1943

Thromboangiitis obliterans : its etiology and pathogenesis

Joseph Delmar Beck
University of Nebraska Medical Center

THROMBOANGIITIS OBLITERANS:

Its Etiology and Pathogenesis

by

JOSEPH D. BECK

SENIOR THESIS

Presented to the
College of Medicine,
University of Nebraska
Omaha, Dec. 1943

TABLE OF CONTENTS

INTRODUCTION

The task of selecting a topic for a senior thesis has been for the most part a bewildering one to me, and I am sure, to my fellow classmates. Those who have passed before us have adequately limited the field and scope of our endeavor. Some of us have chosen current subjects such as have arisen out of four years of World War II. I can not, however, make claim to such originality and it is with apologies that I offer my paper, upon a subject ofttimes reviewed by my predecessors at the University of Nebraska College of Medicine.

In anticipation of the day when I must make such a selection, I have for some time toyed with the idea of a topic from the realm of peripheral vascular disease. I think my interest in this fertile field was first stimulated by a paper presented at the last meeting in Omaha of the American College of Surgeons. Lt. Col. Edgar V. Allen's paper was one based upon personal experience and observation at the Mayo Clinic and dealt in general with the whole field of peripheral vascular disease. The scope of Dr. Allen's paper is obviously too vast to

be considered in a paper of this kind. It is with consideration of this fact that I have been forced to make very definite limitations, and I admit that this thesis is confined to what will seem an infinitesimal part of peripheral vascular disease.

I have chosen for my subject Thromboangiitis Obliterans, with special reference to its etiology and pathogenesis. I have attempted to review all of the literature pertinent to this controversial topic and will endeavor to present such material as I deem noteworthy.

HISTORY

The clinical entity now known as thromboangiitis obliterans is certainly not one of recent origin; yet, we find that little was known of the disease prior to the turn of the century. It seems probable that it had been described many times in the literature under the general term, spontaneous gangrene of the extremities. A detailed history, therefore, is impossible in view of the scope of so-called spontaneous gangrene, which necessarily included diabetic and arteriosclerotic gangrene as well as thromboangiitis obliterans, Raynaud's disease and others. It was not until an adequate description of the pathology had been made that thromboangiitis obliterans became a definite clinical entity, and thus emerged from the realm of confusion.

The fact that this disease was poorly understood is perhaps best exemplified by the great variety in nomenclature to which it has been subjected. It has been designated acroparesthesia, multiple neurotic gangrene, sclerodactlia, scleroderma, Russian disease, Jewish, Yiddish or Jiddaesche Disease, Friedlander's disease, Raynaud's disease, non-syphilitic endarteritis

obliterans, psuedo-erythromelalgia, paralysie vasomatrice des extremities, acrophacelus, acroasphyxia, acrocyanosis, local asphyxia of the extremities, obliterating endarteritis, spontaneous gangrene, presenile gangrene, juvenile gangrene, Gängstockung, intermittent claudication, erythromelalgia, dysbasia angiosclerotica, and Buerger's disease. (Jablons, 1925; Bean, 1923).

Felix von Winiwarter is said to have been the first to describe this disease. He(1879) reported the case of a fifty-seven year old male who developed spontaneous gangrene of one extremity in which amputation was necessary. After studying the vessels of the amputated limb von Winiwarter designated the process endarteritis obliterans. He had concluded erroneously that the pathogenesis was due to intimal proliferation which led to complete occulsion of the vessel.

A few years later Wwedensky(1898) reported the high incidence of an obliterating type of arteritis in certain regions of Russia where the climatic conditions were particularly severe. His description of the clinical course of this so-called arteritis obliterans is such that these cases appear to have

been what is now recognized as thromboangiitis obliterans.

Buerger(1908) was the first to accurately describe the pathology of the disease and the first to recognize it as a distinct clinical entity. He was able at this time to report some thirty such cases. It was he who gave this disease the name it now bears and out of courtesy to him it is often referred to as Buerger's disease.

DEFINITION

Thromboangiitis obliterans is a chronic disease of the peripheral arteries and veins occurring chiefly in adult males; characterized clinically, by intermittent claudication, postural color changes, and trophic disturbances and pathologically, by inflammation, thrombosis and organization.

The whole symptom complex of this disease is one directly attributable to a failing peripheral circulation. It may best be summarized by a quotation from Buerger(1924): " So then it may be correctly said that patients afflicted with thrombo-angiitis obliterans do not usually suffer from the disease itself but from the disastrous occulsive thrombosis which signalizes Nature's method of healing a vascular lesion that has long since disappeared." A period of claudication induced by exercise is usually the first manifestation of the disease, appearing in varying degrees from a mild sense of excessive fatigue to distinct cramp-like pains. Postural color changes signified by rubor in the dependent position becomes evident as the circulatory disturbance progresses. Finally, trophic disturbances appear in the form of fissures, non-healing ulcers and frank gangrene.

The superficial veins of the lower and upper extremities are those characteristically involved; however, the occulsive process may occur at any site in the vascular system. Buerger(1924) observed the typical lesions in the spermatic vessels. Hauser and Allen(1940) reported from a series of five hundred patients afflicted with thromboangiitis obliterans, coronary involvement in fifty-seven per cent and cerebral vascular involvement in two per cent of the cases. Buerger(1924), who is responsible for much of our present concept of the disease, has emphasized two pathological stages which correspond with definite phases of the clinical picture. One, the healed stage, in which thrombotic occulsion has given away to organization and canalization, corresponds with active symptomatology. The second, the acute stage, corresponds with definite evidence of an inflammatory process. He enumerates the lesions in chronological order as follows:" (1) an acute inflammatory lesion with occulsive thrombosis, the formation of miliary giant cell foci; (2) the stage of organization or healing with the disappearance of miliary giant cell foci, the organization and canalization of the clot, and the disappearance of the inflammatory products; (3) the development of fib-

rotic tissue in the adventitia that binds together artery, vein and nerves." The lesion of the affected vessel varies with the duration of the process in both its gross and microscopic appearance. Grossly, early changes consist of thickening of the wall, induration of the adventitia and varying degrees of thrombosis. Microscopically, the acute stage is essentially that of an inflammatory reaction with polymorphonuclear infiltration plus the formation of a red clot in the lumen. Foci of giant cells are pathognomonic of this stage but they later undergo replacement fibrosis. This fibrotic process finally produces the total occulsion of the healed stage, and organization takes place by virtue of the small vessels included within the proliferating connective tissue.

