CORONARY ENDARTERITIS IN ACUTE RHEUMATISM

BY

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Various observers have described intimal changes in the coronary arteries of the heart in acute rheumatism.

Krehl¹, in 1890, was the first to note the occurrence of fibrous intimal thickening in the smaller arteries of the heart in chronic valvular disease of rheumatic origin. Later Romberg² drew attention to this intimal thickening and also reported the finding of hyaline thrombi in many of the small arteries of the heart in two cases of acute rheumatism. No change was found in the walls of the thrombosed vessels nor in the tissues surrounding them, and the presence of fissures between the thrombus and the vessel wall showed that the vascular occlusion was sometimes incomplete. Romberg's comment on the absence of muscle tissue infarction in relation to the occluded arteries was that either the hyaline thrombi formed just before death or that the good collateral blood supply of the myocardium prevented muscle necrosis.

Rabé³, in an examination of the heart of a child, aged five, who died of rheumatic fever, found proliferative endarteritis accompanied by medial degeneration (*mésartérite*) in the small and medium sized coronary arteries. Aschoff^{4, 5}, who has shown that the walls of the small coronary arteries are sometimes involved in the inflammatory nodules which are named after him, has stated that most of the scars in the rheumatic myocardium are due to ischaemic necrosis caused through the consequent sclerotic narrowing of such vessels. Takayasu⁶, who examined the heart of a girl, aged eight, dying of acute rheumatism, found what he described as canalized emboli in many of the small coronary arteries at or near the apex. These emboli were considered by Takayasu to have come from the vegetations on the valves of the heart.

Geipel⁷, in 1909, reported a case of acute rheumatism in which there was marked endarteritis of the small and medium sized coronary arteries. Stenosis or complete occlusion, through the presence of fibrin masses and proliferated endothelial and subendothelial cells in the vascular lumen, was frequently noticed and some small infarcts in the myocardium were attributed to this. Geipel considered that the fibrin masses were in the nature of emboli derived from the vegetations on the heart valves and that the intimal changes were secondary to the embolic plugging of the vessel.

Coombs⁸ has described the endothelial and subendothelial cell proliferation which so frequently occurs in the myocardial capillaries and arterioles, and has further remarked on the fibrous intimal thickening so often to be seen in the smaller and some of the larger coronary arteries in rheumatic carditis, an observation recently confirmed by Perry⁹.

Wätjen¹⁰, in his examination of a case of rheumatic myocarditis, found that all the layers of the coronary artery wall could be involved in the territory of the specific inflammatory nodules, and that nodules occurring in the intima destroyed the internal elastic lamina and involved, more or less strongly, the media. In other instances a diffuse eosinophil cell infiltration of the intima without recognizable nodule formation was observed. The lumen of vessels affected in this way was either

partly or quite filled with fresh thrombus masses or fresh or old organized tissue. Wätjen was of the opinion that this obliterative process in the vascular lumen was caused by the changes in the vessel wall and was not embolic in nature.

Pappenheimer and Von Glahn¹¹, who have described certain lesions in the intima of the aorta which they consider to be of rheumatic origin, found in one of their cases similar changes in the intima of a coronary artery. In their examination of the heart of a boy aged fifteen who died of acute rheumatism the intima of the left coronary artery close to its orifice was found to be represented by a loose tissue apparently derived from the endothelium together with a few wandering cells, including a fair number of polymorphonuclears.

Klinge and Vaubel¹², who believe that the initial change in the rheumatic lesion is a fibrinoid transformation of the ground substance of the connective tissue and that this is followed by cellular proliferation and infiltration, have shown that the intima of the small coronary arteries may be thus affected.

Present investigations.

The purpose of this report, which deals with the histological examination of the coronary arteries of four patients dying of acute rheumatism, is to present further evidence of the occurrence of a specific type of coronary endarteritis in rheumatic disease of the heart. Mention will first be made of the intimal age changes which take place in these vessels, since there is reference to them in the descriptions which follow.

