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Thrombo angiitis obliterans with special reference to etiology

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THROMBO-ANGIITIS OBLITERANS:
WITH SPECIAL REFERENCE
TO ETIOLOGY

SENIOR THESIS
UNIVERSITY OF NEBRASKA
COLLEGE OF MEDICINE

MAX COE
1936
INTRODUCTION AND HISTORY

In covering the subject of thrombo-angiitis obliterans I will place special emphasis on its possible etiological factors. Relatively little space will be devoted to pathology, symptoms, diagnosis and treatment. After giving a brief historical review followed by a classification of peripheral vascular diseases, I will discuss the disease under the following sub-heads: Etiology, which will make the greatest bulk of the thesis, Pathology, Symptoms, Diagnosis and Treatment.

The disease first found its way into the literature in 1856. Czerna (14) refers to cases reported by Savory having signs and symptoms of the same sort as Buerger (9) describes. Billroth in 1869 amputated the leg of a patient with gangrene from this cause and turned the specimen over to Winiwarter, who gave the first precise pathological report on this type of circulatory disturbance in 1879, calling it "endarteritis obliterans".(36) Jablons (23) claims priority of description for Charcot who in 1856 called attention to Bowley's description of the same thing in animals some years before. A case which was diagnosed in 1907 as "angiokeratoma with bony changes" was a number of years later reported on under the diagnosis of thrombo-angiitis obliterans. (49) Buerger (9) in his book on the subject gives an outline of the historical
2.

background in which he describes the two schools of thought which originally dealt with the matter: one, that of Winiwarter, which regarded the vessel occlusion as due to proliferative changes in the intima, and the other that of Von Montenffel which regarded it as a peculiar type of arteriosclerosis in which desquamation of the endothelium in the popliteal artery gave rise to white clot. Sinkoe (53) cites Burrow in 1867 and Jasche in 1865 as having described these lesions, but left the accurate pathological description of them to Friedlander in 1876.

Various and numerous names have been applied to thrombo-angiitis obliterans: dysbasia angiosclerotica, erythromelalgia, vasomotor neurosis, angina cruris, intermittent claudication, gangstöcking, juvenile gangrene, pre-senile gangrene, spontaneous gangrene, obliterating endarteritis, local asphyxia, acrocyanosis, acrosphyxiā, acrosphacelus, paralytic vasomotorice, pseudo erythromelalgia, non-syphilitic endarteritis obliterans, Yiddische krankheit, Friedlander's disease or progressive sclerosis (Osler) of the arteries, and finally Buerger's disease (23).

Definition: Thrombo-angiitis obliterans is a chronic disease of the blood vessels occurring more commonly between the ages of 25 to 50, resulting in thrombosis and gangrene, and involving one or both extremeties (32).
3.

CLASSIFICATION OF PERIPHERAL VASCULAR DISEASES (41)

A. Primary vasomotor disturbances
   a. Vasoconstrictor disturbances
      (1) Raynaud's disease
      (2) Acrocyanosis
   b. Vasodilatory disturbances
      (1) Erythromelalgia
      (2) Acute painful osteoporosis (?)

B. Primary organic diseases of the arteries
   a. Traumatic (chemical and thermal)
      (1) Embolism and simple thrombosis
      (2) Arteriovenous aneurysm
      (3) Phenol and all caustics
      (4) Frost bite
   b. Inflammatory (toxic)
      (1) Thrombo-angiitis obliterans
      (2) Specific arteritis (Syphilis, tuberculosis, periarteritis nodosa pyogenic)
      (3) Non-specific arteritis (exanthemata, typhus, typhoid and pneumonia
      (4) Non-specific arteritis (chronic toxemia, ergotism)
      (5) Endarteritis obliterans (cause undetermined)

C. Degenerative changes
   (1) Arteriosclerosis (senile, diabetic and Mönckeberg)
ETIOLOGY

The cause of thrombo-angiitis obliterans has not as yet been definitely determined. Many possible etiological factors have been discussed such as (1) infection, (2) tobacco, (3) race and birthplace, (4) sex, (5) exposure to cold, (6) occupation, (7) age, (8) carbohydrate metabolism, (9) ergotism, and (10) heredity. Each factor will be taken up separately.

Infection as an etiological factor: According to Buerger (9) the disease is not an endarteritis obliterans but an occluding thrombotic process involving the superficial and deep veins and arteries of the upper and lower extremities. The early stage of the disease manifests itself in an inflammatory lesion which exhibit purulent foci and suggests infection as an etiological factor.

It was Buerger's (10) first belief that the acutely inflamed veins and nodosities of thrombo-angiitis obliterans could furnish the material in which an infectious agent virus or micro-organism might reside and be brought to light, and also that these foci might be utilized for the reproduction of the disease, or, at least, of some of the acute lesions of the malady. He conducted researches over a period of years with little success until 1929. He found that it is possible to reproduce lesions identical with those of acute thrombo-angiitis obliterans. The lesion produced was an acute inflammation with miliary giant cell
foci in the superficial veins of the upper extremity of man, by transplantation of the coagulated contents of acutely affected veins when in the phase of migrating phlebitis. These experiments were conducted in persons without (a) vascular disease, (b) without thrombo-angitis obliterans, and (c) persons with moderately pronounced arteriosclerosis.

Rabinowitz (39) describes an organism he has isolated from a patient with proven thrombo-angitis obliterans. The organism was a gram negative, facultative anaerobic, freely motile bacillus, medium sized, rod-shaped and beaded, bipolar in appearance, containing metachromatic granules, measuring about five-tenths of a micron in diameter and from five-tenths to one micron in length. It forms no capsules and produces no spores. Flagella have not been demonstrated. They stain readily with ordinary aniline dyes, though not intensely, and grow on the ordinary media but most luxuriantly on Loeffler's media. The organisms ferment glucose, saccharose, and mannitol producing gas and acid, but do not ferment lactose. On agar, the colonies are scanty, raised, and smooth, rather translucent, colorless, and round, with a sharp border. After 24 hours incubation at 37°C the colonies attain a diameter of about one-half millimeter. In both there is a uniform clouding, a characteristic cadaveric odor, and a moderate flocculent sediment. In gelatin stab, the growth is filiform along
the lines of puncture. The organism grows best at 37°C, maximum temperature 50°C, minimum at 20°C.

