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NODULAR ENDARTERITIS OF THE AORTA ABOUT THE INTERCOSTAL ARTERIES.*

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Endarteritis is one of the most prominent and widespread reactions of the arterial tree. It is found in arteries of all sizes, and it is mainly through it that circulatory disturbances (referable to arterial disease) in different viscera are brought about. The variety of types of this disease have been repeatedly indicated (Virchow, Thoma, Friedemann, Jores, Chiari, Buerger), and although the disease process has been classified according to its gross character (diffuse, nodular, obliterating, thrombosing), this classification only takes cognizance of the fully developed lesion, when such changes as may readily be observed by the naked eye are recognized.

In endarteritis we must recognize a reaction which is very commonly seen on the intimal surface of the arteries, under most varied conditions. Not only have types of endarteritis been found associated with different systemic diseases (nephritis, Friedemann; lues, Heubner; acute infections, Simnitsky), but it is a very frequent accompaniment of a variety of other reactions in the arteries themselves. In known inflammatory processes of the arterial wall, particularly in syphilis, as well as in periarterial tuberculosis, an endarteritis is the rule, while an endarteritic process overlying an area of fatty degeneration in the deep intima is also common. On the other hand, small plaques of chronic endarteritis may appear in a vessel without evidence of a periarterial or medial inflammation and in the absence of any processes of degeneration in the deep intima which could be suggested as the causative factor in stimulating the overgrowth of the superficial layers. Recognizing, therefore, that the overgrowth of the superficial intimal tissues may be a response to irritants of different kinds, it was determined to study a series of vessels in the

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earliest stages of the process, as well as to collect observations upon the possible presence of reaction in a variety of infectious diseases, where naked eye lesions were not to be found. For the latter, studies were particularly carried out upon arteries of young individuals (ten to eighteen) who had just died of an acute infection (pneumonia, infective endocarditis, peritonitis, typhoid fever). The tissue for study which was selected was the aorta in the vicinity of the intercostal arteries. Moreover, similar studies were made upon individuals of more advanced years (thirty to sixty) who likewise had died of an acute infection. Here it was desired to observe the reaction, if any, which developed in or upon preëxisting nodular areas of the intima.

The presence of button like areas of chronic endarteritis about the mouths of the intercostal arteries has been commented upon frequently. Similar isolated areas of endarteritis are observed about the mouths of other vessels branching from the aorta, but in frequency of distribution the descending thoracic aorta shows the nodular endarteritic thickening more commonly than the remaining portions of the central vessels. Their position upon the posterior wall and particularly about the intercostal arteries is characteristic, but difficult of explanation. For the distribution, particularly when it is recognized that their position is along the best supported portion of the aorta, the mechanical theory alone is wholly inadequate. That the intimal reaction is not in reponse to a medial weakening we hope to demonstrate in the subsequent discussion. And further, that we are not dealing with a process of response to simple "wear and tear" will, we believe, also be evident from this study.

We wish it to be clearly understood that the study here detailed deals with cases of infection and the cases have been selected on that account. We do not wish to have our conclusions misinterpreted as meaning to indicate that all processes of endarteritis have this origin, but rather to demonstrate that endarteritis may have an infectious origin, in which an inflammatory reaction, having a course not unlike that in other tissues and accompanied by fatty and

other degeneration, may be observed. Here again it may be well to indicate that the mode of origin or the previous course of a fully developed plaque of endarteritis cannot be determined by a study of the old lesions alone, and it is futile to hold controversy over such an indeterminable problem. A study of the earliest stages of the lesions in the tissues of man is still the most secure upon which to base conclusions. Animal experiments in our own hands have given inconstant results, though an endarteritis has been produced in very young rabbits by the inoculation of B. typhosus, streptococci, and staphylococci (Crog, Klotz, Saltykow). Hence when in young individuals, tissue reactions in the arteries may be demonstrated in association with a definite systemic disease and infection, and the ear-marks of these reactions are comparable to the known reactions of these bacteria in other tissues, we are justified in indicating a direct or indirect relation between the vascular lesions and the systemic disease.

Whether the lesions discussed in this paper are to be spoken of as arteriosclerosis may not find universal agreement, and is dependent upon the interpretation by the many observers of the nature of the arteriosclerotic process. For my own part (as well as Marchand, Faber and others) the term arteriosclerosis is generic, not defining any one particular disease, but a process induced by a variety of factors whose end-result is a hardening of the arteries. I would, however, point out that although inflammatory reactions induced by bacterial irritants are, for the most part, of a productive (so-called regenerative) kind, they are commonly accompanied by degenerative processes. Fatty degeneration is prone to follow the various chronic productive lesions of the intima, where, by the very nature of the normal structure, a disturbance by thickening of its surface layer leads to nutritional depression. In luetic arterial lesions this degenerative reaction, even though the intima is much thickened, is often lacking, as the nutritional disturbance by the thickening of the inner coat is compensated by the extensive development of new vessels from the vasa vasorum.

