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THE FATE OF THE CLAUDICATOR

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Arterial insufficiency of a limb presents either with pain or with gangrene. The former usually occurs only after exercise—that is intermittent claudication—but may be present at rest. The fate of the gangrenous leg is known; unless the circulation can be improved by direct arterial surgery or a sympathectomy, amputation is the usual outcome. The prognosis for the claudicator, with or without additional rest pain, is not so well documented, but is more favourable.

The natural history of such patients regarding their arterial disease forms the subject of this investigation. It describes the initial assessment and progress of patients who attended with symptoms and signs of atherosclerotic arterial disease in one or both lower limbs. The patient's doctor was then sent a standard letter which requested information on the patient's survival, the state of the affected limbs, manifestations of atherosclerosis in other parts of the body, and, if applicable, the date and cause of death. Where necessary, details of date and cause of death were obtained from the Registrar-General's records.

Clinical Material

A total of 359 patients were taken at random from the vascular index at this hospital. All were first seen before 1958, to allow for a minimum follow-up period of two years. This represented approximately half of all the patients who attend the vascular clinic during this period. The follow-up period was taken to begin with the first hospital attendance at which a definite diagnosis was made. Diagnosis was based on history and signs of impaired circulation. Incipient or actual gangrene was present in 62 patients. To confirm the clinical diagnosis 205 arteriograms were carried out. Patients thought to have Buerger's disease (thrombo-angiitis obliterans) were excluded, the diagnosis being made on the younger age, the episodic course, the occurrence of attacks of superficial thrombophlebitis, the common localization of the arterial lesions in the distal vessels of upper and lower limbs, and sometimes by arteriography.

There was no other selection of cases, all patients conforming to the above-mentioned criteria being included.

Patients with femoro-popliteal thrombosis and with aorto-iliac stenosis and thrombosis are considered separately. Where applicable, joint figures are presented subsequently.

Femoro-popliteal Thrombosis

There were 250 patients in this group, of whom 222 (87%) were men and 28 (13%) women. The mean age was 58 years (34–81). This age-and-sex distribution is similar to that quoted by many authors (Hines and Barker, 1940; Berry *et al.*, 1955). Diabetes mellitus was present in 16 (8.2%) patients.

Blood-pressure readings were available in 179 patients: 97 (44%) were above 150/90 (Platt, 1959); 119 (54%) were above normal for their age according to Hamilton *et al.* (1954).

Results of Follow-up.—Follow-up was completed on 219 (88%) patients. The diagnosis was made on clinical assessment alone in 105 patients and confirmed by arteriography in another 114. Direct arterial surgery or lumbar sympathectomy was carried out in suitable patients with severe disease (Rob, 1956). The remaining patients were given vasodilator drugs and general advice about the care of their limbs. As the value of the latter measures is uncertain (Semple, 1953), those patients are considered under the heading "Nil" in Table I and subsequently. The mean follow-up period was 37 months. Of 114 patients who received only conservative treatment, 109 were improved or remained unchanged. A further 13 patients required amputation for progressive ischaemia during the period of observation.

TABLE I.—*Results of Follow-up (Survivors)*

	Direct Arterial Surgery or Sympathectomy	Nil	Total
Improved	33 (6)	40 (16)	73
No change	19 (3)	69 (30)	88
Worse	—	5 (2)	5
Total	52	114	166

Figures in parentheses refer to the "other leg" (see below).

"Other Leg" Thrombosis.—Bilateral disease was present from the beginning of observation in 58 patients. One developed gangrene in the other leg during the follow-up period, requiring amputation. The fate of the remaining less-affected limbs is given in parentheses in Table I. There were 57 such limbs. Of these, 46 improved or remained unchanged without surgical treatment. The appearance of ischaemia in a previously normal limb was assumed to be due to arterial thrombosis. Such changes in the "other leg" were noted in 17 patients: 10 had claudication, 2 developed ischaemic ulcers, and 5 required amputation.

Myocardial Ischaemia.—There was evidence of previous ischaemic heart disease in 51 (24%) patients. Of those, 36 had E.C.G. changes of past ischaemia and 15 had a definite history of angina or coronary thrombosis. During the follow-up period a further 51 patients had episodes of myocardial ischaemia; 25 were fatal and 26 non-fatal. Of this group 36% had previous coronary disease, compared with 24% in the whole series. The incidence of raised blood-pressure in this group was about the same as in the whole series.