Further experimentation by Rabinowitz in which he took hemolyzed blood from an affected extremity by means of a sterile leech and then extracted and emptied it into a sterile test tube, centrifuged, and incubated. The hemolyzed blood was then injected into the right ear of two rabbits. One week later the vessels about the site of injection were completely thrombosed, and, at the end of ten days, a gangrenous area, with its long axis parallel to the length of the main vessel, with a sharp line of demarcation, appeared in the ears of both rabbits. In the left ear non-hemolyzed blood from the same patient was introduced and used as a control, this produced no lesions, not even engorgement of the vessels. Cultures from the gangrenous areas showed a gram negative, freely motile bacillus, with the same cultural characteristics as that of bacillus isolated previously.

Bacteriologic studies on segments of veins, resected while clinically acute have been studied by Rosenow and Nickel (7). Organisms have been definitely isolated, from a small series of cases; in one instance, an organism quite similar to that described by Rabinowitz was found, the culture of which injected into a rabbit produced an auricular thrombus.

Horton and Dorsey (22) of the Mayo Clinic, in 1932 found by injecting organisms cultured from affected vessels
of a thrombo-angiitis obliterans patient at sites adjacent to the femoral vessels or by embedding segments of vessels from affected humans adjacent to the femoral vessels in rabbits that they could produce in 23 to 24 percent of animals, pathologic lesions which appeared to be identical with those seen in human beings with thrombo-angiitis obliterans. The organism used was a gram positive pleomorphic streptococcus. Their study suggests that thrombo-angiitis obliterans may be of infectious origin and that the streptococcus may be an etiological factor.

Orr (35) states that in every case under his care there was found focal infection of the tonsils or teeth or both; he is quite convinced that the disease is due to an infection which has its source in a chronic infection elsewhere in the body. He made cultures from the extracted teeth of one of his patients with thrombo-angiitis obliterans which killed rabbits in twenty-four to forty hours. No lesions could be produced in the blood vessels of these rabbits though there were vegetations on the heart valves. Attempts to obtain cultures from the vessels and thrombi contained in them, after amputation were negative. In a series of Chinese patients suffering from thrombo-angiitis obliterans, Melene~y and Miller (32) report that pyorrhoea alveolaris was common. Brown, Allen and Møhorner (7) state that in 75 per cent of 85 cases in which the teeth were examined by x-ray they showed signi-
cant periapical infection. In eighty-five percent of these cases, the tonsils were present, most of them being infected. In fifty-two percent of another group of forty-six cases prostatitis was present. Animals were inoculated with cultures from the prostatic secretions in several cases but with negative results.

In a series of eighty-five cases in which Buerger (11) has studied the pathology of the resected vessels, he states that all stages of the process were observed, from the finished organized product back to the early thrombotic lesions where arteries and veins were filled with red clot. The earliest or "acute" stage of the disease was found in the vessels of only two of the patients. In many vessels the wall was diffusely infiltrated with leukocytes, being more marked in some places than others, and the presence of a red thrombus in which certain characteristic foci, "miliary giant cell foci" were present. Buerger states that when these were first studied by him their significance was not understood, except that they were specific for thrombo-angiitis, not having been seen in thrombosis due to other causes. He now explains these as an attempt at healing the suppurative areas.

Nearly all authors have mentioned the inflammatory appearance of the lesions. The course of the disease is usually that of a relapsing process involving the arteries, veins and possibly the capillaries. Changes
in body temperature, pulse rate and leukocyte count are absent or minimal. The absence of systemic reaction does not necessarily mean that the disease is not infectious, since there may be an interference in absorption due to the pathologic process. If the process is of infectious origin, it is due, undoubtedly to a very low grade type (7).

Syphilis has been considered as a causative factor, but in thirty cases worked up by Buerger and Koliski (12); they have shown that leues is not responsible. Perla (37) states that previous infection apparently played no part in a series of forty one consecutive cases. Syphilis did not occur in any of the cases; thirty-six gave a negative Wassermann reaction and a seven plus minus reaction. Typhus fever occurred in but four of the forty-one cases.
Tobacco is a probable predisposing factor and is regarded by most authors in causing at least some alteration in the vessels that makes them open to the inflammatory process and thrombosis. Buerger (9) states that only one percent of his cases denied smoking. Meyer (33) concluded that thrombo-angiitis obliterans is at least partially due to tobacco smoking and that the vascular changes are secondary to saturation by tobacco smoke. He thinks that such products as nicotine, pyridin, cyanic hydrogen, carbon monoxide and other poisons in tobacco smoke cause the secondary vascular changes.

Barker (4) of the Mayo Clinic, in a series of 350 cases, all males between the ages of twenty-five and fifty-five attempted to evaluate the tobacco factor. He compared this group of patients to a so-called control group - 350 male patients between the ages of twenty-five and fifty-five years who had been examined in the clinic and who did not present evidence of peripheral vascular disease. The consumption of tobacco was graded as follows: one to seven cigarettes or one to two cigars (grade 1); eight to nineteen cigarettes or three to five cigars (grade 2); twenty to twenty-five cigarettes or six to eight cigars (grade 3); and thirty or more cigarettes or nine or more cigars (grade 4). Pipe smoking and chewing were
graded on a corresponding basis.