Strangely enough Nature apparently has no time schedule to meet in the repair of these vascular lesions. Weeks, months or even years may elapse between the onset of the inflammatory process and the trophic disturbances which mark the terminal stage.

It will have been noted that no mention of etiology was included in the definition. That was an intentional omission on the part of the author, not an over sight. The question of the etiology of

thromboangiitis obliterans has been and still is a controversial one. It is with a hope of clarifying some of the possible etiological and developmental factors that this paper is presented.

ETIOLOGY AND PATHOGENESIS

Trite as the saying may be, it still holds that until the cause of a disease is understood, preventive measures and therapeutics are at best experimental. The more complex and baffling the problem, the more varied will be the theories and concepts expounded to explain that particular situation. The etiology of thromboangiitis obliterans serves as an excellent example of medical science's search for an unknown entity.

We will consider here those concepts advocated in the literature and designed to explain the origin and development of the disease. They will be presented separately with respect to what the author considers they contribute to the subject as a whole.

Infectious origin: Buerger(1908), in view of his work upon the pathological process, concluded that the disease is essentially inflammatory in nature. He was, however, unable to demonstrate the irritant. The perivascular changes suggested the Spirochaeta pallida as a possible etiological agent. This supposition was later discredited by Buerger(1910) at which time he had increased his original series of thirty cases to eighty.

Working with Oppenheimer he was able to demonstrate syphilis in but two of the eighty patients. Twenty nine of the cases, followed over a period of one year, repeatedly showed negative complement fixation tests. It remained for Smith(1927) to reawaken the question of syphilis as an etiological agent. Smith considered Buerger's report excluding syphilis inadequate in view of the number of cases which were not given complement fixation tests; remarking that in most instances the disease had been excluded merely upon a basis of failure to find the spirochete within the affected vessels. He reported a case of thromboangiitis obliterans in a British subject which appeared to be of syphilitic origin. He failed, however, to support his contention in subsequent articles. It would seem, therefore, that the occurrence of thromboangiitis obliterans together with syphilis in the same patient is purely coincidental.

After repeated failure at isolating a causative organism, Buerger(1914) stated that he thoroughly believed this disease to be of infectious origin in which a specific type of organism is the etiological agent.

Goodman(1916) formulated an interesting hypothesis following a visit to Breslau where he noted the

relative frequency of thromboangiitis obliterans and typhus in soldiers, who had participated in the Bulgonian campaign. He attempted unsuccessfully at this time to show a serological relationship between these concurrent diseases. Undismayed by his unfavorable results, Goodman(1937) reported that he still holds to his original hypothesis. He has developed a cutaneous test which, being uniformly positive in persons who have had typhus or Brill's disease, is almost uniformly positive in those suffering with thromboangiitis obliterans and negative in a group suffering from arteriosclerosis and diabetes melitus. Wolbach(1922) described the pathological process of typhus as a distinct condition of the blood vessels, particularly those of the skin and central nervous system, beginning as a proliferative reaction of the endothelium followed by thrombosis and possible complete occulsion. When we consider the difficulty encountered in the culture of the Rickettsial organisms, it becomes evident that further investigation of this group might be fruitful.

Rabinowitz(1923) believed after ten years of studying the disease that its infectious origin is manifest in all its stages. His convictions were

based upon observations that increased blood supply via transfusion does not bring relief to persons afflicted with thromboangiitis obliterans. This statement was contrary to one previously advanced by Buerger that the symptomatology of the healed stage is a mere manifestation of vascular occulsion. By the use of leeches applied to the aseptically prepared limb of a patient, Rabinowitz was able to isolate specific organisms. He described these organisms as gram negative, aerobic, facultative anaerobic, fully motile bacilli, mediumsized, rod shaped and beaded, bipolar in appearance and containing metachromic granules. The injection of a pure culture of this organism, according to Rabinowitz, reproduced the same lesions in the ears of rabbits as that present in thromboangiitis obliterans. Rabinowitz's work proved an impetus for further investigation.

Buerger(1929) said it is possible to reproduce the lesions seen in acutely affected veins by transplanting their coagulated contents into the apparently normal lumen of a ligated vein. Henery(1923)reported a persistent leukocytosis in an early case of the disease. This finding would tend to substantiate the

infectious theory but unfortunately its incidence has not been reported a second time in the literature. Allen and Lauderdale(1936) gave support to Buerger's report of intentional transmission. They cited the case of a Scotish surgeon who was an accidental victim of the disease by transmission. The history revealed that the surgeon had accidentally pierced the third finger of his right hand with a spicule of bone while amputating the toe of a patient afflicted with thromboangiitis obliterans. No local reaction resulted from the accident; however, one month later color changes consisting of cyanosis and pallor on exposure to cold appeared on that particular finger.

