therefore plasma H_2CO_3 . The clinical counterpart of this physiological adjustment is the slow deep breathing on salicylate administration.

It is realized that a single case has been cited as evidence of a possible common action of aspirin and cortisone, but on examination of our records of previous cases of acute rheumatism treated with sodium salicylate we find that frequent reference is made to puffiness of the face and acne-like lesions on the face, front of chest, and back. In fact, puffiness of the face may be observed in almost every patient receiving full therapeutic doses of salicylate, and it tends to be most pronounced in children. Most of these patients also had a reducing substance in the urine which was assumed to be a salicylate fallacy. However, addition of salicylic acid, sodium salicylate, and aspirin to normal urine in concentrations greater than we have ever encountered in the urine of patients under treatment failed to show any reduction of Benedict's solution. This does not exclude the presence of reducing substances other than glucose, but it may well be that the reductions previously observed were partly if not wholly due to glucose. These retrospective observations suggest that the development of mild Cushing's syndrome during intensive salicylate treatment is not uncommon, but there are many points requiring further investigation before any final conclusion may be drawn. Nevertheless, it is thought that this initial report is justified in view of the significance of the findings.

Summary

The clinical and metabolic effects of aspirin in the treatment of acute rheumatism resemble closely those attributed to cortisone.

A case is presented, and others referred to, in which the similarity in action of the two substances is further strengthened by the development under aspirin treatment of side-effects suggesting a mild Cushing's syndrome.

The effects observed were rounding of the facial contours, acne, diminished glucose tolerance, glycosuria, and alteration of the mental state.

Some important considerations arising out of this conception are discussed.

We thank Professor J. W. McNee for his advice and generous help in providing facilities for this work. We are also indebted to Mr. S. L. Rae for the ketosteroid estimations.

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The British Standards Institution has issued a British Standard for one-mark bulb pipettes. Sixteen sizes of pipette from 1 ml. to 100 ml. capacity are specified, being those most in demand for general laboratory use. Full dimensions are given, but, in accordance with current practice in British Standards for laboratory glassware, only the essential ones are listed as mandatory, the remainder being given for the guidance of manufacturers. Standard methods are included for the determination of capacity and delivery time, and tolerances listed for both. An appendix gives the sizes of glass tubing recommended for the manufacture of these pipettes. Copies of this standard may be obtained from the British Standards Institution, Sales Department, 24, Victoria Street, London, S.W.1 (2s. post free). The Institution has also issued standards for hospital beds and other hospital equipment, and for paper boxes for pills, creams, powders, pastes, etc.

EVALUATION OF TREATMENT IN INTERMITTENT CLAUDICATION*

BY

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Arteriosclerosis is by far the commonest cause of intermittent claudication, and numerous drugs and operations have been advocated for the treatment of this condition. Any effective treatment must increase the distance a patient can walk, either by increasing the blood flow to the affected muscles or by reducing the pain which occurs on exercise.

Direct measurement of the distance a patient can walk is the common method of assessing treatment. This has two disadvantages. First, if improvement does occur it is impossible to say whether this is due to an increased blood flow to the muscles or to a pain-relieving action of the drug. Secondly, it does not allow the limbs to be tested separately. Often both legs are affected by the disease, but the earlier onset of pain in the more severely affected one may stop the patient walking before pain is felt on the other side.

An alternative method for evaluating treatment is described which does not suffer from these disadvantages.

Methods

The method employs an ergograph to determine the amount of work a patient can perform and a venous occlusion plethysmograph to enable the blood flow through the calf to be measured after the exercise.

The ergograph has already been briefly described (Shepherd, 1950). The patient, by depressing a foot-board on plantar flexion, raises a weight. The foot-board is so arranged that the axis of its movement passes through the ankle-joint (Goetz, 1942) and, as the leg is kept horizontal, with the knee flexed through an angle of about 60 degrees, the posterior calf muscles perform most of the work.