<table>
<thead>
<tr>
<th>METHOD OF USAGE</th>
<th>CONTROL GROUP</th>
<th>THROMBO-ANGIITIS OBLITERANS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>350 CASES</td>
<td>350 CASES</td>
</tr>
<tr>
<td></td>
<td>CASES</td>
<td>PERCENT</td>
</tr>
<tr>
<td></td>
<td>PERCENT</td>
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<tr>
<td>Non-tobacco users</td>
<td>91</td>
<td>26.0</td>
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<tr>
<td></td>
<td>5</td>
<td>1.4</td>
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<tr>
<td>Chewers (non-smokers)</td>
<td>17</td>
<td>4.8</td>
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<tr>
<td></td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Smokers (pipe &amp; cigar only)</td>
<td>45</td>
<td>12.8</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>6.8</td>
</tr>
<tr>
<td>Smokers (cigarettes)</td>
<td>197</td>
<td>56.4</td>
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<tr>
<td></td>
<td>320</td>
<td>91.5</td>
</tr>
</tbody>
</table>

| DEGREE OF USAGE                      |               |                             |
|                                      | Grade 1       | Grade 2                     |
|                                      | 53            | 89                          |
|                                      | 15.2          | 35.4                        |
|                                      | 20            | 110                         |
|                                      | 5.6           | 31.5                        |
|                                      | Grade 3       | Grade 4                     |
|                                      | 91            | 26                           |
|                                      | 26.0          | 7.4                         |
|                                      | 158           | 57                          |
|                                      | 45.2          | 16.3                        |

The large number of grade 3 and grade 4 smokers in the thrombo-angiitis obliterans group compared to the small incidence of non-smokers and grade 1 smokers indicate that tobacco may be a definite predisposing factor in the disease. It was noted that the heavier the smoker the more likely was the disease to run a malignant course.

Results of experiments in which nicotine was injected intravenously in rabbits produced lesions in the blood vessels especially of the aorta which were of a necrotic nature. The lesions were neither an endarteritis nor a mesarteritis, but a distinct arterio-
necrosis affecting primarily and mainly the inner muscular layers of the media (1).

Sensitivity tests made by Harkavy (2) in 1933 showed that 76 out of 87 cases of thrombo-angiitis obliterans between the ages of twenty two and fifty eight were found to be hypersensitive to various tobacco extracts, and incidence of eighty seven percent. He suggests that tobacco sensitiveness may play an important role in thrombo-angiitis obliterans, and that the patient may belong to the category of allergic individuals. Sulzberger (54) in a series of skin tests confirmed Harkavy's findings. He also found that nicotine is probably not the important sensitizing substance in tobacco. Many individuals showing a skin reaction to tobacco did not react to skin tests of nicotine.

Maddock and Coller (31) studied the effect of cigarette smoking on the skin temperature of the digits of twenty normal individuals. He found a rather prompt and definite, although transient drop. This temperature drop was not noted in the control experiments in which cubebbs were substituted for cigarettes or the tobacco smoke was passed through a layer of cotton moistened with ferric chloride. Barker (5) repeated the studies of skin temperature during cigarette smoking employing patients with thrombo-angiitis obliterans. Twenty patients were studied and compared with twenty normal persons. The procedure consisted of, first, a
control period, a period of going through the motions of smoking with an unlighted cigarette, then the smoking of three cigarettes in rapid succession. The room temperature was controlled thermostatically and varied less than 100. Fourteen of the twenty normal subjects gave evidence of significant vasoconstriction in the digits, as shown by a fall in cutaneous temperature. Thirteen of the twenty patients who had thrombo-angiitis obliterans exhibited similar effects.

It has been brought out that tobacco as an etiological factor must be carefully evaluated because in some cases smoking is taken up or accentuated as the disease reaches the point of causing pain, nervousness and insomnia (7).

The type of tobacco smoked was at first thought to be of some significance. A report on a series of 150 patients studied at the Mayo Clinic showed that American and foreign blends of tobacco were used equally, showing that the kind of tobacco was probably not a factor. The degree of smoking by Hebrews and Gentiles was about the same (7).
RACE AND BIRTHPLACE AS AN ETIOLOGICAL FACTOR

The Mayo Clinic (7) reports that there was a definite predominance of thrombo-angiitis obliterans among Hebrews, especially the Polish, Bohemians, Austrians and Russians. Eighty-six percent of the Hebrews and twenty-five percent of the Gentiles of the group were foreign born. In a control series of cases with diseases other than thrombo-angiitis, seventy-five percent of the Hebrews and twenty-eight percent of the Gentiles were foreign born. This shows that birthplace was probably not a significant factor.

Meyer (38) stated that all of his patients suffering from the disease were Jews of the poor classes who had immigrated from Russia, Poland and Roumania. He (33) believes also that individuals are pre-disposed to the disease, i.e., a pre-disposition of the nervous system. He thinks that the centuries of persecution under which generations of these Jews have gone through have left their imprint in the form of hereditary neurasthenia. It was first believed that the disease attacked only people of Jewish descent, but reports in the literature on the subject definitely showing this trend of mind to be changing. The Mayo Clinic (7) report a decreasing frequency of thrombo-angiitis obliterans among the Jewish patients and an increasing frequency among Gentiles. Tilford and Stopford (55) say definitely that the disease
is by no means peculiar to the Jewish race; all of their cases were of pure British blood. Meleney and Miller (32) have described twenty-four cases from Peking and Whyte (58) in two papers has reported many cases in Chinese patients. He says that the disease occurs in nearly all the provinces of China. Pertaining to the Hebraic tendency Rubenstein (46) states:

"It seems that if in a series of two hundred cases, fifty percent were either Austrian, German, Scotch, Irish, English, Dutch, Greek, Finnish or American this theory is no longer tenable".

He goes on to say that the Hebrew predominates in Buerger's experiences, but Buerger's practice is largely made up of Jews.
16.

SEX AS AN ETIOLOGICAL FACTOR

The occurrence of the disease almost exclusively in males has been noted by most authors. The marked discrepancy in the incidence of the disease in the two sexes is unexplained. Several possible explanations for variation in sex have been brought out (7). One is endocrine glands, another the difference in the occupation of the two sexes, the male requiring greater use of the extremities and greater exposure to excessive weather changes. Smoking is more common among males, but the increased smoking among women has not increased the incidence of the disease among them. A difference in anatomy of the two sexes has been considered with a conclusion that the prostate gland may act as a foci of infection. The incidence of foci of infection in other tissues common to both sexes appeared to be equal.

Only eight acceptable cases of thrombo-angiitis-obliterans occurring in women have been reported in the literature. Buerger (9) in 1924, made a clinical diagnosis of the condition in two women without pathologic proof. Meleney and Miller (32) in 1925 reported that they had observed a Chinese woman with thrombo-angiitis obliterans. Study of the occluded vessels confirmed their diagnosis. Horton and Brown (21) in 1932 reported three occurring in women; the diagnosis was approved by pathological study of the occluded arteries and veins. The most recent cases in women were reported by Silbert(50) in which he discusses two cases.
OCCUPATION AND EXPOSURE TO COLD AS ETIOLOGICAL FACTOR

Occupation is apparently not an etiologic factor. The Mayo Clinic (7) reports that about every type of occupation was represented in their series of cases. Perla (37) in his series of cases, reports almost identical findings as regards occupation.

