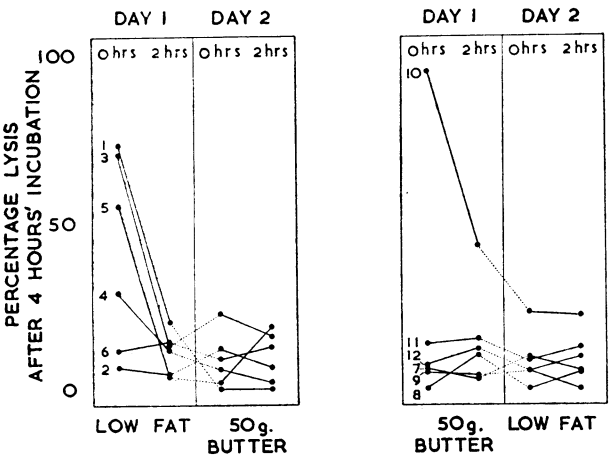
initially which fell to normal or near normal levels at subsequent venepunctures. This is shown graphically in the Chart. Clinically these subjects appeared anxious



Effect of alimentary lipaemia produced by 50 g. of butter on plasma fibrinolytic activity.

at the time of the initial venepuncture and the findings illustrate the importance of taking into consideration the effect of anxiety in causing an increase in fibrinolysis. Clearly there is no evidence from the results presented that 50 g. of butter inhibits plasma fibrinolytic activity two hours after its ingestion. Indeed, if the effect of anxiety on the initial reading is ignored the conclusion would be that a low-fat breakfast inhibited fibrinolysis in four of the six subjects (Table V), while 50 g. of butter produced this effect in only one out of six subjects (Table VI).

Discussion

This study has provided no evidence that alimentary lipaemia produced by 85 g. of animal fat, 85 g. of vegetable fat, or 50 g. of butter inhibits fibrinolysis as measured by the lysis of diluted plasma clots. It cannot, therefore, support the hypothesis that the relationship between high-fat intakes and coronary artery disease can be explained in part by the effect of dietary fat on fibrinolysis.

It does, however, provide an example of how anxiety in the experimental subject may lead to a false interpretation of results. We have already shown that transient anxiety results in a substantial increase in fibrinolytic activity and that such anxiety is usually most prominent at the time of the first venepuncture of a series (Ogston *et al.*, 1962). It is clear that the inclusion of a number of anxious subjects in a group who are given the test fat meal on the first day of an experiment may produce results leading to the conclusion that fat meals inhibit fibrinolysis. Few studies have stated the order in which the high-fat and low-fat meals were given, and this makes it impossible to assess the significance of some of the results reported.

Summary

The diurnal increase in plasma fibrinolytic activity found in the 3½-hour period after a low-fat breakfast was not significantly altered by the alimentary lipaemia produced by meals of 85 g. of animal fat or 85 g. of vegetable fat.

Anxiety at the time of the initial venepuncture was associated with high fibrinolytic activity. If the effect of anxiety was ignored the fall in fibrinolytic activity at subsequent venepunctures could lead to the false conclusion that the test meal had inhibited fibrinolysis.

A study of patients receiving 50 g. of butter and a low-fat meal on alternate days showed that butter-induced lipaemia also did not affect plasma fibrinolytic activity.

We are grateful to Sister I. M. Cowie, Ward 1, Aberdeen Royal Infirmary, for help in the preparation of fat meals, and to the patients for their co-operation. We thank Alfonal Ltd. for the gift of their products.

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ANTERIOR TIBIAL PAIN

BY

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The two patients whose cases are described here suffered from a complaint which is superficially similar to the common intermittent claudication. However, by contrast they were both young men, the pain was felt over both anterior tibial regions, it was relieved by rest only after 20 to 30 minutes, there was no evidence of vascular disease, and they were cured by operation. In describing these cases to friends and colleagues it has become clear that the symptom is not rare among healthy young people, as has been noted previously (Griffiths, 1956). It may interfere with sport, and in America a condition which presents with pain of this description is known to coaches as " shin splints." " Every athletic coach is well acquainted with the tenderness and pain in the pre-tibial muscles that occurs when runners, broad-jumpers, and hikers begin to train. The affected muscles become firm and swollen " (Pearson *et al.*, 1948). In a women's college in this country the complaint is known as " fresher's legs " (M. B. Matthews, personal communication, 1961). However, we could trace only one case in the literature which appeared to be similar to our own (Mavor, 1956).

Another condition in which pain occurs in the front of the legs is peritendinitis crepitans, but the presence of crepitus on movement is a diagnostic sign (Howard, 1937) and is not a feature of the condition discussed here.

Pain is also the presenting symptom in infarction of the anterior tibial muscles, which is known as the anterior tibial syndrome. Reports of such cases have appeared only in the last 15 years. Rarely the peroneal muscles alone may be involved (Blandy and Fuller, 1957). The literature was reviewed by Lytton and

Blandy (1960). Occasionally it is due to injury, peripheral vascular disease, or embolus, but in the majority of cases there has been no evidence of arterial disease and often the arteries have been shown to be normal.

A possible relationship between shin splints, anterior tibial syndrome, and the condition described here is discussed later.

