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VASCULAR CHANGES IN PERIPHERAL NERVES AND SKELETAL MUSCLES IN RHEUMATOID ARTHRITIS

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Problems connected with the pathology and therapy of rheumatoid arthritis are constantly in the foreground of research, on account of the facts that the pathogenesis of that condition is practically unknown, its rheumatic aetiology questionable and, apart from recent results with Cortisone, its response to therapy poor. The disease progressing slowly for decades represents a heavy burden for both patient and community.

Morpho-pathological research may present means to clarify several problems of rheumatoid arthritis, such as the following ones.

[1.] Is it justified to distinguish between a primary and a secondary form of chronic polyarthritis ? Are these not two forms of chronic rheumatism, identical in pathological character and differing only in clinical course ?

[2.] What is the underlying cause of the extraarticular symptoms of rheumatoid arthritis which suggest the presence of the a generalized diesase ? Such symptoms are the atrophy of muscles and skin more marked than expected, the cool, moist skin, the dermographism, the sensation of pain and numbness, inclination to sweating, the hypersensitivity to cold, and, finally, the helpless and adynamic state of the patient.

[3.] Is it justified to ascribe rheumatoid arthritis to neurogenous factors ? According to that theory, based partly on the above symptoms, the condition would be due to a disease of the nervous, and particularly of the central nervous system. [1, 2, 3.]

Earlier histopathological investigations did not provide answers to the above questions. On the ground of the basic investigations of Aschoff [4] and Talalajev [5], Klinge [6] in 1933 arrived at the conclusion that while in rheumatic fever widespread characteristic changes could be found throughout the body in the form of the so-called rheumatic nodules, in chronic polyarthritis rheumatism was in the first place confined to the joints, just as in chronic rheumatic carditis it was localized to the heart. Klinge denied the existence of any histological evidence justifying the classification of chronic polyarthritides into primary and secondary groups.

After such preliminaries, great interest was aroused when in 1942 Freund

et al [7] reported to have found inflammatory nodes in the peripheral nerves in 3 of 5 patients suffering from rheumatoid arthritis. The structure of the nodes was similar to the nodules observed by Klinge in rheumatic fever ; there was a central area of fibrinoid necrosis of the connective tissue surrounded by a ring of granulation tissue, which in its turn was encircled by a ring composed of lymphocytes and plasma cells. Blood vessels abounded in the nodes : number and localization of the nodes were independent of the duration and localization of the disease.

It also was reported by Freund and his collaborators [8, 9] that similar nodes composed of lymphocytes, but exhibiting no characteristic structure, could also be found in muscles. These observations stimulated a great number of histo-pathological studies in the period between 1947 and 1951 [10, 11, 12, 13, 14, 15, 16, 17, 18, 19]. Mostly specimens obtained from patients by means of muscle biopsy were studied and it was concluded from carefully controlled investigations that the nodules found in muscles could not be considered specific for rheumatoid arthritis, as similar changes may be present in other pathological conditions, such as collagen diseases, or even in normal individuals.

In comparison with muscle studies, the number of investigations concerned with the nervous system is still small [14, 16], owing to the fact that such examinations can only be carried out on autopsy material. It has been reported that in 75 per cent of cases of rheumatoid arthritis signs of focal inflammation could be detected in the peripheral nerves. In some instances degeneration of nerve fibers and fragmentation of myelin sheaths could also be observed.

It has also been reported [13, 15] that in some cases of rheumatoid arthritis the wall of thearterioles showed a concentric thickening with consecutive narrowing of the lumen. The development and significance of this phenomenon in the pathomechanism of rheumatoid arthritis has not been clarified. No change ascribable to rheumatoid arthritis could so far be demonstrated in the central nervous system [7].

Thus in the past few years the view that in rheumatoid arthritis chronic inflammatory lesions were present in the nerves and muscles gained widespread acceptance. Although the discovery of these changes has transferred rheumatoid arthritis into the group of collagen diseases, it did not significantly enhance our knowledge of the aetiology and pathomechanism of the condition, nor did these investigations succeed in providing satisfactory answers to the questions listed in the introduction. The relationship between rheumatoid arthritis and other rheumatic dieases is still subject to controversy, the cause of extraarticular symptoms is still obscure and there is no decisive morphological evidence supporting the neurogenous theory of rheumatoid arthritis.

