MUSCLE LESIONS IN RHEUMATOID ARTHRITIS*

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Recently certain pathological investigations have indicated that there is frequently widespread involvement of the neuromuscular system in rheumatoid arthritis, and it has been suggested that this may be responsible for the prominent neuromuscular clinical features of the disease.

Curtis and Pollard (1940) were the first to describe the non-articular lesion which was common to all their eleven cases of rheumatoid arthritis, including four cases with " Felty's Syndrome ". In every one of their eleven cases these authors found small perivascular infiltrations of lymphocytes in the muscles.

Steiner and others (1946) performed muscle biopsies on seven cases of rheumatoid arthritis and demonstrated inflammatory nodules in each of the cases. The nodules were situated in the perimysium and in the endomysium, rarely in the epimysium. The nodules consisted of collections of lymphocytes and plasma cells and the authors termed the lesion " nodular polymyositis ". Similar lesions were encountered in the muscles of two cases which were examined at autopsy. The size of the nodules varied from very small ones (consisting of " twenty or less lymphocytes ") to large ones visible to the naked eye in the stained sections. They also noted definite arteritis and peri-arteritis in the small muscular vessels in some of their cases. In addition to the nodular inflammatory lesions they noted the occurrence of various stages of degeneration and atrophy of the muscle fibres and considered that these degenerative changes, when present, were always secondary to the inflammatory changes. The lesions were found in muscles which were not adjacent to affected joints, and were present even in long-standing cases of rheumatoid arthritis which were " seemingly burnt-out ". They suggested that these findings were specific to rheumatoid arthritis.

These results were soon confirmed by other investigators. Gibson and others (1946) noted the presence of these nodular inflammatory lesions by biopsy in each of eleven cases of rheumatoid arthritis. De Forest and others (1947) found similar characteristic lesions in twelve out of sixteen muscle biopsies. Clawson and others (1947) demonstrated these characteristic lesions in seventeen out of forty-four deltoid muscle biopsies. Desmarais and others (1948) reported the results of muscle biopsies on a further fifty-six cases of typical idiopathic rheumatoid arthritis. Thirty-four of these cases showed round-cell foci and blood-vessel changes. Like Steiner and others, they noted " positive " biopsies in cases which appeared " burnt-out ", in cases without muscle wasting, and in muscles remote from affected joints. Bunim and others (1948) stated that they found the characteristic small nodules in the " large majority " of the muscle biopsies performed on twenty-five cases of typical rheumatoid arthritis.

It thus appears, when these results are analysed, that " positive " muscle biopsies (with " nodular myositis ") occurred in 40 to 100 per cent. of cases of rheumatoid arthritis. If the results are totalled it appears that, on the average, approximately 60 per cent. of muscle biopsies in rheumatoid arthritis reveal the characteristic lesions described by Steiner and others (1946).

Morrison and others (1947) examined the muscles of fourteen cases of rheumatoid arthritis at autopsy and encountered varying sizes of inflammatory nodules in eight instances.

Results of Muscle Biopsy in Thirty-four Cases of Rheumatoid Arthritis

Muscle biopsy was performed under local anaesthesia with 2 per cent. procaine on thirty-four cases of chronic rheumatoid arthritis. The deltoid muscle was selected in thirty-three cases and the gastrocnemius in one case. The cases were typical examples of " idiopathic " chronic rheumatoid arthritis, the durations varying from one year to forty-five years. The size of an average piece of muscle removed by biopsy was approximately 1·8 cm. in length, 0·6 cm. in breadth, and 0·6 cm. in

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thickness. The biopsy specimens were fixed in corrosive sublimate and embedded in paraffin wax. Three sections were cut from each specimen and were stained with haematoxylin and eosin.

Attention was chiefly focused on the inflammatory changes in the muscles. It was sometimes difficult to distinguish with certainty between degenerative changes in the muscles and changes resulting from the trauma of removal. As the inflammatory changes, not the degenerative ones, are those which have been regarded as probably of diagnostic value in the disease, the degenerative changes are mentioned more briefly.

Characteristic inflammatory lesions were found in fourteen cases (40 per cent.) in the series. The muscle biopsies were " negative " in the remaining twenty cases.

A single focus was present in six cases; two to seven foci were found in the other eight cases.

The Fourteen " Positive " Biopsies

The results of the microscopic examinations of the sections of the fourteen " positive " biopsies are tabulated and illustrated below.

