Remarks

ON THE

RESULTS OF LUMBAR SYMPATHECTOMY IN
THROMBO-ANGIITIS OBLITERANS

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We have, since April, 1931, performed upwards of fifty operations on the autonomic nervous system by cervical-dorsal ganglionectomy or excision of the lumbar cords and ganglia. These operations have been done for a variety of conditions, chiefly thrombo-angiitis obliterans, Raynaud's disease, "acrocyanosis," anterior poliomyelitis, Hirschsprung's disease, and scleroderma. Of the patients treated we have, for the purpose of this communication, chosen the first sixteen cases of sympathectomy done for thrombo-angiitis obliterans, believing that a sufficient time has elapsed to warrant an opinion on the result of the operation. No case operated upon later than August, 1932, is included in this study.

The cases were all males, the average age being 47 years. Only three of the sixteen were of Jewish blood. The alleged predominance of Jews as victims of this disease is, as we have already pointed out, nothing more than a geographical accident. Of the sixteen, only two followed outdoor occupations in which they were exposed to the weather; the remainder were engaged in sheltered work within doors. Close questioning as to habits of pipe or cigarette smoking does not support the contention that this is a causal factor. The Wassermann reaction was negative in all but one case: syphilis has no relation to the disease. Routine observations on serum calcium and coagulability time have yielded nothing of interest. As regards duration of the disease, the patients show the extreme differences which exist in the rate of progress in individual cases. The longest history was one of twenty years, while in the shortest symptoms developed which became crippling within the brief space of eight months. The average interval between the onset of symptoms and operation was six and a half years.

SYMPTOMATOLOGY

It is not easy to obtain accurate histories of the onset. With most patients the first complaint is intermittent claudication, with sensations of severe pain, rigidity, or constriction about the calf of the leg. In the more intelligent patients, however, a history of initial coldness, usually in attacks, is given, and these patients describe the feet as "dead white" during the attacks. This is important, because it suggests that there is an early stage of the disease in which vasospasm is the chief feature. In most of the cases claudication is the first complaint, and the walking distance is progressively lowered to 150 or 200 yards. In one of the cases (No. 6) the limit was as low as five yards.

The cases were all bilateral, though as a rule more complaint was made of one leg than of the other. Some of the patients showed the condition which has been pointed out by other writers—namely, that the leg in which the disease is first evident may eventually prove the better limb of the two. This sequence is, however, by no means invariable. It is interesting to note that of the sixteen cases suffering from thrombo-angiitis obliterans in

the lower extremities no fewer than seven made complaint of vascular disturbance in the hands. These disturbances were invariably of a spasmodic Raynaud type, and thrombosis was never clinically evident. It may be argued that these are simply instances of thrombo-angiitis obliterans in the upper limbs, but it is significant that one of our cases (No. 15) developed most classical symptoms of Raynaud's disease in both hands, three months after lumbar sympathectomy for thrombo-angiitis obliterans. In all cases the feet were very cold. The colour was usually slightly dusky owing to cyanosis, but in some cases the skin was dead white. In a few, a cadaveric appearance was observed in the feet after walking a short distance. The dependent position of the limb produced some degree of rubor in nearly all cases, whilst elevation commonly produced a distinct blanching of the foot. Most of the patients had discovered for themselves that the dependent position, together with cool air, gave them the most comfort, and were accustomed to try to get sleep by hanging the limbs out of bed.

Palpation of the pulse showed that in four of the patients no pulse could be felt at any point below Poupart's ligament, while in twelve a strong pulse was present in the common femoral artery, but this pulse ceased abruptly about the division of the artery into the superficial femoral and profunda arteries. One case showed perceptible pulses throughout both limbs, excepting that in both thighs the superficial femoral artery was silent and could be felt as a hard cord. A similar solid thickening of the arteries could be felt in most of the cases, whilst three patients showed a very evident deep thickening in the popliteal space, suggesting that the neuro-vascular packet had become one firm fibrous mass. The presence of a good, often thumping, pulse in the common femoral artery in twelve out of the sixteen cases is of interest, as it may help to throw light on the nervous origin of the disease. The point at which the pulse ceases is the point at which the sympathetic supply to the vessel has been shown to change over from a perivascular plexus to a supply which is derived from the peripheral nerves. This very usual preservation of the pulse in the common femoral artery thus comes into line with the preservation of the pulse in the subclavian and major portion of the axillary arteries of the upper extremity in those instances of cervical rib which give rise to vascular complications.

