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FATTY DEGENERATION OF THE INTIMA OF ARTERIES.*

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The tendency for the arterial tissues to undergo a fatty degeneration,† and the importance of the process in the pathogenesis of arteriosclerosis, has been repeatedly commented upon, but different views have been taken on the immediate part which the degeneration plays in relation to other tissue changes of the arterial coats. Moreover, no unity of opinion has been reached as to the tissues which suffer this degeneration, or in indicating which type of cell, in the state of degeneration, is of prime importance in bringing about serious structural alteration, the end result of which is commonly discussed as atheroma. Prior to Virchow's classification of the fatty changes in the arteries, these were all discussed under steatomatosis, a term which was not alone applied to fatty degeneration of the arteries, but also to similar tissue changes of the organs. To-day in making the pathological distinction between fatty degeneration and infiltration, this term has been dropped.

Desirable as it may be to make a firm distinction between fatty degeneration and fatty infiltration of all tissues showing the accumulation of fat or lipoid bodies under pathological processes, difficulty is yet encountered in differentiating a hyperphysiological process from truly pathological degeneration. All tissue cells are not equally active or sensitive in dealing with fatty materials in their nutrition, some being unusually prone to indicate a slight intra- or extra- cellular disturbance by the accumulation of granular or globular fat in their protoplasm. Such unusual overloading of their protoplasm by foreign fat may occur without any demonstrable degenerative processes in the cell structure. On the other hand, the presence of fat within a cell which otherwise also

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† The term fatty degeneration is used to indicate the abnormal accumulation of Sudan staining substances in cells and tissues.

shows processes of decomposition in protoplasm or nucleus, may be accepted as indicative of a true fatty degeneration, in the sense that the metabolism of fats cannot be properly accomplished in the functionally incapacitated cell. It is probable that the accumulation of fat in excess, in the tissues of the arteries, owes its presence both to true degenerations as well as to processes of a hyperphysiological nature. On the other hand, an accumulation of fat may occur within a tissue, in which its presence is not associated with cell activity or inactivity, but in which the living cells play no direct part, the fatty materials accumulating in the vitally inactive intercellular substance through chemical affinity. These extracellular deposits play no small part in the localization of lipoid masses in the arterial walls. We have recently pointed out the affinity of old amyloid deposits for fat, a process which appeared in part physical rather than chemical. We will later refer to a similar affinity for fat possessed by the hyaline intercellular substance of chronic endarteritis. In these latter instances, the fat is found to deposit only as the tissue changes of the vessels have passed from one state to another, until the nature of the degenerative process is such as to attract fat or lipoid bodies to itself.

In the arteries the important tissue changes associated with the deposit of fat occur in the intima. The muscle cells of the media may also show fat granules in their protoplasm, and, in fact, demonstrate these in the aorta of all individuals over fifty years, but no such important significance may be attached to this medial degeneration as a similar process in the intima. Virchow made a distinction between the superficial fatty deposits (fatty degeneration) of the intima and atheroma. The former he claimed was a process of fat accumulation within cells which remained superficial, while the latter was destructive and deep, lying upon the inner zone of the media. Jores has pointed out, and we believe rightly, that the distinction thus given is superfluous, and that many areas of superficial fatty changes may continue to increase and by the development of a fibrous plaque over the surface, come to take a deeper

position from the vessel lumen. It is quite probable that not a few atheromatous processes have their beginning in the superficial fatty streaks which are so prone to develop in the course of acute systemic infections. It is of importance, however, to indicate that not all superficial fatty streaks, particularly of the aorta, give rise to atheroma, for prominent and common as these are in acute infectious diseases (typhoid fever, septicemia, pyemia) and intoxications (following extensive burns, cholemia, uremia), they in great part disappear upon recovery from the acute illness. The problem of the permanency of these degenerative lesions is to a great extent associated with the nature of the process, and, as we shall point out later, superficial fatty streaks in which the fat is found within the protoplasm of tissue cells, disappear much more readily than masses of lipoid materials in the interstitial substance or in the elastic or connective tissue fibers. Where fat accumulates in undue quantities within cells, which though degenerated are still living, the subsequent disposal of it is controlled by the cell. After removal of the noxious agent the cell on recovery utilizes or discharges the fat in a form which does not localize in its vicinity. On the other hand, the presence of fat or lipoid substance in the relatively inactive tissue fibers or in the tissue spaces, is disposed of only by chemical combination, less frequently by decomposition, through the agency of the tissue fluids. Soluble compounds may be the result, but too frequently insoluble compounds with calcium (Klotz, 1905) are the result. It is mainly this which determines the development of atheromatous masses from the superficial fatty streaks. We would thus prefer the use of the term fatty degeneration (as regards arteries) for those processes in which an undue amount of fat is present within cells or their fibrillar processes, while the term atheroma may be applied when the fat lies free in the tissue spaces where it may be recognized both macroscopically and microscopically as a smeary, gruelly mass. From the very nature of the process where cells have undergone fatty degeneration with subsequent death, the atheromatous area not alone contains