Horton and Dorsey(1930) attempted to confirm the work initiated by Rabinowitz. They were able to obtain in pure culture nine cases with gram positive pleomorphic streptococci and two cases with a green producing streptococci from affeted arteries and veins. Innoculation of these organisms into rabbits and dogs produced the typical lesions of thromboangiitis obliterans in a small number of rabbits. They were not in any instance able to recover the organisms from test animals and thus satisfy Kock's postulates. Two years later these same investigators reported

similar findings from a series of seventeen cases; four of which produced the pleomorphic streptococci, two, the green producing streptococci. Other cultures yielded staphylococci and gram positive bacilli. They were also able to isolate gram positive pleomorphic streptococci from the vessels of extremities amputated from ten patients with arteriosclerosis. These streptococci proved to be morphologically identical and for the most part had the same cultural characteristics as those cultured from the vessels of patients with thromboangiitis obliterans.They concluded, therefore, that if any significance can be attached to these organisms, emphasis should be placed on the pleomorphic streptococci. The other organisms probably represent contamination or the secondary invaders to a gangrenous process.

Brown, Allen and Mahorner(1928) advocated foci of infection as a possible etiological factor. They found only three of forty-six cases were free of demonstrable infection in teeth, tonsils or the prostate gland. In view of the preponderance of the disease in males, they suggested that an infectious origin from the prostate is entirely possible, since the incidence of foci of infection in other tissue common

to both sexes is equal.

The consideration of fungi as [illegible] possible causative agents brought a new concept within the scope of infectious etiological factors. Kaunitz (1932) thought ergot worthy of investigation. He had observed that the incidence of the disease is higher in Russia, Poland, Ukraine, East Prussia and other areas where rye bread constitutes a staple article of diet. Rye is known to be especially prone to contain ergot. He admitted that little was known of the pathology of ergot, which appears to be a contraction and thickening of the vessel with thrombosis of the lumen, and followed by gangrene of the extremity. The lesions are more acute in ergotism, yet it is possible to correlate some of the vascular changes with those occurring in thromboangiitis obliterans. Kaunitz(1930) attempted to produce vascular lesions experimentally in roosters. He reported that he was able to produce a lesion of the comb much the same as that seen in thromboangiitis obliterans. He admitted, however, that he did not know the constituent of ergot which has the toxic effect upon the vascular system. He felt that it is not either ergotamine or ergotoxin but rather the putrefactive substances, histamin,

tyramin and the choline bodies. Tyramin acts pharmacologically as a powerful arterial constrictor, while histamin acts as a capillary dilator. In conclusion he suggested that extensive studies of ergot and its constituents might throw new light on the subject. McGrath(1935) attempted to confirm Kaunitz's work using injections of ergotamine tartrate. He was unable to state that the lesions so produced definitely were identical with those seen in thromboangiitis obliterans. This does not necessarily eliminate the possible significance of other constituents of ergot. Further research into this subject has not been recorded in the literature, so final judgment has not yet been made.

Thompson(1941) was of the opinion that dermatophytosis should be investigated as a possible cause of vascular disease. He had no experimental evidence with which to support his theory, so it was forthe most part based upon speculation. He attempted to explain his hypothesis by a body sensitivity to a fungus antigen, and remarked that the Shwartzman reaction is often accompanied by hemorrhagic lesions. He rationalized that dermatophytosis, like tuberculosis, is a universal disease, yet the average individual is able to combat

tuberculous infection successfully. Therefore, it is possible that certain sensitive individuals may develop vascular lesions as a response to dermatophytosis while others do not. Naide(1941) is of a similar opinion. He seems to have made some actual clinical investigation while working in the perivascular clinic at the University of Pennsylvania. He found a higher incidence of dermatophytosis and more frequent reaction to trichophytin in those with thromboangiitis obliterans than in control groups. He also states that he has observed patients in whom acute dermatophytosis immediately preceded attacks of migratory phlebitis.

The literature thus reveals much that would tend to suggest that thromboangiitis obliterans is of infectous origin; yet, nothing really conclusive has been uncovered. Colonel Edgar V. Allen(1943), who is perhaps one of the world's leading authorities upon diseases of the peripheral vascular system, is of the opinion that the disease is due to a specific bacterial organism or virus. He readily admits, however, that he has no definite evidence which would support his contention.

Tobacco: The introduction of a theory that tobacco may have etiological significance in the production of thromboangiitis obliterans opened a new field for speculation and research of which investigators have written copiously. Earlier workers attempted an explanation largely upon the direct response of the cells of the sympathetic nervous system to nicotine as shown by Langley(1905). A more recent contribution has arisen in the field of allergy.

Buerger(1924) had early come to regard tobacco as a probable predisposing factor, although one per cent of his cases denied smoking in any form. He did not believe tobacco to be the sole etiological agent. He stated that the use of tobacco may render the vessels more susceptible to toxic agents. Meyer(1920) came to believe that abuse of tobacco is primarily responsible for the disease, thromboangiitis obliterans. The secondary vascular changes, according to Meyer, are the result of tobacco toxins in the blood stream which consist of nicotine, pyridine, cyanic hydrogen, carbon monoxide and other poisons. It appears that his opinions were largely influenced by those of his contemporaries because two years previously he had reported glycophilia to be the real

causative factor. Frauenthal(1920) did not agree that tobacco is of importance in the production of the pathological state. He pointed out that if it were a significant causative agent, the disease should then be common in the American Indian, who was to be sure a heavy smoker. Brown(1932) was of a similar opinion and stated that the disease is seldom seen in cigar or pipe smokers, although the tobacco in one cigar is equivalent to eight or ten cigarettes. Colonel E. V. Allen(1943) has said that from his experience with such cases at the Mayo Clinic he believes tobacco to be more importance therapeutically than etiologically. He had previously observed, in conjunction with Brown and Mahorner, that the incidence of thromboangiitis obliterans has not increased in women in recent years despite a very marked increase in women smokers.

