SPONTANEOUS CARDIOVASCULAR DISEASE IN THE RAT *

II. Lesions of the Vascular System

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In a previous article [1] on this subject it was pointed out that information concerning spontaneous vascular disease in the rat is inadequate and incomplete. Duff [2] in a recent review lamented the fact that so little is known concerning natural vascular disease in common laboratory animals. Because of this lack, interpretation of the results of experimentally induced vascular changes is rendered uncertain. Most of the general articles on vascular disease in animals have omitted reference to the rat. Wolkoff [3] included studies on the arteries of 3 rats in different age periods, the oldest of which was 2 years. She was unable to find any very definite changes in the intima or elastica other than slight splitting of the latter in the abdominal aorta of 1 animal. Hueper [4] reported briefly on the incidental finding of changes in the pulmonary arteries associated with calcification in 12 of 75 adult rats.

Spontaneous intimal atheromatous lesions similar to those of man are apparently of limited occurrence in any other species except birds. Minimal and somewhat questionable lesions of this type have been described however in a few mammals, including monkeys and dogs (Fox [5] and others). Löwenthal [6] has reported impregnation by lipoid of arterial walls in several mice but no definite intimal plaques. Nevertheless the absence of such lesions in the rat has never been conclusively established.

Some of the problems of senescence are best approached by the study of animals such as the rat whose natural life span is relatively brief. Alterations of the vascular system, particularly of its elastic tissue component as an indicator of old age have attained almost proverbial acceptance. However, it has always been difficult to distinguish those changes that are the inevitable result of aging from the consequences of disease processes. Lesions that are common to senile animals of many species are more apt to be the

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true expression of senescence than those that are peculiar to only a few. How much such changes depend on simple time factors and how much upon the physiological status of the animal remains unknown. In man with a maximum life span of about 90 years it takes many decades for evidences of senescence to appear. It would be interesting to know if the tempo of these changes is accelerated in animals with short life periods, such as the rat, so as to reproduce a picture similar to senility in man. Obviously if this were so, senescence would depend less upon the simple aging of tissues and more upon intrinsic, less readily explainable phenomena directly related to the natural life span of each species.

In an attempt to shed light on some of these problems a systematic study of vascular changes in a group of 487 rats kept under constant conditions over their entire natural life span was undertaken. The source and nature of this material as well as the vital statistics concerned have already been detailed.[1] Descriptions of the lesions affecting the coronary arteries were included in this earlier report on cardiac disease in the rat. In the present study the vessels of the lungs, spleen, liver, pancreas, adrenals, kidneys, pelvic organs, stomach, neck organs including thyroid and parathyroid, and brain were routinely studied in every case by means of single microscopic sections through each of the organs enumerated. Portions of the ascending aorta were included in every heart section. In addition, in many instances the entire aorta was sectioned. The blood vessels in other tissues such as the testes, intestine, mesentery, pituitary, bone and bone marrow were also frequently examined. Those of the extremities were not investigated.

Aorta

The normal rat's aorta is a delicate, thin walled tubular structure only slightly thicker and larger at its root than at the bifurcation. Microscopically the media contains a series of parallel, slightly wavy elastic fibers varying in number from 8 to 14. The individual elastic fibers are approximately as thick as those in the media of the human aorta but they are never quite so sinuous even in young animals. The elastic fibers are separated from each other by a double layer of smooth muscle cells so that they never overlap in an entangling fashion and the course of each fiber is readily

traced. At infrequent intervals short connecting elastic fibers branch off at acute angles from the main fiber to extend between the smooth muscle cells and anastomose with immediately adjacent ones. The proportion of elastic tissue to smooth muscle is much less than in the human aorta. Connective tissue is scanty and the reticulum is delicate but forms a uniform pattern as it ensheaths the coarser elastic fibers. The most internally situated elastic fiber is separated from the overlying endothelium of the intima only by delicate reticulum. The intima therefore consists of little more than the surface endothelium and its basement membrane. The adventitia is delicate and is composed of acellular loose connective tissue. Nutrient vessels never penetrate the media even at its outer aspect and indeed are not seen in the adventitia itself throughout the entire length.

With advancing age the aorta developed only relatively mild changes. It was somewhat increased in length and circumference. The adventitia was thickened and its connective tissue more compactly arranged. The media was also considerably thicker but its architecture was essentially unaltered. The intima remained as delicate as in young animals. The only lesion of note was the rare occurrence of small masses of calcium usually in the inner third, sometimes protruding into the lumen through disrupted elastic lamellae although always surmounted by intact endothelium. Such calcification was observed in 12 aortas from 9 males and 3 females. All except 1 of these were older than 700 days. The most common sites were in the lower abdominal region, near the bifurcation, at the upper limits of the sinuses of Valsalva and at the angles formed by the orifices of large branches. The calcified masses rarely exceeded 100 μ in diameter and never were more than three such deposits found in any one aorta.

One of the few invariable consequences of aging in man is alterations in the elastic tissue, chiefly a straightening and loss of waviness of the individual fibers. This is associated with enlargement of the vessels and loss of inert elasticity. It has been shown [7] that this change is directly proportional to age and is not affected by intimal atheromas. For this reason the pattern of the elastica of young and old rats was compared to see if analogous changes occurred in the 3 year period that constitutes the life span of this species. Obviously if at the end of this period the rat has under-

gone changes comparable to senility in man one might well expect its elastic tissue to show evidences of degeneration.

