PERIARTERITIS NODOSA IN EXPERIMENTAL HYPERTENSIVE RATS AND DOGS*

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In the course of a procedure to test the effect of certain renal extracts upon experimentally produced hypertension in rats and dogs, it was discovered at autopsy that many of the animals had periarteritis nodosa. The lesions found in these animals appeared to be identical in gross and microscopic morphology and in distribution with those of human periarteritis nodosa. A study of this condition in these animals was begun with the hope that it would add to our knowledge of the occurrence of similar lesions in man.

LITERATURE

A summary of the reported occurrence of periarteritis nodosa in animals is presented in Table I, inspection of which reveals that the disease has been found in a wide variety of animals, including cows, pigs, deer, dogs, rabbits and rats. Spontaneous occurrence of isolated cases in animals has been recognized for many years. Wilens and Sproul found many cases in very old rats fed a special diet.

Periarteritis nodosa has been described recently in rats in which hypertension was produced either by placing a silver clamp on one renal artery (Wilson and Byrom), or by wrapping one kidney with cellophane (Friedman, Jarman and Klemperer), or by various other operative procedures to induce hypertension (Cromartie).

Only 3 cases of periarteritis have been described in hypertensive dogs. Child reported its occurrence in 1 hypertensive dog following production of an Eck fistula. Goldblatt † states that he has found the disease in only 2 of more than 1000 dogs examined, while Graef and Page did not mention its occurrence following the production of hypertension by cellophane perinephritis.

No reports have been found of the occurrence of periarteritis nodosa in animals in which the blood pressures were proved to be normal, or in which the kidneys were proved to be free from pathologic change.

METHODS

Clinical and pathological studies were made on 100 rats and 8 dogs used for routine assays of the blood-pressure-lowering activity of cer-

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† Personnal communication.

TABLE I

Reported Occurrence of Periarteritis Nodosa in Animals

Animal	Author	Year	Arteries involved	Remarks
Calf	Guldner	1915	Heart, skeletal muscles	Spontaneous occurrence in a 4-weeks-old animal
Cow	Nieberle	1928	Heart, kidney, liver, spleen, lymph nodes, udder, gall-bladder	Spontaneous occurrence in a 3½-year-old animal
Deer	Lüpke and Jaeger	1906 and 1909	Abdomen, heart, vasa vasorum	This disease appeared in a herd of 100 10-year-old axis deer, born and living in a park in Ludwigsburg; the etiologic factor was thought to be bacterial but attempts to isolate organisms were unsuccessful; the disease was not found in other similar herds in Calcutta and Hamburg.
Dogs	Baló	1924	Heart	Spontaneous occurrence in a 4-year-old male fox terrier, which had acute gastritis, parenchymatous nephritis and chronic mitral endocarditis
	Child	1938	Widespread, especially in heart and mesentery	One of 12 dogs with experimental hypertension produced by constricting renal artery; in this animal an Eck fistula, produced after hypertension was maintained for 6 months, was followed by a slow rise to 300 mm. Hg, ending in hemiparesis and death
	Goldblatt	1941*	"Most manifest in the heart"	Occurrence in 2 of more than 1000 dogs examined; both were hypertensive with uremia
Pigs	Joest and Harzer	1921	Heart, kidney	Spontaneous occurrence in a 12-month-old animal which was lame and had pseudomembranous inflammation in the mouth and throat
	Collins and Goldie	1940	Heart, kidneys, mesentery, synovial membranes	Occurred in 5 of a group of animals given *Erysipelothrix rhusiopathiae* to produce arthritis; absent in controls and in those injected with streptococci
Rabbits	Harris and Friedrichs	1922	Lung, liver, heart, kidneys	Authors made an emulsion from kidneys of a typical human case of periarteritis nodosa, injected it into ear veins of rabbits which then developed suggestive lesions; emulsions of their involved organs were passed through Berkefeld filter and the filtrate injected into the ear vein of another rabbit which subsequently presented "typical lesions"