Case 1

This patient was an apprentice electronic engineer and a keen amateur soccer and rugby player aged 21. Five years before he was seen he had had to give up ice-skating because of pain in the front of his lower legs. This recurred three years later when he started training for football. At first it was felt only after prolonged exercise, but later became more easily provoked. He gave up soccer, but continued to play rugby, which he found less likely to produce his symptoms, and he noted that walking brought on the pain more readily than running.

He did not report to his practitioner for five years from the onset of the first symptom. The amount of exercise required to bring on his pain varied considerably, and at times walking a distance of only 200 yards was sufficient. Rest relieved the pain, but only after 20 minutes to half an hour. Twice he experienced pain in bed, once following a game of rugby and once after the left anterior tibial muscle had been exercised and infused with 20 ml. of saline in the course of investigation. When free from pain he was unaware of any weakness in his legs or in the movements of his feet. At first the pain was felt only in his left leg, but later the right was equally affected.

His father claimed to have had similar pain in his youth, but according to his recollection it had been less severe and had "worn off" with continued training and exercise.

The patient was 5 ft. 4 in. (1.6 m.) tall, weighed 12 st. (76.2 kg.), and was broad, with very well developed muscles. The muscles of the anterior tibial compartment were prominent. There was no weakness or neurological abnormality. The popliteal, dorsalis pedis, and posterior tibial pulses were normal.

As there were no abnormal signs at rest, observations were made when the pain was present. It was found that cycling the equivalent of several miles on a fixed machine did not cause pain. Walking brought on the pain, but it was found more convenient to reproduce the pain by repeated dorsiflexion of the foot against resistance. Examination of the leg when the patient was lying down then showed that the anterior tibial group of muscles was firm, almost bony hard. Alongside the tibial margin there were three circular elevations, less than 1 cm. in diameter and raised 1–2 mm. above the surface at their centres. They were tense but compressible. Attempted aspiration proved that these bulges were not distended veins. They conformed with the textbook description of muscle herniae (Perkins, 1961). There was also a visible and vigorous pulsation of the front of the legs, best seen when the leg was viewed obliquely.

During the first few minutes after standard exercise, pain reached a peak of severity, remained severe for up to 10 minutes, subsided, and then ceased after 20 to 30 minutes. The pulsation was detectable up to an hour later. The pulse in the dorsalis pedis artery was always palpable, but was smaller after exercise. No crepitus was felt during exercise and there was no change in colour of the skin over the muscles. Temperature of the skin was not measured, but no alteration was detected clinically.

Femoral arteriography showed normal anterior tibial arteries both at rest and when pain was present after exercise. No satisfactory film of the venous phase was obtained.

Electromyography of the anterior tibial muscles showed potentials of normal amplitude and duration during exercise, and the muscle was electrically silent at rest before and immediately after exercise.

Treatment.—As a result of further investigations, described later, the patient was recommended treatment by excision of the pretibial fascia. Immediately before operation one leg was exercised until pain was felt and pulsation was prominent. At operation the fascia of both legs was tense. No other abnormality was detected and in particular the two sides appeared similar to the naked eye. Microscopy of the muscle biopsies was normal. There was no constriction around the blood-vessels as they passed through the interosseous membrane.

The patient resumed full activity, including sport, one month after operation and had remained symptom-free until he was last seen 7 months later.

Case 2

The second patient was a male aged 25. For three years he had been unable to play tennis and other games because of pain over the front of the lower legs. When he was seen this pain would occur after walking about 300 yards and would compel him to stop or to walk very slowly for 15 to 20 minutes. Both legs were equally affected. The pain never occurred at rest and no one in the family had a similar complaint.

The patient was slight in build; he was 5 ft. 3 in. (1.57 m.) in height and weighed 9 st. (57 kg.). There were no abnormal physical signs. In particular, there was no weakness or neurological abnormality in the legs, and the popliteal, dorsalis pedis, and posterior tibial pulses were present and equal. When the leg was exercised by repeated dorsiflexion of the foot against resistance the patient had to stop because of fatigue. No pain was present at this time, but shortly afterwards he walked until he could go no further on account of severe pain, which was felt in the previously exercised leg only. In ordinary circumstances pain appeared in both legs simultaneously. Examination then showed that the anterior tibial muscles had become very hard and there were tense bulges over the anterior tibial region similar to those seen in Case 1. There was a prominent pulsation over the front of each leg. The foot pulses were unaltered. The symptoms and signs were so similar to those of the first patient that it was not considered justifiable to perform arteriograms. Electromyography was also not carried out.

Treatment.—A strip of each anterior tibial fascia was excised as in the first patient. Five months after operation there had been no further pain. He had climbed hills that he could not climb prior to operation, had played tennis, and had taken part in all ordinary activities.

Methods of Investigation

Exercise.—In the first patient and in controls (14 males and four females, aged 21–40) exercise was standardized to raising an 11-lb. (5 kg.) weight over a pulley once every two seconds by dorsiflexion at the ankle. Exercise was continued to fatigue, which was usually accompanied by pain. The weight was then removed from the foot. As already mentioned this form of exercise did not reproduce the pain in Case 2. Observations on this patient were therefore also made after walking and the results were compared with those obtained from normal subjects.