Such a comparison offers difficulties for two reasons. First, the elastic fibers of young rats are not so coiled as in the young human aorta, possibly because in the former the aorta does not undergo as relatively great an excursion with each pulsation. Secondly, the relatively large proportion of smooth muscle tissue in the rat's aorta may serve to hold the elastic fibers in unnatural positions after death. The degree of contraction and postmortem rigor would thus play a more important rôle in the rat than in the human in determining the appearance of the elastic fibers. Nevertheless, examination of a large number of preparations stained by Weigert's elastic tissue method revealed mild but constant losses in waviness of the elastic fibers in old rats, as compared to those of young ones. If this change be considered an expression of senescence, then a 3 year old rat is in a physiological state comparable to that of an old man, at least as far as its aortic elastica is concerned. Moreover, the changes in these fibers are not necessarily the result of simple physico-chemical reactions occurring at fixed time intervals but are dependent upon natural life span of the species.

The Arteries

In general, the arterial system of the rat developed no such constant morphological changes with increasing age as that of man. The only two exceptions were the coronary and pulmonary arteries. All other vessels, including the renal and cerebral arteries, usually retained the same characteristics in the senile rat as in the adolescent one. The intima remained thin and delicate. The elastica did not become frayed or reduplicated. The smooth muscle of the media was essentially unaltered. The vessels increased slightly in size but were never stiffened or tortuous.

The failure to form definite lipoid-containing atheromas in the intima was striking when contrasted with the usual findings in man. This did not appear to be associated with inability to deposit cholesterol in other sites. Indeed it was a common occurrence to find considerable quantities of cholesterol free, in crystalline form, and finely divided in droplets within phagocytes in areas of old inflammation. This was particularly true in the walls of old pul-

monary and uterine abscesses. Occasionally, even in otherwise normal lung tissue, there were found groups of subpleural alveoli filled with fat-laden phagocytes. The failure of atheromas to develop would therefore seem to depend less upon the inability to mobilize and deposit cholesterol than upon local factors obtaining within the arterial system. Special lipoid stains were not prepared routinely so that it is impossible to exclude the possibility of subintimal impregnations by lipoid, such as were described by Löwenthal [6] in a number of mice. Some of the mouse deposits were associated with inflammatory changes of the vessel walls.

TABLE I

Incidence, Age and Sex Distribution of Calcification of Arteries

Artery	No.	Per cent	No. of males	No. of females	Average age	
					Males	Females
					days	*days*
Spermatic	49 *	58.4	–	–	745	–
Pulmonary	224	46.0	114	110	724	768
Coronary	17	3.5	14	3	756	850
Aorta	12	2.5	9	3	803	911
Renal	8	1.6	8	0	754	–
Mesenteric	6	1.2	3	3	843	864
Cerebral	2	0.4	2	0	792	–

* The testes of only 83 males were examined microscopically.

Calcification of Arteries: Although generalized manifestations of degeneration were usually lacking, the one most common pathological alteration observed was calcification. In order of frequency calcification was noted in the spermatic, pulmonary, coronary, renal, mesenteric and cerebral arteries, as well as in the aorta itself. The calcium was usually deposited in small solid masses. The earliest portions of the vessel involved were the inner layers of the media, sometimes with impregnation of the elastic lamella alone. Larger deposits extended throughout the media and protruded through the intima into the lumen. The calcification was never very extensive and seldom did more than 3 arteries in any 1 animal have such deposits. In Table I the incidence, age and sex distribution of the findings are recorded. Males showed arterial

calcification more frequently than females. The average age for each group exceeded that of the entire series which was 702 days for males and 746 days for females.

The intratesticular branches of the spermatic artery were calcified in 49 of 83 testes that were examined microscopically. Not only was this the most frequent site but the extent of calcification was greater than elsewhere. The calcification was confined to the media which was frequently converted into a continuous ring of calcium. The deposits occurred in vessels that were otherwise normal, the intima remaining intact and delicate. They were seldom detected in animals less than 500 days old at death. The adjacent tubules did not show changes comparable to those of the senile testis in man. The basement membranes were thin, spermatogenic epithelium abundant, and interstitial cells not increased. Next in frequency of calcification were the pulmonary arteries. Here the process appears to be definitely related to sclerotic changes in the vessel wall and will therefore be described separately in detail. Identical lesions have been briefly described in 12 out of 75 adult rats by Hueper.[4]

Pulmonary Vascular System: The pulmonary arteries of the rat were peculiarly susceptible to degenerative changes. These were not unlike the ones involving the coronary arteries but were often more widespread and severe. The essential lesion consisted of atrophy of the smooth muscle coat and replacement by fibrous tissue leading to irregular thickening of the wall. In less involved areas the smooth muscle often appeared hyperplastic. The chief differences from the coronary artery lesions were that they were found in almost every rat over 2 years of age and were commonly associated with calcium deposition. The lesions developed at all points in the course of the vessels and were even continuous throughout to the smallest arteriolar radicles. Usually, however, the proximal supravalvular portions were not conspicuously involved.

The pulmonary veins were unchanged but they did exhibit an anatomical peculiarity already described in the literature by Lauche [8] and by Takino.[9] The outer aspect of the pulmonary veins consists of several layers of cardiac muscle bundles having all the characteristics of ordinary heart muscle. Sections through the pulmonary veins at their entrance into the heart show that this

muscle is directly continuous with that of the left auricle. Even deeply within the pulmonary tissue the smaller veins have an outer coat of cardiac muscle. This is separated internally from a quite thin and uneven layer of smooth muscle by loose connective tissue. The significance of the extra coat of aberrant cardiac muscle is not apparent but perhaps cardiac impulses are directly transmitted to the pulmonary circulation.

