>Control</td>
<td>DCA-treated</td>
<td>Control</td>
</tr>
<tr>
<td>Early Period</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.31 ± 0.06</td>
<td>0.50 ± 0.01</td>
<td>0.35 ± 0.02</td>
<td>0.38 ± 0.01</td>
<td>1.11 ± 0.08</td>
</tr>
<tr>
<td>2</td>
<td>0.55 ± 0.33</td>
<td>0.42 ± 0.01</td>
<td>0.42 ± 0.01</td>
<td>1.04 ± 0.01</td>
<td>0.97 ± 0.01</td>
</tr>
<tr>
<td>3</td>
<td>0.36 ± 0.01</td>
<td>0.81 ± 0.05</td>
<td>0.32 ± 0.03</td>
<td>0.43 ± 0.03</td>
<td>0.97 ± 0.06</td>
</tr>
<tr>
<td>Middle Period</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.65 ± 0.09</td>
<td>0.41 ± 0.06</td>
<td>0.41 ± 0.06</td>
<td>0.92 ± 0.11</td>
<td>0.54 ± 0.06</td>
</tr>
<tr>
<td>5</td>
<td>0.35 ± 0.01</td>
<td>0.31 ± 0.03</td>
<td>0.46 ± 0.03</td>
<td>0.80 ± 0.06</td>
<td>1.03 ± 0.06</td>
</tr>
<tr>
<td>Late Period</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.97 ± 0.04</td>
<td>0.53 ± 0.04</td>
<td>0.53 ± 0.04</td>
<td>0.96 ± 0.09</td>
<td>0.65 ± 0.03</td>
</tr>
<tr>
<td>7</td>
<td>0.34 ± 0.03</td>
<td>0.89 ± 0.04</td>
<td>0.37 ± 0.05</td>
<td>0.55 ± 0.05</td>
<td>0.77 ± 0.05</td>
</tr>
</tbody>
</table>

* Results are expressed as mean values with standard errors.
** Body weight at the time of sacrifice was used. Previous weight was applied in the case which showed extreme loss or gain prior to death.

Microscopic Findings

No abnormalities were observed in the control animals throughout the whole experimental periods. The lesions noted in each period of DCA treat-

![Fig. 3. Severity of necrotizing damage shown in the various organs of the DCA-treated rats.](image-url)
ment were as follows. The character and distribution of vascular lesions are summarized in Fig. 3 and Fig. 4.

1) Early Period

There was early and focal involvement in the glomeruli of the kidney represented by the increased mesangium and thickening of the basement membranes in the rats killed at the 1st week of the treatment. At the 2nd and 3rd week the most distinctive and striking feature was widespread vascular damage which was most common in the afferent arterioles, adjacent to the glomeruli, and was represented by acute necrosis throughout the arterial walls with formation of globules of PAS positive amorphous material corresponding
Fig. 5. Glomerulus with the afferent arteriole in a DCA-treated rat, 2 weeks, showing remarkable fibrinoid necrosis throughout the arteriolar wall. Note same homogenous material at the surrounding connective tissue (hematoxyline and eosin stain).

to what was termed 'fibrinoid necrosis': as it extended accumulation of the material spread through the adventitia and perivascular tissue with leaking of the red blood cells and infiltration of the round cells (Fig. 5). Glomerular capillary tufts were partially obliterated with diffuse or granular, PAS positive deposits of hyalinoid material both on the wall and in the lumen and they lost their delicate architecture almost completely. But in general glomerular involvement was less severe than that of the arterioles. In the interlobular and arcuate arteries the point of branching was most frequently diseased where fibrinoid necrosis of the medial smooth muscle cells localized segmentally at the external layer of the media on occasion circumferential (Fig. 6 and 7). Thickening of the medial coats with enlargement, altered polarity and hyperchromism of the muscle cell nuclei and, at times, the swollen or shrunken endothelium were observed. Elastic tissue stains showed complete loss or focal segmental loss of the external and, in many cases, internal elastic lamina in the involved area. In disagreement with the findings of

Fig. 6. Typical damaged arterioles in the kidney of a DCA-treated rat, 3 weeks. Acute fibrinoid necrosis is remarkable at all coats of the wall, in a part, at the perivascular area (see arrow). (Mallory's azan stain).
many observers inflammatory reactions such as endoarteritis or periarteritis were not prominent.