Muscle Blood Flow.—Effective blood flow through muscle was estimated by the rate of disappearance of injected radiosodium (Gemmell and Veall, 1956). Approximately 5 μc contained in 0.1–0.2 ml. of isotonic NaCl was injected to a depth of 2 cm. into the middle of the anterior tibial muscle. A Geiger-Müller end window counter was directed towards the site of injection and attached to the leg with adhesive tape. Counts per minute were recorded on a Panax ratemeter and transferred to graph paper by an automatic pen-writing recorder. Records were taken for 10 minutes with the

subjects at rest. In both patients and in 10 students the leg was then exercised to fatigue with the counter in position and recording was continued for a further 15 to 20 minutes. In Case 2 and in four controls ^{24}Na was also injected after walking. The counter was rapidly fixed in position and recording, which commenced within a minute, was continued for 20 minutes. The counts were plotted semilogarithmically against time in minutes. When the clearance constant was estimated it was obtained from the slope of the graph by the formula $\log C_1 - \log C_2/0.4343 (T_2-T_1)$ where C_1 and C_2 are the counts at time T_1 and T_2 respectively (Kety, 1948, 1949).

Tissue-Pressure in Anterior Tibial Compartment.—Pressure within the anterior tibial compartment was measured by the method of Wells *et al.* (1938). A 26-gauge needle attached to capillary glass tubing of about 0.2 mm. internal diameter was connected to a saline manometer. Air was introduced to create a meniscus within the glass tubing. The needle was then inserted into the leg and the meniscus viewed with a hand lens. The height of the reservoir was raised until the meniscus began to move towards the leg. Movement was immediately arrested and the reading recorded. Free communication with the tissue space was assumed only when each reading could be reproduced to within a few mm. of saline several times in each half-minute. At higher pressures, movements of the meniscus corresponding with the arterial pulse could be seen. The reservoir was lowered at the end of each experiment to ensure that the tip of the needle was not in a blood-vessel. Less than 0.05 ml. of saline was infused during any one experiment. Pressures were recorded before and after exercise on two separate occasions in Case 1, one in Case 2 and in each of the 18 normal subjects, and again in both patients after treatment. In Case 2 the pressure was also measured after walking, both before and after his operation.

Application of a Thigh Cuff.—The time of onset of pain in the leg of Case 1 was observed when exercise was taken with the circulation impeded by a thigh cuff inflated to pressures of 80 and 200 mm. Hg. In addition, tissue pressures were measured while a thigh cuff was applied at 80 mm. Hg for 20 minutes.

Results

Exercise.—Towards the end of the exercise the excursions became progressively less and normal subjects gave up on account of fatigue after an average of 40 lifts (range 30–50). Fatigue was often accompanied by pain which disappeared within a matter of seconds to a few minutes after removing the weight.

The first patient gave up after an average of 35 lifts on account of pain which persisted for 20 to 30 minutes.

Rate of removal of ^{24}Na During a 10-minute Period Before Exercise (k_1) and after Exercise (k_2) in 10 Normal Subjects Compared with Case 1 Before and Two Months After Operation

Subject	Clearance Constant before Exercise (k_1)	Clearance Constant after Exercise (k_2)	k_2/k_1
Control N.	0·051	0·188	3·68
,, H.W.	0·034	0·200	5·88
,, T.	0·069	0·165	2·38
,, A.	0·028	0·097	3·47
,, S.C.	0·043	0·137	3·19
,, P.	0·036	0·137	3·82
,, F.	0·037	0·169	4·68
,, M.	0·069	0·230	3·32
,, E.	0·022	0·205	9·20
,, O.	0·045	0·176	3·92
Mean	0·043	0·170	4·35
Case 1 before operation:			
1	0·083	0·123	1·48
2	0·053	0·046	0·88
3	0·037	0·032	0·88
Mean	0·058	0·067	1·08
Case 1 after operation	0·040	0·149	3·68

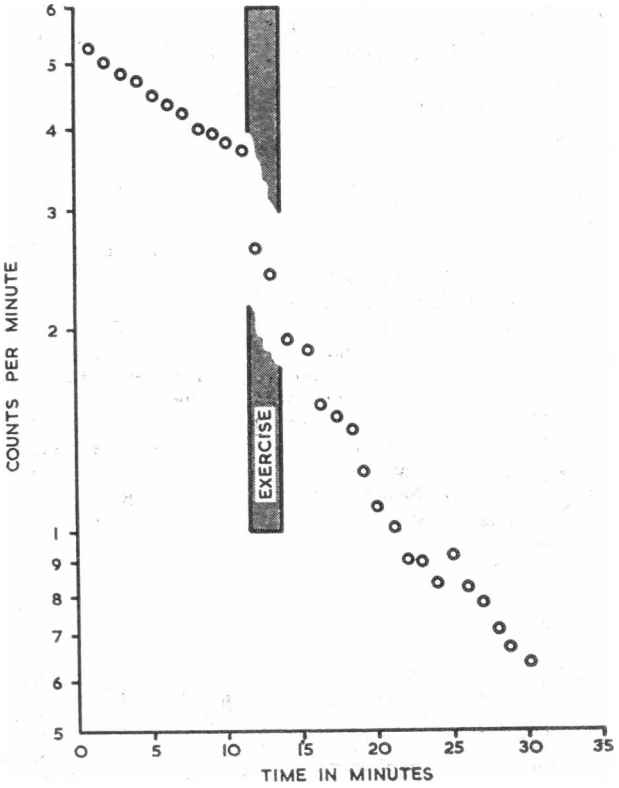

FIG. 1.—Effect of exercise on clearance of ^{24}Na from the anterior tibial compartment in normal subject (P).