Direct connection between the deposition of calcium and the severity of local sclerotic changes in the artery wall could not always be established. Often calcium masses were found in vessels that were otherwise normal. More often still such changes as could be recognized in the adjacent vessel wall might well have developed subsequent to calcification. The calcium showed a striking tendency to deposit at points of bifurcation or in the angle formed by the origin of a large branch. Another prominent feature was the projection of the calcium as jagged spurs into the lumen and over which no endothelial covering was detected. In many instances these deposits completely bridged the lumen, being attached to the artery wall at opposite sides and subdividing the original lumen into two smaller ones. Yet in no instance did such obstructing plugs incite the formation of thrombi. It was not unusual to find several calcified arteries in a single microscopic section. The larger arteries at the hilus of the lung were most often involved. No relation to the frequently coexistent bronchiectatic lesions could be demonstrated. Calcified arteries were found in 24.1 per cent of the animals whose pulmonary tissue was entirely normal. Arteries traversing the walls of large old abscesses were no more frequently calcified than those remotely situated.

Calcification of the pulmonary arteries was found in 224 or 46 per cent of the rats. The incidence would undoubtedly have been still greater if a more extensive microscopic examination had been carried out. 50.7 per cent of the males were involved and only 40 per cent of the females. The lesion was seldom found in animals less than 400 days of age at death and became progressively more prevalent until the 700th day of life, when its maximum incidence was attained.

The composition of the diets on which the animals were fed varied in calcium content, depending on the relative proportions of wheat and whole milk powder in the ingredients. Sherman and

Booher [10] have shown in this strain of rats that the total amount of body calcium in the growth period varied directly with the amount consumed. For this reason it was suspected that calcification of arteries might be influenced by the calcium content of the diet. When the animals were separated into two groups, one that had received diets containing about 0.19 per cent calcium, and the other with 0.33 per cent calcium, no difference in the incidence of arterial calcification between the two groups was noted. 55.4 per cent of those fed with the higher and 55.6 per cent of those with the lower calcium-containing diets had calcified pulmonary arteries. The reason why the percentage of calcification of both these groups is higher than that of the total series is that many of the animals dying at a young age were fed diets whose calcium content was not ascertained and are therefore excluded. Although the variations in calcium content cited above are not marked enough to exclude a possible dietary influence on the development of this lesion, it is obvious that in the present series its presence or absence did not depend upon the difference in calcium intake. It seems more likely that arterial calcification was a manifestation of local disturbance of calcium metabolism. The tendency to precipitate this mineral in extravascular situations as well, was quite prominent. Renal and vesical calculi were common and the bronchial cartilages were often calcified. The walls and contents of old abscesses were usually impregnated. The nature of this disordered calcium metabolism is not apparent. Although the parathyroid glands of senile rats often appeared enlarged and hyperplastic the bones showed no evidence of demineralization. The vitamin D content of the diet was not excessive.

Periarteritis: The arterial system of the rat is subject to a specific, often widespread inflammatory disease that has many of the attributes of periarteritis nodosa as it occurs in man. Lesions of this nature have been described in many different species. Nieberle [11] cited reports of its occurrence in cattle, swine, dogs and wild deer. Löwenthal [6] described several instances in which single arteries of old mice showed inflammatory changes of the same type. However no record of the lesion in the rat has been found.

In the present series 47 animals or 9.7 per cent exhibited evidence of the disease. Its preponderance in the female is noteworthy. 30 were females with an average age at death of 856 days

and 17 were males averaging 700 days in age. The incidence in different age groups was as follows: under 500 days, 0 per cent; from 500 to 700 days, 3 per cent; from 700 to 900 days, 13.1 per cent; and over 900 days, 15.7 per cent. Like so many of the other cardiovascular disorders in this species, the lesion was not found until late middle life and became more prevalent as age increased.

The lesion was apparently a long standing one and various stages in its development could be recognized. In 19 animals only acute or subacute lesions were found. In 6 there were only completely arrested and healed residua. In the remainder both healed and fresh lesions were intermingled. This latter finding was an indication that the disease may progress by a series of recrudescences. The extent and distribution of the process varied considerably although there were certain sites of predilection. When only 1 or 2 vessels were involved the process was classified as localized. When more than 2 arteries in different organs showed changes it was designated as generalized. 26 fell into the former category and 21 into the latter. Such a division is only approximately accurate since recognition of the lesion depended to a certain extent upon fortuitous microscopic sections. The changes were recognized grossly when the mesenteric arteries were extensively involved or when small aneurysmal outpouchings of arteries occurred elsewhere. The mesenteric arteries often showed striking alterations. The entire mesentery was enlarged and traversed by ropy, thick tortuous vessels which often appeared entangled with one another. The individual arterial branches were greatly enlarged. In fact they often exceeded the aorta itself in diameter. All along their course they were beaded by nodular protrusions which on closer examination were revealed as a series of aneurysmal dilatations. Many of these were occluded by thrombi. The earlier, more acute lesions were detected only on microscopic study. As a rule both large and medium sized arteries were attacked, the smaller arteries less often and the arterioles almost never. The aorta itself was spared. Lesions were at one time or another identified in almost every organ and tissue which were regularly examined save only in the lungs and brain. The frequency of involvement of various arteries was as follows: unidentified mediastinal and cervical, 21; mesenteric, 15; coronary, 15; pancreatic, 14; splenic, 11; renal, 11; gastric, 4. In addition the bronchial, hepatic, adrenal, uterine,

spermatic, ovarian, peripelvic and subcutaneous arteries showed the lesion on one or two occasions.

