With experienced control serious haemorrhage is very rare nowadays, and minor haemorrhage, though not infrequently seen with adequate therapy, does not call for cessation of treatment. Vitamin K₁ is invaluable in the control of haemorrhage due to overdosage with anticoagulant drugs, but it must be used with caution, and in very small doses, as it is so potent.

Certain drugs enhance the effect of oral anticoagulants or may cause haemorrhage. As a result, the administration of oral antibiotics, particularly the broad-spectrum drugs such as the tetracyclines and to a less extent penicillin, may call for a reduction in the dose of the anticoagulant drug. Aspirin, phenylbutazone, and probably quinine should not be given at the same time as anticoagulant therapy, and liquid paraffin is also best avoided.

With skilled laboratory and clinical control, emergency surgical procedures, including major operations, can be carried out on patients still receiving adequate anticoagulant cover without the necessity for the treatment to be stopped altogether. This is particularly important in relation to long-term therapy.

In experienced hands anticoagulant therapy has proved so beneficial in thrombo-embolic disorders that everything possible should be done to ensure that the treatment is carried out to the best advantage and that adequate anticoagulant cover is maintained throughout the illness. To-day, with the increasing use of long-term anticoagulant therapy, there is perhaps justification for a special unit in large hospitals for the control of this treatment.

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A TECHNIQUE FOR INVESTIGATING THE BLOOD SUPPLY OF MUSCLE DURING EXERCISE

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One of the major difficulties in investigating problems of diagnosis and treatment in intermittent claudication has been the lack of a suitable objective test for measuring blood flow in the calf muscles during exercise. Plethysmographic studies of muscle are relatively easy to perform with the patient at rest, but such investigations do not help in patients with claudication, because resting blood flow is usually adequate. It is only when exercise leads to a demand for blood greatly above the resting flow that claudication is manifest, and during exercise plethysmography is extremely difficult to perform.

The test described in this paper is based on experimental work carried out over the last few years and has been in use by this clinic for four years, some 200 patients having been investigated. As in the case of any test, it is essential to appreciate the basic factors concerned and to be aware of the limitations of the method. It is proposed in this paper to describe the technique which has been evolved and to discuss the interpretation of the results obtained in the light of experimental findings.

In 1948 Kety published a paper reporting the measurement of the local clearance of radioactive sodium pre-

viously injected into a tissue, and suggested that this might prove to be a method for the experimental study of the peripheral circulation. As a result of an investigation of the clearance of injected radioactive sodium from muscle it was established (Walder, 1955) that with certain provisos changes in the clearance rate were linearly related to changes in blood flow (Fig. 1). The clearance rate of radioactive sodium is expressed as the "clearance constant" K.

FIG. 1.—Relationship between blood flow as measured with a conventional type of plethysmograph and radioactive sodium clearance constant K in the human gastrocnemius muscle during the immediate post-exercise period.

$$K = \frac{\log C_1 - C_2}{0.4343 (t_1 - t_2)}$$

where C_1 and C_2 are the percentage activity of the injected ^{24}Na remaining at the two times t_1 and t_2 after the first measure of activity, which is taken as 100%. Hence, by calibration of clearance rate against blood flow measured at rest, the method can be developed in such a way that it becomes easy to measure blood flow during exercise.

While the problems of measuring blood flow in muscle during exercise were being investigated it was noticed that in the case of patients suffering from peripheral vascular disease the ^{24}Na clearance curve during the type of exercise used showed a characteristic pattern such that there appeared to be no flow through the muscle during the period of exercise. This observation allowed considerable simplification of the clinical test for vascular sufficiency during exercise to be made, since it is only changes in blood flow that are required and it becomes unnecessary to measure the absolute blood flow at any stage of the test.