The common mode of onset of grave trouble in thrombo-angiitis obliterans is by an onychia rather than by gross massive gangrene. The onychia is usually of the great toe, and is no doubt related to the frequency of an ingrowing nail in this toe. Usually the nail has been removed under a mistaken diagnosis, whereupon the nail-bed is transformed into an intractable, callous, and painful ulcer, with no tendency to heal or to form a new nail. It sometimes happens, however, that the onychia proves the starting-point of a massive gangrene. Of the sixteen cases under review eight showed neither infection nor loss of tissue, four showed extensive gangrene of two or more toes, and in one instance of the heel as well, while four were admitted with callous ulcers of a toe following avulsion of its nail. In three of the sixteen cases the superficial thrombo-phlebitis which is occasionally found in thrombo-angiitis obliterans was present.

The various methods of treatment hitherto attempted have included such procedures as perivascular sympathectomy (with or without simultaneous ligation of the femoral vein), attacks upon the suprarenal gland, and injections of substances such as typhoid vaccine, acetylcholine, and muscle extract. Palliation by heat, electricity, diathermy, etc., have usually been tried. The only thing common to these is that they have utterly failed to prove of any permanent benefit in the treatment of the disease.

THE OPERATION

Owing to the fact that thrombo-angiitis obliterans contains an element of vasospasm which is, according to one view, the essential cause of the disease, and according to another merely a superadded factor, surgeons have suggested and tried various forms of sympathectomy. Having had under observation since 1924 a very large number of patients suffering from thrombo-angiitis obliterans we decided to try the effects of an extensive sympathectomy in a consecutive series of cases as they came under our observation. The operation consists in removing on both sides a section of the lumbar sympathetic cord which includes the second, third, and fourth lumbar ganglia. The approach is by the transperitoneal route, which has been admirably described by Adson. The only modification of this which we would suggest from our experience is that we have found it much easier to proceed on the right side by an incision of the posterior peritoneum lateral to the caecum and ascending colon than by the incision, as figured by Adson, between this portion of bowel and the inferior vena cava.

Owing to the invariably bilateral nature of the disease it is necessary to remove both the right and the left cords at the operation. This is, of course, easily done by a transperitoneal approach, but in five of the sixteen cases the route used was the extraperitoneal, restricted to one side. The reasons for this were that in three cases one limb had already been amputated in mid-thigh and in the other two the patients had very obese abdomens. In a very stout abdomen the transperitoneal route will be found difficult, but access to the lumbar cord can be easily obtained on either side behind the peritoneum by the use of an enlarged Abernethy incision.

Before operation we have, in all cases, made careful observations with an electric surface thermometer on the change in surface temperature of the limb induced by the spinal anaesthetic. The rise of temperature so obtained is a direct measure of the result which may be expected from the operation, and we find throughout our cases that this rise of temperature has corresponded very exactly with the quality of the post-operative result. For example, Case 14 complained of severe claudication at eighty yards. On clinical examination both legs were found to be affected by thrombo-angiitis obliterans, but the right was clearly worse than the left. Under the spinal anaesthetic the temperature on the right side rose by only $0.8^{\circ}\text{C}.$, but on the left it rose $5^{\circ}\text{C}.$ (These figures are, of course, much below those to be obtained in normal limbs. In healthy patients the rise of temperature in the feet under spinal anaesthesia may attain as much as $10^{\circ}\text{C}.$) When seen four months after the operation the man stated that he could walk any distance if he went slowly, but if he hurried he had some pain in the right calf. He regarded the left leg as completely well.

DETAILS AND RESULTS

In attempting to assess the clinical results we have grouped them as follows:

Good.—Free from pain and able to walk well.

Fair.—Improvement as regards pain and general condition, but little as regards working capacity.

Unsuccessful.—No improvement, or subsequently requiring amputation.

An analysis of the cases on these lines shows: good, 9; fair, 3; unsuccessful, 4.