The field of allergic response and hypersenitivity is one still in its comparative infancy and one that is receiving ever increasing attention in the field of medical research. Harkavy was one of the first to call attention to an allergic reaction as a possible causative agent in the production of thromboangiitis obliterans. His work has since stimulated the interest of other investigators. Klein,

Cohen and Rudolph(1932) noted the characteristic histological picture of an allergic response and thus provided a basis for reading skin tests. They pointed out that an eosinophilic exudate, reaching its height in half an hour, is the most characteristic sign of an allergic reaction following intradermal injection of an antigen. Harkavy(1934) attempted to show the relative skin reactions in persons suffering from thromboangiitis obliterans and in control smokers. He found eighty-nine per cent of one hundred and three cases of the former group were skin positive: while only twenty per cent of three hundred contols were skin positive. The same year he carried on an investigation to demonstrate the relative skin sensitivity to tobacco pollen and tobacco seed in the two groups. He found that of the control group thirty-two percent reacted to tobacco seed and pollen, while thirty-eight per cent reacted to extracts of the leaf. Fifty-nine per cent of those afflicted with the disease reacted to the pollen and seed, while seventy eight per cent reacted to the extract of the tobacco leaf. In the control group, however, no reaction to tobacco pollen occurred without a concomitant reaction to other pollens. He interpreted these concomitant

reactions to be part of a general allergic response, characterized by multiple sensitization. In general, skin reactions in those suffering from the disease occurred six times as frequently to tobacco pollen as to pollens of ragweed and timothy hay. Harkavy (1938) later attempted unsuccessfully to demonstrate a difference in the allergic response to tobacco antigen and other common antigenic substances.

Sulsberger(1934) confirmed Harkavy's statement that persons suffering with thromboangiitis obliterans show allergic skin reactions to tobacco twice as commonly as normal subjects. He considered this evidence highly suggestive that the disease is in some manner associated with hypersensitiveness to tobacco. He pointed out that certain allergens are known to involve certain tissues and even those specific tissues within localized areas of the body. Thus, he concludes that the tobacco allergen may logically have a predilection for the peripheral vessels of the extremities.

Friedlander, Silbert and Laskey(1936) were able to produce gangrene in the toes of thirty-three of a total of forty-eight rats by the injection intraperitoneally of sixty per cent denicotinized tobacco.

It is interesting to note that they were only able to produce this effect in male rats. Twelve female rats were unaffected by such a procedure. The question of the incidence of thromboangiitis in the two sexes will be considered later.

Trasoff, Blumstein and Marks(1936) attempted to carry on the work initiated by Harkavy, but they found that they could not justify his contention that hypersensitiveness of the vascular sysyem to tobacco is the mechanism concerned it the pathogenesis of the disease. They were forced to explain the effects of tobacco upon the pharmacological action of nicotine. They concluded, therefore, that the vasoconstriction, increased pulse rate, increased blood pressure, and decreased surface temperature are all due to the action of tobacco and its derivatives upon the sympathetic nervous system.

Maddock, Malcolm and Coller(1942) carried on a series of experiments in order to determine whether persons who show skin sensitivity to tobacco have a greater vasoconstriction from smoking than those who are skin negative. They found that smoking causes the same decrease in surface temperature in men and women, and that smoking causes a more marked decrease

in surface temperature in Jewish males than in Gentiles. They concluded that the harmful effect of smoking as manifest in thromboangiitis obliterans is the result of decreased blood supply to an already ischemic area, not the result of an allergic vasoconstriction.

Westcott and Wright(1938) were able to demonstrate nothing of significance by the use of skin tests in a series of thirty-five cases. They regarded the positive skin reactions reported by Harkavy and Sulsberger to be the result of non-specific irritations.

Silbert(1942) was under the impression that tobacco plays an important role in the management of the disease at least from a clinical and therapeutic standpoint. In reviewing a series of thirteen hundred cases, he states that in no instance was a typical case seen in a non-smoker. He has observed that the cessation of smoking while still in the early stages of the disease has brought marked relief of symptoms and improved circulation to many patients.

Brown, Allen and Mahorner(1928) were of the opinion that tobacco is not the sole cause of thromboangiitis obliterans but that evidence strongly

points toward it as a contributory factor.

Metabolic Disturbance: The possibility that some metabolic disfunction may play a role in the production of thromboangiitis obliterans is one which has received consideration from time to time. Ochsner (1915) was perhaps the first to attribute the disease to a disturbance of metabolism. He thought an inability of the body to handle a diet high in salt, such as that of the Swedish and Jewish peoples, might be contributory.

Meyer(1918) studied the blood chemistry of patients afflicted with the disease and postulated a theory of glycophilia; which, however, he abandoned two years later. His idea was that the hyperglycemic state produced increased blood viscosity which resulted in occulsion by "erythrocytosis and stasis". He naturally concluded that a defective carbohydrate metabolism was the causative factor. Meyer's theory was shattered by Bernhard(1920), who found that ninety two per cent of his cases had a normal glucose tolerance curve, while three of fifteen cases actually had a decreased curve of tolerance.

Meyer's observation of increased blood viscosity was destined to receive more attention than that of

decreased glucose tolerance. Silbert, Kornzweig and Friedlander(1930) reported a series of sixty-nine cases of thromboangiitis obliterans in which they found an average reduction of blood volume of twenty-one per cent per kilogram body weight, with an apparent concentration of hemoglobin. They believed the blood to be generally concentrated in the disease. Friedlander and Silbert(1931) demonstrated a transient rise in blood volume by the use of thyroid extract.

This relative increase in blood viscosity eventually lead to the question of whether there is any relationship of thromboangiitis obliterans and polycythemia vera. A case in which the two diseases occurred concomitantly had been reported by Horton and Brown(1929). This apparent association was assumed to be coincidental by Norman and Allen(1937), who reported no incidence of thromboangiitis obliterans in ninety-eight cases of polycythemia vera studied at the Mayo Clinic.

The intravenous injection of insulin free pancreatic extract by Nuzum and Elliott(1931) was noted to produce some favorable therapeutic results.

