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Mycobacterium leprae in the Striated Muscle of Patients with Leprosy*

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Biopsies of striated muscle from leprosy patients showed the presence of *Myco. leprae* in 16 out of 20 biopsies from lepromatous cases, 3 out of 4 borderline, and 5 out of 9 tuberculoid cases; in most cases the bacilli lay chiefly within muscle fibres. Bacillary counts performed on homogenates of 22 skin and muscle biopsies (13 lepromatous, 3 borderline and 6 tuberculoid) showed that the concentration of bacilli in lepromatous cases was from 100 to 1000 times greater in skin than in muscle, but that in this group of treated patients a higher proportion of muscle bacilli were solid staining. In tuberculoid leprosy the total number of bacilli may be greater in muscle than in skin. Muscle involvement in human leprosy may precede the appearance of skin lesions and could also play a significant part in the development of relapse and drug resistance.

INTRODUCTION

When mouse footpads are inoculated with *Mycobacterium leprae* (Shepard, 1960; Rees, 1964), the bacilli are placed in the hypodermis close to the intrinsic muscles; they are not injected into the muscles or into the dermis of the skin. Nevertheless, they enter muscle fibres remarkably quickly, being found within them after as short a time as one hour, but they are not found in the dermal nerves until 12 to 14 months later (Weddell *et al.*, 1970).

During the early months of active bacterial multiplication which follow such inoculations, there is local spread of *Myco. leprae* from muscle to muscle in the footpad. This probably takes place *via* blood vessels, for bacilli are also found in the endothelial cells of intramuscular blood capillaries. However, at this stage by far the greatest number of bacilli is found within muscle fibres, and there is little cellular response to their presence (Palmer *et al.*, 1965). Other mycobacteria, including *Myco. "Charbotier"*, *Myco. "Chatterjee"*, *Myco. lepraemurium*, *Myco. marianum*, *Myco. tuberculosis*, *Myco. ulcerans* and BCG, do not behave in this way when tested under the same experimental conditions (Rees and Weddell, 1968).

By contrast, striated muscle involvement in patients with leprosy has been recorded only on very few occasions (Ishihara, 1959; Convit *et al.*, 1960), and then as lepromatous infiltration between muscle fibres rather than bacilli within muscle cells. However, the observations in mice summarized in the foregoing paragraph have stimulated the investigation of both smooth and striated muscle as possible sites of election for bacillary multiplication in man. It is well known that the arrectores pilorum muscles often contain bacilli when the latter are scanty or absent elsewhere in hairy skins, and Harman (1968) has shown that bacilli are also present in other skin sites containing abundant smooth muscle, e.g. the foreskin, the dartos muscle, and the nipple. Moreover, he noted that in many cases a higher proportion of bacilli were solid-

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staining within these muscle fibres than in the surrounding tissues, which suggested that smooth muscle was, to some extent, at least, a protected zone where bacilli could either survive or multiply more readily than elsewhere.

Job *et al.* (1969), also stimulated by the findings in mice inoculated with *Myco. leprae*, examined a series of biopsies of human striated muscle from 6 patients with lepromatous leprosy and reported the presence of bacilli within the muscle fibres of all of them.

The consistency with which striated muscle is found to be a site of predilection and multiplication for *Myco. leprae* in both normal and immunologically handicapped mice (Rees and Weddell, 1970), together with the observations of Harman (1968) and Job *et al.* (1969) in man, led us to predict that *Myco. leprae* might well be safe from cell-mediated immunological attacks provided they remained confined within muscle fibres and did not multiply sufficiently to destroy their host cells. If this hypothesis is correct, then we might expect to find bacilli in striated muscle not only in patients with lepromatous leprosy, but also in patients with other forms of the disease. To test this we undertook a comparative histological and bacteriological study of biopsies from striated muscle in treated and untreated patients with all types of leprosy, from lepromatous through borderline to tuberculoid. The results of this investigation are reported below.

MATERIALS AND METHODS

Biopsies were taken from Malay, Chinese, Indian and Gurkha patients. They were processed for examination as follows.

(1) Biopsies from 22 patients were fixed and processed for histological examination only. (2) Biopsies from 11 patients were subdivided. A small segment from each was fixed and processed for histological examination and the remainder was homogenized and used for bacterial counts. (3) Biopsies from 9 patients were homogenized and used for bacterial counts only.

TABLE 1

Type of leprosy, treatment and reactional status of patients studied

*Type of disease**	*Untreated*		*Treated*		*Total*
		ENL	*DDS resistant*	*ENL+ DDS resistant*	
Lepromatous (BL; LI; LL)	8	10	4	3	19
Borderline (BB)	4	–	–	–	1
Tuberculoid (BT; BT/TT)	10	–	–	–	1

*Classification according to Ridley & Jopling (1966); Ridley and Waters (1969).

The form of the disease from which the patients were suffering is set out in Table 1. Briefly, there were 8 untreated cases of lepromatous, 4 of borderline, and 10 of tuberculoid leprosy. Of the treated cases, 19 were lepromatous and of these, 10 had erythema nodosum leprosum (ENL).

The use of proportionately larger numbers of biopsies from patients with treated lepromatous leprosy with and without ENL, including patients who had developed sulphone-resistant infections, was deliberate because we thought that such patients might be particularly liable to harbour bacilli in their muscles despite anti-leprosy treatment.

