Thrombo angiitis obliterans : its etiology, pathology, symptomatology and differential diagnosis

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THROMBO-ANGIITIS OBLITERANS

Its Etiology, Pathology, Symptomatology and Differential Diagnosis

Arthur M. Greene

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INTRODUCTION

It is a well known fact that clinical interest in a given field is usually proportional to its therapeutic possibilities. Consequently it is not surprising that until recently the common arterial diseases of the extremities have attracted comparatively little attention. Thus many of the leading systems of medicine containing hundreds and even thousands of pages devote but a few pages to chronic arterial diseases of the extremities, and many fail to even mention thrombo-angiitis obliterans! On the whole, internists and surgeons have neglected the problem of peripheral arterial diseases in their early stages, attention only being focused on an extremity showing actual or threatened gangrene. A certain fatalism has characterized the attitude of the medical profession toward peripheral arterial diseases. It is the main purpose of this thesis to give a better idea of vascular diseases of the extremities, especially in their early stages, so that earlier diagnoses can be made before the impending gangrene stages, and thus earlier treatment can be established. For, only with a better knowledge of the disease and the establishment of early correct treatment will the present fatalism of the profession toward the outcome of these diseases be proven incorrect.
2.

HISTORY

Thrombo-angiitis obliterans was first correctly and exhaustively described in reference to pathology and symptomatology by Leo Buerger in 1908. Before that time, knowledge of peripheral arterial disease was truly a bedlam of scattered and incorrect data. In 1832, M. Victor Francois of Mons recognized this fact and adeptly stated that "Everything regarding spontaneous gangrene is in a state of distressing uncertainty."(1)

That organic occlusion of arteries might be the cause of peripheral gangrene was hinted at by Quesnay (1739), Hebreard (1817) and Avisard (1819) but no actual proof or follow-up work was presented and so these ideas were immediately forgotten.

Dupuytren and Roche stimulated much interest in arterial occlusion, and also are called the fathers of the theory of arteritis. Allibert (1828) stated that arteritis might be the effect and not the cause of thrombosis. Behr (1861) noted the important facts that arterial obliteration causes dry gangrene, venous obliteration causes moist gangrene.

Then came Maurice Raynaud in 1862 with his famous thesis, "On local asphyxia and symmetrical gangrene of the extremities" in which he proved that gangrene may be produced in disease of the arterial system without organic arterial obliteration. This was a great forward step for arterial diseases, and his work was so well recognized that the disease he described was named after him.

The first report of the disease now known as thrombo-angiitis obliterans was made by von Winiwarter (in 1879) who called it endarteritis
and endophlebitis, although the disease was probably known long before this time. Winiwarter described a fairly typical case; fourteen years later (1893) Dutyl and Lamy reported another case emphasizing the syndrome of intermittent claudication, pulseless arteries in legs, pain, cyanosis, coldness and then gangrene.

Vvedensky (1898) first noted the prevalence of the disease in districts of Russia where weather was severely cold; also that the disease occurred more in males, and that pain in legs during exercise and disappearance with rest was a characteristic sign; also that all symptoms were worse in cold weather. He noted that after exercise, muscle spasm, pallor or cyanosis, subnormal temperature, absence or diminished arterial pulsation in feet, and diminished sensation in toes occurred, and stated that a complete cure had never occurred.

In 1908, Leo Buerger of Mount Sinai Hospital, New York, wrote his first paper in which he gave an orderly analysis of the pathological findings and symptomatology of the disease, and suggested the name thromboangiitis obliterans. In 1912, Todyo reported five cases with complete pathological studies in which he correlated and corroborated the findings of von Winiwarter and Buerger.

The latest great contribution to the knowledge of the disease was a book written by Buerger, published in 1924. In this book he gave a most accurate description of the pathology of the disease and came to the conclusion that the disease is an acute inflammation of vessels, leading to thrombosis, subsequent organization and canalization. He described a second stage as a process of healing, characterized by disappearance of
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Inflammatory products, organization and canalization of the thrombus; and an end stage fibrosis of the adventitia and conversion of vessels to fibrous cords.

In spite of the notable studies of Raynaud, von Wiiniarter and Buerger, etc., there is still much confusion in diagnosis and treatment of peripheral arterial diseases.

The literature on Buerger's disease is very confusing due to the fact that many cases of thrombo-angiitis obliterans have been described under other names, and many other diseases have been described as thrombo-angiitis obliterans. Thrombo-angiitis obliterans has been called the following names: dysbasia angiosclerotica, erythromelalgia, crural angina, intermittent claudication, gangstocking, juvenile gangrene, presenile gangrene, spontaneous gangrene, obliterating endarteritis, local asphyxia of extremities, acrocyanosis, acroasphyxia, acrosphacelus, paralysie vasomatricae des extremities, pseudo-erythromelalgia, non-syphilitic endarteritis obliterans, Raynaud's disease, Friedlander's disease, Russian disease, Jewish disease, Yiddish disease, scleroderma, sclerodactyilia, multiple neurotic gangrene and acroparesthesia, gangran spontan, primary endarteritis obliterans, arteritis obliterans, obliterative arteritis of the young, arterio-phlebitis obliterans, endophlebitis and endarteritis, non-syphilitic obliterative arteritis of the Hebrews, and Tokuhatsu dasso gangraena spontanea, and, of course, Buerger's disease. (2)(3)(4)(5)
Definite conclusions as to the etiology of Buerger's disease cannot as yet be drawn, but here the various ideas and theories of causation are going to be discussed, and an attempt is going to be made to evaluate their various merits.

(A) Tobacco smoking as a causative factor.

When Buerger first described the disease, he noted the frequency of inveterate cigarette smoking in those who suffered from this malady. He considered it as one of the prime factors in etiology. Meyer in 1920 wrote several extensive papers on this phase of the disease in which he made the following observations. He stated that the characteristics of patients who are particularly prone to thrombo-angiitis obliterans seem to indicate a hereditary weak sympathetic nervous system. Hence, function of the kidney, innervated by that system, is subnormal. When the system of such a patient is kept incessantly flooded with tobacco smoke poisons over a long period of time, the elimination of poisons by the kidney will fall behind, and the system will gradually become saturated with these poisons. This starts vicious circles of various types, a general upset of physiological balances in the blood is established and causes, secondarily, blood vessel lesions which lead to the symptom complex. Since he noted that most of his cases were in Hebrews, he recommended prophylactic instruction to this race not to smoke. (6)(7)

Nicotine, cyanic hydrogen, carbon monoxide, pyridine, and ammonia are the poisonous products of smoking according to Meyer. He states that the absorption of tobacco smoke poisons into the system does not seem to depend so much upon the amount and quality of tobacco used as upon the manner
of using it, the absorption rising from cigar to pipe to cigarette. His reasons are that cigarette smoking requires more frequent aspirations of air, and the cigarette has the most quickly progressing and the hottest fire; hence, the most steam developed from the moisture of the tobacco, the most effective dry distillation in the zone adjoining the fire, and the greatest volume of smoke reaching the mouth of the smoker from a given weight of tobacco in a given amount of time. Also, smoke is inhaled more by a cigarette smoker than by a cigar or pipe smoker. His statements seem reasonable, and certainly help to explain the fact that thrombo-angiitis obliterans is rarely seen in cigar or pipe smokers, even though the nicotine in one cigar is equivalent to that of eight cigarettes.

Silbert says, "Whatever the underlying cause, smoking is the immediate causative factor in the production of the disease."(8) Weber said he never saw a case in a non-smoker, and Meyer goes so far as to say that non-smokers who manifest the symptoms of thrombo-angiitis obliterans haven't this disease. At first it was thought that only Russian tobacco could cause the trouble, but later they found that all kinds of tobacco could be the cause. W. J. Mayo thought that something in the vapor of burning cigarette paper might be the cause.(9) Langly showed that nicotine in doses larger than those gotten by smokers causes vaso-constriction.

However, that cigarette smoking is the primary and single causative factor can not be accepted. In a series of 350 consecutive cases of Buerger's disease in the Mayo clinic, five persons were total abstainers from the use of tobacco, and many only smoked very moderately. However, it
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must be admitted that in a control group of patients of the same age, sex and nationality not having Buerger's disease, much less tobacco was used than by those suffering from Buerger's disease. In evaluating the amount of tobacco used, one must take into consideration the amount used before the severe pains started, for often the consumption of tobacco increases markedly when the pains start. It must also be noted that statistics prove that the disease runs a more malignant course if patients were heavy smokers, gangrene and amputation being far more common in this group.(10)

Therefore, in summarizing the tobacco factor, let us assume that it is not the primary etiological factor (for proven cases of the disease have occurred in non-smokers) but is probably a large contributing factor.

(B) Race, Birthplace and Family

When Buerger first described thrombo-angiitis obliterans, he stated that nearly all cases occurred in Jews, and most of these had migrated from Russia or south-central Europe. However, recently more and more statistics show that the disease isn't confined to any particular race. The error made by Buerger and other contemporaries was in the fact that most of their clientele were Jewish (most of Buerger's work being done at Mount Sinai Hospital, New York City). The disease has been found to occur in Hebrews, Swedes, Chinese, Japanese, Koreans, Turks and Negroes. However, the statistics so far seem to show that the disease predominates in Hebrews of Polish, Bohemian, Austrian and Russian extraction. T. G. Orr reports nineteen consecutive cases, all gentiles, all American born, and two negroes.(11) Gemmill also reports a case in a negro.(12) Koyano reported 120 cases of
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Buerger's disease in Japanese.(13) At the Mayo Clinic where the clientele is not especially Jewish, more cases are found in gentiles. It therefore appears that there is no essential race factor associated with the disease, even though up to this time more cases have been reported in Jews of Russian or south-central Europe extraction.

There is very little, if any, evidence that the disease is familial. Horton and Brown report three brothers having Buerger's disease. Samuels reported three families in which brothers were affected with no direct evidence of inheritance. I have found no other reports of the disease in families.

(C) Age and Sex

The great majority of patients with Buerger's disease are between the ages of 25 and 55 years. However 25 and 55 are not age limits of the disease. Cahill reported a typical case in a two year old child (14), and Frauenthal reported a probable case in a three year old (3). To the other extreme, Horton and Brown report three typical cases in men of 63, 65, and 73 years of age.(15) Nevertheless, the greatest number of cases occur in young and middle adulthood.