the fat substances of the cells, but also the protoplasmic detritus of their bodies. The composition of the atheromatous deposits is hence very mixed, while the lipoid contents of the living cells is relatively simple.

The importance of fatty degeneration in the intima of arteries, though commented upon by all investigators of the subject of arteriosclerosis, was particularly emphasized by Jores. For him, fatty degeneration of a distinct form was an essential part of arteriosclerosis, and conversely it is to be taken from his attitude that arterial lesions lacking this process are not to be classed as arteriosclerosis. In his earlier work (1903) upon which the present-day definition of arteriosclerosis of his school still rests, he indicated that the essential features of arteriosclerosis are a splitting of the internal elastic lamina and a hypertrophy of the longitudinal muscle layer accompanied in all instances by a fatty degeneration of these muscle cells. Connective tissue proliferation may subsequently invade the damaged musculo-elastic layer or give rise to a plaque over the areas of degeneration. Fatty degeneration of the intima he claimed was always primary in the deep muscle layer and was never primary in the superficial connective tissue plaque of the intima. This we have found to be erroneous, and being so, seriously opposes the narrow and incomplete viewpoint of the pathogenesis of arteriosclerosis as defined by Jores.

In the intima we have found that every type of cell and tissue normally present in this structure may undergo fatty degeneration and, what is more important, may show this degenerative process in the absence of any constant preceding lesion. Thus at times the elastic fibers, the muscle cells, the connective tissue cells, the connective tissue fibers or the lining endothelial cells may first show deposits of fine or coarsely granular fat in their substance, and, in a recent analysis of the intima of the aorta in the vicinity of the intercostal arteries, we have been surprised to find the frequency with which the connective tissue cells and fibers have contained fatty materials in the absence of degenerative change of the deep muscle layer. This is true also for the

elastic fibers, which may undergo an alteration in their composition with the gradual impregnation by fatty substances. There is, however, another type of cell which appears to be foreign to the normal intima, but which under conditions of disease makes its appearance in the superficial or even deep portion of the intima and is characterized by an abundant fat content of its protoplasm. Recently this type of cell has received particular attention by those studying the experimental intimal lesions induced by feeding cholesterin mixtures to herbivorous animals. By Anitschkow it is referred to as the "cholesterinesterphagocyte," while we have spoken of it as an endothelial or lutein-like cell. This cell deserves special attention as it is a common structure in human arteries and may be present in such numbers and clusters as to be recognized by the naked eye.

Fatty processes of various kinds are not alone of importance because of their frequent presence in different types of arteriosclerosis, their association with the development of atheroma, the variety of tissues attacked, but also because they constitute a type of change which, after middle life, is constantly found in the muscle tissues of some of the arteries, and indicates a diminished functional capacity of the vessel wall. This is particularly true of the aorta, where on the whole fatty degeneration both of the intima and media are more frequent than in the peripheral vessels. Moenckeberg reported the frequent finding of severe medial disease of the peripheral arteries in which no evidence of fatty lesions of the intima were to be found. Likewise Hallenberger found an absence of fatty change in the intima of the radial artery even where this inner coat was greatly thickened. Similar observations are reported by Jores, where the intima was thickened under a process of "connective tissue hypertrophy" or true endarteritis. We have also noted the presence of moderate and even severe intimal thickenings in which no demonstration of a fatty degeneration was possible, but we can by no means assert that these proliferative processes without degeneration are unique in their pathogenesis or structure, which differentiates them from those with fatty

