Pathogenesis of Polyarteritis Nodosa in Hypertensive Rats

By GEORGE J. RACE, M.D., AND ERNST PESCHEL, M.D.

The pathogenesis of the vascular lesions of polyarteritis nodosa found in young rats with experimental renal hypertension is described. The panarteritic lesion was a product of the combination of renal injury and feeding sodium chloride. It began with a fibrinoid necrosis of the intima and media which was followed by an extensive inflammatory reaction with subsequent fibrosis of all layers of the vessel wall.

During the course of investigations of the effects of dietary factors upon young hypertensive rats, a characteristic panarteritis rather frequently developed in animals receiving varying amounts of supplementary sodium chloride in the diet. This lesion is not unlike the lesion of human polyarteritis nodosa. Similar lesions have been previously reported in aged rats as a spontaneously occurring vascular disease,1 in young rats with renal damage due to alloxan and use of a 10 per cent sodium chloride diet,2 in rats given desoxycorticosterone and sodium chloride,3 and in rats made hypertensive by varying experimental procedures. In addition, an acute necrotizing arteritis has been produced by purely mechanical, transient elevation of the blood pressure.4 The etiology of the panarteritic lesion has been considered by the above authors and others.5, 6

Inasmuch as the arterial lesions observed by us have many similarities to, but also notable differences from, the lesions described by the previous authors, a morphologic description of the pathogenesis is deemed worthwhile.

**Experimental Procedure**

Twenty normal and 80 hypertensive female rats of the Osborn-Mendel strain were used. The latter were made hypertensive by the technic of renal encapsulation and subsequent contralateral nephrectomy. Details will be included in a subsequent paper.7 At the time of nephrectomy, the animals were approximately 40 days of age and had a systolic blood pressure of from 100 to 120 mm. Hg. Subsequently, the blood pressure rose within four to seven days to 180 to 220 mm. Hg, often followed by rises to 300 mm. Hg or more. The animals were then fed varying diets containing varying amounts of sodium chloride, as outlined in table 1. The hypertensive animals were allowed to die spontaneously. No selection for microscopic study was made except for group II; these represent animals with a survival time similar to that of the other groups. The normotensive controls were killed at varying intervals to match the average age at death of the hypertensive rats. Complete autopsies were done and histologic sections prepared from all organs, including the peripheral vessels, and, in addition, from the arterial lesions where they were observed grossly. All arterial lesions were stained with hematoxylin and eosin, and representative examples were stained with the Verhoeff-Van Gieson elastic tissue stain, the periodic acid-Schiff stain, the Masson trichrome stain for connective tissue, and the McCallum bacterial stain.

**Results**

The hypertensive rats died spontaneously at an average age of 127 days. A contributing cause of death in many cases was bronchopneumonia. The incidence of polyarteritis nodosa in this series of young animals was 31.2 per cent (as contrasted with 9.7 per cent occurring in the aged rats with an average age of 856 days).8 No instance of polyarteritis occurred in the 20 normal control rats. The distribution of the lesions, in order of frequency, was: mesentery, pancreas, spleen, extremities, ovary, and heart.

Grossly, the lesions were detected in the mesenteric and occasionally in pancreatic
PATHOGENESIS OF POLYARTERITIS NODOSA

TABLE 1.—Correlation of Diet, Survival Time, Degree of Hypertension, Heart Weight and Incidence of Polyarteritis in 80 Rats with Experimental Hypertension

<table>
<thead>
<tr>
<th>Group No., and Diet</th>
<th>No. of Animals</th>
<th>Avg. age at Death (Days)</th>
<th>Blood Pressure Avg. (systolic, mm. Hg)</th>
<th>Heart Wt. in % of Body Wt.</th>
<th>Incidence of Polyarteritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Normotensive Controls. Dog Chow (20 Gm./Day, Containing 200 mg NaCl)</td>
<td>20</td>
<td>130 (31-413)</td>
<td>112</td>
<td>0.40</td>
<td>0</td>
</tr>
<tr>
<td>II. Rice, Plus 25-50 mg. NaCl Daily throughout Life</td>
<td>10</td>
<td>135 (57-454)</td>
<td>100</td>
<td>0.62</td>
<td>1</td>
</tr>
<tr>
<td>III. Rice 50% with Meat, Plus 25-75 mg. NaCl Daily throughout Life</td>
<td>12</td>
<td>114 (54-259)</td>
<td>190</td>
<td>0.59</td>
<td>1</td>
</tr>
<tr>
<td>IV. Rice, Plus 75 mg. NaCl Daily (NaCl for 1-3 Weeks Only)</td>
<td>18</td>
<td>127 (58-271)</td>
<td>195</td>
<td>0.71</td>
<td>7</td>
</tr>
<tr>
<td>V. Different Foods Consisting of Carbohydrate and Small Amounts of Protein, Plus 75 mg. NaCl Daily through Life</td>
<td>18</td>
<td>123 (54-204)</td>
<td>223</td>
<td>0.71</td>
<td>8</td>
</tr>
<tr>
<td>VI. Rice, Plus 50-250 mg. NaCl Daily throughout Life</td>
<td>22</td>
<td>133 (55-302)</td>
<td>237</td>
<td>0.74</td>
<td>8</td>
</tr>
<tr>
<td>Totals for Hypertensive Animals</td>
<td>80</td>
<td>127 (54-454)</td>
<td>211</td>
<td>0.69</td>
<td>25</td>
</tr>
</tbody>
</table>