Microscopically there was much individual variation in the appearance of the lesions. A reconstruction of the pathogenesis of the process interpreted from all available material is as follows: The earliest change was the appearance of inflammatory cells in the adventitia often in eccentrically placed crescentic masses about the larger arteries and completely circumventing smaller ones. Multiple but discrete formation of such granulomas might appear along the course of a single vessel, producing a beaded effect. The cells consisted of mixtures of lymphocytes, plasma cells, monocytes, polymorphonuclear neutrophils and usually a few eosinophils. Often their nuclei became pyknotic and fragmented so that recognition of cell types was difficult. The cells lay between connective tissue fibrils, spreading them apart. Often the inflammatory changes encroached upon the outer aspects of the media, destroying smooth muscle cells. Before it penetrated the entire width of the media the endothelial lining might be elevated by a subintimal deposit of fibrin.

Still later the changes became continuous throughout the entire vessel wall, obliterating normal structures, destroying the media completely, disrupting elastic lamellas, and causing marked irregular thickening and narrowing of the lumen. The latter was often partly or entirely thrombosed. In some areas where the fixed tissue was most severely damaged aneurysmal widenings were common and there were sometimes hemorrhagic foci. Complete rupture was not seen. Usually by the time the process reached this stage considerable connective tissue had been formed in the adventitia providing new support. Healing was accomplished by a disintegration of the infiltrating leukocytes and replacement by dense scar tissue. The thrombi became organized and sometimes recanalized. The fibrous tissue assumed a hyaline appearance and on occasion calcium deposits were superimposed. There was some regeneration of smooth muscle but only fragments of the elastica persisted. All stages of development could be found in one animal and sometimes in a single artery. Areas of healing were not immune to secondary flareups and often an early fresh lesion was added to an older organizing one.

Save only in the case of the kidney, secondary manifestations

in the viscera due to obstructed blood supply were surprisingly infrequent. The gut was sometimes mottled by hemorrhagic areas. Focal necroses and interstitial scars appeared in the spleen, pancreas and myocardium. Definite infarction was not encountered. In the kidneys, however, there were often widespread tubular and glomerular changes indistinguishable in many respects from true glomerulonephritis. The convoluted tubules were widely dilated, lined by flattened epithelium, and obstructed by hyaline casts. Other areas of interstitial fibrosis and tubular atrophy although usually less frequent did distort the normal architecture. The glomeruli were in various stages of fibrosis and irregularly distributed in the cortex. Some were enlarged, others shrunken and completely hyalinized. Adhesions of tufts to the capsules of Bowman were numerous. The basement membranes of the capillary loops were thickened and the tufts themselves ischemic. Epithelial proliferation and cellular infiltration were never pronounced. Such changes in the kidney closely simulating if not identical with true glomerulonephritis were found in 9 of the 47 cases. In 13 others there were isolated areas of renal atrophy and fibrosis not unlike the scars resulting from arteriosclerosis of large renal arteries in man.

The etiology of this disease was not determined. Suppurative lesions were extremely common. In 18 of the 30 females there were large uterine abscesses. Similar foci of suppuration occurred with equal frequency in the absence of inflammatory arterial disease. Except for the involvement of the coronary arteries there was no association with endocardial or other intracardiac lesions. A possible relation to diet is disclosed by the fact that the disease appeared in only 1 animal out of 75 receiving meat and vegetables. In this animal the process was localized in the mesenteric artery. Among 356 rats known to lack either of these ingredients in their diet, there were 46 cases. The diet of these animals was less varied and consisted largely or entirely of dried milk powder and ground wheat. This discrepancy cannot be attributed to differences in longevity as 48 of the 75 animals in the first group survived longer than 700 days. Neither can it be ascribed to differences in susceptibility to suppurative infections since these occurred with approximately equal frequency and severity in both. It is thus suggested, although by no means proved, that dietary differences

may influence the incidence of this disease. It would require more extensive observations on a larger series of rats with the diets regulated from this point of view to establish the proposition.

There are many circumstances which make it seem probable that this disease is closely related to periarteritis nodosa in man. Certainly the histological features, the distribution of the lesions, the mode of onset and development, and the permanent residual deformities are closely analogous to those of the human disease. The pulmonary and cerebral arteries in both species are seldom involved. The mesenteric, renal and coronary arteries in both are often damaged. Again the vulnerability of medium sized arteries is a finding common to both. Renal lesions closely resembling glomerulonephritis have been described in association with the human form of periarteritis nodosa.[12] The occurrence of similar vascular lesions in many other species may indicate that they are all etiologically related. The only striking dissimilarities of rat to human periarteritis are in age distribution and incidence. The human disease occurs at all periods of life, whereas the rat lesion is pretty well limited to old animals. Human periarteritis is comparatively rare but in the rat it is one of the most common forms of systemic vascular disease. Neither of these discrepancies offers insurmountable evidence against the identity of the two processes.

Renal Lesions: The kidneys of senile rats are seldom entirely normal. In addition to the 9 cases of nephritis associated with periarteritis, there were 10 others in which the kidney cortex showed evidence of widespread degeneration involving both tubules and glomeruli. The only essential difference from human glomerulonephritis was the paucity of either proliferative or exudative reactions in the glomeruli and the fact that the kidneys were not contracted. Fine granulations of the cortical surface were sometimes visible with a hand lens. Another finding of high incidence was pelvic calculi leading to hydronephrotic atrophy. The kidneys were also subject to bacterial infection in many cases. Some of the older areas of scarring and atrophy were undoubtedly due to healed pyelonephritis.

