Thromboangiitis obliterans (TAO = Buerger's Disease)

Conclusions from a review of 27 published papers

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1. Introduction

I was provided with copies of 27 papers thought to be of relevance to TAO. A list of references of these papers, together with a brief summary/commentary on each is attached as an Appendix to this note. Below I comment on the general conclusions that can be drawn, taking into account strengths and weaknesses of the available evidence.

2. Clear message from 40 years ago

Having read through nearly all the papers, I reached that by Silbert (23), based on his experience of over 1400 TAO patients in New York during a twenty-year period. Although written in 1945, it struck me forcibly that this paper gave us a number of very clear conclusions that all the subsequent literature has only served to reiterate. Since the paper was clearly written and based on a much larger number of patients than any subsequent paper on the subject, it is obviously a "landmark" paper.

The main messages of Silbert's paper were these:

1)   TAO occurs virtually exclusively in men - only 12 of his cases, less than 1%, were in women.

2)   TAO only occurs in those who had smoked - every single one of his 1400+ cases had done so.

3)   If smokers continue to smoke, their disease is almost uniformly progressive.

4)   If smokers stop smoking permanently, the disease is immediately and completely arrested.

5)   TAO is a disease of the young - in 100 case histories he cited, the ages of onset varied from 20 to 44 with a median of 33.

6)   It is important to distinguish TAO from what he called presenile atherosclerosis, particularly in the age group 40-55.

7)   Because no other infection is known to be sex-linked, Silbert believed that infection was unlikely to be a cause of TAO. Rather a sex-linked constitutional special sensitivity to tobacco seemed a much more plausible explanation to him, though he had no concrete evidence here.

In the following sections we consider the further evidence on these main messages and also some other relevant points.

3. Distinction from other forms of peripheral vascular disease (PVD)

Silbert (23) emphasised the importance of distinguishing TAO from presenile atherosclerosis or what others refer to as arteriosclerosis obliterans (AO) or arterial occlusive disease. Both diseases present with symptoms of intermittent claudication (IC), rest pain and numbness of the extremities. In both conditions the local signs, the absence of pulsations, the reduced temperature of the feet and the presence of ulcers or gangrene may be the same.

The major difference is that TAO relates to an inflammatory process while AO results from a generalised arteriosclerosis. Both Silbert (23) and McPherson et al (14) discuss the distinction in detail. Discriminators in favour of TAO are agreed to be a history of superficial thrombophlebitis, absence of calcification of vessels on X-ray, absence of clinical evidence of aorto-iliac occlusive disease, absence of clinical evidence of heart disease and presence of ischaemic lesions of the fingers. Silbert also mentions a relatively low blood pressure, a generally young appearance, normally pigmented hair, no arcus senilis, low blood pressure, soft radial and temporal vessels, low blood volumes and rareness of albuminuria, while McPherson et al include a normal serum cholesterol and a history of tobacco smoking. Silbert goes on to note that care must also be taken to exclude instances of PVD due to syphilis, embolism, trauma, polycythemia, poisoning from ergot or arteritis due to influenza, typhus or rheumatism.

McPherson et al point out that some have vigorously challenged the concept of TAO as a diagnostic entity. They demonstrated clearly a difference in prognosis between 149 patients, classified as TAO definite or probable and 119 classified as ASO definite or probable. 10 year mortality in the TAO groups was similar to the national average, but that in the ASO groups (mainly from ischaemic heart disease) was over 3 times higher, suggesting they were indeed different diseases.

The frequency of TAO is not clearly stated in any of the papers, though it is obviously rare. Liedberg et al (12) notes that it seems to account for only a very small proportion of amputations among patients with arterial occlusive disease, while Nielubowicz et al (17) states TAO patients were only 3.3% of all presenting with peripheral arterial pathology.

In discussing the role of various factors in TAO, the importance of not treating studies of patients with AO, with IC or with PVD generally as of direct relevance to TAO is underlined, as is the importance of bearing in mind the possibility that in some studies patients referred to as having TAO may include some misdiagnosed AO cases.

4. Sex

The percentage of male patients seen in the major studies are given in the table overleaf. It can be seen that the evidence is clear that TAO patients are predominantly male, certainly over 90% and probably more like 98% or 99%, with the lower percentages being due to some misclassification of diagnoses. The male/female ratio is less marked in other forms of PVD.

Author	Ref	Country	N/Disease		% men TAO	% men other
Barker	1	USA	350	TAO	100.0*	
Begg	2	Scotland	294	IC		>90.0**
Birkenstock et al	3	S.Africa	390	PVD		73.1
Hill et al	8	Java	106	TAO	99.1	
Hughson et al	11a	England	60	IC		78.3
	11b	England	160	IC		61.9
Liedberg et al	13	Sweden	188	Amputees		53.2
McPherson et al	14a	USA	149	TAO	94.6	
	14b	USA	119	AO		95.8
Nielubowicz et al	17	Poland	102	TAO	92.2	
Shionaya et al	21	Japan	148	TAO	98.7	
Shionaya	22	Japan	115	TAO	98.3	
Silbert	23	USA	>1400	TAO	>99.1	
Wong et al	26	China	105	TAO	96.2	

*   It was not clear whether Barker had no women with TAO or only described male data.