These considerations, as well as the small number of histopathological

studies hitherto performed, have induced us to carry out detailed morphological investigations in the few cases autopsied by us and to report the findings.

Material and methods

Four cases of chronic polyarthritis have been subjected to detailed histopathological studies, using four cases of chronic rheumatic carditis as control. Data of the polyarthritis cases are as follows.

Case 1. Female, 40 years of age. Rheumatoid arthritis of 16 years' duration, leading to deformation, ulnar deviation and atrophy of the interosseous muscles in both hands. The small joints of the feet were less markedly deformed. The patient had been admitted to the hospital with symptoms of uraemia and had died within a few hours. In addition to rheumatoid arthritis, a chronic glomerulonephritis was also found at autopsy.

Case 2. Female, 66 years of age. Chronic polyarthritis of 4 years' duration. Both hands deformed, elbow joints swollen and fixed in adduction. Cachexia. Autopsy revealed rheumatoid arthritis and ulcero-caseous and acino-nodose tuberculosis of both lungs.

Case 3. Male, 66 years of age. Onset of symptoms 18 months ago, with rise of temparature. First the knee and ankle joints had been involved, then the disease had spread to the hands. The condition deteriorated in spite of treatment and finally deformation, subluxation and ankylosis of both hands developed. The movements of the small joints of both feet were restricted. Multiple subcutaneous nodules of the size of a small nut could be palpated at many sites. Cause of death, heart failure and sclerosis of the coronary arteries.

Case 4. Male, 37 years of age. Rheumatoid arthritis of 15 years' duration. Onset of symptoms in both knee joints, then gradual involvement of nearly every small joint, leading to deformities in spite of treatment. At autopsy subchronic glomerulonephritis, erysipelas of both lower extremities and septicaemia were found.

The age of the control cases was 13, 15, 22 and 52 years. The history in each of these cases included acute polyarthritis ; at autopsy marked chronic endocarditis involving one or more orifices was found in each case. In all four cases the cause of death was heart failure.

In all cases detailed histopathological studies have been carried out on specimens taken from various parts of the brain and spinal cord, intervertebral ganglia, brachial and lumbar plexus, as well as from various parts of the peripheral nerves, skeletal muscles and internal organs. An average of 300 sections have been prepared from each case. Haematoxylin and eosin, Azan, Gömöri's reticulin stain and, for the nerve preparations, Einarson's and Woelke's (for myelin sheaths) stains were used.

Observations

From among the four cases of rheumatoid arthritis the most marked lesions were found in cases 1 and 2. In case 3 changes were slight and in case 4 no lesions worth mentioning could be found in the muscles and nerves. It must be noted that cases 1, 2 and 4 were undoubtedly typical of rheumatoid arthritis, while in case 3 the clinical picture was not so characteristic as to enable us to differentiate between primary and secondary polyarthritis.

In cases 1, 2 and 3, small, loose accumulations of lymphocytes could frequently be found in the perineurium and endoneurium of peripheral nerves. In some cases the accumulations consisted of a few cells ; in other cases, especially in longitudinal sections of nerves, the cells formed longer chains between the nerve fibers (Fig. 1). The cellular accumulations were frequently located in

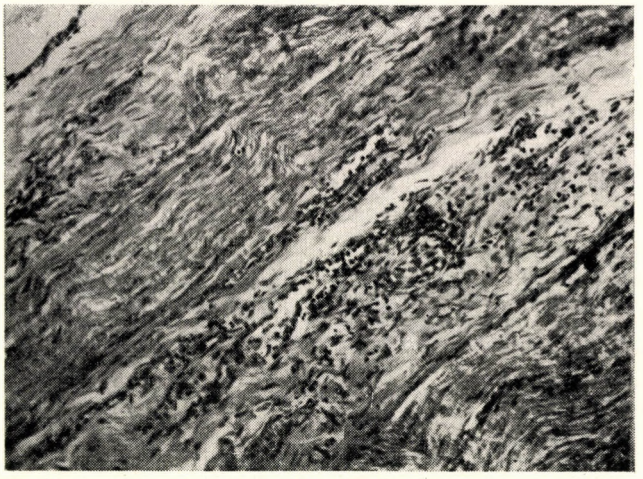

Fig. 1. Loose lymphocytic infiltration in the interstitial connective tissue of the radial nerve. Haematoxylin eosin stain

the proximity of small vessels and arterioles, but without involving the vessel itself.

