Thromboangiitis Obliterans

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Thromboangiitis obliterans (TAO) has been a recognized clinical entity for more than half a century (Buerger, 1908). Distal arterial occlusive disease and/or recurrent superficial thrombophlebitis occurring in an adult male smoker, in the absence of known cause, constitutes a distinctive and unmistakable syndrome (Brown, Allen, and Mahorner, 1928). However, the existence of this disorder has been questioned because it was not being encountered clinically, and meticulous examination of unselected amputated limbs did not reveal the characteristic microscopical changes (Wessler *et al.*, 1960). For these reasons, it was suggested that the diagnostic category of thromboangiitis obliterans be discarded (Wessler, 1961).

If the question of the existence of this disorder had no practical importance, arguments about it could be regarded as exercises in medical pedantry and be dismissed. We feel, however, that this syndrome is separate and distinct, and that failure to recognize it will deprive patients of correct advice and proper treatment. In our opinion, the lack of plentiful characteristic histological changes and the failure to detect such cases clinically are not sufficient arguments to deny what is a clear clinical syndrome. This study was undertaken to emphasize the clinical, radiographic, histological, and prognostic features of Buerger's disease and the differences from other forms of vascular disease.

SUBJECTS AND METHODS

All patients seen in the section of peripheral vascular disease from April 1961 to July 1964 with the diagnosis of TAO are included. In addition, the records of patients given this diagnosis in the Department of Medicine of Henry Ford Hospital during the period from 1950 to 1962 were reviewed.* Criteria for

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* This series represents patients of the Department of Medicine and does not include cases of TAO seen in other Departments of the Hospital.

inclusion as a case of TAO were applied rigidly. These included the initial appearance of symptoms or signs of occlusive arterial disease in an extremity distal to the popliteal or brachial arteries, Raynaud's phenomenon, and recurrent superficial thrombophlebitis, in the absence of detectable cardiac or cerebral vascular disease, peripheral vascular calcification, hyperlipidaemia, hypercholesterolaemia, diabetes mellitus, cervical ribs, scalenus anticus syndrome, scleroderma, systemic lupus erythematosus, or periarteritis nodosa. Such conditions were excluded as effectively as possible either at the time of initial diagnosis or at subsequent visits to the outpatient clinic. Each patient was contacted and 32 of the 41 patients were examined by one of us (I.J.S.). Haemoglobin, fasting blood sugar, uric acid, serum cholesterol, total lipids, serum protein electrophoresis, and 12-lead electrocardiogram studies were performed.

RESULTS

Age and Sex Distribution (Table I). All patients were male and at the onset of their symptoms they smoked heavily. No ethnic preponderance was noted. The disease was observed in one Negro; all of the rest were Caucasian. The average age at the onset of the symptoms was 31.2 years, with the range being 18 to 49 years. The majority of patients were between the ages of 26 and 35 years at the onset of symptoms.

TABLE I
AGE AT ONSET OF SYMPTOMS

Age	No. of patients
18-25	9
26-35	16
36-45	15
46-49	1

Average age 31.2 years.
Range 18 to 49 years.

Initial Complaints (Table II). Manifestations of ischaemia were the presenting symptoms or signs in 32 patients. The remaining 9 patients initially

TABLE II
INITIAL PRESENTING COMPLAINT

	No. of patients
Ischæmia	32
Intermittent claudication of calves or arches	21
Rest pain or ulceration	8
Raynaud's phenomenon	3
Phlebitis	9
Total	41

appeared with episodes of thrombophlebitis. Intermittent claudication of the calves or arches occurred in 21 patients initially, and ischæmic rest pain or ulceration with rest pain was observed in 8 patients. In 3, Raynaud's phenomenon of the fingers was the first symptom.

Clinical Course (Table III). The disease progressed at a variable rate in all patients before they stopped smoking: 33 eventually developed intermittent claudication; 29 had ischæmic ulceration (8 in the upper extremities); Raynaud's pheno-

TABLE III
CLINICAL FEATURES OF ISCHÆMIA

	No. of patients	
	Upper extremities	Lower extremities
Intermittent claudication	1	32
Ulceration	8	21
Raynaud's phenomenon	7	1
Rest pain without ulceration	2	8
Diminished or absent pulses	22	32

menon was observed in 8 and ischæmic rest pain without ulceration in 10 patients. Distal pulses were diminished or absent in the upper extremities of 22 patients and in the lower extremities of 32.