Object of the Test

The object of the test is to detect vascular insufficiency in human muscle. It allows such insufficiency to be demonstrated at a very early stage in its development, and in those instances where patients describe symptoms which may or may not be attributable to muscle ischaemia during exercise the test enables a firm decision to be made one way or the other. Since any one muscle can be selected for testing it enables the exact location of the ischaemic muscle to be determined, a point which opens up the possibility of performing localized neurectomies as treatment for some cases of claudication. Finally, provided that the test is performed under properly controlled conditions, it offers objective evidence of the state of the circulation in a muscle and a record which can be used for comparison later with subsequent tests following treatment. This latter point is of importance in that it provides an objective means of assessing the results of treatment for a condition where the patient's desire to be better and the doctor's enthusiasm can so colour the picture.

Technique of the Test

In its simplest form the apparatus for the test consists of an end-window geiger counter tube (Type GM4) mounted in a simple sorbo rubber strap (Fig. 2) and a ratemeter (Fig. 3).

An injection of 0.2 ml. of radioactive isotonic NaCl containing approximately 20 μ C of ^{24}Na is made through a 26-gauge 2-in. (5-cm.)-long hypodermic needle into the belly of the muscle to be tested. The GM counter is then strapped into position over the site of the injection and the rate of

FIG. 2.—Geiger counter tube (type GM4) mounted for strapping on to the calf over ^{24}Na injection site.

clearance of the ^{24}Na determined. The ratemeter indicates the gamma-radiation intensity of the injected mass of ^{24}Na remaining in the muscle at any one time and with the first reading taken to represent 100% activity. The percentage activity is plotted every 30 seconds on a logarithmic scale with time as the abscissa. (Correction is made for the natural decay of the radioactive sodium, which is occurring approximately at the rate of 0.5% every six minutes.) The slope of the resulting graph is an indication of the rate at which the radioactive sodium is being carried away from the injection site.

As an alternative but rather simpler method of recording the rate of clearance of the ^{24}Na the ratemeter can be connected to a recording milliammeter. The records obtained in this way give exponential curves, but changes in clearance rate can still be easily detected (Figs. 4 and 5).

As the test is most often used in investigating the blood supply of calf muscles the technique for this procedure will be described in detail. As a routine it has been the practice to test the lateral head of the gastrocnemius muscle first. The patient is prepared for the test by getting him to don a pair of running-shorts in place of his pants and trousers. He keeps on his outdoor shoes and his socks. After a half-hour period of rest he is asked to stand up and steady himself with his hands against a suitably placed horizontal bar. The injection is now made into his calf and the counter strapped on. Readings are begun at once, recordings being taken every half-minute. As soon as the clearance rate at rest is seen to be steady over a period of 3-4 minutes the patient is asked to raise the leg not under test clear

FIG. 3.—Subject ready for test.

FIG. 4.—Normal subject.

Comparison of records of ^{24}Na clearance from the lateral head of right gastrocnemius muscle as obtained simultaneously by (a) plotting against time the log of the percentage activity remaining at the injection site, and (b) using a direct recording milliammeter connected to the ratemeter.

FIG. 5.—Patient with claudication.

of the ground so that he is standing on one leg. He is then asked to exercise by raising himself up on to the toes of the leg under investigation and down again in time with a metronome which beats every second. He thus completes one cycle of up on to the toes and down again every two seconds. He continues to exercise for two minutes unless stopped previously by pain. When he stops he places both feet on the ground and remains standing at rest for a further few minutes until the resting ^{24}Na clearance rate is re-established. The test for that particular muscle is then ended. A muscle in the other leg or another muscle in the same leg can then be tested.

As a rough guide it is estimated that the amount of radiation that a patient will receive from the two doses of radioactive sodium used in testing two muscles will be about equal to that received from one chest radiograph. It has been the policy not to give more than two injections of radioactive sodium on any one day and not to retest until eight weeks have elapsed.

FIG. 6.—Record of height to which subject raises himself every two seconds. (Changes in the mean height are also shown.)

One refinement of the test, which although not essential gives useful information, is to measure the work done by the patient during the test. This can be done very simply by measuring the height in feet to which the patient raises himself on each occasion when he rises on tiptoe and multiplying the total of

these heights by his body weight in pounds. The result gives the work done in ft./lb. The height to which the patient raises himself when on his toes is recorded on a kymograph drum by a writing-point connected to a board which rests on the patient's head and moves up and down as he raises or lowers himself (Fig. 6).