It is to be remembered also that degenerative changes of the intima develop not only as a result of nutritional disturbances, but also through the action of noxious agents directly upon tissues and cells. It has been amply demonstrated that a variety of tissues and cells of the intima become involved in fatty degeneration, the sum total of which make up the areas of atheroma visible to the naked eye.

The materials studied comprised a series of twenty cases, ranging in age from ten to fifty-six years. The cases were selected with particular reference to the presence of a systemic infectious disease. In many of these bacteria were demonstrated during life by blood culture or at autopsy from the heart, peritoneum or lung. Control observations were made upon tissues obtained from a number of non-infectious cases.

Case.	Sex and Age.	Cause of Death.	Infection.
1	M. 10	Scarlet fever and otitis media.	
2	M. 11	Scarlet fever and suppurative angina.	
3	F. 13	Acute verrucose M. endocarditis (chorea).	Strept. salivarius.
4	F. 13	Appendicitis.	
5	F. 15	Acute verrucose M. and A. endocarditis.	Strept. fecalis.
6	M. 17	Acute verrucose M. endocarditis.	Strept. salivarius.
7	F. 18	Acute lobar pneumonia.	Pneumococcus.
8	M. 20	Appendicitis.	
9	F. 23	Typhoid fever and peritonitis.	B. typhosus; strept. pyog.; B. coli.
10	M. 25	Typhoid fever.	B. typhosus.
11	M. 26	Recurrent M. and A. endocarditis.	Strept. mitis.
12	M. 28	Typhoid fever.	B. typhosus.
13	M. 29	Appendicitis.	
14	M. 30	Acute lobar pneumonia.	Pneumococcus.
15	F. 33	Typhoid fever.	B. typhosus.
16	M. 34	Acute lobar pneumonia.	Pneumococcus.
17	M. 39	Acute dysentery with peritonitis.	B. dysenteriæ (Flexner varians); B. coli.
18	F. 48	Acute lobar pneumonia.	
19	M. 55	" " "	Pneumococcus.
20	M. 56	Strangulated hernia and peritonitis.	Strept. pyog.; B. coli; Staph. aureus.

Sections were cut of the aorta in the neighborhood of the intercostal vessels. These sections were made by cutting the blocks (paraffin) in different planes, transverse, longitudinal, and on the flat. An opportunity is thus given to study the disposition and grouping of cells, which cannot be

obtained by a study of one set alone. Particularly valuable were the sections cut and mounted serially, which were obtained by cutting on the flat, beginning with the intima and ending in the adventitia. These blocks were taken so as to leave an intercostal artery in the center. By observing the tissues about the mouths of the intercostal vessels, and following the reactions in the vessel as it passed through the aorta, a good picture could be gained to indicate the nature of the process which terminates in nodular endarteritis. These sections made from flat portions of the aorta demonstrate an entirely new character to the deposition of the elements in the arterial wall. The arrangement of the cells in each succeeding layer is well brought out, while any alteration from the normal character or the presence of foreign cell elements is the more striking and quickly recognized.

The alternate sections of the paraffin blocks of each series were stained with hematoxylin and eosin, and by Verhoeff's method for elastic tissues. At the same time frozen sections were also made from adjoining areas of the vessel wall and stained with Sudan III. and hematoxylin, and a double stain of Sudan III. and Verhoeff's. The frozen sections of the aorta on the flat, stained by Sudan and hematoxylin were unusually instructive. The disposition of and the elements involved in the process of fatty degeneration were readily recognized.