They found that this extract inhibited the pressor effect of adenalin in experimental animals, and they believed that it effective in the relief of pain through a decrease in arteriolar spasm. Rabinowitz and Kahn(1936) were of a different opinion as to the basis of its therapeutic action. They believed the effectiveness of this extract to be due to its influence upon a disturbance in phospholipin metabolism. Their investigation leading to this belief is interesting, and their reasoning appears to be sound froma physiological basis. They found that persons with thromboangiitis obliterans have an increased amount of cephalin and lecithin in the blood as well as a decreased phospholipid content in the calf muscles. They reported the muscle content of phospholipin to be but one half that of normal for controls. They contend that the high content of cephalin in the blood would tend to explain intravascular clotting by reason of hemolysis and decreased coagulation time. Claudication, they contend, is not the result of impaired circulation but rather the result of muscle fatigue due to a deficiency of creatine phosphate. Furthermore, they maintain, increased plasma cephalin speeds up oxidative processes during exercise,

thus incurring an oxygen debt which results in a longer period of recovery. Finally, they believe the physiological basis for using insulin free pancreatic extract is sound since it may influence phospholipin metabloism. Favorable results have been reported from this type of therapy in fifty cases by King(1941).

It remained for the Mayo Clinic group, however, to bring forth evidence which makes this well organized theory of a faulty phospholipid metabolism appear to be of little consequence. Roth, Maclay, and Allen (1938) studied the blood chemistry of one hundred and five patients with thromboangiitis obliterans. They reported the blood levels for serum lecithin, serum phosphorus, serum calcium and serum protein all to be within normal limits, In most instances they found the blood volume was essentially normal. They doubt that any relationship exists between the disease and hemo concentration. These figures also tend to discount some work by Conwell(1933). Conwell had believed a subnormal serum calcium to be significant. He reported favorable results from the use of parathyroid extract subcutaneously given in conjunction with calcium gluconate orally. In view of some recent investigation, these results might be interpreted upon a basis of

the calcium gluconate alone.

Race and Heredity: Early writers considered the disease to be one limited to persons of Jewish descent. We find evidence ot this contention in the varied terminology. Jiddaesche Krankheit and Jewish Disease are specific examples within the varied nomenclature. Buerger(1908) remarked in his original monograph that the disease is one which appears to be limited to Hebrews. It was not long, however, as the disease came under wider study that reports were made of its occurrence in other peoples. Frauenthal(1920) stated that he had seen thromboangiitis obliterans in the inhabitants of all nations, and that it is not confined to Jews. Friedman(1920) reported the disease in Russians and Esthonians;Ochsner(1915), in the Swedish people. Forty cases were reported by Ludlow(1931) in Korea. Meleney and Miller(1925) reported the wide spread distribution in China, and twelve cases were recognized in the Siamese by Noble(1931). Telford(1924) reported four cases of thromboangiitis obliterans in patients of British descent. Orr(1925) reported six cases in non-Jewish patients in our neighboring state, Kansas. It would seem, therefore, that no great significance

can be attached to race or nationality, although the Jewish people do appear to be especially prone to the disease. Kaunitz(1932) remarked that more cases are found in the Jewish people but "the Jews are more prone to make known their ailments than more phlegmatic and less sensitive peoples". The literature as yet has offered no explanation for the apparent predilection in Jewish people.

Thromboangiitis obliterans and susceptibility to the disease are believed not to be inherited. Jablons's(1925) series of cases totaled thirteen hundred of which he had observed only six that were related. Sounds(1932) observed three families in which the disease occurred in brothers in five hundred cases, but was unable to elicit no family history of thromboangiitis obliterans in any instance. Weber(1937) reported that he was caring for a Hebrew cabinet maker, age fifty-eight, and his son, age thirty-three, both of whom were afflicted with the disease. Heredity appears, therefore, to have no significance.

Climate and Country of Birth: In view of the general consensus of opinion, climate and country of birth are of little importance from an etiological stand-

point. The literature reports the prevalency of the disease in all parts of the north temperate zone. Some emphasis has been placed upon the climate in those areas where the winters are particularly severe, but thromboangiitis obliterans is by no means limited to those regions. With the exception of Noble's report of the disease in Siam, no example of the incidence in the tropics has been cited.

Place of birth was for a time considered contributory, yet such now seems improbable. Thromboangiitis obliterans is now believed to be a universal disease. Meleney and Miller(1925) reported a fairly even distribution through out all parts of China. Much has been written upon the incidence in central and eastern Europe. Many cases have been recorded in the British Isles and cases i n the United States are numerous.

Sex: Thromboangiitis obliterans is described in the text books as a disease of adult males. This perhaps denotes the influence of Buerger's early conception of the disease. It is now known not to be confined to the male, although it is found to a great preponderance in the male sex. The literature reveals many

instances of sporadic cases occurring in women. The apparent predilection for the male has naturally given rise to the question of a possible hormonal influence which protects the female from the ravages of the disease. Working upon this assumption McGrath (1935) was able to protect female rats from the gangrene of ergotism by the injection of theelin, but could produce no such protection in male rats. Little significance can be attached to McGrath's work because he was unable to demonstrate an etiological relationship between ergotism and thromboangiitis obliterans. The intraperitoneal injection of nicotine was shown to produce gangrene of the toes of male rats while female rats were unaffected. (Friedlander, Silbert and Laskey,1936).