It is known that cold has a deleterious effect on patients with thrombo-angiitis obliterans. In seventy-one percent of a group of cases reported (7) the symptoms were noted first in cold weather. The effect is probably due to vasoconstrictor action on an already diminished blood volume to the part. Symptomatic improvement has been noted in some patients who went to warmer climates. Tilford and Stopford (55) mention the fact that it is worthwhile to take note of any suggestions made by the patients themselves; four of their patients have attributed their condition to prolonged exposure to cold and wet. They state further that it is not likely that their exposure is a direct cause, yet possible to act as a predisposing factor in susceptible patients.
AGE AS AN ETIOLOGICAL FACTOR

In one group of one hundred-fifty cases reported (7); the age groupings were as follows: 15 to 20 years, one case; 20 to 25 years, six cases; 25 to 30 years, eighteen cases; 30 to 35 years, thirty-one cases; 35 to 40 years, thirty-three cases; 40 to 45 years, thirty-one cases; 45 to 50 years, thirty-one cases; 50 to 55 years, fourteen cases; 55 to 60 years, three cases; 60 to 65 years, two cases. The youngest patient with a pathological proved diagnosis was seventeen, the oldest sixty-four.

Perla (37) in his paper on an analysis of forty-one consecutive cases in which the age of onset
ranged from 20 to 45 shows the following figures. The youngest case was that of a man of 20; 3 were under 25; 16 from 25 to 30; 5 from 30 to 35; 11 from 35 to 40; and 5 from 40 to 49. The greatest percentage occurred between 25 and 30 and the average age of onset was 32.5. Frauenthal (17) observed a patient whose symptoms began at the age of nine. Buerger (9) found the age of onset in his large series to range from seventeen to fifty-six years, with an average age of thirty-two. He states, however, that the figures are much too high since it is very difficult to estimate the exact age at which the disease began, because of the insidious nature of the onset and because of the fact that it is overlooked in many cases.
CARBOHYDRATE METABOLISM AS A POSSIBLE ETIOLOGICAL FACTOR

Meyer (34) reports that in all of his cases studied so far a decreased sugar tolerance shows, i.e., 100 grams of glucose, after a brief fasting period has produced hyperglycemia. He proposed naming the disease "glyeophilia", the similarity of the name to "hemophilia" was intended to point to sex limitation and other obscure features of the disease. Meyer further states that the general clinical aspect shows so many similarities to diabetes mellitus that their classification as "near diabetes" appears justifiable. Bernhard (6) confirms the presence of a decreased sugar tolerance in thrombo-angiitis patients. Other chemical blood findings by both Meyer and Bernhard were found to be within normal limits.

Studies on patients made by Meleney and Miller (32) do not bear out Meyer's theory with regard to a disturbance of carbohydrate metabolism. In twenty cases the fasting blood was tested; fifteen were within normal limits; the other five were slightly increased. Eight of these cases were tested again one hour after the ingestion of 100 grams of glucose. Six of these were normal and the other two returned to normal in another hour. The urine was never positive for glucose. Allen and Brown (3) also report normal figures for blood sugar in a series of 200 cases suffering from thrombo-angiitis obliterans.
ERGOTISM AS AN ETIOLOGICAL FACTOR

According to Kaunitz (26) thrombo-angiitis obliterans and ergotism have many points in common especially of their vasomotor, trophic and sensory symptoms and signs. The resemblance pathologically is namely thrombosis with obliteration of the vessel lumina. He also goes on further to say that the nationalities and races affected with thrombo-angiitis obliterans are from those countries where rye bread is the stable article of the diet, generally in the northern Slavic countries - Russia, Poland, Ukraine, East Prussia Luthiania.

The incidence of thrombo-angiitis obliterans in the female is very low as is ergotism as brought out by Krysinsky (28), Renauldin (42), and Tessier (56). In spite of the tremendous quantity of ergot consumed in this country - 170,000 to 264,000 pounds imported yearly one rarely hears of a case of gangrene in women due to ergot. It is interesting to note that even in fowls, Kaunitz encountered and increased susceptibility to ergot in males. Gittinger and Munch (18) in an assay of ergot by the Cock's Comb method, found that the hens had no value, their combs showing slight blanching or no effects whatever; while of the control, 90 percent of the cocks gave satisfactory results.

Thrombo-angiitis obliterans as mentioned before occurs most frequently in young and middle-aged men as
epidemic ergotism of the gangrenous form as reported by Krysinsky (28).

One author (43) has reported on the symptom of ergotism found among the Jewish people of Manchester as the result of eating rye bread. The general symptoms complained of were coldness of the extremities, numbness and lack of sensation in the fingers, headache, depression, gastric disturbances, shooting pains, twitching in the limbs and staggering gait. None of the symptoms complained of were observed among that portion of the Jewish population who ate white bread. It was found also that the symptoms were much more pronounced in the Russian, Polish and German born Jews than in the English born Jews. The latter usually ate white bread, whereas the former partook of rye bread almost exclusively.
HEREDITY AS A POSSIBLE ETIOLOGICAL FACTOR

Samuel (47) in an examination of 500 cases of thrombo-angiitis obliterans has observed three families in which it occurred in brothers. In none of these families has there been any history of disease in parents, grandparents on the maternal or paternal side, nor has there been any evidence of the disease in other blood relatives. In one family three brothers were affected - the older, a heavy cigarette smoker, first noticed symptoms at the age of 33; after walking a long distance he began to experience pains in the calf of the left leg. Upon examination the left foot was found to be colder than the right and the left dorsalis pedis pulse could not be felt. Another brother affected by the disease gave a history of symptoms beginning at the age of twenty four with numbness of the left leg. The youngest brother, who began to smoke at the age of seventeen and has smoked about fifteen cigarettes a day since then, gave first evidence of the disease at the age of twenty four with a typical superficial migrating phlebitis of both legs.