change. Regardless of the associated structural alteration which may accompany, precede or follow the fatty degeneration of the intima, the deposit of fat within the cells or their fibers is the result of a nutritional change, an asphyxia, or an intoxication, and in the different cases the damaging factor is very various. In some cases fatty degeneration may be a very early sign, in others only a very late one. Bacterial intoxications, though not even constant with the same organism, may lead to an unusual fatty degeneration of several kinds of cells in the intima with very little evidence of a proliferative reaction (typhoid). In others again, where the tissue response is slower, as in syphilis, and where a proliferative reaction of the intima is accompanied by the development of new capillaries from the vasa vasorum and only follows the medial disease, relatively little evidence of fatty degeneration is found. The commonly recopied statement that no fatty degeneration occurs in the syphilitic endarteritis is incorrect. Microscopical analysis of such lesions will demonstrate in the majority a greater or less amount of fat in the newly developed connective tissue cells, their hyaline interstitial substance as well as in the greatly altered elastic fibers. It is seldom, however, that the degeneration leads to the liberation of such quantities of fat as to constitute atheroma.

To Jores we are indebted for pointing out that the muscle fibers of the deep intima which undergo hyperplasia, in response to a prolonged increase of the blood pressure, are very liable to fatty degeneration. It is in fact this combination of circumstances which, along with the splitting of the internal elastic lamina which bounds them, constitutes for him arteriosclerosis. The liability of tissues, after undergoing extensive hyperplasia in response to a continuous acting cause, to suffer degenerative processes may be observed in a variety of structures of the body (kidney, heart, liver). It is probable that the work-hypertrophy which appears in the musculo-elastic layer in response to the greater circulatory stress thrust upon the vessel walls, suffers fatigue, when owing to the limit of hypertrophy in relation

to the available local nutrition, having been reached, the hyperplastic tissues suffer an asphyxia and starvation. These hyperplastic processes of the musculo-elastic layer are not accompanied by any increased vascularity of the tissues but it is probable that the not uncommon connective tissue overgrowth, which becomes associated with this process, still further interferes with such nutrition which the intima obtains from the lumen of the vessel. We have in several instances observed the presence of fatty degeneration of the cells of the intima and the inner layer of the media, opposite a complete thrombosis of the arteries of the extremities, while in the peripheral parts of the arterial coat, as well as in the artery lying proximal to the point of occlusion, evidence of a fatty change in the tissues was wanting. By this it is suggested that the arterial wall is in part at least dependent for the nutrition of its inner layers upon a direct absorption from the lumen of the vessel.

By whatever means the tissues of the intima suffer and tend to accumulate fatty materials, be it through the harmful action of bacterial toxins (B. typhosus, streptococci), exogenous or endogenous poisons (tobacco, lead, adrenalin, absorption products from severe burns), mechanical stress (high blood pressure) or direct nutritional disturbances, the process may be best understood in the light of an asphyxia of the cellular elements. In each instance the functional activity of the cells is depressed to a degree that a proper intracellular metabolism is no longer possible. The fatty materials brought to the cells in a state of solution are absorbed but not completely worked over, with the result that the unfinished products form a deposit within the cells. Obviously some tissues are more easily influenced by certain factors than others, and will hence show the presence of this abnormal product at an earlier period Nor do we always find the cells exhibiting fat in the same order or sequence, for at times the muscle, at others the connective tissue or the lutein-like cells may first demonstrate the deleterious influence of the particular agent. At all times, the particular agent and its selective action upon tissues, as well as the

intensity of its influence, must, to a great extent, determine the character of the degeneration.