Well demarcated, larger accumulations, real »nodules« also occurred in the nerves. These lesions were characteristic in structure, exhibiting layers around a centre consisting of cells. The nodules frequently extended into the adventitia of the vessels, the media of which exhibited no pathological change (Fig. 2).

In the peripheral nerves of cases 1 and 2, a small number of marked vascular lesions could be detected (Fig. 3). The media of the arterioles of the nerves was transformed circularly or partially into a homogeneous or granular fibrinoid substance, staining a vivid red with eosin and a dark red with Azan.

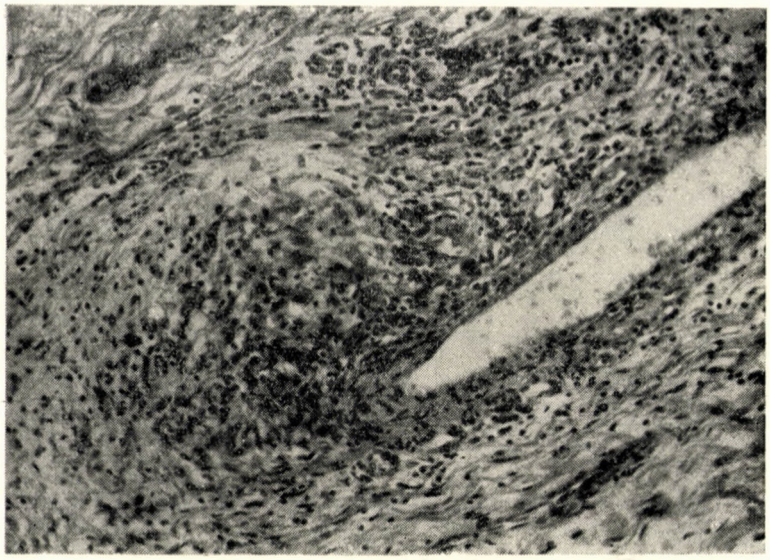

Fig. 2. Nodule composed of proliferation tissue in the adventitia of a small vessel. Haematoxylin eosin stain

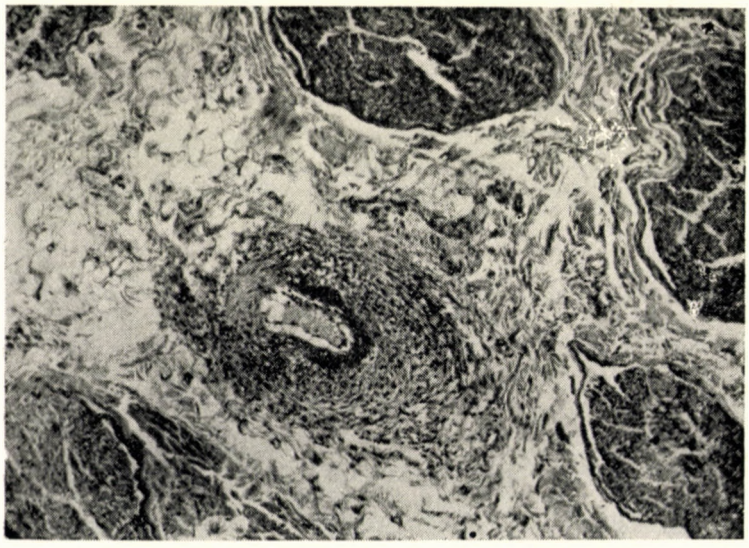

Fig. 3. Necrotising arteritis in the interstitium of the sciatic nerve. Major part of the vascular wall necrosed, surrounded by an area of leucocytic infiltration. Haematoxylin eosin stain

Mural and perivascular inflammatory infiltrations composed mainly of leucocytes occurred in the necrosed vascular walls. In some cases, signs of proliferation were already present around the leucocytic infiltration. Inflammatory cellular accumulations were also found containing in the centre remnants of a necrosed arterial wall sometimes demonstrable only by staining with Azan (Fig. 4). Occasionally the lumen of circularly necrosed arterioles was also filled with proliferation tissue (Fig 5).

