FATTY STREAKS IN THE INTIMA OF ARTERIES.[1]

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WITH a view of determining the earliest stages of the arterio-sclerotic process our attention was attracted to those minute yellow streaks and dots which are so frequently observed in the arteries of young individuals. It is quite useless to argue the questions concerning the development of intimal scleroses if we study and discuss the late stages of the disease alone. We have ourselves fallen into this error, but, as has been recently pointed out, if we wish to gain a true insight into the complex question of arterio-sclerosis we must attempt to follow the lesion from its earliest beginning. This offers many difficulties, especially in the study of human material alone, while the relation of certain artificially induced arterial diseases in animals to those in man is not at all times evident.

Thus the problem reduces itself to one of the study of the many minute changes occurring in the walls of the arteries, in an attempt to find in one or more of them a succession of changes leading from the early and minute damage to the fully developed arterial lesion. It is well to point out that in studying such a lesion or lesions the successive stages are observed in the vessels from the different individuals, and possibly or even probably those individuals have not suffered the same disease or diseases of like severity as the preceding. The observer can therefore offer very little information from a single specimen of an artery as to the factors at work in the given lesions.

The type of disease which we have under discussion does not, at first sight, appear to have any bearing on Thoma's discussion of arterio-sclerosis. We are nevertheless drawn into direct contact with his work when, as we will show later, the outcome of some of these lesions with early fatty streaks is a condition which is indistinguishable from the later stages of true endarteritis. Thoma has recently reiterated his view concerning the arterio-sclerotic process. He still believes that the thickening of the intima by connective tissue is dependent upon the slowing of the blood current. Exactly in what

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manner the slowing of the blood stream acts upon the intima, and more particularly the connective tissue, he does not state. He suggests that the slow current may be associated with a poorer metabolism, that the stagnant metabolic products may irritate, or that the alteration of the current too may have a tugging action on the walls of the arteries. We must concede that these are all possible; but we must further indicate that each of these factors may be called into play without any previous alteration in the arterial wall, and particularly in the media. Thus it is obvious that the different postures of the body have an enormous effect in altering the hydrostatic conditions of the circulation. It is true, as Thoma indicates, that under certain conditions of the rate of flow of the blood when properly balanced with the peripheral resistance, the current of the blood is axial and the outer boundary of the stream is more or less at rest. It may be that with all the conditions given the plasmatic layer resting upon the inner circumference of the artery is immobile. That state, however, is changed immediately with the new conditions in which any one of the factors is altered. Thus the natural dilatation of the peripheral arteries in vasomotor inhibition will alter the relation of the lumen of an artery to the quantity of blood which is supplied to it. Muscular exercise constantly influences the relative size of the arteries, both by the direct excitation of the arteries and by muscular pressure on various vessels. Again, the alteration in the viscosity of the blood will tend to alter the rate of flow of the blood even when all the other factors determining the rate are kept constant. It is evident, then, that the circulation may readily undergo many changes in the rate of flow without any preceding structural alteration in the artery. True it is that the majority of these variations in the blood flow are transient; still, the recumbent position for recurrent periods of eight hours' sleep at a time must alter the hydrostatic conditions in the aorta very greatly. Moreover, the fallacy of these surmises, that local or more widespread slowing of the blood current, developing upon medial dilatation, is invariably the cause of connective-tissue development in the arteries, can be indicated by experiments and observations.

This study concerns itself only with processes in the intima of the arteries which are *degenerative* from the beginning. We wish to differentiate clearly such lesions from those which may begin as *productive* lesions on the surface, and which later develop into lesions having more or less degenerative characters about them. The beginning of each type can be clearly differentiated during the early stages of their development, while, later, much difficulty may be experienced in determining the nature of the earliest process.

The observations in this study were made on the arteries of a series of cases ranging in age from 1 to 73. The majority of the cases, however, were between the ages of 20 and 30. The vessels were obtained at autopsy, where

they were carefully examined for macroscopic evidence of superficial fatty streaks. Histological examination was then also undertaken, the specimens being cut frozen or in paraffin. For our purposes the freezing method was mainly used, although for cell study the thinner paraffin sections were more satisfactory.