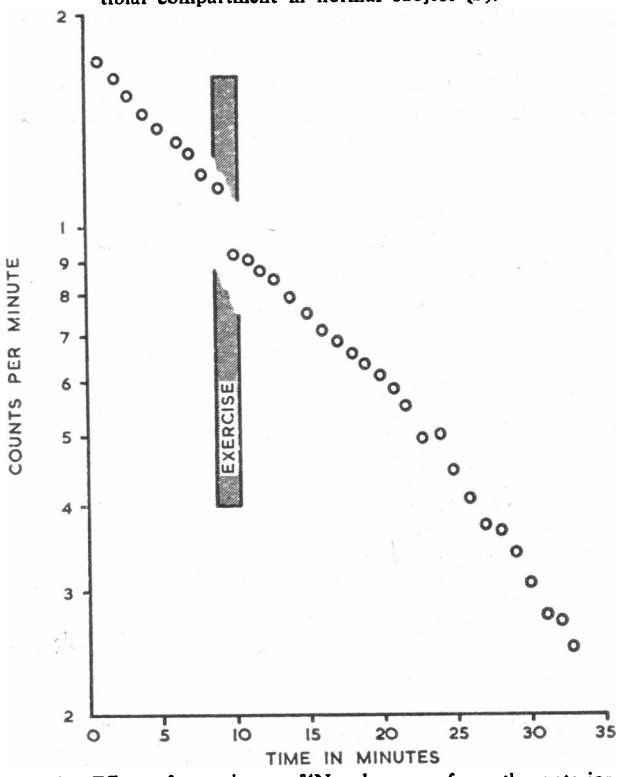

FIG. 2.—Effect of exercise on ^{24}Na clearance from the anterior tibial muscle of Case 1 before operation.

In Case 2 pain developed after walking 300 yards at a fast rate; similar exercise had no adverse effects upon the controls.

Muscle Blood Flow.—The clearance constants at rest (k_1) were similar in the patient and in the controls. In Case 1 clearance after exercise (k_2) was unchanged, but in controls it was increased by 2½ to 9 times (Table, and Figs. 1 and 2). In Case 2 the value for k_2 was within the normal range on several occasions. This was after exercise which did not reproduce his symptoms. After walking, however, the rate of clearance was not maximal until 8 to 10 minutes after the end of exercise. In four control observations it was maximal immediately after exercise and became less rapid 8 to 10 minutes later (Fig. 3).

In Case 1, after treatment the rate of removal of ^{24}Na at rest was the same as before his operation, but after exercise it now increased by more than 3½ times (Fig. 4). Measurements in Case 2 were not repeated after his operation.

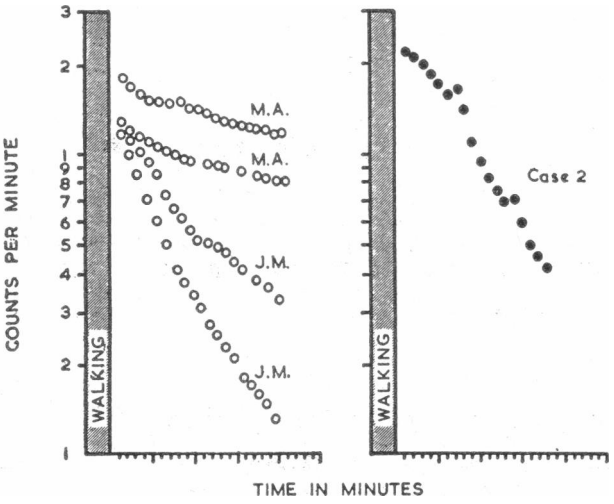

FIG. 3.—Clearance of ^{24}Na after walking. Case 2 is compared with two observations each on two normal subjects. Eight minutes after exercise the rate increases in Case 2 but decreases in the controls.

Tissue-pressure Within the Anterior Tibial Compartment.—Normal resting values for tissue-pressure ranged from 3 to 35 cm. of water. Exercise resulted in a rise of pressure of 6 to 32 cm. of water except in two females in whom there was no change. The return to resting values took from 7 to 30 minutes from the end of exercise (Fig. 5). In Case 1 the tissue-pressure at rest was 25 cm. of water; it rose to 79 cm. on exercise and took 150 minutes to return to the resting level. On another occasion the pressure was 30 cm. at rest; the early part of the record after exercise was missed owing to a block in the needle, but it took 100 minutes to return to the resting level (Fig. 5).