**   Begg only described data on males, but stated that women account for less than 10% of cases.

5. <u>Age</u>

The age distributions reported in the major studies were as follows:

TAO			Other		
<u>Ref</u>	<u>Age</u>		<u>Ref</u>	<u>Disease</u>	<u>Age</u>
1	25-55		2	IC	77% developed in 50's and 60's
8	15-60 mean 32 at onset		11a	IC	40-79
14a	Mean 37 at onset*		11b	IC	35-90 mean 68.6
17	<40 mainly 21-30 at onset		13	Amputees	Mainly 70-90
22	19-49 mean 36 at onset		14b	ASO	Mean 41 at onset*
23	<50, median 33 at onset				
26	<45, median 33 at onset				

* Only patients under age 45 were considered.

It is clear that TAO is a disease of the young, with onset commonly in the 30's and rarely over 50. This is in distinct contrast to IC patients generally. it is not totally clear (to me at least) whether the fact that TAO is virtually never diagnosed in those aged over 50 represents the true situation or to a tendency for older patients, who are more likely to have evidence of gneralised arteriosclerosis, to be diagnosed as not being TAO. If the (more likely) former, this would be consistent with there being a susceptible minority who, if they smoke, get symptoms of TAO within 10-20 years (with others being able to smoke with immunity) since virtually no-one starts smoking other than before age 30 at latest.

6. Smoking in relation to onset of TAO

Smoking habits of TAO and other PVD patients in the various studies were as follows:

TAO			Other			
Ref	% Ever Smoked	% Current Smokers	Ref	Disease	% Ever Smoked	% Current Smokers
1	98.3		2	IC	99.0	96.0
8	100.0	100.0	3	PVD		83.4
14a		100.0*	11a	IC	98.3	98.3
17		84.0**	11b	IC	89.7	
22		100.0*	13	Amputees	45.2	28.2
23	100.0		14b	AO		93.3
26		96.2				

* Current smoking was part of the definition of TAO.

** Heavy smokers - total % of smokers not given.

Though many of these studies did not have control groups, it is clear that the 100% or virtually 100% incidence of smokers among TAO patients would not have been because everyone smoked in the countries where and when the studies were carried out (although the Indonesian study of Hill (8), had a 95% reported smoking in his controls). Bearing in mind the possibility of some misclassification of smoking habits or misdiagnosis (smoking rates though high in the other groups are not so high), the data are in fact consistent with risk of TAO being totally confined to

smokers. One cannot exclude, however, the possibility that there is a very small risk in non-smokers, perhaps due to some undiscovered rare cause.

While none of the studies are prospective (in view of the rarity of the disease), the association between smoking and TAO cannot be plausibly explained by an increased recall of smoking in diseased rather than disease-free patients. Such an explanation may be relevant to explain some excess of smokers, not a 100% incidence of smokers.

6.1 Extent of smoking

Barker (1) found a clear relationship of risk of TAO to degree of usage, with risk over 5 times higher in 30+ cigarette smokers than in smokers of 1-7 a day. An even stronger dose-response was reported by Hill et al (8) with over 20% of cases, as compared with about 2% of controls, smoking over 40 cigarettes a day at peak consumption. The same study also noted a marked tendency for TAO cases to start smoking at a younger age. The Polish study (17) reported 84% of TAO cases were heavy smokers, but gave no control data. Shionaya from Japan (22) stated all his TAO cases were heavy smokers but did not define "heavy".

6.2   Type of product smoked

Barker (1) found that risk of TAO was some 3 times higher in smokers of cigarettes than in smokers of pipes and cigars.

6.3   Unsmoked tobacco

In a large study in   Tennessee   by Smith (25), no intermittent   claudication   at   all   was   reported   in   1500 non-smoking users of snuff or chewing tobacco with oral changes.   Nor were any snuff users or tobacco chewers found in 50 patients with intermittent claudication.   The Mayo Clinic study of Barker (1) found only 1 non-smoking tobacco chewer in 350 TAO cases.   There appears to be no relationship of unsmoked tobacco to TAO.

7.   Other factors

If one accepts that, to all intents and purposes, all TAO sufferers are smokers, does this mean smoking causes TAO? Certainly it is not a sufficient cause, since all smokers do not get TAO (indeed hardly any do), but it is difficult to argue plausibly that it is not a necessary cause.

Normally, in smoking-related diseases, an association with smoking may, in theory, be actually a result of some other (confounding) factor, which is both the true cause and is positively associated with smoking.   For example, smokers get more liver cirrhosis, because smokers drink more alcohol and

alcohol causes liver cirrhosis. In this case, however, one cannot really suggest the association could be secondary to a confounding factor since one would require this factor to be something that smokers (or at least some smokers) do and that non-smokers never do. And, as far as we know, no such factor exists - there are plenty of correlates of smoking but no 100% correlate of smoking.

One is therefore left with the conclusion that smokers with TAO would not have got the disease had they not smoked. Study of other factors should not be seen as looking for a possible confounder. Rather it should be seen as looking for an explanation as to why some smokers get TAO and others do not. it is still eminently plausible that smokers in fact run no risk at all of TAO unless some other factor is present.

