

THE ETIOLOGY AND PATHOLOGY OF THROMBO-ANGEITIS OBLITERANS.

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The intense interest which in recent years has centred about the problems presented by peripheral vascular disease has adequately demonstrated the meagre limits of the present knowledge of the nature of these maladies. Particularly is this true of thrombo-angietis obliterans. From a study of the literature it seems that most research has been directed towards the establishment of the pathology of thrombo-angietis obliterans, but there is as yet no clear knowledge either of the character of the initial lesion in the disease or its chronological development. It is the object of this paper therefore, to consider those etiological factors which are definitely known to be associated with this condition, and also, to consider the existing schools of thought with regard to its pathology.

Etiology.

Age Incidence. The maximum case incidence of thrombo-angietis obliterans is between the ages of twenty and forty-five years. It is a pre-senile peripheral arterial disturbance.

Race Incidence. Statistics show that, contrary to what was formerly thought, the disease is by no means peculiar to the Jewish race. Telford and Stopford describe numerous cases amongst people of pure British blood. Meleney and Miller describe twenty-four cases from Peking. White has reported many cases in Chinese patients, and states that the disease occurs in nearly all the provinces of China.

Sex Incidence. Buerger has stated that the disease is so rare among females that he doubts the possibility of its occurrence outside the male sex. Up to March, 1937, twenty-one cases of thrombo-angietis obliterans have been reported, but in many of these cases, although running a similar course as it does in the male sex, the disease has not only been mild, but it has been atypical. This difference in sex incidence of thrombo-angietis obliterans may be related to some endocrine basis peculiar to the male sex which could play a dominant part in the causation of the disease, or, it could be related to some focus of infection peculiar to men. Horton and Brown have shown that in sixty per cent. of their cases of thrombo-angietis obliterans, prostatitis was present, but that no direct causal relationship could be proved between this focus and thrombo-angietis obliterans.

Relation of tobacco to thrombo-angietis obliterans. Much has been written about the relationship of Buerger's disease and the use of tobacco. Barker's analysis of the use of tobacco in men in 350 cases of thrombo-angietis obliterans has shown that three per cent. have never used tobacco and twenty per cent. had used it in small quantities. He has also called attention to the fact that the disease apparently is more serious if tobacco is freely used. If tobacco is an important factor, one would expect a changing incidence of thrombo-angietis obliterans among women, with its increasing use by this sex. In a series of ten cases reported among women only three used tobacco.

Friedlander, Silbert and Lasky (1936), demonstrated that a gangrenous process could be produced in male rats by daily intraperitoneal injections of denicotinised tobacco extracts. None of the female rats developed this lesion. The fact that a gangrenous process could be produced only in the male is interesting in connection with the almost exclusive occurrence of thrombo-angietis obliterans in men.

Infection as an etiological factor. In the past much effort has been directed towards the establishing of an infective agent for thrombo-angietis obliterans. Rabinowitz claims to have isolated a gram negative, rod-shaped and beaded organism, and to have produced by the bacillus, the same lesion in the ears and feet of rabbits as that which was present in the leg of the human being. Again, Buerger has been able to reproduce typical lesions in apparently healthy ligated veins by paravascular implantation of clot from cases of thrombo-phlebitis. It has not been possible, however, to isolate a specific infective agent from superficial veins, the seat of acute thrombo-phlebitis.

The etiology on an anatomical basis. Popoff (1934) has considered the etiology of thrombo-angietis obliterans from an anatomical viewpoint. He has suggested that a congenital anatomical abnormality may be the basis of the disease. In the cases of thrombo-angietis obliterans that he studied, he found in the digits, abnormal arterio-venous anastomoses, that are different from the normal ones. He states that these abnormal anastomoses are found in the peripheral network of the digital vascular system. By diverting blood directly and continuously into the veins they diminish seriously the amount flowing from the capillary bed. As a result of this self-limited circulatory disturbance, the peripheral digits suffer chronic and unrelievable anoxia with consequent development of the

trophic changes and other manifestations characteristic of obliterating thrombo-angeitis. Both arteries and veins of the affected extremities undergo structural changes, and, depending on the duration of the disease and the size of the abnormal arterio-venous anastomoses, the entire vascular system of the body may show signs of involvement.

It seems that Popoff has described an effect of thrombo-angeitis obliterans which he considers to be the cause. One knows that a limb, the seat of thrombo-angeitis obliterans, may be warmer than its fellow of the opposite side, which increase in surface temperature is due to the development of numerous superficial collateral channels. It is possible therefore that the arterio-venous anastomoses that have been described by Popoff are merely such compensatory collateral circulatory vessels.