The inflammatory cellular accumulations, the »nodule« accompanying vascular lessions sometimes appeared as if it were located in the proximity of a vessel and as if the participation in the inflammatory proliferation process of the vascular walls were only secondary. Especially misleading were sections in which the nodule had been cut through at a point remote from the vascular lesion. In such cases, however, serial sections revealed the connection between nodule and vascular lesion.

Finally, arterioles with a thickened wall were also found in the nerves (Fig. 6). Their lumina were markedly narrowed ; in their wall, in addition to a moderate round cell infiltration, cross sections of numerous small vessels could be seen. The latter corresponded to newly formed and dilated vessels of the proliferation tissue.

No signs indicative of degeneration could be detected in the nerves by means of myelin sheath staining.

In the striated muscles, changes closely resembling those found in the nerves were observed. It was conspicuous that the lymphocytic nodules were larger and occurred in a higher number in the muscles than in the nerves (Fig. 7). The nodules of the muscles were frequently located in the proximity of vessels, but were not associated with vascular lesions. Very occasionally an arteriole with a necrosed wall and infiltrated by leucocytes could be observed in the muscles as well (Fig. 8). Formation of proliferation tissue, organization and signs of cicatrical thickening could be detected in a number of arterioles in the muscles.

The elastic fibres of the vessels presented a characteristic appearance. At the border of the fibrinoid necrosis the elastic fibres were broken off, and in the necrosed area only their granular traces remained (Fig. 9). In the thick wall of vessels with a narrowed lumen the continuous layer of elastic fibres characteristic of the normal vascular wall was absent ; only a few thin fibres were detectable in the cicatrized vascular wall (Fig. 10).

Vessels of the central nervous system and those of the parenchymal organs exhibited none of the changes described above. In cases 1 and 4, signs indicative of a chronic glomerulonephritis with hyalinous degeneration of part of the glomeruli were detected in the kidneys. In the cases of chronic rheumatic carditis serving for controls, multiple accumulations of lymphocytes

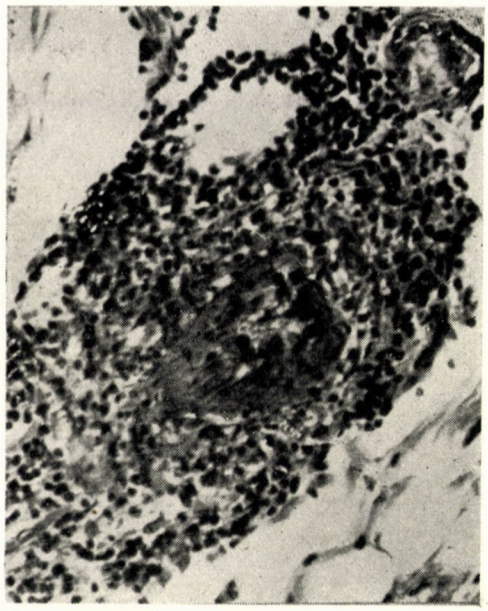

Fig. 4. Hardly recognisable remnants of a necrosed arterial wall in the centre of an inflammatory nodule. Median nerve. Haematoxylin eosin stain