Case 1.—A 51-year-old man had rheumatoid arthritis for three years. Two large oval nodules consisting of about 100 cells each and one small nodule consisting of about 40 cells were present in the endomysium and were perivascular in distribution. The cells were practically all lymphocytes.

Case 2.—A 60-year-old woman had rheumatoid arthritis for seven years. One small nodule consisting of about fifty lymphocytes was situated in the endomysium on the edge of the section.

Case 3.—A 61-year-old woman had rheumatoid arthritis for twenty years. One nodule consisting of about fifty small round cells (chiefly lymphocytes with a few plasma cells) was found in the perimysium.

Case 4.—A 66-year-old woman had rheumatoid arthritis for five years. Very extensive lesions were present in the muscle. Three tiny blue foci were visible in the section on naked-eye examination, varying in size from a pin-point to a pin-head. Microscopically, four smaller foci could also be detected. The nodules consisted of small round-cells, chiefly lymphocytes with a few plasma cells, but in one focus plasma cells were the prominent cells. Scanty eosinophils were present in the nodules. The shape of the nodules varied: some were oval, others elongated, and several were fusiform. One nodule was very large and replaced a large area of muscle (Fig. 1). It was situated in the endomysium, and collections of cells straggled out from the main nodule between the adjacent muscle fibres. A few small portions of muscle fibre were isolated in the centre of this large nodule. A second nodule was about half the size of this large nodule, while an oval-shaped third nodule (Fig. 2) was about one-third the size of the large nodule. This latter nodule was closely related to a few small blood vessels (Fig. 2). The remaining smaller nodules each consisting of about 100 cells were present in the endomysium and were perivascular in distribution. The blood vessel was usually situated near the end of the nodule, not in its centre.

Case 5.—A 40-year-old woman had rheumatoid arthritis for five years. Extensive lesions were present but not to quite the same degree as in Case 4. Four of the five nodules present could be identified in the sections with the naked eye. The nodules were situated in the endomysium. Only one of the five nodules was perivascular in distribution; the others were not related to any blood vessels. They were chiefly spindle-shaped (Fig. 3). In one area the cells could be seen surrounding the muscle fibres in transverse section (Fig. 4). The size of the nodules varied. The smallest nodule consisted of about a hundred cells, while the largest contained several hundred. Lymphocytes comprised the vast majority of the cells in each case. The muscle fibres often showed fragmentation at the sites of the muscular infiltration.

Case 6.—A 35-year-old man had rheumatoid arthritis for eight years. One irregularly-shaped perivascular nodule consisting of about seventy-five lymphocytes was present in the perimysium.

Case 7.—A 39-year-old woman had rheumatoid arthritis for six years. Two small nodules, each consisting of about forty-five small round-cells, were situated in the endomysium.

Case 8.—A 57-year-old woman had rheumatoid arthritis for eight years. Six small nodules, each consisting of about forty to sixty small round cells, were present in the endomysium. The nodules were perivascular in three instances.

Case 9.—A 44-year-old man had rheumatoid arthritis for twelve years. Two large triangular perivascular nodules, each consisting of about two hundred cells, were present in the perimysium. The cells were chiefly lymphocytes, but a few plasma cells were also present. An occasional arteriole in other parts of the section showed some slight perivascular infiltration with about ten to fifteen lymphocytes, and scanty round-cell infiltration was present between some muscle fibres.

Case 10.—A 39-year-old man had rheumatoid arthritis for two years. Six small nodules, consisting of thirty to forty small round cells, were distributed perivascularly in the endomysium and in the perimysium.

Case 11.—A 47-year-old woman had rheumatoid arthritis for one year. One perivascular nodule consisting of eighty small round cells and three smaller nodules, each consisting of thirty to forty cells were found.

Case 12.—A 46-year-old man had rheumatoid arthritis for eight years. One paravascular spindle-shaped nodule consisting of about eighty lymphocytes was present in the endomysium.