In the human subject the surface endothelium of blood vessels commonly shows the presence of fat in acute inflammation. Particularly is this noted in the small arterioles and capillaries in the vicinity of an acute or subacute reaction, and may be observed in appendicitis. Such evidences of fatty degeneration appear to have little significance and rapidly disappear after healing has been complete. It may be suggested that the granules of fat have been phagocyted by these cells, but in the absence of similar deposits in distant parts, it may rightly be assumed that these cells have been influenced during the inflammatory process to alter their functional activity. Seldom do these deposits of fat amount to more than granular accumulations about the nucleus, and their presence is only recognized by the microscope. Under similar conditions, but particularly in the presence of subacute and chronic inflammation, is observed an endothelial type of cell which becomes loaded with a simple form of fat. These cells we have recently described arising in the intima of the aorta during processes of connective tissue hyperplasia. They are endothelial in character in as far as the cells are large with a centrally placed nucleus and a wide protoplasmic border. The nucleus is round and stains quite distinctly. The protoplasm appears granular or vacuolated when treated with alcohol, and resembles the character of the lutein cells. We are, in fact, of the opinion that these cells bear a close relation to similar large cells found beneath the peritoneum as well as in the musculature of the Fallopian tube during chronic inflammation. It is not probable that these lutein-like cells have an association with the lining endothelium of the blood vessels. Their nuclei are smaller and stain more intensely, and the protoplasm is decidedly more granular. The fat content, too, is much greater and its distribution is uniform, not being isolated to the vicinity of the nucleus. True phagocytic properties have not been observed in association with this

type of cell. Anitschkow suggests a lymphocytic origin to these cells.

Up to the present the lutein-like cell has been most frequently encountered in the intima of the aorta, but has also been observed in areas of fatty degeneration of the peripheral vessels. Their presence is with difficulty determined in transverse sections through the arteries, where they may easily be confused with swollen connective tissue cells. When early (preferable to late) areas of superficial fatty degeneration are cut on the flat these cells may be observed in clusters, either near the surface or in the connective tissue layer close to the internal elastic lamina. The closely packed clusters show no evidence of stroma but appear to form groups lying in large spaces (Figure 1). These cells contain such an abundance of fat that their walls are indistinct, and the nucleus is frequently overshadowed, so that groups of these cells may be mistaken for atheromatous areas with only extracellular fat. Alcohol treated sections will demonstrate the individual cells in the groups as well as the spongy character of the protoplasm.

The origin of these cells is still indefinite, but they play an important part in the development of the fatty streaks of the aorta, as well as the subsequent atheroma arising from a breaking down of their cell bodies with the liberation of free fat into the interstices of the tissue.

We have observed these cells under conditions of inflammatory hyperplasia of the intima, but have missed them where pure hyperplasia of the musculo-elastic layer of the intima alone was present. Moreover, we have never found them in the deep media or the adventitia. Their presence in the connective tissue layer of the intima alone, and particularly under conditions of reaction where this layer is in a process of hyperplasia, suggests their development through the influence of an irritant acting upon the inner coat of the artery. The presence of these cells in the same tissues of animals under experimental conditions is of great interest. Ignatiobraski, Anitschkow, Saltykow and others have found similar cells in the aorta of rabbits when fed with cholesterin

containing food. Under these circumstances fatty plaques appear in the intima which are to a great extent made up of lutein-like cells. In the early stages the fatty compounds within these cells have doubly refractile characters, and undoubtedly in part at least, the double refractile bodies observed in atheromatous masses have their origin from these structures.

In the human arteries, however, evidence of fatty degeneration not only occurs in this peculiar type of cell, but also in the connective tissues themselves. We have never missed its presence, in at least microscopic quantities, in the aorta showing even the earliest hyperplasia when the connective tissue thickening was associated with the occurrence of the large endothelial-like cells. Whether, as is suggested by some, there is a genetic relation between the connective tissues and the cells above described we are not able to say at this time. The degeneration of the fibrous tissue cells has the character of a fat deposit in the protoplasm, not only in the body of the cell, but also in its stellate processes (Figure 2). The fat is in the form of granules or small globules which do not coalesce, and which, even when the quantity is of fair amount, does not bring about a distortion of the cell body. The position of the nucleus remains unaltered. Hence, when cut on the flat, the connective tissue cells of the intima may always be distinguished by their morphology from other types. The character of the fatty degeneration here closely simulates the appearance of degenerating connective tissues grown in vitro.