Up to 1932, there were ten cases of thrombo-angiitis obliterans in women in a series of 700 cases of this disease at the Mayo Clinic. This means that 98.2% of Buerger's disease occurred in men. Of the ten cases in women, the diagnosis was definitely proven by pathological reports in three of these; three were Jewish, seven gentile; four smoked excessively, the others not at all. The disease in the women ran a similar but definitely
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milder course. (16) Buerger (1908) stated, "So rare is the disease in the female that doubt has been cast upon the possibility of its occurrence outside of the male sex." Buerger had only seen three probable cases. Telford and Stopford described two cases in women and noted that both of these were affected more in the upper extremities. (17) Various theories have been expounded as to the predominance of this disease in men:

1. Endocrine differences in the sexes - no evidence for this theory of causation.

2. Difference of occupation - men, due to their type of work, use their extremities more than women, and also they are exposed to cold more than women.

3. More smoking in men. It will be interesting to see if more cases of Buerger's disease develops in women in the next decade due to the increase of indulgence by the fairer sex.

4. Difference of anatomy of the two sexes - however, idiopathic and post-operative phlebitis is more common in women.

5. Infections of the prostate - if Buerger's disease is definitely microbic, the prostate might be the focus for the infection.

6. Perhaps women have the disease as much as men, but it may run a milder and even subclinical form.
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(D) Infection

When Buerger described thrombo-angiitis obliterans, he stated that the cause was probably of infectious or toxic nature. He proved nothing, however, and was only drawing these conclusions from the type of pathology found in the infected vessels, i.e., lymphocytic infiltration and giant cell foci.

Although syphilis may be present in one having Buerger's disease, it is certainly not an etiologic factor. In the Mayo Clinic series, 3% of their cases had syphilis, a percentage not higher than that of other groups of patients not having Buerger's disease. The few reports of patients improving when under anti-luetic (arsphenamine) therapy are probably due to the fact that arsenicals act the same as foreign protein injections and stimulate the circulation to the affected parts. (18)(3)(19)

Rabinowitz isolated a hemoglobinophilic bacillus from the blood stream of a patient with thrombo-angiitis obliterans, which organism when introduced into a rabbit's ear vein produced the same lesion in the ear and leg vessels as in human leg vessels. This was proven by microscopic examination. The bacillus requires hemolyzed blood for cultivation and isolation, from the blood stream; Rabinowitz used leeches to extract the blood from the affected limb, the hirudin from the buccal glands of the leeches preventing coagulation. Five weeks after inoculation into the rabbit's ear veins, typical lesions on the plantar surfaces of the toes of three rabbits were found, thus showing specific tissue predelection. The bacillus was described as gram negative, rod-shaped, aerobic, freely motile, medium-sized, beaded, bipolar, and containing metachromatic granules.(20) Unfortunately,
his work has never been corroborated.

Horton and Dorsey (21) obtained acutely inflamed arteries and veins from 34 fresh biopsy or amputation cases. In nine cases, gram positive, pleomorphic streptococci in pure culture were found, and in two cases, green producing streptococci. Negative cultures were obtained from twenty-four normal subjects. The organisms found were injected into experimental animals in the following manners:

(a) Intravenously
(b) Into the femoral muscles near the femoral artery
(c) Imbedding parts of vessels from humans in positions adjacent to femoral vessels
(d) Imbedding vessels into the pulp cavity of the teeth of dogs.

The pathological lesions were found in a small number of rabbits. Thirteen rabbits were given intravenous injections of the organism and two showed typical lesions. However, these experiments fall far from fulfilling Koch's Postulates.

Goodman (1917) was convinced that typhus fever was the main etiologic factor, and that thrombo-angiitis obliterans was a later manifestation of the disease. He called attention to the fact that typhus attacks the blood vessels of the extremities especially, causing endarteritis and thrombosis and fragility of blood vessels, and that the disease occurs more in Russia, Japan, Austria, and Bulgaria. He found three out of twenty-one cases of Buerger's disease who presented positive compliment fixation and agglutination tests to typhus fever. (22)(23) This theory has been disproven, however, in recent years.
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Lowered local resistance following exposure to cold with superimposed focal infection might be the cause of the disease.\(^{(24)}\) In a large series of cases collected by Dumas, 75% had periapical infection of the teeth, 52% had prostatitis and many had infected tonsils. However, no very conclusive evidence is yet to be had to back up this assumption.

There are some excellent arguments, also, against the infectious nature of thrombo-angiitis obliterans. Variation from normal of the pulse rate, number of leukocytes, and temperature is absent or minimal in this disease. Even with marked gangrene and secondary infection, fever is often absent. Also, no systemic reactions occur as do in inflammations such as syphilis or tuberculosis.

In conclusion, one must state that infection can not as yet be satisfactorily proven as an etiologic factor, but certainly it must be kept in mind as a probable cause.

(E) Ergotism

Now we come to the most recent, most interesting, and most logical theory of causation of Buerger's disease, i.e., its relation to chronic ergotism. Kaunitz wrote an article in 1930 about the similarity between thrombo-angiitis obliterans and endemic ergotism in which he pointed out the following likeness:

(a) Both thrombo-angiitis obliterans and the the gangrenous form of ergotism occur most frequently in people of the same age, sex, and social position.

(b) Symptoms and physical signs may be the same in both diseases.
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(c) Pathological findings are the same in both in early stages.

(d) A main article of diet in both conditions is rye bread.

He noted also that ergot is a common infection of all grains, particularly rye, in all continents, and also that the probable difference between thrombo-angiitis obliterans and gangrenous ergotism is in chronicity. (25)

In a later paper, Kaunitz points out that gangrenous ergotism affects males only, the females being affected with convulsions, headache, nausea, vomiting, uterine cramps, sterility or abortion, but never with circulatory symptoms. (26)

J. Klein recently reported on the same subject. He also noted that Russian and Polish Jews are in the habit of eating rye or "pumpernickel" bread instead of white. Symptoms of ergotism have been found in the Jews of Manchester, England, who ate rye bread; such symptoms are: nausea, vomiting, dysentery, headache, depression, coldness of the extremities, numbness and lack of sensation in the fingers, formication, shooting pains, twitching in the limbs and staggering gait. None of these symptoms were found in the Jews eating white bread. The rye grain examined at Manchester showed an incidence of 1% ergotized rye. When rye bread was discontinued, the symptoms quickly improved. The symptoms of ergotism are due to contamination of corn or rye with "Ustilago maidis" or "Claviceps purpurea" (ergot) which are grain fungi parasites.

If Buerger's disease is a manifestation of chronic endemic ergotism, then more careful cleaning of rye seed before planting and milling
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is indicated. Also, storing grain for a long time decreases the toxicity of ergot, if present.

(F) **Miscellaneous**

Many other things have been accused of causing Buerger's disease. Let us mention a few.

(a) Exposure to cold. The first symptoms of the disease are generally manifest in cold weather, and many patients get better in warm climates. However, many patients who have always lived in the semi-tropical south have the severest type of the disease.

(b) Occupation - 80% are in active occupations, 20% in sedentary.

(c) Hyperglycemia - due to a disturbance of glands of internal secretion. (28)

(d) Coagulation time of blood shortened.

(e) Increased viscosity of the blood.

(f) Glandular dysfunction.

All of these have been proven incorrect.

The exact cause of the disease has yet to be found, or should I say proven. When that time comes, I am sure we will be able to attack the disease more intelligently both as to prophylaxis and treatment.
The first accurate and complete description of the pathology of thrombo-angiitis obliterans was made by Leo Buerger in 1908. So excellent were his observations at that time, that at the present time his description has been found but slightly erroneous, and is still accepted almost to the letter.

Perhaps in the attempt to describe the pathology of Buerger's disease, one should first briefly describe the histology of blood vessels and the changes which occur in them with advancing age. There are three coats or layers of all blood vessels with the exception of capillaries. These are from without inward, the adventitia, media, and intima. The adventitia is the outer layer of the vessel, being composed of fibro-elastic tissue, the elastic element being small in youth and increasing with age. It is in this layer that most of the vaso vasorum are found, except in very large vessels where they are also found in the media. This outer layer anchors the vessel to surrounding tissue. The elastic fibers are thicker at the inner zone of the adventitia, thus forming the external elastic lamina.

The media or middle layer is composed of circumferentially arranged smooth muscle cells with very little connective tissue, and some elastic fibers which increase in old age. The elastic fibers collected in the zone between the intima and the media and forms the very prominent internal elastic lamina. In only the larger vessels does the media also contain the nutrient vaso vasorum.

The intima or inner layer at an early age consists of only one or two layers of cells, the cells lying with their long axes circumferentially
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and their nuclei are elongated. With advancing age the number of cell layers increases and the intima becomes thicker, and elastic tissue increases internal to the internal elastic lamina. These changes are normal as they exist in all people and are the onset of arteriosclerosis. When arteriosclerosis is more fully developed, the intima is greatly thickened, nuclei are sparse and small, the tissue is dense, cell outlines become indistinct, and the tissue has a glazed, homogeneous appearance. Calcium salts are found occasionally. There is an abundance of elastic tissue in the intima, and the internal elastic lamina becomes distorted and split.

The media in arteriosclerosis atrophies and there is some replacement by connective tissue. Calcified areas are numerous. Lymphocytes are sometimes found and may be the result of atrophy, and rarely giant cells are found near calcified areas (foreign body giant cells). In arteriosclerosis, retrogressive changes predominate, these changes being alike in senile as well as diabetic processes.

Gross vessel changes in thrombo-angiitis obliterans

These changes depend on the stage of the process when the vessel is examined. The predominant features are noticeable thickening of the walls of the vessels, even in the absence of occlusion. In advanced stages, there is extensive induration of the adventitia and surrounding zones, and artery, vein and nerve become closely adherent. Arteries are more frequently obliterated than their accompanying veins. Occlusion of the vessels extends for variable lengths and then stops. Sometimes there is occlusion at two different levels and the lumen between is patent.
If the disease is progressing, and the occluded vessel is opened longitudinally, you see first a soft, red, adherent thrombus which may be replaced a short distance away by a firm, yellow, brown material (a sign of beginning organization) and the lumen here is much smaller. This may run for a short distance and be replaced by the newer red thrombus again. If the lesion is very far advanced, a dense yellow white material will completely occlude the lumen so that it is impossible to open the vessel in longitudinal section. The vessels are not brittle as in advanced arteriosclerosis, nor in the patent lumina are there irregular encroachments (as atheromatous processes) projecting into the lumina. Vessels are indurated and are bound to nerves by scar tissue.