On the return stroke, as the ankle is dorsiflexed, the speed of the falling weight is controlled by a brake (Fig. 1). Alternate contraction and relaxation of the muscles is therefore possible, the posterior calf muscles being relaxed on dorsiflexion instead of having to resist the descent of the weight. This is important, because it leads to a large difference between the amount of work that can be done by the normal and the arteriosclerotic subject. The normal adult male of whatever build can make 500 contractions at a rate of 24 a minute and show no sign of fatigue or pain at the end. The number of contractions that can be made by arteriosclerotics with symptoms of claudication varies according to the severity of the disease, but even mild cases are generally forced to stop by pain and fatigue in the affected muscles before they have completed 200 contractions. The ergograph could also be adapted for testing the extensor muscles of the leg so that work is performed on dorsiflexion only. In practice this has never been done, as in all our patients pain on exercise was limited to the posterior calf muscles. The movement of the foot-board is transmitted to an indicator. A mark is placed on a scale behind the indicator, and by pushing to this mark the foot-board moves through an angle of 33 degrees and the subject lifts a 5.5-kg. weight a distance of 26 cm. By arranging

*This work was carried out during tenure of a British Medical Association scholarship.

the pointer of a metronome to move parallel to this indicator the subject, guided by the metronome, works at a constant rate. This allows accurate comparisons to be made.

Blood flows are recorded through the calf of the leg after exercise by means of a light celluloid plethysmograph (Shepherd, 1950) applied to the leg before exercise. Grant (1938) pointed out that any material departure from the resting forearm blood flow after local exercise can be attributed to a change in muscle circulation. It is probable that the same is true of the calf, and that recordings made after exercise represent mainly muscle blood flow. With the technique described, the first recording can be started within a second of the cessation of exercise.

FIG. 1.—The ergograph. Framework made from light angle-iron and attached to the end of a couch so that the machine overhangs one end. Pulleys A, B, and C are mounted on axle D. Pulleys B and C are connected through a free-wheel device free from back-lash; A and B are permanently fastened together. A wooden block E encircles pulley C and the frictional force can be adjusted by means of two wing nuts. The brake-block is shown cut away to enable pulleys to be seen. The foot is strapped to the footplate O; the plate swings about the axles P. The footplate and attachments are counterbalanced by a weight not shown.

As the foot is plantar-flexed the connecting rods N move towards the right and pull lever H, which can swing about axle J, also towards the right. Roller K, attached to lever H, pushes to right a second lever L, swinging about axle M. A leather belt F, one end attached to lever L, passes round and is fastened to pulley B. As lever L moves to right the belt causes pulley B to rotate, and with it pulley A. Pulley C is kept stationary by means of the brake-block. A second belt G, one end attached to pulley A, carries a hanger on which the 5.5-kg. weight is placed. The rotation of A causes the weight to be raised.

On the return stroke, as the foot moves backwards and the weight falls, all three pulleys move together, the speed of the falling weight being controlled by the brake. This enables the foot to return to the dorsiflexed position without a y force being exerted on it by the falling weight, since levers H and L can move independently.

Results

Observation of the number of contractions that a subject can make on the ergograph, working at a rate of 24 contractions a minute, with the limb circulation both free and occluded, combined with a study of the calf blood flow after exercise, enables the deficiency of the circulation to the muscles to be assessed.

In the occasional case in which the cause of the pain is in doubt this procedure may enable vascular deficiency to be ruled out. The following case is an example.

A man aged 49 complained of having had attacks of cramp in the left calf for two and a half years. He was able to make 500 contractions without pain or fatigue. The plethysmographic record showed normal pulsations. The immediate post-exercise flow was 23.2 ml. per 100 ml. calf a minute, and this was followed by a return to the resting level in two minutes. In addition, when exercise was carried out with the circulation occluded by a thigh cuff inflated to 200 mm. Hg. which was released just before the first post-exercise recording, the immediate flow was 33.4 ml., indicating that a considerable potential reserve was available (Fig. 2). This is a normal response to these tests.

