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Thrombo angiitis obliterans, with special reference to the etiological diagnostic, therapeutic and prognostic aspects of the nervous system

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THROMBO-ANGIITIS OBLITERANS, WITH SPECIAL
REFERENCE TO THE ETIOLOGICAL, DIAGNOSTIC,
THERAPEUTIC AND PROGNOSTIC ASPECTS OF THE
SYMPATHETIC NERVOUS SYSTEM

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INTRODUCTION

There has in recent years been an ever-increasing interest in the disease now recognized as an entity and termed after Buerger's suggestion, Thrombo-angiitis obliterans, or, as it is often termed in view of the excellence of the large amount of work done by him on this condition, Buerger's Disease. This increasing interest has been due to several factors. First, the disease is of rather recent recognition, not being recognized as a definite entity until the twentieth century, largely due to the efforts of Leo Buerger. Second, the peculiar age and sex frequency, the disease being almost limited to young adults to middle-aged individuals of the male sex, presents many interesting questions for study. The answer to these questions has not yet been obtained. Third, the peculiar racial predilection of this disease, if indeed such predilection does exist, is another question which is as yet unanswered. Fourth, there seems to be indications that the incidence of the disease is increasing. The number of cases reported is rapidly increasing. This may be due in large part to recognition of

many cases which in earlier years would have remained undiagnosed or have been incorrectly diagnosed. Whichever the case may be, it is highly probable that there will be a steadily increasing number of cases of Buerger's disease which will come to the attention of the medical profession. Finally, the increasing interest in thrombo-angiitis obliterans has already begun to pay dividends in the recognition of the disease in its earlier phases when therapeutic procedures are more efficacious, and also in the development of valuable conservative measures, which, combined with early recognition of the disease is restoring an ever-increasing number of sufferers to useful places in the world without major amputations and without the nerve-wracking pain so characteristic of this disease. Probably no truer concept of the trends and aims of the profession today in regard to this disease can be gained than by consideration of Finney's comment that anyone can "amputate an extremity, but that it takes a good physician to save one."

It is not the purpose of this paper to discuss this disease fully in all its aspects. Several excellent monographs^{19, 11} have been written on this disease and any attempt at a shorter discussion of this sort would not be fruitful. In this paper, the work done on etiology, pathology, symptoms, diagnosis, and general therapeutics of thrombo-angiitis obliterans will be only briefly summarized, special attention being directed to one of the newer and quite promising approaches, namely the sympathetic nervous system.

HISTORY

The discussion of history will, for the sake of convenience be divided into clinical and pathological.

History (clinical)¹¹

Early literature regarding spontaneous gangrene of the extremities was quite confusing.

Quesnay (1739) hinted that organic occlusion of arteries might cause gangrene. This was definitely stated by Hebreard (1817) and enlarged upon by Dupuytren & M. Roché who have been termed the fathers of the theory of arteritis. Allibert (1828) suggested that arteritis might be the cause rather than the effect of thrombosis. Virchow's description of embolus and thrombosis was the most significant of much writing on the formation of blood clots in situ and the effects of transmission of these clots in the circulation. Behier (1861) formulated the idea that arterial obliteration caused dry gangrene and venous obliteration moist gangrene. Kaynand (1862) attempted to prove that there is a disease of the arterial system which might produce gangrene in which arterial obliteration is not present.

Although the condition now recognized as thromboangiitis obliterans had probably been known for many years, the first report on the subject was that of von Winiwarter (1879) who used the term endarteritis and endophlebitis. He quoted Jaesche (1865), Larivière (1866) and Friedlander

(1876) as having noted cases similar to his. Dütyl and Lamy (1893) reported a case in which Charcot made a diagnosis of intermittent claudication. These authors described the pain, cyanosis, cramps, and coldness which were present before gangrene occurred. There were further examples reported by Weiss (1895) and Manteuffel (1895). Borchard (1897) reported six cases. Wwedensky (1898) reported that arteritis obliterans of the lower extremities is a disease which is particularly prevalent in districts of Russia where the weather is severe. He believed it occurred almost exclusively in males between the ages of fifteen and sixty. He noted typical symptoms and decided that complete cure had never been observed or was very rare. Bunge (1901) reported cases of arterial occlusion which were probably artero-sclerotic disease. Buerger in 1908¹² studied the arteries and veins in eleven amputated limbs and suggested the name thrombo-angiitis obliterans. Todyo (1912) reported five cases with complete pathological studies. He did not believe the lesions of the nerves were sufficient to explain the severe pain. His pathological studies correlated the observations of von Winiwarter and Buerger. Gilbert and Coury (1922) reported the "first case" in France.

HISTORY (Pathological)¹¹

All treatises refer first to the article of von Winiwarter (1879) which is so complete that it forms the basis

of our knowledge of the pathology of this disease. He designated the process endarteritis obliterans. He noted the very active intimal proliferation. He also noted the cellular occluding mass in the lumens of the vessels, the penetrating new vessels, and the thrombi in the vessels.

Widenman (1892) noted the intimal proliferation, thrombosis, and lymphocytes and believed the thrombosis was caused by the slowing of the blood stream due to intimal thickening.

Weiss (1895) observed the thrombosis and believed this and not the intimal proliferation to be responsible for the vascular occlusion. He did not believe that the cellular thickening of the intima proceeded to complete closure of the lumen. Manteuffel later agreed with Weiss as to pathogenesis.

Hoga (1898) investigated twelve cases and described intimal thickening, mural and occluding thrombi, newly formed elastic tissue in the intima, giant cells in the wall of the vein, and patchy lymphocytic infiltration of nerves.