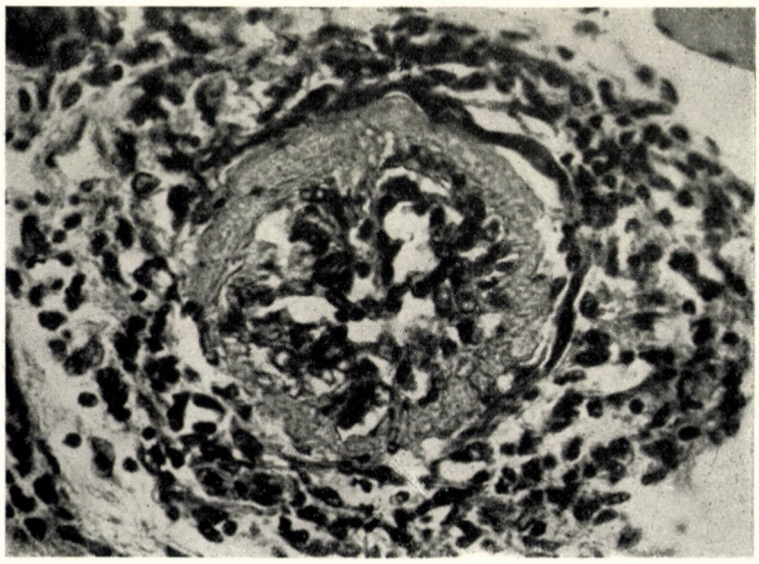

Fig. 5. The lumen of a vessel with circular necrosis is filled with proliferation tissue. Lumbar plexus. Haematoxylin eosin stain

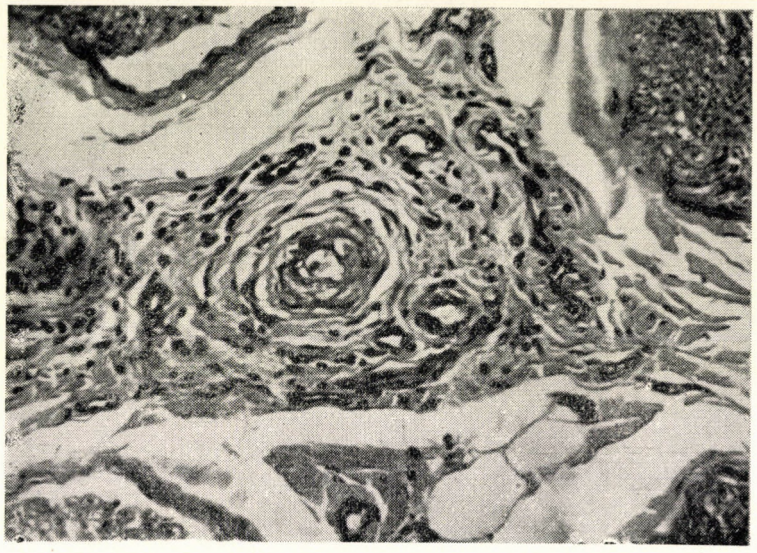

Fig. 6. An arteriole with thickened wall and narrowed lumen in the interstitium of the radial nerve. Dilated vessels in the thick vascular wall. Haematoxylin eosin stain

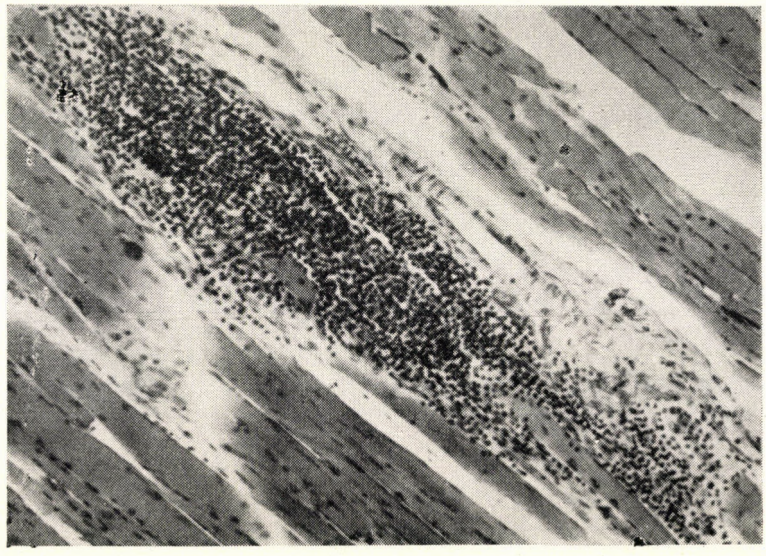

Fig. 7. Large accumulation of lymphocytes with blurred outlines in the muscle of the forearm. Haematoxylin eosin stain