arteries. They usually formed tortuous, adherent, nodular masses. The degree of involvement was extremely variable and ranged from a single 3 mm. node to extensive accumulation of nodules which included the entire mesenteric arterial system. The diameter of the nodules ranged from 1 to 10 mm. The affected vessels were of medium to small size. Gross examination alone failed to reveal the lesions in peripheral vessels or parenchymatous organs.

Microscopically, the arterial changes were invariably those of a panarteritis. Three stages of development, based on necrosis, presence and type of inflammatory exudate, and degree of healing, were observed: an acute, a subacute, and a healing stage.

The acute lesions were seen in the heart and mesenteric arteries. The most acute change observed was a complete recent fibrinoid necrosis of the entire vessel wall without evidence of inflammatory reaction. This occurred in smaller blood vessels and might be interpreted from morphologic appearance alone as similar to the process which occurs in human malignant hypertension. Other acute, but slightly older and less severe lesions were characterized by fibrinoid necrosis of the intima and inner layers of the media with accumulation of fibrin in subendothelial spaces. Also there was edema of the outer media and adventitia, and infiltration by many polymorphonuclear leukocytes, and a few lymphocytes and macrophages. Elastic tissue stains showed fragmentation of the elastica interna and externa. The fibrinoid material was demonstrated to be positively stained by the periodic acid-Schiff stain. The Masson trichrome stain showed the presence of connective tissue only in the adventitia. McCallum bacterial stains failed to demonstrate bacteria within the arterial walls.

The subacute lesions were characterized by a mixed inflammatory infiltrate and early evidence of healing. This stage of panarteritis was observed in pancreas, intestine, and ovarian arteries. Here the entire wall of the vessel was disorganized so that it was impossible to define the limits of the intima, media and adventitia. The elastica interna and externa were fragmented and often laminated. The vessel wall was infiltrated throughout with polymorphonuclear leukocytes, macrophages, lymphocytes, and a few plasmocytes. Also, some proliferation of endothelial cells was observed. The peculiar fibrinoid material beneath the intima seen in the early lesion was no longer present, and there was marked fibroblastic proliferation and organization of the entire wall. Masson trichrome
stains demonstrated the marked degree of fibroblastic proliferation and the virtual absence of the musculature of the media. Thromboses were observed, both recent and organizing.

In the healing phase, fibrosis of the entire vessel wall was the predominant feature. The intima was greatly thickened by fibrosis, and the lumen of the vessel was reduced to about one-fifth of its previous diameter, or it was completely occluded by organizing thrombus. The muscle of the media was replaced by fibrous tissue which blended imperceptibly with the scarred adventitia. A few chronic inflammatory cells were present in the fibrous vessel wall. Some thrombi were recanalized. Calcification
of the intima was common in occurrence. In one mesenteric artery, there was a healing lesion adjacent to a late acute lesion. Generally, however, the age of the lesions as confined to one animal was about the same in all locations.

DISCUSSION

The panarteritis herein described was produced by a combination of renal injury and feeding sodium chloride. The initial injury to the vessel produces a fibrinoid necrosis of the
intima and sometimes the entire vessel wall. We consider this to be the initial lesion because it is immediately followed by a polymorphonuclear leukocytic exudate. Furthermore, the early fibrin accumulation on the surface of, and beneath the endothelium, is evidence of endothelial damage. This concept in pathogenesis is in opposition to the concept of Zeek and associates, who state that the initial stage is one of fragmentation, degeneration and edema of the adventitial collagen, which in turn is followed by fibrosis of the adventitia and subsequent necrosis and degeneration of the inner media and intima. Such a sequence of events is difficult to explain if this arterial disease is considered to be a reaction to injury. Our observations coincide with those of Selye and of Chute and associates, who describe a change in all layers of the vessel wall. However, it is thought that the intimal necrosis observed in our animals is of an acute fibrinoid type rather than a hyalinizing degeneration of the collagen over a long period of time. In agreement with the observations of the previously quoted authors, the repair following the injury, which we noted in our animals, was characterized by fibroblastic proliferation throughout all layers of the wall, eventually leading to extensive scarring.

**Summary**

Polyarteritis nodosa can readily be produced in hypertensive young rats by feeding diets containing sodium chloride. The incidence in this series was 31.2 per cent. The arterial injury was characterized by severe panarteritis. Pathogenetically, it began with a fibrinoid necrosis of the intima and media, which was followed by an extensive inflammatory reaction with subsequent fibrosis of all layers of the vessel wall.

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