Buerger's first paper¹², brought out a new concept of pathogenesis. His book in 1924¹⁹ is a most detailed clinical and pathological study. He concluded that the disease is an acute inflammation of the vessels, leading to thrombosis, with subsequent organization and recanalization.

He described the second stage as a stage of healing, characterized by the disappearance of the miliary giant cell foci and the inflammatory products, the organization and recanalization.of the thrombus and finally the fibrosis of the adventitia and conversion of the vessel into a fibrous cord.

Todyo (1912) compared material from thrombo-angiitis obliterans with that from senile gangrene, thrombosis in pneumonia, and one case of beriberi. He advanced progressive mural thrombosis as a theory of pathogenicity and agreed with certain of the views of both von Winiwarter and Buerger.

DEFINITION AND PATHOLOGY

Thrombo-angiitis obliterans is a disease of the blood vessels, arterial and venous, probably of a chronic inflammatory etiology, characterized pathologically by an occlusive thrombosis that subsequently gives way to a stage of healing or organization, the final result being the complete closure of arteries and veins over a large extent of their course by vascularized and canalized connective tissue. The disease is characterized clinically by pain in the extremities, intermittent claudication, coldness and numbness in the extremities, pallor on elevation and rubor on lowering of the extremity, and an absence of pulse in the lower arteries. The condition may limit itself or go on to a progressive gangrene which may require amputation.

The concept of the pathology in thrombo-angiitis obliterans is quite definite and generally agreed upon. This concept has changed very little since Buerger's earliest work. In 1904¹⁴, he states, with reference to involvement of the veins, that the disease is often associated with thrombophlebitis of the superficial veins of the arms and legs, and that this disease of the superficial veins may be subsidiary or may dominate the clinical picture. There may be a migrating thrombophlebitis which gives no symptoms, the signs referable to the deep veins being of the most importance. There are many cases characterized by certain peculiar nodosities of the skin.

Buerger in 1920¹⁸ refers to the healed stage and to the acute stage, calling attention to the fact that with all the well-known manifestations of the disease we may still be dealing with arteries that are healed so far as the disease thrombo-angiitis obliterans is concerned. In the healed stage the thrombotic occlusion of the vessels, both arteries and veins, has given way to organization, canalization, and connective tissue formation in the occluding clot, with conversion of the arteries by an obliteration process into hard cords. In the acute stage he finds definite evidences of inflammation. He believes we are dealing here with phenomena which go hand in hand with an active inflammatory invasion of arteries and veins--"phenomena that afford the true clue to the investigator for researches on etiology." He lists the lesions in their chronological order as follows; first, an acute inflammatory lesion with occlusive thrombosis, the formation of miliary giant cell foci; second, the stage of organization or healing, with the disappearance of the miliary giant cell foci, the organization and canalization of the clot, and the disappearance of the inflammatory products; third, the development of fibrotic tissue which binds together the artery, vein and nerves.

Perla⁴⁷ does not find the acute specific lesion described by Buerger in the vessels of amputated extremities. In his studies he found that the deep arteries and veins in

the affected limb show various stages in the process of organization and recanalization of the thrombotic lesions. Acute phlebitis was not uncommon. The capillaries were normal. Arteriosclerosis was sometimes associated. He found that death may occur from thrombo-angiitis obliterans of the aorta and coronary vessels.

Meleney and Miller⁴⁰ state that the process appears to be inflammatory, attacking large and small arteries and veins in an irregular manner and causing thrombosis and obliteration. It is not necessarily progressive from below upward or from above downward. He believes that the severe pain which is so often present may be at least in part explained by the frequent attack on the nutrient arteries of the nerves. He noted also that an extensive collateral circulation develops which in some cases can keep pace with the obliterative process and in other cases can not.

Brown, Allen and Mahorner¹¹ in presenting the results of their study of fifty amputated cases agree almost to the finest detail with the views of Buerger. They emphasize the idea that thrombo-angiitis obliterans is fundamentally a chronic inflammatory condition 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 vasa vasa-

rum and other vascular channels to establish a collateral circulation. At times acute inflammation is superimposed on the chronic process. The nerves are involved apparently by virtue of their relationship to the vessels and by ischemia in the distal portion.

The disease usually affects the larger vessels of the extremities, the lower more often than the upper. The arteries chiefly involved are the Dorsalis pedis, Anterior tibial, and Dorsalis hallicus. It does not as a rule reach the level of the Popliteal artery. Other vessels, however, may be affected, and there is scarcely a region or organ in the body which has not been the site of this disease. Meyer⁴¹ reports a case of thrombo-angiitis obliterans of the intestine in a man aged 47 who had sixteen years previously both lower extremities amputated for Buerger's disease. Clinically, the case presented severe intermittent and later continuous pain, associated with enormous enlargement of the colon, severe constipation, occasional vomiting, and visible peristalsis. Exploratory operation revealed pulseless mesenteric arteries. Sprunt⁶² presents the data from eighteen cases of thrombo-angiitis obliterans with autopsy to show that it seems to be a widespread arterial disease and not confined to the arteries of the extremities. He states there is further indication that patients with this disease usually die of some vascular

complication. Raube⁶⁴ calls attention to the distribution of the lesions other than of the extremities, tabulating twenty-six cases from the literature, of lesions affecting other blood vessels than those of the extremities and adds to this list two cases of his own, of intermittent claudication of the mesenteric vessels.

ETIOLOGY

In the study of the etiology of thrombo-angiitis obliterans we encounter quite an interesting situation. The early workers had very definite and it might even be said, dogmatic ideas regarding the etiology of this disease, especially regarding racial predilection and the role of tobacco. As more work has been done and an ever-increasing number of cases have come under observation, some of these etiological factors have come to be seriously doubted and many new factors suggested.