**Microscopic vessel pathology in Buerger's Disease**

**Adventitial changes:**

(a) One of the earliest changes in the vessel wall is the presence of lymphocytes in the adventitia; these lymphocytes are usually around the vaso vasorum, but occasionally are in the surrounding tissue. They persist even when the occlusive lesion is old.

(b) Simultaneous with the appearance of lymphocytes, changes occur in the intima of the vaso vasorum which consist of increase in the size of the nuclei of the endothelial cells, and the endothelial cells become more numerous.

(c) Fixed connective tissue cells exhibit increased proliferation.
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(d) Later changes in adventitia:–

(1) Increase of connective tissue of adventitia and surrounding tissue.

(2) Cell thickening of intima of the vaso vasorum

(3) Fibrosis between artery, vein, and nerve.

(4) Rarely, polymorphonuclear leukocytes are found in adventitia.

(5) Blood channels in adventitia become large, an attempt to establish collateral circulation.

Medial changes:–

(a) Leukocytes and lymphocytes usually are absent, but may be present (less than 50%).

(b) Vaso vasorum are found inside external elastic lamina, an attempt to establish collateral circulation.

(c) Muscle cells are generally well preserved, except with old occlusions when they may be atrophic.

(d) Increase of interstitial connective tissue of media; it may occur even before occlusion of lumen. The connective tissue cells may be young fibroblasts or mature cells.

The media in arteriosclerosis shows quite different changes. There is an atrophy of muscle cells; cell outlines are indistinct; cells appear to fuse and nuclei become smaller; there is replacement of muscle cells with connective tissue and also interstitial fibrosis; deposits of calcium are found; lymphocytes are rarely found; and small new vessels are not so common.
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Intimal changes:-

(a) Active proliferation and thickening are found. The thickening is characteristic in that it is very cellular, especially on the free border, and cell nuclei are often prominent, large and oval. No mitotic nuclei are found.

(b) Lymphocytes are sometimes found in the intima.

(c) Cells have their long axis radial when the cell borders the lumen.

In arteriosclerosis, the cells are not so numerous, nuclei are small and shrunken, and the cells are arranged circumferentially; deposits of calcium are found in intima and the intima is converted into a homogeneous glazed tissue. In other words, retrogressive changes are faster than proliferative.

Changes in elastic tissue:-

In thrombo-angiitis obliterans concentric layers of elastic tissue are often found, but never in very cellular intimas. The internal elastic membrane is not split, and often the elastic tissue is very abundant. On the other hand, in arteriosclerosis, the internal elastic lamina is distorted and split, and new elastic tissue appears in the intima.

Normally, there is an increase in the elastic tissue of vessels in old age; perhaps I should modify this statement and say that there is an increase in substances which stain with Weigert's elastic tissue stain; but there is a loss of elasticity of the vessel, therefore this tissue probably has no elastic properties.
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New vessels in the occluding mass:

When cellular masses occlude the lumina of vessels, new formed blood channels appear in these masses with intimal and medial layers. A secondary cellular thickening of the new formed intima appears. Well-defined elastic lamina also appears. Thus elastogenic and myogenic properties must be inherent in the cells that organize the thrombus.

Oclusion of the vessels

Although it is definitely proven that thickening of intima occurs to a tremendous degree in thrombo-angiitis obliterans, yet there is great doubt if in itself the thickening would produce complete occlusion of the vessel without the intervention of a thrombus. It is well known that thrombosis occurs. In the late stages, there is a dense cellular occluding mass in the vessel's lumen, and this gave the old pathologists the idea that the disease was an endarteritis obliterans. It is conceivable that proliferation of the intima could cause complete occlusion, and this hasn't been disproved, but unmistakable thrombus is frequently found and it is at least the most common method of occlusion. Buerger described acute inflammation of the vessel with thrombosis as the initial lesion of the disease, but his concept of the pathogenicity has never been corroborated. Although acute inflammation sometimes occurs in these vessels, it is probably not the fundamental process. The process is probably chronic with acute inflammation superimposed as is evidenced by the following:

1. Although there may be many leukocytes in the wall of a vessel and in the occluding thrombus, there are also lymphocytes and fibroblasts.
(b) Lymphocytes occur in the adventitia without thrombosis and without infiltrating polymorphonuclear leukocytes.

(c) Changes of chronic character are present before thrombosis occurs.

(d) Evidence of acute inflammation is rare and chronic inflammation is also found when it does occur.

(e) Incompletely organized thrombi without evidence of acute inflammation, but with chronic inflammation are often found.

(f) Vessels with chronic inflammation in adventitia without thrombosis are found.

(g) Often miliary giant cell foci are formed in the new thrombus replacing purulent foci in periphery of the clot, and disappear in the stage of organization and healing.

**Organization of the Thrombus**

Organization starts peripherally, and cells grow inward to the center of the clot and form a network. Sinusoids filled with well preserved erythrocytes but no fibrin are numerous in the organizing clot. Since erythrocytes are found, blood must be flowing through these sinuses for there is no other source for these red cells, and the absence of fibrin suggests a very rapid circulation. The single layer lining the sinusoids is endothelium or modified fibroblasts.

Splitting or autolysis of the central part of the clot occurs while organization progresses in the periphery, and circulation of cells
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through these crevices follows. Fibroblasts grow into a thrombus singly, and line these blood spaces. There is a close relation between fibroblasts and angioblasts, and the cells that line the blood spaces look almost exactly like fibroblasts. There seems to be a metamorphosis between cells which form connective tissue of an organizing thrombus, and those that line its blood channels.

End Stages

The adventitia and surrounding regions are found to have marked increase of connective tissue; cells are mature and closely packed. This perivascular fibrosis causes induration of perivascular tissue, and adherence of artery and vein and nerve to one another. There may be a few lymphocytes in the adventitia. The vaso vasorum are numerous and larger than normal and may have a thickened intima.

The media shows well preserved muscle cells generally, increase in the interstitial connective tissue, and small new blood channels.

The lumina of vessels are occluded by cellular masses containing fibroblasts and occasionally lymphocytes, and new formed blood channels often lined with three coats. Circulation is carried by these vessels in the cellular mass occluding the lumen, and also in the adventitial, and intimal vessels which have increased in number and size, but the capacity of the original lumen is greatly reduced by occlusion.

Changes Occurring in Nerves

These are not constant or definite. The most frequent finding is a change in the character of the connective tissue in the region of the nerve,
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which tissue becomes very dense. This increase of density depends entirely upon the contiguity with blood vessels, and is worse where blood vessel changes are more marked. Occasionally in the smaller nerves of the toes, extensive degenerative changes occur. There is increase in the number of nuclei of the sheath of Schwann, thickening of the perineurium, and absorption of myelin. These changes are probably due to prolonged ischemia, and are also found in arteriosclerosis.

Summary of Pathologic Findings

Gross changes:-

(1) First stage - thickening of the wall of the vessel.

(2) Second stage - occlusion of the vessel by a soft red thrombus.

(3) Third stage - the thrombus is converted into firm yellow white tissue through which course minute blood channels. The adventitia and perivascular tissue become very indurated and in the end stages artery, vein, and nerve are bound together.

Microscopic changes:-

(1) First stage - the earliest changes are the appearance of lymphocytes in the adventitia, and proliferation and thickening and increase of elastic tissue in the intima.

(2) Second stage - thrombosis and complete occlusion of the vessel lumen. The cause of the precipitation of the thrombus is not understood, since it seems that it is not necessary to have an acute inflammation to bring it about.
Pathology

It is thought that chronic inflammation precedes acute, for lymphocytes are found in the adventitia without thrombosis of vessels or leukocytes being present. The thrombus is organized by ingrowth of intimal cells. New vascular channels are found in the intima and media, and the vessels of the adventitia become larger and more numerous.

In the end state, there is marked fibrosis, and a few lymphocytes in the adventitia; the lumen is occluded by cellular connective tissue through which course blood vessels. The media has many new blood vessels and an excess of connective tissue. Nerves sometimes show an increase of connective tissue in the perineurium and epineurium, and sometimes lymphocytes; in the small nerves of the toes, there is often absorption of the myelin, and increase of the cells of the sheath of Schwann.

In conclusion, thrombo-angiitis obliterans is a chronic inflammatory disease of the vessels, accompanied by proliferation of the intima, and resulting in thrombosis with organization and canalization of the clot; fibrosis of the adventitia and an attempt on the part of the vaso vasorum and other vascular channels to establish collateral circulation. At times acute inflammation is superimposed on the chronic process. Nerves are involved only due to their close relationship with vessels, and the pathology is due to the resulting fibrosis and ischemia. (3)(33)(34)(35)(36)(55)(57)(58)(56)
The present concept of most physicians is that thrombo-angiitis obliterans is a disease of the vessels of the extremities only, particularly the lower extremities. This misconception has been opposed by many well trained observers who have filled the literature with cases of the disease which show manifestations of pathology in almost every vessel of the body.

It is true that the vessels of the extremities are more involved than any other vessels, and also that the lower extremities are attacked more often than the upper. However, many reports have been found of cases involving the coronary vessels as well as the vessels of extremities. Linenthal and Barron(29)(30), Lemann(45), Allen and Willius(43), Lawson(38), Samuels and Feinberg(41) report many cases of coronary vessel involvement in thrombo-angiitis obliterans of the extremities, the characteristic coronary thrombosis, or angina pectoris syndromes being present in men too young to be attacked by the usual coronary sclerosis. Both clinical and electrocardiographic findings proved the pathology to be present in the coronary vessels; also a few autopsy reports are found.

Crisp(42) noted the coincidence of gastro-intestinal lesions and Buerger's disease. He reports seven cases of peptic ulcer in 462 cases of Buerger's disease. Although the operative or autopsy pathological findings in the vessels of the stomach were not exactly like those of thrombo-angiitis obliterans, there were many findings similar to Buerger's disease (as thrombosis, proliferation, intimal thickening, etc.)

Taube(39) reports several cases of thrombo-angiitis obliterans with amputation who later had mesenteric thrombosis (intense abdominal pain,
vomiting, rigidity, distention, and on operation a gangrenous bowel); a most interesting case of intermittent claudication of the mesenteric vessels is also reported.

McGreggor and Simson(46) report a case involving the spermatic vessels. Lawson(38), Linenthal and Barron(29), emphasize the frequency of cerebral vessel involvement. Gresser(51) reports a case with partial occlusion of both central retinal arteries and veins in connection with a proven case of Buerger's disease.