These processes in the connective tissues of the intima also constitute a type of superficial degeneration which may be recognized on the inner surface of arteries as yellow streaks. Seldom do these cells show complete disintegration to form atheroma, save when they become involved in the border of a previous area of softening, and it is more than probable that a complete recovery from the process of degeneration commonly occurs. As these cells lie as a loose thin layer beneath the endothelium, the fatty materials are

not aggregated at one point, and the macroscopic appearance of the condition is rather more diffuse than sharply defined. These degenerations are particularly frequent in the aorta suffering the early stages of endarteritis as we have elsewhere described. This early inflammatory process, provoked by bacterial toxins as well as the absorbed poisons of tissue disintegration (extensive burns), is a lesion of the subendothelial connective tissues in which infiltration, proliferation, and degeneration may go hand in hand. It is in these, particularly, that the fatty degeneration of the connective tissues may be found (Figure 3). On the other hand, that form of endarteritis developing as a secondary reaction over deep atheroma may in its early stages not show fatty change. But in this latter type, developing as a slowly progressive sclerotic plaque another form of fatty degeneration of the connective tissues is not uncommon. Here the fibrous tissue is very sparse in cells and nuclei, but the mass consists of a dense aggregation of fine fibrils which have a homogeneous appearance. It is difficult to trace the individual fibers, as the intracellular substance is very abundant and of a hyaline character. Occasionally much flattened and spindle connective tissue cells are found to contain a few fat granules at the ends of the nuclei. Whereas, in the new connective tissue cells fat is seldom found in the fibers or the interstitial substance, the presence of this substance in the hyaline plaques is quite common. The interstitial substance and the fibers undergo definite chemical change by which the hyaline appearance of the areas is produced. In this state there appears to be a greater affinity for fatty materials through which the hyaline area becomes impregnated with fat. The fat which localizes in the hyaline plaques does not appear to owe its presence to cell activity. It forms a slight and diffuse impregnation of the area which, when stained with Sudan III., gives a washed appearance with the presence of very few granules. At other times the fat appears in wavy strands, not sharply demarcated, but yet showing that the fatty material is in or upon an altered connective tissue stroma which lies parallel to the lumen and is thrown into

folds by the contraction of the walls. Elastic fibers are not to be found in these areas, but in a layer which is disposed in lamellæ and which stains well with eosin. The deposition of the fat in this altered connective tissue stroma appears to bear some similarity to the deposition of fat and lipoids in old amyloid deposits. The diffuse fatty materials in the hyaline plaques of arteries appear as relatively simple fats and may be removed by alcohol, ether, and other fat-solvent agents. Its association with the hyaline groundwork is probably a physical or loose chemical combination.

The impregnation of fat into the hyaline connective tissue plaques has an important bearing not only because of the actual presence of this foreign material but in indicating a progressive process of degeneration which has attacked an area of fibrous tissue hyperplasia of the intima. It indicates that a slow destructive process may attack areas of connective tissue thickening, quite regardless of the nature of their origin. It is by the progressive increase of this process that atheromatous masses gradually involve more and more of the overlying connective tissue cap, until an erosion through to the surface has taken place — the atheromatous ulcer.

The elastic tissue of all parts of the artery may be subject to a fatty degeneration, but as Jores has pointed out, the most common and most important type is seen in the internal elastic lamina of the intima. Under conditions of disease of the media, the parallel lamellæ of that coat may show a similar process. Under most varied conditions do we find fat deposits outlining the innermost elastic band of the arteries. Both in the small arteries as well as the aorta and its branches may we observe this structure attacked, and at times it would appear that the greatest damage to the arterial wall at a particular point consists of a fatty degeneration of the intima. However, close observation will indicate that other reactions are also present, of which a hyperplasia of the intima, either of the deep muscle layer or of the superficial connective tissue lamina are the most common. The presence of fatty deposits in the internal elastic lamina

is not to be viewed as an individual process, but rather as an indication of a previous alteration of the elastic structure by which its normal characteristics have been destroyed, so that it no longer reacts in a normal fashion to stains, but has acquired the chemical property of localizing fatty materials in its substance. The morphology of the elastic lamina is altered as has been described by Dmitrijeff, Jores, Fisher, and others. At times the lamina is granular so that its continuity is broken, leaving spaces in which the non-staining strands or fibrils of the elastic substance are seen; granules may appear along the inner border of the band (Aschoff), and particularly when an inflammatory reaction lies beneath the endothelium; the lamina may be broken up into fine fibrils, so that the appearance of a loose untwisted rope is obtained. In the last type the stain for elastin is wanting or is obtained very poorly. The appearance of the structure suggests a loss of the interfibrillar substance with its elastin content, so that the fibrils of the elastic bands are liberated, forming the loose striated bundle. It is probable that the brush-like appearance to the so-called ruptured elastic lamina has its explanation in a similar process. The bands have not mechanically ruptured, but a loss of continuity of the stainable material results, with, at times, a destruction of the fibrillar components of the elastic band, with the result that the partly disturbed elastic fibrils form brush-like extremities. All of these types of change of the elastic fibers, and particularly those resulting from a chronic course in which complete loss of the tissue constituents does not occur, may be accompanied by the deposit of fatty materials. Sudan III. picks out the affected areas very sharply and it is not uncommon to find an altered elastic lamina showing the only fat deposit in the artery. Here again, as in the accumulation of fat in the hyaline stroma of the connective tissue, the deposit depends upon a chemical affinity of the products of primary degeneration and not upon any direct cell activity.