The intercostal arteries are not individual and self-contained structures until the outer border of the aorta is reached. At their mouths on the inner surface of the aorta their boundary consists only of the intima of the aorta which dips downward and continues as the intimal lining of the efferent vessel. The internal elastic lamina of the aorta is also continuous with the innermost elastic layer of the intercostal vessel. Other than this, a thin intimal structure with an outer elastic zone, the intercostal artery possesses no elements of its own during its passage through the inner two-thirds of the aorta. In the outer part of the aorta the perforating artery gradually takes form, and elements from

the wall of the aorta enter into an orderly arrangement imitating a small vessel of the elastic type. The internal elastic lamina becomes more marked, and the media is well supplied with concentrically arranged elastic fibers. Moreover, in the outer part of the aorta, and while still within the media, the perforating intercostal vessel shows a fibrous tissue adventitia in which lymphatics and small blood vessels may be demonstrated. Thus the point of exit of each intercostal artery has a fibrous tissue mass which continues to surround the artery in the outer third of the aortic media. This connective tissue invasion of the aorta simulates that seen about the vasa vasorum, with this difference that the intercostals as they pass through the outer part of the aorta are provided with their own vasa vasorum.

The elastic elements entering into the structure of the efferent vessel vary in their arrangement from the inner surface of the aorta until the artery emerges from the adventitia. The elastic elements of the deep layer of the aorta are continued into the intercostal branches forming a definite boundary separating the elements of the media of the aorta from the intimal tissues of the branches. At times, this inner elastic boundary is sharp and definite, forming an elastic ring as is found in the peripheral arteries. At other times again the inner elastic lamina is an ill-defined layer which does not differ from the elastic elements which surround it on the outer side, and which are essential elements of the media of the aorta. It is observed, however, that as the branching artery passes through the aortic wall the elastic bands take a more definite arrangement to the efferent artery, and become disassociated from the elastic fibers in the media of the aorta. Moreover, in the outer part of the aorta the perforating vessel possesses a definite internal elastic lamina of its own simulating more the arrangement of this tissue in the peripheral vessels.

During the passage of the intercostal arteries through the wall of the aorta they do not possess a true media. The tissues which support the small artery belong to the aorta. The muscle and elastic elements of the media separate at

different angles leaving an oval opening but which, on account of the many directions of the spaces, form a central circular lumen. From these neighboring tissues a number of fibers are given off which enter into the composition of a more or less circular structure, the intimate wall of the efferent artery. In the outer third of the aorta this arrangement becomes more and more a part of the new vessel, until at the point of exit the artery possesses its regular layers. The character of the new vessel is that of the arteries of the elastic type where the media is richly supplied with elastic fibers. However, these elastic elements do not maintain a parallel arrangement to each other as do those in the media of the aorta. At a little distance from the aorta the elastic fibers gradually diminish in number until the media contains only sparse and branched elements as are present in other peripheral arteries.

In a like manner the muscle cells within the wall of the branching artery are but elements derived from the parent vessel. Their course lies parallel with the elastic fibers, some simply diverging from their usual direction to permit the efferent vessel to pass, others taking a somewhat circular course about the perforating lumen. Muscle cells were not noted in connection with the deep layer of the intima.

The intima of the intercostal branches as they lie in the wall of the aorta appeared very simple. An inner endothelial layer lies upon a narrow strip of connective tissue. No other elements than fibrous tissue were observed in this subendothelial coat. The indefinite inner elastic lamina marked the outer bounding of the intima and separated it from the tissues of the media of the aorta. As noted before a true media distinguishable from the tissues of the media of the aorta does not exist for these efferent arteries during their course through the wall of the aorta.

Recently Yamagiwa and Ito have shown that the mouths of the intercostal arteries are each provided with a valve-like lip which projects downwards from the upper border. Such a projection would tend to develop unusual currents about the openings of these vessels and possibly lead to small

whirlpools under the projecting margin. It is claimed that some of these thickened borders contain muscle bundles. We have been unable to demonstrate them.

Thus the exit of the intercostal, as well as the small intervertebral arteries, differs materially in its architecture from that of the large vessels of the arch. The character of the opening on the surface of the aorta, no doubt, gives rise to a different blood current than at the mouths of the larger vessels where a more or less steady stream constantly rushes through. To measure and examine the character of these currents is not possible, and a mathematical determination, dependent upon the size of the lumen of the vessel, is not justified by fact. It is not probable that the different character of the blood stream over the surface of the arteries is alone sufficient to stimulate histological changes in the intima, but it may have a bearing upon the localization of bacteria or the influence of their toxins upon the underlying tissues.

The character of the reactions observed in the walls of the arteries of the cases studied showed a considerable variation. Most instructive were the vessels of the younger individuals where no evidence of a previous reaction or disease was present. In the arteries of older individuals care must be exercised in separating the tissue changes which may be of recent date from those of longer standing and different causes. Attention must, moreover, be paid to all portions of the arterial wall, noting the reactions in the adventitia and media as well as the intima. As we have previously pointed out, an inflammatory infiltration is not uncommonly present about the vasa vasorum, and in our study upon the arterial lesions of acute rheumatic fever particular stress was laid upon this, because of the possible sequelæ of acute destructive mesarteritis or of chronic interstitial mesarteritis. In our former study the slight lesions observed in the intima were not further studied, it being indicated, however, that some reaction of infiltration by wandering cells and proliferation of the connective tissues was evident.

