

himself no prejudice, no sentimentalities, no illusions." But there is no record in his life of any evidence of credulousness to match it and, according to my view, to enable him to make really great discoveries.

Perhaps it is worth mentioning in the present connexion the remarkable epidemic of belief in the cruder aspects of spiritualism that infected several of the leading English physicists early this century: Sir William Barrett, Sir William Crookes, Sir Oliver Lodge, and Sir George Stokes. The number of times the mediums in which they trusted were exposed as frauds made no difference to the tenacity of their beliefs.

#### Psycho-Analytical Considerations

It would not be out of place on this occasion if I concluded with a reference to some psycho-analytical considerations. The only point I wish to bring forward here is the suggestion of a possible correlation between the credulousness on which I have been laying stress and the characteristically receptive nature of genius. A credulous attitude betokens an uncritical, excessive open-mindedness towards environmental stimuli, and this must go hand in hand with a similar uncritical open-mindedness towards the ideas pressing forward from the preconscious and ultimately from the id. It can afford to be uncritical here because of the relaxing of the inner censorship when harmony is established for the moment between the three mental institutions, ego, super-ego, and id. All this, however, represents only the preliminary stage of the process—an essential one, it is true. It is followed by a far more critical stage during the final act of formulating the new theory or conception. In this stage there is a strict criticism of the incoming ideas combined with an exclusion or even oblivion of the outer world when outer stimuli are regarded as a hostile interference, as in the case of Archimedes they certainly were. The intense concentration of this stage may culminate in the state of trance mentioned earlier.

Now in the first stage the passive, almost self-effacing role of the ego in accepting the ideas pressing in from the pre-conscious must surely be associated with the more feminine aspect of the personality or, as Freud preferred to term it, "the attitude of passive aims." It cannot be chance that so many words describing the process are taken from bodily analogies. The very word "inspiration" signifies a taking-in act on the part of the body. Poets often speak of being pregnant with their fancies, and the words "to conceive" and "to produce" equally apply to bodily activities. A writer can describe his mood as being in labour with an idea or actually giving birth to one. Furthermore, it is noteworthy how often, as constantly happened with Freud himself, the fomenting gestation of thought that precedes that final illumination is accompanied by just that kind of bodily discomfort that suggests the pains of labour. That women have more direct means of expressing this instinct would then account for the undeniable fact of major creative thinking being almost a prerogative of the male sex. It is their substitute, the only one available to them, for the gift of bodily creation bestowed on women.

#### Conclusion

I will conclude by recalling your thoughts to the man in whose honour this address is given. It will probably be generations before all the implications of his ideas are fully worked out and the stimuli he provided for us fully acted on. Revolutions in thought such as he brought about do not happen very often in history, and it may well be long before another similar one takes place. We do not even know in what sphere of psychology to expect it; it might be one in the genetics of the mind or, on the other hand, in the field of social psychology. In the meantime what can we feel but gratitude towards the memory of a man who gave so richly and so generously? Truly one may well say with his favourite prince: "I shall not look upon his like again."

## AMNION IMPLANTATION IN PERIPHERAL VASCULAR DISEASE

BY

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The purpose of this article is to report the effect on intermittent claudication of implanting human amnion into the thigh in 40 cases of peripheral vascular disease. This procedure was adopted because it had been observed (Troensegaard-Hansen, 1950; Shaw and Troensegaard-Hansen, 1952) that amnioplasty carried out for the treatment of leg ulcers in cases of peripheral vascular disease was followed not only by healing of the ulcer but also by a reduction in the severity of intermittent claudication. That such reduction might not be due solely to the healing of the ulcer was suggested by the fact that several patients claimed that their claudication was less than it had been before the ulcer appeared.

#### Material

The present series consists of 40 male patients. Their ages varied from 35 to 89, with an average of 60 years. They were selected as being in groups 1 and 2 of intermittent claudication (Professor Boyd's classification). The claudication was due to arteriosclerosis in 38 cases and to Buerger's disease in 2. Symptoms had been present for more than six months in the majority (Table I), and conservative treatment had been applied without significant effect in all of them. Three had been subjected to sympathectomy without effect on the claudication.

The pre- and post-operative condition of the patients was assessed by their tolerance to exercise, the presence or absence of rest pain, the radioactive sodium test, oscillometry, radiography, and skin temperature recordings.

#### Methods of Investigation

*Tolerance to Exercise.*—The criteria for tolerance to exercise were walking distance and ergometry. By walking distance is meant the distance which the patient can walk under controlled conditions before the onset of pain in the calf. By ergometry is meant controlled exercise on an ergometer. Two types of ergometers were used. In the first type, devised by Mr. N. C. Lake, the patient rhythmically depresses and releases a pedal, so raising a known weight through a standard distance once per second. This frequency was indicated to the patient by a swinging pendulum. The second ergometer was of the bicycle type, and was pedalled at a standard rate against a constant resistance. The patients' tolerance to these exercises was expressed as time (seconds) required to produce pain in the calf, and is referred to in Table I under ergometry as pain threshold in seconds. Rest pain was assessed in terms of severity, frequency, and duration.

*Radioactive sodium tests* (see below) were done on normals, on claudicants, and on patients having varied treatment.

*Oscillometry* was carried out, using a Pachon type of oscillometer. The maximum deflections were noted at different pressures and recorded (Table I).

*X-ray examination* of the patients' legs for evidence of arterial calcification was carried out.

*Skin temperature* of the limbs was recorded by means of a mercury skin thermometer.