The second family in which three brothers were affected with thrombo-angiitis obliterans was of Russian Jewish descent. All were born in Russia and came to America at an early age. The oldest had been treated for many years by several outstanding specialists who definitely made the diagnosis. He died suddenly at the age of forty two probably due to a coronary artery
lesion. Another brother died at the age of thirty five in a similar manner as the eldest. He also had been treated by outstanding specialists and the diagnosis definitely made. The third brother at the age of forty suffered from massive gangrene of the left foot. Beginning a few years ago, he also had attacks of precordial distress and dyspnea which were diagnosed as coronary seizures. All three brothers were heavy cigarette smokers. The parents and grandparents had no symptoms of circulatory disturbance of the extremities as far as could be determined.

The third family affected were of Austrian descent. Both members affected, however, were born in America. The oldest had both legs amputated, one at the age of thirty and the other several years later. The younger brother, at the age of forty three had an advanced case of thrombo-angiitis obliterans. Both patients were heavy cigarette smokers. There was no history of circulatory diseases in the extremities of the parents or grandparents as far as could be determined.

The above cases occurring in brothers does not prove, however, that the disease is necessarily one of heredity but are all the same interesting. The possibility of inheriting the susceptibility to the disease must not be overlooked.
Pathologically the disease is essentially of a chronic inflammatory nature, affecting chiefly the larger arteries and veins of the lower extremities. The upper extremities are next in order of frequency and cases of involvement of the cerebral, coronary, mesenteric and spermatic vessels are rare. Early in the disease the adventitia becomes thickened and infiltrated with lymphocytes. The intima proliferates, the cells assume a radial arrangement and a thrombosis fills the lumen. The vasa vasorum undergo similar changes and new vasa vasorum penetrate all coats of the vessel and the thrombus as it undergoes organization. Changes in the nerves of the part are secondary to and dependent upon the changes in the arteries. The earliest manifestation of the disease may be superficial phlebitis. It is usually migratory and recurrent and may be present for years before arterial occlusion becomes sufficient to cause anoxemia. Involvement of a vein may vary from the smallest palpable subcutaneous nodosity to thrombosis throughout its entire length (13).

Grossly the healed vessel is filled with a grayish or yellowish mass that can be differentiated from the intima and shows one or more fine openings. The vessel wall itself is usually contracted so that it appears thickened. If the lesion is old enough there may be some accompanying arteriosclerosis, which parti-
ally obscures the original picture. Characteristically, there is a marked peri-arteritis which binds together accompanying nerves and other vessels which may present the disease in a different stage (19).

Histologically the earliest changes are those of an acute inflammatory process involving all coats of the vessel. The intima, the media, the adventitia and perivascular tissues are infiltrated with polymorpho-
nuclear leukocytes. The lumen of the vessel is completely filled with red thrombi. In the peripheral portions of the thrombus, large or small foci of leukocytes begin to form. The remainder of the clot which shows an infiltration of leukocytes may be seen to be undergoing organization while the purulent areas develop the typical giant cell foci, containing giant cells, endotheliod or angioblasts, and broken down leukocytes (9). The giant cells disappear and new vessels penetrate, the final product being a fibrous nodule containing vessels and some pigment.

The lesions in thrombo-angiitis obliterans are, in chronological order, an acute inflammatory lesions with occlusive thrombosis, the formation of miliary giant cell foci, the stage of organization with with the disappearance of the miliary giant cell foci, the organization and canalization of the thrombus, the disappearance of the inflammatory products, and the development of fibrotic tissue in the adventitia, that
that binds together the artery, vein and nerves (19).

The nutrient blood vessels supplying the nerves may be affected. In a series of cases Meloney and Miller (32) report that all who gave symptoms of pain showed nutrient vessel to be occluded.

Putnam (24) believed that a true neuritis was present. Evidence of true neuritis was found in several cases observed by Allen, Brown and Moborner (7) but not uniformly enough to be of importance. They bring out further that changes in the nerves in thrombo-angiitis obliterans are not very definite or constant; there is often an increase in the connective tissue of the perineurium and epineurium and at times lymphocytes have been found. Absorption of the myelin and an increase in the number of cells of the sheath of Schwann occurs especially in the small nerves of the toes.

Interference with the blood supply and the involvement of nerves give rise to changes in the skin and other ectodermal derivatives. Thickening, hyperkeratosis, and scaling are frequently seen. Alopecia may occur, and the nails show changes varying from mild ridging to marked hyperplasia with deformation and incurvation. Ulcers commonly develop under the nail bed over the tibia, on the plantar surface of the toes, or immediately below the malleoli. When the occlusive thrombotic process becomes too extensive for the collateral circulation to compensate, gangrene of the infarct type develops and spreads with the extension of the thrombus (13).
SYMPTOMATOLOGY

In the early stages, the disease may manifest itself in several different ways. May patients give indefinite pains in the foot or toes while others may complain of coldness and numbness of the toes or foot. Quite frequently the patient will suffer from cramp-like pains in his calf muscles when walking. This is the characteristic pain of intermittent claudication, which is at first relieved by rest, but later becomes more constant as collateral circulation begins to fail (19).

The pain of thrombo-angiitis obliterans has been put into two different types, one produced by exercise and relieved by rest, the other which comes on when the patient is at rest and known as "rest pain". The first type as has been mentioned before is the typical pain of claudication (7). The presence of "rest pain" is frequently not associated with gangrene and is usually limited to the digits. One author (44) attributes this type of pain to the increase in connective tissue around the nerve trunks, another (32) to the obliteration of the nutrient arteries of the nerves, another (24) believed it was due to a true neuritis, and still another (24) thought it was due to constant profound anoxemia approaching the threshold of tissue death. Pain induced by exercise is the result of anoxemia (7).

Some patients give a history of pain, tenderness, and redness over the superficial veins of the extremity; this is due to a migratory phlebitis which Buerger (9)
describes. He claims this symptom occurs in twenty-five percent of the cases.

According to Allen and Brown (3) pain of claudication was the first symptom in fifty one percent. Coldness of the extremities was the first symptom in twelve percent; abnormal fatigue in eleven percent; non-healing ulcer in ten percent; sudden arterial occlusion in seven percent; recurrent superficial phlebitis in four percent; edema in three percent and vasomotor disturbance of the spastic type in two percent.