In our present observations the consecutive changes have

been followed, to indicate the process whereby the mild and early change in the intima gradually assumes the characters so commonly described as chronic endarteritis. In whatever manner the active factor of the systemic disease may act, whether by the bacteria, their toxins or through disturbed metabolism, will not at present be further discussed. We can only indicate that an irritant is present, whose response is a tissue reaction, infiltrative, proliferative, and degenerative.

The earliest response we have observed in the intima is a loosening of the narrow connective layer, simulating an edema. The change may be very slight, but sufficient, nevertheless, to show that the thickness of the tissues on the inner side of the internal elastic lamina (of both central and peripheral vessels) is not uniform. The connective tissue fibers show a fine loose meshwork with clear spaces. Occasional cells of a lymphocyte type are also present, but every evidence of a fatty degeneration is wanting. The internal elastic lamina is usually uninvolved, showing neither splitting nor degeneration. At other times this elastic layer appears granular along its inner border and does not stain uniformly opposite the point of subendothelial thickening. These mild reactions are readily overlooked. The media is uninvolved, save where an occasional vasa vasorum shows a mild edema or collection of a few lymphocytes and plasma cells.

The stellate connective tissue cells of the intima are best seen in the sections cut on the flat. Here they show a meshwork with fairly wide spaces, looking not unlike the fibrous tissue cells of cultures in vitro as have been described by Burrows, Weil, Lambert and Hanes and others. The wandering cells are most frequently found near the surface while few are seen, in the early stages, at the inner border of the media. At this period, too, there is a comparable reaction about the vasa vasorum. This, as we have on a former occasion described, begins in a loosening of the stroma about these small vessels in the adventitia and media, and accompanied by a few lymphocytes and occasional plasma cells and leucocytes. It is to be recognized that normally a few lymphocytes are found about some of these vasa in the adventitia,

but their uniform presence about the majority of nutrient vessels, as well as their occurrence with plasma cells and leucocytes in the outer portion of the media, must be appreciated as distinctly pathological, and in the light of an inflammatory reaction.

In the early stages, the reactions are isolated to the tissues of the intima and those immediately surrounding the vasa vasorum. No changes are to be observed in the inner portion of the media, so that an uninvolved tissue is found to lie between the reactions in the inner and outer portions of the vessel wall. It would thus appear that the early reactions in the intima and about the vasa vasorum are unassociated.

The intensity of the reaction in the intima is not uniform, but is distributed in irregular microscopic patches over the surface. In the aorta these areas are more frequent about the mouths of the efferent vessels, and are particularly frequent at the points of exit of the intercostal arteries. They are frequent just at the ridge over the mouth of the vessel, and commonly extend inwards for some little distance along the lumen of the intercostal branch. These plaques, however, become less frequent in the intima of the intercostal, as this vessel perforates the deep portion of the aorta and passes beyond its confines.

As the process advances the tissue changes become more marked. This is mainly observed in the greater infiltration of cells, lymphocytes, some leucocytes, and a few plasma cells. The greater number of cells are still observed near the surface, although the infiltration now occupies the entire depth of the intima and to some extent the neighboring border of the media. This infiltration is fairly diffuse in the involved plaque, with, besides the more marked aggregation at the surface, occasional groups of cells in the meshes of the connective tissue. Where these groups are found there may also be observed the presence of large mononuclear cells, with vacuolated protoplasm bearing a resemblance to the lutein type of endothelial cells. These large mononuclears lie in groups in the connective tissue of the intima, and in the early plaques are best seen in sections cut on the

flat. With the appearance of these large mononuclears, degenerative changes may be observed. These cells in themselves contain much fat-staining material, and even though the cells are loaded with fat granules, the nucleus remains centrally placed. Free fat is not seen in any part of the intima and no evidence is at hand to indicate that the fat is deposited by a mechanical process as was suggested by Ribbert and Aschoff. On the other hand, other degenerative processes are also occurring in the tissues. The connective tissue fibers are no longer as distinct, but are aggregated in masses of matted fibrils which appear swollen and indistinct. A hyaline appearance is overshadowing the fibrous tissue structure. Fat may also be demonstrated in some of the connective tissue cells, forming wedges of deposit at the ends of the nuclei. Here and there, the elastic bands of the deep layer of the intima have lost their typical staining and are found to contain a fatty material which stains diffusely in the swollen bands.