Cerebrovascular Accidents. — Previous cerebral thrombosis or haemorrhage had occurred in 6 (2.5%) patients. A further 12 (5%) patients were similarly affected during the follow-up period. Of these cases six were fatal and six non-fatal. In this group a previous cerebrovascular accident had occurred in three patients, and raised blood-pressure was present in four.

Mortality during Follow-up Period.—There were 41 (19%) deaths, the causes and distribution of which are given in Table II.

TABLE II.—*Total Number of Deaths in Each Year of Follow-up Period*

	Post-op.	0–1 Yr.	1–2 Yrs.	2–3 Yrs.	3–4 Yrs.	4–5 Yrs.	Total
Coronary thrombosis	1	9	8	6	1		25
Cerebral thrombosis or haemorrhage		2	2	1		1	6
Miscellaneous	3	1		4	2		10
Total	4	12	10	11	3	1	41

Finally, Table III summarizes a number of results of this investigation according to age. The age-groups analysed (45–69 years) comprise 78% of the total follow-up group. The most significant figures in this Table show the greatly increased mortality of patients suffering from peripheral vascular disease.

TABLE III

Years:	45–49	50–54	55–59	60–64	65–69	Total
Total No.	24	36	46	32	33	171
Survivors	23	33	38	26	24	144
Deaths	1	3	8	6	9	27
% Deaths	4	8	17	19	37	Mean 17
Mean survival to death (months)	18	10	29	20	18	Mean 19
Deaths/1,000*	40	80	150	160	370	Mean 170
Registrar-General's deaths/1,000	4·4	7·5	12·5	19·8	31·8	Mean 15.2

* Excluding post-operative deaths.

Aorto-iliac Thrombosis

This group consisted of 109 patients; 94 (86%) were men and 15 (14%) women. The mean age was 53 years (38–77). There were two (2%) patients with diabetes mellitus.

Raised blood-pressure was found in 70 (67%) patients according to Hamilton *et al.* (1954) and was above 150/90 (Platt, 1959) in 51 (49%) patients.

Results of Follow-up.—Follow-up was completed in 103 (94%) patients. The diagnosis was made on clinical signs alone in 12 patients and confirmed by arteriography in 91. The mean follow-up period was 36 months. Table IV summarizes the results during the period of observation. Of 22 patients treated conservatively, 20 were improved or remained unchanged. A further five patients required amputation for progressive ischaemia during the follow-up period.

TABLE IV.—*Results of Follow-up (Survivors)*

	Direct Arterial Surgery or Sympathectomy	Nil	Total
Improved	41 (11)	7 (4)	48
No change	8 (3)	13 (1)	21
Worse	—	2 (1)	2
Total	49	22	71

Figures in brackets refer to the "other leg" (see below).

"Other Leg" Thrombosis.—Evidence of bilateral disease was often found at arteriography and at operation. Only 21 patients had symptoms of ischaemia in both lower limbs at the beginning of the survey. One developed gangrene and required amputation. The fate of the remaining less-affected limbs is given in parentheses in Table IV. Of six patients who received

conservative treatment only, one had increasing claudication. The remaining five limbs improved or remained unchanged. In six patients ischaemia appeared in the previously symptom-free leg: four developed claudication and two required amputation for gangrene.

Myocardial Ischaemia. — Evidence of previous ischaemic heart disease was present in 20 (19%) patients: 15 had E.C.G. changes and 5 had a definite history of angina or coronary thrombosis. During the period of observation there were 20 further episodes of coronary ischaemia, of which 14 were fatal and 6 non-fatal. Of this group, 25% had previous coronary heart disease, compared with 19% in the whole series. Raised blood-pressure was found less often in this group (60%) than in the whole series (67%).

Cerebrovascular Accidents.—Four cerebrovascular accidents occurred during the follow-up period. All were fatal, including the only patient who had suffered a previous cerebral thrombosis. Of this group, two patients had raised blood-pressure.

Mortality During Follow-up Period.—There were 33 (32%) deaths; the causes and distribution are given in Table V. The high proportion of post-operative deaths is due to the greater use of direct arterial surgery in the aorto-iliac group and the magnitude of these operations.