TOBACCO

Silbert^{57,58,59} believes smoking to be the immediate causative factor. Meyer⁴³ believes patients afflicted with similar clinical syndromes do not have thrombo-angiitis obliterans unless they smoke tobacco. He is of the opinion that the disease is caused by the absorbed tobacco-smoke poisons circulating with the blood and in the lymph, and states that "people so constituted as these Hebrews should not smoke." Weber reported he had never seen a case in an individual not an habitual smoker.

Erb believed smoking to be a significant contributing cause. Buerger¹⁸ believes it to be only a contributory factor. Gray²⁹ states his belief that tobacco is only a predisposing factor.

On the other extreme we find those who hold that tobacco plays no part whatever in the etiology. In this group we find Perla⁴⁷, and several others. Meleney and Miller⁴⁰, Jablons³¹, Koyano and others have reported cases in individuals who were not smokers, and many workers have found a large percentage of patients who were only moderate smokers.

If tobacco smoking is to be designated the most important cause of this disease, it leaves several peculiar facts unexplained. Why is there not a higher incidence of the disease, in view of the universality of smoking? Why are such a large percentage of the moderate smokers afflicted while the great majority of those who smoke far to excess do not have the disease? With the very high percentage of women who are smoking in recent years, why is thromboangiitis obliterans still almost unknown in the female sex? Another important point to be kept in mind was suggested by Brown, Allen, & Mahorner.¹¹ They observed that occasionally tobacco smoking is initiated and frequently accentuated after the disease has progressed to the point of causing pain. Thus, erroneous conclusions may easily be drawn from the tobacco smoking status of patients with well advanced disease.

Another view which was advanced early was that the type of tobacco was a factor. When this disease was first

widely studied clinically, it was thought that all patients smoked Russian tobacco, which might contain ergot. This has been disproved. Jones in a controlled study of one hundred fifty cases found that the type of tobacco was not a factor, although his comparison showed that the subjects with thromboangiitis obliterans showed a higher incidence of smokers and used larger amounts of tobacco.

Experimental studies on the effect of nicotine on the blood vessels of rabbits have not been very helpful. Langley³⁶ showed that nicotine in larger doses than that received in smoking produced vasoconstriction. Adler and Hensel¹ found that the effects on the blood vessels of rabbits following nicotine injection were of a degenerative rather than of an inflammatory nature.

Thus, in the present status of this etiological factor, it is found that while the majority of workers find smoking to be a significant contributory factor and a few believe it to be the primary cause, there are yet some who find it of no influence whatever.

RACE AND BIRTHPLACE

Buerger¹⁵, Meyer⁴³, and Perla⁴⁷ have reported almost exclusive occurrence in Hebrews. Cases have been reported in Swedes by Ochsner, in Chinese by Meleney and Miller⁴⁰, in Japanese by Koyano and Ito, in Koreans by

Ludlow, and in Turks by Wieting.

In a series of more than three hundred cases in the Mayo Clinic from 1922 to 1927, Brown, Allen, and Mahorner¹¹ found slightly more than fifty percent occurred in Hebrews which is many times the percentage of this race registering at the clinic. The belief of Meyer⁴³ that all patients with Thrombo-angiitis obliterans had migrated from a narrow belt from the Black Sea to the Baltic Sea was disproved by this study. At the Mayo clinic a decreasing frequency has been observed among Hebrew patients and an increasing frequency among Gentiles. It is quite generally believed that the almost exclusive occurrence in the Hebrew race reported by the early observers was due to the fact that their patients were resident in New York City where the Hebrew percentage of the population is high. Most studies in this country have shown a higher incidence in Hebrews than in Gentiles.

SEX

Exclusive occurrence in males has been reported by all authors except Buerger¹⁸, Koyano, Meleney and Miller⁴⁰, and Telford and Stopford⁶⁵. Meleney reported a case in a woman of forty-eight with a five year history. The microscopic picture is characteristic. The other cases reported are questionable because of lack of proof.

Evidence for explanation of the higher male incidence on the basis of endocrine function seems rather in-

adequate¹¹. Differences in occupation is suggestive but has yielded nothing definite. Though smoking is predominant in the male sex, the disease is extremely rare among women in spite of their increasing use of tobacco.

If the disease is infectious in origin, the prostate gland might serve to explain the overwhelming predominance in the male, the incidence of foci of infection in other tissues common to both sexes seeming to be about equal.

FOCI OF INFECTION

Brown, Allen & Mahorner¹¹ believe their series provides evidence that is at least suggestive regarding the significance of distant foci of infection. Seventy-five percent of their patients showed significant periapical infection; eighty percent still had tonsils, most of which contained fluid pus or plugs; fifty-two percent of the patients in whom the prostate was examined by the method of von Lackum, prostatitis graded 2 to 4 was found. Animal inoculation of cultures from prostatic secretion gave negative results. Only three patients were free of demonstrable infection.

INFECTIOUS NATURE OF THE DISEASE

Most observers have been impressed with the inflammatory appearance of the lesions. Buerger has

repeatedly^{15,16,17,18}, stated his belief that the disease is the result of some specific infectious or toxic agent.

Rabinowitz⁴⁸ isolated an organism from the blood of patients with which he produced characteristic lesions in rabbits not only at the site of injection (the ear) but also on the plantar surfaces of the feet. Bacteriological studies on segments of veins resected while clinically acute were carried out by Rosenow and Nickel. In a small series apparently similar organisms have been isolated. In one instance an organism probably similar to that described by Rabinowitz was found, the culture of which when injected into a rabbit produced an auricular thrombus.

AGE

Various authors agree as to the almost constant occurrence between the ages of twenty-five and fifty. Frauenthal's report²⁵ of a case of bilateral spontaneous gangrene of the hands in a boy aged three years does not present conclusive data. Koyano described a case which began at 9 years of age.