Recently Pemberton and Mahorner(47) reported two cases of aneurysm of the popliteal and axillary arteries associated with thrombo-angiitis obliterans. In both cases, the aneurysms were bilateral and symmetrical. The subacute or acute inflammation of the wall might weaken it enough to cause aneurysm, so the cases were probably not just coincidental.

Various other diseased states have been reported occurring simultaneously with thrombo-angiitis obliterans but probably having no relationship with it. Carcinoma of the recto-sigmoid(48), diabetes(50), polycythemia, and traumatic myelitis(44) and nearly any disease may be associated and complicate the diagnosis tremendously.

The lower extremities do not necessarily have to be involved, but they generally are involved primarily or secondarily. Yartan and Van Duzen(40) report several cases of the disease only in the fingers. Kessel(37) states that ulceration of the toes is usually more frequent in the first or fifth, for centrally placed toes get blood supply from two sources. Dyer(31) noted that the left leg and foot were more frequently involved, and that the posterior tibial was attacked more frequently than the anterior.
Horton(54) and Reichert(52) injected metallic mercury into recently amputated limbs and then took X-rays. A few cases appeared normal but some showed that the original arterial tree had been occluded and replaced by a collateral circulation. From the appearance of the X-rays, it would seem that thrombosis of a vessel occurs, then collateral circulation develops above it, and then another segment closes. The X-ray also shows the poverty of collateral vessels around a region of gangrene. In arteriosclerosis, generally the main arteries in the leg and foot were patent but reduced in caliber, and collateral circulation was small or absent. Also, in both Buerger's disease and arteriosclerosis there was a lowering of the amount of fluid that could be pumped into the vascular system.

Friedlander and Silbert(49) and Kornzweig(53) found that there was a reduction of 21% in the blood volume in a series of cases with Buerger's disease, this reduced volume probably being more concentrated because there is an increase in the total ash content, total protein, calcium and cholesterol per 100 c.c. of blood; a high hemoglobin and increased viscosity of the blood is also found. Since patients with Buerger's disease have a low blood volume and also a low basal metabolic rate (and since patients with myxedema who have a low blood volume increase their volume when thyroid extract is administered) thyroid therapy was introduced and found to increase blood volume in thrombo-angiitis obliterans.

Bernhard(59) in a study of the chemical blood findings in Buerger's disease found no sign of departure from the normal.

In concluding the clinical side of the pathology of Buerger's disease, let us emphasize the following:
Clinical Pathology

(a) From a mechanical point of view, and from the standpoint of symptomatology, thrombotic occlusion is the most important phenomenon.

(b) Lesions occur in the superficial as well as the deep veins and are identical.

(c) Any vessel in the body may be involved.

(d) Progression of the thrombotic processes takes place rather in attacks or sudden exacerbations than by gradual ascent(34).

(e) The process is a migrating thrombosis of the deep and superficial vessels and is often associated with superficial phlebitis of lower or upper extremities (an early symptom).
SYMPTOMATOLOGY

The symptomatology of Buerger's disease is fairly characteristic and although a diagnosis of the disease can hardly be made from the history of the symptoms alone, nevertheless the symptomatology should at once make one place Buerger's disease in the differential diagnosis list. In 75% of cases the history of symptoms is as follows: A man of about 35 to 40 years of age notices that he has pains in his feet or legs when exercising, but is relieved when he sits down to rest; his legs tire easily; later he notices that his feet are very red when dependent, and very pale when elevated; soon a new type of burning, intractable pain comes on even when he is resting, and to obtain partial relief, he hangs his feet out of bed when he sleeps at night, or else sleeps in a chair just so his feet are dependent; later trophic changes occur such as ulcers, fissures, non-healing incisions, and gangrene associated with severe pain, result. It generally takes from one to ten years to develop this syndrome.

Let us analyse in detail some of the important symptoms.

(1) Intermittent claudication, or pain in extremities during exercise but relief upon resting, is perhaps the commonest single symptom of the disease, and occurs as the first symptom in about 50% of the cases. It is often preceded by excessive unilateral or bilateral fatigue of the muscles of the calves of legs, arches, ankles, or under the knees; it is also often accompanied by a coldness of the feet, or perhaps numbness or tingling. At first there is only a mild aching in the muscles following exercise, but gradually a true cramping pain sets in. After the patient has exercised for a certain length of time, the pain becomes more and
more unbearable until finally he has to sit down and rest. He obtains almost instant relief except for a residual soreness, tenderness and fatigue, and after a few minutes can start to exercise again. However, as the disease progresses, the rest periods become longer and more frequent, and the exercise periods shorter.

The claudication is a varied symptom, but is usually described as a "cramping" pain. It is not a continuous pain, but only occurs at the place in the step when the weight of the body is thrown on the ball of the foot, and it is relieved as the foot is carried forward. The pain darts up and down the calf muscles generally, usually more severe on the inner aspect. A residual soreness is left in the leg not supporting the body.

Claudication can occur in various sites, the following list being in order of frequency of involvement - calf muscles, arches, ankles, and single digits. The duration of claudication is from a few months to many years, the average being about four years. The pains of claudication in the ankles, toes or balls of feet is described as a sensation of walking barefoot on gravel or cobblestones.

Claudication pain and abnormal fatigue are both due to deficient supply of arterial blood to remove the excess metabolic products of muscle action during exercise; yet this supply is sufficient to remove metabolic wastes produced during rest, thus relieving the pain. Lactic acid is the cause of the slowing down and fatigue. It is produced normally when muscle contracts but is largely converted to glycogen (to be used as energy for more muscle activity) by a good blood supply. But lactic acid is only neutralized by alkaline salts and an unknown buffer when the blood supply is deficient and therefore a large part of quick muscle food (glycogen) is lost.
Symptomatology

The speed of removal of lactic acid from a working muscle is directly proportional to oxygen supply; thus with a poor blood supply as is present in thrombo-angiitis obliterans, lactic acid reaches a high concentration.

Finger or toe claudication suggests distal arterial occlusion; arch claudication, occlusion at or above the ankle; calf claudication, occlusion at or above this region. Claudication is infrequent above the knee due to the rich collateral circulation here.

Frequently patients experience periods of claudication, and then periods of relief. This can be explained on the basis of arterial occlusion, then the establishment of good collateral circulation, and then further arterial occlusion again, etc. If collateral circulation is good enough, all main arteries may be occluded without claudication occurring.

The pain of claudication may vary from day to day, probably due to changes in weather (heat or cold).

Experimentally, intermittent claudication can be produced by placing a sphygmomanometer cuff around an extremity and inflating the cuff to 5 m.m. above arterial pressure and then exercising the extremity, thus proving that poor circulation is the cause of the pain.

Before finishing the discussion of the symptom claudication, we should not fail to mention that it can occur in parts other than the extremities. Meyer (68) describes a case of a man who had had his legs amputated for sixteen years when he began to have severe intermittent and later continuous pain in the abdomen, with severe constipation, occasional vomiting, distention of the bowel, visible peristalsis, and an enlarged colon. Autopsy findings showed typical vessels of Buerger's disease. Also,
Symptomatology

perhaps coronary sclerosis with anginal symptoms might be a sign of the disease. Generally, a history of extremity involvement simplifies the diagnosis. (70)(63)(64)(62)(65)

2. **Rest pain** in contradistinction to the pain of claudication occurs without exercise. It may or may not be associated with gangrene, and it is usually limited to the digits. It is variable in type and severity. In most cases it is present before trophic changes appear and is greatly accentuated by these changes. The pain may be so severe and intractable that amputation is often necessitated even though no trophic changes are present. Severe pain occurs only in the digits, but occasional milder pains occur in the dorsum of the foot or ankle. After major trophic changes occur, pain is usually limited to the gangrenous or ulcerated areas, severe trophic changes nearly always giving severe pain.

Early in the disease there is a constant deep seated soreness or aching, or perhaps a sensation of burning, coldness or numbness. The pain might be intermittent and sharp. Partial relief from the pain may be obtained by heat and dependency; elevation and cold increase the pain. The patient may sleep with his feet hanging over the edge of the bed for relief (Buerger's angle of circulatory sufficiency) or sleep tailor-fashion sitting up. The patient generally dreads the night; he doesn't sleep much but just rubs his feet and smokes many cigarettes.

Generally the pain becomes so severe that the patient loses weight, doesn't eat much and is gaunt and hollow cheeked. He shows little or no response to large amounts of opiates. The pain is often so severe that he begs for amputation if he knows that this will relieve him.
Symptomatology

Rest pain is probably due to constant profound anoxemia approaching the threshold of tissue death. This explanation is not entirely adequate for it doesn't explain the small amount of pain in arteriosclerosis with profound anoxemia, nor does it explain the absence of pain in some cases of thrombo-angiitis obliterans with gangrene. The inflammatory nature of the lesion is probably contributory. Many explanations have been given for rest pain, none of them as yet being proven. Some say it is due to increase of connective tissue around nerve trunks, and to true neuritis; but these can not be the whole explanation for these processes occur in the nerves throughout the whole extremity in most cases, and yet there is pain in only the toes in 95% of cases. Also pathological changes in nerve trunks seem inadequate to explain the pain on this basis.

In discussing pain, it should be kept in mind that different nationalities are found to stand pain in varying degrees. The hypersensitive Jewish race suffer terribly with small trophic changes; the stoic Chinese allow gangrene to auto-amputate without much complaint.

As a prognostic point, absent or mild pains indicate slow occlusion and slow progression which allows establishment of sufficient collateral circulation, and thus gives a good prognosis. Severe pain of short duration indicates a rapid type of occlusion with inadequate establishment of collateral circulation and gives a poor prognosis. However, as a prognostic point, severity and duration of rest pain is not always accurate, for spontaneous amputation may occur without any pain.

3. Lowered temperature in the extremities is the first symptom of the disease in 11% of cases. It may be present for from one to five years before other symptoms appear. The lowered temperature is due to
decreased arterial inflow into the extremity, and is distinguished therefore from non-vascular coldness of extremities by diminished or absent warming up of the part with increased environmental temperature, and also by the development of progressive coldness of the limb during the progression of the disease.

4. Postural color changes. Excessive rubor of the extremity when dependent generally follows soon after claudication but may occur at any time. It is generally simultaneous with subjective coldness of the extremity. Rubor is common in both Buerger's disease and Raynaud's disease, but is more marked in Buerger's.