**Radioactive Sodium Test**

The radioactive sodium test as described by Kety (1949) and modified by D. Walder (1953) was used for estimating the variations in blood circulation of the limb. This test has been used to determine changes in the arterial blood flow occurring after the use of certain vasodilators. As small variations can be detected the test is suitable for indicating changes that might occur following the treatment devised. Forty radioactive sodium tests have been done up to the time of writing, in 16 cases both before and after implantation. 24 cases had only post-implantation tests, as these were early cases before the radioactive sodium test had been started.

In this test from 0.06 to 0.15 ml. of saline containing 30 microcuries of radioactive sodium was injected into

the calf muscle to a depth of 2.5 cm. from the surface, and its rate of disappearance from the area was judged by the decrease in counting rate from a Geiger counter strapped to the calf, this being recorded on a ratemeter. For the first four minutes the patient stood at rest; he was then exercised by making him rise on his toes once per second, timed by a swinging pendulum for a period of two minutes. Finally, the readings were continued while he was at rest for a period of five to eight minutes. The fall in radioactivity was plotted logarithmically against time. In normal patients (Fig. 1) the fall was regular and the rate of fall increased during exercise. In a patient with intermittent claudication the graph deviated from the normal during the period of exercise (Figs. 2 and 3). The occurrence of the "hump" (A and B in Fig. 2) was thought to be due to poor arteriolar

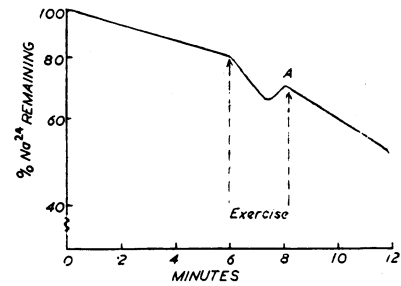
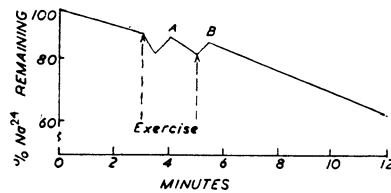
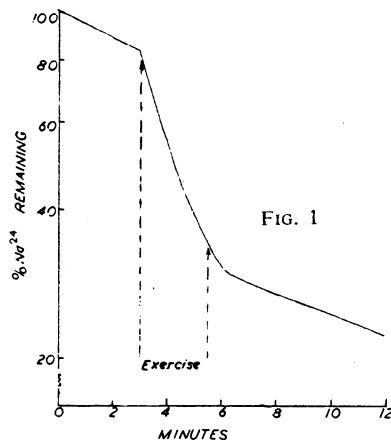


FIG. 1.—Normal curve of left leg showing straight line in inter-exercise period. Return to pre-exercise level within one minute. FIG. 2.—Before treatment, showing claudication. A denotes inter-exercise hump. B denotes post-exercise hump. FIG. 3.—Claudication curve before treatment showing notched inter-exercise period.

TABLE I.—Data Following Amnion Implants in Intermittent Claudication

Case No.	Age	Diagnosis	Duration of Disease	Ergometry Pain Threshold in Seconds		<sup>24</sup> Na (Radioactive Sodium)		Pain Threshold to Walking		Oscillometry in Deflections		Follow-up and Results	Date of Implant
				Pre-op.	Post-op.	Pre-op.	Post-op.	Pre-op.	Post-op.	Pre-op.	Post-op.		
1	55	Arteriosclerosis	7 mths.	20	None	Claudicating graph	Normal	10 yds.	½ mile	Flicker	Flicker	First implant septic. No improvement Reimplanted—satisfactory. Back at work. 8 months since implant. Good result	9/2 55 26 9 55
2	56	"	1 yr.	45	240	"	"	75 "	½ "	½	½	First implant septic—no improvement Reimplanted. Over 7 months since implant. Result good. Working as postman	19 5 54 5 1 55
3	67	"	2 yrs.	90	300	"	"	50 "	1 "	Nil	½	Walking well. No pain at all. 9 months since implant	2 11 55
4	66	Arterioscler. + coronary thrombosis	4 "	40	None	"	"	100 "	1 "	½	1½	First implant septic: no improvement. No calf pain at all. Reimplanted. Foot aches after 1 mile walking quickly. 8 months since implant	17 5 55
5	57	Arteriosclerosis	1 year	30	"	Not done	"	10 "	3½ miles	1	5	Very good result. Completely normal. 3 years since implant	31 10 52
6	53	"	1 "	20	150	"	"	50 "	1 mile	R. 1 L. 5	R. 5 L. 8	Completely normal. 1 year 7 months since implant	24 3 54
7	78	"	13 yrs.	18	90	"	Not done	10 "	½ "	R. 3 L. 2	R. 3 L. 4	Walking briskly. No pain when last seen. 1 year since implant	6 10 54
8	70	"	6 mths.	50	None	Cl. graph	Normal	100 "	7 miles No pain	R. ½ L. 0	R. 3 L. 4	Walking normally. Back to work. 7 months since implant	13 4 55
9	50	"	2 yrs.	50	"	graph Not done	"	100 "	½ mile	½	½	Walks ½ mile up a slope with no pain. Pulsation previously absent in the foot is now felt. Excellent result. 1 year since implant	7 12 54
10	53	"	4 "	12	50	"	Not done	50 "	2 miles	0	2	Walked 2 miles a day for 10 days with no pain at all. Started running after discharge from hospital with complete relapse. Classed as a failure	11 12 51
11	89	"	3 mths.	Not done	Not done	"	"	Bedridden		0	0	Had a static senile gangrene of one toe. Within 10 days of implant gangrene became moist and spread over the foot. High amputation followed. Classed as a failure	12 4 54
12	35	Buerger's disease	2 yrs.	14	90	"	Normal	50 yds.	½ mile	1	1	Result fair. 15 months since implant. Buerger's disease has been complicated by cerebrospinal meningitis and wasting of affected leg with bilateral deep thrombosis	12 5 54

Continued overleaf

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TABLE I.—Data Following Amnion Implants in Intermittent Claudication—contd.