7.1   Race

The relationship of TAO to smoking has been reported in a wide range of nationalities, creeds and ethnic groups. Some early studies pointed to a preponderance of cases in Jews, but there was no evidence in those papers to support this contention. Thus McPherson et al (14) found a similar proportion of Jews, about 16%, in both TAO and ASO cases in Minnesota (though no corresponding figures for the normal population are given). No relationship of TAO to ethnic group was seen in the Javanese study (8).

7.2   Diet

Hill et al (8), in the study which looked at most other possible factors for TAO, noted that diet was generally poorer in TAO cases than in controls in their study in Java, but no clear vitamin-deficiencies were seen. Otherwise diet does not seem to have been studied.

7.3   Occupation

No obvious relationship to occupation was seen in studies of TAO (8,23,26) or of IC(2). The study in Java (8) noted that TAO predominated in the lowest socia-economic groups.

7.4   Alcohol and drugs

Hill et al (8) noted alcoholism was not seen in his Javanese TAO cases. Wang et al (26) found that 75% of his patients drank alcohol, most being only social drinkers and that 15 patients took narcotics regularly. Their personal habits did not differ from those of general surgical patients.

7.5   Geography and climate

As none of the papers give clear data on prevalence of TAO it is not possible to easily compare different countries. None of the papers referred to their country being a high risk area, and the impression is that this is a rare disease everywhere.

Hill et al (8) found no evidence of clustering of cases in Java with patients having a similar geographic and climatic distribution to controls.

7.6   Family history

Hill et al (8) found evidence of familial aggregation TAO in 2 (of 106) patients. However, one patient with an identical twin brother who smoked was normal.

The Scottish study by Begg (2) found no clear relationship of family history of atherosclerosis to risk of IC, the only possible exception being that patients had marginally significantly ($p < 0.05$) more brothers with IHD than the controls.

7.7   Classical coronary risk factors

Since cholesterol and blood pressure are used to discriminate TAO and other forms of PVD, it is not surprising that in general studies of TAO patients did not report increased cholesterol or hypertension (8), but that studies of IC patients did.

The study of Begg found IC patients tended to be somewhat less obese than average (2).

7.8 Past illness

Hill et al (8) found that his TAO cases and controls had a similar history of trauma, infectious disease and food and drug allergy.

7.9 Cold injury

In the study in Java (8), each respondent was read a story of an Indonesian farmer who had suffered from an episode of trench foot. 23 of the cases, but not of the controls, recognised having suffered a similar episode before onset of TAO. In most of these cases the episode had been followed by a temperature. A further 7 cases had also suffered some other form of cold injury, in general associated with working with feet immersed in water for long periods of time.

7.10 Mycotic infection

The Javanese respondents were also shown coloured photographs illustrating various forms of mycotic infection. More than 40 patients claimed they had had tinea pedis, a fungal infections between the toes, as against only 16 controls.

7.11 Studies of hypersensitivity

Because only a small proportion of smokers contract TAO, some studies have been carried out looking at the possibility that the disease may only occur in a subset of smokers.

A group in New Delhi found that, compared with normal controls, the circulatory immune complexes of TAO patients had a higher protein content and that their immunoglobulins in the immune complexes were predominantly of mixed type and were biologically active (6). They also found that TAO patients had significantly lower leukocyte migration inhibition and a somewhat reduced lymphocyte proliferative responsiveness in response to specific arterial and tobacco antigens, suggesting development of cell-medicated immunity (20). A study in New York found that 83% of TAO patients had reactions after being injected with tobacco extracts, as compared with 9% of control smokers (7). TAO patients were also more sensitive to other agents, though not so frequently.

A Yugoslavian study found no difference in skin sensitivity to nicotine or tobacco extract between TAO smokers and ex-smokers and controls smokers and nonsmokers (24). They did however demonstrate a vastly increased incidence of antinuclear antibodies in continuing TAO smokers compared with TAO smoekrs who had given up, and a decreased IgG immunoglobulin level and increased general and cellular body responsiveness.

The problem of course, wth all such studies, is that they are after the disease, and the observations made may in theory be a result of the disease and not a cause of it. Ideally one would like to see a prospective study of healthy subjects, in which hypersensitivity to tobacco could be linked to

subsequent onset of TAO, but this is unlikely ever to be carried out because of the rarity of TAO.

7.12   General conclusions in relation to other factors

The evidence from the Javanese study that TAO patients report past cold injury (in particular trench foot) and tinea pedis far more after than controls is strongly suggestive that some form of initial damage may be required to start off the disease process. Even then it seems clear that this initial damage will not progress to TAO unless it ocurs in a smoker.

It also seems very plausible that a genetic (probably sex-linked) hypersensitivity is involved. Although there is no very convincing detailed evidence that this is so, there are a number of pointers from the specific studies of hypersensitivity that this might be the case. Furthermore, although the fact that all smokers do not get the disease does not per se imply hypersensitivity to tobacco must be involved (Russian roulette victims are not hypersensitive, just unlucky!), the distribution of age of onset is suggestive of there being a small susceptible minority who all get the disease if they continue to smoke (and in whom the disease will progress if they do not stop).