Elastic fibers (internal elastic lamina) showing the presence of fat in their substances are, as above stated, not normal in their morphology or composition. The staining

reactions are sufficient proof for the latter. The tendency to enlarge in their diameter, to show their internal fibrillar structure and the separation of many fasciculi is an evidence of the former. It is suggested that an altered nutrition (Jores) or the changes induced by the undue stress of work, as well as the direct action of toxins (Katsurada) or poisons may so affect the elastic tissue as to bring about these appearances. Those changes observed in them under conditions of inflammation are to be classified under toxic effects, taking place synchronously with the inflammatory reaction.

As the degenerative processes of the elastic fibers of the arteries are so commonly associated with the accumulation of fat, it is quite easy to follow the different stages in the disintegration of the elastin materials by means of special stains (Weigert, Verhoeff, Sudan III. and others). The definite chemical change in the composition of the elastic structure and the character of the fat deposit suggests that the accumulation of lipoids in amyloid, hyaline and elastic structures is closely related.

We have previously mentioned the occurrence of a fatty degeneration of the muscle elements of the deep intima (Figure 4). The actual evidence of fatty bodies in the intimal muscle elements themselves is not commonly observed, for it is only seen by those who search carefully the vessels of middle-aged people and who have the good fortune to obtain specimens in which the longitudinal muscle cells may be unmistakably differentiated. The mere presence of spindle-shaped cells in the region of the musculo-elastic layer even though those cells show fatty degeneration is insufficient to make a diagnosis of degenerated muscle cells. Lately through the influence of Jores' work we have, without further verification, spoken of all forms of fatty degeneration in the deep portions of the intima as of this type. We would here repeat that, although it has been amply demonstrated that a proliferative response on the part of the musculature of the arteries, and particularly by the muscle elements of the deep intima, occurs to physical and mechanical stress (increased blood pressure) and that processes of degeneration are liable

to develop in the hyperplastic layer, we must also appreciate, as we have above described, that several other tissues also suffer a similar reaction, and when lying near the musculo-elastic layer may lead to much confusion in the pathogenesis of the lesion. In short, we can by no means assume that deep degeneration of the intima is necessarily a process in the musculo-elastic layer, nor that such reactions are indicative of a common causative factor. That atheroma may result from deep muscular degeneration of the intima (Jores) as well as from a similar lesion in other tissues of the intima we have indicated above.

Thus it is seen that a degeneration may involve every type of tissue in the intima. Nevertheless, our interest is stimulated as to the frequency and importance of the processes, as well as the relation of the lesions to arteriosclerosis. It has been our finding that endarteritis of true inflammatory origin both in its subacute and chronic stages is accompanied by fatty degeneration of the connective tissue, the endothelial or lutein-like cells as well as the elastic fibers, while reactions of hyperplasia of the deep muscle layer associated with unusual functional activity and with intermittent high blood pressure are also prone to suffer similar changes. Hence in considering both forms of response, arising in connective or muscle tissues associated with fatty degeneration, as types of true arteriosclerosis, the important bearing in the recognition of each is readily appreciated. Both types may advance to atheroma and its accompanying process of calcification and "ulcer."

The difficulty in recognizing the exact type of cell involved in the degenerative process is not so great in the smaller arteries as in the aorta, in which the intima is a complex structure. We have found, however, that by the method used in this study, of preparing the microscopical sections by making flat sections from the inner surface of the artery, a much better picture of the relation and character of the cells was obtained. The features of fatty degeneration of the intima, as we have described above, are then readily recognized.