In Brown Allen, and Mahorner's series¹¹ of one hundred fifty cases, the youngest with pathologically proven diagnosis was seventeen, the oldest sixty-four. One hundred forty-four cases were in patients of age twenty-six to fifty.

MISCELLANEOUS

Exposure to cold seemingly has a deleterious effect on thrombo-angiitis-obliterans, often producing the first symptoms. A warm climate in some cases causes symptomatic improvements.

The series of Brown, Allen and Mahorner showed eighty percent in active occupations and twenty percent in sedentary occupations. The control group showed the same percentage group of occupations.

Meyer⁴² in 1918 reported defective carbohydrate metabolism and suggested the name "Glycophilia."

Gray²⁹ believed that thrombo-angiitis obliterans is the end-result of an intestinal putrefaction, with resultant toxins in the blood stream having a selective action on the vascular intima.

Telford and Stopford⁶⁵ state that "we are probably on safe ground in regarding the disease as spasm followed by thrombosis."

Goodman and Bernstein believed that latent Typhus fever was an etiologic factor, but later work by Perla⁴⁷, by Meleney and Miller⁴⁰, and others has failed to show any causal relationship between this condition and Typhus or Malaria.

SUMMARY

None of the etiological factors suggested fulfills the requirements of a direct causal agent.

The etiological relationships of the sympathetic nervous system have been left until later in the paper where special reference will be made to the sympathetic nervous system.

DIAGNOSIS

The diagnosis of thrombo-angiitis obliterans in its latest stages with the long history of intermittent claudication, exercise pain, coldness and numbness of the extremities, later "rest pain," and finally ulceration and gangrene, along with the physical signs of pulseless arteries and pallor on elevation and rubor on depression of the extremity, has never presented any difficulties since the work of Buerger, it was first recognized as an entity. The differential diagnosis is not difficult. Two general types of disease of the peripheral arteries of the extremities are recognized, vasomotor or functional, and obliterative or organic. The former are divided into vasospastic and vasodilator forms seen clinically as Raynaud's disease and erythromelalgia, respectively. The organic diseases are chiefly thrombo-angiitis obliterans and arteriosclerosis. The prime requisite in the clinical differentiation of vascular disease of the extremities is the determination of the vasomotor or organic nature of the process. This is readily accomplished in most cases by palpation of the arteries of the extremities and careful consideration of the symptoms. Perla⁴⁷ states that absent pulsation of the palpable arteries of the extremities comes on months or years before the onset of gangrene and is the most important

physical sign in thrombo-angiitis obliterans.

This we see that early diagnosis, which so many writers, Samuels⁵¹, Perla⁴⁷, Silbert⁵⁹, Allen⁴, and many others have emphasized as being so important in the prognosis and therapeutic efficacy is not difficult. The early signs and symptoms of arterial occlusion are not elusive or equivocal, but constitute a syndrome as pathognomonic as obtained in the occlusive lesions of the coronary arteries.

Samuels uses two diagnostic tests which he finds quite valuable. One of these tests is based on the same principle as intermittent claudication. Both feet are elevated to ninety degrees. Pallor of the affected extremity and pain in it upon rapid flexion and extension of the foot at the ankle joint are the diagnostic signs. The other sign is the oscillometric index⁵⁰ which gives the amount of pulsations of the vessels and an idea as to the amount of occlusion present in vessels.

The discussion of some of the special diagnostic signs of reference to the sympathetic nervous system will be reserved for that portion of the discussion.

TREATMENT

The past ten years has brought about a marked change in the treatment of patients with thrombo-angiitis obliterans. Previous to this time medical treatment was largely neglected and surgical treatment followed the dictum of "high and early amputation." This was justified at the time in the belief that small trophic ulcers progressed eventually to gangrene and amputation, and that little could be done to prevent these disastrous sequelae. As late as 1925, Meleney and Miller⁴⁰ recommend conservative operation (local amputation or debridement of gangrenous area in cases in which there is general and local evidence that the collateral circulation can keep pace with or outrun the obliteration process, and radical amputation in other cases). He states that only in borderline cases can conservative general treatment be expected to be of much aid.

In the last ten years, however, several facts have become apparent; (1) in selected cases amputation is successful at a low level; (2) in many cases severe pain can be relieved by medical measures; (3) in many cases without trophic changes gangrene can be prevented; (4) small trophic ulcers can be healed frequently and the total volume flow of blood increased; (5) Lumbar ganglionectomy is of value in

selected cases; and (6) frequently patients go through the entire course of the disease without trophic changes or gangrene and eventually reach a stage of adequate compensation of volume flow of blood to the extremities.

The changed concept of the treatment of thromboangiitis obliterans has been brought about largely by the view that the disease is self-limited and that if the treatment can be instituted early extensive gangrene can often be prevented.

The most fundamental principles of the conservative line of treatment are (1) to prevent the ischemia from doing harm and (2) to aid the collateral circulation to keep pace with the obliterative process. The former purpose is in part accomplished by (1) rest, (2) postural treatment and exercise (3) relief from pain, and (4) prophylaxis against infection.

If occlusion is shown to be the greatest causative factor of the obstruction, by methods which will be discussed in the next section on the Sympathetic Nervous System, not a great deal can be done about it except to aid the more peripheral distribution of the small amount of blood available.

Many workers have attempted to accomplish this by attempts at reversal of the circulation, by methods varying

from venous ligation to anastomosis of the femoral artery and vein as first suggested by Lilienthal. The results have not been too gratifying although a few workers report good results. Pearse of Rochester, N. Y. has found venous ligation a valuable procedure, while others contend that the good results of such procedures are solely those of bed rest and general care during the post-operative period. Buerger stated his objections to this form of treatment, and he believes that "experimentally it is practically impossible to convert veins into arteries and furthermore the clinical reports do not justify us in recommending such a procedure."

