BRITISH MEDICAL JOURNAL

LONDON: SATURDAY, APRIL 27th, 1935

THROMBO-ANGIITIS OBLITERANS

WITH SPECIAL REFERENCE TO ITS PATHOLOGY AND THE RESULTS
OF SYMPATHECTOMY

BY

E. D. TELFORD, B.CHIR., F.R.C.S.

PROFESSOR OF SURGERY, UNIVERSITY OF MANCHESTER

AND

J. S. B. STOPFORD, M.D., F.R.S.

PROFESSOR OF ANATOMY, UNIVERSITY OF MANCHESTER

This mysterious disease, formerly described under a bewildering variety of names, owes its present title to the work of Buerger, whose observations culminated in his important book, published in 1924.

The disease is a chronic, occlusive lesion, which affects, in the first instance, the medium-sized arteries, especially of the lower limb, and it is to Buerger that we owe the statement that thrombo-phlebitis is not only found in association with some cases, but may actually precede the development of clinical signs of arterial obstruction. The work of many observers since 1924 leaves no doubt that thrombo-angiitis obliterans is a definite clinical entity, belonging to the vasospastic group of vascular lesions.

The following study is based on personal observation of some 200 cases, and is largely concerned with the results obtained by sympathetic cord ganglionectomy. To this end we have taken as a basis of assessment those patients who were operated upon by us in the three years April, 1931, to April, 1934. The number is forty-eight, and in a recent review the present condition of each one has been ascertained.

Occurrence

Thrombo-angiitis obliterans is pre-eminently a disease of the male. Every writer insists on its rarity in women. A report of the Mayo Clinic mentions ten cases in women, Buerger gives only three, and we have seen but two undoubted cases. It is evident from the literature of the subject, which at this date includes several large and important series of cases, that less than 1 per cent. of the patients are women. Earlier writers stressed the frequency of the disease in the Jew, but more extended observations show that this suggested preponderance is merely fortuitous, and important lists of cases have been reported in Chinese and Siamese natives. Our own series contains no greater proportion of Jews than one would expect in the mixed population of Manchester.

Occupation appears to have no direct relation to the disease. We have thought that an undue proportion of our cases arose in men whose work as navvies, slaters, etc., exposed them to much wet and cold, but it is clear that this can be no more than a contributory or aggravating factor.

The disease is almost invariably first seen in the legs, and appears to begin in the medium-sized arteries, such

as the dorsalis pedis and the posterior tibial. It is rarely seen in the arms. We have seen only two patients in which there was thrombosis of the arteries of the arm. It is significant that many of our patients complain of a Raynaud type of symptoms in the hands. This is present in one-third of the cases, and it has been seriously suggested that the symptoms of Raynaud's disease in the hands of a man will be followed by thrombo-angiitis obliterans in the legs. It would, however, need observations over many years to estimate the truth of this suggestion.

Instances of the disease have been described by other writers in the mesenteric, spermatic, and coronary arteries. In one of our cases (reported below), a man who died suddenly in a tram at the age of 26 showed at post-mortem examination the lesions of thrombo-angiitis obliterans, both macroscopical and microscopical, in his coronary arteries.

Age of Onset and Clinical Course

It is difficult to estimate the real age of onset because it is rarely that a patient comes under observation before the claudication has crippled him, and by this time the arterial disease is far advanced. It has taken perhaps months, more probably years, to reach the stage of claudication. The average age at which claudication was observed in our series is 45 years. It is likely that the disease commonly begins about 40 years, or even in the later years of the third decade.

After the age of 50 years occlusive lesions of the arteries are likely to be due to atherosclerosis rather than to thrombo-angiitis obliterans. It is important to stress this point, since the two lesions are quite different, and the atherosclerotic cases are not likely to benefit from sympathectomy.

Once established, the course of the disease is very variable. It is usually chronic, tending to progress by exacerbations with long periods of arrest. It is this factor which not only makes prognosis difficult, but renders it risky to lay too much stress on the value of any one particular line of treatment.

The variable course of the disease is well illustrated in our series. In one case a man aged 42 years was admitted on account of a thrombo-phlebitis of the right internal saphenous vein. He gave a history of claudication of less than seven months. On examination no pulse

was detected either at Poupart's ligament or in the iliac fossa on each side, and in seven days he was dead from a thrombosis ascending from the aortic bifurcation, which produced sudden obstruction of the inferior mesenteric artery. On the other hand, we have seen a man of 52 years whose claudication had lasted more than twenty years, and in spite of this he had never suffered any serious complication beyond the loss of small portions of two toes.