Case No.	Age	Diagnosis	Duration of Disease	Ergometry Pain Threshold in Seconds		<sup>24</sup> Na (Radioactive Sodium)		Pain Threshold to Walking		Oscillometry in Deflections		Follow-up and Results	Date of Implant
				Pre-op.	Post-op.	Pre-op.	Post-op.	Pre-op.	Post-op.	Pre-op.	Post-op.		
13	71	Arterio-scler.	3 mths.	Not done	Not done	Not done	Not done	Not done	Not done	Not done	Not done	Static senile gangrene. Became moist, with rapid spread up foot within 10 days of amnion implant. High amputation. Classed as failure	14.7.55
14	74	"	3 "	"	"	"	"	50 yds.	1 mile	"	"	Good result. No claudication when last seen, has malleolar ulceration, which is healing. Ulceration impedes his capacity for walking. 6 months since implant	1 9 53
15	64	"	6 "	90	None	"	Normal	200 "	1½ miles	R. 4 L. 5	R. 8 L. 7	Very good result. Walking well. No pain. Over 5 months since implant	4 5 55
16	53	"	2 weeks	45	300	Cl. graph	"	40 "	1 mile	R. 0 L. 2	R. 2 L. 3	Eight months since implant. Good result. Walking well. Back at work	15 12 54
17	60	"	1 yr.	50	None	Not done	"	20 "	1½ miles	R. 1 L. 1	R. 1 L. 2	17 months since implant. Walking well. Implant went septic. Gets slight cramp after 1½ miles, occasionally after less than 1½ miles. Back at work. Result fair	10 3 54
18	64	"	2 mths.	35	135	"	"	50 "	1 mile	R. 1 L. 3	R. 2 L. 3	Very good result. There was some doubt whether this case was a typical claudication. 12 months since implant	8 10 54
19	71	"	2 yrs.	45	135	"	"	100 "	1 "	R. 1 L. 1	R. 2½ L. 1½	Very good result. After 1 mile quick walking is tired, but no pain in the calf. Untreated left leg still shows some claudication. He is due for another implant. 7 months since implant	5 1 55
20	69	"	6 mths.	Not done	Not done	"	Not done	Not done	Not done	Not done	Not done	Bilateral claudication. Implant done 2 years ago. Within 10 days of implant, existing dry gangrene spread. High amputation. Failure	18 12 53
21	73	"	6 "	"	"	"	"	20 yds.	1½ miles	"	"	Over 2 years since implant. Claudication completely dispersed. His hands, which were white (Raynaud's) are now pink and warm with no Raynaud's phenomenon. Result excellent	18 11 53
22	71	"	3 yrs.	1	75	"	Normal	20 "	1 mile	R. 2 L. ½	R. 2 L. 3	Result very good. Eight months since implant. Is walking well. No pains	22 12 54
23	59	"	1 yr.	Not done	Not done	"	Not done	Could not walk	2½ miles	Not done	Not done	Very good. Lost right leg earlier owing to gangrene. Despite sympathectomy this patient had claudication in his left leg. 4 years after implant. No claudication at all	1 8 51
24	59	"	2½ yrs.	26	None	"	Normal	100 yds.	250 yds.	R. ½ L. ½	R. ½ L. ½	Old case of bilateral Achilles tenotomy which prevents quick walking. Claudication was present, but abolished after implant. 15 months since implant	19 5 54
25	52	"	10 "	45	130	Cl. graph	"	100 "	½ mile	R. ½ L. ½	R. ½ L. ½	Eight months since implant. Right leg excellent; left leg only fair. His last left implant went septic. Needs another implant. Right leg—painless	12 10 55
26	49	"	9 mths.	90	260	Not done	"	50 "	1 "	R. 1 L. 1	R. 2 L. 1	Very good result. Can now walk up a steep slope. No pain at all. 8 months since implant	7 12 54
27	51	"	1 yr.	R. 90 L. 69	None	R. N. L. Cl.	R. N. L. N.	50 "	2 miles	R. 3 L. 0	R. 4 L. 2	Excellent result. Can go shooting or fishing for miles	16 8 55
28	54	"	14 yrs.	R. 45 L. 66	120 None	R. Cl. L. N.	R. N. L. N.	100 "	¾ mile	R. ½ L. 1	R. ¾ L. 1	Result good. No pain on walking ¾ mile	12 10 55 2 3 55
29	58	"	4 yrs.	R. 90 L. 65	"	R. Cl. L. Cl.	R. N. L. N.	200 "	3 miles	R. 1 L. 1	R. 2 L. 2	Had bilateral sympathectomy—R. no improvement. Excellent result. Walks 3 miles easily	12 10 55
30	26	Buerger's disease	4 "	R. 60 L. 200	" 200	R. Cl. L. not done	R. N. L. N.	400 "	2 "	R. 0 L. 4	R. 3 L. 4	Left sympathectomy 1953—deteriorating left side. Very good result. Walks 3 miles	4 10 55
31	61	Arterio-scler.	4 "	R. 28 L. 26	180 None	R. Cl. L. Cl.	R. imp. L. N.	100 "	1 mile	R. 0 L. 0	R. 1 L. 0	Achilles tenotomy. Good result. No claudication after 1 mile	29 11 55
32	51	"	10 mths.	R. 60	R. None	R. poor clearance	R. N.	80 "	400 yds.	R. 4-5	R. 4-9	Good result; walks 400 yards comfortably. Feels great improvement in spite of short distances	1 7 55
33	68	"	3 mths.	L. 60 R. 180	L. " R. "	L. — R. poor clearance	L. N. R. N.	200 "	1½ miles	L. 7-11 R. 0	L. 7-11 R. 5-8	Oscillometry increase—no pain on walking 1½ miles	7 12 55
34	68	"	2 yrs.	L. None R. 90	L. " R. "	L. — R. Cl.	L. N. R. N.	50 "	1 "	L. 4-5 R. 0	L. 5-10 R. 1	Very good result. No complaints	2 11 55
35	66	"	2 "	L. 65 R. None L. 15	L. " L. 240	L. Cl. L. Cl.	L. N. L. N.	10 "	½ mile	R. ½ L. 0	R. 5-6 L. 5-6	Left implant. Left leg normal. R. Fair result. Can now do her shopping. Stops at 150-200 L. yards, but quickly walks on	16 11 55 8 1 56
36	66	"	3 mths.	R. None L. 60 R. 50	R. None L. "	R. N. L. Cl. R. poor clearance	R. N. L. Imp. R. Imp.	20 "	2 miles	R. 2 L. 0 R. 1	R. 2 L. 2 R. 3	Good result; back at work. Poor radioactive sodium clearance	9 11 55
37	63	"	1 yr.	R. 60	R. "	R. poor clearance	R. N.	200 "	3 "	R. 1	R. 3	Good result. Feels quite normal. Poor radioactive sodium clearance	16 11 55
38	74	"	3 yrs.	L. None R. 75 L. 60 R. 60	L. " R. " R. "	L. N. R. Cl. L. Cl. R. Cl.	L. N. R. N. L. Cl. R. N.	½ mile	1½ miles	L. 0 R. 0 L. 0 R. 0	L. 2 R. 4-8 L. 5-6 R. 2	Walks 1½ miles. 1 mile briskly. R. Result very good	26 10 55 14 12 55
39	61	"	6 mths.	R. 60	R. "	R. Cl.	R. N.	½ mile	1½ miles	R. 0	R. 2	Excellent result in spite of sepsis and only improvement on sodium test	5 4 55
40	58	"	6 "	L. None R. 120 L. 80	L. " R. 180 L. 180	L. — Cl. graph	L. Imp.	300 yds.	1½ "	L. 4-6 R. 4½ L. 0	L. 4-9 R. 4½ L. 3-4	Results have been dramatic. Can now walk ½ mile up a steep slope. Has walked 1½ miles without pain	