In the heart there were numerous islets of hyalinization of the myocardial fibers mainly situated within the wall of the right ventricle. The subendocardial portion or the entire thickness of the wall was involved. The myocardial fibers became swollen and vacuolated: some fibers lost their striations and reduced to masses of necrotic material.

Small vessels showed focal or complete fibrinoid necrosis with extravasation of a homogenous, hyalinoid substance in the perivascular tissues and interstitial round cell infiltration. Vascular lesions of the small intestines, stomach, pancreas and mesenteric arteries slightly differed in appearance of damage and the subsequent proliferative reaction from those of the kidney and heart. Homogenous, PAS lightly positive material was accumulated between the endothelium and internal lamina, the vessels lumen being reduced
in size with the loosened endothelium (Fig. 8). In some places hyaline material infiltrated into the outer coat of the vessels or was in direct contact with the intravascular plasma mass.

Arteriolar fibrinoid necrosis was present in variable degree in the liver, ovary, brain and spleen. Microscopic cerebral bleeding was observed in a few cases. In general, there was no other significant change of the parenchymal tissues.

2) Middle Period

In the kidney interstitial cells and fibers proliferated in the involved afferent arterioles and their vascular lumen was partially or completely obliterated. The walls of the vessels often lost their fine structures and changed to onion-like granulomatous masses (Fig. 9). There were progressive hyalinization, eventual complete fibrous obliteration of the glomeruli, and atrophic or fibrotic change of tubules secondary to damage of the glomeruli. The glomeruli

Fig. 9. Glomerulus and afferent arteriole of a DCA-treated rat, 5 weeks, showing fibrinoid necrosis of the arteriolar wall extends to the glomerular loops. Note onion-like lesion around the involved area, consisting of cellular and fibrous proliferations (PAS stain).

Fig. 10. Right ventricular myocardium of a rat treated with DCA for 6 weeks, showing extensive fibrous lesion which contains the several affected vessels. Collagen fibers laminate both in the adventitia and perivascular area (Mallory's azan stain).
without damage of the afferent arterioles were either obliterated or greatly distended by accumulation of blood and hyaline materials exudated into the Bowman’s spaces. Degenerated tufts were frequently adherent to the Bowman’s capsules whose epithelial cells were swollen. The proximal convoluted tubules and, occasionally, the collecting tubules contained hyaline casts with resultant atrophy or hydropic degeneration of the epithelium.

In the heart the hyalinized myocardium was replaced by the fairly dense connective tissue which could be detected grossly as grayish-white nodules (Fig. 10).

In the lesion of the mesenteric arteries the walls and surrounding interstitial tissues were disrupted by the marked proliferating and granulomatous tissue, consisting of polymorphnuclear leucocytes, mononuclear cells and fibroblasts, which resembled periarteritis nodosa.

3) Late Period

In the kidney interstitial cells and fibers proliferated extensively surrounding the involved glomeruli, tubules and vessels all together. Laminated, circumferential collagen fibers were noted in the adventitia and perivascular tissues of the affected small arteries and arterioles, at times with concentric hyperplastic thickening and fibrosis of all coats of the walls (Fig. 7 and 10). Of particular interest is that actively necrotizing damage was recognized at the same time at the center of onion-like granulomatous lesions and in both the intima and media of the small vessels adjacent to or inside healed lesions. Besides the findings described above, the thickening of the intima and media of the small vessels and other hyperplastic arteriolosclerotic changes were noted in all hypertensive animals.

The incidence of the diseased rats and the average severity of vascular damage in the kidney and heart at each week of DCA treatment are summarized
Necrotizing damage was prominent at the 2nd and 3rd week and then maintained the same level throughout the experimental period. Fibrous proliferation followed to necrotizing damage and increased linearly (Fig. 11). The incidence of the diseased rats was approximately 50 to 60% continuously after the 3rd week.

**Relation between Blood Pressure and Necrotizing Vascular Damage**

Blood pressure elevated rapidly in the early period and necrotizing damage was also predominant at the 2nd and 3rd week. In the middle and late period blood pressure continued to rise and maintained the level of 200 mm.Hg but contrarily the evolution of vascular damage diminished. All animals treated with DCA developed hypertension, although vascular damage was induced in only half.