It is so common as to be almost the rule for the disease to begin first in one leg and later in the other, whereupon the second leg to be attacked shows the disease in a worse degree. It should, further, be realized that the disease is always bilateral. It is usual for a patient to complain of claudication in one calf and to state that the other leg gives no trouble in walking. The truth is that the worse leg pulls him up first, and the other leg, although probably on the verge of claudication, has no opportunity to display the symptom.

Symptoms

The first symptom to attract attention is the claudication. After walking some distance the patient is arrested by severe and crippling pain. The cramp-like pain is felt usually in the calf of the leg, sometimes in the foot, and may be described by some as a tense, constricting ring just below the knee. A rest of two or three minutes, often spent gazing into a shop window, relieves the pain, and the patient resumes his walk only to be pulled up again, often within a distance slightly shorter than before. His walking distance gets shorter and shorter as time goes on, and in one of our patients it was no longer than five yards. Should the patient hurry or be walking up-hill the claudication comes on earlier. The "walking distance" at which claudication begins is of little or no value in estimating the severity, depending as it does on such factors as speed of walking, inclination of ground, and the patient's own idea of distance. It is possible to obtain an exact measure of claudication by a simple machine constructed from an old-fashioned wooden back-splint with a foot-piece. The foot-piece is hinged, and the patient is asked to plantar-flex the foot to its full extent against a constant resistance and at a constant rhythm. In this way the symptom is reduced to a definite figure, comparable for all cases. For example, in a recent case pain began to be noticed and blanching to be seen at forty excursions, whilst at sixty-five all movement was arrested by severe pain, and the foot was seen to be of a cadaveric whiteness.

A few of the more observant patients have noticed before the onset of claudication that their feet felt at times intensely cold, and have observed that whilst in this condition the feet appeared very white. This blanching suggests that the initial lesion is vasospastic, and is akin to the first stage of a Raynaud attack. If these patients are examined immediately after walking, their feet will be found to be very white.

Blanching of this kind is, of course, not necessarily to be accepted as evidence of spasm. In these limbs, which already suffer from a diminished entry of arterial blood, the blanching may be due to a too rapid emptying of the veins as a result of muscular action. There are, however, certain observations, to be mentioned later in the section on examination of the pulses, which do suggest that a spastic condition of the arteries is not only present but may vary in intensity from time to time.

At a variable interval after the onset of claudication the patient notices that his foot becomes discoloured when hanging down. The colour is of a dull brick-red hue, beginning in the toes and spreading to the dorsum. If the foot in this condition is raised above the level of the heart the rubor disappears, and is replaced by a paper-

white blanching. The rapidity with which these colour changes can be elicited is a measure of the arterial obstruction—the more rapidly they come and go the more advanced is the disease.

At length the patient begins to complain of pain whilst at rest, especially when warm in bed. He usually discovers that his pain is eased by exposure to cold air and by the dependent position. Many patients manage to secure some sleep by hanging the bare limb over the side of the bed.

Sooner or later the debilitated tissues invite the onset of "trophic" lesions. Not all cases develop these; the incidence is probably just under 50 per cent. of all patients. The most common is a chronic intractable onychia, usually of the great toe. In most cases the nail has been removed in an attempt at treatment, and the patient presents a deep callous ulcer of the nail-bed. This type is more common in the younger patients. In the more severe cases a black spot of gangrene appears, usually on a toe, sometimes on the heel, and is apt to take on a moist type, spreading rapidly to the foot and leg.

Thrombo-phlebitis, though an integral part of the disease, is by no means seen in all cases. In our experience it is relatively rare, and has been found in not more than 10 per cent. of the patients. Very exceptionally thrombo-phlebitis may appear as the first symptom of the disease, but in such cases we have not as yet seen a patient who did not show evidence of arterial obstruction. We have observed it usually only as a superficial lesion. In one patient only have there been symptoms of deep intermuscular phlebitis. It is found most often in the form of multiple patches in the smaller venous radicles of the leg, but at times considerable stretches of the saphenous veins, in both legs and thigh, may be affected.

Examination of the Pulses

In a case of average severity examination commonly shows an absence of palpable pulse in the dorsalis pedis, posterior tibial, popliteal, and superficial femoral arteries. It is usual to find a good pulse for a distance of some two inches below Poupart's ligament. This observation is of interest, because it is generally recognized by anatomists that it is in this district that the nerve supply of the arterial wall changes over from a perivascular to a peripheral origin.