The vessels from various parts of the body were examined, but it was soon found that particular attention had to be concentrated upon the aorta and the vessels arising at the arch. In all instances the changes when present were found in these arteries, and of these the aorta showed the greatest frequency of the lesion. A few instances were observed in which fatty changes were alone present in the carotids, and these changes were noted, as Chiari has pointed out, at or near the bifurcation. This author has found lesions at the bifurcation of the common carotid in individuals under twenty-five years of age where no changes were to be noted in the aorta or other vessels.

It is unusual to have a wide distribution of this superficial fatty lesion in the peripheral arteries. Changes do occur in many arteries simultaneous with fatty streaks in the aorta and carotids, but these changes are not of the same character as the fatty lesions, although both may have the same etiological factor. Thus small pearly thickenings of the intima were observed in the peripheral arteries, particularly in the renal and mesenteric arteries, while only yellow streaks were found in the aorta. In some of the older individuals there were easily recognisable old processes in the outer coats of the arterial walls, while the more recent changes were seen on the inner surface of the intima. Nodular and pearly thickenings around the mouths of the intercostal arteries were often observed in older persons, while in the same vessel the fatty streaks were arranged longitudinally in the thinner portions of the artery. Old calcareous deposits were present in a few cases, but never close to the more recent fatty streaks.

There are definite age periods when fat in superficial streaks is most commonly found in the intima. Between the ages of 20 and 30 the condition is very frequent; it is unusual before the age of 10 or after the age of 50. The frequency of this condition, therefore, does not increase with advancing age, as, apparently, does nodular arterio-sclerosis. We have observed the lesion four times before the age of 10 (6, 8 (twice), and 9 years respectively); each of these was found in an autopsy on a scarlet fever patient.

Naturally the most interesting cases for study are young individuals. In them the various causative factors are more readily approached, particularly when the individual has been robust until the final illness. It might not be safe to suggest that the final illness was the agent leading to the changes found in the arteries at death, but when we find with such regularity that typhoid fever is accompanied

by fatty streaks in the aorta and vessels of the neck we cannot but feel that the infection had something to do with the lesion.

Ages.	Number of Cases Examined.	Frequency of Fatty Streaks.
1–10	16	4 cases
11–20	12	8 ,,
21–30	15	12 ,,
31–40	22	7 ,,
41–50	15	4 ,,
51–73	10	1 ,,

In our experience these superficial fatty lesions were found most frequently in cases which had died of typhoid fever. In this disease it could be looked for with fair certainty in all individuals under 30 years of age. Frequently the condition was very marked, and it was only very infrequently that a considerable yellow streaking of the descending thoracic aorta was not found. In our records on typhoid fever in which the lesion was looked for at autopsy we have noted its absence in two cases only. This covers a series of thirty-five cases of typhoid fever. At one time it was thought that the intensity of these fatty streaks suggested the diagnosis of typhoid fever or a closely related infection. This, however, does not hold true in all cases. The lesion in typhoid is most frequently seen in the descending aorta and occasionally in the mesenteric artery. These lesions varying in intensity are also to be observed in pneumonia, in acute osteomyelitis, puerperal endometritis, scarlet fever, pernicious anæmia, and severe cachexias. We have found, however, that the frequency and intensity of the condition in these last two diseases is much less than for infections, particularly severe septicæmias.

On the other hand, in cases of accidental sudden death, two of typhoid fever and one of toxæmia of pregnancy all before the age of 20, and three of scarlet fever before the age of 10, there was no evidence of fatty change of the intima.

In general, the appearance of the condition is fairly uniform. The lesion consists of narrow yellow lines running longitudinally and lying close beneath the endothelium. When closely examined these fine streaks or lines are slightly raised above the inner surface of the vessel. At times the lines seem to be made up of multiple small points or dots which have, in part, coalesced. Besides these yellow streaks, many fine pale lines and dots are found scattered between

them. The position of the lesion is fairly constant. They are almost always found along the posterior wall of the aorta, lying between the pairs of intercostal arteries or close to their outer borders. The anterior and outer walls of the aorta are usually free from change. There are instances in which the process extends beyond the posterior wall and becomes quite diffuse. Nevertheless, the most intense lesions are to be looked for along the posterior border of the aorta.