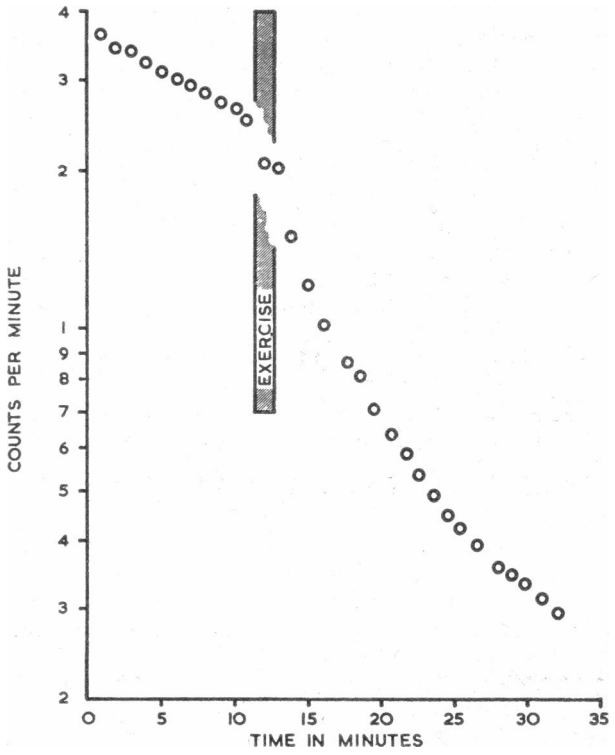

FIG. 4.—Effect of exercise on ^{24}Na clearance from the anterior tibial muscle of Case 1 after operation.

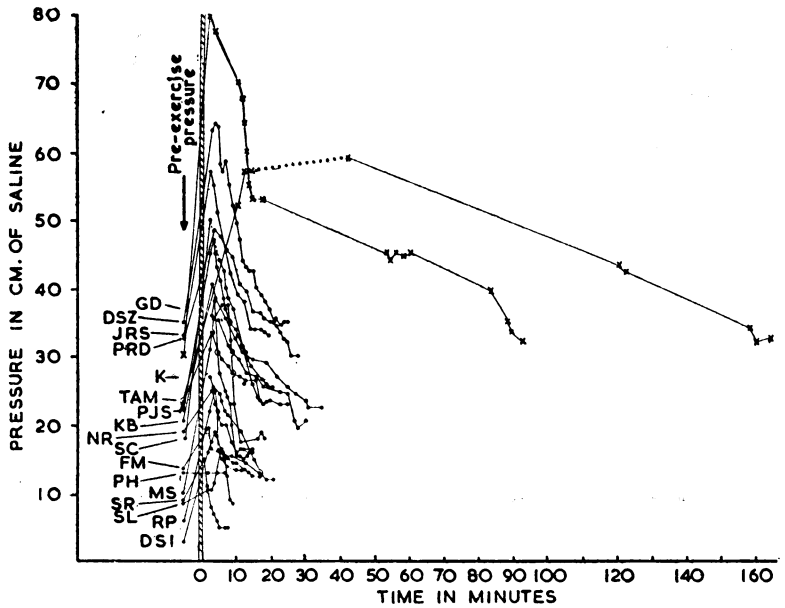

FIG. 5.—Effect of exercise on tissue-pressure in the anterior tibial compartment of Case 1 before treatment (×——×) and of 18 controls (●——●).

In Case 2 the resting pressure was 20 cm. of water. When pain had been produced by walking, pressure rose to 136 cm. of water and took 150 minutes to return to the resting value (Fig. 7). Repeated dorsiflexion of the foot which did not reproduce the pain only raised the pressure to 40 cm. of water, which is in the normal range.

Two months after treatment the pressure in Case 1 rose from 20 cm. to 40 cm. of water after exercise and fell to the resting level in 30 minutes (Fig. 6).

When Case 2 was re-examined two months after operation the muscles were soft even after twice the amount of exercise which had previously produced pain. The pressure immediately after such exercise was only 11 cm. of water (Fig. 7).

Application of a Thigh Cuff in Case 1.—(*a*) *At 80 mm. Hg.* Exercise immediately after the application of a thigh cuff at 80 mm. Hg caused pain no earlier than

when the circulation was free. Under both conditions he raised the 11-lb. (5 kg.) weight 35 times. Venous congestion caused a gradual rise in tissue-pressure to 80 cm. of water at 15 minutes (Fig. 8). This was the same pressure as was observed after exercise in Case 1. When the cuff was released pressure fell instantly to near

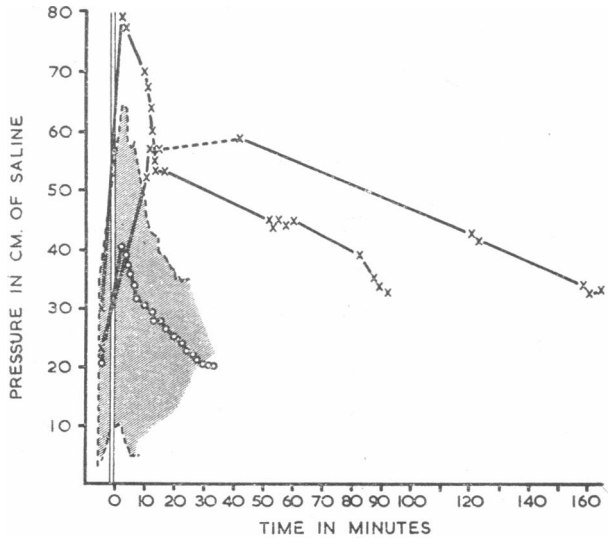

FIG. 6.—Effect of exercise on tissue-pressure in the anterior tibial compartment of Case 1 before treatment (×——×) and after treatment (O——O). The shaded area represents the range in 18 controls.