The stage at which the fatty degeneration makes its appearance in the arterial coat is dependent upon the factor inducing the lesion as well as the character of the reaction in the wall. When by a process of high blood pressure there develops a hyperplasia of the deep intima, the fatty degeneration appears as a secondary process in the nearby muscle cells, as has been described by Jores. These newly developed muscle cells so alter their environment that nutrition is not available in sufficient amount and it may be that "overstrain" and "stress" (Adami) as the causative factor plays an important part in acting upon this tissue. These factors, purely nutritional and mechanical, can and do lead to this form of degeneration. On the other hand, active agents of a chemical nature (bacterial toxins, poisons, protein decomposition products) may directly influence the tissue cells with the accumulation of fatty materials within the cells. In the case of selective poisons, particular types of cells may be picked out and show the fatty change, or when the irritant induces inflammatory reactions, the tissues acted upon may synchronously show the presence of an exudate and the intracellular deposit of fatty granules. Even in the early stages of endarteritis where fatty degeneration is already present, it is often very difficult to indicate the sequence of change, particularly to determine at what stage in the reaction the fat made its appearance. There appears to be a type of reaction in the intima of arteries in which a connective growth is secondary to the fatty process. It has been shown (Jores) that where fatty degeneration of the deep muscle cells leads to the liberation of the fatty material and the development of an area of atheroma, a cap-like thickening of connective tissue gradually forms over its surface. The response in the connective tissues is not accompanied by an inflammatory infiltration, nor does this new layer contain elastic fibers. Here we must admit that in respect to the endarteritic plaque the fatty degeneration has been primary. In nearly all other cases of fatty degeneration of the intima the process develops either simultaneously with or secondary to other tissue reactions of

the arterial wall. Thus, in truth, whether the important factor in arteriosclerosis is of a mechanical, bacterial or chemical character, the degenerative reactions in each play an important part in the progress of the disease. In the late atheromatous softening, with its complex chemical constituents, the deposition of calcareous salts is directly associated with the presence of these fatty bodies. Such atheromatous areas have their beginning in and their progressive enlargement due to the destruction of a variety of cells which by disintegration liberate their fat content.

BIBLIOGRAPHY.

Anitschkow. Ziegler's Beiträge, 1913, lvi, 379.
Aschoff. Verhand. d. d. Path. Gesell., 1910, xiv, 123.
Dmitrijeff. Ziegler's Beiträge, 1897, xxii, 207.
Fisher. Ziegler's Beiträge, 1900, xxvii, 494.
Hallenberger. Deut. Archiv. f. Klin. Med., 1906, lxxxvii, Ht. 1, 2.
Ignatiobraski. Virchow's Archiv., 1909, 192.
Jores. Arteriosklerose, Bonn., 1903.
Idem. Cent. f. Path. Anat., 1903, xiv, 865.
Klotz. Jour. Expl. Med., 1905, xxxiii, 633.
Idem. Jour. Med. Research, 1914, xxx, 373.
Moenckelberg. Virchow's Archiv., 1903, clxxi, 141.
Ribbert. Verhand. d. d. Path. Gesell., 1904, vii.
Saltykow. Verhand. d. d. Path. Gesell., 1910, 140.
Virchow. Cellular Pathology. New York, 1858, 380.

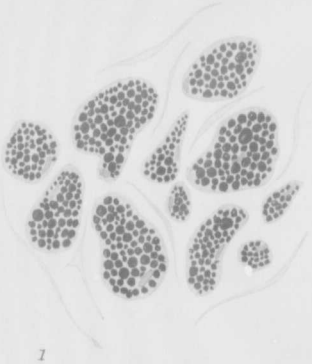
DESCRIPTION OF PLATE III.

FIG. 1. — Large lutein or endothelial-like cells in the intima heavily loaded with fat.

FIG. 2. — Stellate connective tissue cells with fat deposits.

FIG. 3. — Spindle-shaped connective tissue cells of the intima containing much fat.

FIG. 4. — Fatty degeneration of the muscle cells in the musculo-elastic layer of the intima.



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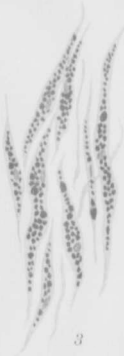

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Klotz

Fatty degeneration