The biopsies used only for histological examination were taken in the following way. A routine diagnostic skin biopsy was removed under local anaesthesia (2% procaine). Next, using a clean set of instruments, the incision was deepened to reach the underlying muscle and a discoid fragment about 0.5 cm in diameter was cleanly removed with fine scissors. The excised skin and muscle were fixed for immersion in buffered 10% formaldehyde solution (Richardson, 1960).

The material for bacillary counts was taken in the same way, but the amount removed was larger. The biopsies were placed on wet ice in a vacuum flask and despatched by air to the National Institute for Medical Research, London, where they were weighed, homogenized,

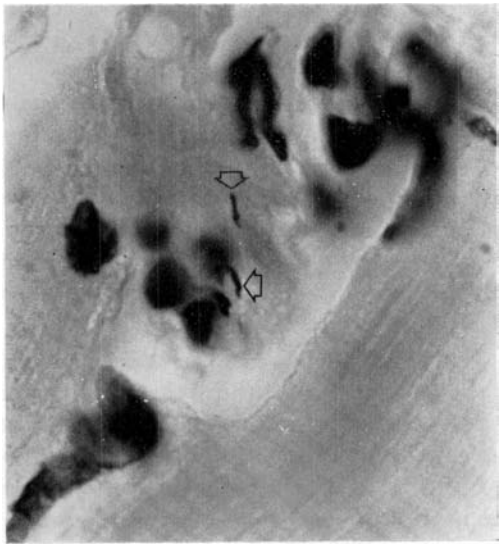

FIG. 1

Acid-fast bacilli in striated muscle (arrows). They lie close to an intramuscular capillary and are solidly stained; muscle fibres containing bacilli tend to be friable and this is no exception.

FIG. 2

Acid-fast bacillus in a muscle fibre in transverse section.

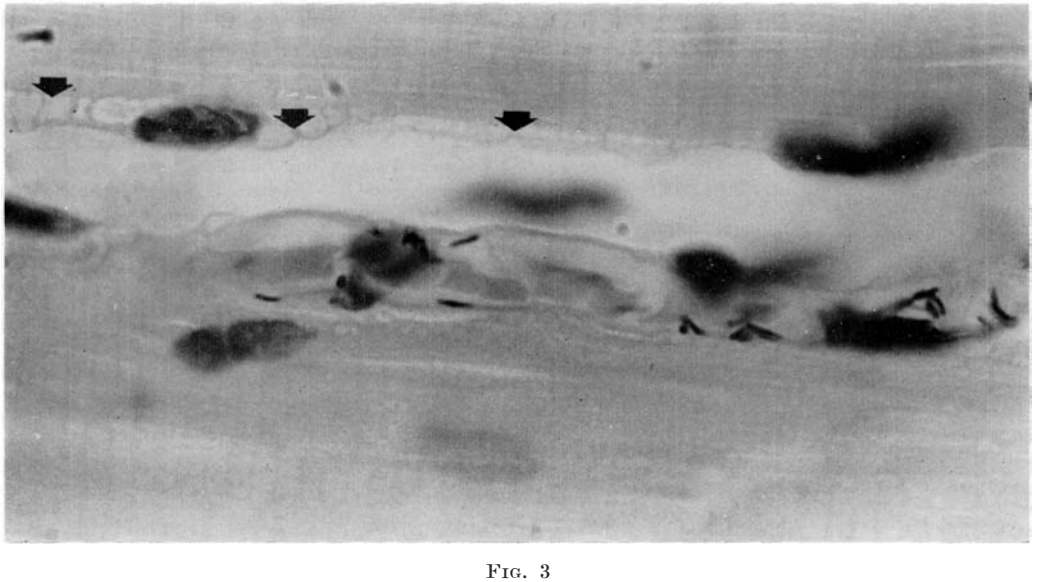

FIG. 3

Bacilli, chiefly in the endothelial cells of an intramuscular capillary. Note lipofuchsin granules at points of arrows.

and bacillary counts performed on the skin and muscle fractions separately by the method used for mouse footpad tissue (Rees, 1964). In order to increase the sensitivity of the technique, however, these tissues were homogenized in minimal volumes of fluid, not more than 2 ml being used for the skin and only 1 ml for the muscle. As a result, counts of as little as 3.4×10^3 bacilli per g tissue homogenate could be detected.

The muscle biopsies came from the triceps brachii or quadriceps femoris muscles in all but 3 cases; in these 3 they came from the deltoid, platysma, and frontalis muscles respectively.

In 3 cases, outside this series, we obtained biopsies from muscles in patients with lepromatous leprosy undergoing surgical operations. Two came from the internal oblique muscle during hernia repairs and one from the peroneus longus muscle during an orthopaedic operation. All these specimens were processed for examination by light microscopy as described above.

RESULTS

Histological observations

1. *Muscle.* A total of 33 muscle biopsies were taken from 32 patients (see Table 2). One patient suffering from ENL was biopsied twice, the biopsies being a year apart. Acid-fast bacilli were found in 11 out of 12 biopsies from patients with lepromatous leprosy, but not in reaction, and in 5 out of the 8 biopsies from patients with ENL. They were also found in 3 untreated cases with borderline leprosy, but not in the treated case, and finally in 5 of the 8 patients with tuberculoid leprosy, but none in the patient who had had treatment. Bacilli were, therefore, found in 24 of the 33 biopsies taken.