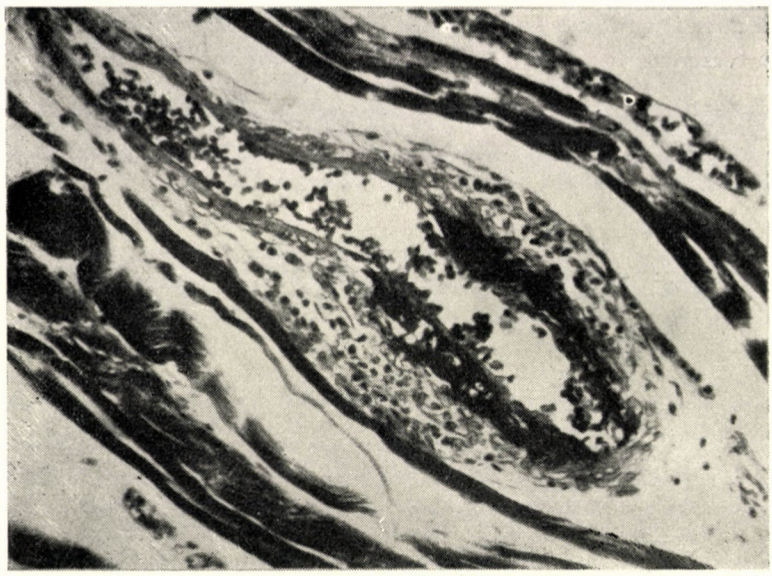

Fig. 8. Fresh necrosis in the wall of au arteriole ; in the longitudinal section of the vessel the acute demarcation line and the surronnding area of infiltration are visible. Gluteus muscle. Azan stain

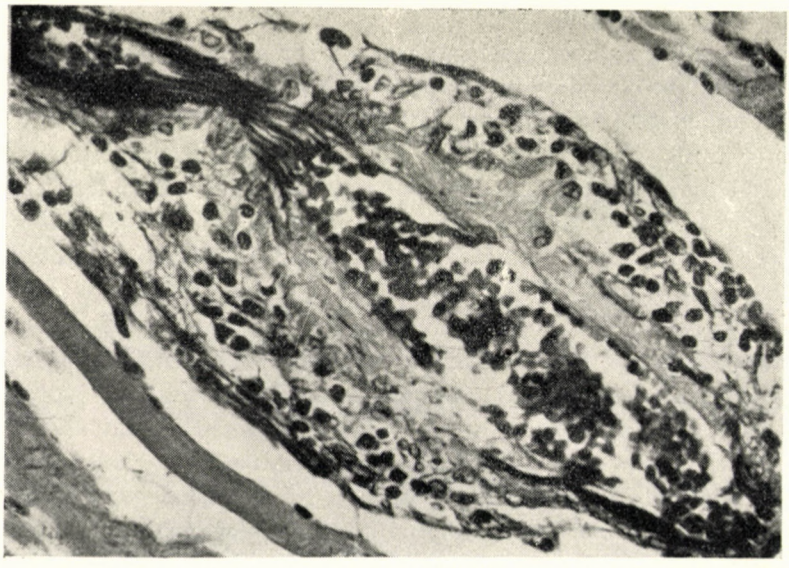

Fig. 9. Same vessel as shown in Fig. 8, stained with elastic stain. The elastic fibres are disrupted at the border of the necrosed area with an acute line. Fuchselin neutral red stain

were present in the nerves and muscles, but neither fibrinoid necrosis, nor any of the other vascular lesions described above could be detected.