Because of these complicating factors it was difficult to establish the extent to which the degenerative lesions encountered were dependent upon vascular disease. The major renal arteries seldom

deviated from normal although calcification was noted 8 times. The intima in senile rats was not thickened and the elastic fibers did not split or become multiple as is so often the case in adult man. Nevertheless there were many instances of linear or wedge shaped scars in the parenchyma directed at right angles to and retracted below the cortical surface. These had all the attributes of arteriosclerotic scars in the human kidney. In addition, a few scattered glomeruli were often hyalinized. Lesions of this nature were found in 65 males and 51 females, a total incidence of 23.8 per cent. They were uncommon in animals younger than 700 days at death and present in 34.6 per cent of those surviving more than 900 days. Because of the absence of sclerotic changes in the renal arteries it is impossible on morphological grounds to associate the scarring with impaired circulation. Some must have resulted from healed pyelonephritis, others possibly from pressure on the arteries in the peripelvic tissue exerted by intrapelvic calculi. This latter suggestion is not entirely implausible inasmuch as the peripelvic tissue in the rat is lacking in adipose tissue which might cushion and protect the vessels. The arterioles in and about the scars often seemed to have thick muscular walls and only minute lumens, but hyaline necrosis was not observed.

The Arterioles

In general, the arterioles showed little pathological change. In no instance were arteriolarsclerotic lesions disseminated throughout the splanchnic area, as is seen so frequently in association with human hypertension. There is no reason for believing that any of the rats had had elevated blood pressures comparable to a primary hypertension. Hypertrophy of the heart occurred only in conjunction with other cardiac lesions or in animals that had severe renal lesions. As previously noted, in scarred kidneys the arterioles sometimes appeared thickened and tortuous. Definite hyalinization of the renal arterioles was observed in 3 cases and in only 1 of these were the changes striking. In this particular animal, a 1005 day old female, there were associated widespread glomerular changes which might have been secondary to the arteriolar lesion. The renal changes were suggestive of arteriolar nephrosclerosis but extrarenal arteriolar lesions were not observed.

The splenic arterioles were examined closely inasmuch as these

are so constantly altered in man. In only 1 animal, an 800 day old female, were comparable lesions found. In the spleen of this particular animal practically every follicular arteriole was thickened and contained a subintimal accumulation of deeply eosinophilic, homogeneous material. In the spleen of 1 other rat, an 850 day old male, a few central arterioles showed similar changes. In all the other old animals the splenic arterioles were perhaps thicker and more tortuous than normal but there were no definite sclerotic changes.

The pulmonary and bronchial arterioles often exhibited striking muscular hypertrophy. This, however, was usually associated with more profound changes in the larger arteries.

The Veins

The only finding of note in the veins was the occasional thrombosis of the hepatic, adrenal, splenic, renal, uterine and pulmonary vessels. The thrombi were at times secondary to lesions in the adjacent tissue but also formed in normal tissue without obvious cause. Small pulmonary emboli were present in a few cases and were probably derived from such thrombi. With advancing age none of the veins examined showed degenerative changes of any consequence.

Summary and Conclusions

The pathological manifestations of vascular disease in 487 rats of all ages in which death occurred as the result of natural causes are described. Intimal lesions of the arteries comparable to those of man and birds, or those experimentally induced in rabbits following cholesterol ingestion, or in the coronary arteries of rats with administration of excessive doses of vitamin D (Ham and Lewis [13]), were not observed. The elastic fibers in the aortas of senile rats were thicker and less undulating than those of young ones. Except for the absence of fraying and splitting, this change is analogous to that in the elastic fibers of man with advancing age. If it be interpreted as an indication of reduced elasticity, the assumption can be made that degeneration of elastic tissue is dependent upon the natural life span and not upon simple aging of this tissue. Since intimal thickening did not accompany this medial change, as it so commonly does in man, it seems likely that the two

are unrelated and that the latter is not a true phenomenon of senility.

Only the coronary and pulmonary arteries were commonly the seat of degenerative changes. These consisted of fibrosis of the media and thickening of the wall. In the pulmonary arteries the lesion was frequently associated with calcification. Calcification was found also in other arteries, particularly the spermatic.

A specific inflammatory disease of arteries identical with or at least closely resembling periarteritis nodosa in man was found in 9.7 per cent of the animals.

Renal lesions similar to arteriosclerotic atrophy in the human kidney were described but their association with vascular disease could not be established. The arterioles showed evidences of sclerotic changes in only a few exceptional cases and in none was generalized arteriolarsclerosis recognized.

All of the lesions encountered were influenced by age, few of them being observed before the 700th day of life. All of the non-inflammatory lesions were more common in males.

The absence of amyloidosis in all of the animals is particularly noteworthy in view of the success with which this change has been experimentally produced in rodents by a variety of methods.[14] The circumstances would seem to have been especially propitious for its development spontaneously in these animals. Chronic suppurative lesions were very common and one of these, infection of the auditory bullae, was often associated with osteomyelitis of the adjacent bony structures sometimes with extension into the cranial cavity.