TABLE V.—*Total Number of Deaths in Each Year of Follow-up Period*

	Post-op.	0–1 Yr.	1–2 Yrs.	2–3 Yrs.	3–4 Yrs.	4–5 Yrs.	Total
Coronary thrombosis	5	2	1	2	3	1	14
Cerebral thrombosis or haemorrhage		1	2			1	4
Miscellaneous	7	2	3		2	1	15
Total	12	5	6	2	5	3	33

Finally, Table VI summarizes a number of results of this investigation according to age. The age-groups analysed (45–69 years) comprise 91% of the whole series, and the figures again demonstrate the high mortality of atherosclerotic patients.

TABLE VI

Age:	45–49	50–54	55–59	60–64	65–69	Total
Total No.	20	28	23	17	5	93
Survivors	18	22	13	12	1	66
Deaths	2	6	10	5	4	27
% Deaths	10	21	43	29	80	Mean 36
Mean survival to death (months)	26	29	23	21	26	Mean 27
Deaths/1,000*	50	180	340	290	800	Mean 366
Registrar-General's deaths/1,000	4·4	7·5	12·5	19·8	31·8	Mean 15·2

* Excluding post-operative deaths.

Anticoagulants

We have used long-term treatment with anticoagulants (phenindione) for several years, for reasons that have been similar to those justifying its use after coronary thrombosis (M.R.C., 1959). All patients in this series who had been on continuous anticoagulant treatment from 1957 or earlier were analysed and the results are presented in this section. No specific control group is offered, but the figures for the phenindione series are compared with those of the whole follow-up group, the constitution of the two series being similar. Patients with femoro-popliteal and aorto-iliac disease are presented jointly.

TABLE VII.—*Results of Phenindione Treatment*

	Phenindione Group	"Control"
Improved	69%	51%
No change	26%	45%
Worse	5%	4%
Thrombosis in "other leg"	6%	7%

There were 70 patients in the phenindione group. The figures in Table VII show that there was no significant improvement in the prognosis for the affected limbs as a result of this treatment. Angina or coronary thrombosis developed in 15 (21%) patients during the follow-up period, and was fatal in 6 (40%) cases. The corresponding figures for the whole series are 71 (22%) patients with angina or coronary thrombosis, of whom 39 (55%) died of the latter. Thus, long-term anticoagulant therapy did not reduce the incidence of coronary ischaemia, although the number of deaths due to coronary thrombosis was less.

Discussion

A postal follow-up has obvious disadvantages. However, as the principal complications looked for—gangrene, cardiac or cerebral ischaemia—are all of such a nature that medical aid would be sought immediately, it was thought unlikely that many would have been overlooked. Regarding the severity of claudication, the results were again considered to be accurate enough for the purpose of this survey, especially as there is no intention to prove the value of any particular form of treatment and as replies through an intermediary are probably less subject to observer bias.

Notable among the results are the large number of cases in which leg symptoms remained stationary or were improved without active treatment (180 limbs). Similar results are reported by Hamilton and Wilson (1952), Massarelli and Estes (1957), and DeWolfe *et al.* (1954). On the other hand, Gillhespy (1957) found in his series of femoro-popliteal thromboses that "most untreated patients deteriorated." Similarly, Beaconsfield and Kunlin (1953) write of their aorto-iliac group that "sooner or later bilateral above-knee amputation will be required."

We consider that in many patients intermittent claudication is a relatively benign condition, and that with proper selection only a proportion of patients suffering from this condition will require active surgery. Gangrene will still lead to immediate amputation in some patients, although many limbs can be saved by direct arterial surgery.

Myocardial ischaemia is frequently present in patients with peripheral atherosclerosis, as described by McDonald (1953), Spaulding (1956), and Richards (1957). This is confirmed in the present series, where 71 patients had pre-existing ischaemic cardiac disease and a further 71 episodes of coronary ischaemia occurred during the follow-up period.

The value of long-term anticoagulant therapy is not proved. The figures presented in this survey do not demonstrate any definite improvement due to this measure. A case can be made for continuing the use of long-term anticoagulants in the hope that further results will show an improvement in the prognosis for life and limb.

Summary

219 patients with femoro-popliteal thrombosis and 103 patients with aorto-iliac thrombosis were observed

for an average period of three years after their first attendance at hospital. The results of treatment are analysed, showing that claudication in a large number of patients remained unchanged or improved on conservative treatment only. Angina and coronary thrombosis were common during the follow-up period, and the general mortality of this atherosclerotic group is high. The position of long-term anticoagulant therapy is discussed.