The above symptoms are those which accompany the early stages of the disease and may persist from a few weeks to even years. Following the so-called early stages, trophic changes or gangrene may appear. The most common sites for ulceration are on the outer or inner margin of the big toe adjacent to the nail, the outer aspect of the little toe, the middle of the second toe, the middle of the dorsum of the foot, the inner aspect of the ankle inferior to the internal malleolus and on the anterior aspect of the leg over the tibia (19).

Erythromelia may make its appearance at any stage of the disease; this sign is a peculiar blush which begins on the affected toe or toes and then gradually extends up the dorsum of the foot. It can best be observed with the foot in the dependent position. Ischemia can be plainly elicited when the affected
extremity is brought above the horizontal position (7).

The cause of this rubor has been explained in three different ways, one advanced by Buerger (9) is the dilatation of the capillaries and this acting as a compensatory measure in supplying maximal amounts of blood to the tissues. A second explanation of the color change was that of capillary dilatation due to presence of metabolites formed as a result of a greatly diminished blood supply (16). A third explanation is based on the lowered temperature of the extremity which may be below that necessary for the free oxygen exchange. The oxygen content of the dilated capillaries would be high and an increased redness result (7).

Palpation will reveal in later stages a loss of pulsation in the dorsalis pedis, posterior tibial, and sometimes the popliteal or even the femoral arteries. The surface temperature is markedly lowered (19).
First tobacco must be discontinued and cessation of its use is the most important part of the treatment \((51),(47),(30)\). Lowenstein \((30)\) states that he has repeatedly seen exacerbations of symptoms and progression of the disease when smoking was resumed, while its discontinuance has regularly resulted in arrest unless too far advanced.

Silbert \((51)\) reports remarkable results obtained by the use of repeated intravenous injections of hypertonic salt solution. He gives a series of 524 patients over a ten year period, that have been treated by this method. Of 524 patients, 434 were improved, 88 unimproved, and in 40 amputation of the affected extremity was necessary. The method consists of the use of a five percent sodium chloride solution prepared in freshly distilled water, filtered and sterilized. Injections are given by the gravity methods into a superficial vein at the antecubital space. The initial dose is 150 cubic centimeters and all subsequent injections are 300 cubic centimeters. The fluid is allowed to run in slowly, about ten minutes usually being required for the injection. The injections are at first given on alternate days, three times a week, later twice a week and the length of intervals is further increased as the patients improve. The total duration of treatment varies from six weeks to two years, depending upon the severity of
the individual case.

Certain measures having for their aim the improvement of collateral circulation and the increasing of blood supply are valuable. Buerger (9) employs certain postural exercises. The patient lying in bed elevates the affected limb from 60 to 90 degrees above the horizontal for 30 seconds to three minutes. As soon as blanching occurs the limb is allowed to hang over the edge of the bed for from two to five minutes until reactionary rubor or hyperemia sets in. The extremity is then placed in the horizontal position for about three to five minutes. These exercises should be taken for fifteen minute periods three or more times daily.

A simply procedure which may give relief in many cases is the use of some baking apparatus capable of producing mild heat, a suitable one may be made by suspending two ordinary carbon light bulbs from a cradle. The length of time of exposure is gradually increased to three or more hours a day, precaution being made to prevent burning (19).

The use of contrast baths, by which the extremity is immersed alternately in hot and cold water is valuable especially in the absence of open lesions but is considered severe treatment and may be overdone (19).

The use of foreign protein injections has been advocated in an attempt to produce a rise in body temperature with a cutaneous dilatation (8).
The injection of typhoid vaccine has been used to some extent and at times has produced marked improvement of trophic lesions, ulcers and gangrene, and a diminution in the severity of the rest pain. The method should not be used in the presence of marked arteriosclerosis because of the danger of thrombosis (7).

Roth, Barker and Brown (44) report a very high percentage of relief from pain of claudication by the injection of an insulin-free substance from the pancreas. The substance has vasodilating properties, lowers blood pressure, and is antagonistic to epinephrine. The extract was first standardized so that one unit was that amount which barely produced perceptible evidence of a drop in blood pressure on the tracing, when the substance was injected into the jugular vein of a rabbit weighing two kilograms. Later the Sharpe and Dome laboratories made a standard in which one unit would neutralize the pressor effect on anesthetized dogs of 0.001 mg. of epinephrine. The results of the work done with this extract, show that the probable therapeutic value of the pancreatic tissue extract lies first in the fact that its use is safe and without disagreeable or toxic effects in the doses used (which was 30 units), and second, that it is the only substance now known which has had definite and striking effect on the symptoms of intermittent claudication. The individuals working with this extract state that its use for thrombo-
angiitis obliterans and arteriosclerosis of the extremities probably will be restricted to those cases in which intermittent claudication is the most prominent symptom.

In the last few years treatment by use of alternate suction and pressure on the affected extremity has been instituted with some success. The extremity is enclosed in an especially constructed box (29),(40). Treatment to be successful must be begun before the pathologic conditions have too greatly reduced the normal capacity of the blood vessels to dilate. Very good results have been reported by this method of treatment.

Surgery on the sympathetic system has been advocated by some. A sympathetic neuréctomy which is a perivascular stripping was first performed by Jaboulay in 1899 (25). This procedure was based on the conception that the vasomotor nerves reached the distal parts of the extremities along the adventitial coat of the main vessels and by destroying a segment of the perivascular structure an interference would be produced in the vasomotor paths with resultant vasodilatation of the extremity. The results of this type of procedure in thrombo-angiitis obliterans have not been remarkable.

Operation on the lumbar sympathetic trunks has met with a fair amount of success. Operations on the lumbar sympathetic rami were advised by Royle in 1924 (45).
Adson (2) modified the technique of the operation by adopting the abdominal route and removed the second, third and fourth lumbar ganglia. The most striking effect observed post-operatively was the increased and maintained temperature of the feet. It was thus concluded that the diminished blood supply in certain cases of thrombo-angiitis obliterans depends on two factors: the occlusion of the main arterial channels and associated vasoconstriction. The increased irritability of the vasomotor mechanism may be explained by inflammation in the peripheral vascular structure which gives rise to afferent impulses which are followed by vasoconstriction (51).