Other than a somewhat more marked cellular infiltration about the vasa vasorum and the presence of a few wandering cells at the inner border, the media shows little evidence of further change. Evidence of degeneration is only present in the muscle cells and the elastic fibers of the media in the immediate vicinity of the vasa vasorum.

With the development of early fatty degeneration in the intima there is observed a change in the elastic elements in the outer portions of the intima. In the aorta and still better seen in the larger peripheral vessels the internal elastic lamina undergoes splitting. The elastic lamina becomes granular and may even show the presence of fat in the areas of degeneration, while the muscle fibers on its inner side appear more prominent through the presence of fine fat droplets within them. In our preparations the splitting of the elastic lamina and the early development of a fatty degeneration in the cells of the immediate vicinity, though appearing a little later than the first changes in the inner connective tissue layer, are a progressive accompaniment of the inflammatory process. The development of fine elastic

fibrils, in the intermediate zone between the intima and the media and which extend later into each of these layers, is also an early reaction in these lesions.

In the later stages of the systemic disease much of the reaction, particularly the edematous swelling of the intima and the cellular infiltration, may disappear. This is particularly evident in the disappearance of the visible intimal change after typhoid fever. Almost complete restitution of the tissues results. Even much of the products of degeneration is removed so that neither fatty deposits nor hyaline change can be recognized on the posterior wall of the aorta where they are prone to occur. On the other hand, even where naked eye evidence of perfect repair presents itself, some permanent alteration of the tissues of the intima may be recognized microscopically. The superficial layer of connective tissue of the intima is slightly increased in amount forming a thin laminated structure parallel to the surface. An increase in very fine fibrils of elastic tissue is also evident in the intima as well as in the inner media adjacent. Furthermore, the not uncommon splitting of the inner elastic lamina remains as a permanent alteration, though the accumulation of fat granules in the different types of cells may, to some extent, disappear.

The presence of new connective tissue in the intima becomes definite with the progress of the lesions, and in some specimens it would appear that a certain amount of hyperplasia of the subendothelial layer continues even after all evidence of the acute stage has disappeared. The reaction which takes place is a process lying entirely within the intima and does not result as the organization of an exudate upon the inner lining of the artery. Moreover, although wandering cells, chiefly of the lymphocytic variety, constitute the early reaction, a true process of interstitial organization is not the mode of repair in the intima. We have not observed the presence of capillaries in this structure, nor any attempt on the part of the vasa vasorum to send branches towards the lesion in the intima. The tissue changes are progressive and the connective tissue cells take part directly by proliferation.

At the withdrawal of the wandering cells, the new connective tissue establishes itself as a permanent mass of new fibers forming a greater or less thickening of the coat.

In the specimens of older individuals, evidence was at hand of a former connective tissue thickening of the intima. These were accompanied by tissue changes of degeneration as are commonly observed in chronic endarteritis. In some, the deep fatty change was evident to the naked eye, while the connective tissue hyperplasia formed a hyaline pearly plaque over it. Moreover, the various types of change in the musculo-elastic layer were recognized in many. In such specimens it is impossible to say in what manner the old endarteritic process was brought about. Was it primarily the result of an inflammatory reaction as we have indicated in the above observations, or did it develop only as a connective tissue hyperplasia, secondary to the fatty deposit in the deep layer? That the latter type of reaction does occur in the intima we feel fully convinced and have previously discussed elsewhere.

However, in the present series we have observed that the areas of old connective tissue thickening of the intima may become the seat of new and more acute reactions. An infiltration by wandering cells begins from the surface and extends into the superficial connective tissue which has again become quite loose. The reaction may remain quite superficial or may advance deeper into the old connective tissue plaque. The area of fatty degeneration in the base of the lesion may show the presence of a lymphocytic infiltration in the surrounding stroma. It is, however, of particular interest to observe the reactions which take place in the upper layer of the intima, where the progressive changes simulate those previously noted in younger individuals. The infiltration by cells, though mainly lymphocytic, also contains plasma cells and occasional leucocytes. Passing through stages of edema and infiltration it can finally be seen that a new increase of connective tissue has taken place. This new hyperplastic layer lies as a cap over the former compact and hyaline connective tissue area of the intima. Thus old lesions may become the site of new attacks of endarteritis.