8.   <u>Progression of the disease</u>

No formal randomized intervention trial has been carried out, presumably because it would be unethical not to tell a patient presenting with symptoms of TAO to stop smoking. However, there are a number of studies confirming Silbert's finding that giving up smoking halts progression of the disease.

Birkenstock (3), in a study of 390 PVD patients given instructions on foot care, exercise, diet and smoking, and given vitamin E tablets, which generally reported much better prognosis in those who gave up smoking. Only 10 were classified as TAO and in the 7 who stopped smoking their ischaemia improved, while symptoms got worse in those who did not.

Hill and Smith (9) carried out a retrospective longitudinal analysis of 97 Javanese smoking TAO patients. They found progression was more markedly rapid in those who smoked heavily and continuously. It was also worse in those who smoked Indonesian "Kawlung" cigarettes and who worked in wet and cold conditions.

As noted above for the Birkenstock study, giving up smoking is also associated with better prognosis for PVD generally. Supportive evidence for this was seen in the study by Hughson <u>et al</u> in Oxford (11).

Some studies have looked at the effects on outcome of various forms of surgery, and the way in which continuing to smoke has interfered with this.

Naik et al (15) described the prognosis of 14 Indian bidi smokers who underwent adrenalectomy and sympathectomy for TAO. The only patient to show a "poor" result was the one who continued smoking in the immediate postoperative period.

In Japan, Nakata et al (16) noted that improvement of TAO patients in response to sympathectomy was much better for those who gave up smoking that for those who did not.

Nielubowicz et al (17) concluded that such surgery was of little value, but gave no information on possible effects of giving up smoking. Indeed it was not stated that smokers were advised to give up.

Again in Japan, Shionaya et al (21,22) noted that long-term patency following vascular reconstruction surgery for TAO was strongly associated with stopping smoking.

In a study of Ohio patients undergoing bypass grafts for aortoiliac occlusive atherosclerosis, Wray et al (27) found that all late thromboses occurred in continuing smokers.

It is clear that, although patients with TAO (and indeed PVD generally) are usually advised to give up smoking, not all do so.

A Californian study (5) compared personality and behaviour in cooperative and uncooperative TAO patients. Uncooperative patients, in terms of neglect in following medical advice, were much more often described as hostile, negativistic, complaining, dependent and aggressive and less often as friendly, considerable, reliable and self-confident.

Only one study by Clyne et al (4), used blood carboxyhaemoglobin levels to show that PVD patients who report stopping smoking are usually fairly honest in their statements. However, only 7 out of 40 actually stopped, so the possibility of misclassification cannot be excluded. No data were presented on whether stopping smoking (or COHb reduction) was associated with an improved prognosis.

APPENDIX

Detailed reviews of the 27 papers

TAO	Thromboangiitis obliterans = Buerger's Disease
RR	Relative risk
IC	Intermittent claudication
PVD	Peripheral vascular disease
PEG	Polyethylene glycol
ASO	Arteriosclerosis obliterans
IHD	Ischaemic heart disease
HLP	Hyperlipidaemia
LMI	Leukocyte migration inhibition
LPR	Lymphocyte proliferative responsiveness
PA	Presenile arteriosclerosis
DNCB	1-Chlor, 2,4 dinitrobenzene
IgA,G,M	Immunoglobulins A, G, M

1. Barker (1931) compared the smoking habits of 350 men aged 25-55 with clinically diagnosed definite TAO with those of 350 similarly aged men attending the Mayo Clinic with no evidence of PVD. Results were as follows:

	Cases	Controls	RR
Never used tobacco	5	91	1
Chewers (non-smokers)	1	17	0.96
Smokers (pipe and cigar only)	24	45	9.71
Smokers (cigarette)	320	197	29.57

While the results were not standardised for age or any other factors, it is impossible to believe the very strong association between smoking (but not chewing) and TAO would have been materially

affected. Indeed, the use of hospital patients as controls would have tended to underestimate the association.

An analysis is also presented showing a dose-related relationship, with RR's varying from 6.9 to smokers of 1-7 cigarettes or 1-2 cigars a day up to 39.9 to smokers of 30+ cigarettes a day or 9+ cigars a day. Non-users or light smokers were also much less likely to have ulcers, gangrene or an amputation than heavy smokers.

Interestingly, the author notes that the fact that 5 TAO patients denied ever having used tobacco (and that 20 used it only in small amounts) is evidence against the hypothesis that tobacco is the primary cause of TAO. In this context, one should bear in mind the possibility of misclassification - 5/350 is only 1.4%, and the data on tobacco consumption came from hospital records.

2. Begg (1965) studied 294 men with IC in Glasgow. 116 healthy men drawn from various occupations in a large manufacturing firm were used as controls. Of 100 cases, nearly all were smokers:

	Cases %	Controls %	RR
Never smoked	1	21	1
Ex cigarette smokers	3	11	5.73
Pipe smokers	3	15	4.20
Less than 20 cigarettes/day	51	28	38.25
More than 20 cigarettes/day	42	24	36.75

Begg noted that the "men with IC are almost inevitably smokers, but often quite moderate smokers. This is consistent with the hypothesis that smoking is not a prime cause of peripheral arterial disease, as

it seems to be of bronchial carcinoma, but is a significant co-factor in its development in all cases."