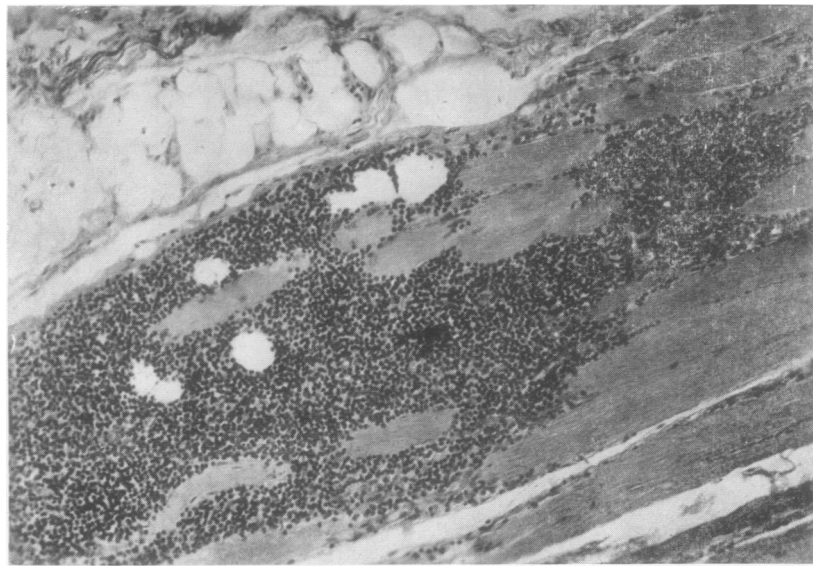

FIG. 1.—Case 4. Very large inflammatory nodule, consisting chiefly of lymphocytes. It is situated in the endomysium, and linear collections of cells extend between adjacent muscle fibres. A large part of the muscle is replaced by the " nodular myositis ". (Haematoxylin and eosin, × 130.)

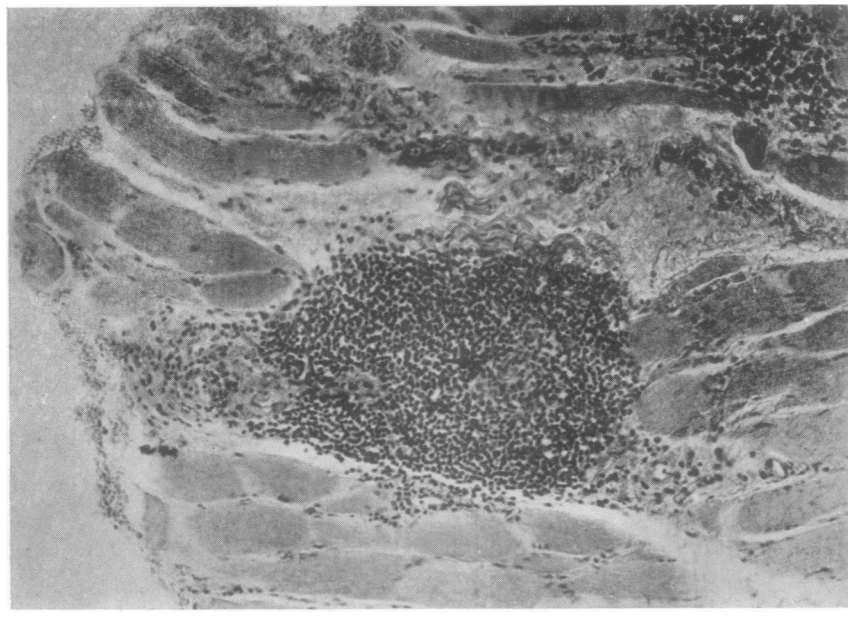

FIG. 2.—Case 4. A large focus consisting of small round cells replaces part of the muscle. Small blood-vessels are present at one edge of the focus. (Haematoxylin and eosin, × 130.)