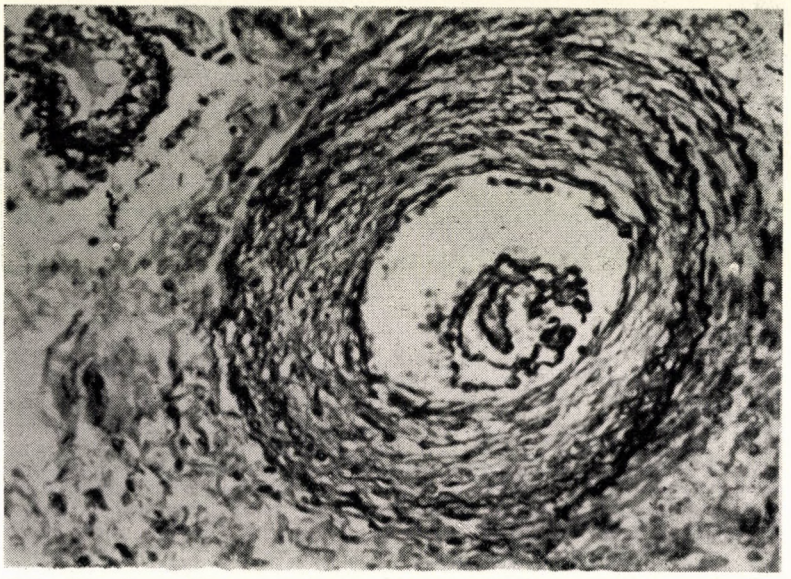

Fig. 10. Only thin elastic fibres can be found in the thickened vascular wall. Sciatic nerve. Fuchselin neutral red stain

Discussion

On basis of the above observations the opinion was formed that the lesions observed should be classified into two groups. The first group embraces changes consisting of lymphocytic accumulation located in the endoneurium, perineurium or in the endomysium and perimysium. The accumulations, although frequently situated in the proximity of vascular walls, never lead to vascular involvement. Such cellular groups were present, although in a smaller number, also in the controls ; this observation is in agreement with data of the literature. According to both our own observations and to literary data, it appears that the presence of these loose accumulations of lymphocytes is of no special significance in rheumatoid arthritis, since such lesions may appear in other pathological conditions or even in normal individuals.

It is endeavoured sharply to distinguish between the above changes and those related to vascular lesions. To the latter group belong part of the nodules exhibiting a characteristic structure, further the »necrotising arteritis« and arterioles possessing a thick wall and lacking elastic fibres. In our opinion, these lesions may play a rôle in the pathomechanism of rheumatoid arthritis.

According to our observations, it seems that the fibrinoid necrosis of

the arterioles of nerves and muscles provides the basis for further vascular changes. The inflammation at first acute, then proliferative, following the circular necrosis of the vascular wall leads to a grave narrowing of the lumen or even to its complete obstruction. In the latter case the remnants of the vascular wall subsequently disappear in the inflammatory granulation tissue. In case of a partial, segmental necrosis, the nodule is located next to the vascular wall, and is connected with it.

It is beyond doubt that Freund and other investigators had also noticed that the nodules were often located around or next to the vessels. Working further along these lines, in the course of our investigations we came to the conclusion that it is the involvement of the arterioles which is primarily responsible for the major part of the lesions observed in the nerves and muscles.

According to the view generally accepted, the necrotising arteritis is an allergic phenomenon due to hypersensibility. It is well known that the condition is mostly encountered in collagen diseases, such as rheumatic fever [6], periarteritis nodosa [20], disseminated lupus erythematodes, Libman-Sachs' syndrome, diffuse sclerodermia [22] and malignant nephrosclerosis. It is also known that certain drugs, such as the sulphonamides, may also give rise to necrotising arteritis. Experimental necrotising arteritis was produced by Holman [23] by means of the so-called standard fat diet, as well as by Selye [24] and his collaborators by means of cold stress, administration of anterior pituitary extract, desoxycortiscosterone acetate and with the aid of the so-called endocrine kidney. According to Selye, the essential factor in the process is not a necrosis of the vascular wall but the deposition under the damaged vascular endothel of a hyaline substance, and therefore he uses the term hyalinosis to denote the condition.

In the literature at our disposal we have found two data on the occurrence of necrotising arteritis in association with rheumatoid arthritis. Dawson [25] has found in the subcutaneous nodules of patients suffering from rheumatoid arthritis necrosis of vascular walls with destruction of elastic fibres, thickening and recanalization of the walls. More recently, Sokoloff, Wilens and Bunim [26] have reported necrotising arteritis in muscle biopsy specimens taken from patients with rheumatoid arthritis. The lesions described are completely similar to those observed in our material. However, to our best knowledge, necrotising arteritis occurring in the central nervous system of patients with rheumatoid arthritis has not been reported. The reason for this is to be sought in the extreme rarity of acute vascular lesions.