There is one difficulty which arises in attempting to estimate the success of the operation. In these patients, although the disease is bilateral, one extremity is commonly in a much more damaged condition than its fellow. It may therefore happen that after sympathectomy no improvement is seen in the worst limb, but a decided

gain is obtained in the better one. Case 13 is an example of this: this man's right leg was, on clinical examination, decidedly worse than the left. Ten weeks after sympathectomy it was necessary to amputate the right leg for gangrene, but the condition of the left leg is so far improved that it seems likely to give no further trouble. Such a case is, however, classed as "unsuccessful," since the operation failed in what is, after all, its main object—the recovery and preservation of the limbs.

We have paid particular attention to the question of the possible return of pulsation in arteries previously silent. In three of the cases we have observed that the pulse, after the operation, has extended a few inches lower down the limb than had been before observed. Beyond these, there is no evidence that the operation has resulted in any return of the pulse in previously silent arteries. Nor is it to be expected when one considers the firm fibrous tissue with which the lumen of these vessels is choked. Sympathectomy clearly produces its good results by dilating collateral vessels, and evidence that this has happened is afforded in several of our cases by a pulse in a dilated muscular branch in the popliteal space, and a distinct pulsation in a muscular branch of the superficial femoral artery about three inches above the patella. It is evident that the better results are given by the younger patients, in whom not only is the disease likely to be less advanced, but the younger arteries dilate more easily after sympathectomy than do those of the older patients.

Whilst cases of onychia have showed rapid healing, the outlook for sympathectomy when gangrene is actually present is not good. The operation is here hardly worth while, excepting that a sympathectomy may render it possible to amputate at a level lower than the customary above-the-knee operation. Many of these patients suffer from well-nigh intolerable "rest-pain," which causes a rapid depreciation of their general health. In such cases it is well worth while to consider a sympathectomy even if the vascular condition of the limb offers but scanty hope of success as regards function. The relief of pain after the sympathectomy is often complete, and we have found this one of the most striking and gratifying results of the operation. It is a point of great practical interest to know to what extent sympathectomy is likely to arrest the march of the disease. In a condition so chronic and so erratic in its progress as thrombo-angiitis obliterans, it will be very long before any opinion can be safely ventured on this point. All that we can say is that if the disease be, as we think it is, the result of vascular spasm, there is good ground to hope that sympathectomy will arrest its further progress. It is somewhat surprising that so extensive a removal of the lumbar sympathetic cord can be done without any sign of harmful effect. We have repeatedly cross-examined our patients in a search for any altered function or deleterious effect of the operation: none has been found, and, in fact, the only difference apparent is that the patients will often state that action of the bowels is more regular than before. It can only be surmised that a sufficient sympathetic supply to pelvic organs is provided by the fibres which descend from the intermesenteric plexus by the so-called middle root of the presacral nerve.

In view of the statements made by Hunter and Royle, we have made some observations on the muscular condition of sympathectomized limbs; it is quite evident that when judged by ordinary clinical and functional tests these limbs show not the slightest difference from the normal.

Thus we believe from our experience that, in most cases of thrombo-angiitis obliterans, sympathectomy is well worth while, and should be done in all cases which show some improvement in circulation (as measured by surface temperature) under spinal anaesthesia. It is quite plain

that in the earlier cases in which thrombosis is not excessive the operation can do much good, and in the more advanced cases the relief of pain which follows may, of itself, fully justify the intervention. We think that sympathectomy will take an established place in the treatment of thrombo-angiitis obliterans. The operation would appear at present to be passing through a phase which is common to the history of many now well-established procedures. These, in their earlier days, had to justify themselves in advanced and seriously complicated cases. They reached their full achievement only when the cases came earlier to the surgeon. Almost without exception our patients have been sent to us when all other forms of treatment have been tried and found wanting. If, then, the results from such material can be described as encouraging, they will be infinitely better when the operation is not regarded as a last resource, but is offered to the patient as soon as the diagnosis is definitely made.