	Wilson and Pickering	1938	Intestines, stomach, suprarenal gland, liver, heart, eye	Experimental hypertension produced by constricting renal arteries with silver clamps; lesions described as periarteritis nodosa, but not so designated; lesions seemed to be related to rapidly developing severe hypertension
	Rich and Gregory	1943	Widespread	Lesions occurred in 12 of 14 rabbits in which hypersensitivity to horse serum was induced experimentally; controls were not described; 10 of the 14 rabbits had acute diffuse glomerulonephritis; blood pressure studies were not reported
Rats	Mets	1931	Kidneys, lungs, heart, brain, liver, skin, skeletal muscle	Lesions occurred in white rats following injections of *Streptococcus hemolyticus*, sterile toxin and nonspecific protein antigen, to which, respectively, the animals had been highly sensitised
	Masugi	1935	Kidneys, intestines, lungs, heart, aorta	Lesions occurred in rats which had been injected with rabbit anti-rat-kidney serum.
	Wilens and Sproul	1938	Widespread	Lesions found in 47, or 9.7%, of a large series of rats studied for cardiovascular disease; these animals were old rats used in a dietary experiment, in which the diet consisted of dried milk and ground wheat; suppurative lesions were common; younger rats on meat and vegetable diet did not develop the lesions
	Ham	1940 1941*	Mesentery and spleen	Lesions occurred in animals given a single massive dose of activated ergosterol which caused calcification in the kidneys, which in turn was thought by the author to have led to renal ischemia, hypertension and then periarteritis nodosa
	Wilson and Byrom	1941	Most marked in mesentery	Lesions occurred in 28 rats made hypertensive by placing a clamp on one renal artery; animals were well below the age limit of those used by Wilens and Sproul
	Friedman, Jarman and Klemperer	1941	Pancreas, mesentery, intestines, heart, testes and unwrapped kidney	Lesions described as periarteritis nodosa but not so designated; hypertension produced by cellophane-perinephritic method, using one kidney; inflammatory necrotising arterial lesions in animals having rapid, severe rise in blood pressure
	Cromartie	1943	Widespread	Typical lesions were found in 15 of 37 rats in which hypertension had been produced by various operative methods; 12 of the 15 were infected; another 12 were infected but showed no periarteritis nodosa

* Personal communication.

tain kidney extracts. The dogs and rats were housed in laboratories in different buildings. The rats were fed Rockland Rat Diet, while the diet for the dogs consisted of dog biscuits, cooked meat scraps and bones, and occasionally milk.

Autopsies were performed on all of these animals and microscopic sections of heart, liver, spleen, kidney, pancreas, mesentery and occasionally other organs and tissues were studied.

Hypertension was induced in the rats by wrapping both kidneys with silk according to the technic described by Kempf and Page. Healthy rats of either sex, all under 6 months of age and weighing 150 to 200 gm., were used. The procedure of wrapping the kidneys was carried out in two stages: one kidney was wrapped with silk and 7 to 10 days later the other kidney was wrapped in similar fashion. Although the silk was autoclaved and the instruments soaked in alcohol, no special additional aseptic precautions were employed. Both stages of the operation were done under ether anesthesia, and the incisions closed with skin clips.

In rats, systolic arterial blood pressure determinations were carried out according to the indirect method of Williams, Harrison and Grollman. The blood pressure readings reported represent triplicate determinations after the animals had been heated in a box at 60° C. for 5 minutes. Blood pressure determinations were made usually three or more times a week.

Arterial blood pressure determinations in dogs were made by puncturing the femoral artery with an 18 gauge needle connected directly to a mercury manometer by pressure tubing. Such determinations were made weekly or oftener.

A number of the animals which became hypertensive were treated with kidney extracts designed to lower blood pressure. The extracts were prepared by modifications of the methods published by Page, Helmer, Kohlstaedt, Fouts, Kempf and Corcoran. These extracts were sterile by bacteriologic test and were administered orally, intramuscularly, or intraperitoneally, and in a few instances intravenously. The dosage varied according to the response elicited. An evaluation of the ability of these extracts to reduce the blood pressure will be presented separately. Evidence will be presented in this paper to show that treatment with these extracts did not cause periarteritis nodosa.

