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THE MORPHOGENESIS AND SIGNIFICANCE OF DEGENERATIVE VERRUCAL ENDOCARDIOSIS (TERMINAL ENDOCARDITIS, ENDOCARDITIS SIMPLEX, NONBACTERIAL THROMBOTIC ENDOCARDITIS) *

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This paper is concerned with a lesion of the cardiac valves which has been variously labeled terminal endocarditis, marantic thrombosis, nonbacterial thrombotic endocarditis, endocarditis simplex, thrombo-endocarditis cachectica, etc. The valvular lesion has long been treated with a diffidence considered appropriate for a condition having no clinical significance. The alteration has been regarded simply as a bland thrombus deposited from the blood within a cardiac chamber onto a normal or thickened valve, the surface of which is either intact or superficially degenerated.[1-5] The cause of the condition has not been established but investigators have inconclusively implicated a variety of factors, including toxins, abnormal metabolism and a terminally sluggish circulation.

A minority point of view opposing the thrombotic concept began to take form when Neumann,[6] in 1896, indicated that the thrombotic excrescence was in reality degenerated valvular collagen which histologically simulated fibrin. He therefore applied the term "fibrinoid" to this substance. Several years later (1903), Königer[2] conceded that the base of these excrescences was probably degenerated collagen but maintained that their major portion consisted of thrombotic deposits. Königer's has remained the prevailing concept.

In 1939, in a discussion incidental to an elucidation of the mechanism of localization of vegetations of bacterial endocarditis,[7] attention was called to the valvular genesis of the verrucae of "terminal endocarditis." Repeated observations over the past 6 years have fortified the impression that these verrucae are not accretions of thrombotic material deposited onto valves but rather that they are composed of material derived from the valve itself. It is our opinion that this material con-

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sists primarily and predominantly of swollen, degenerated valvular collagen with occasionally an admixture of varying amounts of plasma and blood-cellular elements which have exuded from the valvular vessels. Furthermore, we submit that the determination of the morphogenesis of these lesions is not a mere academic nicety inasmuch as we feel that they constitute the first stage in the sequence of events leading to the development, in many cases, of bacterial endocarditis.[8] Because of this concept of the relationship of "terminal" to bacterial endocarditis it seems important to try to clarify certain histologic details and to integrate seemingly discordant facts into a unified, comprehensible picture. It is with this aim that we have undertaken a systematic study of the basic endocardial lesion generally designated as "terminal endocarditis."

Materials and Methods

There were available for study the clinical histories, gross specimens and microscopic preparations of 66 cases in which there was no evidence of bacterial endocarditis or of acute rheumatic carditis. Of these, 50 cases had active lesions of "terminal" endocarditis; the remainder were examples of healed lesions. The criteria for evaluating activity are outlined below. Multiple sections from each heart were examined and, in certain indicated instances, six sections were taken according to the procedure of Gross, Antopol and Sacks.[9] However, in every case, sections of the base of the heart (M.V.P.)* were included.†

The tissues were fixed in a 20 per cent Formalin (8 per cent formaldehyde) solution except for one case in which Zenker's solution was used. The stains included hematoxylin and eosin, the Mallory-Heidenhain azocarmine, Mallory's phosphotungstic acid hematoxylin, van Gieson's combined with Weigert's, and the silver stains of Wilder and of Bielschowsky as modified by Foot. In addition, the lesions of 3 cases were subjected to serial digestion with trypsin following which they were treated with van Gieson's stain. In three instances, serial sections 6μ thick were cut.

Findings

Relationship to Malignant Tumors. "Terminal endocarditis" has been considered to be associated with patients dying of malignant tumors. In our small series, such neoplasms were present in 28 per cent

* M.V.P. = Mitral valve posterior.

† In this connection, Gross's own investigation[9] indicates that the incidence of Aschoff bodies in rheumatic hearts could have been determined from the examination of the two sections from the base of the heart only, inasmuch as no additional cases with Aschoff bodies were discovered by the study of the four remaining sections.

of 50 cases (Table I). This incidence appears strikingly high and yet, in the general autopsy material of the hospital, 23 per cent of 2000 patients died with malignant tumors. If there were no selection of patients with malignant growths by terminal endocarditis, cancers would be expected to occur with the same frequency in our 50 endocardial cases as in the general post-mortem material, namely, 23 per cent. This was essentially true inasmuch as the difference between 28 and 23 per cent is so small that when subjected to the X^2 test of statistical significance, a positive correlation between patients with malignant tumors and those with "terminal endocarditis" was not dem-