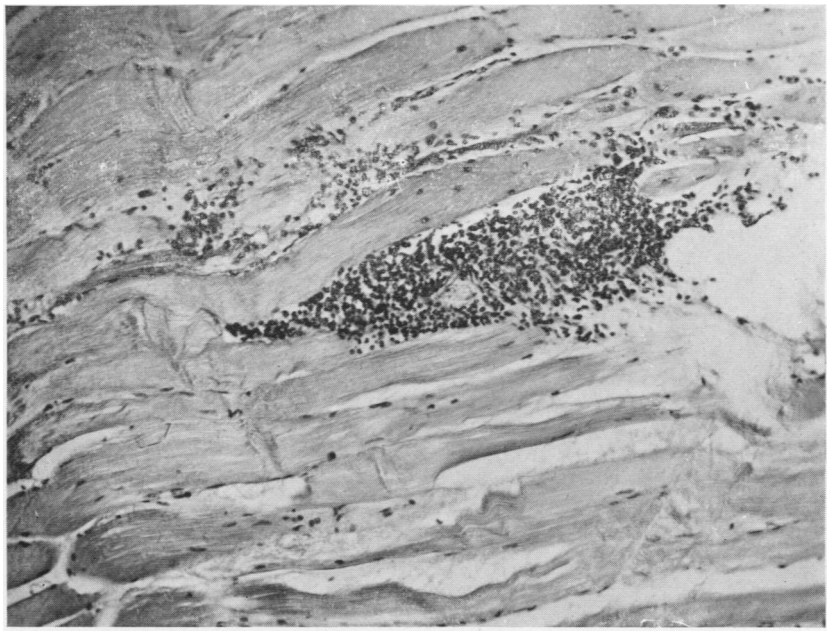

FIG. 3.—Case 5. Spindle-shaped focus of lymphocytes in endomysium. (Haematoxylin and eosin, × 130.)

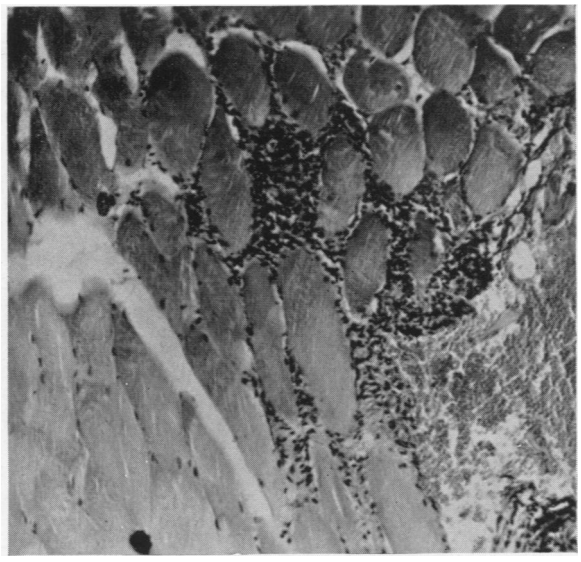

FIG. 4.—Case 5. Collections of lymphocytes seen encircling muscle fibres in transverse section. (Haematoxylin and eosin, × 130.)

Case 13.—A 60-year-old woman had rheumatoid arthritis for one year. A small irregularly-shaped collection of about forty small round cells was seen encircling a muscle fibre.

Case 14.—A 70-year-old woman had rheumatoid arthritis for four years. One small paravascular nodule consisting of about forty-five small round cells was present in the perimysium.

Discussion

The results of the deltoid muscle biopsies were " positive " in approximately 40 per cent. of the thirty-four cases examined. These findings thus confirm the reported incidence of the inflammatory foci and nodules in the muscle in rheumatoid arthritis. The incidence encountered in this series is lower than that noted by most of the investigators, but corresponds closely to the results recorded by Clawson and others (1947) in their forty-four biopsies.

A striking feature was the ease with which the inflammatory nodules could be recognized and identified. They appeared in sharp contrast to the surrounding muscle fibres, and could be easily detected. In two instances (Case 4, Figs. 1 and 2 ; and Case 5), the nodules were sufficiently large to be visible in the stained sections on naked-eye examination.

The nodules varied in size from small foci consisting of approximately thirty small round cells to very large nodules visible macroscopically. Fig. 2 illustrates the appearance of such a very large nodule, whilst Fig. 4 illustrates a smaller collection of cells. The shape of the nodules varied. Some were round, others triangular, others oval, others elongated, and others spindle-shaped. The edges sometimes " tailed off " between adjacent muscle fibres (Fig. 1). The nodules were encountered in the endomysium and in the perimysium. They were often perivascular or paravascular in situation, but some nodules occurred without any obvious relation to a blood vessel.

The cells consisted mainly of lymphocytes, with a variable number of plasma cells and a few eosinophils in some nodules. The muscle fibres at the edges of the larger nodules often showed atrophy and fragmentation. In some nodules muscular remnants could still be recognized. However, there was no close parallelism between the degree of inflammatory change and the degree of muscular atrophy.

There was no close relationship between the finding of " positive " muscle biopsy and the degree of " activity " of the arthritis. Case 9, for example, was clinically " burnt-out ", and had a normal sedimentation rate, yet two large inflammatory nodules were seen in the muscle biopsy sections. There were no clinical differences noted between these cases with " positive " biopsies and those cases with " negative " biopsies.