The factor of spasm. The ultimate histopathological picture of thrombo-angeitis obliterans is that of a subacute or chronic lesion indistinguishable from one resulting from inflammation. Although this may be so, it does not necessarily follow that the final histological features of the disease process is an indication of its pathogenesis, because it is known that any thrombotic lesion will present a picture of an inflammatory process, and that in the surrounding tissues there is also evidence of inflammatory reaction. Again, in the early stages of thrombo-angeitis obliterans it has been demonstrated by means of skin temperature reactions that the arterial obstruction may be partially or entirely due to vaso-spasm. The maintenance of this spasm leads eventually to damage of the vessel wall and subsequent thrombosis. There are cases on record where the vasomotor irritation from a cervical rib has resulted in thrombosis of the radial and brachial arteries with maintenance of the circulation in the subclavian and axillary arteries. The mechanical pressure effects can be entirely excluded in such a case. The thrombosis and associated gangrene in one or more digits was due entirely to arterial spasm. This evidence together with that of a similar thrombosis resulting after long periods of frequent angiospastic attacks in Raynaud's disease provide conclusive proof that continued spasm favours ultimate thrombosis in the spastic vessels.

Further, it has been shown experimentally (Rothlin 1923, Kaunitz 1930, MacGrath 1935, and Freed, Prag and Suzman 1936) by means of the administration of ergot or of certain of its preparations, that the production of continuous arterial spasm leads to a clinical condition and

pathological picture indistinguishable from the stages of the disease observed in thrombo-angeitis obliterans, namely, spasm, cyanosis, thrombosis and trophic lesions such as ulceration and gangrene. Moreover, it has long been known that poisoning with ergot (endemic ergotism) leads to intense vascular spasm followed by organic arterial obliteration with subsequent trophic changes.

With this evidence we feel that information with regard to the etiology of Buerger's disease could be obtained by investigations directed towards the establishment of those factors which produce continuous arterial spasm.

Pathology.

Notwithstanding the fact that most of the work on Buerger's disease has been concerned with its pathology, there is still no unanimity of opinion amongst students of the disease regarding its morbid histology. Two major schools of thought exist. The one holds that the disease begins as an acute panarteritis, associated with thrombosis, the process gradually becoming chronic and being characterised by periods of acute exacerbations relieved by stages of quiescence. The second group believes that thrombo-angeitis obliterans is a chronic process from the outset, beginning as a chronic inflammatory reaction in the adventitia of the vessels associated with intimal proliferation and secondary thrombosis; that all coats of the vessel wall are progressively involved, but that the disease always remains an essentially chronic disturbance.

Buerger, in his description of the pathogenicity and chronological pathology, postulated the following series of events: there is an initial acute inflammation with polymorphonuclear leucocytic invasion of the peripheral tissues and of all the coats of the vessel wall. Synchronously, thrombosis occurs in the area of inflammation. This is followed by replacement of the inflammatory cells by connective tissue, organisation and canalisation of the thrombus and finally a great overgrowth of connective tissue in and about the adventitia binding the artery, the vein and the nerve together. Mahorner, Telford and Stopford, and others, have expressed the opinion that the earliest pathological process consists in the invasion of the adventitia by lymphocytes. This change is associated with cellular proliferation of the intima. Subsequently a thrombus forms, completing the occlusion of the vessel. The thrombus becomes organised and canalised with replacement of the inflammatory cells by connective tissue. The lesion progresses to a fibrous matting together of the artery, vein and

nerve. In their opinion, the disease is essentially chronic rather than acute, and that the intimal proliferation probably precedes the deposition of the thrombus rather than occurring simultaneously with it.

We have reviewed the etiology and pathology of Buerger's disease and in the etiology of this condition particular emphasis has been placed on the factor of spasm. Although it is, perhaps, still too early to correlate the element of spasm with the histo-pathological features of Buerger's disease, the present day trend is towards the establishment of such relationships.

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Increase in the viscosity of the blood and vasospasm are found both in Buerger's disease and arteriosclerosis. The aim of treatment in both conditions is to increase the supply of blood to the extremities. This is done, firstly, by relieving vasospasm, which results in the dilatation of those vessels with resilient walls, and, secondly, decreasing the viscosity of the blood, which results in its easier passage through even narrow and rigid vessels.

Treatment of Vasospasm.

- (1) No tobacco.
- (2) Diet high in calcium and vitamins.
- (3) Eliminate worry.
- (4) Physical exertion should be commensurate with the diminished peripheral blood supply. Buerger's postural exercises are done three to four times daily.
- (5) Avoid exposure to cold.

Reduction in blood viscosity is obtained by intravenous clays of 250 ccs. of 2% sodium citrate solution, daily at first, and then reduced to three or two a week as improvement progresses.

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