The relief of pain appears as the general condition improves. In the pre-gangrenous stage when the pain is very severe or when a large ulcer is present which causes a great amount of pain, more direct methods of relief are necessary. One method is to isolate the nerve supplying sensory fibers to painful areas and inject it with alcohol. This causes a complete anesthesia of the area lasting for three to six months and has been found to aid greatly in the cases having painful, slowly healing ulcers. This allows thorough dakinization and a removal of the necrotic tissue. Because of the poor circulation and the resulting slow healing of the operative wound, the nerves should be isolated above the ankle in all cases (38). Another method for relief of pain caused by ulceration was exposing and sectioning the peripheral
nerves. The nerves are exposed by small incisions above the ankle, sectioned, and immediately sutured. Silbert found that primary union of the operative wounds was almost invariably obtained. Relief of pain was complete in practically all cases. The wound surfaces following the section become anesthetic and can be dressed and cleaned without pain and thus allow for more rapid healing. Reports of cases in which this therapy has been used, no trophic ulcers resulted and a return of sensation in the feet took place in about one year (52).

Indications for amputation are much narrower than formerly. There are practically only two: (1) the presence of extensive gangrene preventing the saving of a useful foot, and (2) a spreading infection threatening the patient's life (30). The gangrene of thrombâ-angiitis obliterans tends to be a self-limiting process and extreme conservatism even in the severe forms of gangrene result in an intact extremity (48).

Instructions to the patient for the care of his feet are quite important. It may be summed up, "keep your feet clean, dry and warm", but it is usually necessary to give the patient specific details. The shoes should be properly fitted and not too tight and any corns or callouses must not be cut. It is advisable to avoid circular garters or anything that
might interfere with circulation (51).

In selecting the type of treatment, one must consider the clinical syndrome presented by the patient. One author puts the cases roughly into one of the five following groups (7):

1. Extensive gangrene with or without rest pain. The treatment in these cases is amputation.

2. Mild trophic changes with severe rest pain. The treatment consists in medical measures for relief. If these are successful then medical and physical measures to heal the trophic ulcers by increasing the circulation should be used. Lumbar ganglionectomy in suitable cases is a prophylactic measure. Amputation is carried out in cases not suitable for lumbar ganglionectomy if the rest pain can be relieved.

3. Mild trophic changes without rest pain - the treatment consists of mechanical and physical measures to increase the circulation and heal the trophic ulcers, careful prophylaxis, and lumbar ganglionectomy in suitable cases.

4. Severe rest pain without trophic changes - the treatment is the same as in the second group.

5. Cases without rest pain or trophic changes - the treatment consists in prophylactic and medical measures to increase the circulation of the part and to prevent gangrene.
DIAGNOSIS

The diagnostic features which are characteristic in this disease are: (1) almost all of the patients are males (2) the age of the patients affected is variable but with an average of 42, (3) its predilection for Jews has been brought out by several authors and discounted by others, (4) its occurrence in individuals who use tobacco excessively is quite obvious, (5) the disease in most cases affects one extremity first then the others; in 90 percent or more of the cases the condition is essentially bilateral (8).

Errors arising most frequently in the diagnosis are mistaking the pain of claudication in the foot for arthritis or fallen arches and the redness or rubor of the toes for an infectious process. A superficial phlebitis occurring in a male, if spontaneous, should make one suspect thrombo-angiitis obliterans. An important point to establish in the presence of symptoms referable to the hands,feet or legs, is whether they are due to disease of the vessels and if so, whether the trouble is vasomotor or occlusive. The differentiation of vasomotor disturbances and occlusion may be made by simple palpation, the presence or absence of pulsation in the four palpable arteries of the leg or in the two palpable arteries of the wrist (30).

The extremities should be examined in a good light and variations from the normal color noted. Edema or other swelling, trophic changes such as glossy or fissured skin,
"corns" and callouses, irregular, ridged or poorly developed nails should be looked for. The temperature of the affected part should be noted and compared with the opposite extremity. Any differences on the two sides or zones of sudden change should make one suspicious of circulatory impairment. The skin temperature changes may be shown by means of the skin thermometer of the electric thermocouple, but practically any significant variation can be detected by the hand of the examiner (30).

One method of checking upon the circulation as used by Buerger (9) was in estimating the angle of circulatory sufficiency which is "based on the supposition that the normal limb, when elevated so as to be perpendicular to the horizontal plane, that is, 180 degrees, still retains most of its color. When the circulatory mechanism is defective, and the limb is elevated to the vertical, a variable degree of blanching of the foot occurs. If the leg is then gradually depressed, the angle at which a reddish hue returns (angle of circulatory sufficiency) will be found to vary with the state of the vessels permitting the reestablishment of visible circulation in the skin.

The intracutaneous salt solution test in the diagnosis of peripheral vascular disturbances was first used in 1924. It normally takes thirty to sixty minutes for an intradermal wheal of physiological salt solution to become absorbed. In cases of diminished vascularity to a part the solution will be absorbed and the wheal
disappear very rapidly as a result of low tissue fluid. The rapidity of absorption and point on the extremity denote the height and degree of occlusion (38).

Another method in which one may test the vascularity of a part is by the injection of histamine. In 1927 it was found that the histamine reaction consisted of three distinct factors: (1) a local dilatation of the capillaries, venules and arterioles by direct action, which caused a purplish spot to appear, (2) a widespread dilatation of the surrounding arterioles by local reflex action, which was visible as a red flare, and (3) a local increase in the permeability of the walls of the minute vessels by direct action, which caused a wheal at the site of injection. It was shown also that if the circulation was completely occluded only a purple spot would form but no wheal or flare, and that coldness of the extremity retarded the reaction (38). The test as reported by de Takats (15) is the intradermal injection of 0.1 cc. of 1:1000 histamine solution (ergamine acid phosphate). It was found that normally the skin reaction to histamine is at its height in from two and one-half to five minutes. Changes which suggest an insufficient circulation are (1) delay in appearance of the reaction, (2) delay in appearance plus a reduction in the intensity of the reaction, (3) failure of either flare or wheal to appear, (4) failure of both the flare and wheal to appear and the reduction to consist of only
a purple spot which was a sign of complete obstruction. The resulting wheal normally is irregular but sharply defined and is usually one half to one cc. in diameter. The flare about it is also irregular but not raised and extends for one to two cc. in each direction. The test is said to be quite accurate as a means of determination of circulatory efficiency agreeing closely with the oscillometric readings and the surface temperature as determined by the skin thermometer (38).
**DIFFERENTIAL DIAGNOSIS (30)**