A number of other factors were studied. Compared with the controls, cases had more hypertension (21% vs. 6%), higher serum cholesterol (by about 25 mg/100 ml on average), were marginally less obese (contrary to the heart disease pattern), showed no obvious difference in social class distribution and no clear difference in family history of atherosclerosis.

3. Birkenstock et al (1975) studied 390 patients in Cape Town with PVD who were neither eligible for, nor fit to undergo, surgery, 98 of whom had severe ischaemia, presenting with ulcers, rest pain or gangrene. Patients were given instructions on foot care, exercise, diet and smoking (stop!) and given vitamin E tablets, and followed up for an average of 2 years. Smoking habits were not recorded initially, but it was calculated that, of 332 patients assessed, 277 (83%) smoked initially. 164 of those stopped smoking (some further claims of stopping being countered by observations by the Sister!). 72% were assessed as having improved. Among the 332 patients with smoking recorded, patients who continued to smoke had a 20% chance of improvement as against while those who stopped or were non-smokers did vastly better, 85% and 69% respectively. The RR of improvement in relation to stopping vs. continuing can be calculated as 22.8 for all the patients and 34.0 for those with severe ischaemia.

Only 10 of the patients were classified as fulfilling the strict criteria for TAO, it being noted that "many cases previously

diagnosed as such were, in fact, cases of atherosclerosis." 7 of these stopped smoking and their ischaemia improved. Symptoms got worse in those who did not and returned in those who started smoking again.

4. Clyne et al (1982) compared 43 men in Southampton who smoked and had PVD (Group 1) with 25 age, sex, and weight matched smoking controls with no signs or symptoms of PVD (Group 2) and 25 similarly matched non-smoking controls (Group 3). Smoking habits in Groups 1 and 2 were similar at the start of the study. COHb levels were, as expected, significantly lower in Group 3 than in the other groups but interestingly were also lower (p<0.001) in Group 2 than Group 1. The PVD patients were instructed to stop smoking. 3 months later, 7 (of 40 reattending) reported they had given up. Their COHb levels significantly reduced, all being below 3% at the second visit. There was also a highly significant association between reducing consumption (reported by nearly all the remainder) and reduced COHb levels.

    While the study showed (given accuracy of the chemical methods) that PVD patients would reduce consumption, and in some cases give up, on advice to do so, no data were presented on whether this had an effect on their symptoms or prognosis.

5. Farberow and Nehemkis (1979), in a study in California, compared personality characteristics and behavioural phenomena in 26 uncooperative TAO patients and 26 matched cooperative TAO patients. Cooperation was measured in terms of neglect in following the medical

regimen, disregard of suggestions to avoid undue exposure to cold and refusal to abstain from smoking. All but 1 of the uncooperative patients and 2 of the cooperative patients smoked before the illness was diagnosed. Half the cooperative patients gave up and the rest reduced, in contrast to the uncooperative, where 23 of the 25 smokers continued. Uncooperative patients were more often described as hostile and negativistic (16 vs. 0), complaining, demanding and manipulative (12 vs. 0), passive and/or dependent (15 vs. 5) and having aggressive behaviour (7 vs. 0). Cooperative patients were much more often friendly, pleasant, helpful, considerate, grateful, responsible, reliable, self-confident and active (11-23 vs. 0 or 1). Alcohol consumption did not vary.

In a further detailed comparison of 12 uncooperative and 12 cooperative patients, the uncooperative patients (who, though of similar age, had had the disease for a shorter time), did not seem to value time nor be interested in achievement.

6. Gulati et al (1984) carried out an immunological study, comparing 25 Indian male TAO patients with 20 age matched normal males. Half the controls were smokers. Whether all the TAO patients smoked is not stated, but seems implied. Circulatory immune complexes were estimated in the sera by precipitation with polyethylene glycol (PEG). The TAO patients showed a significantly higher mean protein content of the PEG precipitate, and their immunoglobulins in the immune complexes were predominantly of mixed type and were biologically active. The authors postulate that smoking might be the cause of these differences seen in TAO patients, though they admit

other factors may be responsible for the initial vascular damage or change in antigenic character, since all smokers do not get the disease.

7. Harkavy et al (c.1935) compared tobacco hypersensitivity in 68 TAO patients and 122 control smokers in New York. 75 of the controls were Russian Jews aged 26 to 68 with a smoking history comparable to the cases; the remainder were 47 healthy college students. Subjects were injected on the outer arm with extracts of tobacco. 83% of the cases reacted to one or other extract, with reactions varying in intensity. 9% of the controls reacted, each reaction being not marked. In contrast, only 2 (of 68) TAO patients reacted to ragweed and, though in a further more detailed study of 15 patients multiple sensitizations were commonly seen (10 to horse epithelium, 9 to tomato and 6 to rice were the most frequent), none were as frequent as to tobacco.