Results

The lesions were similar in rats and dogs and consisted of varying degrees of fibrinoid necrosis and inflammatory exudate in the walls of small and medium-sized arteries, particularly those of the mesentery, hilar regions of abdominal viscera, and in the epicardium of the right

ventricle. Acute, subacute and chronic stages were seen. The early phase consisted of fibrinoid necrosis of the media and adventitia with perivascular edema and the appearance of a few large cells resembling macrophages or histiocytes, which frequently contained many blue granules in the cytoplasm. The lesions spread to involve all three coats of the vessel walls (Fig. 1), producing a necrotizing panarteritis with pleomorphic inflammatory cellular exudation in which eosinophils were prominent. In more chronic cases, extensive granulomatous nodules were found in and around the vessel walls (Figs. 2 and 4). Frequently there was thrombosis of the lumina with varying degrees of vascular occlusion and aneurysm formation, which produced gross nodularity and angulation of vessels (Fig. 3). The mesenteric arteries were often enlarged to many times their normal caliber.

The process was largely confined to the small arteries; the arterioles only rarely were affected and when involved the lesions were not prominent. In a few cases with long-standing hypertension and extensive renal destruction, such as infarction, there was found the type of arteriolar necrosis described by Goldblatt and Kahn. Such lesions can be differentiated from those of periarteritis nodosa by the amount and type of inflammatory cellular exudation, the size of vessels involved and, to a lesser extent, by the distribution of the lesions. In arteriolar necrosis inflammatory reaction is rare, but when it occurs the cells are predominately neutrophils. In periarteritis nodosa inflammatory reaction is a prominent part even of early lesions, and the reaction is pleomorphic with neutrophils playing a minor rôle. In the abdominal viscera, arteriolar necrosis is most commonly seen in the nutrient arterioles within organs, while periarteritis nodosa is best seen in the smaller arteries in the hilum of an organ. In fact it is often limited to this site.

In the majority of the animals with periarteritis nodosa the lesions were widely distributed. Microscopic evidence of the disease was found in every organ except the lung. In a few cases of limited distribution the coronary and hepatic arteries were the vessels most frequently involved. For some unknown reason the arteries in the heart which most frequently presented lesions were those in the epicardium of the right ventricle about halfway between the apex and the atrioventricular junction. The size and histologic structure of vessels may be an important predisposing factor in the localization of the lesions.

Findings in Rats

In order to correlate various experimental factors with the occurrence of periarteritis nodosa, the 100 rats studied were divided into the following groups (the numbers of animals are noted):

A. Rats which were not treated with renal extracts and were not operated upon (28).

B. Rats which were treated with renal extract but were not operated upon (10).

C. Rats in which hypertension was induced by wrapping the kidneys with silk, but which received no renal extract (26).

D. Rats in which hypertension was induced by wrapping the kidneys with silk, but which subsequently received renal extract (36).

Group A served as controls for the other groups in regard to sex, age, strain, species, diet and environment.

Table II gives the number of cases of periarteritis nodosa found in

TABLE II

Occurrence of Periarteritis Nodosa in Animals Subjected to Various Controlled Procedures

	Number of animals	Periarteritis nodosa	
		Present	Absent
Group A. No operation, no extract	28	0	28
Group B. No operation, extract treated	10	0	10
Total	38	0	38
Group C. Silk-perinephritis operation, no extract	26	6	20
Group D. Silk-perinephritis operation, extract treated	36	20	16
Total	62	26	36

each of the four groups of rats. Of the 38 which were not operated upon, none showed evidence of the disease either grossly or microscopically, while 26, or about 42 per cent of the animals which were operated upon, subsequently developed periarteritis nodosa. The odds against this association occurring by chance are greater than 16,000 to 1.*

Of the 62 rats with perinephritis induced by silk, 27 were males and 35 were females. The lesions of periarteritis nodosa were found in 14, or 52 per cent, of the males and in 12, or 34 per cent, of the females. This difference is too small to be considered significant with this number of animals.

In Table II the greater proportion of animals with periarteritis among those treated with extracts after operation is explained by the fact that extracts were given to the animals with the higher blood

* Computed according to the formula for a four-fold table as described by Raymond Pearl (Introduction to Medical Biometry and Statistics, W. B. Saunders Co., Philadelphia, 1930, ed. 2, p. 317).

pressures, and, as will be pointed out later in this report, animals with periarteritis tended to have higher blood pressures than the ones without it.

