Rheumatic Nephrosclerosis

With Special Reference to Rheumatic Endarteritis

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THE occasional development of nephrosclerosis as a late sequel of rheumatic fever has been suggested by Fahr.1,2 But Fahr did not follow up this observation with detailed microscopic examinations, and the question remained unsettled as to the significance of the coarsely granular renal surface, often interrupted by deep depressions (infarcts). The histologic observations reported below revealed that nephrosclerosis in patients with rheumatic cardiac disease is the result of a widespread rheumatic obliterating endarteritis, involving particularly the medium-sized and small renal arteries.3 The term endarteritis rather than arteritis is preferred because the chronic vascular process is limited to the endothelium, in contrast to the acute type of rheumatic vascular disease with involvement of all the coats of the vessel wall.4-7 Blood vessels of the same size in other organs, especially in the brain8,10 and the myocardium,7,11,12 may be similarly affected.

Rheumatic occlusive vascular lesions were incidentally observed in 1890 by Krehl11 in the myocardium of patients with chronically diseased rheumatic heart valves. These observations were later confirmed by Karsner and Bayless12 and Gross et al.,7 who described distinctive vascular lesions in active as well as inactive cases of rheumatic fever. Von Glahn and Pappenheimer8 systematically investigated all the peripheral vessels (except in the brain) of patients with rheumatic carditis, and described “specific” vascular lesions in various organs in 10 of 47 such cases. Usually, isolated vessels were affected, but in the kidneys the lesions were widespread. In the brain, late rheumatic vascular disease, mostly occurring in the form of an obliterating endarteritis, has been extensively studied by Bruetsch2,9,10 in material from mental patients with chronic valvular lesions.

Report of Cases

Case 1

A woman was admitted at the age of 44 to Central State Hospital because of psychiatric difficulties diagnosed as a schizophrenic reaction. Physical examination revealed well-compensated rheumatic mitral stenosis and hypertension. Despite antihypertensive drugs the pressure increased from 210/100 in 1955 to 280/125 in 1960, when she died of a cerebral hemorrhage. The urine frequently contained a slight trace of albumin and a few hyaline and granular casts, but at other times was negative. The plasma nonprotein nitrogen remained within the upper limits of normal. From 1955 to 1957 leukocyte determinations occasionally were elevated between 11,000 and 17,000, although there were no arthralgia, sore throat, colds, etc. The sedimentation rate was moderately elevated during this period. In the 3 years antedating death, the white-cell count did not exceed 10,000.

Postmortem observations revealed advanced rheumatic mitral stenosis with scattered areas of lymphocytes present in the thickened mitral leaflets. The heart was hypertrophied and weighed 515 Gm. A single Aschoff nodule was found in a serial examination of 14 myocardial tissue blocks.

The kidneys revealed rheumatic nephrosclerosis (fig. 1), with granular surfaces and large deep depressions, representing infarcted areas. On the cut surface some of the smaller infarcts confined to cortex were dark red and apparently recent. Microscopic examination of the infarcted areas showed completely or partially occluded medium-sized arteries (fig. 2). The occlusion of these vessels was due to former endothelial proliferation, now presenting itself as dense connective tissue, conventionally termed intimal hyperplasia. The continuing or recurring endothelial proliferation could still be observed in some of the partially obliterated vessels in the form of groups of 8 to 12 and more proliferating endothelial cells, some of these dividing

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Case 1. Rheumatic nephrosclerosis in patient with rheumatic mitral stenosis. The surface of the kidney is granular and there are several large sunken areas (infarctions).

Case 1. Two medium-sized renal arteries from an infarcted area, revealing old occlusive rheumatic vascular disease. The lumen is filled with dense fibrous tissue. Toluidine-blue stain; × 100.

by amitosis and invading the remaining lumen (fig. 3). In the infarcted areas, there was tubular atrophy and condensation of glomeruli in all stages of fibrosis. Throughout the grossly non-infarcted but granular regions of the renal cortex many small arteries showed endarteritic changes in all phases of evolution (fig. 4). There was a moderate degree of arteriolar sclerosis with endarteritic occlusion of some of the arterioles but with a minimum of arteriolar hyalinization. Other arterioles were entirely normal.