The color varies markedly and is modified by posture of the extremity and temperature of environment. With room temperature, the color is deep red or crimson, often erroneously being interpreted as inflammatory reaction. With lowering of the temperature the skin becomes more red-blue or cyanotic. Early it occurs only in the tips of the toes and is only a slightly exaggerated normal reaction occurring when the foot is lowered. It then progresses and involves the distal and then proximal part of the foot. The color changes as the disease advances from a pink to an extreme red to a red-blue color, and is more intense in the toes and distal half of the foot.

Buerger stated that the rubor of thrombo-angiitis obliterans is a sign of defective circulation in the deeper vessels, and that its chronicity and dependence on the dependent posture of the limb should differentiate it from rubor of vasomotor origin. Rubor of the skin in occlusive arterial disease as is shown by biomicroscopic studies of the surface.
capillaries is due to a large number of open dilated capillaries and venules and to a red oxygenated blood. Buerger explained this phenomenon by assuming that dilatation of the capillaries is compensatory in nature, attempting to supply maximum amounts of blood to tissue in which the total volume flow of blood is low. That rubor doesn't disappear when good circulation has been re-established might be explained by a partial paralysis of the capillaries' contractability power due to prolonged dilation. The fact that the blood remains oxygenated (red) in a tissue needing oxygen might be explained by the fact that the temperature of the tissue may be reduced to a level below that necessary for free oxygen exchange.

Associated with the rubor of dependency is pallor of extremities upon elevation. The pallor may be diffuse, patchy or spotted, or involve only single digits. The pallor is an extreme death-like color and is relieved by lowering the extremities. The rapidity of return to normal from rubor or pallor is inversely proportional to the degree of arterial occlusion.

5. Cyanosis. With impending gangrene, cyanosis may persist despite prolonged elevation. Continuous cyanosis in one or more digits is sometimes present and often associated with symptoms suggesting sudden thrombosis (pain in the digit, sudden onset, and sharply defined cyanosis). The color of the other toes may be normal or slightly red.

Occasionally various grades of cyanosis are present instead of rubor; this is probably due to better use of oxygen by the tissue cells, thus causing an unoxygenation of the slow flowing capillary blood in the dilated capillaries.
36.

**Symptomatology**

Sudden onset of cyanosis and pain in one or more digits may suggest Raynaud's disease, but lack of symmetry, severe pain, sudden onset, and sex of patient should rule it out.

6. **Trophic disturbances.** In 10% of the cases, non-healing ulcers on the extremities are the first signs of the disease. These may exist for years before other symptoms appear.

After claudication pain and postural changes appear, shallow ulcers, dry gangrene, or non-healing incisions generally follow. Surgical intervention (made erroneously for ingrown toenails or deep-seated infection in the toes which really was the rubor and pain of thrombo-angiitis obliterans) often causes non-healing incisions.

Minor trauma often precipitates trophic changes; new shoes, corn plasters, objects falling on toes are examples. In cases of long duration, excessive callouses over weight bearing areas or corns over areas subject to friction always appear.

Removal of toenails causes indolent shallow ulcers, and amputation or incision of toes leaves gapping, sloughing wounds. Gangrene is usually spontaneous and progresses slowly. Due to the fact that thrombo-angiitis obliterans occurs often in very young adults in whom both the vis-a-tergo and the cardiac power are adequate for compensation, and in whom blood vessels are very elastic, gangrene occurs very much later or may be absent in spite of vast extensive obliteration of arteries and veins.

7. **Superficial phlebitis** is the first symptom of Buerger's disease in only 4% of cases, although Buerger stated that early thrombo-angiitis obliterans often manifests itself as a migrating phlebitis; he states that
recurrent idiopathic superficial thrombo-phlebitis in the arms or legs should arouse suspicion as to the deep veins. Often months or years after superficial thrombo-phlebitis, circulatory obstructive symptoms will appear.

Superficial phlebitis is rare in the upper extremities. It is generally found in the main trunk of the internal saphenous vein below the knee, but branches over the dorsum and lateral aspect of the leg and foot may be affected.

Evidence of inflammation varies from one to four weeks. As inflammation subsides, the thrombosed vein feels like a hard cord, which condition persists for a long time.

Instead of linear involvement of veins, the same process may be seen as tender red circular areas called "cutaneous nodosities" by Buerger. These are probably localized inflamations at the site of valves in the veins.

Superficial phlebitis is often recurrent in different veins. The signs are tenderness, redness, heat, and soreness made worse by motion; absence of fever, tachycardia and leukocytosis is characteristic.

8. Vasomotor changes occur at any time in the course of the disease. They occur in 30% of the cases and may mask the primary disease for they may be the first sign of the disease (2%). Generally they accompany other occlusion symptoms.

Usually one or two digits on the same extremity are involved, the hands being more frequently involved than the feet. The vasomotor changes are never as uniformly bilateral as in Raynaud's disease, and they are invariably precipitated by exposure to cold. Psychic influences and ingestion of cold foods or fluids don't bring on the attack as in Raynaud's disease.
Symptomatology

The change generally is striking pallor ("dead finger"), but minor grades of pallor or cyanosis may occur. Recovery of color can be induced by massage or heat. A part of one finger or many fingers may be involved. Numbness and dull aching accompanying the pallor, and burning or tingling during recovery are common. The hand appears normal between attacks.

By biomicroscopic study on the skin, it is found that during blanching of the skin there is a disappearance of many of the capillary loops, the visible loops are small and contracted, and the blood in them flows sluggishly and is cyanotic. When cyanosis is present, the number of visible loops is increased, and the loops are dilated and contain larger amounts of motionless, cyanotic blood.

These vasomotor disturbances are probably only an accentuation of normal reactions due to hyperirritability of peripheral vasomotor nerves following inflammation in perivascular tissues.

9. Edema may be the first evidence of the disease, occurring as the first symptom in 3% of cases. It is rare in the upper extremity, but common in the legs and feet particularly when the clinical course is rapid and rest pain is severe.

The causes of edema are:

(a) Obstruction of the deep veins due to thrombo-phlebitis

(b) Dependent posture

If it is due to long dependency it is relieved by elevation in a short time. Edema is serious when it accompanies major trophic changes or
moist gangrene, and amputation generally must be resorted to.

10. Sudden arterial occlusion symptoms are sometimes the first signs of the disease (7% of cases). A sudden sharp pain is felt in the extremity, and extreme pallor and coldness soon follows. The pain subsides gradually in twenty-four to seventy-two hours. The pallor gradually disappears and is replaced by rubor or cyanosis in the ends of the toes or fingers. Claudication or other symptoms generally follow in several months. A tentative diagnosis of thrombo-angiitis obliterans should be made in all cases of sudden arterial occlusion in young adult males.

11. Miscellaneous. Often the disease is characterized by periods of remissions for months to years in which the patient may be free from all symptoms.(61)

The right leg is said by some to be most often involved.(67)

Thomas (60) has found persistent leukocytosis in early stages of the disease. This has not been corroborated, however.

Primary involvement of the upper extremities does occur. In a series of 94 cases at the Mayo clinic, only 24 showed clinical signs in the upper extremities, and in only four of these cases was the symptomatology primarily and mostly in the upper extremities. In nearly all cases primary in the upper extremities, the lower extremities are sooner or later involved. Buerger's disease of the upper extremities rarely leads to gangrene of more than a few fingers; in this manner it is thus much less mutilating than the disease attacking the legs.(66)

While thrombo-angiitis obliterans often only attacks one extremity, it is in many cases bilateral. The usual history is that while the patient is under observation for one extremity, the other becomes involved.(71)
In conclusion, it must be made emphatic to all who attempt to make a diagnosis of Buerger's disease that no one or group of symptoms must be present to clinch the diagnosis. Also, although the symptomatology aids in making the diagnosis, the physical examination and tests finally confirm the diagnosis.
Not all cases of thrombo-angiitis obliterans follow the same course, i.e., the disease is not like lobar pneumonia with its definite stages, but it has many courses which it may follow in this way being similar to pulmonary tuberculosis. Perhaps a detailed discussion of the various types will illustrate this point.

Type I - Slow progression type.

This is by far the most common type, the course lasting from four to eight years. Cold feet is generally the first symptom, followed soon by excessive fatigue of single digits, and later of ankles, wrists, legs and forearms. Soon claudication appears with increasing debility. Posture changes, rest pain and trophic lesions develop. Finally gangrenous areas increase in extent requiring amputation, or healing may occur in some in whom the pain can be relieved. In this type pulsation of arteries is diminished or absent.

Type II - Absence of Progression

In this type excessive fatigue and mild claudication are present but progress slowly for a while and then become stationary. The extremities are cold, have absent or diminished arterial pulsation, and postural changes are present, but trophic changes other than proliferation of nails and corns over weight bearing areas don't occur. Disability is minimal even though symptoms may have been present for eight to twelve years.

Type III - Circulatory Compensation

This is a fairly common type. The patients may originally belong to Type I in which the pain of trophic changes is quite mild or relieved by
Clinical Types

medical measures or amputation. Gradually the symptoms disappear and leave the patient with an 80% adequate extremity.

Type IV - Acute Fulmination

This is similar to Type I, but the progress is more rapid and severe. Claudication appears suddenly and progresses rapidly with severe rest pain, gangrene, edema, fever, and often leukocytosis soon following. The pain is unbearable and intractable and gangrene progresses very rapidly so that amputation is necessary. The whole process may be completed from three months to one year.

Type V - Extensive Gangrene without Rest Pains

This is a very rare type and is only diagnosed by pathological studies.

Type VI - Venous Involvement at first; years later, Arterial Involvement

This is not an infrequent type. The first sign is recurrent idiopathic superficial phlebitis for many years before other symptoms appear. Years later deep phlebitis as is shown by edema and tenderness over deep veins follows. Not all cases of idiopathic recurrent superficial phlebitis later becomes a true thrombo-angiitis obliterans, but prophylactic treatment should be established in all males having this symptom.

Type VII - Buerger's Disease with normal arterial pulsation

Diagnostically, this is the most confusing type because all arteries pulsate normally. The clinical course of this type is that of acute arterial occlusion in one or more toes followed by color changes suggestive of Raynaud's disease. Gangrene generally follows and necessitates
amputation of the toes and healing follows due to normal blood supply proximal to the affected areas. Other digits may be affected in the same way, and later obliteration may extend more proximal. The diagnosis of this type depend on the age, sex, and nationality of the patient, and the presence of superficial phlebitis, and rest pain or claudication.