Intimal age changes in the coronary arteries.—The coronary intima, which consists at birth of the internal elastic lamina covered by endothelium, begins in early life to undergo various structural alterations which lead to progressive thickening. An inner layer of elastic tissue called the boundary stripe layer splits off from the internal elastic lamina and between these two elastic boundaries there develops a longitudinal musculo-elastic layer of tissue into which medial muscle cells pass, through gaps which appear in the internal elastic lamina. Internal to the stripe there forms a circular layer of fibrous tissue which is rich in elastic fibres and is called the elastic hyperplastic layer. These two layers gradually increase in thickness and, as age progresses, a third layer appears internal to the elastic hyperplastic layer. This innermost layer is composed for the most part of collagenous fibres and is called the fibrous layer.

Wolkoff¹³, who has made a study of the structure of the coronary arteries of normal hearts at different age periods, considers that this process of intimal thickening is much more marked in these arteries than in the other arteries in which age changes have been described. At the age of seven years, according to Wolkoff, the intima of the main coronary stems may be half as thick as the media, while at eighteen years the three layers may be present, the intima then being as thick as or thicker than the media. This thickening occurs in small areas at first but after the thirtieth year it affects the whole circumference of the vessel. In the medium-sized and smaller coronary branches similar changes occur but at correspondingly latter ages.

Wolkoff observed no intimal changes in the smaller myocardial arteries, but Gross¹⁴ and his co-workers have recently shown that these also undergo somewhat similar age period changes which bring about intimal thickening.

Case histories and autopsy records.

Case 1.—Female, aged 8 years, who was admitted with rheumatic heart disease and attacks of severe abdominal pain with vomiting. Signs of fluid in the pericardium were detected a week after admission. During the first twelve days in hospital there were ten attacks of pain in the epigastrium. Each attack of pain lasted from five to ten minutes and was accompanied by vomiting. Later these attacks of pain became less frequent but increased in number again in the last few days before death, which occurred a month after admission. The temperature varied from 100° F. to 101° F. until a week before death when it dropped and remained at 99° F., with a drop to subnormal just before death. The blood Wassermann test was negative.

PREVIOUS HISTORY. When four years old the child complained of pains in the elbows and knees. These pains disappeared after some months and her health remained apparently good until about the age of seven-and-a-half years, when the parents noticed twitchings of the face and jerkings of her head, arms and legs. Later she complained of pain in the knee joints and when brought to hospital was admitted with a diagnosis of rheumatic arthritis, carditis and chorea. At the end of six weeks her condition had much improved and she was discharged to attend, but was readmitted three weeks later on account of the sudden onset of attacks of severe abdominal pain and vomiting.

FAMILY HISTORY. There are two other children in the family, a boy of six with rheumatic heart disease and a boy of three who is apparently quite healthy. The parents are in good health and have no history of rheumatism or specific disease, and in each case the blood Wassermann test was negative.

AUTOPSY RECORD. The pericardial sac was markedly distended with turbid yellowish fluid showing the following cell count: polymorphs 40 per cent., lymphocytes 23 per cent., endothelials 37 per cent. No micro-organisms were seen in the direct smears made from this fluid and all cultures remained sterile. A thin fibrinous exudate was present on the surface of the visceral and parietal pericardium, more marked around the base of the heart. Hypertrophy and dilatation of the heart was found with thrush-breast appearance all over the inner surface of both ventricles. Rheumatic endocarditis of the mitral, tricuspid and aortic valves was present. Cultures made from the vegetations remained sterile. A fair amount of yellow fluid was found in the peritoneal and pleural cavities. There was chronic venous congestion of the viscera and moderate fibrosis of all heart-valve leaflets.

Case 2.—Male, aged 9 years, was admitted with pericarditis. He had always been a weakly child and during the six months previous to admission had suffered from frequent attacks of pain in the chest and abdomen with headache and vomiting. These attacks occurred at intervals during periods which lasted from one to two weeks. The last illness was of a similar nature but the symptoms were much more severe. Death took place nine days after admission. The blood Wassermann test was negative.