Experimental Evidence on Which the Test is Based

Full details of the experimental basis for this test have been previously published (Walder, 1953; Walder, 1955). Animal experiments were carried out on the isolated skinned limbs of cats and rabbits, and it was found that changes in the rate of clearance of radioactive sodium injected into the muscles as isotonic NaCl were directly related to changes in the rate of blood flow through the muscle as estimated by direct measurement. This relationship held good within the physiological range of blood pressure and flow rates.

In man the relationship between change in muscle blood-flow rates and clearance rates of radioactive sodium was investigated during post-exercise hyperaemia, when flow rates as high as 30 ml./100 g./min. could be obtained and a statistically highly significant linear relationship demonstrated.

Interpretation of Results

In a subject with a normal circulation the changes in clearance rate during a test are as follows. First, during the initial period of standing, ^{24}Na is seen to be cleared from the muscle at a constant but comparatively slow rate. Once the patient starts to exercise, the rate of clearance shows a sharp increase, which persists during the exercise period. When the exercise stops, the clearance rate decreases and within a very short time has returned to its resting clearance rate (Fig. 4).

In a subject with vascular insufficiency of the calf muscles the clearance rate during the initial standing period is not

appreciably different from that of a normal patient; but as soon as the exercise starts, instead of an increase in blood flow there is a complete cessation of clearance, and as soon as the subject stops exercising (either because he is told to do so or because he is forced to by the severity of the ischaemic pain of muscle) the clearance of ^{24}Na is re-established and there is a period of several minutes when the clearance rate is high (higher, that is, than the initial standing period rate). This high rate gradually subsides, until eventually the resting conditions are re-established (Fig. 5).

Discussion of Results

In the subjects with a deficient blood supply it is often noted that at the beginning of exercise there is a sudden drop in the counting rate preceding the period when no clearance occurs; then as the patient tires towards the end of the exercise period the counting rate gradually rises, sometimes almost to the pre-exercise level, until finally, after the patient has stopped exercising, the counting rate falls again and the post-exercise phase of rapid clearance is established. Occasionally, if the patient with a deficient blood supply is able to maintain a constant degree of exercise right up to the end of the exercise period, there is a sudden increase in the counting rate almost to the pre-exercise level after the patient has stopped exercising and before the phase of rapid clearance is seen.

At first it was thought that these changes might be explained by the sudden ejection of a large volume of venous blood containing radioactive sodium at the first contraction of the muscle with the reflux of this radioactive blood into the muscle at the end of the exercise phase. However, this explanation cannot be substantiated by experimental evidence; on the contrary, by using special apparatus consisting of multiple counters surrounding the limb under test, it can be shown that the sudden decrease in counting rate sometimes seen at the beginning of the exercise phase, the rise in counting rate towards the end of the exercise, and the sudden rise in counting rate after the patient stops exercising are due to axial movement of the sodium source in relation to the counter as the muscle belly moves with the contractions. The contractions become less as the patient tires towards the end of exercise (Fig. 6), and finally the muscle returns to its resting position when the exercise stops.

The physical characteristics of the recording milliammeter used in this work are such that its frequency response is rather low, and consequently only the mean of these axial movements is recorded. When a more sensitive recording instrument such as an oscilloscope is used with a higher frequency response these axial movements can be demonstrated (Fig. 7).

FIG. 7.—Record of ^{24}Na clearance from the gastrocnemius muscle of a patient with intermittent claudication made during exercise using an oscilloscope with camera as the recording instrument.

An interesting fact which emerges from these experiments is that in a patient with peripheral vascular disease affecting the muscles there is often a complete cessation of blood flow during the type of exercise used in this test. Since there is a very rapid clearance rate as soon as the exercise is stopped, it would appear that the muscle vessels are opening up normally during exercise; but presumably the internal resistance of the muscle during contraction is too great for

the available head of pressure in the arterial blood at the entrance to the muscle to force the blood through during exercise.