Bacilli were found within muscle fibres in 20 of the 24 biopsies in which they were present (Figs 1 and 2). In 4 of these 20 cases bacilli were also found in the endothelial cells lining blood vessels (Fig. 3), in macrophages scattered along the neurovascular bundles between groups of muscle fibres and extracellularly between muscle fibres. In 4 biopsies only were no bacilli found lying within muscle fibres; in one of these they were lying extracellularly in connective tissue, in 2 others in endothelial cells of muscle capillaries (Fig. 4) and in the remaining case large numbers of bacilli were seen in the Schwann and perineurial cells of an intramuscular nerve bundle as well as in macrophages and an endothelial cell of a muscle capillary.

TABLE 2
Summary of histological findings in all muscle biopsies

*Type of disease**	*No. of biopsies*		*Tissues in which acid-fast bacilli were found*				
	Total	*With AFB†*	*Muscle fibres*	*Blood vessel wall*	*Nerves*	*Macrophages in NVB‡*	*Extra cellular*
Lepromatous							
(a) Untreated	6	5	5	1	0	5	1
(b) Treated	4	4	3	2	0	0	0
(c) ENL	7	4	3	1	1	1	0
(d) DDS resistant No ENL	2	2	2	0	0	0	0
(e) DDS resistant ENL	1	1	0	1	0	0	0
Borderline							
Untreated	3	3	2	1	0	0	1
Treated	1	0	0	0	0	0	0
Tuberculoid							
Untreated BT	5	3	3	0	0	0	2
Untreated BT/TT	3	2	2	0	0	0	0
Treated BT		0	0	0	0	0	0

*Classification according to Ridley & Jopling (1966); Ridley and Waters (1969).
†Acid-fast bacilli.
‡Neuro-vascular bundles.

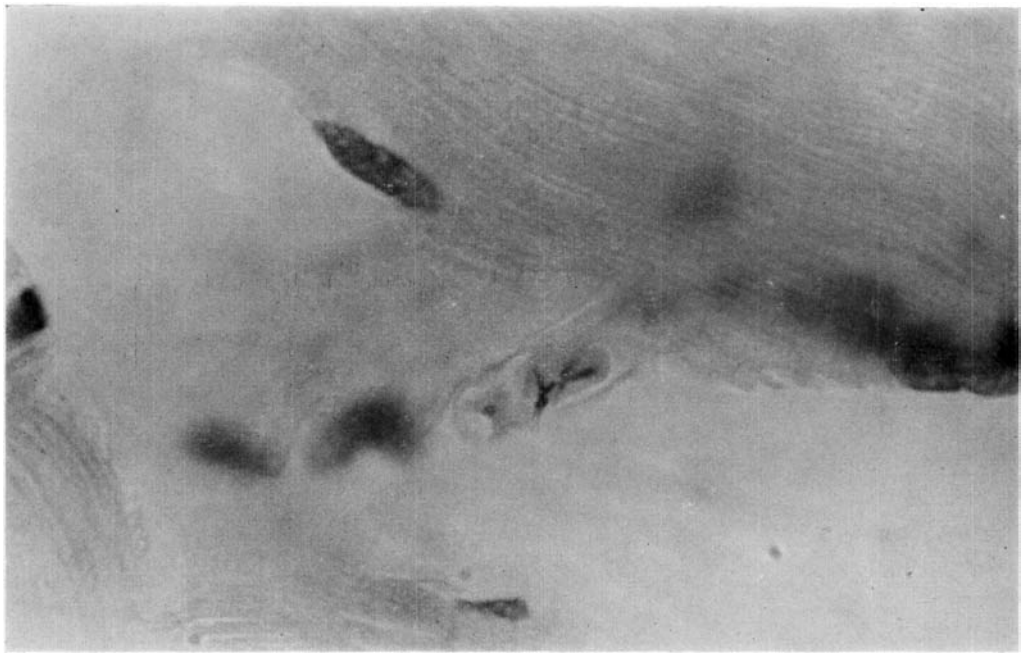

FIG. 4

Solidly stained bacilli in the endothelial lining of a blood capillary. The capillary has been torn from the muscle fibre and the bacilli are lying close to a segment of muscle which has come away with the capillary. The nuclei of the capillary lining cells are more darkly stained than the muscle fragment.

In all patients with either tuberculoid or borderline leprosy the intramuscular bacilli lay singly, and there were no inflammatory cells near the muscle fibres in which they were situated. This was not always so in biopsies from cases of lepromatous leprosy. Indeed, in one patient there were zones in which muscle fibres had been replaced by foam cells (Fig. 5), and in half the specimens there were well-defined areas where the muscle fibres had been so severely damaged that they were difficult to identify without examining the tissue under phase-contrast conditions. Macrophages were sometimes present in these zones, and in 2 cases bacilli were present in these sites in higher concentration than elsewhere in the specimen and were present in micro-colonies as well as singly (Fig. 6). There were never many acid-fast bacilli in these muscle biopsies; in 10 of the 24 positive specimens, for example, only one such bacillus was found after several hours of searching, but in very few of our cases were inflammatory cells present.