SUMMARY OF CASES

1. M. B., aged 45 years, joiner. History of fifteen years. No pulse felt in either leg, excepting the common femoral, which is normal on right, but very weak on left. Claudication of both legs at 300 yards. Severe rest-pain. A large sloughy ulcer immediately above left medial malleolus; this has been present for fourteen months. Operation: bilateral lumbar sympathectomy, January 13th, 1932. Temperature rose on right 3° C. and on left 1.4° C. The immediate result was very promising, and the ulcer was completely healed in six weeks. He returned to work, but still has claudication on exertion, though with a much longer interval than before. The scar of the ulcer occasionally breaks down. General condition much improved. Result classified as "fair."

2. A. B., aged 52 years, cabinet maker. History of twenty years, during which the following amputations have been done for gangrene: first right toe, 1914; fifth left toe, 1918; first left toe, 1923. On admission the second right toe showed a gangrenous ulcer, with protrusion of the distal phalanx. No pulse present in either leg, excepting common femoral. Severe rest-pain in right leg. Operation: extraperitoneal excision of right lumbar cord, August 23rd, 1932. The pain disappeared and the ulcer healed, with exfoliation of bone in six weeks. The local circulation was much improved. Result classified as "good."

3. S. B., aged 45 years, mechanic. History of two years. Left leg had been amputated through thigh three months before admission. Admitted with gangrene of two toes on remaining foot. No pulse felt anywhere in the limb. Operation: extraperitoneal excision of right lumbar cord, April 27th, 1931. There was some improvement in pain and in the gangrene, but three months later the limb was amputated owing to rapid spread of gangrene. Histological examination of the vessels of the limb showed the changes which are present in thrombo-angiitis obliterans. Result classified as "unsuccessful."

4. R. C. F., aged 46, clerk. History of two and a half years; claudication at 100 yards; no rest-pain. No pulse felt in left leg, but in right all pulses felt, though very feeble. Operation: transperitoneal excision right and left lumbar cords, March 3rd, 1932. Temperature rose on right 3.7° C. and on left 2.8° C. The after-history is completely satisfactory on right, less satisfactory on left. Claudication is still present, but is much less, and he has returned to work. Result classified as "fair."

5. H. G., aged 35 years, capmaker. History of two years; onychia first right toe during the last six months. Claudication marked, and no pulse felt in either leg below the apex of Scarpa's triangle. Operation: transperitoneal excision right and left lumbar cords, November 5th, 1931. Temperature rose on right 1.6° C. and on left 3° C. The onychia was slow in healing, and the toe was amputated through the distal joint. Histological examination of the vessels of the toe showed the typical picture of thrombo-angiitis obliterans. Healing was prompt. He is now free from pain, walking well, and at work. Result classified as "good."

6. R. H. J., aged 53 years, salesman. History of one and a half years. Claudication extreme. He can only walk five yards, when he comes to a stop and both legs are rigid.

All pulses are present, excepting the superficial femoral on each side. The artery can be felt on each side as a solid cord. Operation: transperitoneal excision of right and left lumbar cords, December 16th, 1931. He is now at work, standing or walking all day, and is apparently quite normal. Result classified as "good."

7. E. L., aged 62 years, salesman. History of three years. Claudication at 200 yards, and much rest-pain. Pulses entirely absent in both legs. No sign of atheroma. Operation: transperitoneal excision right and left cords, August 13th, 1932. Temperature rose on right 1.4° C. and on left 1.2° C. There was cessation of rest-pain and improvement in colour and condition of both feet. Now walks much better, but claudication is not entirely lost. Result classified as "fair."

8. J. L., aged 57 years, shopkeeper. History of four years. In September, 1930, left leg was amputated for gangrene of foot. On right side no pulse could be felt, excepting a slight one in the common femoral. Total gangrene of fourth toe. Operation: extraperitoneal excision of right lumbar cord, November 21st, 1931. There was a slight improvement for a time, but on January 5th, 1932, the limb was amputated for spreading gangrene. Result classified as "unsuccessful."

9. J. N., aged 57 years, printer. History five years. A very rapid onset, with severe claudication of both legs, so that he was entirely crippled. In January, 1932, the right leg was amputated for a rapid moist gangrene. Histological examination of the vessels of the limb showed the typical picture of thrombo-angiitis obliterans. On admission the left leg showed no pulse, excepting a good common femoral. There was severe rest-pain. Operation: extraperitoneal excision of left lumbar cord, April 28th, 1932. Temperature rose 4° C. Patient is now walking well with an artificial limb. The left leg gives neither pain nor trouble. Result classified as "good."