It has been repeatedly indicated and more particularly discussed by Jores and later by Aschoff that the amount of the superficial connective tissue layer is not constant, and that at different ages a considerable variation may be noted. Thoma laid particular stress on the progressive increase of this connective tissue in the "nabelblutbahn," which may be looked on as a physiological process. Subsequently others have found that this connective tissue growth is not isolated to the "nabelblutbahn" system but may be seen in varying degree in other arteries. Moreover, Jores has pointed out that a sharp demarcation of this physiological growth of connective tissue cannot be made from the early pathological processes of this subendothelial layer. He does, however, insist that when the growth of connective tissues not alone involves the superficial layer but also spreads into the deep musculo-elastic layer, the process is always a pathological one.

The presence of the physiological connective tissue increase is not accompanied by degenerative changes, but when hyaline change is observed in the superficial layer or fatty degeneration is present in the deep portion of the intima, a simple process of tissue growth is not to be thought of. We would, however, indicate that all forms of fatty degeneration found in the intima in association with a connective tissue overgrowth are not a common process. As Jores has shown, a mixed type of hyperplasia of the musculo-elastic layer showing fatty degeneration with a superimposed connective tissue "regeneration" is not uncommonly noted. Furthermore, however, fatty degeneration may accompany the process of connective tissue growth of the intima without any involvement of the musculo-elastic layer. These degenerative changes are found in the connective tissue cells and in the large endothelial-like cells, which aggregate in small groups in the tissues of the inner layer of the intima. The presence of fatty deposits within the elastic fibers of the intima has also been observed in the absence of proliferative changes in the musculo-elastic layer.

Jores has restricted the term arteriosclerosis to the one type of intimal change in which an hyperplasia of the

musculo-elastic layer and a splitting of the internal elastic lamina is accompanied by fatty degeneration of the longitudinal muscle fibers. Where a superficial thickening of the connective tissues occurs over this process it is viewed by him as always secondary. Furthermore, the fatty degeneration which develops in the layer of connective tissue thickening is viewed as secondary to degenerative processes in the deep musculo-elastic layer. From our observations this does not always appear to be the case. We have repeatedly seen proliferative changes in the superficial connective tissue without involvement of the musculo-elastic layer, in which the newly developed tissue showed fatty deposits in the connective tissue cells as well as showed the presence of cells apparently foreign to the intima, the large lutein-like cells, which were loaded with fat. Under the Virchow classification, this would constitute a simple fatty degeneration of the intima, a passive process as opposed to atheroma which develops in the deepest part of the intima and is viewed as an active process. We must agree that in this stage of fatty degeneration when the fat is still contained within living cells the term atheroma is inapplicable, and it is even more than probable that many of these cells containing fat may recover their normal function with the disappearance of much fat from the tissues. On the other hand, a continuation of the deleterious influences upon the vessel wall must bring about destruction of the involved cells with the deposition of free fat in the tissues. Such deposits must be viewed as atheroma. Furthermore, the presence of these masses of free fat may further stimulate, as is suggested by Jores, Faber and others, the further proliferation of connective tissue in its vicinity.

I would draw particular attention to the presence of the large endothelial-like cells (lutein-like cells) which occur in the connective tissue layer of the intima under conditions of proliferation. Much has been said by recent observers concerning the presence of these cells in the vessels of experimental animals fed with cholesterin and lipoids. In fresh preparations doubly refractile lipoid bodies (cholesterin-esters) have been demonstrated within these cells

(Anitschkow). Similar cells may commonly be demonstrated in human arteries where the fatty degeneration occurs in the superficial layers of the intima, and when such specimens are cut (frozen) on the flat, they are seen as compact aggregations in which the lipoid substance is almost entirely intracellular. That this type of fatty degeneration of the intima forms an important factor in the subsequent development of atheroma, even in the absence of hyperplasia and degeneration of the muscle layer of the intima, appears obvious.

Rokitansky was among the first to view the nodular thickening of the arteries in the light of a pseudo-inflammatory process, although he did not believe that the intima itself, being a nonvascular tissue, was capable of undergoing true inflammation. The intimal plaques, he believed, were the result of a blood deposit upon the surface, which subsequently became converted into a tissue mass by cells derived from the blood. Others soon opposed this view, Engel, Crisp, and Naumann each finding that the intima was capable of an inflammatory process. Particularly, however, was Rokitansky's attitude attacked by Virchow, who not only demonstrated that the intima, like other nonvascular tissues, may be the seat of inflammation, but that a proliferation of its own cells leads to the nodular masses on the surface. He compared nodular endarteritis with chronic endocarditis where an inflammatory thickening results mainly in connective tissue proliferation without an extensive cellular infiltration. Cohnheim, Engelhardt and others also accepted this view, differing, however, in minor points respecting the origin of the leucocytic infiltration. Traube found that the white cells, infiltrating the intima, were derived directly from the blood stream, while Friedlander and Koester believed their origin to be from the vasa vasorum. Koester's findings are particularly interesting in that he noted the simultaneous cellular infiltration about the vasa vasorum and in the intima. His descriptions even indicate that under inflammatory conditions the capillaries of the media extend closer to the intima, and a rich lymphatic system extends from the media