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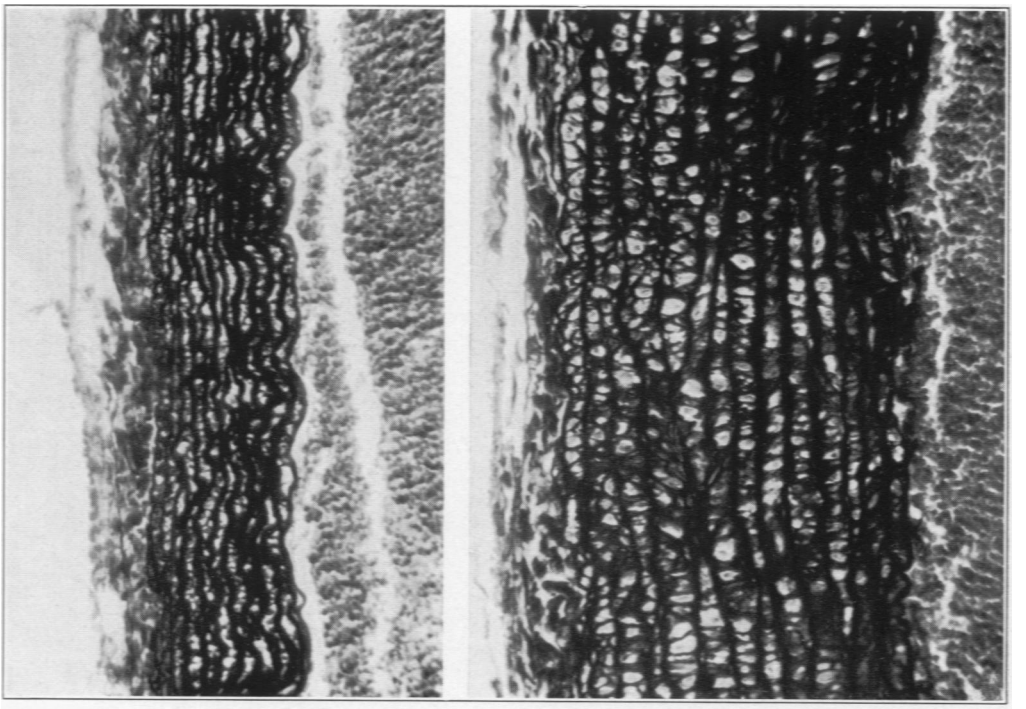
DESCRIPTION OF PLATES

PLATE 40

FIGS. 1 and 2. Elastica in media of aorta. The photographs are from comparable points in the ascending aorta. Fig. 1 is from a 93 day old and Fig. 2 from a 1021 day old rat. In the senile animal the media is much broader, the individual lamellae slightly thickened and much farther apart. The most striking change, however, is the stretching and loss of undulation of the elastic fibers in Fig. 2, as compared to those in Fig. 1. Weigert's elastic tissue stain. × 300.

FIG. 3. Calcification of pulmonary artery. Two solid masses of calcium are embedded in the intimal surface of the sclerotic vessel. The wall of the artery at this point is irregularly thickened by dense fibrous tissue which has replaced the smooth muscle. × 300.

FIG. 4. Calcification of abdominal aorta. At the orifice of a large arterial branch a solid mass of calcium is deposited and protrudes into the lumen. × 100.



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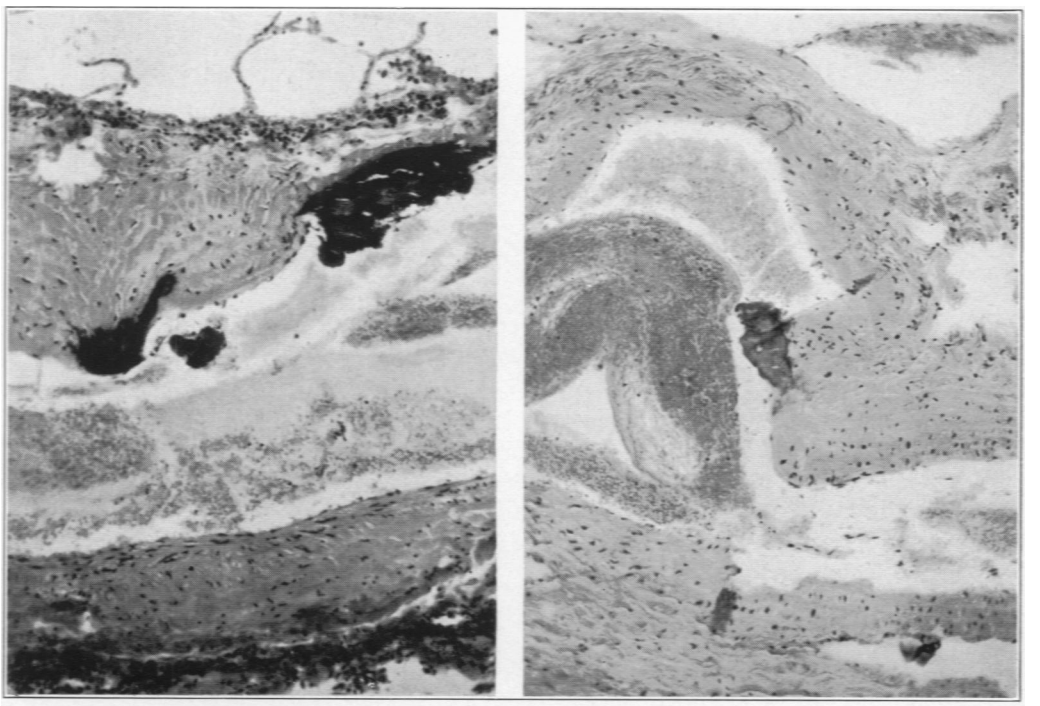

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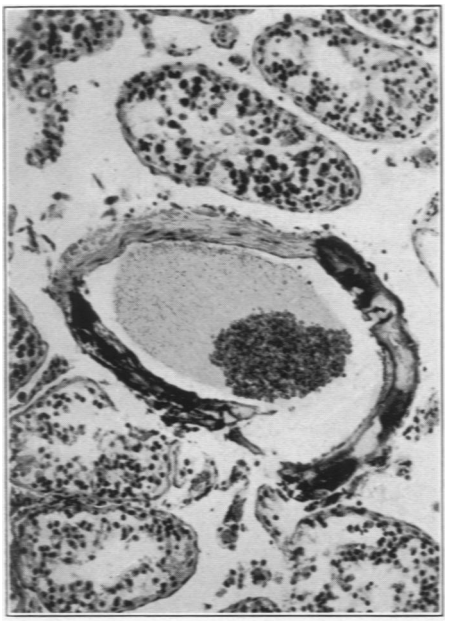
PLATE 41

FIG. 5. Calcification of spermatic artery. Calcium is deposited as curved plates in the media of the vessel without causing the latter to become thickened. × 110.