In the brain, a large fresh hemorrhage extended from the white matter of the left frontal lobe through the left basal ganglia and into the midbrain and pons. In about 50 per cent of the cortical tissue blocks, taken from the hemisphere not affected by the terminal hemorrhage, there

Figure 1

Figure 2

Figure 3

Figure 4

Case 1. Recurrent rheumatic endarteritic changes in small renal artery. The greater part of the lumen is eccentrically filled with old fibrous tissue. At the edge toward the narrowed lumen there is a recent deposit of fibrin, similar to that seen occasionally on rheumatic heart valves. From this area actively proliferating intimal cells, represented by small nuclei, are invading the remaining lumen. Toluidine-blue stain; × 260.

Case 1. Small artery from renal cortex. Obliterating rheumatic endarteritis (old process). The lumen is obstructed by proliferated endothelial cells, having produced a fairly cellular fibrous tissue. Toluidine-blue stain; × 320.
were so-called acellular areas in which all the ganglion cells had disappeared. These ischemic areas, also termed areas of pallor, represented incomplete microscopic softenings. Nevertheless, the gross appearance of the convolutions was normal. There were a few small cortical vessels with mostly old and usually slight rheumatic endarteritic alterations. One meningeal artery did reveal old occlusive rheumatic endarteritis (fig. 5). In contrast to the kidneys, the vascular and parenchymatous rheumatic changes in the brain were slight.

Rheumatic obliterating endarteritis of a few small arteries was present in the myocardium, in the pancreas, and in the submucosa of the stomach.

**Case 2**

A 56-year-old Negro woman died after 11 years in a state of dementia. Physical examination 2 years prior to death revealed a blood pressure of 140/80 and in the urine a trace of albumin and numerous hyaline and granular casts. Cardiac murmurs were not noted.

Postmortem examination revealed evidence of recurrent rheumatic endocarditis of the mitral valve with a rather large verruca and a continuous, barely visible layer of verrucous tissue along the closing border. The heart weighed 310 Gm. Microscopically, a tiny area of calcification was seen in the base of the mitral verruca. Recent deposits of fibrin were attached to the surface of the verruca and to other parts of the slightly thickened closing border. At various places young fibroblasts were growing into the fibrin. Lymphocytic cells were scattered in the verrucous tissue. One small artery in the myocardium was completely occluded by old connective tissue (rheumatic endarteritis). One distinct Aschoff body was seen.

The kidneys showed rheumatic nephrosclerosis (fig. 6). Only a few isolated areas of the renal surface had retained a normal, smooth appearance. Most of the outer aspect of both organs was interrupted by deep narrow depressions, by sunken areas with broad bases, or occasionally circumscribed granular areas. On the cut surface, in the region of the depressions, the renal cortex had completely disappeared and microscopically corresponded to wedge-shaped infarcts, extending through the entire cortex. Near such a small infarct was the medium-sized artery of figure 7, occluded by old fibrous tissue. Numerous other medium-sized and small arteries were seen, displaying concentric or eccentric intimal hyperplasia; adjacent vessels were often entirely normal. Prolonged search detected additional completely obliterated vessels. No such changes were observed in the arterioles, which had mostly a normal appearance.

The brain contained circumscribed areas in the frontal and parietal-occipital region of "granular appearance" while other areas were completely infarcted (fig. 8). The granular appearance of the cerebral cortex was the result of innumerable, retracted, minute infarcts, brought about by rheumatic endarteritic involvement of small meningeal and cortical vessels. As in the kidneys, the obliterated segments of the involved vessels of
the brain were difficult to find and necessitated search in serial sections.

In the remaining organs, occluded rheumatic endarteritic vessels were rarely observed.

Case 3

A 43-year-old man was admitted to the mental hospital because of a psychosis associated with epileptic convulsions. The seizures had started at the age of 30. The patient was otherwise considered in good health. No cardiac murmurs were recorded. The Wassermann reaction on the blood and the cerebrospinal fluid was negative. Unfortunately, no blood pressure reading was available. He died at the age of 57 of a large rheumatic pulmonary infarction.

Chronic rheumatic mitral disease was found at autopsy. Along the closing border of the mitral valve was an elevated ridge of firm, yellow-gray, verrucous tissue. In one place was a large, partly calcified, roughened, bacteria-free vegetation. Histologically, the mitral leaflet had a characteristic rheumatic appearance. The heart was moderately hypertrophied, weighing 490 Gm. In the myocardium were minute connective-tissue scars and a few obliterated small arteries (rheumatic endarteritis). Intensive search detected an occasional Aschoff nodule in the stage of organization.