Thrombophlebitis occurred in 20 patients, and was recurrent in 15 of these (Table IV). The superficial veins were involved in 20 patients and the deep veins in 4. Phlebitis was noted in the upper extremities in 6 and in the lower extremities in 19 patients.

TABLE IV
CLINICAL FEATURES OF THROMBOPHLEBITIS IN 20 PATIENTS

Site	No. of patients
Superficial veins	20
Deep veins	4
Lower extremities	19
Upper extremities	6

Three major clinical phenomena were apparent: ischæmia, thrombophlebitis, and Raynaud's phenomenon. Ischæmia alone was noted in 15 patients during the course of the illness (ischæmia is defined arbitrarily as denoting intermittent claudication, ischæmic rest pain, or ischæmic ulceration). In 20 patients symptoms or signs of ischæmia plus evidence of single or recurring episodes of thrombophlebitis occurred. In 8 patients ischæmia plus Raynaud's phenomenon were present and in 3 all three major clinical patterns were observed.

Therapy. The response to tobacco abstinence was specific. Symptoms and signs of the disease abated without recurrence in 20 of the 21 patients who stopped smoking permanently. Some of these patients have been followed more than 20 years without evidence of progression of the disease. On the other hand, new clinical phenomena were observed in all 20 patients who continued to smoke (Table V).

TABLE V
TOBACCO AND BUERGER'S DISEASE

Patients	Disease arrested	Disease progressed
Stopped smoking permanently	21	1
Continued to smoke	20	20

Thus the treatment of TAO had, as its cornerstone, avoidance of tobacco. Ancillary measures were of value only when used in conjunction with this simple manoeuvre. These included attempts at overcoming vasoconstriction by chemical block or surgical removal of sympathetic chains, provision of adequate warmth, protection and bed-rest for the affected extremity, and suppression of infection by appropriate antibiotics. Amputations of digits or extremities were necessary in 9 patients: each of them had continued to smoke.

Prognosis. One patient died and at necropsy there was histological evidence of TAO in the peripheral vessels and marked atherosclerosis in the aorta and renal arteries. The cause of death was thrombosis of the renal arteries and abdominal aorta. Two other patients have manifested evidence of ischæmic heart disease with typical electrocardiographic changes subsequent to their initial examination. Both patients are now in their fifties and have continued to smoke.

Radiographic Findings. Arteriograms were made in several patients, but reconstructive arterial surgery was applicable in none. The most common finding was an occlusion of one or more larger

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 1.—Arteriogram of the right lower leg, which shows a channel proceeding distally from an obstructed popliteal artery to form a network of collaterals which supplies stumps of the posterior tibial and of the peroneal vessels. These arteries in turn are obstructed lower in the leg so that only fine tortuous branches proceed distally.

FIG. 2.—Arteriogram of the left femoral system showing corrugation of the superficial femoral artery, and a block at the level of Hunter's canal with smaller branches proceeding distally.

FIG. 3.—Portions of an arteriogram showing marked corrugation of the right superficial femoral artery, with a diagrammatic representation of the vessel.

branches of the popliteal artery, most commonly within a few centimetres of its origin or in the region just above the ankle. The appearance of the occlusion was not characteristic. In many cases one or more tortuous collateral vessels extended distally from the region of the occlusion either uniting with the distal portion of the affected vessel bridging a gap or more commonly continuing inferiorly as a smaller vessel than the occluded vessel. Occasionally stumps of the distal vessels were well filled

by the collaterals (Fig. 1). In one patient an arteriogram of the upper extremity revealed an occlusion of both the radial and ulnar arteries at their origin from the brachial artery. The circulation to the forearm and hand was maintained by the volar and dorsal interosseous arteries.

Corrugation of the major arteries and branches of the deep femoral artery is of interest (Fig. 2 and 3). The nature of the change which produces this appearance is not known, but it has been noted

TABLE VI
PATHOLOGY IN BUERGER'S DISEASE

Acute lesion	..	..	..	..	..	2
Chronic lesion	..	..	..	..	..	7
Negative muscle biopsy	..	..	..	..	..	3
Number of patients						12

TABLE VII
HISTOLOGICAL DIFFERENTIAL DIAGNOSIS

	Inflammatory cells	Thrombosis	Medial calcification	Atheroma	Veins and other tissue involved	Int. elastic lamina
TAO—Early	+	+	—	—	I	U
Late	±	+	±	—	?I	?U
Arteriosclerosis obliterans	—	±	+	±	U	I

+ = Present — = Absent I = Involved U = Uninvolved

by other investigators (Sutton, 1962; Theander, 1960).