AUTOPSY RECORD. Fibrinous pericarditis was present, the pericardial layers being adherent but easily separated. Rheumatic endocarditis of the mitral, aortic, and tricuspid valves was found but no obvious fibrosis of the valve leaflets. There was a little clear yellow fluid in the pleural cavities and chronic venous congestion of the viscera. Cultures made from the vegetations on the heart valves remained sterile.

Case 3.—Female, aged 15 years, was admitted to the surgical ward for erysipelas of the face. The erysipelas cleared up in a few days and she was then transferred to the medical ward on account of the condition of her heart, which was diagnosed as rheumatic heart disease. She was discharged improved at the end of two months but was readmitted six weeks later with oedema of the feet and legs and a fibrillating heart. She died two days after admission. There was a history of an attack of acute rheumatic fever at the age of eleven. The blood Wassermann test was negative.

AUTOPSY RECORD. There was hypertrophy and dilatation of the heart with an adherent pericardium and rheumatic endocarditis of the mitral and aortic valves. The mitral valve leaflets were fibrosed and there was a moderate stenosis of the valvular orifice. Much clear yellow fluid was present in the peritoneal and pleural cavities. There was chronic venous congestion of the viscera. Cultures made from the vegetations on the heart valves remained sterile.

Case 4.—A female, aged 27 years, was admitted in an acutely ill condition with pericarditis and oedema of the feet and ankles. Death occurred twenty-four hours later. Eighteen weeks previous to admission the patient had a severe quinsy from which she never quite recovered and six weeks after the onset of the quinsy her condition was diagnosed as acute rheumatic fever. She was confined to bed and became progressively worse. There was no previous history of rheumatism. The blood Wassermann test was negative.

AUTOPSY RECORD. There was a large dilated heart with rheumatic pericarditis and endocarditis of the mitral and aortic valves and wall of the left auricle. Much clear yellow fluid was present in the peritoneal and pleural cavities. The lungs and liver showed chronic venous congestion. The spleen was double the normal size, and the cut surface showed a firm hyperplastic pulp. There was cloudy swelling only of the kidneys. Cultures made from the vegetations on the heart valves and the auricle wall remained sterile.

Histological examination.

There were numerous Aschoff nodules in the myocardium in all four cases but the outstanding feature was the condition of the coronary arteries. These showed a characteristic type of intimal inflammation with or without involvement of the media and some degree of periarteritis. The lesions were not necessarily nodular in distribution but might involve long stretches of the vessel, although in places there might be some variation in the intensity of the inflammatory reaction.

In case 1 both main coronary stems and many of their branches even to the smallest twigs were affected, the left coronary to a much greater extent than the right. In case 2 the condition was present in the main stem and some of the branches, both large and small, of the left coronary artery only, while in case 3 and 4 only a few of the smaller arteries in the wall of the left ventricle and in the basal third of the interventricular septum were affected. The histological picture of these vascular lesions corresponded with that generally recognized as the tissue reaction to the presence of the virus of acute rheumatism, namely, the Aschoff nodule.

In the precapillaries and the small arterioles the endothelium was raised up into the lumen through the deposition of fibrin in the subendothelial space. Sometimes this fibrin was more abundant at one point so that small projections were formed which might almost occlude the lumen (fig. 1). These formations might be mistaken for hyaline thrombi, if their origin was not clearly shown in the section. Even then, however, a close inspection showed that the fibrin mass was surrounded by a layer of endothelial cells, separated from the intact vascular endothelium by a space containing red blood cells. Accompanying this deposition of fibrin there was usually some proliferation of the endothelial and subendothelial cells and even of the cells of the rest of the vessel wall and surrounding tissues. Many of these proliferated cells

were of large size and showed basophil cytoplasm, and some were multinucleated (fig. 2). Even when the subendothelial space was full of these cells the normal endothelial lining to the vascular lumen might remain intact.