circulation with a capillary reflux, thus raising the sodium level. Although the curves are as a rule reproducible it has been found so far impossible after implantation to reproduce the pre-implant "hump" in three cases in spite of their being exercised to exhaustion. The slope of the curves varies, and it was thought the steeper the slope the greater the vascularity of the limb. However, it must be considered that the site of

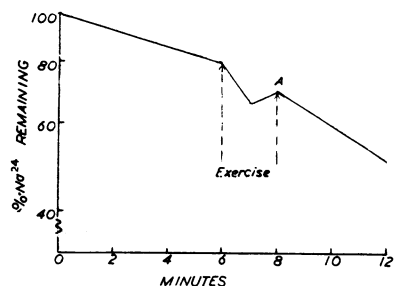


FIG. 4.—Same case as Fig. 3. Right leg after control implant, showing claudication curve. Note inter-exercise hump at A.

the injection must in some way be responsible for the slope; thus an injection made into vascular muscle must give a steeper clearance than one made into fascia, fat, or areolar tissue. Lastly, we have tried to find some explanation of the hump of the claudication graph. Accordingly, radioactive isotope sodium was injected into the calf of a normal patient. The arterial flow in the thigh was blocked by a sphygmomanometer cuff, the pressure of which was raised above the systolic blood pressure. The graph compared with that of a patient suffering from mild intermittent claudication. In the same case

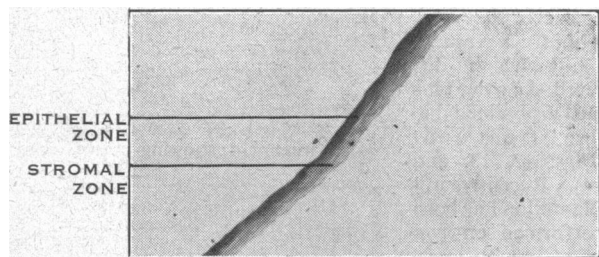


FIG. 5.—Macerated inactive amnion showing loss of cell nuclei. ( $\times 175$ .)

the venous flow was then occluded by a sphygmomanometer cuff with a pressure just sufficient to block the venous return. The radioactive sodium test in this case, however, showed no hold-up. It is therefore assumed

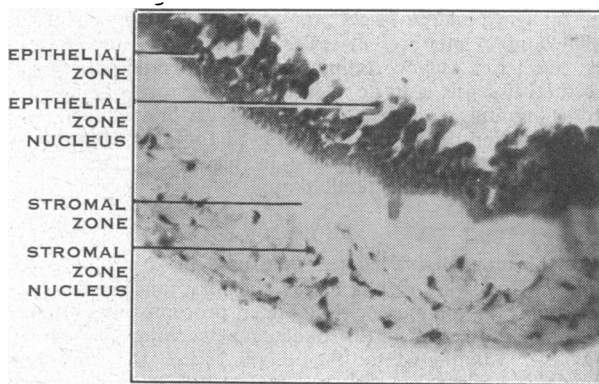


FIG. 6.—Active amnion with nuclei in stroma and epithelium. ( $\times 175$ .)

that the features of the radioactive sodium test are attributable to arterial flow and its variations, and not to venous occlusion.