FIG. 6. Acute periarteritis of small artery. The entire adventitia of the vessel is heavily infiltrated by lymphocytes, polymorphonuclear leukocytes, large mononuclear cells and pyknotic nuclei. The media is degenerating and a subintimal deposit of fibrin has been precipitated. The lumen is still patent. × 460.

FIG. 7. Acute periarteritis of large peripancreatic artery. An acute inflammatory reaction attended by the fragmentation of nuclei of infiltrating cells is apparent in the adventitia and outer aspects of the media. The nodular character of the lesion is self evident. × 110.

FIG. 8. Chronic periarteritis of mesenteric arteries. The arteries throughout the mesentery to their points of entrance into the intestinal wall are greatly enlarged, twisted, tortuous and nodular. Aneurysmal dilatations are numerous.



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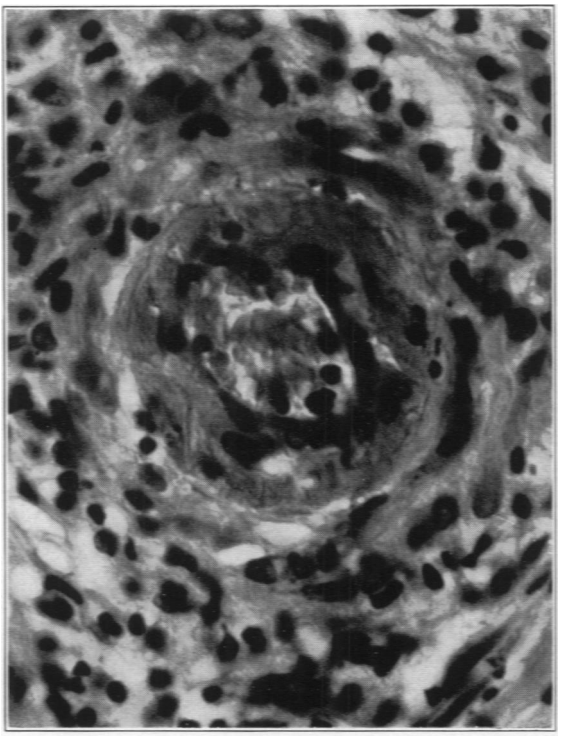

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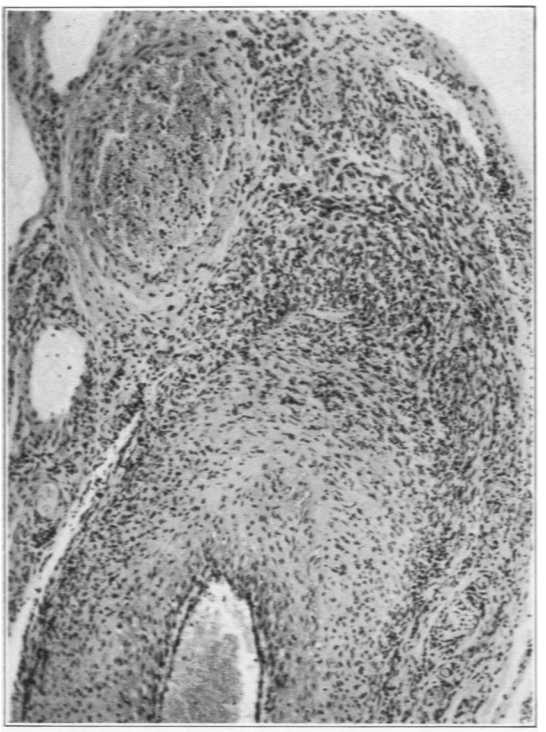

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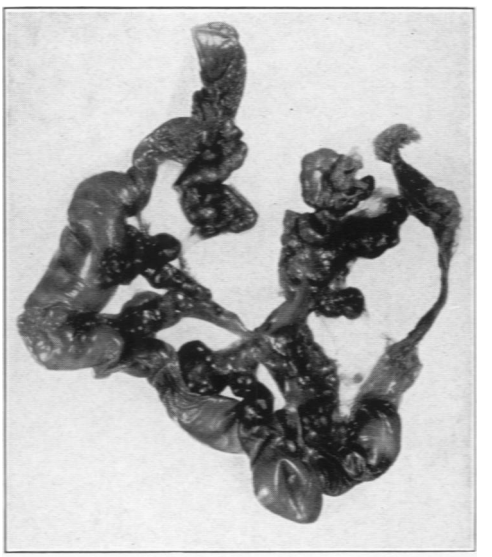