The pattern of the calf blood flows after exercise in patients with arteriosclerosis and symptoms of intermittent claudication falls into two main groups (Shepherd, 1950).

Group A.—The plethysmographic record shows pulsations, but they are usually smaller than in normal subjects. The immediate post-exercise flow is lower than in the normal individual, and the flow subsequently declines very slowly to the resting level (Fig. 3). Ischaemic exercise carried on to claudication does not increase the post-exercise flow.

Group B.—The plethysmographic record shows either very small pulsations or none at all. The immediate post-exercise flow is much lower than in the normal subject, but instead of declining slowly to the resting level it gradually increases to a maximum some time after the cessation of the exercise and then declines to the resting level. The maximum level reached in these cases is invariably much less than the immediate post-exercise flow in normal individuals (Fig. 4). This pattern and the initial flow are unchanged if the exercise is carried out with the circulation arrested in the leg.

Treatment of Intermittent Claudication with "Padutin"

Werle and Multhaupt (1937) found that the injection of padutin, an insulin-free pancreatic extract, caused an

FIG. 2.—Patient aged 49. Normal pattern for the calf circulation. Normal pulsations on plethysmogram. 500 contractions of left calf without symptoms. Initial high flow with a rapid recovery to resting level. With 60 ischaemic contractions of left calf the immediate post-exercise flow is higher than with 500 normal contractions, indicating the potential reserve available.

increase in the skin temperature of the fingers. On the other hand, Abramson *et al.* (1941) found no change in the resting blood flow to the hand, leg, or forearm after the intramuscular injection of four biological units. Allen *et al.* (1946) state that the exact mechanism of relief of the pain of claudication by tissue extracts is not well understood, but that the extract seems to prevent in some way the chemical changes which produce pain in exercised ischaemic muscles.

In the present experiments the effect of padutin has been tested on eight male patients with arteriosclerosis whose ages ranged from 44 to 57 years, average 52. The primary complaint in all cases was intermittent claudication. None were diabetic, and the skin in all cases was healthy. The calf blood flow after exercise showed a Group A pattern in four, and a Group B pattern in four. Treatment lasted from 12 to 21 weeks, average 16.

The general routine was as follows. The patient made five visits before any treatment was started. On the first visit he practised on the ergograph in order to become familiar with the exercise, but no observations were made. At each of the following four visits the claudication index and the calf blood flow after exercise were measured. By claudication index is meant the number of contractions the patient could make before pain and fatigue in the affected muscles forced him to stop. Owing to the dependence of the claudication index on the determination of the subject, it was thought desirable to have four baseline observations.

The drug was given by weekly intramuscular injection: usually 1 ml. (three biological units) weekly for the first

two weeks, then 2 ml. weekly until the last four weeks, when the dose was usually increased to 3 ml. In addition, the patient took the drug by mouth (10 biological units per ml.): 10 drops three times a day for the first two weeks, then 20 drops increased to 30 drops in the last four weeks. The claudication index and post-exercise calf blood flows were usually determined at weekly or occasionally fortnightly intervals throughout the period of treatment. Recordings were made about 15 minutes after the injection, but in some cases were also made before the injection was given, in order to rule out the possibility of the injection itself reducing the claudication index. No undesirable symptoms were reported.

In neither group was there any evidence that the drug relieved the claudication or increased the calf blood flow after exercise. Fig. 3 shows the post-exercise calf blood flow before and at the end of treatment in a patient with a Group A pattern. The pattern and the extent of the blood-flow response were unchanged and the average of the four determinations of the claudication index before treatment was not materially different from that at the end of treatment. Fig. 4 shows the post-exercise calf blood flow in a patient with a Group B pattern before and after treatment. The results of all the tests on this patient are shown in Fig. 5. It will be noted that there is no marked change in the calf blood flow or claudication index during the treatment.