A similar type of lesion is also seen at the base of the aorta just above the aortic ring. Here the yellow dots do not take any definite arrangement, but seem to lie more transversely to the vessel than in the descending thoracic aorta. Similar dots and streaks with a partial longitudinal arrangement are found in the large vessels arising from the aorta, and occasionally they are seen in many of the branches of the vessels of the abdomen.

All these lesions, when seen during the acute stage of the disease which apparently gives rise to them, are found to be immediately beneath the endothelial lining. In some instances the small elevations can be incised with a knife and some fatty material expressed from them. On the other hand, when the lesion is seen toward the end of the causative disease they appear to have a thicker layer of cells covering them, and at times there is a fairly smooth and glistening membrane forming a pearly nodule. Still other lesions are observed in which the yellow streaks are only slightly raised above the surface, and where the degenerative process appears to lie at some little distance below the surface lining.

In a microscopical examination of the vessels showing the superficial fatty streaks of the intima we have found that the process may begin in one of two places. In some instances, changes with the early deposit of fat are seen in the subendothelial layer of connective tissue alone. In other instances this layer may show little or no change, but the fatty change may be confined to the musculo-elastic layer, or what is more common the degenerative changes are found in both layers of the intima. We have noted that in either case an œdematous appearance develops early in the intima in both its superficial and deeper portions. The connective-tissue cells stand widely apart, and there is an indefinite granular material lying in the interstitium of the cells. The connective-tissue cells no longer occupy any particular relation to each other or to the direction of the lumen. In some instances the œdema of the strip of the subendothelial connective tissue makes the layer appear less cellular. On the other hand, it was particularly noted that in a later stage, when fat was being deposited in the tissue, the number of cells to the part increased considerably. The nuclei of these cells were usually oval and stained quite intensely. The cells developed fibrils which stained like those of connective tissue. Beside this were found a few widely scattered lymphocytes in and about the area of degeneration.

The fat earliest deposited in the subendothelial layer lies within the cells. Cells having the same character as the mature connective-tissue cells of this layer are seen to have an accumulation of fatty material, often extending in a wedge-shaped mass at one or both ends of the nucleus, and for some distance from the nucleus. This fat first appears as fine discrete granules, and in cells containing a greater quantity of this material the fat is aggregated into larger masses or globules.

We have not been able to demonstrate that in this process of cell proliferation of the intima any of the fat-containing cells have been derived from the endothelial layer. We have observed repeatedly that the lining endothelium which so commonly is shed after death has produced a narrow layer of loosely attached cells upon the surface. However, there was no evidence that these proliferated cells entered into the formation of the thickened and fatty layer of the subendothelium.

In the later stages of fat accumulation within the subendothelial cells it is noted that these cells retain their shape and the nucleus remains in the centre until the cell substance is widely distended, almost to bursting, with the accumulation of fat. Cells of various shapes are seen—oval, spherical or spindle shaped. These same spindle cells when cut transversely appear fairly circular. In the still later stages the cells with their nuclei disappear and leave the fat in the interstitial spaces. Specimens are not infrequently seen in which a few circular or spindle-shaped spaces are filled with a fatty material. This fat then lies between the tissue fibres and cells, and naturally in this condition it is difficult to state its exact origin. However, as the process of gradual accumulation of lipoid substances can be observed, and as the degeneration of the cell may also be followed, it seems fair to assume that the free fat comes from cell disintegration.

During this period, in which the subendothelial cells show the accumulation of fat, the elastic fibres in the hyperplastic zone show the faint yellow tinge of a fatty change. At first the colour change appears to be diffusely spread through the fibre without the appearance of granules. Later, fine granules appear when it is difficult to determine whether these are within or only on the surface of the elastic fibres.