TABLE I

Cause of Death in 50 Unselected Cases of "Terminal Endocarditis" (Active)

Cause of death	No. of cases
Malignant tumor	14
Congestive heart failure	10
Major operation	7
Pneumonia	4
Acute and subacute glomerulonephritis	2
Pulmonary embolus	2
Acute suppurative pyelonephritis	2
Congenital polyposis	2
Ulcerative colitis	2
Blood dyscrasia	2
Coronary occlusion	1
Periarteritis nodosa	1
Congenital heart disease	1
Total	50

onstrated. Additional information of the same order would have been furnished by the converse data; namely, the comparative incidence of "terminal endocarditis" among a large series of patients with cancer, pneumonia, glomerulonephritis, and other conditions. These data are not available at present.

Association with Acute Diseases. Of great significance is the fact that these endocardial lesions are found in persons who have died after an illness of only a few days' duration; for example, in patients dying of pneumonia or following a recent operation (Table I). In other words, the lesion does not require the background of a long, wasting disease. Furthermore—and this is of great importance—the lesion may accompany diseases which are by no means always fatal. That is to say, inasmuch as "terminal endocarditis" occurs in patients with pneumonia, nephritis, and other diseases which often are not fatal, it is reasonable to presume that "terminal endocarditis" may occur during the course of diseases which the patients may survive for years. This

fact is of prime concern in connection with the subsequent superimposition of bacterial endocarditis, a point which will be elaborated further.[8]

Age and Sex Incidence. In this small series, 70 per cent of the cases of "terminal endocarditis" occurred in persons above the age of 40 (Table II). This does not indicate a selectivity for the older age group inasmuch as 67 per cent of all those in the general autopsy material of the hospital were in the same age group. The difference between 70 and 67 per cent is not statistically significant. Similarly, 46 per cent of our cases occurred in females and 54 per cent in males. The corresponding distribution of sexes in our autopsy population is

TABLE II

Age Distribution of "Terminal Endocarditis" (Active)

Decade	No. of cases
1–10	1
11–20	7
21–30	2
31–40	5
41–50	8
51–60	11
Above 60 years	16
Total	50

41 and 59 per cent respectively. The difference between these sets of figures, again, is not beyond the range of chance variation as determined by the X^2 test.

In summary, it appears from an analysis of our material that the lesion of "terminal endocarditis" occurs in random distribution at all ages and in both sexes as well as in a great variety of diseases, both acute and chronic, with possibly a very slight tendency to favor those patients with malignant tumors, although statistical proof thereof is lacking.

Distribution of Lesions. In 34 of our 50 active cases (68 per cent), the lesions occurred on valves that were thickened by chronic rheumatic valvulitis. In 12 of the remaining cases the valves were moderately sclerotic but rheumatic cardiac stigmata were absent. The valves of 4 cases were apparently normal except for "terminal endocarditis."

The distribution of the valvular lesions of "terminal endocarditis" parallels fairly closely that observed in rheumatic and bacterial endocarditis. The mitral valve was involved most frequently and with about twice the frequency of the aortic valve. The right side of the heart was rarely the site of a lesion and, in this series, the pulmonic valve was spared. In six instances, lesions were found on two valves of the same heart.

GROSS EXAMINATION

It is generally assumed that the lesion of "terminal endocarditis" is a single, small verruca. However, the lesions may assume a wide range of gross patterns, including those of rheumatic and bacterial endocarditis, so that differentiation by inspection may be impossible in some instances. In general, the lesions have one of five patterns:

1. The small univerrucal type. This group consists of lesions that are barely visible, or measure up to about 3 mm. in height. They are light gray-brown to dark brown and usually firmly attached to the valve as if a part thereof rather than a superficial deposit. These are practically always found on previously thickened fibrotic valves. They are seen characteristically at the line of closure. On the aortic valves, the corpora arantii are especially vulnerable, quite as in rheumatic or bacterial valvulitis. (The term "univerrucal" is applied also to those valves with two or three verrucae in which the lesions are isolated, as in Figs. 1 and 2.)

2. The large univerrucal type. These are tawny, usually very finely granular and firmly adherent to the valve proper (Fig. 2). In unusual instances, they are so decidedly shaggy as to make gross differentiation from bacterial endocarditis a mere guess. In other instances, the surface may be smooth and the lesion soft and polypoid. This latter form is found usually to differ histologically from the preceding type.