Samuels^{52,53} advocates conservatism. He believes that the disease is self-limited, that the only indication for amputation in this disease is total destruction of the foot, so that a weight-bearing stump is unattainable; that sympathectomy is unnecessary and unwarranted, and that under his treatment the condition will quiet down without the necessity for amputation or other major operation. He believes the obstruction is due in large part to an abnormally high viscosity of the blood which can in a measure be corrected by repeated injections of large quantities of hypertonic saline solution intravenously. His treatment consists of a careful coordination of rest in bed, prohibition of

smoking, intravenous injections of hypertonic saline solution. He has had quite convincing results in a large series of cases. This same line of treatment is followed by Silbert^{57,58,59}. He agrees with Samuels that thrombo-angiitis obliterans is not a progressive disease if patients discontinue the use of tobacco. He reports that of the five hundred twenty-four patients he has treated by this method in the past ten years, eighty-three percent have obtained improvement as manifested by cessation of pain, improvement in walking, increase of oscillometer readings, increased temperature of extremities, healing of ulceration, and reopening of an obliterated extremity. Of his series six and seven-tenths percent have required amputation of an extremity.

Steel⁶³ is of the opinion that a factor in pathogenicity of thrombo-angiitis obliterans is a decreased clotting time of the blood, and used intravenous injections of sodium citrate solution, in conjunction with ten grains of potassium iodide three times daily throughout the entire course of treatment, along with such other measures as rest, hot air or electric light bath, daily leg massage and gradually increasing exercise. He reports three years use of this procedure with encouraging results.

Frauenthal²⁵ states that by exposure of the diseased extremity to white light he has saved about sixty-five percent of cases from amputation and had a number of cases that

had remained well for over seven years.

Landis and Hitzrot^{34,35} report "good" and "fair" results in sixty-four percent of cases treated with alternate suction and pressure therapy. They obtained good results when occlusion had progressed to the point at which arterial flow was no longer helped by vasodilation. Symptoms and signs of ischemia were relieved when other conservative measures proved ineffectual.

The Schwartzman's of Odessa and London have reported good results from the use of the angioidilating drugs acetylcholine and muscle extracts.

Allen and Myerding⁶ group the surgical treatment in forty-five cases as follows:

- (1) Incision of toes or removal of toe nails-successful in one case out of fifteen
- (2) Amputation of toes-successful in four cases out of six.
- (3) Amputation below the knee-successful in nine cases out of twelve.
- (4) Amputation above the knee-successful in six cases out of seven.

SYMPATHETIC NERVOUS SYSTEM

RATIONALE OF SYMPATHETIC ATTACK

It was mentioned in the section on treatment that it is of importance in determining the amount of obstruction due to vasoconstriction in relation to the amount due to occlusion. Obviously, an attack on the vasoconstrictor supply of the arteries is of no use if the obstruction is mainly due to organic occlusion. There are some workers, notably Davis and Kanavel²⁴, and Samuels⁵³ who are opposed to any attack on the sympathetic nervous system.

Davis and Kanavel report lumbar sympathectomy in two cases of thrombo-angiitis obliterans, the first of which was erroneously diagnosed as erythromelalgia. In this case there was no relief. Amputation was done because of intense pain and advancing gangrene. Examination of the vessels showed the organic changes of thrombo-angiitis obliterans. In the second case a periarterial sympathectomy had been performed elsewhere nine months previously. There was no gangrene. Lumbar sympathectomy gave no relief. The diagnosis was verified by examination following amputation. They say "Recognition of the lesion and a thorough understanding of the organic changes in the vessel wall are sufficient contra-indications to an attack on the sympathetic innervation of an extremity. One cannot expect to dilate

or constrict an arterial wall so altered by a pathological process such as Buerger has so carefully described in this disease."

Samuels states that sympathectomy and ganglionectomy have no place whatever in the treatment of any phase of thrombo-angiitis obliterans. The spastic element in this disease plays such a minor role as to be negligible in the consideration of therapy. Much more can be accomplished by the employment of comparatively simple recognized surgical principles. The risk attached to the operation of lumbar sympathectomy is unwarranted in any case of thrombo-angiitis obliterans.

The majority, however, of those authors, who refer to sympathetic attack, believe that this approach, in one form or another is of value.

Allen⁵ states that thrombo-angiitis obliterans has a tendency to be a self-limiting disease; in a certain number of cases it does not progress, apparently, beyond a certain point, or the development of adequate collateral circulation keeps pace with the disease. In the cases that he found to show a high vasomotor gradient, "the operations on the sympathetic nervous system as advocated by Adson certainly constitute the best form of therapy." Matas³⁹, Scott and Morton⁵⁶ Archibald⁷, and Telford and Stopford⁶⁵, see beneficial results from the sympathectomy as advocated by Adson. There are other

writers who advocate various of the other sympathetic attacks. Archibald states his belief that no procedure has yielded such uniformly favorable results as the bilateral sympathectomy of Brown and Adson. Telford and Stopford believe ganglionectomy not only is to be recommended, but in those cases in which the spasmodic element is clinically well defined as evidenced by reaction to exercise and by the customary preliminary vasodilation tests is the only procedure which offers any hope of permanent cure.