10. A. W. O., aged 59 years, salesman. History one year. Rapid onset of severe claudication. On admission, dry gangrene of anterior half, and heel, of left foot. No pulse perceptible in this limb, but very weak pulses present in right limb. Operation: transperitoneal excision right and left lumbar cords, February 6th, 1932. Temperature rose on right 0.6° C. and on left was unchanged. Right leg is much improved, and remains well, but left was amputated six weeks afterwards. Result classified as "unsuccessful."

11. G. O., aged 46 years, spinner. He lost a portion of first toe of left foot in 1917, but has become rapidly worse in the last six months. Can walk only 100 yards owing to claudication of left calf. He makes no complaint of right leg. No pulse felt anywhere in left leg. All pulses present in right leg. Operation: transperitoneal excision right and left lumbar cords, March 18th, 1932. Temperature rose on right 3.1° C. and on left 1° C. This man can now work all day and walk four miles. Result classified as "good."

12. D. O., aged 25 years, engineer. History six years. Began with claudication of left calf, and soon afterwards of right calf. Nine months before admission onychia developed in first and second left toes. The nails were avulsed, but the ulcers have never healed. He spent seventeen weeks in bed under treatment, with no change. No perceptible pulse in either leg, excepting a good common femoral in both. Operation: transperitoneal excision right and left lumbar cords, August 23rd, 1932. Temperature rose on right 1.6° C. and on left 3.4° C. Both feet are now warm and of good colour. All pain disappeared immediately after the operation. The ulcers were healed in three weeks. Result classified as "good."

13. V. S., aged 37 years, clerk. History eleven years. Gradual deterioration, with claudication in both legs. Severe rest-pain. No pulses felt in either leg, excepting a weak one in Scarpa's triangle on left side. Operation: transperitoneal excision right and left lumbar cords, November 29th, 1931. There was only slight improvement in the condition of the leg. Pain continued severe in right leg. Ultimately the left leg did very well, and lost all pain, but the right leg was amputated for gangrenous ulcers in October, 1932. Histological examination showed the changes of thrombo-angiitis obliterans to a very advanced degree. Result classified as "unsuccessful."

14. R. T., aged 52 years, clerk. History of three years. Claudication began three months ago in right leg between

200 and 300 yards. The patient is very worn and tired from severe rest-pain. On the right side there is a feeble pulse to apex of Scarpa's triangle, but the femoral artery is felt as a solid cord below this point. On the left side all pulses present, but very weak. Operation: transperitoneal excision right and left lumbar cords, July 4th, 1932. Temperature rose on right 0.6° C. and on left 5° C. This man walks well and is free from pain, excepting a slight cramp of the right calf if he hurries. His general condition is greatly improved. Result classified as "good."

15. E. W., aged 31 years, chemist. History eight months. Began with claudication of left calf and thrombo-phlebitis of internal saphenous vein. All pulses in each leg are so feeble as to be doubtful, excepting the common femoral, which is strong on both sides. Operation: transperitoneal excision right and left lumbar cords, December 12th, 1931. Temperature rose on right 1.8° C. and on left 0.8° C. He is now free from pain, "can walk miles," and is playing cricket. He has, three months after the operation, developed Raynaud's disease of both hands. Result classified as "good."

16. J. W., aged 55 years, taxi-owner. History of sixteen years. Began with pain in left calf. Has got steadily worse and now has claudication at 200 yards. Has had onychia of first toe of left foot for two years. A callous ulcer has been present the whole of this time. There is much rest-pain. All pulses were perceptible in right leg, but no pulse was felt in left leg, excepting good common femoral. Operation: extraperitoneal excision of left lumbar cord, August 8th, 1932. Temperature rose on right 4° C. and on left 2.8° C. There was immediate improvement in the condition of the left foot. The ulcer healed quickly. Result classified as "good."