**Procedure of Amnion Implantation**

Human amnion was collected immediately after delivery and stored at 0° C. for five days. It was then cleaned on the chorionic side only, care being taken not to damage the epithelial layer. The tough adherent mucus was removed, after which the membrane appeared to be clear. The amnion was boiled for three minutes and was then ready for immediate use. For storage purposes this procedure must be followed by stretching and drying in warm air, with subsequent re-boiling before use to ensure sterility, but this does not seem quite so effective as the former method for immediate use.

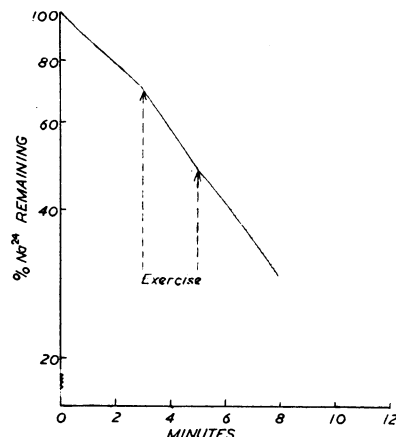


FIG. 7.—Same case as Figs. 3 and 4. Normal curve after satisfactory implant.

The amnion was then implanted under local analgesia in the form of two pieces each 7 by 5 cm. tightly rolled

TABLE II.—Details of Six Specimen Control Cases

Case No.	Age	Diagnosis	Duration of Disease	Ergometry Pain Threshold in Seconds		<sup>24</sup> Na (Radioactive Sodium)		Pain Threshold to Walking		Oscillometry in Deflections		Follow-up and Results
				Pre-op.	Post-op.	Pre-op.	Post-op.	Yards	Miles	Pre-op.	Post-op.	
1	55	Arteriosclerosis + Diabetes. Coronary disease	7 mths.	20	No change	Cl. graph	Cl. graph	10 yds.	No change	Flicker	No change	Patient states no change. Claudication as severe as before
2	56	Arteriosclerosis	1 year	45	..	..	..	75 ..	..	½	..	No change
4	66	Arteriosclerosis + cor. thrombosis	4 years	40	..	..	..	100 ..	..	½	..	.. ..
7	78	Arteriosclerosis	13 ..	18	..	..	..	10 ..	..	0	..	.. ..
16	53	..	2 weeks	45	..	..	..	40 ..	..	R. 0 L. 2	..	Improved for ten days, then relapse
18	64	..	2 mths.	35	55	..	..	50 ..	..	R. 1 L. 3	..	Two months slight improvement. Relapse after 14 days

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together. The "pencil" so made was implanted deep to the fat lying on the fascia lata on the lateral aspect of the thigh, and in our present series we have used the affected leg. A strict aseptic technique in an operating theatre is essential if sepsis is to be avoided. Under sepsis is included reddening and, of course, induration with or without actual pus formation. Bed rest was allowed for only 48 hours in some cases, but was usually less in this series. The stitches were removed on the tenth day.

**Controls**

Certain control procedures were used in 20 of the cases, with the following results before the final implant was carried out: (1) Simple incision under procaine anaesthesia: this had no effect. (2) Subcutaneous injection of 0.5 mg. of histamine into the thigh raised the threshold for claudication for a period of from 10 to 90 minutes, with subsequent return of the initial condition. (3) Implantation of amnion which had been so treated as to remove the epithelium with loss of all cellular and nuclear structure (Table II and Figs. 4 and 5): intermittent claudication was unaffected and the radioactive sodium test gave a claudication curve (Fig. 4). These patients were led to believe that the control measures would give relief to their symptoms. This was done in order to exclude the possibility that any benefit that was derived might have been the result of psychological influences. In Cases 16 and 18 slight changes occurred (Table II), but in the other 18 cases no change followed control treatment. There was both subjective and objective improvement when the same cases were later implanted with a similar quantity of amnion prepared by our own methods (Figs. 6 and 7).

**Results**

In Table I are recorded the results of this treatment. When the site of an implant was excised three weeks later and examined microscopically, there was no sign of the amnion and there was a considerable degree of vascular reaction in excess of that normally found round a foreign body (Fig. 8). After a successful implantation the patient usually experiences no change for 72 hours, then finds that the legs, and especially the implanted one—that is, affected leg—feels warm and less numb. The skin temperature rises, cramp becomes less, and effort tolerance is steadily increased. Four cases (Nos. 1, 2, 4, and 17) showed sepsis at the implant site with no improvement either subjectively or objectively, and these were subsequently satisfactorily re-implanted with good results. It has also been found that some amnion is ineffective for reasons yet unknown. It is possible that in the preparation of the amnion the epithelial layer has been damaged or the nucleated element destroyed by heat-drying. All cases that have shown no improvement

after implantation have been reimplanted until claudication disappeared. One case had to be reimplanted four times before a satisfactory result followed. After satisfactory implantation claudication disappeared in 29 cases, became less in 7, and persisted unchanged in 4; of these failures one was in group 2 claudication, and the three other failures had pre-existing gangrene, which we now know contra-indicates implantation.