Since not all of the animals with silk-induced perinephritis developed periarteritis nodosa, the possible etiologic effect of the extracts was considered. Ten rats not operated upon received the extracts and none developed periarteritis nodosa. Thirty-six rats operated upon were subsequently given extracts. In 16, or about 45 per cent, periarteritis nodosa did not develop. Therefore, the extracts, either alone or in combination with the operation, failed to produce periarteritis nodosa in 26 animals. On the other hand, 6 rats which were operated upon but received no extracts developed periarteritis nodosa. It was concluded, therefore, that the treatment with extracts did not cause periarteritis in these rats. The possible effects of the extracts upon blood pressure will be discussed in a subsequent report.

Many of the rats of this series, both with and without periarteritis nodosa, presented extensive infectious processes, particularly suppurative lesions within the perinephric membrane. In those animals which presented periarteritis there was usually binding together of abdominal viscera by chronic granulomatous inflammation in which pockets of caseous necrosis and suppuration were found.

In the animals which did not present periarteritis nodosa the reaction around the silk was usually limited to a thin layer adjacent to the renal capsule, with very little or no involvement of the surrounding organs and tissues. Pockets of necrosis and infection were frequently not found. In some animals the reaction was so slight that the perinephric membrane was semitransparent. Sections of silk-wrapped kidneys were difficult to cut on the microtome; therefore it was considered impractical to make numerous microscopic sections of all kidneys to determine accurately the incidence of perinephric infectious processes.

Infections elsewhere in the body, such as lobular pneumonia, occurred occasionally in each group and were considered to be of no etiologic significance.

A distinct difference between the two groups of animals was disclosed by the blood pressure studies shown in Table III. In order to rule out the effect of possible errors in blood pressure readings, the mean pressures of the two groups were compared. In Table III the differences in the mean blood pressures between the rats with and without periarteritis are indicated. Statistical analysis permits the conclusion that the mean pressure of the periarteritic animals each month during

the period of observation was significantly higher than that of the non-periarteritic animals.*

The range of normal pressures was determined from 707 readings on 83 rats before operation or extract treatment. Ninety-nine per cent of the readings were between 100 and 139 mm. of mercury, the average being 122 mm.

TABLE III

Mean Blood Pressures of Rats Each Month after Last Operation

Interval after last operation		With periarteritis nodosa (A)	Without periarteritis nodosa (B)	Significance of differences $\left(\frac{\text{Mean}_A - \text{Mean}_B}{\sqrt{(\text{P. E.}_A)^2+(\text{P. E.}_B)^2}}\right)$
1st month	Mean pressure and P. E.	178.7 ± 0.8	167.8 ± 0.4	12.2
	Number of pressures	224	345	
	Number of animals	22	33	
2nd month	Mean pressure and P. E.	176.6 ± 0.6	165.0 ± 0.4	16.1
	Number of pressures	409	422	
	Number of animals	24	32	
3rd month	Mean pressure and P. E.	175.0 ± 0.6	165.3 ± 0.5	12.4
	Number of pressures	326	195	
	Number of animals	22	26	
4th month	Mean pressure and P. E.	173.4 ± 0.7	166.9 ± 0.7	6.6
	Number of pressures	164	143	
	Number of animals	15	16	
5th month	Mean pressure and P. E.	176.1 ± 1.1	168.9 ± 0.9	5.1
	Number of pressures	100	95	
	Number of animals	6	10	
6th month	Mean pressure and P. E.	189.1 ± 1.3	168.0 ± 0.8	13.8
	Number of pressures	78	69	
	Number of animals	5	6	

Findings in Dogs

Eight dogs were operated upon. One kidney was wrapped with silk and the other kidney removed. Of these animals four developed periarteritis and only one of these received renal extract. The other four did not develop periarteritis nodosa.

As shown in Table IV, the blood pressures of dogs with periarteritis were decidedly higher than of those without this condition.

In three of the dogs with periarteritis there were suppurative foci in the perinephric membrane and beginning abscess formation in the renal substance.