8. Hill et al (1973), in a study in Java, carried out a complete interrogation and physical examination on 106 TAO patients and 106 individually age, sex, race and socio-economic status matched controls. All patients were continuing cigarette smokers when the disease started, all but 1 were men and all but 6 developed the disease before age 45. 95% of the controls were also cigarette smokers. TAO patients started smoking earlier (p<0.01), and smoked more cigarettes a day (p<0.001) compared to controls. 13 of 19 patients who stopped smoking and 15 of 16 who reduced consumption showed improvements in symptoms. All patients were from the poorer

section of the community and none could even be judged middle class by Indonesian standards.

No significant case/control differences were seen in respect of race, occupation, geographic or climatic distribution, past history of trauma or infection or food or drug allergy. Alcoholism, hyperglycaemia and hypercholesterolaemia were not seen in cases or controls and only 2 patients were positive for syphilis.

There was evidence of familial aggregation of TAO in two families. However, one patient with an identical twin brother who smoked was normal.

Diet was very poor in protein in rather more cases (58) than controls (42).

The only striking case/control differences other than smoking habits were that 23 cases, as against zero controls, reported suffering from an episode of trench foot (after having a case described to them), with a further 7 reporting some form of cold injury. Also more than 40 patients claimed, after seeing coloured photographs, that they had had tinea pedis (fungal infection between the toes) as against only 16 controls (p<0.001).

9. Hill and Smith (1974), using the same database, investigated the clinical course and prognosis of TAO by a retrospective longitudinal analysis of the history of 97 male Indonesian patients all of whom smoked. Starting with the time at which symptoms started, the

probability that they still only had symptoms, had digital disease or had amputation was calculated at times 3, 6, 9, 12 and 15 years since onset in relation to a number of factors. Overall, an estimated 58% of patients would have had an amputation after 15 years from first symptoms. Progression was found to be more markedly rapid in those who smoked Indonesian "Kawung" cigarettes, who smoked heavily and continuously, or who worked in wet and cold conditions. All these appeared to be independent factors, though a full multivariate analysis had not been attempted. An association between lower social class and poorer progression was thought to be secondary to these factors.

10. Based on the same subjects, Hill (1974) developed what was described as a rational basis for management of patients with TAO. He noted that the disease was characterized by acute exacerbations (attacks) with long remissions. For some patients, the attacks occurred "out of the blue" but 60% of patients related them to increased tobacco consumption and 23% to excessive exposure to cold. Hill recommended prophylaxis by advising young men not to smoke if they have any combination of: migratory thrombophlebitis, excessive hyperhidrosis, persistent fungal infection between the toes, an episode of cold history or frostbite, a job involving excessive exposure to cold and wet or a family history of the disease. Similarly, those already with the disease, should stop smoking and avoid cold exposure.

11. Hughson et al (1978) described the results of 2 Oxford studies of IC patients. In the first series of 60 patients, only 1 reported never having smoked, the rest all being current smokers. All were

strongly urged to discontinue smoking. 11 stopped and 9 reduced. Those who stopped or reduced were much less likely to have an adverse effect (death, amputation, onset of IC in a previously asymptomatic leg, onset of rest pain in a limb previously free of rest pain, MI or stroke, operation) than those who continued. Those who stopped or reduced smoked similar numbers of cigarettes originally and were similar in respect of age at onset, age at referral, claudication distance and other risk factors. Presence of IHD, hyperlipidaemia or hyperglycaemia did not affect prognosis, though the authors felt the data were not adequate to pick up a possible effect.

In the second study, 160 PVD patients were followed up for 8 years after first hospital admission. 94 had died, their death rate being much higher than the general population at each age. they also had a high hospital admission rate and reconstructive surgery rate. Age, coronary artery disease, cerebrovascular disease and diabetes were associated with an adverse outcome. The effect on outcome of giving up or reducing smoking could not be determined due to inadequate data.

12.   Kjeldsen (no date) reported results of a study relating COHb and serum cholesterol levels in smokers to the incidence of occlusive arterial disease. This does not seem directly relevant to the question of TAO.

13.   Liedberg and Persson (1983) studied the distribution of smoking, diabetes and age in 188 Swedish patients with lower limb amputation for arterial occlusive disease. These were compared with age and sex

matched population controls and with patients having hip fractures. In males, 45% of amputation cases were current smokers, as against 21% of population controls and 28% of hip fracture controls. In females, the figures were 9%, 3% and 6% respectively. There was a much higher incidence of diabetes in cases (29% men, 36% women) than in population controls (5% men, 8% women). The relevance of these findings to TAO is not direct. The authors note that TAO among smokers seems to account for only a very small proportion of amputations.

14. McPherson et al (1963) categorized 268 Minnesota patients into definite or probable TAO and definite or probable ASO (arteriosclerosis obliterans) based on the following criteria:

TAO 1.   History or clinical evidence of superficial thrombophlebitis.