In the three latter cases, all suffering from a relatively dry senile gangrene, amnion implantation was followed by an advancing wet gangrene, and each patient subsequently had high amputation (Nos. 11, 13, and 20). In the cases where claudication disappeared there was an improvement of the arterial circulation as evidenced by (1) improved exercise tolerance (Table I), and (2) increase in the dispersion rate of radioactive sodium from the calf (Figs. 2 and 9, and 10 and 11), with incidental increase in the skin temperature. In seven cases oscillometric increases were noted with changes from one to two deflections before treatment up to five deflections after treatment. In seven cases returning dorsalis pedis pulsation was noted. In six of the successful

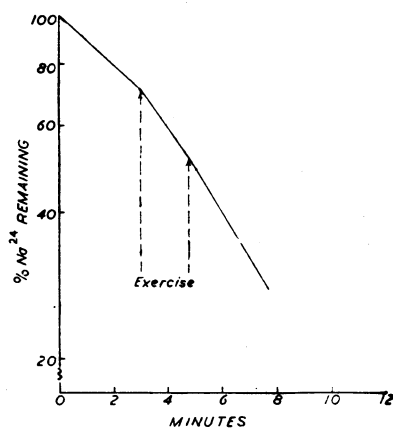


FIG. 9.—Same case as Fig. 2. Right leg after treatment, showing normal curve.

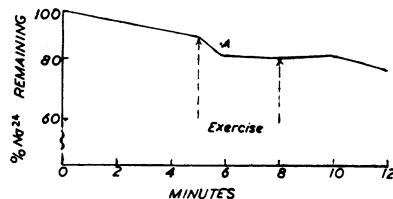


FIG. 10.—Right leg after septic implant showing claudication. Shallow curve levelled off at A.

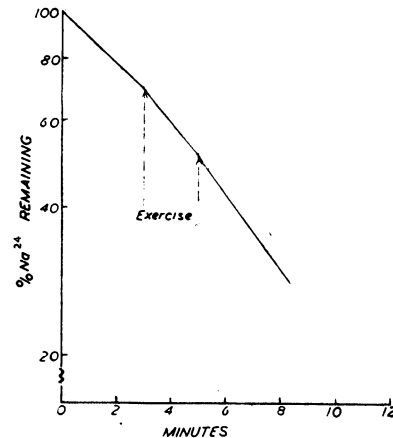


FIG. 11.—Same case as Fig. 10. Right leg after satisfactory implant, showing a normal curve.

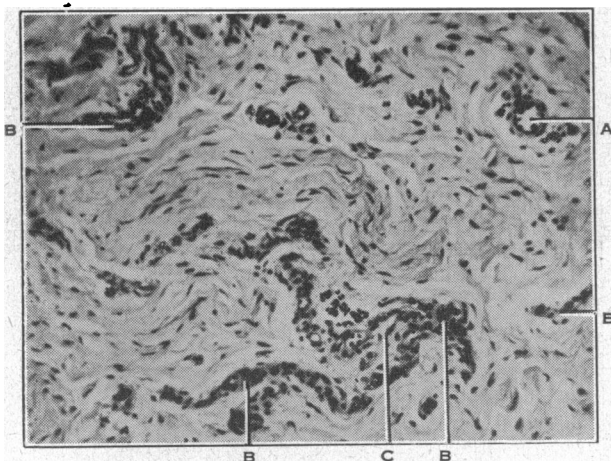


FIG. 8.—Section of amnion implant. A and B, small blood vessels. C, endothelial cell. Numerous capillaries with hyperplastic endothelium. No foreign body reaction is visible. (×210.)

Of the patients whose condition was improved by implantation, the six who had shown previous rest pain stated that this symptom disappeared 72 hours after the implantation. All cases successfully treated have been free from symptoms for periods as follows: two cases

over three and a half years, seven cases over one year, and the remainder for eight months, and it is worthy of note that no vasodilator drugs have been administered, and smoking is permitted in moderation.

**Discussion**

It is always difficult to assess the value of a particular form of treatment on peripheral vascular disease because of the natural tendency of the untreated case to fluctuate in severity from time to time and in view of the symptomatic improvement which sometimes follows non-specific forms of treatment or even bed rest alone. There has been a certain consistency, however, about the response to implantation of the amnion prepared in the way described above. The factors which cause intact amnion (Fig. 6) to call forth a reaction greatly in excess of what occurs with macerated amnion (Fig. 5) seem to be associated with the nucleated elements of the epithelial and stromal layers of the amnion. It would appear from these observations that the introduction of relatively intact human amnion (Fig. 6) in the

manner described does influence the circulation in the limb treated. Beneficial effects on the opposite limb have been noted in six bilateral cases (Table I). Note also the changes in the radioactive sodium tests in Case 27 and the fact that patients suffering from Raynaud's phenomenon of the hands (two cases) and intermittent claudication who were treated for the latter had subjective improvement of the former complaint.

It is of interest that in three cases of relatively stationary dry gangrene subjected to amnion implantation all showed subsequent spreading wet gangrene, a result similar to that following application of warmth to a dry gangrenous limb. It can always be argued that any surgical intervention might influence tissue changes and could be responsible for the conversion of dry to wet gangrene. In attempting to explain these results, it is not unreasonable to suppose that the superficial circulatory changes following amnion implanta-

tion, as evidenced by the feeling of warmth and rise of temperature in the limb concerned, might also include the muscle vessels, so giving relief from claudication. The finding of relief from night pains is not inconsistent with this possibility.