**Relation between Body Weight Changes and Necrotizing Vascular Damage**

On the basis of the degree of weight loss between 2 and 4 weeks, the animals were divided into 3 groups: (1) lost 6 to 12%, (2) lost 1 to 5%, and (3) continued to increase. Their blood pressure, the incidence and severity of lesions are compared in Table IV. No significant difference was recognized in the height of blood pressure at the end of the 3rd week, but the rats which lost 6 to 12% were all seriously diseased and none of those which continuously gained weight revealed vascular damage.

**Table IV. Relation of Body Weight Loss between 2 and 4 Weeks of Treatment to Blood Pressure, Incidence and Severity of Lesions**

<table>
<thead>
<tr>
<th>Loss of Weight in Percent</th>
<th>No. of Rats</th>
<th>Changes in Body Weight</th>
<th>Blood Pressure at the End of the 3rd Week mm. Hg</th>
<th>% Incidence of Lesions</th>
<th>Severity of Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-12%</td>
<td>9</td>
<td>Failed to gain or even lost more</td>
<td>170.8 ±9.9</td>
<td>100</td>
<td>2.8</td>
</tr>
<tr>
<td>1-5%</td>
<td>9</td>
<td>Regained</td>
<td>175.3 ±8.4</td>
<td>33</td>
<td>0.8</td>
</tr>
<tr>
<td>No Loss of Weight</td>
<td>8</td>
<td>Continued to increase</td>
<td>169.7 ±11.4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**DISCUSSION**

**The Evolution of Vascular Damage**

The histological structures of vascular damage, the incidence and severity of lesions observed in the animals killed periodically were highly suggestive that acute necrotizing vascular damage appears in bursts at the 2nd and 3rd
week of DCA treatment, and diminished thereafter as shown schematically in Fig. 12. Weight loss noted between 2 and 4 weeks also supported the evidence that the changes originated in that period or earlier. On the other hand, interstitial cells and fibers proliferated in the necrotizing lesions and accumulated in parallel with time. The severity of fibrous proliferation increased linearly though that of necrotizing damage maintained approximately the same level throughout the experiment after the 3rd week. Cells and fibers proliferated not only in the affected places but became extensive forming laminated structures and composed in splanchnic arteries the peculiar features similar to periarteritis nodosa. What can be inferred from these facts is that these are not merely the healing reaction of damage but play an active part in the progress of lesions probably through the mechanism of 'antigen-antibody reaction'. At the same time fresh necrotizing damage noted within fibrotic lesions in the late period offered the possibility that overproduction of fibers may disturb the metabolism of the vessels and interstitial tissues, thereby intensifying the damage.

The kidney shows more extensive lesions because vascular damage produced in early weeks resulted in secondary destruction of the glomeruli and tubules, and because hyaline materials exuded into Bowman's space as a consequence of increased capillary permeability, distributed widely to the tubules and elicited diffuse damage of the epithelial cells. The increase of urinary protein excretion in the later weeks also supports the evidence of renal damage. From the view that the animals which lost considerable weight in the early period failed to regain it or even lost more, continuous aggravation of the disease may be justified. It is also in accordance with the observation that discontinuation of DCA treatment is followed by a definite decrease in blood pressure but persistence of nephrosclerotic lesions.
Hypertension as a Factor in Causing Necrotizing Vascular Damage