EFFECT OF PASSAGE THROUGH GLOSSINA ON THE RESISTANCE OF A TRYPARSAMIDE-FAST TRYPANOSOME*

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In previous papers (1930-2) we have shown that if laboratory animals infected with a pathogenic trypanosome are treated with appropriate doses of an aromatic arsenical or antimonial compound—for example, atoxyl, tryparsamide, arsacetin, neosalvarsan, stibenyl, etc.—strains possessing a high degree of "drug resistance" (or "drug fastness") are produced. These various resistant strains are similar in that each is resistant not only to the drug used to produce it, but also, broadly speaking, to all the other aromatic arsenical or antimonial compounds commonly employed in the therapy of trypanosomiasis, and also to the acridine dye, acriflavine; but each is just as sensitive to the non-aromatic compounds of arsenic (sodium arsenite) and antimony (tartar emetic) and to "Bayer 205" as is the normal parent strain. For example, an atoxyl-fast strain is resistant not only to atoxyl, but also to arsacetin, orsanine, tryparsamide, halarzol, salvarsan, stibenyl, and acriflavine; but it is normally sensitive to sodium arsenite, to tartar emetic, and to "Bayer 205." If the resistant strains are passaged through mice the resistant character is preserved unchanged for prolonged periods. Our atoxyl-fast strain has been passaged through a series of 280 mice since it was last exposed (in August, 1930) to the action of any drug, and it is still as resistant to atoxyl and other aromatic arsenicals as it was two and a half years ago.

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Contrary to the generally accepted view, we have found that the resistant character of a trypanosome is not modified by transference of the parasite from one vertebrate host to another. A strain of trypanosomes made resistant by treating infected mice or rabbits with atoxyl or tryparsamide retains its resistance when transferred to other hosts. In short, it appears that resistance to the aromatic arsenicals is a stable character, which is inherent in the trypanosomes themselves; it persists unchanged for prolonged periods when the parasite is passaged through laboratory animals, and it is in no way modified by changing the vertebrate host. Finally, no method has as yet been discovered whereby the acquired resistant character can be destroyed: our attempts to confirm Citron's (1930) statement that salvarsan resistance can be removed by sodium thiosulphate have been fruitless.

DRUG RESISTANCE OF TRYPANOSOMES IN MAN

Apart from its academic interest, the problem of drug resistance is a matter of immediate practical importance in so far as it probably has a very important bearing on the treatment of human trypanosomiasis. When once a strain of trypanosomes has attained to a certain degree of atoxyl- or tryparsamide-resistance it is impossible to cure any laboratory animal infected with that strain by the administration of even maximum doses of any aromatic compound of arsenic or antimony. If a resistant strain is developed in the course of arsenical treatment of a human case of trypanosomiasis (and as such strains can be produced in the treatment of infected mice, rats, guinea-pigs, or rabbits with equal facility there seems no reason to doubt that under suitable conditions they will likewise develop in man), then from analogy of the laboratory observations it will prove a hopeless task to attempt to cure such a patient with any aromatic arsenical or antimonial compound. An examination of the factors (size of dose, frequency and number of doses, etc.) which govern the production of drug resistance in trypanosomal infections of animals and man is consequently a matter of first importance.

That a drug-resistant strain of trypanosomes retains its resistant character, not only throughout the life of the host in which it first becomes resistant, but also throughout the lives of hundreds of other hosts through which it is passaged by means of direct inoculation of infected blood, is obviously a fact of considerable importance. It is, however, of relatively little practical significance in comparison with the question whether a drug-resistant strain of trypanosomes preserves its resistant character after it has passed through its cyclical development in its intermediate host—*Glossina*.

PERSISTENCE OF DRUG RESISTANCE IN INTERMEDIATE HOST

That this fundamental problem has received very little attention is probably due to two main reasons. In the first place, ever since Kleine in 1909 discovered that *T. brucei* underwent a biological development in *G. palpalis*, there has undoubtedly been a general consensus of opinion that one of the most important results of this process was to maintain constant the pathogenicity and other biological characters of the trypanosome; it was considered that the alternate passage through the insect and vertebrate hosts which takes place in nature prevents such changes in the trypanosome as are known to develop in the parasite when it is passaged through a series of laboratory animals by means of blood inoculation. In the second place, notwithstanding the great amount of work which has been devoted to the problem of drug resistance in trypanosomes since the fundamental discovery of the phenomenon by Franke and Roehl in 1907, we have had until recently but little precise knowledge of