<table>
<thead>
<tr>
<th>THROMBO-ANGIITIS OBLITERANS</th>
<th>ARTERIOSCLEROSIS</th>
<th>RAYNAUDS DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age - between ages 30-50 - average 42</td>
<td>Chiefly after mid-life</td>
<td>Between 17 and 35</td>
</tr>
<tr>
<td>2. Sex - males about 98 percent</td>
<td>Males predominate.</td>
<td>Females - 95 percent</td>
</tr>
<tr>
<td>3. Race - Jews about 28 percent</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>4. Rest pain - often very severe</td>
<td>Usually mild</td>
<td>Usually absent</td>
</tr>
<tr>
<td>5. Intermittent claudication - usually present</td>
<td>Usually present</td>
<td>Absent</td>
</tr>
<tr>
<td>6. General appearance - often younger than age</td>
<td>Often older than age Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>7. Upper extremities - frequently involved</td>
<td>Seldom involved</td>
<td>Frequently involved</td>
</tr>
<tr>
<td>8. Postural changes - Rubor when dependent pallor on elevation</td>
<td>Rubor when dependent pallor on elevation</td>
<td>Absent</td>
</tr>
<tr>
<td>9. Edema - frequent</td>
<td>Uncommon</td>
<td>Absent</td>
</tr>
<tr>
<td>10. Arteries - Pulseless or of diminished volume, Coronary sclerosis rare.</td>
<td>Pulseless or of diminished volume. Coronary sclerosis rare.</td>
<td>Normal</td>
</tr>
<tr>
<td>11. Veins - frequently involved. Often migrating phlebitis</td>
<td>Rarely involved</td>
<td>Normal</td>
</tr>
<tr>
<td>12. Roentgenogram of vessels - usually negative. Aorta normal</td>
<td>Frequently calcification of vessels.</td>
<td>Possible elongation of aorta</td>
</tr>
</tbody>
</table>
CONCLUSIONS

The etiology of the disease remains unsolved, but there are a few factors so constantly associated with it that they appear inseparable. It is practically limited to males between the ages of 30 to 50. Cases reported in females are very few and most of these lack pathological substantiation. Smoking is almost universal among the affected. The increase in the use of tobacco and the possible increased incidence of the disease may bear relationship, although this far from explains its rarity among females. Contrary to previous beliefs the disease is more or less equally divided among the races and occupations. Much evidence has accumulated which points toward infection as an etiological factor. Several individuals claim to have isolated organisms from the diseased vessels but this has not been accepted as yet because of the lack of others to verify the results. Buerger has produced a lesion identical to the one present in thrombo-angiitis obliterans by transplantation of the coagulated contents of acutely affected veins when in the phase of migrating phlebitis. Rabinowitz, Horton and Dorsey and Rosenow and Mickel claim to have isolated bacteria from the affected vessels. A large percentage of cases show foci of infection, which together with the inflammatory appearance of the lesions seem to point to an infection or bacterial toxic foundation as the etio-
logical factor. It has been mentioned that ergotism may be of etiological importance in thrombo-angiitis obliterans. They have many points in common especially of their vasomotor, trophic, and sensory symptoms and signs. Heredity as referred to previously probably doesn't play a big role in the disease although inheriting the susceptibility to the disease is not an impossibility. A lowered sugar tolerance has been shown to exist in most of the patients by a few authors while others do not find this to exist. This factor has yet to be more regularly shown before it becomes of any significance.

The pathology of the disease is one of a chronic inflammatory nature affecting chiefly the large arteries and veins of the lower extremities and frequently the upper extremities. There is a proliferation of the intima, the adventitia becomes thickened and infiltrated with leukocytes. There is thrombus formation which after a time becomes organized and canalization takes place. The changes in the nerves, skin, nails, etc. are secondary to the changes in the arteries.

The most typical symptom given by the patient is that of severe pain in the muscles of the extremities affected following exercise, and disappearance of the pain after rest. Pain in thrombo-angiitis has been put into two types, one, exercise pain, the other rest pain. The first is thought to be caused by an anoxemia, the latter
to pathology of the nerves. Some patients may give early symptoms of indefinite pains while others complain of coldness and numbness of the distal end of the affected extremity. There is present in all cases the characteristic rubor or erythromelia. A migrating phlebitis is a common symptom affecting especially the superficial vessels. Later trophic changes and gangrene may appear.

Many types of treatment have been reported such as Buerger's postural exercises, the use of alternate suction and pressure, application of mild heat, the use of contrast baths, intravenous injections of hypertonic salt solution (5 percent), foreign protein injections, injections of insulin-free pancreatic extract, and operative procedures which include sympathetic neurectomy (perivascular stripping), isolation of sensory nerves and their injection with alcohol and finally amputation. Selection of the type of treatment is controlled by the clinical syndrome presented as outlined previously. Nearly every author advocates conservatism in the treatment until extensive gangrene compels amputation. General instruction given to the patient should be to stop smoking, to keep the feet clean, dry, and warm, to wear properly fitting shoes, not to cut any corns or callouses, and to avoid circular garters or anything that might interfere with circulation.
Diagnosis is made on the features which are characteristic to the disease, i.e. its occurrence in males, between the age of thirty to fifty, its pre-dilection for Jews which may or may not be of significance, its occurrence in individuals who use tobacco excessively, its unilateral appearance which later becomes bilateral, the presence of pain usually that of an intermittent claudication, the presence of rubor of the distal part of the affected extremity, lack of pulsation in one or all of the main arteries of the extremity, the presence of edema and trophic changes. Some of the methods used in determining the vascularity of the part which were discussed were, Buerger's method of estimating the angle of circulatory sufficiency, the intracutaneous salt solution test, and the histamine test as given by de Takats.
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