In undamaged muscle fibres in 17 out of 20 biopsies from patients with lepromatous leprosy, in one out of 4 biopsies from patients with borderline leprosy, and in 9 out of the 11 biopsies from patients with tuberculoid leprosy there were variable numbers of weakly stained acid-fast granules (lipofuchsin). They sometimes resembled irregularly stained bacilli and some may have originated from them. However, the majority of the granules were paler, more globular and quite unlike fragmented bacilli seen in other tissues. The granules lay just beneath the sarcolemma and mostly close to nuclei, which were often irregular in outline and less basophilic than their neighbours (see Fig. 3). In all such cases there were zones in which muscle fibres contained nuclei which were aggregated into clumps or strung together in chains (Fig. 7). There was no evidence of in-

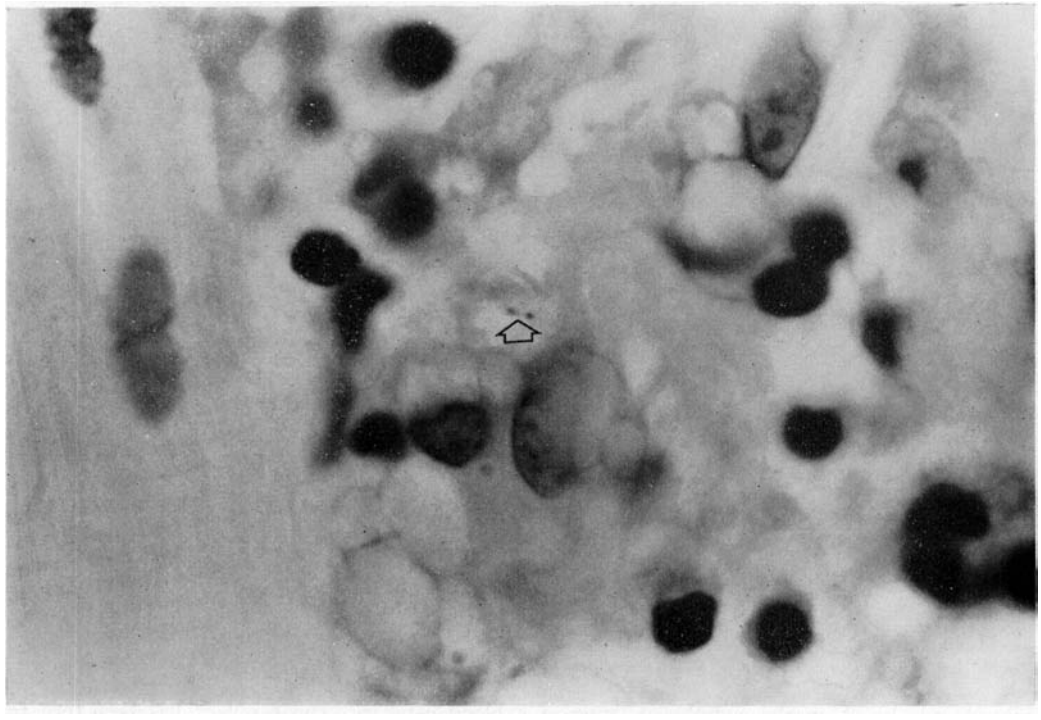

FIG. 5

Foam cells in a neurovascular bundle between muscle fibres. Note the lymphocytes and the characteristic dumb-bell appearance of the irregularly stained bacillus (arrows). Bacilli close to lymphocytes commonly assume this form (Rees and Weddell, 1968).

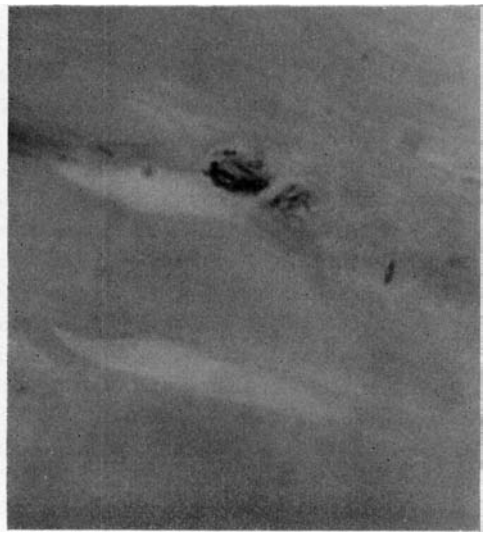

FIG. 6

Microcolony of solidly stained bacilli in a muscle fibre. Note the absence of inflammatory cells.

flammation surrounding any of the muscle biopsies in our series.