The lesions described are doubtlessly similar to the well-known tissue changes occurring in other collagen diseases, particularly in rheumatic fever. The histopathological picture would point to a rheumatic-hyperergic origin of the nerve and muscle lesions although we are well aware of the fact that

a resemblance of the histological pictures does not necessarily mean the identity of lesions and by no means does it indicate a pathogenetical agreement.

Thus we have arrived at the conclusion that in the muscles and nerves of patients suffering from rheumatoid arthritis the continuous influence of some injury of unknown nature gives to constantly relapsing acute vascular changes of small intensity for years or even for decades. Healing of such lesions brings about complete or partial obstruction in more and more arterioles, thus leading to a permanent or transitory functional disturbance. The very small number of acute vascular lesions explains the slow progression of the process. This is not in contradiction with the greater number of granulation tissue nodules, since restitution takes a certain time, and thus changes connected with the restitution process remain demonstrable for longer periods than are acute changes.

It is very difficult to evaluate the consequences of vascular changes and their role in the development of symptoms. It appears that they cause mostly functional disturbances, since no marked morphological changes were demonstrable in the nerves and muscles. Beside chronic inflammatory changes in the tissues of joints, vascular lesions may play a subordinated part in the development of arthritis, although the theory according to which the small joints and muscles of the hand performing precise functions would be more sensitive to changes in the blood supply and innervation than other joints and tissues, is very attractive and should not be left unconsidered [15].

The importance of vascular lesions is accentuated by the known therapeutical efficacy of Cortisone in rheumatoid arthritis. It is known that the effect of Cortisone in cases of periarteritis nodosa and disseminated lupus erythematodes manifests itself in the rapid healing of vascular lesions [24,27]. So far no satisfactory explanation for the efficacy of Cortisone in rheumatoid arthritis has been put forward. The rapid improvement may to some extent be due to the favourable influence exerted upon the vascular changes discussed.

Summary

1. Lymphocytic nodules unrelated to vascular changes occurring in nerves and muscles of patients suffering from rheumatoid arthritis cannot be considered specific for that condition.

2. In the interstitium of nerves and muscles a very small number of foci of acute necrotising arteritis could be observed. The vascular change leads to the formation of inflammatory proliferative nodules. When the vascular necrosis is circular, the nodules are located around the vessels; when the necrosis is partial, they are found next to the vessels.

3. In the vessels involved, destruction of the elastic fibres with consequential thickening of the vascular wall and narrowing of the lumen can be observed.

4. Number and localization of acute vascular lesions are independent of the duration and localization of the disease.

5. The histological structure of vascular changes point to a rheumatic-hyperergic aetiology of rheumatoid arthritis.

6. The widespread vascular changes in nerves and muscles throughout the body may play a role in the development of extraarticular symptoms of rheumatoid arthritis.

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ИЗМЕНЕНИЯ СОСУДОВ В ПЕРИФЕРИЧЕСКИХ НЕРВАХ И МЫШЦАХ ПРИ РЕВМАТОЙДНОМ АРТРИТЕ

Б. Раднай

Резюме

1. При ревматойдном артрите в периферических нервах и в мышцах встречаются скопления лимфоцитов, не зависимые от изменений сосудов. Эти скопления не являются специфическими для ревматойдного артрита.

2. В промежуточной ткани нервов и мышц можно наблюдать в небольшом числе острый некротизирующий артерит. Это изменение сосудов ведет при польном циркулярном некрозе и образованию периваскулярных, а при частичном некрозе к образованию околососудистых воспалительно-грануляционных очагов.

3. В поврежденных сосудах наблюдается уничтожение эластических волокон, а затем рубцевое утолщение сосудистой стенки и сужение процвета.

4. Число и расположение острых сосудистых изменений не зависят от времени и расположения болезни.

5. Гистологическое строение сосудистых изменений указывает на гиперэргическое происхождение ревматойдного артрита.

6. Изменения сосудов встречающиеся в нервах и мышцах всего тела, по нашему мнению играют роль в возникновении внесуставных симптомов ревматойдного артрита.