Type VIII - Buerger's Disease with Vasomotor Changes like Raynaud’s Disease

This is a very confusing type if one fails to recognize vasomotor disturbances in organic vascular disease. Often vasomotor symptoms completely dominate the field and the organic nature of the disease is overlooked. The obliterative process is evidenced by absence or diminution of pulsation of palpable arteries of the extremity, excessive postural color changes, superficial phlebitis, fatigue, and the pain of claudication. These signs don’t occur in Raynaud’s disease.

Type IX - Buerger's Disease associated with Arteriosclerosis

In this type there are signs and symptoms of thrombo-angiitis obliterans, but there is roentgenographic evidence of calcification of arteries of the extremities, sclerosed radial arteries, and the age of the patient is high above the age limits of Buerger's disease.

The diagnosis is made on the race of the patient, the presence of superficial phlebitis, rubor of toes, inflammatory area around the gangrenous ulcer, excessive pain and absence of senile changes in the skin of the extremities. Pathological examination has often shown that both diseases may appear at the same time.
Clinical Types

Type X - Thrombo-angiitis Obliterans with no trophic lesions.

Abnormal fatigue, claudication, postural color changes, cold extremities, and absence or diminution of pulsation of arteries are present, but no trophic lesions appear. In some cases rest pains become so severe that even though no trophic changes are present, amputation must be resorted to to relieve the pain.

Type XI - Absence of symptoms in one of two affected extremities

The objective findings in both extremities might be subjective in only one. The reason for this is that the patient rests on account of symptoms from the worst extremity, thus not exercising the better extremity enough to show symptoms of decreased circulation. Partial arterial obliteration in the hands is usually without symptoms. Postural changes are often present without any subjective symptoms.

Type XII - Acute Thrombosis Type

The first symptoms are those of sudden arterial occlusion, such as sudden onset of pain, pallor and coldness. After prolonged rest some color and warmth return and mild rest pain and claudication follow. Vasomotor symptoms (as reactions to temperature changes) are common. These cases then gradually progress to a true thrombo-angiitis obliterans syndrome. (3)(74)

Type XIII - Return of Arterial Pulsation

Return of pulsation to previously pulseless arteries is common in many cases and is due, according to Buerger, to the fact that the arteries may be only collapsed, and with improving circulation through proximal collateral paths, pulsations may be re-established, the blood flowing through devious channels in uninvolved territory. (69)
EXAMINATION

EXAMINATION OF PATIENT SUSPECTED OF HAVING THROMBO-ANGIITIS OBLITERANS

Although there are many mechanical instruments available, accurate observation by eyes and finger tips are adequate and perhaps a better means of examining the patient. Every practitioner has this equipment, and if he uses it well, he will need no other.

Inspection:—Note the color of the extremity in the horizontal position, after elevation, and in the dependent position, for five minutes each. Apply the "circulatory efficiency test": elevate the limb so that it forms a right angle to the bed for three minutes. Then lower the extremity slowly to the angle at which the normal pink occurs. This is the angle of circulatory efficiency and is an indicator of the integrity of the arterial tree. The extremity is then lowered to a dependent position and the degree of abnormal rubor indicates the degree of arterial obliteration. In watching the return of the rubor on lowering the limb from the elevated position, note the rapidity of return and the distribution of the rubor. If the speed of the return of rubor is high, then arterial occlusion is little; if speed of return is slow, then arterial occlusion is great. Irregularity of the distribution of the rubor indicates spotted occlusion.

Look for large or small areas of superficial phlebitis or inflamed nodosities. Also note minor trophic changes as (1) excessive thickening or desquamation of the skin over weight bearing areas of feet, and areas on the hands subject to trauma (2) inequality of the two sides (3) fissures (4) nails showing irregular growth, proliferations, notchings, discolorations, ragged cuticles (5) infections at the nail border (6) muscle atrophy and
Examination

variations in size (7) edema and (8) gangrene.

Palpation: Roughly estimate the surface temperature of all extremities and compare with one another; compare the temperature of the digits. When contemplating amputation determine the point where there is a sudden lowering of the temperature.

Superficial veins should be palpated for thromboses, thickenings, or nodes; also note the degree of distention of the veins.

Brachial, radial, ulnar, femoral, popliteal, posterior tibial, and dorsalis pedis arteries should be palpated and compared with their mates. Note the intermittency of pulsation (often obtained by massaging the vessel). Examine the arteries for thickening, beading, tortuosity, and aberrant pulsations.

Note the presence of arterial tenderness, edema, neuritis, absence or presence of skin atrophy or scleroderma.
It is a well known fact that early diagnosis and the establishment of correct therapy early are essential to a good prognosis. Don't wait for marked gangrene, rubor, and pain to be present before you establish a therapeutic schedule, for at this time your efforts are generally in vain. There are a few points to be borne in mind in connection with early diagnosis. Let us briefly list these.

(1) Abnormal fatigue of the muscles of the extremities is one of the earliest signs, particularly if there is a difference between the two extremities. The fatigue is intermittent in the early stages and disappears at once after a short rest, but reappears soon after exercise again. Usually the fatigue is in the posterior part of the leg, peroneal or tibial muscles, or in the arch of the foot, but it may be in the ankle or heel.

(2) Pain of claudication may occur in all parts of the extremity, single digits, arches, wrists, ankles, forearms, peroneal, tibial or calf muscles, and rarely in the thigh muscles. Early claudication pain is mild and is associated with abnormal fatigue, and it is brought on by exercise and relieved by rest. Sciatic neuritis often simulates claudication but there is tenderness over the course of the nerve, and also reflex and sensory changes.

(3) Superficial phlebitis - any spontaneous recurrent superficial phlebitis in an adult male is probably early Buerger's disease. Always examine the arteries and do postural tests with these cases.

(4) Rubor is not an early evidence of the disease, but indicates an advanced state, however it is often the symptom which brings the patient to the doctor. The extreme redness may involve all of the digits of one
extremity, and is often bilateral but one side may be redder than the other. Replacement by pallor on elevation and absence of heat makes the diagnosis.

**Common Inexcusable Diagnostic Errors**

Perhaps the most common error is the diagnosis of flat feet when the patient comes in complaining of pain in the arches. In cases like this always try the water foot-print test for flat feet which is often negative in Buerger's disease. Also the pain in the arches is relieved by rest, even though the patient remains standing on his feet, in Buerger's disease; this is not so in flat feet. Arch supports give no relief in Buerger's disease. The temperature of the extremity is low in Buerger's disease, normal in flat feet; postural color changes and decreased arterial pulsation are also present only in Buerger's disease.

Abnormal or excessive fatigue in the extremities is frequently ignored, or considered a part of a general fatigue syndrome. Variation in the degree of fatigue in the extremities, or lack of evidence for adequate explanation on another basis should give a clue to the proper diagnosis.

Rheumatism and arthritis are often diagnosed for Buerger's disease. Remember that rheumatic pains are not relieved by rest; that definite wet weather attacks of pain occur in rheumatism; and that the temperature, postural changes, and pulsation of arteries are always normal in rheumatism.

Rubor and rest pain have often been thought to be deep infections of the toes or ingrown toenails, and many injudicious incisions have been made which never heal and lead to extensive sloughing and gangrene. The presence of rubor in other toes, and coldness of the reddened area should
Diagnosis

prevent such an erroneous diagnosis. Also testing of arteries and postural tests should be precautionary measures.

Although gangrene is nearly always diagnosed as such, too often no attempt is made to determine the cause of the gangrene. This accounts for many of the amputations done too low where reamputation must be done later.

Idiopathic recurrent superficial phlebitis in males is often treated as such, with no attempt to figure out the possible etiology, or to establish early treatment.
DIFFERENTIAL DIAGNOSIS

To make an accurate differential diagnosis of arterial diseases of the extremities, it is essential to know the outstanding characteristics of all these diseases. In this section I shall attempt only to mention the most important diseases of this class and to point out characteristics of these diseases which would distinguish them from thrombo-angiitis obliterans.

First, let us classify arterial diseases of extremities. They may be divided into two main parts, motor or functional, and organic or obliterative.

<table>
<thead>
<tr>
<th>Functional or Vasomotor Types</th>
<th>Vasoconstricting types</th>
<th>Vasodilating types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Distribution</td>
<td>(a) Raynaud's disease or multiple phase color reaction</td>
<td>(a) Erythromelalgia</td>
</tr>
<tr>
<td></td>
<td>(b) One phase color reaction; or acrocyanosis, dead finger, local syncope</td>
<td></td>
</tr>
<tr>
<td>General Distribution</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vasoconstricting types -</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Primary or essential hypertension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vasodilating types -</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Primary or essential hypotension</td>
<td></td>
</tr>
</tbody>
</table>
Differential Diagnosis

Local Distribution

1. Arteriosclerosis with or without gangrene, diabetic gangrene
2. Thrombo-angiitis obliterans
3. Simple thrombosis or embolism
4. Arteritis of known infectious origin (rheumatism, lues)
5. Aneurysm with or without thrombosis

Organic Types

Arteriosclerosis

1. Primary
2. Secondary types due to hypertension, lead poisoning, etc.

The first thing to be done in making a differential diagnosis is to determine whether the disease is a vasomotor or an organic process or both. Palpation of arteries and symptomatology generally decides the point. Absence or diminished pulsation of palpable arteries always indicates organic disease, even in the presence of vasomotor symptoms also. Symptoms of vascular insufficiency as excess fatigue, claudication, and postural color changes are not found in vasomotor diseases. It is indeed very confusing to meet a case with pronounced vasomotor symptoms secondary to underlying organic disease. No less confusing is the case showing trophic changes, gangrene, postural changes and severe pain in the digits, with normally pulsating palpable arteries. (This occurs in 5% of the cases.)
In vasomotor types secondary to organic occlusion, the diagnosis should be made clear by the absence of symmetry and failure to recover when the part is placed in a warm environment. The symptoms of vascular insufficiency in the group with normally pulsating arteries are limited to the areas distal to the point of normal pulsation, usually the digits. One or two toes are usually affected with severe pain, become cyanotic, and cold, and show vasomotor symptoms. It can be differentiated from Raynaud's disease because Raynaud's always affects digits symmetrically, doesn't produce severe pain, rarely causes gangrene except in late stages and occurs more in females.