The surfaces of both kidneys were coarsely granular (fig. 9) as the result of a diffuse proliferative rheumatic vascular process, involving the middle-sized and small cortical arteries; they were in all stages of occlusion (fig. 10). In some vessels the rheumatic endarteritic process was active, evidenced by proliferating endothelial cells with reddish (basophilic) cytoplasm when stained with toluidine blue. An occasional intimal cell was dividing amitotically. The endarteritic process extended occasionally into an arteriole, often thickened or occluded by recently proliferated endothelial cells. There was no arteriolar necrosis; most arterioles were normal. The parenchymatous tissue displayed extreme disorganization with innumerable areas in the cortex containing collapsed tubules. These areas were at times infiltrated with lymphocytes and Aschoff cells, the latter being identified by a highly basophilic cytoplasm. The disorganized areas, which represented microscopic infarcts, alternated with regions of normal tissue.

In the brain the gross appearance of the convolutions was normal, despite numerous ischemic foci in the cortex, ranging from areas of paling (acellular areas), to microscopic softenings of recent date. Only a few of the minute cortical infarcts had progressed to the cystic stage, retracting the remaining overlying tissue. Consequently, the convolutions had not yet assumed a "granular appearance." Rheumatic endarteritic alterations of the small meningeal and cortical vessels were infrequent and usually of long standing. There were also a few instances of recent endarteritic changes, as shown by the reddish cytoplasm of the proliferating endothelial cells. On the intimal layer of one small meningeal artery, a verruca-like formation was observed, protruding into the lumen. Such structures have been termed arteritis verrucosa by Gross et al.\textsuperscript{7} and Holst.\textsuperscript{13} These arterial verrucae are probably identical with those on rheumatic heart valves.

Other organs in which a few rheumatic endarteritic vessels were noted were the lungs,
Discussion

The "embolic contracted kidney" is widely recognized as a manifestation of rheumatic cardiovalvular disease. Rheumatic nephrosclerosis is less widely appreciated.

Rheumatic vascular disease, as a sequel of rheumatic fever, has been slow to find general recognition, although occasional reviews have been published.\textsuperscript{14, 15}

Rheumatic endarteritis of an occasional small artery may be found in almost every part of the body;\textsuperscript{8} the kidneys and the brain are most frequently involved. In both organs the cortex particularly is involved because of its similar vascularity.

In the kidneys the occlusion of the small and medium-sized arteries produces innumerable microscopic infarctions, causing a granular or nodular external surface with some large sunken areas due to occlusion of larger vessels.

In the brain the same vascular process involves the small meningeal and cortical arteries followed by "granular atrophy" of the cortex (fig. 8). The granular appearance of the convolutions is usually confined to circumcribed areas of the brain, where the rheumatic vascular changes with their dependent microscopic cortical infarctions retract the surface. In the kidneys, on the other hand, the entire surface may be coarsely granular (fig. 9). In some instances, the areas with a granular appearance alternate with large areas of smooth normal-appearing external surface, indicating that the granulation is not the result of hypertension, often present in these cases. Similar observations were made by Denst and Neubuerger.\textsuperscript{16}

The outstanding feature of rheumatic endarteritis is proliferation of endothelial cells that may be confined to a segment of the inner circumference or, more rarely, a verruca-like formation. At a later date the proliferating process may resume activity leading to further narrowing (fig. 3). In other instances endothelial proliferation originates from the entire wall proceeding to complete occlusion at once, or it may stop halfway, causing a concentric narrowing ring of fibrous tissue on the inside of the intima.

This process can be observed in sections stained with hematoxylin and eosin, but the utilization of alcohol-fixed tissue embedded in celloidin and stained with toluidine blue, after Nissl, enables one to see details that cannot be easily seen otherwise. If endothelial proliferation is active, the cytoplasm of these
cells assumes a distinct reddish tint. Similarly, the cytoplasm of the Aschoff cells of the myocardium stains the same reddish color. The microscopic renal and particularly the incomplete cerebral infarctions, the so-called acellular areas of the cortex, are also better demonstrable with this method.

Summary

Three instances of rheumatic nephrosclerosis are described in patients with chronic rheumatic valvular heart disease. The underlying mechanism of this renal lesion consists of an obliterating rheumatic endarteritis, involving mainly medium-sized and small arteries of the renal cortex. The arterioles take relatively little part in these changes. The widespread occlusive vascular disease gives rise to innumerable microscopic infarctions, resulting in a coarsely granular external surface of the kidneys.

A similar granular appearance of cerebral convolutions may or may not occur in these cases, depending on whether the small meningeal and cortical vessels of the brain are extensively involved.

References

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