       2.   History of tobacco smoking at onset of disease!

       3.   Significant decrease of arterial pulse in fingers.

       4.   Absence of clinical evidence of heart disease.

       5.   Absence of clinical evidence of aorto-iliac occlusive disease.

       6.   Normal serum cholesterol.

       7.   Absence of arterial calcification on X-ray.

ASO 1.   Clinical evidence of aorto-iliac occlusive disease or atheromatous calcification of arteries on X-ray.

       2.   Absence of ischaemic lesions of fingers.

95% of patients in all 4 groups were men. 16% were Jewish, again similar in all groups, contrary to a once-held view that most cases

were in Jews. 93% of ASO probable and possible smoked. 12% of ASO were diabetic as against only 0.7% of TAO.

These patients were then followed up to 10 years after diagnosis. 13 deaths out of 149 (8.7%) occurred in the TAO groups, a survival rate similar to the national average. In contrast, 39 deaths (31 from IHD) out of 119 (32.8%) occurred in the ASO groups. Finger and toe amputation, ulceration and gangrene rates were much higher in the TAO groups, but leg amputation rates did not differ much according to diagnosis. The authors conclude that TAO is a useful diagnostic category which should not be discarded.

15. Naik et al (1978) describe the follow-up of 14 Indian cases of TAO (all bidi smokers) who underwent adrenalectomy and sympathectomy. In the immediate postoperative period, 10 patients showed "good" results (being asymptomatic with no evidence of ischaemia), 3 patients showed "fair" results (with claudication still present but improving and no ischaemic ulceration), while 1 patient showed a "poor" result. This last patient continued smoking in the immediate postoperative period against medical advice and needed amputation. 9/11 patients remained with no symptoms and reduced disability after 6 months, while 6/8 did after a year. Sympathectomy alone, on the other hand, did not apparently increase the time lag between onset of disease and amputation of limb, although this was based on a small sample of the cases in a different hospital. The authors discuss evidence that adrenaline was responsible for onset of the disease.

16. Nakata et al (1975) describe the clinical response to lumbar
     sympathectomy in 88 Japanese patients with TAO. 52% of patients with
     a sensation of coldness, 58% of those with ulcer and 64% of those
     with rest pain improved. These data are difficult to interpret
     without control data since TAO patients' symptoms vary naturally over
     time. Effects were better in those with less severe disease
     initially - thus of those with coldness or numbness only, all showed
     improvement, whereas of those with coldness or numbness,
     claudication, ulcer and rest pain, 18% got worse and 36% were
     unchanged. Clinical response was much better in those who were
     non-smokers (86% improved) and those who gave up smoking (93%
     improved) than in those who continued (51% improved). Unfortunately,
     data are not given on numbers by initial smoking habits, though we
     can deduce from their Figure 4 that there were 14 (or perhaps 28)
     non-smokers. In view of the mass of evidence from other studies that
     the % of non-smoking TAO patients is very small (0.1%), this suggests
     that the diagnosis of TAO is in doubt (or that there is some other
     important factor in Japan).

17. Nielubowicz et al (1980) described the characteristics and progress
     of 102 patients with TAO, 20% of whom were treated by vasodilators,
     80% of whom were operated on (sympathectomy, adrenalectomy,
     stellectomy, amputation). It is noted that TAO cases formed only
     3.3% of all who present with peripheral arterial pathology, that 92%
     of patients were male, that 78% of cases present before age 30 and
     that 84% were heavy smokers (unfortunately no data on light smoking
     vs. non or ex-smoking are given). The authors concluded that none of
     the treatments were of any obvious value, and that patients had a

risk of getting sick of other diseases similar to the general population.

18. Patil et al (c.1970) described the pathology and pathogenesis of 25 Hindu males aged less than 40 with TAO who had had an amputation above or below the knee for gangrene. All were smokers, of cigarettes, pipe or bidis. There was no evidence of CHD or diabetes. From their observations, they concluded that TAO was a distinct clinicopathologic entity, changes seen in small and medium sized blood vessels being distinctive from those seen in other vasocclusive conditions. The authors considered the pathogenetic mechanism to be obscure. They felt the possibility of allergy to tobacco smoke was likely, though this study did not provide evidence here.

19. Rubba et al (1984) studied 143 Italian asymptomatic men aged 20-60 who had been referred for the evaluation of plasma lipids. 42 of them were normocholesterolaemic, the rest had varying degrees of hyperlipidaemia (HLP). The HLP group showed significantly increased signs of early arteriosclerosis obliterans (AO), as measured by digital pulse plethysmography. Within both HLP and non-HLP men, signs of early AO were significantly increased in smokers. This paper is of little direct relevance to TAO.

20. Sharma et al (1985) compared leukocyte migration inhibition (LMI) and lymphocyte proliferative responsiveness (LPR) against specific arterial and tobacco antigens in Indian male TAO patients, presumably all smokers, and age and sex matched healthy controls, mainly non-smokers. LMI was significantly lower in TAO patients than in

controls against both human arterial and tobacco antigens (the latter being prepared from bidi tobacco). LPR was somewhat higher in TAO patients, though not significantly. In controls, LMI and LPR did not vary significantly by smoking. While numbers were small, 17 or 18 TAO cases, 13 controls and only 3 or 5 controls depending on the test, the authors feel the results are consistent with development of cell-mediated immunity in response to these antigens. They suggest that this develops first in response to tobacco, which, in combination with vascular damage from smoking, probably changes the antigenic character, subsequently affecting response to other antigens.