The changes in the musculo-elastic layer are of quite similar order to those in more superficial portions of the intima where changes, as above described, are being brought about. In the former tissue there is evidence that the interstitial spaces become wider and are filled with a homogeneous or finely granular débris. The cells in the musculo-elastic layer appear more prominent, so that this band of muscle fibres is more readily recognised than under normal conditions of the vessel. Whether an actual increase in the number of muscle cells takes place is hard to say, but it is apparent that the

longitudinal muscle fibres are much more prominent and occupy a wider zone. The degenerative changes, which are recognised by the fat stains, occur in the muscle cells by the accumulation of fat granules in a greater or less quantity. The fine elastic fibres which are present between the muscle cells and the muscle bundles are also found to be attracting a fatty substance to them. These fibres eventually appear quite granular with the yellow lipoid bodies. Where the degeneration is advanced the muscle fibres become less numerous, and masses of fat granules are found to lie in the positions which the muscle cells formerly occupied. In no instance have we observed evidence of inflammatory cellular infiltration in the musculo-elastic layer during these processes.

The affected area of the superficial intima occasionally showed a slight reaction of proliferation with scattered lymphocytes. An acute inflammatory reaction was not observed either in or about the tissues showing the fatty change. On the other hand, the vasa vasorum of the adventitia and of the outer zone of the media were repeatedly observed to have a cellular infiltration about them. Lymphocytes and plasma cells were most abundantly present, with stray polymorpho-nuclear leucocytes. In these situations, however, there was no evidence of the accumulation of fat in the tissues. The media and adventitia showed no other evidence of change which could be associated with the condition arising in the intima. In fact, in young individuals no alteration of any other tissues was observed, while in adults, and in particular those beyond middle age, varying lesions were observed, common for this period of life, in one or other of the arterial coats. In no instance was a former lesion found to influence the character of the recently acquired fatty streaks.

One feature, however, of sclerosed arteries was evident, that the vessels with former intimal sclerosis, either nodular or diffuse, rarely showed fatty streaks even when the patient had suffered from a disease which in the young adult would have been followed by these lesions. It would appear that where the subendothelial layer had been thickened with the production of connective tissues it no longer reacted to irritants as formerly. Degenerative changes do, of course, develop in the thickened fibrosed intima, but these occur in the progressive process of intimal sclerosis.

The fat, as we have observed, is at first deposited within the living cells and in the elastic fibres. Later, free fat is found between the tissue cells and lying as fine droplets upon the different fibres. In some of these deposits anisotropic globules, like myelin, were seen. The fat and fat-like substances could be dissolved from the tissues by alcohol and ether, while no lipoid substances insoluble in these solvents were observed. All of the fat stained after the manner of neutral fats.

From our observations it appears quite definite that fat may be

deposited in streaks either in the subendothelial layer or in the deeper musculo-elastic layer. Or again, both layers may be affected at the same time and the lesions coalesce, so that a condition of "fatty degeneration" extends from the endothelial layer to the innermost lamella of the media. What process governs the laying down of fat in this or that layer of tissue, or why certain areas in the arteries are the sites of predilection, has not been determined. The main interest that attaches itself to the study is the relation of the fatty streaks of the aorta to the more severe and extensive atheromatous processes.

We have repeatedly observed that as fat accumulated in the subendothelial or musculo-elastic layer, the superficial portion of the intima became thicker and formed a small nodule of flat and parallel cells over it. This was particularly evident in those cases where the process had developed to the degree in which the fat-laden cells were destroyed and liberated their contents into the interstitial spaces. The degree of proliferation varied greatly, but the same compact mass of an almost hyaline-looking tissue was always produced. We were not able to determine whether these new cells were of endothelial origin or were derived from the layer of subendothelial connective tissue immediately beneath this.

As we study these lesions in succession we come upon some in which we can no longer distinguish the sequence of events. The subendothelial thickening forms a definite nodule of long and narrow spindle cells with much hyaline material between them, in which delicate elastic fibrils are found. Below this proliferative nodule is an isolated or diffuse fatty degeneration of the musculo-elastic layer or of the hyperplastic layer. This process, even in the presence of fatty streaks of the intima, makes it difficult to make a positive statement as to whether or no the degenerative condition has been primary. We believe that some, at least, of these lesions have their origin in a primary degeneration of the deeper portions of the intima, with a secondary proliferative reaction close to the endothelial lining.