Froma review of a few of those cases occurring in women, it would seem that the hormone balance of the normal menstruating woman may be significant. Those cases reviewed by Telford(1927), Jablons(1925), Horton(1932), Herrell(1936), Elliott(1937) and Meleney (1925) all appear to have occurred in women past the menopause. That reported by Herrell is questionable since the ageof the patient was forty-one. On the other hand, Millman(1938) has recorded the case of a twenty

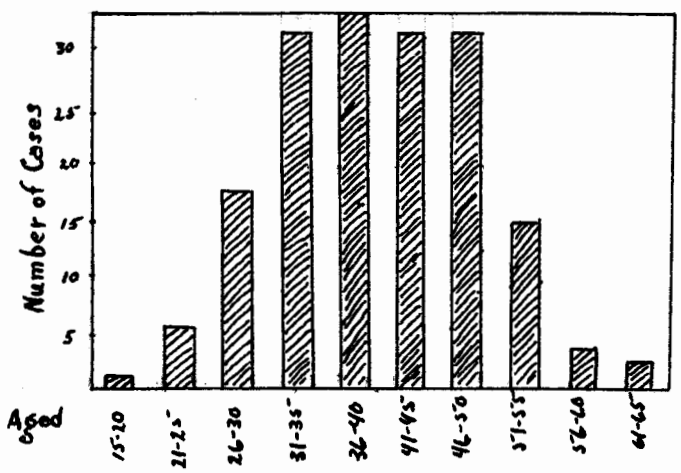
seven year old Jewess who developed the disease. The author is not prepared to say just what may be the relationship of the sexual factor to the incidence and causation of thromboangiitis obliterans, but it seems plausible that there may be a basis for further investigation in the field of endocrinology.

Occupation: German writers have remarked about the similarity of thromboangiitis obliterans and a disease of the peripheral vessels which they call "air hammer disease". Jablons(1925) believed occuption to be an important predisposing factor, noting that only four of his entire series of cases were mental workers. Brown, Allen and Mahorner(1928) estimated that eighty per cent of their cases were engaged in active occupations while only twenty per cent were engaged in sedentary occupations. A control group of miscellaneous patients showed the ratio to be approximately the same, so they concluded that occupation is probably of little importance if any.

Oxygen Want: The question oxygen want was raised by McDougall(1935). He reported the case of a veteran of t he first World War, a victim of gassing, who was seen

with chronic bronchitis, emphysema, and thromboangiitis obliterans as a complication. It appears that the development of thromboangiitis obliterans in this man was a mere coincidence and not a comlication of gas injury. It has been pretty well disproved that the hemoglobin is concentrated in Buerger's disease, a fact which would be evident were oxygen want a real causative factor.

The Age Factor: The relation of age to susceptibility to the disease deserves little more than passing mention. It appears to be a disease of early adulthood and middle life in males. No definite compilation of figures are available to show the relative age incidence in women. The author believes such an age chart for women would show the greatest incidence to be at the end of reproductive activities. The following chart was reconstructed from Brown, Allen and Mahorner(1928).



Vitamin Deficiency: I suppose no discussion of the possible etiology and pathogenesis of a disease could be complete today without mentioning a possible avitaminosis. The author naturally does not wish to be guilty of such an infraction.

The literature contains nothing specifically relating to vitamin deficiency in thrombo-angiitis obliterans, but contains at least two articles which proclaim the value of vitamins therapeutically. Bernheim and London(1936) reported marked improvement in patients following massive doses of vitamins A, B, C and D. In addition to the vitamins they included a diet high in calcium and in several instances gave sodium citrate intravenously. Dubnove (1942) believes that vitamin A and the "B" complex are of importance in the treatment of peripheral vascular disease as a whole.

The author hesitates to comment upon the wonders of vitamins, but wonders if Bernheim's results wouldn't have been very similar had he omitted the vitamins entirely.

SUMMARY

1. The theory of an infectious origin of the disease has received the support of the majority of authorities. Goodman believes the causative organism to be Reckettsial in nature. A pleomorphic streptococcus has been cultured on at least two occasions, but general confirmation is lacking. Accidental transmission in man lends support to the concept of an infectious origin. Fungi have been considered but convincing evidence is lacking.

2. The possible role of tobacco in the production of the disease has been studied both in relation to the pharmacological action of nicotine and individual hypersensitivity to the constituents of tobacco. Cessation of smoking is of definite therapeutic value by virtue of the pharmacological reaction. The investigation of individual hypersensitiveness has as yet uncovered nothing conclusive.

3. Recent laboratory data tends to discount the role of hemo concentration and possible association of thromboangiitis obliterans with polycythemia vera. The theory of a disturbance in phospholipid metabolism

explains rather nicely some of the clinical manifestations of the disease but confirmatory evidence has not been reported. The rationale of the use of insulin free pancreatic extract therapeutically has its basis in this theoretical metabolic disturbance.

4. Reports of world wide incidence have devaluated the significance of geographical and climatic conditions. With the possible exception of those cases reported in Siam, thromboangiitis obliterans has not been reported in the tropics.

5. Heredity plays no important role other than that the disease seems to have a predilection for persons of Jewish descent. Frauenthal reports the peoples of all nations to be afflicted.

6. Although there have been scattered reports of the disease occurring in women, it is predominately one of males. The possible significance of the sex hormones has not been sufficiently investigated.

7. Thromboangiitis obliterans is a disease of early adulthood and middle life.

8. Persons engaged in active occupations are not more susceptible to the disease than sedentary workers.

9. Oxygen want is a manifestation, not a causative factor.

10. Avitaminosis seems improbable.

BIBLIOGRAPHY

Allen, E. V.: Thromboangiitis Obliterans, Bulletin New York Academy of Medicine, 18:165-189, 1942

Allen, E. V.: Personal Communication

Allen E. V., and Lauderdale, T. L.: Accidental Transmission of Thromboangiitis Obliterans From Man To Man, Proc. Staff Meetings Mayo Clinic, 11:641-648, 1936

Brown, G. E.: Discussion: Thromboangiitis Obliterans Among Women, Proc. Staff Meetings Mayo Clinic, 7:109, 1932

Brown, G. E., Allen, E. V., Mahorner, H. R.: Thromboangiitis Obliterans, W. B. Saunders Company, Phila., 1928

Bean, Harold C.: Thromboangiitis Obliterans, Boston Medical and Surgery Journal, 188:427-431, 1923

Bernhard, Adolph: Summary of the Chemical Blood Findings in Thromboangiitis Obliterans, Medical Record, 97:430-431, 1920