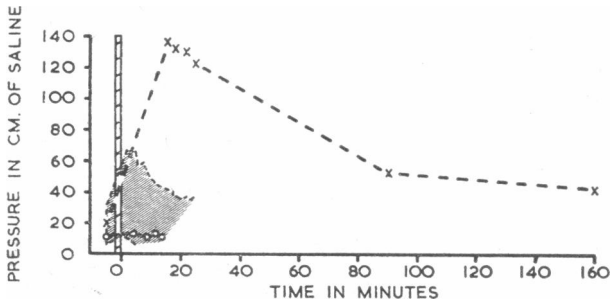

FIG. 7.—Effect of exercise on tissue-pressure in the anterior tibial compartment of Case 2 before treatment (×——×) and after treatment (O——O). The shaded area represents the range in 18 controls.

resting level. At no time did the patient complain of pain. (*b*) *At 200 mg. Hg.* The patient was able to raise the weight only 15 times before he was compelled to stop by pain. The cuff was released and the pain cleared immediately.

Discussion

Our observations upon these two young men suggest that after exercise the normal increase in blood flow through the muscles of the anterior tibial compartment is prevented by an unusual rise in tissue pressure.

Firstly, there were three indicative clinical signs when pain was present: (1) hardness of the muscles; (2) tense localized bulges over the muscles; (3) pulsation visible over the front of the legs. Secondly, there were two findings which differed significantly from normal subjects on investigation after exercise: (1) there was a higher and more prolonged rise in pressure in the anterior tibial compartment; (2) the increase in the rate of removal of ^{24}Na was absent or delayed. Thirdly, both patients were completely relieved by operation.

The high tissue-pressure adequately explains the hardness of the muscles and the tense bulges. Similar bulges, though less tense, were seen in a few normal subjects. Pulsation can also be explained by high tissue-pressure, and the amplitude is maximal when compression is about equal to diastolic blood-pressure. This is the basis of the oscillometric method of measuring blood-pressure. Pulsation also clearly indicates that the arteries are patent. It can be seen to some extent in normal subjects with tissue-pressure in the higher range. We believe that the cause of the abnormally high tissue-pressure is swelling of the muscle on exercise in an unusually tight anterior tibial

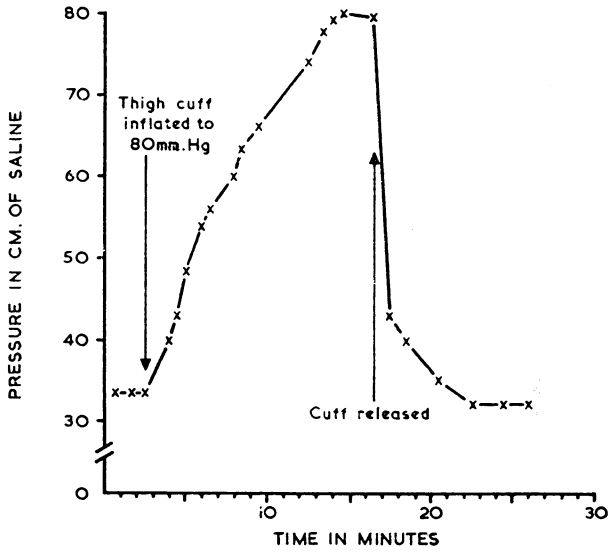

FIG. 8.—Effect of venous congestion on pressure in the anterior tibial compartment of Case 1 before treatment.

compartment. Attention has been drawn to anatomical features which are peculiar to this region, namely that the muscles are surrounded by inelastic structures—bone, interosseous membrane, and thick fascia (Hughes, 1949). Even in normal people, tissue-pressures are higher here than in the gastrocnemius (Wells *et al.*, 1938). Any increase in the bulk of the contents of this compartment is liable to be accompanied by an excessive rise in pressure.

One factor causing an increase in bulk is swelling of the muscles. Barcroft and Kato (1916) exercised one gastrocnemius of the anaesthetized dog by stimulating it to contract every 0.3 second for 15 minutes. As long as $7\frac{3}{4}$ hours later the muscle felt firm, had a specific gravity of 1062, and weighed up to 20% more than the resting muscle, which had a specific gravity of 1073. Thus, it was clearly shown that exercised muscles absorb water. Previously Fletcher (1904) had shown that a fatigued muscle became heavy when suspended in an isotonic solution, whereas resting muscle did not—demonstrating that this effect is due to osmosis.

The other factor which might contribute to an increase in bulk is an increase in the volume of blood in the vessels. Arterioles and capillaries supplying muscle dilate on exercise, but this is unlikely to be responsible for a rise in pressure persisting for up to $2\frac{1}{2}$ hours. Blood flow after exercise of the forearm for one minute normally returns to resting level in less than 10 minutes (Grant, 1938). In addition, full vasodilatation alone cannot account for the high pressure, since ischaemic exercise was not followed by pain after release of the occluding cuff. Distension of veins due to venous obstruction we also consider to be an unlikely cause in

these cases, as no evidence of it could be seen in the exercised leg at operation. Small additional points are that (1) pain was not felt any sooner when the subject was exercised with a cuff on the thigh at 80 mm. Hg, and (2) tissue pressure fell to near the base level very rapidly after the release of a thigh cuff which had been on for 16 minutes. We do not think that the pain can be attributed to the stretching effect of the high pressure or to the localized bulges, because both were reproduced by venous occlusion and maintained for 45 minutes without the production of pain.