2. *Muscle biopsies from patients taken during surgical operations.* These all came from patients with lepromatous leprosy receiving antileprosy treatment, none of whom had any clinical signs of muscle involvement. In the 2 biopsies which were taken from internal oblique muscles of the abdomen the findings were comparable with those in our series from the quadriceps femoris and triceps brachii muscles. There were single isolated solid-staining bacilli in muscle fibres and in one of the cases there were micro-colonies of bacilli. However, in neither case was there any inflammatory cells present among the muscle fibres. The biopsy from the peroneus longus muscle of the leg, however, was full of bacilli. In focal zones around blood vessels there was a great deal of muscle destruction (Fig. 8). Fibres had been completely or partially des-

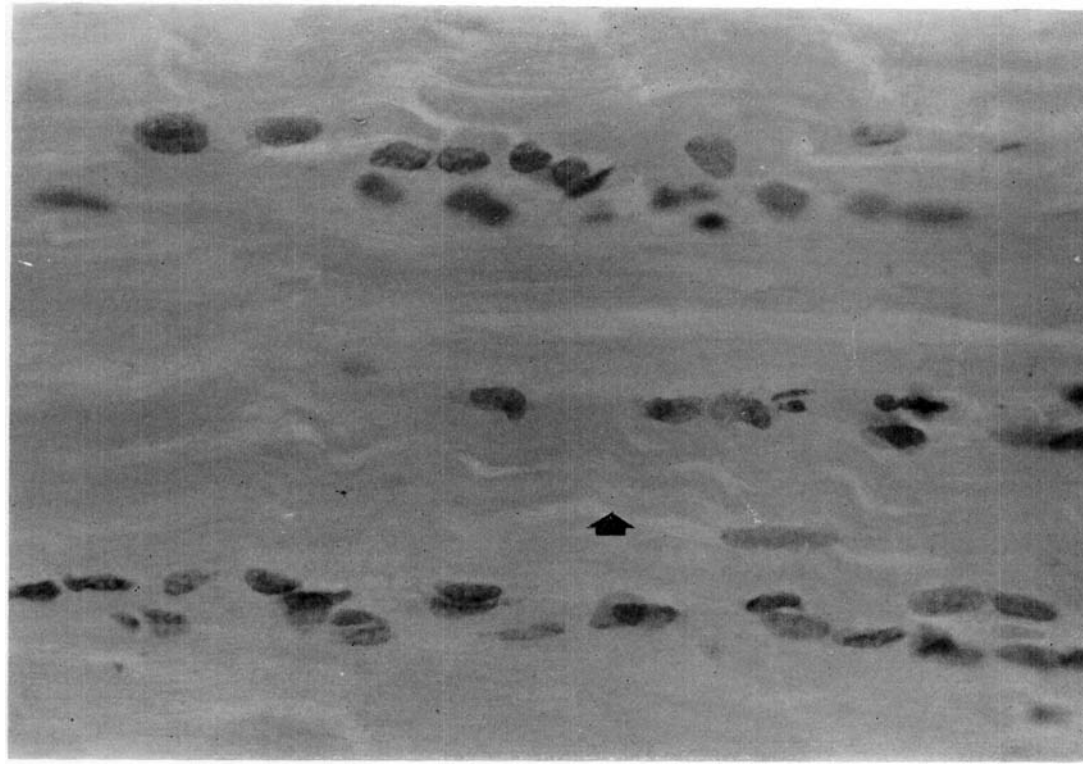

FIG. 7
Bunched nuclei in muscle fibres lying between bundles of collagen fibres which have a characteristic wavy appearance (arrow). They have undoubtedly replaced destroyed muscle fibres.

TABLE 3
Presence of acid-fast bacilli; comparison of skin and muscle histology

Type of leprosy	*Presence of acid-fast bacilli*			
	Muscle		*Skin*	
	Positive	*Negative*	*Positive*	*Negative*
Lepromatous				
(BL; LI; LL)	10	3	10	3
ENL	4	2	4	2
No ENL	6	1	6	1
Borderline				
(BB)	3	0	2	1
Tuberculoid				
(BT; BT/TT)	5	0	2	3

*Classification according to Ridley and Jopling (1966) and Ridley and Waters (1969).