It was often difficult to reconcile the patient's own assessment of changes in his condition with the objective measurements in the laboratory. Some patients thought they were improved about the middle of treatment, and two said that they could walk a mile whereas formerly they could walk only 200 yards. All, however, at the end of treatment felt there was no substantial improvement. Even during the time of alleged improvement the laboratory measurements showed no increase in claudication index or post-exercise blood flow.

All the patients smoked from 8 to 35 cigarettes a day, the average consumption being 20. Four ceased smoking for almost two months during treatment, with no important difference in their claudication index or their calf blood flow after exercise. Four patients, at one of their tests, smoked a cigarette and inhaled the smoke during exercise, with no change in the calf blood flow or the number of contractions carried out. In seven of these eight cases treated with padutin the circulation through the other calf was tested. Four showed a normal response, two a Group A response, and one a Group B response (Fig. 6).

FIG. 3.—Group A pattern. Post exercise calf blood flow before and after 14 weeks' treatment with padutin in a patient aged 44. No change in blood flow and little alteration in number of contractions that can be made on the ergograph.

FIG. 4.—Group B pattern. Post-exercise calf blood flow before and after 20 weeks' treatment with padutin in a patient aged 55. There is no increase in blood flow as a result of treatment. Note that in this case the immediate post-exercise flows are lower than the average resting flows.

FIG. 5.—Claudication indices and calf blood flows of same patient as in Fig. 4. Black circles represent immediate flow after the exercise, and the open circles the maximum flow attained. The amount of padutin given is shown at the top of the figure. This patient received the maximum dose for a longer period than the average.

FIG. 6.—Post-exercise blood flows through the right and the left calf of same patient as in Figs. 4 and 5. Right calf shows a normal response, left calf a Group B response.

Prediction of the Effects of Sympathetic Neurectomy

In a series of 10 cases of arteriosclerosis with a healthy skin, whose primary complaint was claudication, an attempt was made to determine the effect of acute release of sympathetic control on the calf blood flow after exercise. Five of these cases had a Group A response to exercise, and five a Group B. Two methods were used. In the first the claudication index and the post-exercise calf blood flow were measured before and after heating the subject by wrapping him in blankets and immersing one arm in stirred water at 43° C. (Gibbon and Landis, 1932). Heating lasted one hour, unless the resting calf blood flow reached a steady maximum sooner. In the second method the claudication index and the calf blood flow after the exercise were first determined, and, after allowing one hour for recovery, the subject was asked to make the same number of contractions, during the last 18–24 of which 500 mg. of tetraethylammonium bromide (T.E.A.B.) (Acheson and Moe, 1945, 1946) was injected intravenously.

The calf blood flow was again determined immediately after the exercise. This procedure was used because of the brief action of T.E.A.B.

In four patients both these methods were used on separate occasions, in three T.E.A.B. only, and in three indirect heating only. In no case did either method increase the calf blood flow after the exercise, nor did indirect heating increase the claudication index.

Effects of Lumbar Sympathectomy

Eight cases have been examined before lumbar sympathectomy, including three from the series just described. Four of these were in Group A and four in Group B. These patients also were non-diabetic and had healthy skins; their primary complaint was of intermittent claudication. Five had one cold foot, but the skin temperature of the toes of this foot rose to 31.5–34.5° C. in response to indirect heating (Gibbon and Landis, 1932). The other three also showed a similar rise on the more affected side.

After lumbar sympathectomy there was in no case any conclusive evidence of improvement either in calf blood flow after exercise or in the claudication index. Fig. 7 shows, for example, the blood flow before and eight weeks after sympathectomy in a patient with a Group A response. The blood flow was also determined at 5, 14, and 19 weeks after the operation, with similar results. The claudication index averaged 77 before and 79 after operation. A typical patient who showed a Group B response made 173, 120, 150, and 150 contractions 7, 8, 8½, and 9 weeks after the operation respectively, whereas his previous best was 140 contractions. There was no improvement in his calf blood flows in any post-operative test (Fig. 8). All these patients said that their exercise tolerance had not been improved by the operation.