Buerger, L.: Thromboangiitis Obliterans; a study of the vascular lesions leading to subcutaneous gangrene, American Journal of Medical Science, 136:567- , 1908

Buerger, Leo and Kaliski, D. J.: Complement Fixation Tests in Thromboangiitis Obliterans, Medical Record, 78:665-669, 1910

Buerger, L.: Is Thromboangiitis Obliterans An Infectious Disease?, Surgery, Gynecology and Obstetrics, 19:582, 1914

Buerger, Leo: The Pathology of Thromboangiitis Obliterans, Medical Record, 97:431-437, 1920

Buerger, L.: The Circulatory Disturbances of the Extremities, W. B. Saunders Co., Phila., 1924 pp. 214-279

Conwell, D. V.: Thromboangiits Obliterans: Results of Treatment with Parathormone(parathyroid preparation); 4 cases; Preliminary Report., Journal Kansas Medical Society, 34:465-468, 1933

Dubnove, Aaron: Role of Vitamins in the Etiology and Treatment of Peripheral Vascular Diseases, Hebrew Medical Journal, 1:174-172, 1942

Elliott, A. H.: Thromboangiitis Obliterans: In Woman, Calif. and West. Medical Journal, 47:190-191, 1937

Frauenthal, Henry W.: in Discussion on Buerger, Leo: The Pathology of Thromboangiitis Obliterans, Medical Record, 97:458, 1920

Friedman, G. A.: in Discussion on Buerger, Leo: The Pathology of Thromboangiitis Obliterans, Medical Record, 97: 457-458, 1920

Friedlander, M., and Silbert,S.: Thromboangiitis Obliterans(Buerger)vi Chemistry of the Blood, Archives of Internal Medicine, 48:500-506, 1931

Friedlander, M., Silbert, S., and Laskey, N.: Toe Lesions Following Tobacco Injections in Rats (in relation to the etiology of thromboangiitis obliterans) Proc. Exp. Biol. and Med., 34:156-157, 1936

Goodman, Chas.:(with E. P. Epstein) Presenile Gangrene, Thromboangiitis Obliterans; A Serological Study with Reference to the Possibility of Typhus Fever As An Etiological Factor, Preliminary Report, New York Medical Journal, 103:1073-1075, 1916

Goodman, Chas.: Thromboangiitis Obliterans and Typhus: evidence of etiological relationship, Archives of Surgery, 35:1126-1144, 1937

Goodman, Chas.: Thromboangiitis Obliterans and Typhus Fever, Hebrew Medical Journal, 1-172-163, 1942

Harkavy, J., Hebald, S., and Silbert, S.: Tobacco Sensitiveness In Thromboangiitis Obliterans, Proc. Soc. Exp. Biol. and Med., 30: 104, 1932

Harkavy, J.: Tobacco Sensitiveness In Angina Pectoris and Coronary Artery Diseases, Proc. Soc. Exp. Biol. and Med., 30: 683, 1933

Harkavy, J., and Romanoff, A.: Skin Reactions To Tobacco and Other Allergens In Normal Men and Women Smokers, Journal Allergy, 6:56, 1934

Harkavy, J.: Skin Sensitiveness to Extracts of Tobacco Leaf, Tobacco Pollen, Tobacco Seed and To Other Allergens In Two Hundred Normal Smokers, Journal Allergy, 6:56-61, 1934

Harkavy, J.: Skin Reactions To Tobacco Antigen In Smokers and Non-Smokers, Journal Allergy, 5:131, 1934

Harkavy, Joseph: Hypersensitiveness To Tobacco and Biopsy Studies of Skin Reactions In Vascular Disease, Journal Allergy, 9:475-488, 1938

Hauser, E., and Allen, E. V.:Vascular Clinicsviii. Generalized Arterial Involvement In Thromboangiitis Obliterans, Proc. Staff Meet., Mayo Clinic, 15:7-13, 1940

Herrel, W. E., and Allen, E. V.: Thromboangiitis In Women, American Heart Journal, 12:105-108, 1936

Horton, B. T., and Brown, G. E.:Unusual Cases of Thromboangiitis Obliterans: Their Association with Polycythemia Vera and Traumatic Myelitis; Med. Clinics of North America, 12:1617-1627, 1929

Horton, B. T., and Dorsey, A. H. E.: Thromboangiitis Obliterans; Bacterialogical Studies, Proc. Staff Meet., Mayo Clinic, 5:337, 1930

Horton, B. T., and Brown, G. E.: Thromboangiitis Obliterans; among women, Proc. Staff Meet., Mayo Clinic, 7:107-109, 1932

Horton, B. T., and Dorsey, A. H. E.: Experimental Thromboangiitis Obliterans; Bacteriological and Pathologic Studies, Archives of Surgery, 13:910, 1932

Jablons, B.: Thromboangiitis Obliterans, International Clinics, 3:193-210, 1925

Kaunitz, J.: the Pathological Similarity of Thromboangiitis Obliterans and Endemic Ergotism, American Journal of Pathology, 6;299-309, 1930

Kaunitz, J.: Chronic Endemic Ergotism; its relation to thromboangiitis obliterans, Archives of Surgery, 25:1135-1151, 1932

King, G. S.: Deproteinated Pancreatic Extract; Use in Thromboangiitis, Industrial Medicine, 10:530-532, 1941

Klein, B. S., Cohen, M. B., and Rudolph, J. A.: Histological Changes in Allergic and Non-Allergic Wheals, Journal of Allergy, 3:531, 1932

Kramer, D. W.: Gangrene of the Lower Extremities: Consideration of and Differential Diagnosis, Hebrew Medical Journal 1:162-156, 1942

Langley, J. N.: On the Reaction of Cells and Nerve Endings to Certain Poisons, Chiefly as Regards the Reaction of Striated Muscle to Nicotine and To Curare, Journal of Physiology, 33:374-413, 1905-1906