3. The small multiverrucal type. These lesions are about 3 mm. in diameter, firmly attached to the valve and arranged in a fairly regular, beaded ridge along the line of closure. They may be macroscopically indistinguishable from acute rheumatic verrucal endocarditis. As a rule, however, they are larger and somewhat more friable than rheumatic verrucae. They may, in some cases, suggest bacterial endocarditis but their relative regularity, especially over a large span of the valve, would militate against this diagnosis.

4. The large multiverrucal type (Figs. 3 and 4). This is a striking lesion composed of soft, friable masses beaded along the line of closure for as much as 4 to 5 cm. and measuring up to fully 6 to 7 mm. in height. The verrucae may be as large as many of the vegetations of bacterial endocarditis, but, unlike them, are characterized by a remarkable regularity in size, consistency, color and contour. They may be loosely attached to the valve and when removed may expose an endocardial surface that is only slightly roughened. Such lesions, although nonbacterial, are prone to produce emboli. They generally show a characteristic histologic picture to be described as the "exudative" type.

5. Healed type. Inasmuch as "terminal endocarditis" is seen postoperatively and in cases of pneumonia, glomerulonephritis, etc.; that is,

in diseases not necessarily fatal, it appears plausible that, if the patient survives, the verruca formed during the period of illness will either resolve or become a fibrous tab or nodule, or a focal, slightly bulbous thickening of the edge of the valve. Such changes are found commonly near the free edge of the valves, particularly at the corpora arantii (Lamblian excrescences*) or along the adjacent ridge (Figs. 5 and 6). They are 1 to 5 mm. in length, are covered by smooth endothelium and have the color and consistency of the valve to which they are attached. The "healed" lesions in this study occurred on nonrheumatic valves in 11 cases and in 5 instances on valves that showed evidence of chronic rheumatic inflammation.

MICROSCOPIC EXAMINATION

The histologic patterns of the active lesions appear to fall into two principal groups, differentiated primarily by the amount of degenerated collagen present in the verrucae:

Degenerative Type

The histologic picture characterizing the degenerative type commonly corresponds to the small or the large, granular, densely adherent univerrucal gross type (Fig. 14). It begins as a focus of granular, eosinophilic degeneration in the outer layers of the valve, generally near the free margin (Fig. 13). As a rule, the auricular surfaces of the A-V valves and the ventricular surfaces of the semilunar valves are those selected. This alteration may occur without a grossly visible change in the contour of the valve and hence is often overlooked, as might have possibly occurred in the lesion illustrated in Figure 13. As in any other organ, the altered collagen is appreciably more acidophilic than the adjacent uninvolved collagen. The original focus enlarges and the altered fibers swell and become loosened and fragmented to form a mound of degenerated, soggy appearing collagen. Here and there, small foci of precipitated serum, fibrin, or platelets are observed, as if there had occurred a slight seepage from permeable or eroded valvular vessels. Occasionally, several clumps of red blood cells and leukocytes of various kinds are present, not only in the verruca, but near the verrucal base and obviously within the valve proper. In practically all instances of this type there is no abrupt demarcation of the verruca from the valve; rather, one observes that the eosinophilic, fibrillar, or granular material of the verruca represents the termination of the valvular fibers which fray out into the lesion. To be sure, the

* Lambl. Papilläre Excrescenzen an der Semilunar-Klappe der Aorta. *Wien. med. Wchnschr.*, 1856, 6, 244.

acidophilic alteration may occasionally be seen in the fibers of the valve itself even at a distance from the verruca. With serial sections, it is found that this alteration may occur in the fibers well within the valve, which may or may not be in continuity with the surface, so that the possibility of its representing imbibed thrombotic material from the cardiac chamber would seem to be most unlikely.

With carefully controlled Mallory-Heidenhain stains, there is observed in some instances ragged, ripped, anuclear, collagenous fibers in all parts of the verruca, including its most superficial portion. The absence of fibroblasts about such torn, displaced fibers distinguishes them from fibers formed as a result of a reparatory process. However, fibroblasts and even granulation tissue may be seen in other parts of the verruca, especially at its base, but such foci are easily distinguishable from the degenerated areas. The altered fibers stain various shades of red, orange, or blue, depending on the degree of degeneration. They may resemble fibrin tinctorially but they usually can be distinguished by such structural details as sharpness of contour, the irregular, torn ends, and often by continuity with a collagenous fiber of the valve itself. Indeed, a few foci of fibrin and platelets may be included but most of the granular, platelet-like or fibrinoid substance appears to be derived from collagen. This altered collagen differs from platelets and fibrin, in part by its relative resistance to tryptic digestion, but also by its relationship to disintegrating collagenous fibers which shade off finally into the granular platelet-like débris. In other words, the granular material constitutes an advanced stage of degeneration. One frequently observes an identical change in the dermal lesions of granuloma annulare, for example, or in the subcutaneous rheumatic nodules, in which there is no question that the fibrinoid and platelet-like material are truly products of altered collagen. This feature is illustrated in Figure 15. Additional evidence that this material is not fibrin or platelets is furnished by silver stains and tryptic digestion.