Pathology (Tables VI and VII). Tissue was available for histological study in 12 patients. The following stains were used to study the muscle and connective tissue, cellular infiltrate, and elastic tissue: hæmatoxylin and eosin, Masson trichrome, azure eosin, and orcein azure eosin. Muscle biopsies were available in 3 patients but showed only lymphocytes and occasional eosinophils in the walls and adventitiæ of several arterioles.

Thrombosis and inflammatory cell infiltration of the blood vessels and adjacent tissues were present in 9 patients. The involvement was segmental, and,

except for one small vein, was limited to medium and small arteries. In 2 of the 9 patients, the lumen of a small artery and vein was occluded by inflammatory cells consisting predominantly of neutrophils and lymphocytes, with rare eosinophils and multinucleated giant cells (Fig. 4 and 5). These 2 patients we have classified as having the "acute

FIG. 4.—Recent thrombus in a subcutaneous artery beginning to organize. Elastic lamina is delicate, intact, but split. (Orcein azure eosin. $\times 12$.)

FIG. 5.—Enlargement of Fig. 4. Unlike other thrombi, leucocytes and rare giant cells (A) are the principal components. The media is oedematous, well vascularized, and contains leucocytes. (Orcein azure eosin. $\times 127$.)

FIG. 6.—Organized recanalized thrombus of artery. Except for one area (A), the internal elastica is intact. Adventitia contains more leucocytic infiltrate than the arterial wall. (Orcein azure eosin. $\times 25$.)

FIG. 7.—Leucocytic mantle about an arteriole demonstrates the infiltration of the wall and adventitia. (Hæmatoxylin and eosin. $\times 330$.)

FIG. 8.—Diffuse intimal thickening narrows this small arterial lumen. Media is hypertrophied. (Orcein azure eosin. $\times 128$.)

lesion" of TAO. In 2 patients a thrombus of platelets, fibrin, and leucocytes, with early organization of the periphery was present. The remaining thrombi were organized and frequently recanalized (Fig. 6), making it impossible to determine whether they were originally masses of inflammatory cells or conventional thrombi.

Inflammatory cell infiltration varied greatly and in most instances was overshadowed by the thrombus. Arteries and connective tissue were the sites of major involvement and only rarely did a vein wall contain scattered inflammatory cells. Although neutrophils were seen in the acute thrombi, lymphocytes predominated with infrequent infiltration with eosinophils. Leucocytes were present in great numbers in the extravascular connective tissue, and formed cuffs around arterioles (Fig. 7).

Mast cells were easily recognized with the azure eosin stain. They were most numerous in the adventitia of the blood vessels and connective tissue and less so in the vascular wall and in the organized thrombi. No mast cells were seen within the acute thrombi (inflammatory or platelet).

In those arteries with inflammatory cell infiltration, the media was occasionally oedematous and contained increased numbers of capillaries. Unlike arteriosclerosis, the elastic tissue of the intima and media of the arteries was infrequently and less severely involved. The elastica was generally intact, but in a few thrombosed arteries the internal

elastic lamina was interrupted and sometimes split. Segmental focal intimal proliferation and occasionally arterial muscular hypertrophy of otherwise uninvolved arteries and veins were encountered; in some arterioles intimal thickening and endothelial cell hyperplasia narrowed their lumens (Fig. 8 and 9). Focal medial calcification without other changes was encountered in large arteries of 2 patients.

Peri- and intraneural fibrosis of small intradermal nerves and of a large subcutaneous nerve of one patient were encountered. Demyelination and degeneration of nerve fibres in the large nerve were demonstrated with the Kluver and Bodian stains.

DISCUSSION

A diagnostic category is of practical value to the clinician only if knowledge of the unique characteristics of the disorder provides a guide to prognosis and treatment. Whether classification be made on the basis of aetiology, clinical course, morphology, or response to therapy, categorization of disease has obvious advantages. Often, however, pathognomonic features for diagnosis do not exist; in these cases clinical judgements, and experience in disease patterns, supplant more objective data. That such observations are valid is unquestioned.