Our findings are in accord with those of Jores (1903 [4]), Askanazy (1907 [1]), Benda (1909 [2]), and others.

These observers believed that the superficial fatty streaks of the intima were closely associated with advanced arterio-sclerosis. Jores was the first to show that the small white or yellow streaks of thickening found in young individuals were the beginning of arterio-sclerosis of the aorta. He found much of the fatty change in the musculo-elastic layer, where the elastic fibres in particular were altered in the degenerative process. The thickening of the layer on the surface was a condition arising secondarily to the deeper degeneration. Askanazy, while he admitted that the fatty streaks might progress to definite atheromatous processes, believed that many of them disappeared without advancing into the more serious lesion. On the other hand, Thorhorst (1904 [7]) and Hallenberger did not consider the fatty streaks of the intima as important factors in the production of arterio-sclerosis.

They point out that minute thickenings may be observed in the intima without fatty change.

Thorel (1910[8]) points out that the small fatty areas produce a change in the character of the inner layer of the artery which alters its elasticity and which must be recognised as a definite manifestation of a progressive tissue degeneration. In recognition of this early and progressive change, which combined with it some characters of sclerosis, Marchand (1904[5]) applied the name of athero-sclerosis.

The frequency of these fatty lesions in the vessels of young individuals with acute diseases, and their absence, microscopically, after a year or two, demands some explanation, if we consider they have any association with true arterio-sclerosis later in life. There can be no doubt but that many of these superficial lesions disappear almost entirely and leave the artery in an elastic condition equal to normal. We do believe, however, that although the débris and fat of the degenerative process may in some areas be fully absorbed, the proliferated cells of the subendothelial layer are permanent, and although they do not form isolated nodules assist in producing a more or less diffuse thickening of the intima. On the other hand, the more severe lesions, which have caused the destruction of cells in the musculo-elastic layer and also in the hyperplastic layer of the intima, have a more extensive reaction in the subendothelial layer in producing localised nodular thickenings which are permanent and indistinguishable from endarteritis nodosa. In them, however, the products of degeneration are not readily absorbed, so that these early thickenings of "endarteritis" always have fat and débris in their deepest portion. Such areas have all the characters of chronic endarteritis with early atheroma, and there is no reason to believe that the process cannot go on to atheromatous ulceration.

It is evident, from our finding, that it would be most difficult to determine the process of development of an atheromatous area after it was fully established. From our observations and those of others it is seen that an atheromatous process may be a degenerative lesion from the very beginning, with more or less proliferative reaction above it. On the other hand, Jores and others have determined that the primary intimal hyperplasia may be followed by fatty and other degenerations. We are not familiar with any definite points by which a well-developed atheromatous process may be recognised as coming from one or other process.

In general, the situation of the fatty streaks about the intercostal vessels is the same as the nodular endarteritis. Each is commonly found distributed on the posterior surface of the descending aorta. The thickening of the actual mouths of the intercostal vessels is a process which not infrequently has the condition of fatty streaks of the intima as a forerunner. In such cases the nodular endarteritis is a secondary result of an irritative process.

It is evident from these observations that there is a direct relation

between acute infective diseases and progressive lesions in the intima of the larger arteries. These lesions, though apparently of little account at the beginning, may become autochthonous and develop into definite nodular endarteritis with atheroma. Thus even when the initial factors leading to the fatty streaks are removed a vicious process is established which may lead to a nodular arterio-sclerosis or atheromatous ulceration.

We have found no evidence that before the development of the fatty streaks of the aorta a degenerative or other condition in the media is associated with the growth of connective tissue in the intima; but there is every indication that the production of tissue in the intima is the result of a direct irritation of that tissue by the presence of infection or toxins or of the stimulation by the products of a primary degeneration in that layer.

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