Silver Stain. With silver stains by either the Wilder or Foot modification of the Bielschowsky technic one finds that the quantity of argyrophilic fibers in the lesions varies considerably. In some lesions, they are entirely absent; in others, there are so many closely lamellated argyrophilic fibrils that the verrucae appear almost solidly impregnated. Usually, one observes foci of irregular, anuclear, fragmented fibers, some of which are as fine as reticulum and others fully as thick as ordinary collagenous fibers (Fig. 17). The fibers to which we are referring are, of course, entirely removed from the reticulin of the granulation tissue that may be present at the base of the verruca.

Tryptic Digestion. Unfortunately, there is no stain that will un-

equivocally differentiate all forms of altered collagen from fibrin. We have therefore made use of the digestion of the lesions with trypsin, a procedure dependent on the differential digestive properties of trypsin, which were found informative in previous studies on hyaline material in tumors,[10] in renal glomeruli [11] and in the investigation of so-called aortic thrombi.[12] It is known that trypsin digests collagen with difficulty whereas, on the other hand, clots of platelets and fibrin are easily digestible. We, therefore, determined the relative digestibility of the substance composing the verrucae. The procedure included placing a paraffin section (6 μ thick) of the verruca and a section of blood clot on the same slide. Serial sections were placed in a 0.3 per cent solution of fresh trypsin alkalinized with 0.03 per cent Na_2CO_3 to which chloroform had been added as a preservative. The tissues were then digested for 1 hour at 37°C., after which a slide was removed approximately every half hour for a period of about 3 hours and stained with van Gieson's stain. This time period permitted definite differential digestion of the fibrin and platelets, the verrucae, and the valvular collagen. The order of the rapidity and ease of digestion was as follows:

1. Fibrin and platelets: early and complete digestion
2: Verruca: digested partially and at a later period
3. Collagen of valve: practically undigested during the period of exposure

Exudative Type

The exudative type of verruca occurs relatively uncommonly, having been found in about 10 per cent of our lesions. These verrucae may vary greatly in size but are especially characteristic of the large multiverrucal, soft, friable lesions (Figs. 3 and 4).

They are made up principally of material that superficially seems indistinguishable from serum, platelets and fibrin (Figs. 7 and 8). With the Mallory-Heidenhain stain, one may observe in most of them several haphazardly arranged, blue, isolated, collagenous fibers, again unassociated with fibroblasts and not part of a reparatory process. Similar fibers may be seen with silver stains. In addition, these lesions may contain a few red blood cells, an occasional focus of polymorphonuclear leukocytes, and a few lymphocytes. The components of this type of verruca are as a rule arranged in a completely irregular pattern of clumps of varying size and do not suggest successive accretions of deposits of thrombi. In each instance there is evidence of fibrinoid degeneration of the valve at the base of the verruca.

No elastic tissue is found in these lesions. The tryptic digestion fails to reveal any noteworthy difference between this type of verruca and the fibrin of clots.

Healed Type

As stated, this lesion consists of a fibrous tab, nodule or focal collagenous thickening with rarely a few elastic fibers. Such a lesion may itself undergo degeneration and become the site of a verruca which is practically always of the degenerative type (Fig. 19). In valves thickened by chronic rheumatic inflammation there are no histologic features that distinguish the healed verruca of "terminal endocarditis" from that of acute rheumatic valvulitis.