The conclusion therefore appears to be that one nodule or multiple nodules are commonly found in sections of muscle removed by biopsy in cases of rheumatoid arthritis. The results are all the more striking as only small portions of muscle were removed at biopsy and yet the lesions were readily detected in fourteen of the thirty-four cases examined (40 per cent.). The histological findings in this series of fourteen " positive " biopsies conform to the descriptions of " nodular polymyositis " given by Steiner and others (1946).

However, it must be realized that the results of the reported investigations and of the present investigation have confirmed only one point, that is, the high incidence of " nodular myositis " in cases of rheumatoid arthritis. The other problem, which was immediately presented to Steiner and others (1946) and to other workers, was whether these findings are specific to rheumatoid arthritis or whether they also occur in a variety of conditions. Neurologists, for example, have often described the occurrence of " lymphorrhages " in the muscles of cases of myasthenia gravis (Kinnear Wilson, 1940 ; Russell Brain, 1947), yet this fact appears to have been largely overlooked by various investigators.

Review of the Literature on Control Cases

Steiner and others (1946) examined muscles in a series of controls from 196 routine autopsies. With the exception of one case of dermatomyositis and one case of trichiniasis, they were unable to demonstrate " nodular myositis " in any of these muscles.

Morrison and others (1947) examined a control series of muscles in fifty autopsies ; in a " few cases " of dermatomyositis, disseminated lupus erythematosis, and scleroderma, they found muscle lesions which closely resembled the inflammatory nodules in rheumatoid arthritis, but the rest of the controls were " negative ".

De Forest and others (1947) performed muscle biopsies on ten control cases (excluding the four cases of " non-specific infectious arthritis ", and their one case of osteo-arthritis which " had a history suggestive of rheumatoid arthritis ") and were unable to find any instances of " nodular myositis " in these ten cases.

Desmarais and others (1948), in their series of control muscle biopsies, found characteristic foci of

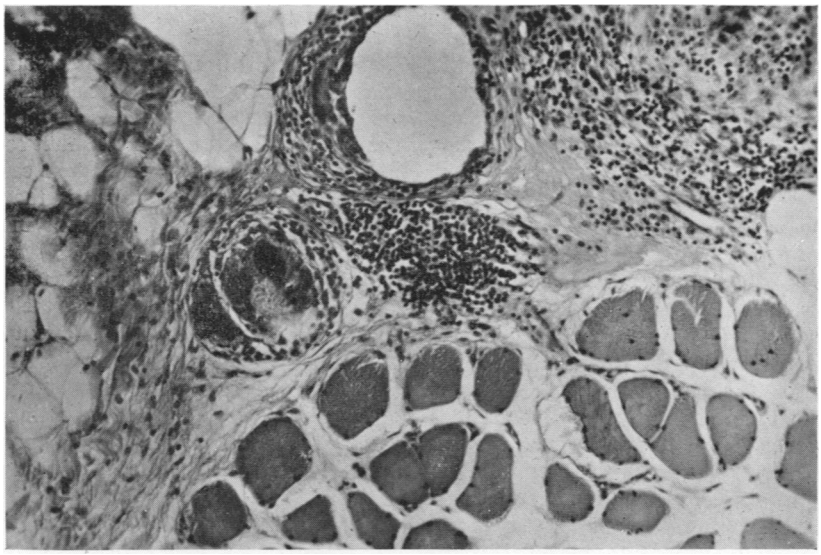

FIG. 5.

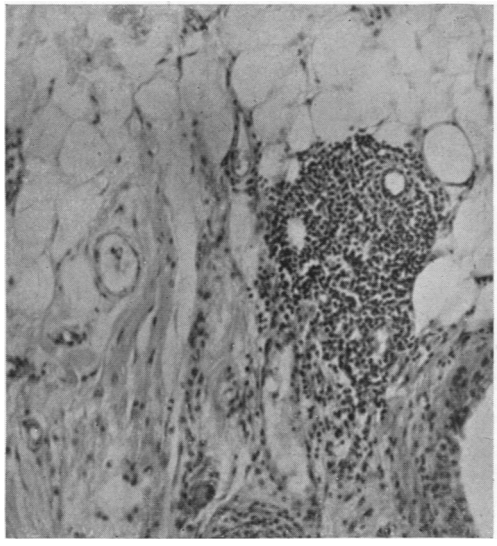

FIG. 6.