Color changes not dependent on posture are of no significance diagnostically for they are common to both vasomotor and organic groups. The red foot doesn't necessarily indicate erythromelalgia, nor does the blue extremity indicate Raynaud's disease. (75)(76)

Let us discuss Raynaud's disease which is often confused with Buerger's disease. The following are criteria absolutely necessary to diagnose Raynaud's disease:

(1) Intermittent attacks of changes of color of acral parts, as pallor, cyanosis or rubor.
(2) Symmetry or bilateral involvement.
(3) Absence of clinical evidence of occlusive lesions of peripheral arteries.
(4) Gangrene or trophic changes if present, limited in a large degree to the skin.
(5) Disease must be present for a minimal period of two years (for early in the course of organic vascular disease, vasomotor manifestations may be the only evidence).
Differential Diagnosis

(6) There must be no evidence of disease to which it could be secondary.

Presumptive Criteria of the Disease

(7) Females - (90%)

(8) Presence of associated scleroderma, arthritis, ulcers, gangrene, recurrent infections. These are only present in the minority of the cases, for the disease usually reaches a standstill and doesn't progress to these complications.

(9) Cure of uncomplicated cases by sympathectomy, and relief in complicated cases.

(10) Age around 25 to 45 years.

(11) Associated functional disturbances (25% of cases) as hysteria, constitutional biologic inferiority, excess nervousness, chronic exhaustion, and neuroses.

(12) Pain absent or mild.

(13) Symptomatology: - Recurrent episodes of discoloration of digits (pallor, cyanosis, rubor) and intervening periods of entirely normal color. The disease may remain stationary or improve; or it may progress with increase in the number of episodes of discoloration, the episodes last longer, disappear less completely, cyanosis may be more or less constant, and years later complications (such as punched out ulcers or gangrene) may occur.

(14) Hands are most often involved; next feet; rarely nose, ears, or chin.
Differential Diagnosis

(15) Lowering of the environmental temperature or emotional upsets cause the attacks.

(16) No postural color changes, intermittent claudication, phlebitis, rest pains.

(17) X-rays often show atrophy of terminal phalanx.\[(77)(78)(79)(80)]

Erythromelalgia is another vasomotor condition which should never be confused with Buerger's disease, but often is. This disease described by Wier Mitchel is of unknown etiology; it is rather a rare vasomotor disease characterized by local vasodilation attacks. There are five fundamental criteria necessary to diagnose the disease.

1. Bilateral burning pain in the extremities.
2. Sharp increase of local heat in the affected parts, with redness, flushing and congestion of affected part.
3. Production and aggravation of the distress by heat or exercise.
4. Relief by rest, cold or elevation.
5. Augmented arterial pulsation during attacks.

Erythromelalgia comes on in paroxysmal attacks of bilateral pain, redness, swelling; motor, secretory and trophic disturbances occur occasionally and hyperesthesia commonly. The redness of the feet is aggravated by dependency and heat, and relieved by elevation and cold. The pain is of intense burning or deep aching type and is referred to ball of foot or heel, the paresthesias being confined to hyperemic areas. The redness is bright with an intense bluish tinge and is accompanied by increased arterial pulsation.
Differential Diagnosis

and distention of peripheral veins. The skin temperature is elevated and there is often swelling due to increased blood supply. Secretory disturbances as increased sweating during attacks, and trophic lesions as blebs, skin atrophy and dystrophies of the nails also may appear, but are rare. No intermittent claudication, ischemia, pulseless arteries or deep gangrene ever occurs. (80)(81)(94)

Arteriosclerosis, no matter of what etiology, is the commonest organic disease from which thrombo-angiitis obliterans must be differentiated. It must be remembered that in Buerger's disease 50% of the people are Hebrews; superficial phlebitis is often an early symptom; there is very little or no sclerosis in the arteries shown by X-ray plates; most patients are from 25 to 55 years of age; rubor is intense; retinal vessels show no pathology; and evidence of general arterial disease is not present. In arteriosclerosis, there is no racial preference, the age is from 50 to 85; no superficial phlebitis is present; definite evidence of arteriosclerosis exists in peripheral and central arteries, as in the fundus and central nervous system; calcified arteries are seen in X-rays of extremities; the gangrenous ulcers are dry; and rest pains are mild. It must always be remembered, however, that arteriosclerosis may be superimposed on thrombo-angiitis obliterans. (80)(96)(93)

Scleroderma, and especially sclerodactylyia, are skin diseases that might be confused with the trophic lesions of Buerger's disease. Scleroderma is a disease of the skin in which thickened, hard, rigid and pigmented patches occur. Scleroderma of the fingers or toes is called sclerodactylyia. Scleroderma is a chronic progressive disease with no pain or
sensory disturbances. It is commonly in the hands. Local asphyxia
dominates the picture before the sclerodermic condition. There is a
hypertrophy of the connective tissue of the corium which is soon followed
by pressure atrophy of the skin vessels and epidermic structures.

Scleroderma is more in women and involves the neck and breast
mostly. When it affects the hands, the patient complains of stiffness and
tension of the hand movements, and there is a brawny induration. Atrophy
of the phalanges generally follows the first stage of induration in sclero-
dactylia. All arteries pulsate normally and there are no inflammatory
symptoms. In the fully developed sclerodactylia, the fingers are symmetrically involved, become deformed, shortened and atrophied due to the
dermal connective tissue overgrowth which caused the strangulation of the
superficial vessels.(85)

Acroasphyxia or acrocyanosis are very rare vasomotor conditions
occurring in neurotic individuals. It is a vasomotor spasm with coldness,
numbness, and pallor of fingers or toes; no pain is present, but hyperesthesia
is common. It is often associated with pulmonary osteo-arthropathy.(82)

Finally, a few miscellaneous conditions must be borne in mind.
Luetic endarteritis leading to occlusion of the peripheral arteries of the
extremities is very rare, and can only be distinguished from Buerger’s dis-
ease by the presence of other evidences of lues (82). A case is reported
by Lapidus of a fracture of some metatarsal bones with evidence of mechanical
impairment of circulation in the digits due to hemorrhage and callous
pressing off the digital blood supply; this case was mis-diagnosed as
thrombo-angiitis obliterans. Emboli of cardiac origin often cause sudden
Differential Diagnosis

acute, unilateral pain which may be exceedingly hard to differentiate from an acute thrombotic type of Buerger's disease. Anourysm also often causes a confusing type of peripheral circulatory insufficiency.
<table>
<thead>
<tr>
<th>Pulmonary Dysfunction</th>
<th>Thrombo-Angiitis Obliterans</th>
<th>Arteriosclerosis</th>
<th>Raynaud's Disease &amp; Similar Conditions</th>
<th>Primary Erythromelalgia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest Pains</td>
<td>Usually severe</td>
<td>Usually mild</td>
<td>Usually absent</td>
<td>Mild to severe</td>
</tr>
<tr>
<td>Type of Rest Pain</td>
<td>Sharp, stinging</td>
<td>Aching</td>
<td>Absent</td>
<td>Burning</td>
</tr>
<tr>
<td>Appearance of Gangrenous Ulcers</td>
<td>Moist, inflamed; discharging</td>
<td>Usually dry</td>
<td>Small punched out areas in early stages</td>
<td>None</td>
</tr>
<tr>
<td>Superficial Phlebitis</td>
<td>30% of cases</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Age</td>
<td>Mostly between 25 &amp; 45</td>
<td>Mostly between 55 &amp; 85</td>
<td>Mostly between 17 &amp; 35</td>
<td>Mostly between 30 &amp; 50</td>
</tr>
<tr>
<td>Sex</td>
<td>Males - 99%</td>
<td>Males - 90%</td>
<td>Females - 95%</td>
<td>Females - 70%</td>
</tr>
<tr>
<td>Race</td>
<td>Hebrews - 50%</td>
<td>any</td>
<td>any</td>
<td>any</td>
</tr>
<tr>
<td>Roentgenogram of Arteries</td>
<td>Usually negative for sclerosis</td>
<td>Usually positive for sclerosis</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Color changes following exposure to cold</td>
<td>30%</td>
<td>15 – 20%</td>
<td>Always</td>
<td>Never</td>
</tr>
<tr>
<td>Temperature of Extremities</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Edema</td>
<td>Frequent</td>
<td>Infrequent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
</tbody>
</table>
As I have stressed before, elaborate apparati are not necessary to make a diagnosis of a peripheral vascular disease, in most instances, but as a last resort they may be of help. A few important measures will be discussed.

I. Spasm of vessels is often an important element in obliterative organic vascular disease. To test just how much of the occlusion is due to arteriospasm, it is simplest to observe the effect of temporarily paralyzing the sympathetic vasomotor fibers. This is done by using local anesthesia to interrupt these fibers at some point between the central nervous system and the terminal vessels. When this is done in a normal individual, there is a marked increase in the local circulation which is shown by an increase in the temperature of the part; but in occlusive vascular disease without spasm there is no increase of the deficient flow under these conditions. Thus if vasoconstrictor spasm plays an important role in producing the circulatory impairment of thrombo-angiitis obliterans, the blood flow is improved in the anesthetic field, and the amount of improvement is in direct proportion to the amount of spasm causing occlusion. This test makes an excellent differential diagnostic means between Raynaud's and Buergar's disease, for in Raynaud's the response after anesthetizing the nerve is up to the same level as normal, while in thrombo-angiitis obliterans the response never reaches normal. It has been found that early in the latter disease spasm plays a larger part in the production of the ischemia (and it is in these cases that sympathectomy produces good results) but later the thrombotic process becomes so extensive that only an insignificant amount of spasm is found. Thus the treatment is
quite different in these cases.\(83\)(90)

II. Special surface temperature recording devices may be used to determine variations of temperature between extremities.