Some experiments on the lines of those reported by Barcroft and Dornhorst (1949) have been carried out on normal subjects and on patients with peripheral vascular disease in an effort to demonstrate how the tension developed in the gastrocnemius muscle affects the blood flow through it.

Measurements of radioactive sodium clearance are made on the calf muscle of a subject who is lying on a couch. Changes in tension within the calf muscle can be brought about by arranging for the subject to depress a weighted pedal with his foot. The weights on the pedal can be varied. In a patient with claudication the circulation stops completely at tensions which in the normal subject result only in a slowing of the blood flow (Fig. 8).

FIG. 8.—Effect on the clearance rate of ^{24}Na from the gastrocnemius muscle of increasingly powerful contractions. The figures 14, 28, and 56 refer to the load in pounds supported by the contracting calf muscle. (a) Patient with claudication; clearance has stopped with a load of 28 lb. (b) Normal subject; clearance still continues with a load of 56 lb.

The results of the clinical experiments carried out in the course of investigating the clearance rate of radioactive sodium serve to emphasize the fact that in patients who have peripheral vascular disease severe enough to give rise to claudication on exercise the blood supply at rest is perfectly adequate to maintain the metabolic requirements of muscle.

These facts become important when considering the use of drugs for the treatment of intermittent claudication. So far no drug tested in this clinic has been found to change the abnormal clearance curve of a patient with peripheral vascular disease to the "normal" type of clearance curve. There is no doubt that some drugs result in vasodilatation of blood vessels in resting muscle even to the extent of doubling the resting blood flow; this does not, however, enhance the flow in exercise, since even when the maximum vasodilatation resulting from metabolites has occurred the flow during contraction is still zero. It is not an increased vasodilatation of muscle blood-vessels that is required but an increased head of pressure at the entry port of the vessels into the muscle so that blood can flow even when the internal tension of the muscle is high owing to contraction.

The operation of lumbar sympathectomy (that is, the removal of a length of lumbar sympathetic chain from above

the first lumbar ganglion to below the third lumbar ganglion) has not been found to affect an abnormal ^{24}Na clearance curve.

A few cases have been followed in which vascular grafting has been carried out for a localized block in a major peripheral vessel. After some successful grafting operations it has been possible to demonstrate the return of an abnormal sodium clearance curve to an apparently normal type of curve, with clinical relief of the claudication (Fig. 9). In these cases it is sometimes possible to re-establish the peripheral blood flow so fully that the pressure head of blood available in the arteries to the gastrocnemius muscles is once again capable of maintaining an adequate flow against the resistance of the contracting muscle.

It is possible for normal ^{24}Na clearance curves for all the calf muscles to be obtained in the presence of claudication, but such cases will have a grossly lowered haemoglobin concentration. Correction of the anaemia will cure the claudication.

Summary

An objective test is described using radioactive isotopes for the evaluation of vascular sufficiency in muscle during exercise. The apparatus is readily available commercially, and in fact is already possessed by most hospital physics departments. This test assists in the diagnosis of intermittent claudication by giving additional evidence in doubtful cases. It enables vascular insufficiency to be detected early. The exact muscle affected can be located. The test also enables treatment to be assessed objectively.

The technique described provides a useful tool for research into the problems of muscle blood flow. Observations made so far using this technique would seem to suggest that the fundamental requirements in claudicating muscles are an increase in the pressure of blood available in the arteries supplying the muscle or a decrease in the tension developed within the muscle during contraction.

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The Ministry of Health has sent to local authorities a new edition of its memorandum entitled *Food Poisoning* (revised 1958, H.M.S.O., 1s.). It brings up to date the 1949 edition but makes no major changes. The memorandum is intended primarily to help medical officers of health. A covering letter stresses the importance to the Ministry of having adequate information about outbreaks of food-poisoning. It also asks local authorities whether there is need to remind medical practitioners "of the value of full and prompt notification of cases of food-poisoning and of their obligations in regard to such notification."

FIG. 9.—Records of ^{24}Na clearance from the right human gastrocnemius muscle made before and after the replacement of a blocked aortic bifurcation by a homograft. (↓ Ex. ↓ indicates period of exercise.)