FIGS. 5 and 6.—*Gout*. Inflammatory foci, consisting chiefly of lymphocytes, were noted in the sections from a deltoid muscle biopsy in a case of gout. The foci resembled those seen in rheumatoid arthritis, but differed in being accompanied by several " foreign-body " giant cells (as in tophi), and by being situated mainly in the subcutaneous tissue, extending into the epimysium. (Haematoxylin and eosin, × 130.)

" nodular myositis " in one case of Still's disease, but the remainder of their controls were " negative " (including four cases of subacute rheumatic infection with cardiac involvement ; one case of rheumatic fever with rheumatic heart disease ; seventeen cases of ankylosing spondylitis ; six cases of gout ; six cases of osteo-arthritis ; three cases of polio-myelitis ; three cases of specific infective arthritis ; one case of Paget's disease ; one case of prolapsed disc ; and one case of amyotonia congenita). One case of Volkmann's ischaemic contracture showed diffuse round-cell infiltration in the fibrous tissue among the muscle fibres, but the cells were not related to blood vessels as in rheumatoid arthritis. Two cases of reaction to muscle trauma had lesions similar to " nodular myositis ". One case of tuberculous spondylitis had a tiny paravascular focus consisting of about twenty lymphocytes. Thus, with rare exceptions (chiefly in post-traumatic cases) their control series did not reveal lesions of " nodular myositis ", and this finding, in their opinion, emphasized the importance of its high incidence in rheumatoid arthritis.

The finding of muscle lesions in such conditions as dermatomyositis, disseminated lupus erythematosus, and scleroderma, indicated that nodules of inflammatory cells in muscles could not be regarded as quite specific to rheumatoid arthritis. These observations do not greatly detract from the value of muscle biopsy in rheumatoid arthritis, as the diseases mentioned above are comparatively rare, and as there might be some as yet undetermined relationship between them and rheumatoid arthritis.

However, Clawson and others (1947) have reported results which, if correct, are irreconcilable with the findings of all the previous investigators. They collected seven muscles from each of 450 autopsies, and in 118 cases (that is 26 per cent.) inflammatory lesions were observed in one or more muscles and of one or more grades ! They divided their inflammatory lesions into four grades : their grade 4 corresponds with one of the large nodules illustrated by Steiner and others, and their grade 1 resembles a small nodule as illustrated by Steiner and others (1946). They noted these " positive " biopsy results in a wide variety of diseases : acute rheumatic fever, bacterial endocarditis, hypertension, coronary sclerosis, accidents and trauma, " tumors ", cerebral haemorrhage, cirrhosis, " gastro-intestinal conditions ", tuberculosis, poliomyelitis, pneumonia, infections of the bladder and kidneys, etc.

These results, if correct, challenge the validity of the results reported by Steiner and others (1946), Desmarais and others (1948), de Forest and others (1947), and Morrison and others (1947) in their series of control cases.

It is difficult to find a possible source of error in Clawson and others' investigations (1947). They admitted that " rheumatoid arthritis may have been present to some extent without being mentioned in the histories " in some of their cases, but statistically it is very improbable that coincidental rheumatoid arthritis was present in more than a fraction of the cases.

Nor can it be said that the criteria employed by Clawson and others (1947) in their diagnosis of " positives " were very different from those employed by former workers. They specifically stated that they did not regard " the presence of but a few lymphocytes " as indicating a " positive result ". Their illustrations of " positive results " appear similar to those shown by previous investigators. Most of their " positive " results were grouped in grades 1 and 2, but many were grouped in grades 3 and 4, and were thus examples of large nodules. Clawson and others commented that the lesions were found more frequently in cases in which death occurred in the upper decades of life.

Yet in an extensive examination of muscles in " control " cases (including approximately sixty muscle biopsies, and the examination of muscles of approximately 250 cases at autopsy), Steiner and others (1946), de Forest and others (1947), Morrison and others (1947), and Desmarais and others (1948) noted no " positive " results with the exception of the few cases of dermatomyositis, etc., mentioned above.