The disease begins in the smaller peripheral arteries—for example, the tibials—and it is worthy of note that these smaller arteries contain relatively more muscular tissue than do the larger trunks, in the walls of which the amount of elastic tissue shows an increase. We have notes of some patients in whom the posterior tibial pulse is at one time distinct and at another time absent. Such a finding is of obvious importance in the aetiology of the disease. It is only in the older, more advanced cases that the thrombosis extends to the external, internal, and common iliac arteries. The silent arteries are often to be felt as solid rods, particularly in the case of the superficial femoral artery. Clinical evidence of extensive perivascular fibrosis can often be obtained on palpation of the popliteal fossa, the contents of which appear lost and merged in one diffuse fibrous mass.

The long-continued pain and lack of sleep produce their inevitable effects in these patients. They are usually very worn and tired.

The Cause

It may be said at once that the cause is unknown. Rabinowitz in 1923 described an organism which he averred was capable of causing the disease in rabbits. No one has so far submitted convincing evidence that the cause is a micro-organism.

We are probably on safe ground in regarding the disease as spasm followed by thrombosis. Some evidence of spasm is afforded by the intermittent attacks of coldness and blanching, often induced by exercise. Moreover, we have seen early cases in which pulsation in the posterior tibial artery is at one time distinct and at another time silent. That persistent arterial spasm will lead to thrombosis we know from the phenomena of ergotism and from our observations on those cases of cervical rib which show arterial complications. As an explanation of the spasm hyperadrenalinaemia has been suggested, and adrenalectomy has been tried as a line of treatment. Overaction of the constrictor mechanism by an irritative lesion of the sympathetic may supply the explanation, but we are as yet without a reasonable suggestion as to the cause of such overactivity.

We have examined many hundreds of sections of sympathetic cords and ganglia, obtained at operation on these patients, and on comparing these with presumably normal ones, obtained at similar ages, we find no evidence of any organic lesion in this part of the autonomic system.

Routine examination of the blood for sugar, urea, calcium, phosphorus, and for coagulability time has yielded no clue. Syphilis has nothing to do with the disease. The excessive use of tobacco, the cigarette being more usually incriminated, is often given as an explanation; both tobacco and paper have been suspected. Maddock and Collier found in tobacco smokers a drop in the cutaneous temperature of the digits which they state is not seen if the smoke be filtered. On the clinical evidence it is plain that, whilst tobacco may be a cause or a contributory factor, it cannot be the sole direct cause. The number of cases which have been seen in both men and women non-smokers prove that other causes must be at work. It is, for instance, said by experienced veterinary surgeons that thrombo-angiitis obliterans is found in horses.

Another clinical fact, difficult to interpret, is the predominance of the disease in men and in the lower extremities. In this respect it is of interest to note that where a large population has been exposed to poisoning by ergot, the toxic phenomena have been in men and in the lower limbs. The work of Pickering is interesting as showing that there are certain differences in the reactions of the arteries of the leg as compared with those of the arm. These observations may prove to have a bearing on the predilection of thrombo-angiitis obliterans for the lower limbs.

Naked-eye and Microscopical Anatomy

The investigation of the condition of the vessels in twenty-six amputations has provided us with the opportunity of studying the pathological changes which are characteristic of the disease, and has caused us to modify somewhat our earlier impressions published ten years ago.¹

Dissection has confirmed the "patchy" nature of the disease, since it is common even in advanced cases to find several inches of normal vessel between two points showing partial or complete occlusion. As is to be expected, the situation of the arterial obstruction has a pronounced influence upon functional capacity. For anatomical reasons occlusion of the upper part of the popliteal artery is most unfavourable.² Dissection also demonstrates clearly that the disease affects primarily the muscular arteries, and that at a later stage the veins may show very little change. Our investigations have proved that the veins are implicated much less than is supposed, and there is considerable evidence to suggest that the histological change in the veins is different from that in the arteries. In the latter the primary change