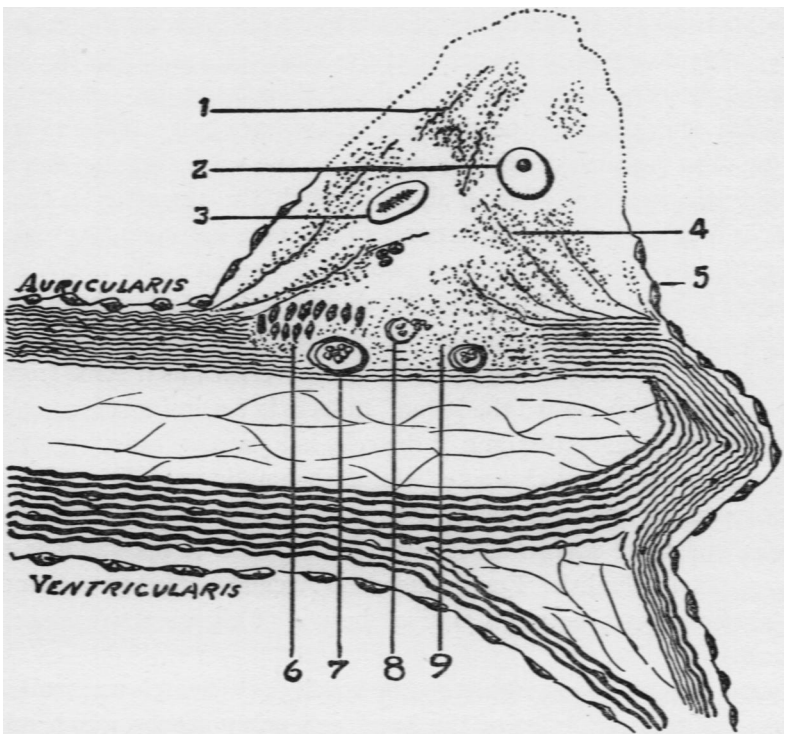
Cellularity of the Verrucae. In the majority of the verrucae no cells, or merely a few shrunken degenerated cells and pyknotic nuclei, are present. In most of the remainder, one sees loosely scattered histiocytes in addition to the degenerating cells, although, occasionally, clumps of polymorphonuclear leukocytes and isolated lymphocytes are seen. In many instances a few foam cells, filled apparently with lipoids, are included in the body of the lesion. In one instance the abundance of these vacuolated cells well within the verruca presented a striking picture (Figs. 10 and 11). Isolated Anitschkow myocytes (myocardial reticulocytes) were observed in the midst of the fibrinoid material in the body of two of the verrucae (Fig. 9). As a rule, there is greater cellularity in the lesion of exudative type than in that of degenerative type (Figs. 7 and 8). The reaction within the portion of the valve forming the base of the lesion was negligible in about one-half the cases but in the remainder took one of two patterns: (1) In some instances, the normal fibrocytes of the valve developed swollen, hyperchromatic nuclei so as to resemble newly formed active fibroblasts; (2) in other cases, there was an actual increase in number of fibrocytes or fibroblasts arranged vertically or obliquely in the direction of the verruca as if some tropism were guiding them toward the lesion. Indeed, in several instances, there was observed actual palisading of the cells in a pattern indistinguishable from that regarded as characteristic of rheumatic valvulitis (Fig. 8). In these cases, the reaction was limited strictly to the base of the verruca and there was no associated inflammation of the valvular ring or interstitial valvulitis. Furthermore, no Aschoff bodies were found in any of these cases notwithstanding the use of the method of section advocated by Gross.[9]

Changes in the Myocardium and Other Organs. Search was made for changes in the remainder of the heart and other organs which might possibly be related to the valvular lesion. We were especially interested in collagenous alterations, vascular lesions and emboli. Focal collagenous granular alterations were found in the walls of small arteries and arterioles of the myocardium in 5 cases, each in association with granu-

lar verrucae in the lumen at the site of alteration. These granular verrucae or "plugs" project into the lumen as knobs or as irregular lobulations. They have been variously described as platelet thrombi, as swollen, desquamated endothelial cells and as emboli from verrucae. They may become organized and canalized. These luminal projections have been observed frequently and their occurrence stressed in acute disseminated lupus erythematosus and in the entity described by Gross and Friedberg [5] as "nonbacterial thrombotic endocarditis." Because of association with, and apparent emergence from, a site of granular degeneration in the vessel wall, they appear actually to be fibrinoid, verrucal swellings of portions of the vascular wall.[13]

Occasionally, portions of verrucae, particularly of the more friable exudative type, break off to produce infarcts, and, rarely, even a fatal encephalomalacia.