The blood flow through the muscles both before and after exercise was assessed by the clearance rate of ^{24}Na. The efficacy of this method has been questioned (Miller and Wilson, 1951) as it does not correlate with other established methods of estimating blood flow. The discrepancy has been attributed to a failure by this method to estimate flow through arteriovenous anastomoses (Barcroft and Swan, 1953). In fact, it is probable that it reflects accurately the capillary or effective blood flow (Gemmell and Veall, 1956). We therefore deduced that in both patients blood flow after exercise did not increase as in normal subjects, thus accounting for the pain.

The evidence derived from the studies on the removal of ^{24}Na supports the clinical impression that the pain was ischaemic in its origin. The persistence of pain in Case 2 even when the clearance of ^{24}Na had reached normal values 8 to 10 minutes after exercise is difficult to understand. It is possible that at 8 minutes this increase in flow was still insufficient to remove the accumulated metabolites quickly enough to relieve the pain. Though the pain may be ischaemic the following facts indicated that the main arteries were patent: (1) the pulses in the foot were easily palpable after exercise; (2) pulsation was visible over the front of the leg; (3) arteriograms were normal when the pain was present; (4) normal function followed operation.

A rise in tissue-pressure reduces the transmural pressure in all the vessels and leads first to a reduction in flow through the smaller ones, in which the internal pressure is lower and the critical closing pressure is greater (Burton, 1952).

In 1956 an account of a case with striking similarities to our own was published by Mavor. The author concluded that a high pressure in a confined compartment must account for ischaemic pain, and he suggested that the herniae of muscle bulging through the fascia were evidence of this. Treatment by incision of the pretibial fascia cured the patient. The author's conclusions were discredited in an editorial of the same issue, particularly with reference to his suggestion that he was dealing with a chronic form of the anterior tibial syndrome, a term applied to infarction of the anterior tibial muscles. In the majority of such cases there is no evidence of direct injury or of arterial occlusion. The condition has usually followed unaccustomed exercise, and various explanations have been put forward to account for it. These include the tearing of muscle fibres with interstitial bleeding, venous obstruction, arterial spasm, and swelling of the muscles. Confinement of the muscles of this region to a compartment with unusually rigid walls has also been emphasized on a number of occasions (Hughes, 1948). By the time infarction has occurred the leg is swollen and painful. On incision of the fascia (which it is recommended should be done as early as possible) the muscles bulge out so that the wound often has to be left gaping. In cases in which the arteries have been shown to be patent the cause of the necrosis has been largely a matter of guesswork. It may be that Mavor's patient and the two reported here were in danger of developing ischaemic necrosis of the muscles, and, indeed, some of the reported cases of acute anterior tibial infarction have given a previous history, sometimes for years, of pain in the front of the leg on exertion.

The two episodes of pain at night of which Case 1 complained are reminiscent of the onset of several of the reported cases of infarction. In this connexion it is interesting to note that in our patients the tissue-pressure remained high after pain had disappeared, and this could be corroborated by persistence of the physical signs—visible bulges, pulsation, and firmness of the muscles. On lying down there is a considerable drop in the arterial pressure in the leg due to the loss of the hydrostatic component. Thus if a patient retires to bed with a sustained rise in tissue-pressure in the anterior tibial compartment the fall in perfusion pressure may account for the occurrence of pain or infarction. The variation in the duration and in the height of the post-exercise pressures of the control group suggests that all degrees of severity of this complaint may be found. There may be a tendency for patients to restrict their activities rather than report their symptoms. It is reasonable to suspect that these hidden cases account for examples of the anterior tibial syndrome when unaccustomed exercise is attempted or is forced upon them as in military service.

Summary

Two cases of intermittent claudication are described in young men in whom pain occurred over both anterior tibial regions.

The cause was found to be a rise in tissue-pressure sufficient to prevent a normal increase in muscle blood flow with exercise. These findings were indicated by the clinical signs observed in the two patients while pain was present.

Both patients have been successfully treated by excision of a strip of the anterior tibial fascia.

Reasons are given which support the suggestion that shin-splints, the condition described, and the anterior tibial syndrome are increasing grades of severity of the same basic abnormality.

We are indebted to Dr. J. A. Simpson for suggesting the relationship to anterior tibial syndrome, to Mr. P. Tothill, Medical Physics Unit, for providing facilities for and advice on isotope studies, to Mr. C. W. A. Falconer, who operated, to Dr. R. C. MacNair and Dr. J. D. Matthews for providing the patients, and to students and patients for their co-operation.

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TREATMENT OF MACROGLOBULINAEMIA

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Macroglobulinaemia was first described by Waldenström in 1944. It is characterized by an abnormal tendency to bleed, anaemia, and an increased liability to intercurrent infections; cardiac failure may complicate the clinical picture. Hepatosplenomegaly and generalized lymphadenopathy are frequent, and various neurological lesions (Logothetis *et al.*, 1960) and an unusual retinopathy (Coyle *et al.*, 1961) are described.

The spleen, lymph nodes, and marrow are infiltrated by lymphocytoid cells and plasma cells (Zollinger, 1958), and Curtain and O'Dea (1959) have shown that the abnormal macroglobulins are produced by the latter. Recently, chromosomal abnormalities have been reported (Bottura *et al.*, 1961).