is undoubtedly to be found in the inner coat, where proliferation of the intima can invariably be demonstrated at the initial site of the disease. Later, thrombosis occurs in the neighbourhood of the intimal irregularities. The size of the clot varies. At first it is often very small and localized, but later increases by additions, and it is often possible under the microscope to recognize three zones—the thickened intima, the organizations of the primary thrombosis, internal to which is to be seen the more recent clot. These changes lead to a narrowing of the lumen, and ultimately to occlusion. When the thrombosis completely fills the lumen the clot often extends in a central direction some distance beyond the site of the original intimal proliferation, and transverse sections of the vessel at this level will fail to demonstrate the primary intimal change. It is suggested that this is why some observers have not recognized the significance of the thickening of the intima. Succeeding proliferation of the intima, and becoming more pronounced as the organization of the clot proceeds, is to be found fibrosis of the media. The increase of fibrous tissue in the adventitia is also associated with the organization of the thrombus. Unlike Buerger³ and some of the other writers, we find nothing characteristic in the process of organization. We have, but only occasionally, seen the collections of lymphocytes to which Buerger has directed such marked attention. In our view the organizing process shows no special features. In veins proliferation of the intima is usually absent, and the primary change there is obstruction by clot. Later this becomes slowly organized, and again the process is not in any way different from that under other circumstances. Our inquiries have caused us to believe that the venous thrombosis is, as a rule, if not invariably, secondary to the arterial changes. The cause of the intimal proliferation in the arteries remains obscure, but we believe that it may be related to the attacks of intense spasm which we have noted clinically.

Treatment

The essentially chronic nature of the disease, with its long periods of intermission, makes it very difficult to estimate the value of treatment, and no doubt explains the good results which writers have, from time to time, claimed for one particular method. Our own experience is that all forms of physiotherapeutics are, at the best, merely temporary palliatives, and unless handled with care may be actually dangerous. No drug by mouth appears to have any effect on the disease. The injection of substances—for example, muscle extract, acetylcholine, typhoid vaccine, and similar vaso-dilator agents—has been extensively tried. The results are temporary, and the patient soon tires of the discomforts of febrile reaction.

Operative treatment of various kinds has been explored by many surgeons. Adrenalectomy, high ligation of the femoral vein, and perivascular sympathectomy have failed to maintain the often enthusiastic claims with which they were introduced. If the disease is, at its root, spastic in nature, and if such spasm is the result of impulses via the vaso-constrictor fibres of the sympathetic, the most obvious and rational operation is cord ganglionectomy.

We began our series in April, 1931, and up to April, 1934, we had performed the operation of lumbar cord ganglionectomy (excision of the second, third, and fourth lumbar ganglia with the intervening chain) in forty-eight cases of thrombo-angiitis obliterans. In forty-two of these the excision was bilateral, and in six a unilateral operation was done, the patients having already suffered amputation of one leg. Convalescence in all cases was straightforward, and there was no death in the series.

The Results

The present condition of these cases has been recently reviewed. Since operation six of the patients have died. The causes of death are: haematemesis from a duodenal ulcer (verified post mortem); alcoholic delirium (verified post mortem); cardiac muscle failure (no post-mortem); and the remaining three from coronary disease (one verified post mortem). In the remaining forty-two we have classified the results as:

Good.—Free from rest pain, able to walk well, and in most cases have returned to work.

Fair.—Improvement as regards rest pain and general condition, but little or none as regards walking and capacity for work.

Unsuccessful.—No improvement in several cases ending in amputation.

The numbers in each case are: good, twenty-five; fair, seven; and unsuccessful, ten.

Many points of interest in the post-operative condition of these patients have already been discussed by us in a former article, and more extended experience has confirmed the opinions there expressed. The object of sympathectomy being to abolish spasm and to dilate such collaterals as are still capable of enlargement, it is evident that the younger patients and the less advanced cases will give the better results. It is in this class of case that the majority of our good results lie. Some writers have taken the line that early cases should not be subjected to sympathectomy because of the gravity of the operation. The operation is, in fact, perfectly straightforward, not particularly difficult, and very safe; it is at least as safe as a simple appendicectomy. Moreover, it is just in these earlier cases, where spasm is pronounced and thrombosis limited, that the operation should be done.

Cases with onychia have healed readily and permanently, but the outlook when gangrene is present is not good. In these advanced cases it is doubtful how far sympathectomy is worth while; the operation will, however, ease pain, and may permit a lower level of amputation than might otherwise have been possible.

The present inquiry is concerned more, immediately with the permanency of the result and the effect of sympathectomy on the progress of the disease. On many of these cases it is perhaps permissible to express an opinion, since they are of more than three years' standing. The operation does appear to have a definite action in arresting further progress of the disease. In only two cases is there any evidence of deterioration, and in one of these a partial amputation of a toe has been necessary. It is interesting to note that attacks of phlebitis may still occur after operation; of this we have had three instances. The effect on the claudication is apt to be disappointing. In a few of the slighter cases this disability has been entirely abolished, but the average result is that although the walking distance may be considerably lengthened the claudication is still present.