A similar deposition of fibrin and proliferation of endothelial and subendothelial cells accompanied occasionally by medial changes and a varying degree of periarteritis might be seen in the smaller and some of the larger coronary branches (fig. 3).

As a rule, however, in vessels of a calibre larger than arterioles the picture varied through the occurrence of reactive intimal hypertrophy. In these vessels the earliest reaction was a simple proliferation of the intimal cells

FIG. 1. Case 4.—Arteriole in the inner wall of left ventricle. Note the fibrin and basophil cells in the subendothelial space and the subendothelial exudation of fibrin simulating a hyaline thrombus ($\times 315$).

which might lead to marked intimal fibrosis, or, if the stripe layer became split off from the internal elastic lamina, to the premature formation of those intimal layers which appear with advancing age (fig. 4). Later cellular infiltration and fibrinous exudation occurred in this thickened intima and the intimal cells around the fibrin masses became large and basophil and in some cases multinucleated.

In rare instances these intimal changes were so marked that the lumen became obliterated by the proliferated endothelial cells, fibrin and altered intimal cells (fig. 5).

At other times opposing endothelial surfaces approached one another and finally coalesced so that small portions might become cut off from the main lumen or the whole lumen might become divided up into several small spaces (fig. 6). Sometimes, if there had been much destruction of the internal

FIG. 2. Case 3.—Small myocardial artery, showing numerous Aschoff cells in the intima ($\times 315$).

FIG. 3. Case 1.—Artery in the auriculo-ventricular sulcus showing intimal changes. A composite type of Aschoff nodule lies between the vessel wall and the heart muscle ($\times 90$).

FIG. 4. Case 1.—Branch of the anterior descending coronary artery. Note the thick musculo-elastic and elastic hyperplastic intimal layers—the latter showing marked leucocytic infiltration ($\times 90$).

FIG. 5. Case 1.—Branching artery in the auriculo-ventricular sulcus showing occlusion of the lumen. The edge of an Aschoff nodule can be seen in the adventitia at the upper part of the section ($\times 90$).

FIG. 6. Case 1.—Intima of a myocardial artery, showing the formation of luminal spaces. The much reduced original lumen is on the left ($\times 315$).

FIG. 7. Case 1.—Artery in the auriculo-ventricular sulcus, showing division of the lumen into four separate spaces. There is degeneration of the internal elastic lamina and stripe layer and much disintegration of the media ($\times 315$).

FIG. 8. Case 1.—Artery in the interauricular septum showing hyperplastic intima and two luminal spaces lying within the degenerated internal elastic lamina ($\times 90$).

FIG. 9. Case 1.—Artery in the auriculo-ventricular sulcus, showing the formation of muscle and fibrous tissue layers around the luminal spaces ($\times 90$).

elastic lamina and disorganization of the media, a few of these luminal spaces appeared to lie within the media. These blood spaces or luminal rests remained lined by intact endothelial cells which might show basophil cytoplasm, and they communicated both with one another and with the vascular lumen above and below the segment thus affected (fig. 7). There was thus some resemblance to canalization of a thrombus, but thrombosis did not as a rule occur at any stage.

The mobile cells taking part in this intimal inflammatory reaction were chiefly lymphocytes, polymorphonuclears, and plasma cells. Eosinophil cells rarely occurred and then only when the other cells were present in great number.

The internal elastic lamina remained more or less intact, or it appeared as a beaded or segmented ring. Occasionally all that remained of this elastic layer consisted of small scattered portions of degenerated elastic tissue. If the stripe layer of elastic tissue had formed it also underwent similar degenerative changes. The media, even when intimal changes were marked, might remain unaffected. More often there were varying degrees of inflammatory-cell infiltration without much tissue damage. At other times there was marked dissociation of the medial cells and fibres accompanied by much muscle cell atrophy. Occasionally fibrin masses were seen in the affected media, and capillary vessels might also be present. Only very rarely was there any change comparable to coagulation necrosis of the media, and degenerated muscle or other cells with pyknotic nuclei were seldom seen.