to the intima. While the acute inflammatory processes were accompanied by a round cell infiltration, he observed that a connective tissue proliferation was present both in the intima and about the vasa vasorum in the chronic stages.

Our own findings have led to conclusions which, to some extent, are similar to those of Koester. The simultaneous presence of a small cell infiltration in the vicinity of the vasa vasorum and the intima may be observed during the acute stages, but we have not been able to demonstrate a constant relation between them in the arterial wall. The localization of one or the other in the artery is not always accompanied by a similar reaction in the other arterial coat opposite to it. In other words, though an inflammatory reaction may be demonstrated about the vasa vasorum in the adventitia and outer portion of the media, a similar process may not lie opposite to this in the intima. Moreover, where the simultaneous presence of a cellular infiltration has been observed in the inner and outer coats of the artery, there has always appeared a strip of media adjacent to the intima which was uninvolved in the inflammatory process. It would, therefore, appear that these reactions are individual, though frequently occurring side-by-side in the same vessel. The cellular exudate found in the intima appears to arise by a direct migration of the wandering cells from the surface of the artery.

Wiesel has made some interesting observations upon the arterial system of individuals under twenty-four years of age who had suffered an acute infection (scarlet fever, pyemia, diphtheria, typhoid fever, pneumonia). A variety of reactions of an inflammatory nature along with degeneration of the muscle cells and the elastic fibers was noted. He suggested the name "arteritis chronica postinfectiosa" for this condition which he believed was not related to arteriosclerosis. Faber also observed a variety of degenerations in the aorta after acute infections, and he suggested that the injury to the media, "dilatation, hypertrophy and hyperplasia of the entire vessel wall might occur." Hansen had recorded similar findings, but, going even further, stated that the acute infections had a direct influence upon the development of atheroma.

In Prag, Simnitsky also had his attention attracted to the presence of intimal thickening, degeneration (fatty), splitting of elastic fibers, in the aorta of young persons who had died of acute infections.

Although inflammatory reactions have been observed in the inner part of the intima under a variety of infectious diseases, the outcome of the process is not the same in all cases. Gradations of intensity of the primary inflammatory process may be observed in the early stages, while the nature of the repair in the older lesions also varies. As we have indicated, it is probable that many of the milder reactions, seen in the acute stage, may disappear without leaving recognizable change, but it is impossible to indicate from the appearance of a given lesion the subsequent outcome of the process in the arterial wall. Inflammatory reactions of the intima of longer duration are always accompanied by a connective tissue disturbance of a proliferative kind, and from them there develop the intimal thickenings of the "hyaline" type. These reactions are frequently of the pure connective tissue variety, but are sometimes associated with hyperplasia of the muscle layer of the intima and splitting of the elastic lamina. Nevertheless, the splitting of the elastic lamina cannot alone be taken as an indication of a hyperplasia of the deep muscle layer, as we have seen it in pure regenerative processes of the inner coat where no proliferative response was seen in the muscle tissue of the intima.

It is obvious that with the degree of the reaction in the intima, the component tissues will take part in bringing about a structural alteration in the involved area, at times proliferative, at others degenerative in kind. When, however, the harmful influences (particularly bacterial toxins) are so great, the proliferative changes give way to processes of degeneration of which the fatty is most easily demonstrated, and which may be recognized in a variety of tissues and cells. Whether all well defined processes of fatty degeneration of the intima shall be called atheroma finds no common agreement. For my own part, when the fatty degeneration of the intima has proceeded to that stage, that not alone

do we find fatty substances within the cells, but also that some of it has been liberated, by the death of cells, into the interstices of the tissue, giving rise to a free greasy deposit, do I speak of it as atheroma. Other products of degeneration, particularly the calcareous, are also mixed with the atheromatous deposit. From our observations it is clear that this atheromatous material may arise not only from the destruction of one type of tissue (deep intimal muscle), but also from degenerative changes in the elastic fibers, connective tissue, and the endothelial-like (lutein-like) cells.