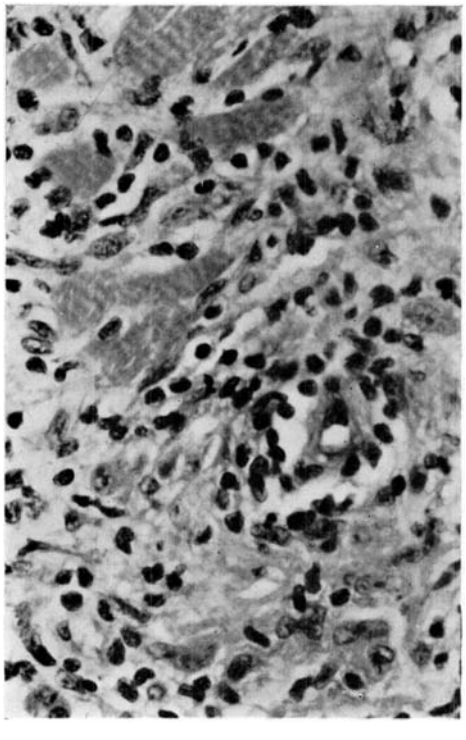

FIG. 8
Muscle fibre destruction around a blood vessel "cuffed" with lymphocytes

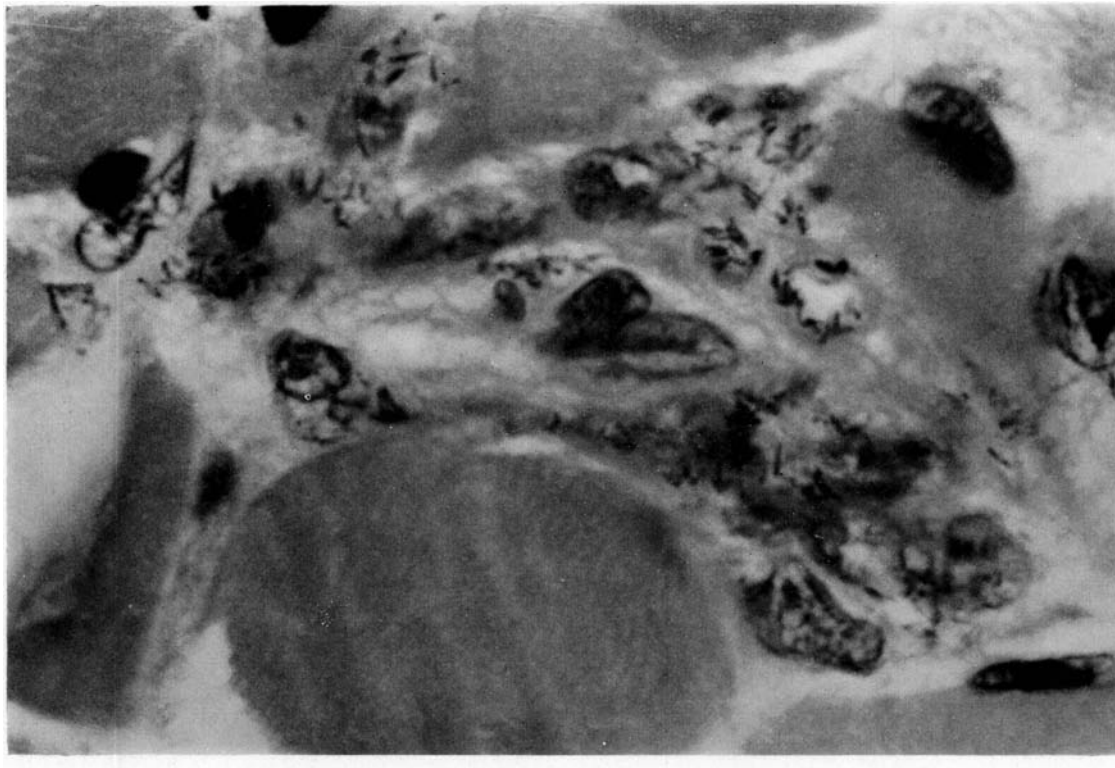

FIG. 9

Muscle fibres undergoing exhaustion and destruction due to the number of bacilli they are nourishing. Note the absence of inflammatory cells. The nuclei seen have all the characteristics of muscle cell nuclei and the bacilli are all solidly stained. A neighbouring muscle cell is quite unaffected.

troyed, a number of macrophages containing irregularly stained bacilli and lymphocytes were present, but most of the bacilli in the muscle remnants were solidly stained. In other regions of the section there were muscle bundles entirely free from infection and it was noteworthy that some muscle fibres in the badly affected zones were also free from infection and looked entirely normal (Fig. 9).

3. *Skin.* When taking muscle biopsies through skin incisions care was taken to see whether, macroscopically, there had been any evidence of spread of the infection from the hypodermis into the deep fascia covering the muscle. In no case from which we took biopsies was there any evidence of such spread.

The skin biopsies were examined histologically and in all cases confirmed the clinical diagnosis. They were next compared with the muscle biopsies, section by section, particularly in respect of the presence or absence of bacilli; the results are set out in Table 3. In some of our cases only muscle biopsies were taken for histological examination, so that this comparison is available for only a limited number of cases. However, as far as they go it is clear that among the cases with lepromatous leprosy, there is a close parallel between skin and muscle with respect to the presence of bacilli. In borderline leprosy, bacilli were found in muscle in 3 cases, but in one of these there was none in the skin. However, the most striking observation is the presence of solid-staining bacilli in muscle in so many cases of tuberculoid leprosy and their relative rarity in the skin of these same patients.

Clearly, histology is not the method of choice

to settle a quantitative issue of this kind. Because of this it was decided to make direct bacterial counts from tissue homogenates and in particular to try to express the results in terms of morphological indices.

4. *Bacilli in skin and muscle homogenates.* Twenty-two combined skin and muscle biopsies were taken from 18 patients for homogenization. Bacilli were found in 15 of the muscle biopsies and in 19 of the skin biopsies. Moreover, as can be seen in Table 4, they were found in muscle

TABLE 4

Presence of acid-fast bacilli in homogenates of skin and muscle biopsies from 18 patients

*Type of leprosy**	*No. of patients*	*No. of biopsies*	*No. of biopsy-homogenates with acid-fast bacilli*	
			Muscle	*Skin*
Lepromatous (LL; LI; BL)	10	13	11	13
Borderline (BB)	3	3	2	3
Tuberculoid (BT; BT/TT)	5	6	2	3

*Classification is according to Ridley and Jopling (1966) and Ridley and Waters (1969).

from patients with borderline and tuberculoid as well as lepromatous leprosy. In Tables 5 and 6 we have set out our observations in greater detail. This was necessary to guard against the possibility that the bacilli found in the muscle homogenates were merely contaminants from the skin. We can be certain that the majority were not, firstly because of our histological findings in the cases from which small segments were available for this purpose; and secondly, though the evidence in the other cases is indirect it is persuasive. It rests on the fact that the morphological indices in muscle and in skin are in sharp contrast and this would be most unlikely if the muscle bacilli had been contaminants from the skin.