Conclusions

Our conclusions are that in the present state of knowledge of thrombo-angiitis obliterans, treatment by cord ganglionectomy is not only to be recommended but is the only procedure which offers any hope of permanent relief. It will give its best results in the younger men, and in those cases in which the spasmodic element is clinically well defined, as evidenced by reaction to exercise and by the customary preliminary vaso-dilator tests. The positional colour changes have seemed to us of great value in determining the extent of the disease; the more they are marked the less satisfactory will be the operative result.

There are two cases which we wish to place on record as presenting features of special interest. In the one

case, thrombo-angiitis obliterans has given, so far, a good result after cervico-dorsal ganglionectomy, whilst the second illustrates death by coronary thrombosis in a man of 26 years, and shows that changes, indistinguishable from those of thrombo-angiitis obliterans, may be present in the heart at this early age.

SUMMARY OF CASES

1. Male, aged 39 years, clerk. First symptoms were in the legs thirteen years ago. Both legs were eventually amputated for gangrene. In February, 1934, he was seen with his right hand white, "dead," and very painful. No pulse was felt from the wrist up to the proximal part of the brachial artery. The right cervico-dorsal ganglion was at once removed. The arm recovered and, although it shows no pulse, it has been warm, useful, and free from pain since the operation. Towards the end of June, 1934, he complained of similar symptoms in the left hand. All pulses were present, but very weak. During the ensuing three weeks the thrombosis was seen to ascend from the wrist to the anterior axillary fold. The left cervico-dorsal ganglion was removed. The hand became warm, useful, painless, and on several occasions a faint radial pulse has been detected. The symptoms, which appeared with great rapidity and threatened the loss of both arms, have, up to the present, been completely arrested.

2. Male, aged 26 years, engineer. He began with claudication as a student at the age of 19, and became steadily worse. Onychia developed in the first and second toes of the left foot before admission. Callous ulcers were present where the nails had been avulsed. He had spent the nine months bed-fast and in much pain. No pulse was to be felt anywhere in the legs excepting in the common femoral artery of each side. After a bilateral sympathectomy in August, 1932, he recovered very quickly and returned to his work, which involved much travelling both at home and abroad. During this time he reported frequently, and seemed very well. Exactly twelve months after his operation, whilst running for a tram, he collapsed and died. Post-mortem examination showed a pericardial sac containing some blood-stained fluid; the heart muscle was heavily infiltrated with blood, and the coronary arteries much reduced in calibre by thrombo-angiitis obliterans. This case is of much interest as showing that the disease may, on occasion, be more widespread than one is apt to imagine. A similar case is reported by Perla.

REFERENCES

- ¹ Telford, E. D., and Stopford, J. S. B.: "Thrombo-angiitis Obliterans," *British Medical Journal*, December 6th, 1924.
- ² Stopford, J. S. B.: "A Cause for the Frequent Occurrence of Gangrene after Ligature of the Popliteal Artery," *Brit. Journ. Surg.*, 1924, xii, No. 45.
- ³ Buerger, L.: *The Circulatory Disturbances of the Extremities*, Philadelphia, 1924.

Discussing the importance of the diencephalic factor in the pathogenesis of epileptic crises, A. Salmon (*Presse Méd.*, March 13th, 1935, p. 405) states that the epileptogenous properties of the diencephalic nuclei are demonstrated by the fact that experimental and pathological lesions of the said nuclei are manifested by convulsive phenomena. This conception, which accords perfectly with the sympathetic and hormonal properties of the nuclei of the tuber explains the pathogenesis of the numerous cases of diencephalic epilepsy reported in recent years. The theory of an epileptogenous centre in the infundibular region does not imply that epilepsy is always connected with diencephalic alterations: cases of cortical origin are much more frequent than those of subcortical. Many clinical facts support the theory that a diencephalic factor exists also in the pathogenesis of epileptic attacks of cortical origin. The latter show a very close relation with the principal diencephalic functions (sleep, heat production, glyco-regulation, diuresis), which are ameliorated and temporarily disappear by the barbiturates having an elective hypnotic action on the nuclei. These facts justify the hypothesis that epileptic crises of cortical origin depend on the very sharp reaction of the diencephalic nuclei, and explain their amelioration by medicaments which diminish the activity of the latter. This accords with the opinion that epilepsy of cortical origin is due to suppression of the inhibitory action of the cortex on the subcortical centres. Cortical changes, through qualitative and quantitative modifications of the cerebral fluid, usually react on the functions of the subthalamic nuclei.