Macroglobulinaemia may occur in association with other diseases, such as multiple myelomatosis, lymphosarcoma, and leukaemia, but in many cases no such association is demonstrable. The course of the disease varies in severity and spontaneous remissions may occur. As normal human plasma contains small amounts of macroglobulins, an important diagnostic criterion is the demonstration by ultracentrifuge studies that they constitute at least 10% of the plasma proteins (Martin, 1960).

We report a case treated by plasmapheresis (the selective removal of plasma).

Case Report

A man aged 55 was admitted to hospital on March 6, 1961, complaining of lassitude, dizziness, ankle-swelling, palpitations, and breathlessness on exertion of three months' duration. Seven weeks previously, prolonged bleeding had followed dental extraction and for two weeks he had noticed blurred vision and deafness.

On examination he was anaemic and breathless, and had slight ankle oedema; the gum margins were bleeding. The liver was palpable 5 cm. below the costal margin, but there was neither splenomegaly nor lymphadenopathy. His deafness consisted in a conduction defect on the left (with a scarred tympanic membrane) and a nerve deafness on the right (confirmed by audiometry). The fundi showed gross papilloedema and venous engorgement with numerous retinal haemorrhages but no exudates or arterial changes. The central nervous system was otherwise normal, as were the respiratory and cardiovascular systems.

Investigations

Haemoglobin, 44% (6.5 g./100 ml.); white-cell count, 5,300/c.mm. (polymorphs 75%, lymphocytes 21%, monocytes 3%, eosinophils 1%); E.S.R., 144 mm./hour (Westergren); reticulocytes, 1%; platelets, 102,000/c.mm.; bleeding-time, over 37 minutes; clotting-time, 8 minutes 20 seconds (Lee and White). One-stage prothrombin time, normal; prothrombin concentration, 64%; two-stage prothrombin value, 90% of normal; Stuart-Prower assay, 76% (a low value probably due to the effect of the abnormal proteins on the incomplete thromboplastin "stypven" used); factor VII assay, 90%; thrombin/fibrinogen reaction, normal; plasma fibrinogen, 0.33 g./100 ml. Thromboplastin generation test showed an inhibitor effect on the formation of intrinsic thromboplastin. Urine, no protein or Bence Jones protein; blood urea, 72 mg./100 ml.; liver-function tests, normal; plasma proteins, 10.3 g./100 ml., electrophoresis showing a large amount of an abnormal protein between the beta and gamma positions with reduction of the gamma globulin and increase of the alpha$_2$-globulin; Sia test, positive; bone-marrow, hypoplastic with an increase in lymphoid cells but no myeloma cells and no evidence of leukaemia. *X*-ray examination of the chest, skull, and dorso-lumbar spine, normal; barium-meal examination, normal. Chromosomes normal in number and morphology. Ultracentrifuge studies of the plasma proteins confirmed the diagnosis.

Progress

On the day after admission he had a haematemesis. After the transfusion of 9 pints (5.1 litres) of blood over the next three days his haemoglobin was 57% (8.4 g./100 ml.) but no further manifest bleeding had occurred. Renewed bleeding from the gums preceded another large haematemesis on April 26 and additional transfusion was required. On May 4 he developed suppurative parotitis with rapidly spreading cellulitis of the neck and upper chest; this responded eventually to incision and antibiotics.

Plasmapheresis was begun on May 30, 42 units of plasma being removed in four weeks (a unit being defined in this article as that quantity of citrated plasma discarded from each pint bottle of venesected blood, and averaging 400 ml.). Improvement was rapid, with increased well-being, return of appetite, cessation of bleeding from the gums, lessening of dyspnoea, improvement in vision and hearing, and regression of the retinal changes. The plasma proteins, initially 9 g./100 ml. (albumin 2.6 g., globulin 6.4 g.) were lowered to 6.8 g./100 ml. (albumin 2.4 g., globulin 4.4 g.).

He was discharged on July 22, but renewed symptoms necessitated readmission on August 8, examination revealing a striking deterioration in the retinopathy with many new haemorrhages. The haemoglobin was 38% (5.6 g/100 ml.) and the plasma proteins were 9.2 g./100 ml. (albumin 2.3 g., globulin 6.9 g.). Transfusion was necessary, and this obscured the results of the subsequent plasmapheresis of 16 units of plasma in five days. Once more marked symptomatic improvement occurred, with regression of the retinal changes. On discharge penicillamine, 300 mg. t.d.s., was started, and was continued for the rest of his life.

A third admission was arranged for September 15, when the plasma proteins were 10.8 g./100 ml. and symptoms had just reappeared. Removal of 18 units of plasma over three days produced improvement uniform with that previously seen.

His final admission, on October 11, was with bronchopneumonia of two days' duration. His condition was poor, the haemoglobin being 43% (6.4 g./100 ml. and the white-cell count 2,000/c.mm. (lymphocytes 99%, polymorphs 1%). Blood cultures grew *Escherichia coli* profusely, and despite energetic antibiotic treatment he died on October 13, 1961.

Post-mortem Findings.—The significant findings were bronchopneumonia, a large spleen (720 g.), and enlargement of the cervical lymph nodes only. The brain was normal. Histologically there was infiltration by lymphocytes and plasma cells of the spleen, lymph nodes, kidneys, portal tracts of the liver, and bone-marrow, which, additionally, showed hyperplasia of all elements, numerous granulocyte precursors, and no evidence of maturation arrest.