Discussion

In order to assess any treatment of intermittent claudication it is desirable to study both the claudication index and the calf blood flow during exercise. The latter may bear no relation to the resting calf blood flow, so that the demonstration of an increase in resting calf flow is of no significance. The flow immediately after exercise is probably similar to that during the relaxation periods in exercise.

FIG. 7.—Group A pattern. Post-exercise calf blood flow before and eight weeks after removal of the first, second, and third lumbar ganglia in a patient aged 50. Similar flows were obtained 5, 14, and 19 weeks after operation. Skin temperature and skin resistance of foot after sympathectomy showed no change in response to indirect heating carried out by immersing the hand, forearm, and as much of the arm as possible in a stirred water-bath at 44° C. In view, however, of the findings of Boyd and Monro (1949) it is unlikely that all the vessels in the leg were completely denervated.

FIG. 8.—Group B pattern. Post-exercise calf blood flow before and eight weeks after sympathectomy in a patient aged 47. Similar flows were obtained seven and nine weeks after operation.

It is a much better, though still indirect, index of the blood flow during exercise than is the resting blood flow. It can also be determined simply and with precision. For these reasons its use is recommended, and it has been employed in this work. The ergograph does not, of course, exactly reproduce normal walking conditions, but it allows the blood flow to be measured after standardized exercise. To do this after walking involves some delay.

The values obtained for the claudication index were not constant for any one patient but varied somewhat on different occasions. In order to reduce these differences as much as possible it is essential for the subject to have a preliminary practice on the ergograph. After becoming familiar with the exercise his claudication index should be determined on at least four separate occasions. It is important to tell him to carry on until compelled to stop.

The knee must be kept at the same angle throughout the series, because when it is more extended the subject is often able to perform many more contractions.

On pooling all results, 95% of the claudication indices and immediate post-exercise calf blood flows before treatment lay between 38% and 17% respectively above and below the mean for each individual. Any increase that was less than these values after treatment cannot be considered significant. The stage of the disease did not seem to affect the range of variation, in the same individual on different occasions, of either the claudication index or the immediate post-exercise blood flow. There was no evidence in any of the patients tested in the present series that padutin or lumbar sympathectomy caused a significant change in the claudication index or the immediate post-exercise calf blood flows.

The patients' own statements during treatment are occasionally misleading. They may, in an attempt to convince themselves that they are getting better, go further by walking more slowly, or overestimate the distance walked, or drive themselves further in spite of pain. For instance, four of the patients in the middle of their course of treatment with padutin said that their walking distance was increased, but their claudication index was found to be unchanged.

Since the condition may be progressive, the fact that the claudication index and the calf blood flow after exercise remained more or less unchanged during padutin treatment might indicate that this drug prevented a deterioration in the patient's condition. Before beginning treatment two of the patients were examined for four and six months respectively, during which time there was no deterioration in the calf blood flow after exercise. However, to obtain definite evidence on this point it would require two large groups, one acting as a control.

If during treatment there had been any definite evidence of improvement in the claudication index in these patients without a change in the calf blood flow following the exercise, it would have been necessary to control the results by treatment with a placebo in order to rule out the possibility of psychological improvement. As no improvement was found, this was not thought to be necessary.

The tests described with indirect heating and T.E.A.B. may be useful in assessing whether sympathectomy can be expected to cause at least a temporary (Barcroft and Walker, 1949; Lynn and Barcroft, 1950) increase in the calf blood flow immediately after exercise. Three patients who had no increase of their post-exercise calf blood flow during heating or after T.E.A.B. also had no increase after sympathetic neurectomy.

Finally, these results deal only with claudication and the calf blood flow, not with the effect of padutin or sympathectomy on the temperature or circulation of the foot. All but one of the sympathectomized patients had a warm foot after the operation, and five of them felt that this made it worth while.