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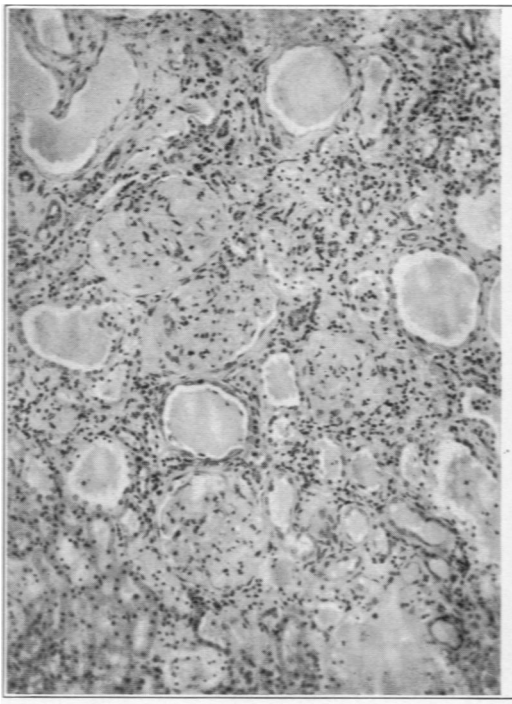
PLATE 42

FIG. 9. Nephritis in periarteritis nodosa. The architecture of the cortex is disarranged. Some of the tubules are enlarged and obstructed by hyaline casts. Others are atrophic and have shrunken into the increased interstitial connective tissue. The latter is infiltrated by lymphocytes. The glomeruli are distorted and swollen so that the tufts obliterate the capsular spaces. The tufts are ischemic, compact and depleted of cells. × 110.

FIG. 10. Atrophy and fibrosis of renal cortex. The edge of a wedge shaped scar borders on adjacent intact renal cortex and merges with the slightly thickened and sunken capsule. The tubules in the scar are completely atrophic and the glomeruli are shrunken and partly replaced by fibrous tissue. A heavy lymphocytic reaction has occurred. × 110.

FIG. 11. Hyalinization of splenic arterioles. The lumens are greatly narrowed. The walls are thickened by dense homogeneous masses of hyaline material lying between the endothelium and the outer layers of the vessel wall. × 110.

FIG. 12. Marked smooth muscle hypertrophy in the media of a pulmonary arteriole. The lumen is greatly reduced. A small capillary is seen as it emerges directly from the arteriole. × 300.



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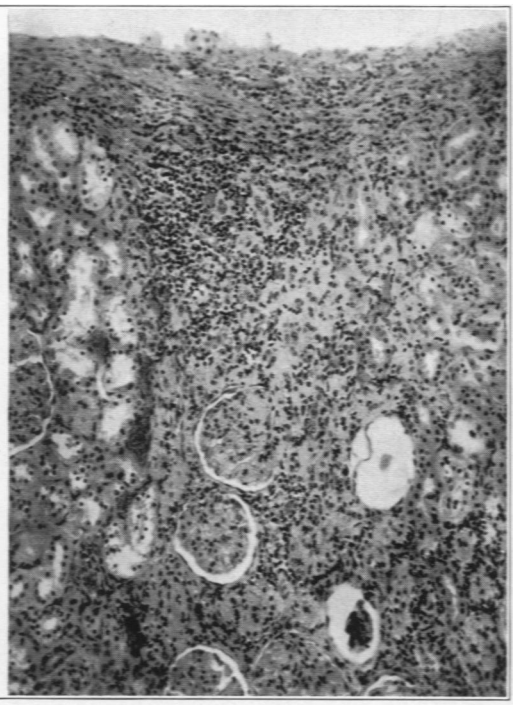

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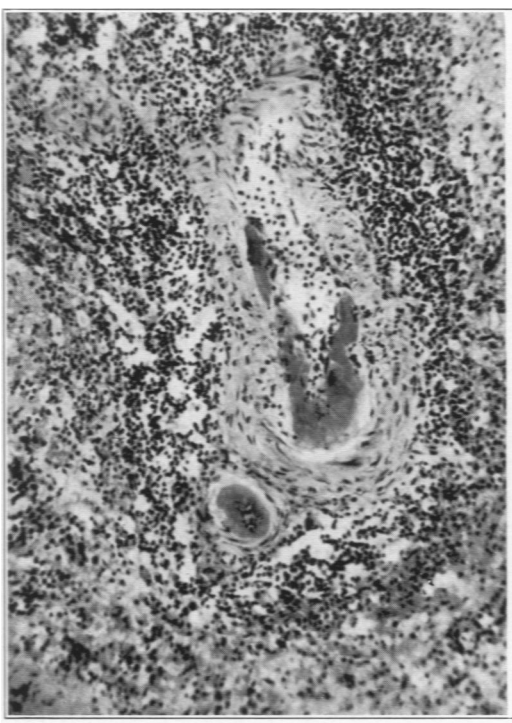

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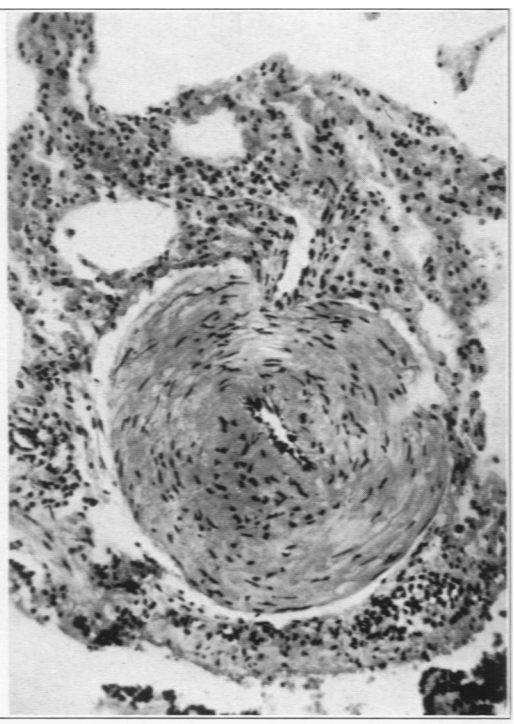

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