Figures for the bacillary counts in the patients with lepromatous leprosy are shown in Table 5. There were 100 to 1000 times more bacilli in skin than in muscle, but there was a higher proportion of solid-staining organisms in the muscle, particularly in patients who were suffering from ENL. The figures for patients with borderline and tuberculoid leprosy are shown in Table 6. The counts were considerably lower, but the same trend is evident.

DISCUSSION

The mouse has been shown to provide a very accurate model for studying the pathogenesis of human leprosy (Rees and Weddell, 1968; Rees and Weddell, 1970). There was one noticeable difference, however—in mice the bacillation and subsequent infection of striated muscle fibres was a prominent feature, whereas this is not thought to be the case in man. The present comparative studies were undertaken because of the overwhelming evidence that striated muscle was an important site of multiplication of *Myco. leprae* in experimental leprosy. Thus, when muscle biopsies from patients with lepromatous leprosy were found to contain acid-fast bacilli, a series of patients with the full spectrum of leprosy was investigated. It is now clear that, in this respect also, the mouse provides a model for the disease in man, and that muscle infection plays a part in the pathogenesis of human leprosy.

All the muscle biopsies were taken through a skin lesion, but the dermal granuloma never extended through the deep fascia. Moreover, the different venous drainage of skin and of muscle makes it impossible for bacilli to pass directly from one to the other. Thus the presence of acid-fast bacilli in both skin and muscle is clear indication of systemic spread. Similarly, although the muscle biopsies were taken from zones of muscle immediately beneath skin lesions this does not mean that these sites are the only ones likely to harbour bacilli.

Some interesting and important points emerge from these studies:

(1) In most lepromatous cases, the concentration of bacilli in muscle was 100- to 1000-fold less than in skin; but the proportion of solid-staining organisms was often 10 or more times greater. This trend was particularly striking in

TABLE 5

Number of acid-fast bacilli (AFB) in homogenates of muscle and skin from 10 previously treated patients with lepromatous leprosy

Case No.	*Treatment*		*Clinical status*	*Muscle*		*Skin*		*Site of bacilli histologically in muscle*
	Drug	*Duration (year)*		*AFB/g tissue*	*Solid staining AFB (%)*	*AFB/g tissue*	*Solid staining AFB (%)*	
(A) (*Histology incl.*)								
9055	DDS	21	DDS resistant; ENL	1.6×10^{6}	18	$1.0\%10^{8}$	2	Nerves; blood vessel walls.
16004	DDS	1.5	ENL	1.8×10^{6}	28	1.3×10^{9}	2	Muscle, neurovascular bundles.
16004 2nd biopsy	DDS	2.5	ENL	Nil	—	2.4×10^{6}	2	None seen.
16030	DDS	2.5	ENL	6.6×10^{4}	2/5 (40)	1.8×10^{6}	1	Muscle.
16107	DDS	0.75	No ENL	1.6×10^{5}	1/9 (11)	5.2×10^{7}	0	Muscle.
16147	DDS	16	DDS resistant	1.3×10^{6}	32	1.3×10^{9}	13	Muscle, blood vessel walls.
(B) (*No Histology*)								
9302	—	Nil for 7 yrs	No ENL	1.2×10^{5}	2/4 (50)	8.1×10^{7}	25	
10607	DDS	18	ENL; DDS resistant	Nil	—	1.8×10^{8}	1	
10835	DDS	17	DDS resistant	5.4×10^{4}	2/8 (25)	9.5×10^{8}	4	
16011	DDS	1.5	ENL	2.1×10^{4}	0/2 (0)	1.7×10^{7}	1	
16217	DDS	10	DDS resistant	4.6×10^{5}	5/17 (30)	1.0×10^{8}	12	
9055 2nd biopsy	DDS	22	DDS resistant	7.1×10^{5}	19	5.4×10^{7}	5	
16147 2nd biopsy	B 663	16.5	DDS resistant	1.1×10^{5}	2/5 (40)	2.1×10^{10}	0	

TABLE 6

Number of acid-fast bacilli (AFB) in homogenates of muscle and skin from 8 previously untreated patients with borderline and tuberculoid leprosy

Case No.	*Type of leprosy**	*Muscle*		*Skin*		*Site of bacilli histologically in muscle*
		AFB/g tissue	*Solid staining AFB (%)*	*AFB/g tissue*	*Solid staining AFB (%)*	
(A) (*Histology incl.*)						
16159†	BT/TT	2×10^{5}	3/4 (75)	0 ($<3.6\times10^{5}$)	—	None seen.
16162	BB	0 ($<7.7\times10^{3}$)	—	4.0×10^{5}	1/17 (6)	Muscle; loose connective tissue.
16164	BT/TT	0 ($<10^{4}$)	—	0 ($<10^{4}$)	—	Muscle.
16173	BT	0 ($<1.7\times10^{5}$)	—	2.1×10^{5}	1/2 (50)	Muscle.
16175	BB	8.9×10^{4}	1/3 (33)	3.0×10^{7}	0	Blood vessel wall.
16253	BT/TT	8.4×10^{3}	2/4 (50)	0 ($<1.4\times10^{4}$)	—	Loose connective tissue.
(B) (*No Histology*)						
16155	BT	0 ($<10^{4}$)	—	1.2×10^{6}	0/13 (0)	
16163	BB	1.5×10^{4}	0/3 (0)	9.9×10^{7}	6	
16173‡ 2nd biopsy	BT	0 ($<1.7\times10^{5}$)	—	2.1×10^{5}	1/2 (50)	

*Classification is according to Ridley and Jopling (1966) and Ridley and Waters (1969).