CONCLUSIONS.

It would appear from the present study that contrary to our opinion previously expressed, the reactions in the intima, in many acute infectious diseases, may occur independently though simultaneously with the inflammatory reactions about the vasa vasorum.

The intimal reactions of the aorta are more marked about the mouths of the smaller vessels, particularly the intercostals, but they do not usually advance along the lumen of the branching vessel.

The reaction is an inflammatory one, in which the infiltration of wandering cells (lymphocytes and some plasma cells and polynuclear leucocytes) may best be observed when the tissues of the intima are cut on the flat.

The inflammatory process is accompanied by progressive as well as degenerative changes in the tissues of the intima. Repair is accomplished by a proliferation of the connective tissues of the inner layer of the intima and may show some hyperplasia of the musculo-elastic layer.

Splitting of the internal elastic lamina into multiple bands occurs in reactions of a purely inflammatory nature in the absence of hyperplasia of the deep muscle layer.

Fatty degeneration is a common accompaniment of the pure connective tissue thickening of the intima, and is found to involve particularly the connective tissue cells, the elastic fibers, and the endothelial-like cells found in the intima.

Deep areas of degeneration also show the involvement of the muscle cells of the intima.

The late stages of the lesion cannot be differentiated from processes of atheroma with superficial endarteritic thickening. It is superfluous to differentiate atheromatous softening of the intima by the particular tissue cells which show fatty degeneration and which on subsequent destruction liberate fatty materials in the intima of arteries.

It is probable that the structural changes brought about in the intima of the arteries in infectious diseases are the result of bacterial toxins, but it is possible that a vicious circle is set up in the affected area by which nutritional alteration and decomposition products of tissues also exert an influence upon the surrounding parts.

The entire process must be classed as one of arteriosclerosis in which proliferative and degenerative reactions are closely associated.

BIBLIOGRAPHY.

Anitschkow. Ziegler's Beiträge, 1913, lvi, 379.
Aschoff. Beihefte zur Med. Klinik., 1908, iv.
Idem. Verhand. d. d. Path. Gesell., 1910, xiv, 123.
Burrows. Jour. Amer. Med. Assoc., 1911, lv, 2057.
Chiari. Verhand. d. d. Path. Gesell., 1905, 326.
Idem. Verhand. d. d. Path. Gesell., 1903, 137.
Crog. Archiv. de Med. Exper., 1894, vi.
Crisp. "On the structure, disease, and injuries of blood vessels." London, 1847.
Cohnheim. Allg. Pathologie., 1877.
Engelhardt. Centralb. f. d. Med. Wissensch., 1876.
Friedemann. Virchow's Archiv., 1900, clix, 554.
Faber. Die Arteriosclerose, Jena, 1912.
Friedlander. Centralb. f. d. Med. Wissensch., 1876.
Hansen. Ref. Faber.
Huebner. Die luetische Erkrankung der Hirnarterien, Leipzig, 1874.
Jores. Ziegler's Beiträge, 1902, xiii, 726.
Idem. Wesen u. Entwickelung d. Arteriosclerose, 1903.
Koester. Berlin Klin. Wochen., 1876, 454.
Klotz. Brit. Med. Jour., 1906.
Idem. "Arteriosclerosis," 1911, Pittsburgh.
Idem. Jour. Path. and Bact., 1913, xviii, 259.
Lambert and Hanes. Jour. Exper. Med., 1911, xiv, 129.

Marchand. 21st Kongress f. Innere Med., 1904, 23.
Idem. Cent. f. Path., 1904, xv, 400.
Ribbert. Verhand. d. d. Path. Gesell., 1905, ii, 168.
Rokitansky. Lehrbuch d. Path. Anat., 1856, ii.
Simnitsky. Zeitschrift f. Heilkunde, 1902, xxiv Ht. 4.
Saltykow. Ziegler's Beiträge, 1914, lvii, 415.
Idem. Ziegler's Beiträge, 1908, xlii, 147.
Thoma. Virchow's Archiv., 1886, cv, 197.
Traube. Berlin Klin. Wochen., 1871.
Virchow. Virchow's Archiv., 1879, lxxvii, 380.
Weil. Jour. Med. Research, 1912, xxvi, 159.
Wiesel. Zeitschrift f. Heilkunde, 1905, xxvi, 107.
Idem. Zeitschrift f. Heilkunde, 1906, xxvii.
Idem. Zeitschrift f. Heilkunde, 1907, xxvii.
Yamagiwa and Ito. Japanese Path. Assoc., 1913, 24.