The skin temperature generally fell by the end of one month, but when the radioactive sodium test was performed six weeks after the implant it showed improved sodium clearance from the calf, the curves reverting to the normal type, as demonstrated by 16 isotope curves before and after treatment. There is possible evidence, so far, of a permanent improvement in the muscle circulation. It may be noted that despite the fall in skin temperature the improvement of claudication persists.

The present uncertainty about the basic nature of claudication imposes great difficulty in attempting to explain the lasting improvement in exercise tolerance which appears to follow amnion implantation. When the limb has lost its pinkness or warmth and the temperature on both sides is the same the significant questions are whether the circulation in the limbs has become permanently increased compared with the pre-operative level, or whether the response to exercise is substantially different in the treated and untreated limbs or perhaps a combination of both.

Examination of pre- and post-implantation radioactive sodium graphs (see illustrations), as indicated by their change from the claudication type to the normal, suggests that the reaction of the muscle flow returns to limits within normality. In view of the fact that the injection of radioactive sodium is intramuscular it may be supposed that the circulatory changes chiefly affect the muscle vessels.

It would be unjustifiable on present evidence to draw any conclusions about the resting levels of the circulation in the muscles concerned before and after treatment. However, it is noticeable that sometimes the slope of the radioactive sodium curve is steeper after implantation than before. This has been interpreted as being due to an increase in the circulation, but it is possible that the slope of the curve may depend on whether the injected radioactive sodium has initially lodged in tissue of high or low vascularity. Patients who complain of claudication state that their pain is diffuse, but if they are questioned carefully one finds the pain localized to the following sites: high in the calf or low down just above the upper limit of the Achilles tendon, the middle of the shin, and the dorso-medial and dorso-lateral aspects of the foot. Only too often do these patients show tender areas which have been corroborated by other workers. It is therefore natural to suppose that certain muscles show signs of ischaemia in preference to others and that special sites are commonly affected.

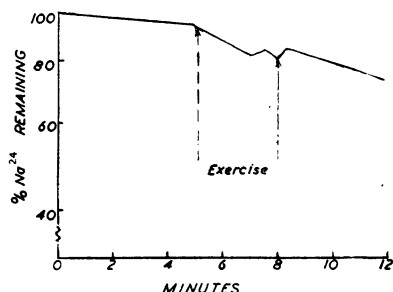


FIG. 12.—Case 27. Left leg before treatment.

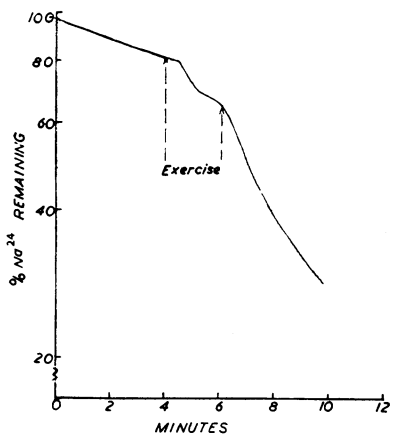


FIG. 13.—Case 27. Left leg after treatment.

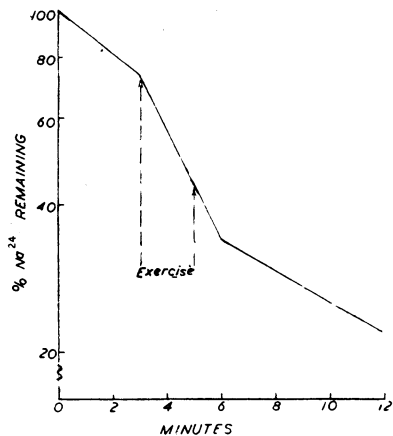


FIG. 14.—Case 27. Right leg after treatment.

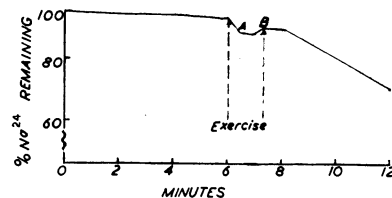


FIG. 15.—Right leg before sympathectomy. Foot cold. Pain stopped exercise. True claudication curve.

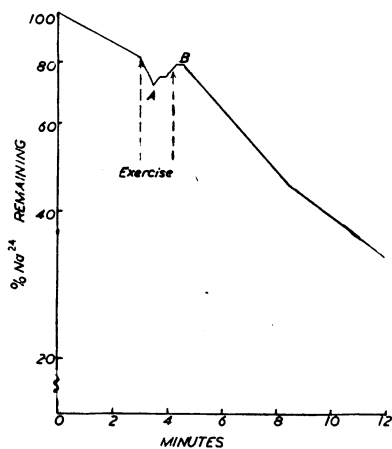


FIG. 16.—Same case as Fig. 15. Right leg after sympathectomy. Foot warm. Pain stopped exercise. True claudication curve.



It must be mentioned that it is well known that some cases have intermittent claudication without the absence of dorsalis pedis pulsation. Thus it is possibly not essential to increase the general circulation of the leg to any great extent provided the local muscle circulation is suitably improved. Several cases are recorded where the superficial circulation has been improved by sympathectomy, with a resulting warm leg and foot without amelioration in claudication (Figs. 15 and 16). It is known that perineural injection of procaine temporarily, and even for long periods, does improve claudication, but it is difficult to give an explanation for this phenomenon. The best explanation is that of a trigger mechanism, a theory supported by Mr. N. C. Lake and others.