Ludlow, A. I.: Thromboangiitis: A Review and Report of the Disease in Koreans, China Medical Journal 45:487-514, 1931. (from Mayo Cininc Monograph, W. B. Saunders Company, Phila., 1928, p. 27

Maddock, W. G.,and Coller, F. A.: Peripheral Vasoconstriction by Tobacco Demonstrated By Skin Temperature Changes, Proc. Exp. Soc. Biol. and Med. 29:487-498, 1932

Maddock, W. G., Malcolm, R. L., and Coller, F. A.: Thromboangiitis and Tobacco: The Influence of Sex, Race, and Skin Sensitiveness To Tobacco on Cardiovascular Responses To Smoking, American Heart Journal, 12:46-52, 1942

Meleny, F. L., and Miller, G. G.: Contribution to the Study of Thromboangiitis Obliterans, Annals of Surgery, 81:976-995, 1925

Meyer, W.: Etiology of Thromboangiitis(Glycophilia), Journal American Medical Association, 71: 1268-1290, 1918

Meyer, W.: A Further Contribution To The Etiology Of Thromboangiitis Obliterans, Medical Record, 97:425-430 1920

Millman, S.: Thromboangiitis Obliterans; in a woman, Amerian Heart Journal, 15:746-748, 1938

McDougall, J. B.: Gassing As An Etiological Factor: Thromboangiitis Obliterans, Lancet, 2:366-368, 1935

McGrath, E. J.: Experimental Peripheral Gangrene, Journal American Medical Association, 105:854-856, 1935

Naide, M.; The Causative Relationship of Dermatophytosis To Thromboangiitis Obliterans, American Journal of Medical Science, 202:822-830, 1941

Noble, T. P.: Thromboangiitis Obliterans: In Siam, Lancet 1:288-291, 1931

Norman, I. L., and Allen, E. V.: The Vascular Complications of Polycythemia Vera, American Heart Journal, 13:257-274, 1937

Nuzum, F. R., and Elliott, A. H.: The Pharmacological Properties Of An Insulin Free Pancreatic Extract and TheCirculatory Hormone of Frey, Journal of Pharmacology and Experimental Therapeutics, 43:463-474, 1931

Ochsner, A. J.: Discussion; Chicago Surgical Society, Surgery, Gynecology and Obstetrics, 21:536, 1915

Orr, T. G.: Thromboangiitis Obliterans A Universal Disease, Journal Missouri Medical Association, 22:174-175, 1925

Rabinowitz, H. M.: Experiments On Infectious Origin Of Thromboangiitis Obliterans and Isolation Of A Specific Organism From The Blood Stream, Surgery, Gynecology and Obstetrics, 37: 353- 362, 1923

Rabinowitz, H. M., and Kahn, J.: Relationship of Phospholipin Metabolism To Thromboangiitis Obliterans and Its Treatment, American Journal of Surgery, 31:329-339, 1936

Roth, G. M., Maclay, E. V., and Allen, E. V.: Blood In Thromboangiitis Obliterans, Archives of Internal Medicine, 62:413-422, 1938

Samuels, S. S.: Thromboangiitis Obliterans: Incidence in brothers, American Journal of Medical Science, 183:465-467, 1932

Silbert, S.: Studies On Thromboangiitis Obliterans: ii The Effectiveness Of Therapeutic Procedures, Journal American Medical Association, 89:964-966, 1927

Silbery, S., Kornzweig, A. L., and Friedland, M.: Thromboangiitis Obliterans(Buerger):iv Reduction of Blood Volume, Archives of Internal Medicine, 45: 948-957, 1930

Silbert, S., and Friedlander, M.: Studies In Thromboangiitis Obliterans(Buerger): viii Effect of Thyroid Administration On Blood Volume, Journal American Medical Association, 97:17-18, 1931

Silbert, S.; Treatment of Thromboangiitis Obliterans, Hebrew Medical Journal, 1: 155-148, 1942

Smith, R. P., and Patterson, D. W.: Thromboangiitis Obliterans in Association With Syphilis, British Medical Journal, 1:227-228, 1927

Sulsberger, M. B.: Recent Immunologic Studies in Hypersensitiveness To Tobacco, Journal American Medical Association, 102:11-13, 1934

Telford, E. D., and Stopford, J. S. B.: Thromboangiitis Obliterans, British Medical Journal,1:1035, 1924

Telford, E. D., ans Stopford, J. S. B.: Two Cases Of Thromboangiitis In Women, British Medical Journal 1:1140-1141, 1927

Thomas, Henry M. J.: Persistent Leukocytosis In The Early Stages Of Thromboangiitis Obliterans, American Journal of Medical Sciences, 165:86, 1923

Thompson, K. W.: The Relationship of the Dermatomycoses To Certain Peripheral Vascular Infections, International Clinics, 2:156-158, 1941

Trasoff, A., Blumstein, G., and Marks,M.: The Immunologic Aspect Of Tobacco In Thrombpangiitis Obliterans And Coronary Artery Heart Disease, Journal of Allergy, 7:250-253, 1936

Weber, F. P.: Thromboangiitis Obliterans In Father and Son, Lancet 2:72-73, 1937

Westcott, F. H., and Wright, I, S.: Tobacco Allergy and Thromboangiitis Obliterans, Journal of Allergy, 9:555-564, 1938

Winiwarter, Felix, V.:Ueber eine eigenthumliche Form von Endarteritis und Endophlebitis mit Gangran des Fusses, Arch. f. Klin. Chir., 23:202-226, 1879

Wolbach, S. B., Todd, J. L., and Palfrey, E. M.: Etiology and Pathology of Typhus, Harvard Press, Cambridge, 1922

Wwedensky, A. A.: Ueber Arteritis obliterans und ihre Folgen, Arch. F. Klin. Chir., 57:98-117,1898