Scott and Morton⁵⁶ give a very clear exposition of their reasons for sympathectomy. They state that when the vasoconstrictor pathway is interrupted in occlusive arterial disease without spasm there is no increase in the deficient flow of blood. But if vasoconstrictor spasm plays a part in the production of the circulatory impairment, the blood flow is improved in the anesthetic area. If the circulation reaches the normal level under such circumstances, the circulatory impairment is dependent entirely on spasm. If it does not, the amount by which it fails to reach the normal level, as measured by the surface temperature, represents the contribution of mechanical occlusion. In every case of peripheral arterial disease, irrespective of the clinical diagnosis, it is essential to determine the relative proportions of these elements before a rational basis for treatment can be established. In different stages of the same disease, the proportion may

Change greatly. Thus it is their experience that most cases of thrombo-angiitis obliterans early in the disease, the role of vasoconstriction is much greater than in the later stages of the disease when the vascular lesions have passed the early acute stage.

TESTS FOR VASODILATION

This leads us to a discussion of the special tests for determination of the role of vascular spasm in production of the spasm, which are essential to any useful attack on the sympathetic nervous system.

The method of Adson and Brown² in arriving at this determination is to hospitalize all patients, administer typhoid vaccine intravenously, and a regional or spinal anesthetic, to determine the degree of vasospasm, and unless an increase in skin temperature over the digits of at least twice that obtained by the mouth temperature during the height of the fever, operation is not done. Kennedy³² also emphasizes the importance of estimation of the amount of vasodilation during fever.

Scott and Morton^{54,55}, realizing the diagnostic and prognostic importance of estimation by spinal anesthesia the amount of vasomotor spasm in vascular lesions in the extremities, sought to simplify the procedure so that it could be applied with minimal discomfort to ambulatory patients. It was already well established that the motor fibers to the vessels of the extremities, as will be dis-

cussed presently. They then undertook to determine what proportion of the increase in peripheral circulation (in normal individuals) seen after spinal and general anesthesia would be obtained under peripheral nerve block. They were chiefly concerned with the foot, which was easily obtained by infiltration about the posterior tibial nerve a little below the internal malleolus. The nerve at this point can almost always be felt after it has passed under the posterior tibial artery. If procaine hydrochloride is infiltrated into this region, conduction block anesthesia of the corresponding skin field involves most of the sole and the plantar surfaces of the heel and of all the toes. They found the vasodilator response to this nerve block quite effective in determination of the vasomotor gradient.

DISTRIBUTION OF VASOMOTOR FIBERS TO THE EXTREMITIES

Hamann, writing in Piersal's anatomy, mentions the distribution of fibers to the subclavian artery and its branches from the ansa subclavia, the distribution of filaments to the volar interosseous artery from the corresponding nerve and to the ulnar artery in the forearm from the palmar cutaneous branch of the ulnar nerve. Paterson in Cunningham's text-book refers to the branch supplied by the musculo-cutaneous nerve to the brachial artery. In Quain's textbook Symington mentions those described by

Paterson in Cunningham's text-book refers to the branch supplied by the musculo-cutaneous nerve to the brachial artery. In Quain's textbook Symington mentions those described by Hamann and also that described by Paterson.

Soulies' description in Poirier's treatise mentions the distribution of filaments from the median nerve to the brachial artery, to the volnar ulnar recurrent artery from the volar interosseous nerve, to the ulnar artery in the forearm from the palmar cutaneous branch of the ulnar nerve, and to the radial artery and vein from the volar terminal branch of the musculo-cutaneous nerve; also the direct supply of filaments to the subclavian artery and its branches from the inferior cervical ganglion.

Kramer made dissections on six upper limbs and found that while there was considerable variation, the constant general plan was as follows:

1. The sub-clavian artery receives its nerve supply directly from the sympathetic chain.
2. The more distal arteries are supplied by sympathetic fibers which have travelled to their distribution along special nerve-trunks and not along main vessels.

Dennis Crile²² cites signs of vasomotor paralysis in the area supplied by the median nerve as a diagnostic sign of a median nerve lesion.

METHODS OF SYMPATHETIC ATTACK

Leriche^{37,38} states that when you remove the sheath of an artery, the primary reaction is the characteristic physiological reaction against excitation. After several hours, varying from three to fifteen there is a local temperature elevation reaching two degrees or even three degrees Centigrade, and an increasing amplitude of oscillation in the pulsations of the artery.

In his cases in which he did his operation for trophic troubles leading to ulcers, twelve out of thirteen were followed by rapid healing. However, he states that relapse is possible if the cause of the trophic trouble is not removed, and that the cause is not always removed by the sympathectomy.

Callander²⁰ differs in certain fundamental principles from Leriche, who seems to consider that the majority if not all the vasomotor fibers to the extremities follow the sheaths of and lie in the adventitia of the larger arteries. Anatomists and physiologists concur in the belief that these fibers accompany and are embodied in the spinal nerves which run to these parts. This view is born out by the fact that in Callander's cases he was able only in one instance to demonstrate any post-operative rise in blood pressure, or increase in surface temperature.

Langley³⁶ found that after section of the sciatic and crural nerves, stimulation of the lumbar sympathetic causes no appreciable pallor of the foot. "Thus peri-arterial section in man, so far as it relieves peripheral vasoconstriction, in all probability does not do so by severing nerve fibers running with the arteries to the periphery."

Weir Mitchell⁴⁴ carries out the experiment of temporarily interrupting impulses through a mixed nerve by freezing his own ulnar nerve, and found an immediate increase in circulation. Brown in 1903 emphasized the vasomotor paralysis with hyperemia and hyperthermia which follows conduction anesthesia. Wiedhopf in 1924 made an extensive study of this hyperthermia, and advised its use in determining the height necessary for amputation.