†This biopsy was made after 3 weeks' treatment with DDS.

‡Repeat biopsies of muscle after 3 and 4 months' treatment with DDS both gave negative counts.

patients who had received previous treatment, and makes it clear that the muscle bacilli were not contaminants from the skin. This ob-observation suggests that bacilli can survive and multiply in striated muscle more readily than in the skin, and that in this site they are less liable to attack, either by the normal defence mechanisms of the body or by drugs. Certainly there was a striking absence of inflammatory cells in relation to the muscle bacilli in almost all our biopsies from human muscle. This finding closely matches the absence of inflammatory response in the early and late stages of the muscle infection in the mouse footpad. However, in some cases of treated lepromatous leprosy there is an inflammatory response in human peripheral limb muscles. The process is symptomless and closely matches the process seen at particular periods in the footpad infection in mice (Weddell *et al.*, 1970). It is interesting that, as in the mouse, a few individual muscle fibres in a bundle are spared and some whole bundles escape. This suggests that *Myco. leprae* multiply more freely in some muscle fibres than others, a point already emphasized by Esiri (1969).

It is also of interest that as long as the muscle fibres are intact the bacilli within them are solidly stained, but once they get into macrophages and in association with lymphocytes they degenerate. A few degenerate bacilli are also found in completely exhausted muscle fibres in the absence of lymphocytes. It is perhaps of more than passing interest that the most heavily infected muscle from man which we have yet seen came from the leg rather than the thigh, arm, or face. It suggests that the more peripheral the infection is, the more the bacilli are able to multiply. This is certainly the case in mice where the footpad musculature is more heavily infected than the rest of the limb musculature, after infection by the intravenous route.

Our observation, then, strongly suggests that muscle offers a protected site where bacilli can lodge and multiply in the early stages of infection, where they could persist after an apparent cure, and from which they might spread to cause a relapse when treatment is stopped. It is also possible that such bacillary reservoirs are related to the development of drug resistance, and they may even play some part in the aetiology of ENL.

Just how *Myco. leprae* enter target cells, i.e. muscle fibres and the perineurial and Schwann cells of nerve fibres, remains a mystery. However, one of the more interesting observations in this series of patients was the presence of so many solidly stained bacilli in the endothelial lining cells of intramuscular capillaries, and this in the complete absence of inflammatory cells. Moreover, bacilli were found in the capillary endothelium of muscle biopsies from patients with tuberculoid as well as from patients with lepromatous leprosy.

It has been found both in mice and in patients, that intramuscular capillaries with bacilli in their wall tend to be more than usually adherent to the muscle fibres in which they are virtually embedded. For man this is illustrated in Figs 3 and 4. It appears, therefore, that capillaries in target organs probably have endothelial lining cells to which circulating *Myco. leprae* readily adhere and subsequently enter.

It is highly significant that bacilli were seen histologically in 5 of 7 biopsies from patients with tuberculoid (BT or TT) leprosy. They were few in number, and it often required 2 or more hours' searching of serial sections before a single bacillus was found, but it was striking that in most cases they were solid-staining, and lay within muscle fibres and capillary walls, neither of which had any inflammatory cells near them. The number of bacilli found in homogenates of skin and muscle from such cases suggests that they are present in comparable concentrations in skin lesions and in striated muscle, but as the bulk of the body musculature is in the order of 100 times greater than that of the skin lesions in a case of tuberculoid leprosy, a greater number of bacilli may well lie within striated muscle.

The significance of these findings is heightened by the small samples of muscle which were examined. They were taken from random sites in

patients who had no symptoms or signs of a muscle disorder, and the weight of each homogenized muscle biopsy was in the order of 0.25 g. The specimens examined histologically were smaller still and only a fraction of a total biopsy could be searched for bacilli in a few hours. Nevertheless, at least one bacillus was seen histologically in 5 out of 8 muscle biopsies from patients with untreated tuberculoid leprosy. In other words, bacilli were commonly found on examining a few milligrams of randomly selected striated muscle taken from patients with tuberculoid leprosy. In one case, bacilli were even found on 2 occasions by the less sensitive but quantitative technique of homogenization. The distribution of bacilliin muscle is uneven; this has been noted in single biopsies and also demonstrated most strikingly in the first biopsy from case 16004, which had the highest count of all in the homogenized muscle, but in which only a single bacillus was found histologically. Nevertheless, muscle bacillation may well play a significant part in the pathogenesis of human leprosy.

These studies were initiated by the finding that when mice were infected with *Myco. leprae*, striated muscle was the first tissue to be affected. The same may be true of human leprosy and our findings are compatible with this hypothesis. That is to say, it is possible that when leprosy becomes clinically apparent and skin lesions are visible, bacilli have previously been multiplying within striated muscle. Further studies, however, including biopsy of muscle from leprosy contacts and footpad inoculation to confirm that these acid-fast bacilli are indeed *Myco. leprae*, will be required to elucidate this aspect of the pathogenesis of human leprosy.

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