In the fourth animal in which periarteritis nodosa was limited to the coronary arteries, no evidence of infection was found in the sections studied. This animal died suddenly 3 weeks after operation, having

* A difference which is three or more times its probable error is considered significant (Pearl, *loc. cit.*).

developed hypertension (215 mm. Hg) 1 week after operation. The cause of death was extensive myocardial necrosis and hemorrhage.

The four dogs which did not develop periarteritis had mild hypertension with no evidence of suppuration in the kidney or perinephric membrane. Two of the four had slight arteriolosclerosis in some of the viscera.

TABLE IV

Monthly Average Blood Pressures of Dogs
(Mm. of Mercury)

Interval after last operation	Mean pressure, probable error and number of readings							
	Dogs without periarteritis nodosa				Dogs with periarteritis nodosa			
	No. 255	No. 360	No. 392	No. 398	No. 314	No. 348	No. 358	No. 367
1st month	155 ± 3 (8)	160 (2)	160 (1)	145 ± 3 (6)	151 ± 8 (10)	210 ± 3 (3)	207 ± 13 (3)	210 (2)
2nd month	145 ± 3 (7)	168 (2)	170 (2)	145 (2)	199 ± 4 (6)		248 ± 4 (6)	275 ± 2 (4)
3rd month	180 ± 8 (3)	140 (2)		165 (1)			238 ± 3 (17)	
4th month	185 (1)		205 (1)				228 ± 5 (12)	
5th month			285* (1)					
6th month	160 (1)							
7th month	155 (1)	125 (1)						
8th month	140 (1)	135 ± 5 (4)						
9th month	173 ± 6 (3)	150 ± 1 (11)						
10th month	163 ± 2 (11)	148 ± 3 (6)						
11th month	172 ± 2 (10)	150 (1)						

* Died on the following day.

Periarteritis nodosa has never been encountered in the large group of dogs which have lived in the same laboratory as the above animals and which have been studied for other purposes.

COMMENT

In reviewing previous reports concerning the occurrence of periarteritis nodosa in animals it has been difficult to attribute the condition to any one factor.

The occurrence of this condition in epidemic form in the herd of axis deer cited in Table I suggests an infectious agent. However, the majority of investigators seem to think that periarteritis nodosa is not a specific disease but represents a reaction (possibly allergic) of the arterial system to a variety of infections and toxemias. Rich and Gregory have reported the occurrence of this vascular lesion in human

patients who have manifested hypersensitive reactions to serums or to a sulfonamide. They also described typical lesions in rabbits in which hypersensitivity had been induced by the administration of horse serum. Most of their animals also had acute diffuse glomerulonephritis. They described no controls or blood pressure studies.

Wilson and Byrom have noted periarteritis nodosa in certain rats made hypertensive by clamping the renal artery, and believe that the factor determining the lesion is the sudden strain imposed on the vessel wall by marked vasoconstriction and the resultant sudden rise in blood pressure. These authors did not investigate the possible relation between periarteritis and the presence of infection in their animals. Cromartie's rats, which developed periarteritis, were all hypertensive and most of them presented infection around the kidneys. Since some human patients with periarteritis nodosa apparently have not had hypertension, it seems that other factors may play a rôle in the genesis of this condition in man.

Since blood pressure levels of the two groups of hypertensive rats of the present series were essentially the same before operation and were within normal limits, it would be interesting to know how soon a significant difference began to appear. Table III shows that the rise in blood pressure following the production of perinephritis by silk had reached a fairly constant level by the end of the first month after operation. Also, this blood pressure level was decidedly higher in rats which developed periarteritis nodosa.

The question arises as to which developed first, the higher blood pressure or the periarteritis. Data are not available to answer this question since the blood pressure of these animals was not measured for 2 weeks following the second stage of the operation. Also, the possible rôle played by hypersensitivity has not been determined. These problems are now being investigated in additional series of animals.

Summary

1. Periarteritis nodosa was found at autopsy in 26 of 62 rats and 4 of 8 dogs which had been made hypertensive by wrapping their kidneys with silk. No evidence of these lesions was found in groups of control animals.

2. In animals presenting periarteritis nodosa at autopsy, the monthly mean blood pressure levels had been higher than in animals in which no periarteritis nodosa was found. This higher level had been manifested within 1 month after the production of perinephritis and had been maintained throughout the 6 months of observation.