While Leriche reports good results from peri-arterial sympathectomy, comparatively few of these results were on patients with thrombo-angiitis obliterans, and many workers, including Ginsburg²⁶, Allen^{3,4}, Scott and Morton⁵⁶, Miller⁴⁵, Archibald⁴, and Callander²⁰, present very discouraging reports of the results of this operation.

Strauss mentions two cases of thrombo-angiitis obliterans which he believes to have been benefitted by

periarterial sympathectomy, but Allen³ calls attention to the fact that one of these patients lost a toe by gangrene and the other required amputation of the leg. He remarks that "the beneficial results in thrombo-angiitis obliterans are not sufficiently lasting to warrant the procedure in this disease."

Muller⁴⁵ reports seventeen cases in which periarterial sympathectomy was done and states that "if permanent relief of pain and the maintenance of the integrity of the limbs be accepted as criteria for cure," he has had only two successful cases. In most cases temporary relief was obtained but relapse occurred after a few weeks or the oncoming gangrene necessitated amputation.

Ginsburg²⁶ states that many cases of thrombo-angiitis obliterans have as a concomitant feature of the symptom-complex pronounced vasomotor disturbances; but it is difficult to conceive how the advanced thrombus occlusion of the blood vessels can be antagonized by section of the vasomotor fibers surrounding the large blood vessels in the thigh.

Smithwick and White⁶⁰ report that pain in the lower extremities secondary to vascular disease can be relieved by alcohol injection of peripheral nerves and that this can be accomplished without paralysis of any important muscles of the leg or foot. Depending on the length of the nerve

trunk injected, the anesthesia produced may last but a few months or may be permanent. They state that the relief of pain has been responsible for the saving of six out of eleven legs otherwise doomed to amputation. It should never be necessary to sacrifice a leg because of pain. After an extremity has been desensitized by this method the foot frequently becomes drier, warmer and previous color changes are eliminated. The surface temperature may rise five degrees F. This is probably due to elimination of sympathetic stimulation both by relieving pain and by interrupting the course of the nerve fibers to their peripheral destinations. The majority of the sympathetic nerves course peripherally with the sensory nerves. They report that after an extremity has been desensitized, ulcerations which previously resisted all methods of treatment will frequently heal. In 1935⁶¹, comparing the results of the first twenty-five cases treated by this method with twenty-five preceding cases by other methods, they find a marked increase in the number of successful minor amputations and a decrease in the number of major amputations necessary in cases treated by nerve block by alcohol injection or crushing of sensory nerves of the lower leg. They found the operation very efficacious on the relief of pain. The circulation to the part may be increased because the anesthetic area is also deprived of vasoconstrictor nerves. The general condition

of the patient improves with the relief of the pain and makes other conservative measures more effective.

Royle in 1924 devised the surgical procedure known as lumbar sympathectomy. Adson² later adopted the abdominal route. The experiences of Adson and Brown with sympathetic ganglionectomy and trunk resection in the treatment of Raynaud's disease led them to employ the same procedure in thrombo-angiitis obliterans when vasomotor spasm was a contributing factor in the production of symptoms. The real problem, that of selection of suitable cases for operation, has already been discussed. In a study of a series of one hundred bilateral sympathectomies four of which required both cervico-thoracic and lumbar operation, they tabulate the results of eighty-nine bilateral lumbar sympathetic ganglionectomies and trunk resections and fifteen bilateral cervico-thoracic ganglionectomies with resection of the upper portion of the thoracic trunk. One of their charts, showing beneficial results of the operation, the complications encountered, and the number of fatalities with the causes of death, is herewith reproduced.

Thrombo-angiitis obliterans
treated by sympathectomy

	Operations	Improved	Average degree of improvement, %	Useful extremity	Complications
Group 1, uncomplicated					
Upper extremity	4	4	81	4	Pneumonia 1 incomplete Operation 1
Disease in lower extremity	19	16	76	16	neuritis, leg amputation neuritis, chordotomy death Death, 1: pulmonary embolism
Group 2, with ulcers					
Upper	1	1	90	1	
Lower	43	39	78	33	neuritis, 1: chordo- tomy neuritis, 2 Pneumonia, 1
Group 3, with gangrene					
Upper	10	10	82	9	incomplete operations 3 Pneumonia, 1
Lower	27	17	73	13	Deaths, 5; due to Pneumonia, 2 Cardiac, 2 Anesthetic, 1 Neuritis, 1
	104	87	80	76	

They found that following sympathectomy the incidence of necessary amputations was definitely lowered.

Since the vasomotor fibers are intermingled with other postganglionic gray fibers supplying sebaceous and sweat glands and pilomotor muscles, it is a necessity that these two be divided during sympathectomy and dryness of the skin is thus produced. This dryness is not serious and serves as an excellent index in determining whether all of the vasomotor fibers have been divided, for if they are not all divided sweating will persist. Lumbar sympathectomy includes postganglionic fibers to the hypogastric plexus, but since these fibers carry inhibition stimuli to the detrusor muscle of the bladder, the musculature of the rectum and contraction stimuli to the internal sphincters of the bladder, complaints are not made by the patient. This is undoubtedly due to the fact that other fibers carrying similar impulses remain uninterrupted in the presacral nerve and that voluntary control to the external sphincters is not disturbed.

Cervicothoracic ganglionectomy and trunk resection produce Horner's syndrome, but when bilateral the apparent enophthalmos, contracted pupils and the narrowing of the palpebral fissure are not conspicuous nor do they interfere with vision.

Telford and Stopford⁶⁵ report a series of forty-eight cases in which lumbar cord ganglionectomy was done, forty-two cases being operated bilaterally. They found the results very encouraging and believe it not only to be recommended, but the only procedure which offers hope of permanent relief.