III. Pachon Oscillometer is an instrument which accurately records the amount or presence of arterial pulsation in a part. It consists of a rubber arm cuff connected to a delicate recording apparatus, which graduates the amount of pulsation which is pumping against the elastic cuff around the extremity being tested. Samuels (94) has pointed out that many erroneous diagnoses have been made in persons on whom no pulsation of the dorsalis pedis artery could be felt on palpation, yet the oscillometer index was at least 15, a high normal. Such errors (which might be due to an anomalous position of the artery) would be eliminated if the oscillometer were used routinely. The oscillometer is also a good prognostic instrument, for if it shows pulsation at the ankle, prognosis is good for relief of symptoms, even if ulceration and gangrene are present. If it shows no pulsation, the prognosis is very poor.\(86\)

IV. To determine if radial or ulnar arteries are obliterated distal to the wrist: have patient hold clenched fists in front of him for about two minutes. Then make pressure on the radial arteries of both hands. Suddenly have the patient release his clenched fists and open his hands wide. If the ulnar arteries are good the pallor will soon be replaced by reactionary rubor, even if the radials are still occluded. If the ulnar arteries are occluded, pallor persists. By repeating the test but compressing the ulnar arteries, the patency of the radial arteries can be determined.\(91\)
V. To determine slight obliteration of vessels of the feet: with patient lying down, flex his legs to 90°; then have him alternately flex and extend his feet on the ankles. If there is even slight occlusion of the arteries, plantar ischemia or toe pallor will appear. Generally it is not symmetrical or not of the same degree on opposite sides. In mildest cases, pallid blotches appear on the normal pink.(92)
A British, white, male, age 29, was a traveler for a tobacco firm for many years. He went to war, and after being discharged at the end of the war, he began to complain of flat feet, which he attributed to his army training. Some time later he began to be troubled with pain in the right calf suggestive of intermittent claudication. This pain was believed to be due to fallen arches. The patient was fond of dancing but two years ago had to give it up; even when golfing he frequently had to sit down and rest. The pain was a cramp-like affair with no sense of numbness. He was never ill in his life. There was no history of chest trouble or venereal disease. He smoked about 25 cigarettes per day.

On May 12, 1927 he was admitted to the Royal Infirmary, Aberdeen, suffering from pain in the right toes. Six months before admission he complained of coldness of the right foot. Shortly after this he tried to cut a corn on his little toe with a safety razor blade and it became septic and failed to heal. The toe became blue and later black.

Physical examination showed the man to be in good general health. Both femoral arteries showed feeble pulsations. The popliteal arteries and other arteries below showed no pulsation. The right little toe was black and gangrenous, the big toe was bluish, and the rest dusky. The skin over the toes did not appear healthy. The urine was negative.

On May 14th, the outer two toes were removed at the metacarpal phalangeal joints, but this gave no relief. May 23rd the leg was amputated at the junction of the middle and upper thirds. The wound healed well. The excruciating pain for which the patient had to sleep with his leg hanging down over the bed was completely relieved. Girwood (96)
Case Histories

This case illustrates the following points: (a) Contact with tobacco and heavy smoking as etiologic factors (b) Flat feet being the common diagnosis first to be made in obliterative vascular disease of the extremities (c) The frequency of corns and the ill-advisability of any surgical incision in a foot with poor blood supply, (d) The necessity of high amputation to obtain relief in severe cases.
Case Histories

II.

J. S., 48, Russian Jew, storekeeper, came into the Beth Israel Hospital for the second time complaining of sudden onset of loss of motion and weakness of the right arm and leg, and some dysarthria. He fell a number of times and he noticed that his speech was slow and thick.

Past history revealed that he was operated for duodenal ulcer ten years ago, a gastro-enterostomy being performed. His symptoms were not relieved and six months later he was operated for gastro-jejunal ulcer. Soon after, he began to complain of severe pain in the calf of his right leg on walking, and a more or less constant pain and numbness in the toes of the right foot. Three years later he developed gangrene of the third toe of the right foot which was soon amputated. The pain continued, and he developed gangrene of the second toe, and amputation below the knee was done. He soon recovered and was sent home. Two months later he re-entered the hospital complaining of severe bleeding hemorrhoids that caused such a severe secondary anemia that transfusion was necessitated. The hemorrhoids were removed. Soon after, he began to complain of some mild pain in the calf of his left leg, and the pulsation of the dorsalis pedis was not felt.

Physical examination at the time of entrance showed a well-developed man, cooperative, rational, with thick and slurring speech. His mouth was pulled over slightly to the left. Pupils were negative. Tonsils were large and slightly reddened. Heart, lungs and abdomen appeared normal. B. P. 114/60 The right knee jerk was more active than the left. No abdominal reflexes on the right, and no cremasteric reflex on the right.
Babinski, Oppenheim, and Gordon reflexes were present on the right. The grip of the left hand was stronger than the right. The patient was unable to move the stump of his right leg.

Laboratory: Wasserman, neg., R.B.C. 5,500,000, Hb. 80%, W.B.C. 7,000, Differential count, normal.

Diagnosis: Cerebral thrombosis of the same type as thrombo-angiitis obliterans of the legs, for no signs of arteriosclerosis were present anywhere. Linenthal & Barron (30)

This case illustrates that thrombo-angiitis obliterans can attack vessels other than those of the extremities. The diagnosis is made generally by a history of the disease in the extremities previously.
Case Histories III

L. S., male, plasterer, 45, came to the hospital complaining of paroxysms of pain in the chest which radiated to neck, chin, left arm and wrist. The pain was accompanied by a sense of constriction about the chest, and came in short paroxysms. Past history revealed that the man had typhoid fever fifteen years before; the rest of his history was inconsequential. He had smoked occasionally for several years. Physical examination showed nothing but hypertension (190/110) but this returned to normal in a year's time. Two bad teeth were removed; later tonsillectomy was performed. He was diagnosed as angina pectoris. His attacks grew less frequent and by a year or two had stopped. A year after he was apparently cured, he had a mild attack of hemiplegia which cleared up very soon with but little residue of disability.

One year later he was seized with a severe pain in his left foot and leg which pain was brought on by walking. He also had a tired feeling in his legs; postural color changes and pulseless arteries were later found. He became very debilitated, and died of cerebral thrombosis within a few months. Lawson (38)

This case illustrates the point that the pathology of Buerger's disease is not limited to the vessels of the extremities, but may involve other vessels, as the coronary or cerebral vessels.
A Scotch lawyer with thrombo-angiitis obliterans had been under the observation of the Mayo Clinic since 1924 at which time he was 30 years of age. A letter from his local physician stated that in January, 1926, he found the patient in collapse, semi-conscious, bathed in cold perspiration and pulseless, with heart rate of 44 per minute. The recovery from the attack was incomplete and two hours later a second similar attack occurred. The precordial pain was severe for the following 24 hours, and this time he vomited twice. During the week before the attack he had slight attacks of retro-sternal pain with dizziness and shaking sensations. On examination in the Mayo Clinic in April, 1926, the heart tones were indistinct, B.P. 119/68; Pulse 80; the electrocardiographic record showed right ventricular preponderance and T wave negativity in the third lead. In December, 1927, while the patient was at home, he had a severe attack but with less pain. He died in five hours. Autopsy was not permitted. Allen and Willius (43)

This case also illustrates the frequency of extra-extremity involvement of vessels in thrombo-angiitis obliterans, and also brings up the possibility of many of these coronary syndromes without disease in the extremities being on a thrombo-angiitis obliterans basis.
P. S., aged 28, Russian Jew, a produce buyer, moderate cigarette smoker, consulted Dr. McGregor on December 14, 1927, complaining of dull, gnawing irritation over the penis, left half of the scrotum, and lower abdominal wall. This recurred daily and lasted for two to three hours, but was not severe enough to interfere with his working.

Past History: On November 15, 1927 the left testis was a little swollen and very painful. The doctor confined him to bed for four days. There was no history of lues or Neisserian infection.

Examination revealed that the left testis was smaller than the right, and the epididymus contained two nodules in the caput and one in the cauda. The cord was thickened proximally. The sensation in the testis was normal. Other systems were normal. Laboratory findings showed the Wasserman to be negative, and the cutaneous tuberculin test positive.

A confident diagnosis of tuberculous epididimitis was made and operation was advised by a urologist. The operation was performed and the testis and cord up to the internal ring was removed. The patient made a good recovery.

On pathological examination, the vas was found normal, the apparent thickening of the upper part being due to firm adhesions of many blood vessels to the periphery of the vas. Microscopic study proved the case to be thrombo-angiitis obliterans of the cord. No abnormalities of the peripheral vessels were found after the report was made, the extremities not having been tested before.
Case Histories

Post operative progress: Slight shooting pains of the right cord were felt which later decreased and disappeared. McGregor and Simpson (46)

Although it was almost impossible to diagnose this case before pathological study, still the case was clinically not typical tuberculous epididimitis, for this disease is usually painless, and thickening of the cord usually occurs first at the lower, testicular part of the epididimus. This case illustrates the peculiar localities which Buerger's disease may strike; perhaps these atypical cases may be more common than we think but are never diagnosed.
A. S., a man of 37 years of age, metallurgist, entered the Mayo Clinic May 25, 1926 complaining of pain in the right arch with exercise. Eight months previously a small ulcer had appeared spontaneously on the distal surface of the second toe of the right foot. It grew larger and a similar lesion appeared on the dorsum of the fourth toe of the left foot, but it healed with treatment locally. Roentgen rays, hot packs, and irrigations with Dakins solution did not change the course of the ulcer on the right second toe; it became painful following a sudden onset of bluish discoloration of the entire toe. The toe was amputated elsewhere, and healing was uneventful, but severe pain occurred in the right arch; it was brought on by exercise, relieved by rest. No superficial phlebitis nor excessive calf fatigue was present. All arteries of the upper and lower extremities pulsed normally; the toes of both feet showed pallor of the second degree on elevation, and second degree rubor when dependent. Laboratory data was insignificant.

A diagnosis was made of thrombo-angiitis obliterans of the vessels of the foot distal to the point of normal pulsation. A section of the amputated toe showed complete obliteration of digital artery by a mass of tissue containing a moderate number of fibroblasts. Newly formed vessels were present in the surrounding tissue. The occluding mass was thought to be the proliferating intima. Allen and Brown (97)
This case emphasizes the fact that Buerger's disease may be present even though all peripheral vessels have normal pulsations, and without intermittent claudication in the calves. Claudication in the arch, postural color changes, and trophic changes should cinch the diagnosis in this case.
In this thesis I have attempted to describe thrombo-angiitis obliterans in such a manner that one unfamiliar with the disease may get a correct conception of it. I have pointed out the outstanding symptoms, the pathology causing these symptoms, and the diseases with which it may be confused. Special attention was paid to the differential diagnosis between vaso-motor and organic diseases of the extremities. I hope that I have shown that vascular disease of the extremities is not in a deplorable state of confusion (as is thought by many) but that the confusion is only on the part of those individuals who have not studied and looked into the problem to sufficient lengths.
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