3. Suppurative lesions were common in the experimentally-produced perinephric membranes.

4. A review of the literature revealed no report of the occurrence of periarteritis nodosa in animals in which the kidneys and the blood pressure were proved to be normal.

5. In the present series of hypertensive animals the two observed differences between those which had and those which did not have periarteritis nodosa were, in the former: (1) higher mean blood pressure levels, and (2) more frequent and more extensive suppurative lesions around the kidneys.

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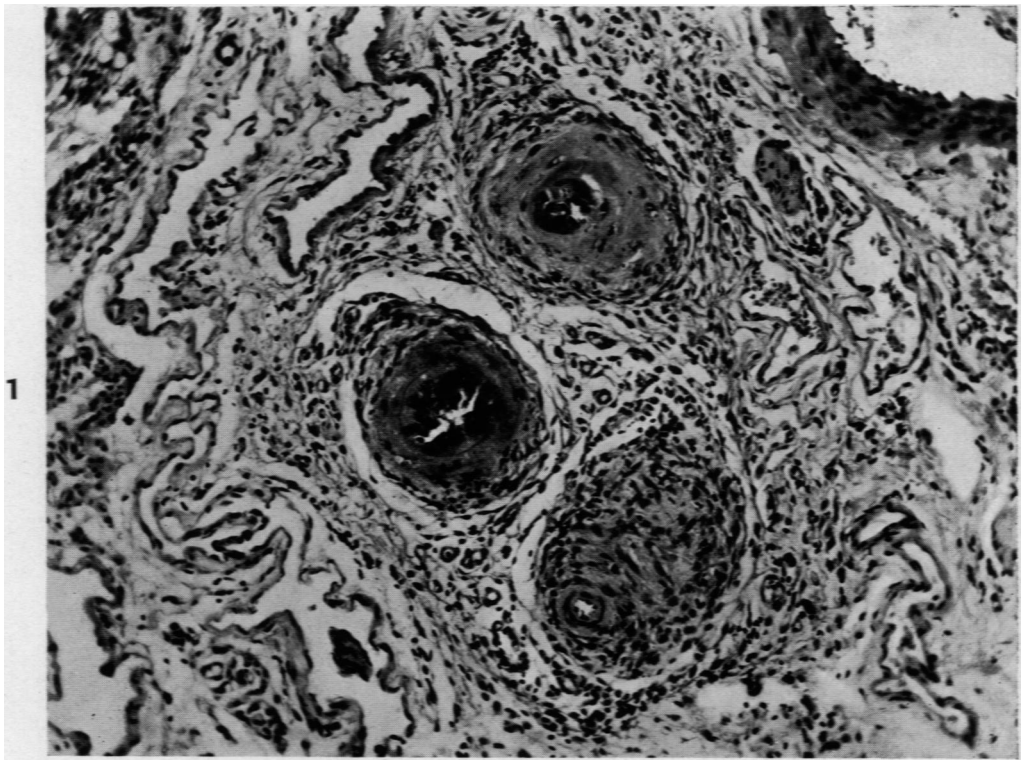
DESCRIPTION OF PLATES

PLATE 139

FIG. 1. Renal pelvis of a rat showing necrotizing periarteritis nodosa with beginning granulomatous changes. × 149.

FIG. 2. Mesentery of a rat showing marked granulomatous changes of periarteritis nodosa. × 78.