Bunim and others (1948) also stated that the characteristic muscular nodules were present in many diseases in their control group. The histological appearances and anatomic locations of these nodules were strikingly similar to, and in some cases indistinguishable from, those seen in rheumatoid arthritis. Their control series included not only cases of rheumatic fever, Still's disease, ankylosing spondylitis, lupus erythematosis, and dermatomyositis, but also cases of gout, osteoarthritis, gonococcal arthritis, tuberculous arthritis, and Pott's disease. Bunim and others therefore concluded that if the nodules occurred in a number of unrelated diseases then they could hardly be considered to be specific for rheumatoid arthritis. Bennett (1948) agreed with these conclusions, although his " observations were limited ".

On the other hand, Freund (1948) has repeated his belief that the nodules of " nodular myositis " are specific for rheumatoid arthritis. He agreed that similar nodules may occur in disseminated

lupus erythematosus, in dermatomyositis, in trichiniasis, and in Still's disease, but denied that the nodules occurred in other conditions such as ankylosing spondylitis, gout, osteo-arthritis, and gonococcal arthritis.

How are these diverse results to be reconciled? It is possible that Clawson and others (1947) detected the high incidence of muscle lesions in numerous diseases on account of their extensive examinations on seven muscles at each of the 450 autopsies, whereas the other observers have examined only smaller pieces of muscle removed by biopsy or at autopsy. Nevertheless, if Clawson and others (1947) and Bunim and others (1948) are correct in their observations, then these observations constitute a very serious obstacle to the claims that these inflammatory nodular foci found in muscle in cases of rheumatoid arthritis are in any way diagnostic of the disease.

Results of Muscle Examination in Twenty Control Cases

Muscle biopsies were performed in twelve control cases. The muscle was obtained from the deltoid in nine cases (consisting of two cases of acute rheumatic fever, one case of osteo-arthritis, one case of "fibrositis", one case of generalized scleroderma, one case of acute diffuse glomerulonephritis, two cases of gout, and one case of acute poly-arthritis of unknown aetiology); from the pectoral muscle of a case of hypertension; and from the sacrospinalis and gastrocnemius muscles respectively in two cases of polyarteritis nodosa.

In addition, muscle was examined at autopsy in eight cases. The gastrocnemius was examined in a case of acute porphyria, and the deltoid was examined in the other seven cases (consisting of two cases of miliary tuberculosis; one case of generalized peritonitis; one case of myocardial infarction; and three cases of death due to violence).

Although the series of control cases is admittedly small, it is interesting that (with three exceptions) no muscle lesions were encountered in the twelve muscles examined by biopsy and in the eight muscles examined at autopsy.

Of the three cases with muscular lesions, two were cases of polyarteritis nodosa in which the expected characteristic vascular lesions were found (Selzer and Horwitz, 1949). They were distinguishable from the lesions of "nodular myositis" in the rheumatoid arthritis series.

The third case with muscular lesions had gout (the diagnosis had been proved by demonstrating the presence of sodium biurate crystals in a tophus removed from the elbow (Horwitz, 1949)). The deltoid muscle biopsy was performed while the patient was suffering from an attack of gout in the knees and ankles. The histological appearances were interesting (Figs. 5 and 6), and have not been noted hitherto in examinations of muscle biopsies. Inflammatory foci were present which closely resembled those seen in rheumatoid arthritis, but it was at once possible to differentiate sections from those of the rheumatoid arthritis series by means of two features: (1) Numerous foreign-body giant cells were present in, or at the edge of, several of the inflammatory foci (Fig. 5). The lesions thus seemed to resemble those seen in tophi and were presumably a tissue reaction to the local deposition of biurate crystals. (2) The majority of the inflammatory foci were situated in the connective tissue on the surface of the deltoid muscle (Fig. 6), extending into the epimysium and sometimes into the perimysium. The situation of the inflammatory foci was thus primarily in the subcutaneous tissue, and the extension into the muscle appeared to be secondary. A deltoid muscle biopsy was performed on a second case of gout, but no lesions were found in the connective tissue or in the muscle. The "positive" result in the first case of gout is interesting as it probably indicates a deposition (in the past attacks or in the present attack of gout) of sodium biurate in the deep subcutaneous tissue, and in the intramuscular connective tissue. It is well known that tophi may occur, not only in joints, cartilage, bursae, and tendons, but also in subcutaneous tissue, and the histological appearances in this case probably represent "a microscopic tophus". (No tophi were present over the shoulders on clinical examination before the muscle biopsy was performed).