The necrotizing vascular damage appeared in the period when blood pressure was elevating rapidly. This led us to consider that the damage may be attributed to the rise in blood pressure. This is also supported by the observation of Gaunt,8) who has demonstrated that treatment of the DCA-treated rats with a depressor drug, hydralazine hydrochloride (apresoline), prevents vascular damage. The investigation by Byrom and Dodson9) in which sudden strain placed on the arterial walls by repeated forced injections of Ringer’s solution into the carotid artery produced focal necrosis of the small arteries of the kidney, must also be considered as an evidence to prove the causal relation between high arterial pressure and vascular damage. The mechanism through which increased arterial pressure may participate in eliciting vascular damage has remained unsolved. It can be assumed that the electrolyte equilibrium in the peripheral vascular bed might be disturbed by DCA and excessive salt intake10,11) so as to enhance the contractility of musculature exposed to chemical pressor substances.12) Although the significance of this metabolic change is far from clarified, the possibility remains that such disturbance may be responsible for both the elevation of blood pressure and the early organic injuries of the vessels. At the same time it is postulated that hypertension and other related hemodynamic changes, resulting in increased permeability13,14) of the arterial intima to blood constituents, may account for the acceleration of damage and form the extensive necrotizing lesions.15) The fact that the afferent arterioles in the kidney and the small arteries and arterioles in the various organs which consist of the main parts of the resistant vessels, are the sites of predominant damage during the early period led us to formulate the concept that the structure or status of musculature, such as its vasocontractility, is an important determinant which conditions the onset of lesions. Filtration of plasma into vessels is also implied by manifestations that lesions are often associated with leakage of red blood cells to the walls, hyalinoid materials in the perivascular tissues which seem to be extrusion of a protein through the necrotic wall and hyalinization of the adjacent muscle fibers in the heart, and that subintimal fibrinoid materials of mesenteric arteries are in direct contact with plasma-like mass in the vascular lumens.

In spite of these supporting evidences there is however some doubt that high blood pressure is the only determining factor because vascular damage was elicited only in half the rats which equally developed hypertension by DCA treatment, and because its evolution diminished in the period when hypertension became established and was sustained in higher levels. One possible explanation for this discrepancy is that hyperplastic arteriolosclerotic changes16) would inhibit the infiltration of plasma into the vessels. The elevation
of blood pressure and its maintenance are not necessarily the same from the pathogenetic stand points; thus the evolution of vascular damage does not always correspond to either the level or the duration of hypertension. Actually in each series of the experiment, widely varying observations are noted of the incidence, severity, the time of evolution of the damage and its interrelation to the elevation of blood pressure. Ooneda et al.\textsuperscript{17} noted acute vascular damage in 4 of 6 cases at the 5th week of DCA treatment (1 mg./day), whose average blood pressure was 200 mm.Hg. Selye et al.\textsuperscript{2} proved periarteritis nodosa, acute nephrosclerosis and granulomatous nodules in the heart after daily injection of 2.5 mg. desoxycortisone for 3 weeks, though blood pressure elevated from 125±5 to 156±6 mm.Hg. Masson et al.\textsuperscript{4} recognized no remarkable change before 3 weeks in rats receiving daily administration of 2.5 mg. DCA, but they found diffuse renal and vascular damage in all rats before 9 weeks. This variability is due partially to the amount of DCA injections but the strain and age of rats and genetic sensitivity to NaCl\textsuperscript{18} are other contributing factors, besides the elevating blood pressure and related change discussed above. Attention has been also brought to the existence of vasculotoxic and humoral substance by Winternitz\textsuperscript{19,20} who noted acute vascular lesions due to saline extract of the kidney in bilaterally nephrectomized dogs and more recently by Assher\textsuperscript{21} who demonstrated a vascular permeability factor of renal origin. On the other hand Masson et al.\textsuperscript{22} proved that chronic treatment with crude or semipurified renin produced both hypertension and renal and vascular lesions in uninephrectomized rats. The vascular damage varies in character depending on the organs, and it has also peculiar localizations such as the small vessel of the right ventricle, the point of branching and the external layer of the media in the small arteries. These facts also suggest that it is necessary to devote more consideration to the anatomical and physiological specificity of the organs and vascular trees.

**Summary**

A series of the DCA-treated rats were unilaterally nephrectomized, given 1% NaCl solution for drinking fluid, and killed periodically to observe the evolution and progress of vascular lesions in relation to the elevation of blood pressure.

(1) Acute necrotizing vascular damage appeared in bursts in the early period of DCA treatment. The evolution of lesions diminished thereafter while interstitial cells and fibers proliferated in the areas involved and continuously accumulated in parallel with time. In the kidney, lesions further extended with destruction of the glomeruli and tubules secondary
to vascular damage.

(2) The necrotizing vascular damage evolved in the period when blood pressure was elevating rapidly. The histological features and localization of lesions highly suggest that the rise in blood pressure, which results in altered vascular permeability, and the status of the musculature of the peripheral vascular bed related to some maldistribution of sodium ion are of fundamental importance in the pathogenesis of the damage.

(3) On the other hand, the fact that the evolution of the damage diminished in the period when hypertension became established points out that high blood pressure is not an only determining factor.

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References