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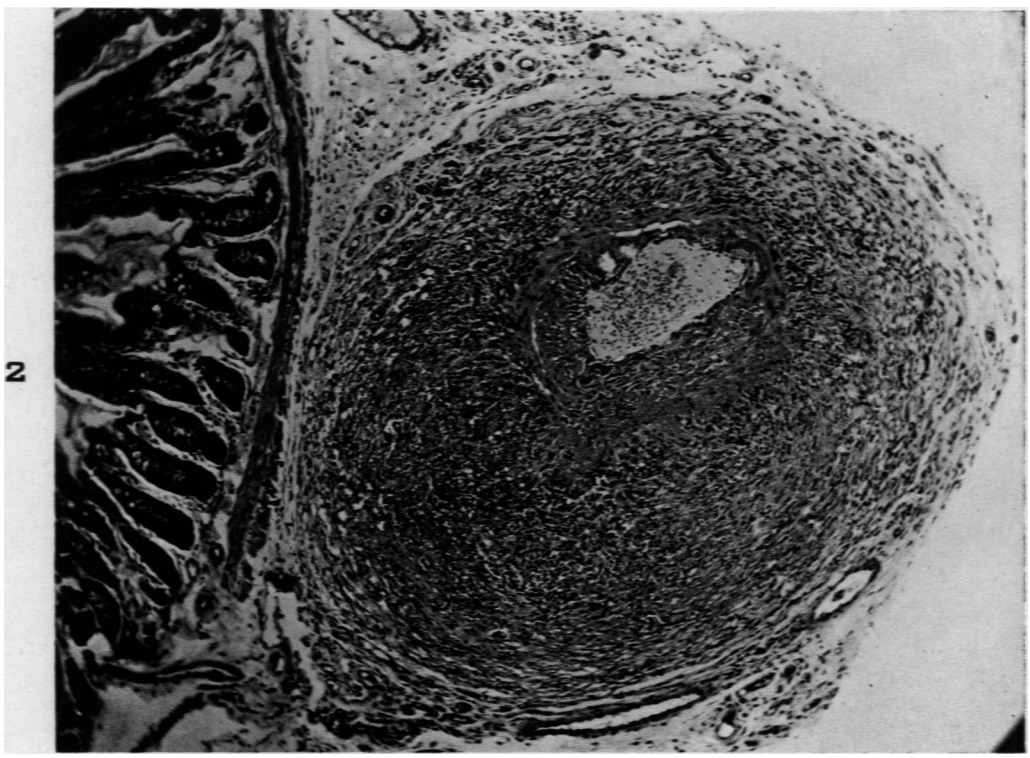

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PLATE 140

FIG. 3. Loop of the small intestine of a rat showing typical lesions in the mesenteric arteries.

FIG. 4. Heart of a rat showing periarteritis nodosa in wall of right ventricle. × 140.

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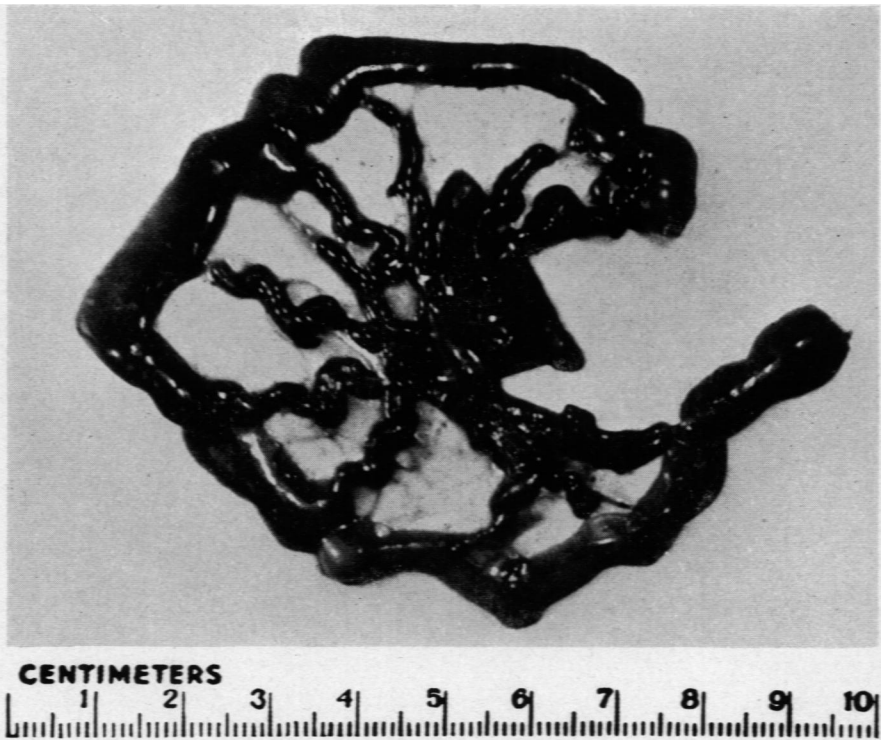

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