Matas³⁹ observes that while in a good percentage of case, ganglionectomy is certainly indicated, a lumbar ganglionectomy or radicotomy is a serious procedure which is not applicable to all patients even when physiologically indicated. Neither, he says is the repeated induction of fever with typhoid vaccines always a satisfactory mode of treatment. Before resorting to the traumatizing radicotomies and ganglionectomies, one should exhaust all the simple and safer methods of physical therapy. In line with these suggestions he directs attention to the irradiation of the lumbar region with x-rays as a vasodilator procedure. These irradiations, advocated by Langeron and Desplats, Morin, Brunet, Zimmerman and others in France are directed to the suprarenals and probably act on the lumbar ganglia as well.

Crile²³ reports that the results of sympathectomy and adrenalectomy in three cases of endarteritis obliterans were negligible. Other opinions regarding lumbar ganglionectomy in its relation to the treatment of thrombo-angiitis

obliterans have been previously discussed.

Scott and Morton⁵⁶ very nicely summarize the various branches of the sympathetic nervous system attack. The following is excerpted from that article.

This operation is the procedure of choice in the young or middle-aged adult when the clinical evidence of a local circulatory deficiency and the functional importance of vasoconstrictor spasm are clearly established. The one important objection to this form of treatment is that it requires a major operation. The peripheral vasodilatation accompanying the systemic reaction to the injection of protein or inorganic chemicals has been advocated as a method of treatment in the milder cases in place of surgical intervention. The effect lasts from a few hours to several days. That this method would be useful as a substitute for operation in the older group of patients concerning the condition of whose myocardium there may be some doubt. It is exactly in these patients, however, that the dangers of such reactions become greater. Consequently, it does not help in the more difficult decision as to the method of choice for overcoming spasm. For these patients, paravertebral injections of alcohol have been advocated. This procedure probably does not give permanent relief; it is usually followed by rather severe neuritic pains, and

would make a later operation, if necessary, more difficult. Periarterial sympathectomy does not have sufficient merit to warrant its use in such cases. Injection of alcohol into the peripheral nerves below the main muscular branches not only relieves pain, but may result in improvement in local circulation when the latter is impaired by vasoconstrictor spasm. The two objections to this method of accomplishing the latter purpose are: First, anesthesia in the peripheral area accompanies the vasomotor paralysis. Second, vasoconstrictor innervation is reestablished in a few months. This method is helpful however in some difficult cases when operation and fever-producing injections are absolutely contraindicated by the patient's condition. The one procedure that permanently overcomes the detrimental effects of sympathetic vasoconstriction in arterial disease is sympathetic ganglionectomy. We hope some day to have a simpler method of removing as satisfactorily arterial spasm in the extremities.

SUMMARY

Although the condition now known as thrombo-angiitis obliterans had probably been known for many years, the first report on the subject was that of von Winiwarter in 1879, who used the term endarteritis and endophlebitis. In the next few years there was much confusion in the literature on this subject, until Buerger's excellent work on the pathology of the disease.

Buerger's classic description of the pathology of thrombo-angiitis obliterans has not been improved upon. There is first an acute inflammatory lesion with occlusive thrombosis, and the formation of military giant cell foci. Second is the stage of organization or healing, with the disappearance of the military giant cell foci, the organization and canalization of the clot, and the disappearance of the inflammatory products. Finally, the development of fibrotic tissue which binds together the artery, vein and nerves.

The etiology of thrombo-angiitis obliterans is not as yet determined. Excessive tobacco smoking is quite generally agreed to be a contributory etiological factor, although some consider it to be the direct cause of the disease and others believe it has nothing to do with the etiology of this disease. There is serious doubt at the present time as to the role of race as an etiologic factor.

Birthplace has been proven to have no etiological importance. Sex is a definite etiologic factor. The disease is almost unknown in females. The disease almost constantly occurs between the ages of twenty-five and fifty. Other suggestions that have been presented are focal infection, specific infection, climate, occupation, defective carbohydrate metabolism, intestinal putrefaction, vascular spasm, typhus fever, malaria, increased viscosity of the blood, and decreased clotting time of the blood. None of the etiological factors suggested fulfills the requirements of a direct causal agent.

The diagnosis of thrombo-angiitis obliterans is not difficult in any stage. There is a history of intermittent claudication, exercise pain, coldness and numbness of the extremities, later rest pain, and finally ulceration and gangrene. The physical signs are diminished or absent pulsations in the arteries of the lower extremity and pallor on elevation and rubor on depression of the extremity. Early diagnosis is of the utmost importance. Determination of the vasomotor gradient is of importance in determining the type of treatment.

There are two fundamental principles in treatment; first, to prevent the ischemia from doing harm; and, second, to aid the collateral circulation to keep pace with the obliterative process. The first purpose is in part accom-

plished by rest, postural treatment and exercise, relief from pain, and prophylaxis against infection. If the vasomotor gradient is low not much can be done with the second purpose except to aid the more peripheral distribution of the small amount of blood available. To this end, the best procedures are intravenous injections of large quantities of sodium citrate solution or hypertonic saline solution. Prohibition of smoking is considered important in treatment. Alternate pressure and suction therapy has given good results in the hands of some workers. Reversal of circulation in the diseased extremity, exposure of the extremity to white light, and the use of angioidilating drugs have also been suggested.

It is now quite generally agreed that in a fairly large percentage of cases, vasomotor spasm is a factor in the production of the obstruction and that vasomotor paralysis of the diseased extremity is of value in these cases. This has been attempted by production of systemic fever, x-radiation of the lumbar region, and periarterial sympathectomy. The best results have been obtained from lumbar ganglionectomy and trunk resection. Crushing or alcohol injections of peripheral nerves is useful in cases in which the more serious operation is not permitted by the general condition of the patient.

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