For many years Buerger's disease was recognized as a distinct syndrome. Recently, however, chal-

FIG. 9.—Arteriole of skin in area of acute inflammation. Fibrous intimal and endothelial cell proliferation distorts and markedly narrows its lumen. (Orcein azure eosin. $\times 390$.)

lenges to its existence as a diagnostic entity have appeared (Wessler *et al.*, 1960; Wessler, 1961). Subsequently, experienced investigators have defended its recognition as a clinical disorder (Barker, 1962; McKusick *et al.*, 1962; Horwitz, 1961). This ventilation of differing viewpoints was the stimulus for us to examine our own experience in this disease.

Analysis of the data uncovers an overwhelming mass of evidence supporting the thesis that TAO is a separate and distinct syndrome. This information may be divided arbitrarily into 5 categories: clinical, radiographic, histological, prognostic, and therapeutic.

(1) *Clinical.* The specificity of distal occlusive arterial disease in young adult male smokers is apparent. The subsequent appearance of recurrent episodes of thrombophlebitis in 20 patients (49%) is not characteristic of premature atherosclerosis or embolic arterial disease. Raynaud's phenomenon is an extremely uncommon symptom in young adult men (I. J. Schatz, unpublished data), yet it occurred in 8 patients. Thus, arterial disease, venous thrombosis, and Raynaud's phenomenon in a young male smoker present a highly suggestive clinical pattern.

Radiography. The number of patients with TAO studied by angiography is insufficient to reflect statistically significant differences from other arterial diseases. However, the data available do indicate that this disorder is usually infrapopliteal in location and that signs of involvement of more proximal vessels with atheroma (as one would expect were TAO due to premature atherosclerosis or distal embolization from proximal sclerotic plaques) are absent. In addition, the corrugation of the femoral arteries noted in the several angiograms is an uncommon phenomenon in atherosclerosis. These findings suggest that characteristic angiographic features may exist in TAO.

Pathology. One of the arguments against the existence of TAO has been the inability by some to demonstrate the histological changes described by Leo Buerger (1908). Tissue from 2 of 12 patients in this study had changes of the "acute lesion" of TAO. This lesion is unlike any histological change of arteriosclerosis obliterans or response to an embolus or thrombus. The fact that such a lesion has been observed in this series, confirms earlier claims about its specificity for TAO, and underscores its rarity (Barker, 1962). In none of the 12 patients was arteriosclerosis present in the peripheral

TABLE VIII
NUMBER OF YEARS FOLLOWED FROM ONSET OF SYMPTOMS

No. of years	No. of patients
<1	3
1-5	9
6-10	11
11-20	13
21-30	3
31 +	2

vessels. The internal elastic lamina was infrequently and minimally involved.

Prognosis. It is clear from this study, as well as others (McPherson, Juergens and Gifford, 1963), that the outlook for life in these patients is distinctly better than that for patients of the same age with premature sclerosis. Table VIII indicates the number of years this group was followed. One death occurred and this was due to atherosclerosis of the terminal aorta and renal arteries; yet this patient had no sign of peripheral arteriosclerosis and had the classical changes of TAO in the peripheral vessels. Two other patients developed clinical evidence of coronary disease. If this disorder is a form of premature arteriosclerosis, the toll of deaths due to cerebrovascular and coronary atherosclerosis would reasonably be expected to be higher than 1 patient in 41.

Similarly, Table V clearly shows that this disease almost always progresses if the patient continues to smoke, and becomes arrested if smoking is stopped. Several patients in this group have had symptoms of ischaemia which have remained stable for over 20 years from the time they stopped smoking. Such lack of progression would be unusual in any other form of vascular disease.

Therapy. The only specific treatment that is apparent on review of these cases is abstention from tobacco. Those adjunctive measures that include encouraging collateral supply, suppressing vasoconstriction, and combating infection in themselves are insufficient to prevent worsening of the condition, unless the patient stops smoking.

CONCLUSIONS

The present study indicates that TAO is a separate and distinct diagnostic category. The importance of its recognition lies in the fact that patients who suffer from it seem no more susceptible to atherosclerosis than do others of the same age, and that almost always the simple abstention from

smoking will arrest this disorder. Accordingly there is considerable practical value in detecting this disease.

SUMMARY

A study of 41 patients with symptoms of distal arterial occlusive disease, and/or thrombophlebitis, and Raynaud's phenomenon was made. This group had a distinct clinical course, and responded to the therapeutic manoeuvre of abstention from tobacco. Characteristic histological and radiological features were observed. The data available support the thesis that thromboangiitis obliterans is a separate clinical entity.

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