The adventitia showed little or no change or it might be involved in the spread of any Aschoff nodules present in the surrounding tissues. More usually there was a diffuse perivascular inflammatory reaction which frequently involved the adventitia, and in such cases there might be some destruction of the external elastic lamina. The cells taking part in this periarteritis were chiefly lymphocytes and polynuclears, but Aschoff cells were frequently seen either singly or as part of a typical nodular area. Often there were numerous capillaries and thin walled blood spaces present and these might communicate with the vessel lumen or what remained of it through capillary channels which passed through the media. A new and accessory circulation was thus established with the collateral blood vessels.

The healing process which followed these inflammatory changes consisted of absorption of the fibrin, disappearance of the mobile and basophil cells and fibrosis. Marked thickening of the intima was produced through the laying down of both collagenous and elastic fibres. The media might become almost entirely replaced by fibrous tissue and there might be marked adventitial and perivascular fibrosis.

The small blood spaces cut off from the vascular lumen sometimes remained and simulated true vascularization of the intima (fig. 8). Occasionally the intimal cells nearest to these luminal rests formed a cuff-like arrangement around them, giving the appearance of somewhat thick walled vessels, in which, so far, it has not been possible to demonstrate the formation

of a new internal elastic lamina (fig. 9). These circularly arranged cells resembled smooth muscle cells in their appearance and staining reactions.

In the later healed stage it might be impossible to differentiate such an affected segment of an artery from a healed and canalized thrombus, except by observing the more acute stages of the intimal lesion at other neighbouring parts of the same vessel or the recrudescence of the acute inflammatory process in the healed segment itself.

Definite evidence of damage to the myocardium as a result of these vessel changes was noticed only in case 1, in which a few microscopical anaemic infarcts were observed here and there along the base of the left ventricle.

Summary and conclusions.

Four cases of acute rheumatism have been described, in which the condition found in the coronary arteries illustrates the occurrence of an endarteritis which is specific in type, the intima undergoing a diffuse inflammatory reaction which reduplicates the histological features of the Aschoff nodule.

The initial change is an intimal cell proliferation which may lead to fibrotic thickening or simple intimal hypertrophy. This is followed by fibrinous exudation or necrosis, mobile cell infiltration, and the appearance of those basophil giant and multinucleated cells which denote the presence of the virus of acute rheumatism. Usually there is marked degeneration of the internal elastic lamina and of any other elastic layers which may have formed in the intima.

Unless complete obliteration of the lumen occurs the vascular endothelium remains intact and thrombosis does not take place. An interesting feature is the occasional isolation of small luminal spaces or even the complete partition of the lumen, which in the later stages leads to the simulation of intimal vascularization or thrombus canalization. Sometimes the intimal cells, in keeping with their mesenchymal origin, reproduce layers of what appear to be smooth muscle cells around these luminal spaces, thus giving them the appearance of thick-walled vessels.

A common accompaniment of this endarteritis is a perivascular inflammation which may be of the Aschoff nodule type or consist of a more diffuse inflammatory reaction with numerous mobile cells, isolated Aschoff cells and many distended blood vessels. Communication between the lumen of the affected segment of the vessel and these perivascular blood vessels is established through the formation of new capillary channels which pass through the media.

The media may remain unchanged or it may be involved through spread of the infection either from the intimal or adventitial side or from both. As a result medial muscle cells disappear and are replaced by fibrous tissue.

Both coronary arteries may be affected and at any part of their course, but the condition is more commonly found in the smaller branches of the left coronary artery.

The vascular lesions observed in these cases show that in acute rheumatism the coronary arteries may be infected not only from the outside, the virus gaining access by way of the perivascular lymphatics, but also from the inside, the virus passing directly into the wall from the lumen.

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