Summary

1. In a series of muscle biopsies performed in thirty-four cases of rheumatoid arthritis, nodules were found in the endomysium or in the perimysium in fourteen cases. The histological appearances closely resembled the descriptions of "nodular myositis" in the literature. The findings confirmed the fairly high incidence of these muscle lesions in rheumatoid arthritis.

2. The lesions were noted in "active" and in "burnt-out" cases.

3. The nodules were detected with great facility on histological examination. In some cases they were sufficiently large to be visible to the naked eye.

4. In an examination of the muscles of a small control series of twenty cases, by biopsy or at autopsy, similar inflammatory nodules were found in only one case—a case of gout. Certain additional features rendered the differentiation possible from

the " nodular myositis " seen in rheumatoid arthritis. Two cases of polyarteritis nodosa showed the characteristic vascular lesions of that disease.

Muscle examinations in two cases of polyarteritis nodosa showed the characteristic vascular lesions encountered in the disease.

5. In reviewing the literature it was noted that some investigators have reported the occurrence of " nodular myositis " in a miscellaneous collection of diseases. If their findings are confirmed, it would indicate that " nodular myositis " is a comparatively common condition in a wide variety of diseases and that it is of no diagnostic value in cases of rheumatoid arthritis.

The number of control cases in this series was too small to enable final conclusions to be drawn, but the results were more in conformity with the " negative " findings noted by most investigators in the examination of muscle in control cases.

I am greatly indebted to Prof. F. Forman, Dr. P. W. J. Keet, and the Hon. Physicians of the Groote Schuur Hospital, Cape Town, for permission to investigate the cases under their care ; to Prof. B. J. Ryrie and Prof. M. van den Ende for assistance and facilities afforded in the Department of Pathology, University of Cape Town ; to Dr. G. Selzer for valuable assistance in the histological examinations ; to Mr. W. Taylor for the histological preparations ; and to Mr. G. C. McManus for the microphotography. A grant from the Staff Research Fund, University of Cape Town, is gratefully acknowledged.

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Lésions Musculaires dans la Polyarthrite Chronique Inflammatoire

Résumé

1. Une série de biopsies musculaires pratiquées dans trente-quatre cas de polyarthrite chronique inflammatoire, a montré, dans quatorze cas, des nodules dans l'endomysium et le perimysium. L'aspect histologique ressemblait beaucoup à ce qu'on décrit sous le nom de " myosite nodulaire " dans la littérature. Les constatations confirmèrent l'assez grande fréquence de ces lésions musculaires dans la polyarthrite chronique inflammatoire.

2. On remarqua ces lésions dans des cas qui étaient en phase évolutive ou en phase de " calme ".

3. Les nodules furent découverts très facilement à l'examen histologique. Dans certains cas, ils étaient assez importants pour être vus à l'oeil nu.

4. Pour une série de vingt " cas témoins " (2 rhumatismes articulaires aigus, 1 ostéoarthrite, 1 cellulite, 1 sclérodermie, 1 glomérulo-néphrite aigüe, 2 gouttes, 1 polyarthrite d'étiologie inconnue, 1 hypertension, 2 périartérites noueuses, 1 porphyrinurie aigüe, 2 tuberculoses miliaires, 1 péritonite généralisée, 1 infarctus du myocarde, 3 cas de mort violente), l'examen des muscles, par biopsie ou à l'autopsie, ne révéla la présence de semblables nodules inflammatoires que dans un seul cas, un cas de goutte. Certaines différences d'aspect permirent le diagnostic avec la " myosite nodulaire " caractéristique de la polyarthrite chronique inflammatoire.

L'examen musculaire de deux cas de périartérite noueuse mirent en évidence les lésions vasculaires caractéristiques rencontrées dans cette maladie.

5. On remarque dans la littérature que certains auteurs ont signalé la présence de " myosite nodulaire " dans une série de maladies diverses. Si leurs constatations sont confirmées, cela semblerait prouver que la " myosite nodulaire " est rencontrée assez communément dans une grande variété de maladies et qu'elle n'a pas de valeur diagnostique dans les cas de polyarthrite chronique inflammatoire.

Dans cette série le nombre des " cas témoins " fut trop faible pour permettre d'en tirer des conclusions définitives, mais les résultats semblent plutôt confirmer l'opinion de la plupart des auteurs à savoir l'absence habituelle des nodules typiques de la polyarthrite chronique inflammatoire en dehors de cette maladie.