It is conceivable that since pain can cause reflex vasoconstriction (Doupe *et al.*, 1937; Travell *et al.*, 1944; Elliott, 1949) the pain caused by a portion of ischaemic muscle in the calf might cause constriction of the immediate collateral circulation with consequent increase of the area rendered ischaemic. If, however, some improvement in the muscle circulation were to occur after an implant then this postulated abnormal response to exercise might be abolished, the local circulation then responding in a physiological manner to the needs of the muscles in exercise.

The clinical effectiveness of the treatment would depend on the extent to which the collateral system is capable of development, while the ultimate duration of freedom from pain following the implant must depend on whether the underlying disease progresses or not. Examples are not rare of patients with peripheral vascular disease who have shown spontaneous improvement after a period of bed rest and have remained well for years, and it is then reasonable to think that the benefits of this local improved circulation would be felt by all the tissues and be maintained for prolonged periods, as shown in Table I, up to five years.

#### A Typical Good Result (Case 5)

A printer aged 57 complained of pain in both calves after walking as little as 10 to 15 yards. The pain was severe in the left calf and moderate in the right. This condition had existed for one year. A diagnosis of intermittent claudication was made one year previously. His treatment had been several courses of nicotinic acid, tolazoline hydrochloride, and Buerger's exercises; but he became worse, and developed intolerance to tolazoline hydrochloride (headache and vomiting).

On examination his left leg was of normal colour but cold, with no pulsation below the popliteal artery. No abnormality was found in the right leg. X-ray examination revealed no calcification. Temperature: right leg, 80° F. (26.7° C.); left leg, 78° F. (25.5° C.); right foot, 78° F. (25.5° C.); left foot, 75° F. (23.9° C.). Oscillometry: right leg, 5 deflections (8-13) at 250 mm. Hg; left leg, 1 deflection (8-9) at 250 mm. Hg. Ergometry: right leg, no discomfort; left leg, discomfort after 30 seconds, unbearable pain after 60 seconds.

Left amnion implant on October 31, 1952. Forty-eight hours after the implant the left leg and foot felt warmer and pain began to diminish. He was allowed to walk about the ward from morning to evening from the day after the implant. No bed rest was allowed. He walked continuously for two hours at a time with no pain and did not need sticks, which he had been using for support during the past year. Pulsation was felt in the left dorsalis pedis artery. On December 3 he could walk 200 yards at a fast pace up a slight incline. Temperature: right leg, 86° F. (30° C.); left leg 86° F. (30° C.); right foot, 80° F. (26.7° C.); left foot, 80° F. (26.7° C.). Oscillometry: right calf, 5 deflections (6-11) at 250 mm. Hg; left calf, 5 deflections (8-13) at 250 mm. Hg. Ergometry: no discomfort in either leg. Radioactive sodium test normal.

Final assessment: walks 3½ miles; perfectly fit; duration of improvement, 2 years 3 months.

#### Summary

Following a chance observation that amnioplasty carried out for the treatment of gravitational ulcers had

a beneficial effect on intermittent claudication, amnion was implanted into the thigh in 40 cases of peripheral vascular disease with claudication.

In 29 cases the claudication disappeared and could not be produced by severe exercise. In seven cases exercise tolerance was increased but mild claudication was experienced during severe effort. There was complete failure in one case. In three cases with early dry gangrene the condition of the limb deteriorated after the implant and high amputation was required. Evidence of tissue necrosis is therefore regarded as a contra-indication for this form of treatment.

Pre- and post-operative studies showed an increase in circulatory efficiency after treatment, as evidenced by increase in walking distance, exercise tolerance by ergometry, loss of rest pain, and the production of a normal radioactive sodium graph, whereas in 20 controls who received macerated amnion there was neither clinical improvement nor change in the results of objective tests. The main difference between the two types of amnion is the presence in the effective form of a well-defined nucleated epithelial and stromal layer.

Implants give rise locally to a vigorous outgrowth of capillaries and are absorbed in about three weeks. Clinical improvement begins in about three days and is maintained for a period that cannot yet be assessed. It has lasted for over three and half years in two cases, over one year in seven, and in the remainder over eight months. There have been four relapses in the series.

A possible explanation of the observed effects of amnion implants is discussed.

If an implant shows any signs of sepsis then generally no improvement is gained, either subjectively or objectively. However, very occasionally some improvement has been seen in spite of sepsis which has been subjective only.

It has been found that some amnion is inactive even after preparation by a standard technique, the explanation of which at present remains obscure. Reimplantation must always be carried out until claudication disappears.

This work has been made possible by a grant from the Clinical Research Subcommittee of Charing Cross Hospital, without whose continued support it could not have been completed. I would like to thank Mr. N. C. Lake and Dr. F. A. Elliott for their help and the reading of my paper; and Professor Paterson Ross, of St. Bartholomew's Hospital, and Dr. J. Lee, of the physiology department, Charing Cross Hospital, for helpful suggestions. I am grateful to Dr. Moore Patterson for his co-operation in the isotope work completed in the radiotherapy department of Charing Cross Hospital; and to Dr. D. N. Walder, of the Newcastle Infirmary, and Mr. N. Ramsay, physicist to Charing Cross Hospital, who enabled the radioactive sodium work to be carried out. I am indebted to the consultants of Charing Cross Hospital, to the many general practitioners who have sent me cases, and to the out-patient department, and to Messrs. Smith and Nephew Research Department for the supply of most of the amnion and for carrying out research on my behalf.

*Addendum.*—Since this work was completed 20 further cases have been treated in the same way, with complete remission of symptoms.

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