21. Shianoya et al (1976) carried out vascular reconstruction surgery in 23 of 148 patients with TAO. In a follow-up of 10 months to 8 years, the overall patency rate was 26%. It was noted that 7 patients with long-term patency of the revascularized segment have stopped smoking, but that 5 patients with late failure of bypass grafting started smoking again postoperatively. The authors emphasise that complete abstinence from tobacco is essential for long-term patency. Further details of smoking habits are not given.

22. Shianoya et al (1983) described 115 Japanese patients with TAO, all but 2 of whom were males. The diagnostic criteria included onset before the age of 50 years, absence of atherogenic risk factors (undefined) and being a smoker. All the patients were stated to be heavy smokers, though no definition of "heavy" was given. Pathological and haematological characteristics were described, as were the results of arterial revascularization, carried out in 20

patients. In these cases, trophic lesions did not recur unless the patients resumed smoking, these results presumably corresponding to those reported in Shianoya et al (1976).

23. Silbert (1945) describes the characteristics of over 1400 cases of TAO seen in his New York clinic and private practice over 20 years. He notes the problems of distinguishing TAO from presenile arteriosclerosis (PA), an "entirely different disease", with a number of common symptoms - IC, rest pain, coldness and numbness of the extremities, presence of ulcers or gangrene. Distinction, for patients between age 40 and 50 years, is made on the following criteria:

	TAO	PA
Appearances	Younger than age	Older than age
Hair	Usually pigmented	Usually grey
Arcus senilis	None	Often present
Blood pressure	Usually low	Often high
Radial and temporal vessels	Soft	Thickened and hard
Involvement of upper extremities	Frequent	Seldom
Closure of femoral arteries	Frequent	Seldom
Calcification of vessels on X-ray	None	Frequent
Blood volume	Usually diminished	Usually normal
Symptoms of coronary artery sclerosis	Rare	Frequent

	TAO	PA
Appearance of aorta on X-ray examination	Normal	Elongated
Albuminuria	Rare	Not uncommon
History of migrating phlebitis	Frequent	Rare

Care must also be used to exclude instances of peripheral arterial disease due to syphilis, embolism, trauma, polycythemia, poisoning from ergot or arteritis due to influenza or rheumatism.

Having made the diagnosis, Silbert noted 4 major points:

(i)   only 12 cases, less than 1%, were in women,

(ii)   every single case occurred in those who had smoked,

(iii)   the disease is almost uniformly progressive in individuals who continue smoking,

(iv)   the disease is immediately and completely arrested in individuals who permanently discontinue smoking. Case histories of 100 patients with TAO who had given up smoking for 10-20 years were cited in support of this - none of them showed progression.

The author considers that TAO is caused by tobacco, probably in conjunction with a sex-linked sensitivity of the blood vessels.

24. Simic and Pirnat (1985) described the results of various immunological tests in Yugoslav TAO smokers and ex-smokers and on control smokers and non-smokers.

Skin hypersensitivity to nicotine sulphate or to tobacco extract was similar in patients and controls, though slightly but not significantly higher in current smokers in both groups.

Antinuclear antibodies in sera of patients in acute stage TAO were much more comon in continuing smokers (91%) than in ex-smokers (5%), consistent with the disease process being active to a far greater extent in continuing smokers.

21 acute stage TAO smokers were exposed to 5% DNCB in acetone and 0.10% DNCB in alcohol. All but one showed a toxic response to the former but reactions were always at most mild to the latter. 21 days later, the second allergy test provoked an allergic response, vulgar eczema, in all but 1 patient. No controls were given this cellular immunity test.

Serum immunoglobulins were compared in 15 smoking and 17 ex-smoking TAO patients. Reduced levels were seen in smokers particularly in IgG and to some extent in IgA and IgM.

The authors suggest that smoking increases the general immunological responsiveness of the body.

25. Smith (1974) reported that in a 10-year follow-up of 1500 non-smoking users of snuff or chewing tobacco in Tennessee who had shown some changes in the oral mucous membranes, none claimed to have pain that could be considered intermittent claudication. Similarly, among a group of 50 patients with IC, all were smokers, and none were snuff users or tobacco chewers. Smith concluded that there is no relationship of unsmoked tobacco to IC.

26. Wong et al (1978) described characteristics of 105 Chinese patients with TAO aged 45 or under. 101 were male. All were cigarette smokers except 4. Three-quarters drank alcohol. Symptoms may begin in the teens but were maximal in the 31-35 years group. About half of all patients underwent both sympathectomy and amputation. No mention is made of advice to give up smoking or its effect on outcome.

27. Wray et al (1971), in Ohio, carried out bypass grafts on 50 patients with aortic aneurysm, 31 of whom were smokers, and 50 patients with aortoiliac occlusive atherosclerosis, 29 of whom were smokers. No late thromboses were observed in the former group, but 9 were in the latter, all in smokers. The authors recommend cessation of cigarette smoking to all patients undergoing vascular reconstruction.

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