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OBSERVATIONS ON PREVENTION AND DIAGNOSIS OF ANAEMIA IN PREGNANCY

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The high incidence of anaemia in women attending the antenatal clinics of two hospitals in North Staffordshire led, in 1957, to a systematic study, the first results of which have already been published (Giles and Shuttleworth, 1958). They showed that megaloblastic anaemia of pregnancy occurred in at least 2.8% of hospital confinements and that there was almost invariably a good response to folic acid. A megaloblastic bone-marrow, however, was found in only a minority of women who presented with anaemia in pregnancy or the puerperium. In the absence of haemorrhage, iron deficiency accounted for the great majority of anaemias and often complicated a coexistent deficiency of folic acid.

In view of the relatively slight marrow changes in some of the milder cases of megaloblastic anaemia and an unexpectedly high serum iron in a few anaemic women with entirely normoblastic erythropoiesis, those authors surmised that folic-acid deficiency might exist in pregnancy even in the absence of megaloblastic anaemia. That this is in fact the case has now conclusively been demonstrated by Chanarin *et al.* (1958, 1959) by means of tests of folic-acid clearance and absorption.

It was therefore decided to administer folic acid prophylactically to an unselected group of women during the last 11 weeks of pregnancy—not only in order to prevent the onset of megaloblastic anaemia, but also to compare the haemoglobin level at term of women so treated with that of a comparable group of controls.

For several years the prevalence of iron deficiency had convinced us that all antenatal patients need supplementary iron, but the onus for its administration had rested with the family doctor. Since the incidence of iron-deficiency anaemia remained high we felt it advisable that iron should be administered by the hospital to all patients from the time they first attended the antenatal clinic. This new regimen was timed to coincide with the therapeutic trial of folic acid in order to eliminate iron deficiency as a variable factor in the investigation.

Method

From July 1, 1958, onwards all antenatal patients, as soon as they first attended the hospital, were given a daily dose of 540 mg. of ferrous sulphate and 75 mg. of ascorbic acid. They were also handed a sheet of instructions and explanation of why it was necessary that iron and vitamin C should be taken regularly. The medical and nursing staff did their best at every visit to ensure that patients took their iron, and advised them how best to take it. Ferrous sulphate was chosen, since trials of different iron preparations (Kerr and Davidson, 1958) had shown that this, the cheapest of all iron compounds, was quite as effective in raising the haemoglobin level of the great majority of patients as other more expensive iron preparations. Intolerance to ferrous sulphate could often be minimized by the simple advice that the drug be taken during the course of a meal rather than afterwards, which is the common practice. Rather less than 20% of women developed gastro-intestinal symptoms—constipation, nausea, abdominal pain, and, occasionally, diarrhoea; and in such cases other forms of iron, such as ferrous gluconate, "colliron," and ferrous succinate was substituted for ferrous sulphate. A small number of patients (less than 1%), who could not tolerate oral iron in any form, were given a course of injections of intramuscular iron-dextran complex ("imferon"). Ascorbic acid was routinely administered. as it has been claimed (Fisher and Biggs, 1955; Steinkamp *et al.*, 1955) that this vitamin facilitates absorption of iron and reduces some of the side-effects of oral iron preparations.

The selection of patients for the trial of folic acid was based entirely on the order in which they were booked in the antenatal clinic; thus every other patient was given a daily dose of 15 mg. of folic acid from the 29th week of pregnancy onwards. This is undoubtedly far more than the daily needs of a pregnant woman (Lowenstein *et al.*, 1955), but in such a large group of cases, which included many women of rather low intelligence, it was obviously simpler to prescribe an equal number of tablets of three different kinds. Subsequent findings have shown that depletion of folic acid may occur before the 30th week of pregnancy, and our more recent practice is to begin the administration of folic acid at the 26th week.

The haemoglobin of all patients was determined at every visit, and packed cell volumes were estimated and stained blood films examined whenever the haemoglobin dropped below 67% (100% = 14.8 g./100 ml.). At the same time a careful search was maintained for cases of megaloblastic anaemia on the lines of the previous investigation (Giles and Shuttleworth, 1958).