Summary

A method is described in which an ergograph and a light celluloid plethysmograph were used to measure the claudication index and the post-exercise blood flow through the calf.

The use of this method in the evaluation of treatment in intermittent claudication is discussed.

In eight cases of arteriosclerosis in which the primary complaint was intermittent claudication, padutin, administered both by mouth and by intramuscular injection over periods of 14-21 weeks, had no effect on the claudication index or the post-exercise blood flow through the calf.

Eight cases of arteriosclerosis with claudication examined before and at varying times after sympathetic neurectomy showed no evidence of improvement in the claudication index or the post-exercise blood flow through the calf.

I would like to thank Mr. E. J. Finnan, M.Sc., of the Department of Civil Engineering, Queen's University of Belfast, who designed and constructed the ergograph; also the patients, who willingly co-operated. I would also like to thank Messrs. Bayer Products, Ltd., for their co-operation and for the supplies of padutin.

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INTRAMUSCULAR HEPARIN

BY

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It is generally considered that heparin is the most efficient and the safest anticoagulant in common clinical use. However, satisfactory therapy with this drug has hitherto necessitated frequent intravenous injections, which are irksome to both patient and doctor. Since heparin cannot be given by mouth, a method of administration which avoids the intravenous route and decreases the frequency of injections would have obvious advantages. Attempts to achieve this have been made in the past with various preparations of "depot" heparin, incorporated in Pitkin menstruum or other media. These have not proved completely successful.

A concentrated aqueous solution of heparin, 25,000 units per ml., for intramuscular injection has recently come on the market. This paper describes trials with this preparation carried out on 20 cases at the Institute of Cardiology.

Methods

All clotting times were determined by the method of Dale and Laidlaw (1911-12). Objections have been raised to this test, since it employs capillary blood. However, most authorities agree that all methods of estimating clotting time are unsatisfactory, and that techniques employing capillary blood are no more inaccurate than those in which venous blood is used. Moreover, the Dale and Laidlaw method is easy to carry out, gives an excellent end-point, and avoids the necessity for repeated venepuncture on the same patient. It was therefore admirably suited to the present type of study. The normal clotting time determined with this technique is two and a half to three minutes.

It was necessary to establish a criterion for adequate anticoagulation when using this method. This was done

by injecting a standard dose of heparin intravenously into normal subjects and measuring by Dale and Laidlaw's method the extra time before clotting occurred.

Fig. 1 shows the average delay of clotting at ten-minute intervals in 16 normal subjects following the intravenous

FIG. 1.—Average curve obtained in 16 normal subjects after an intravenous injection of 100 units of heparin per kg. body weight. Delay of clotting = actual clotting time minus control clotting time.

when given intravenously. After one hour the delay of clotting was two minutes. It was felt that a satisfactory blood level of heparin should exist for one hour after the intravenous injection of a therapeutic dose, and accordingly this was the criterion for adequate anticoagulation adopted in this work.

Results

The usual dose of heparin when given intravenously is about 30,000 units a day. It was reasonable to suppose that intramuscular injection would demand higher dosage, and trial and error showed that a single dose of 35,000 to 40,000 units given intramuscularly would delay clotting satisfactorily for twelve hours. The results obtained were extremely uniform, with only minor variations from patient to patient.

Fig. 2 shows the curves from two patients. After a single intramuscular injection of 37,500 units of heparin (1.5 ml. of solution) the delay of clotting has been plotted for twelve hours. Both these curves differ markedly from that

FIG. 2.—Clotting delay in two patients, followed for twelve hours after an intramuscular injection of 37,500 units of heparin.

obtained following intravenous injection (Fig. 1). With intramuscular injection, clotting is never considerably prolonged even in the initial stages, and the anticoagulant effect is very well maintained. This would seem to show that the drug is absorbed from muscle at a constant