In summary, the lesions of "terminal endocarditis" are observed grossly as single or multiple verrucae, or as healed, smooth, projecting



Text-fig. 1. Schematic drawing of the composite features of nonspecific verrucae: 1 = fragmented, anuclear collagenous and argyrophilic fibers displaced from the valve into the verruca; 2 = foam cell; 3 = Anitschkow myocyte; 4 = granular disintegration of valvular collagenous fibers; 5 = valvular endothelium which has been raised and disrupted by the verruca; 6 = reactive histiocytes; 7 = arteriole; 8 = eroded arteriole; 9 = granular disintegration of collagen within original limits of valve.

tabs, nodules, or focal thickening of valves. Microscopically, they may be divided into three types: the degenerative type, consisting preponderantly of altered, swollen valvular collagen; the exudative type, made up of platelets, serum, fibrin and usually a few fragments of disrupted collagenous fibers; and the healed type representing fibrosis of an active verruca. Of these, the type consisting almost entirely of degenerated collagen occurs with about ten times the frequency of the other form of active verruca.

COMMENT

Morphogenesis

We have thus far presented the histologic details of the nonbacterial verrucae. It is our impression that these observations indicate an origin of the verrucae from the valve. That is to say, we regard the verruca as a focus of degenerated, loosened, swollen, valvular collagen, occasionally puffed out with more or less exuded plasma from the permeable or eroded vessels of the valve itself. However, those who do not distinguish the verrucae from simple thrombi deposited by the blood streaming over the valve, maintain that the collagenous and argyrophilic fibers on which we have laid much stress are observed in ordinary vascular thrombi. They regard the altered verrucal collagen, or fibrinoid, as identical tinctorially with the fibrin of thrombi, and hence conclude, in effect, that verrucae and thrombi are not only indistinguishable but represent essentially the same pathogenetic process.

Verrucae do often closely resemble thrombi in sections stained merely with hematoxylin and eosin. Furthermore, collagen and argyrophilic fibers, and of course platelets and fibrin, are found in vascular thrombi and obviously are not *per se* peculiar to the verruca. But to conclude from this fact that the verruca is a thrombotic deposit is to disregard a fundamental distinction between degeneration and repair. It is to be emphasized that this distinction may be easily missed in a section stained with hematoxylin and eosin, and yet it is on just such routine sections that the general concept of the thrombotic nature of verrucae is based. The verrucal collagen to which we refer has undergone various degrees of degeneration so that with the hematoxylin and eosin stain it appears deeply eosinophilic, anuclear, and occasionally fragmented and granular, thereby closely resembling fibrin and platelets. However, this same degenerated camouflaged material may retain sufficient tinctorial properties of collagen to reveal its identity with appropriate stains. For example, it may show a partial affinity to aniline blue as well as to silver (Fig. 17). In other words, with a

differential stain, one may observe a fiber of valvular collagen continue up into verruca and within the body of the verruca exhibit a gradual loss of affinity for aniline blue and, *pari passu*, a progressively increased azocarminophilia, the latter indicating degeneration of the terminal portion of the fiber. The degenerated anuclear fibers may be fragmented, disrupted and scattered to various parts of the verrucae.[14, 15] This pattern is quite unlike the radiating, more orderly picture of organization within a thrombus, be it in a vein, artery, or cardiac chamber (Fig. 16).

The masking of collagen and its argyrophilic derivatives is a commonplace phenomenon which can be observed in a variety of organs; *e.g.*, in the degenerated foci of granuloma annulare of the skin, in synovial degenerations, in Aschoff nodules, etc. The fact is that one could superimpose many of the verrucae onto the lesions of granuloma annulare, for example, and differentiation of the verrucal material from the areas of cutaneous fibrinoid alteration would be impossible. It therefore appears that the fundamental interpretive discrepancy of those who believe in the thrombotic nature of the verrucae is that they ascribe the origin of the collagen in the verrucae—*i.e.*, the fibrinoid collagen "uncovered" by special stains—to the process of organization notwithstanding the unquestionable lack of evidence of organization in the foci in question in sections stained with hematoxylin and eosin.

Some observers, in order to account for the argyrophilic fibers in fibrinoid material,[16] maintain that serum may seep in through the surface and separate the collagenous fibers into thin fibrils, and that these fibrils by virtue of their thinness acquire an affinity for silver. The evidence from the current studies does not support this combination of assumptions. In the first place, serial sections reveal foci of degenerated collagen with argyrophilic fibers well within the valve and showing no continuity with the surface. Indeed, occasionally such degenerated areas are seen in valves with intact endothelium. It is hardly likely that serum from the cardiac chamber has soaked through an intact valve to collect as a pool within the body of that valve. Furthermore, there were found in the verrucae, degenerated collagenous fibers which were argyrophilic *and yet were distinctly thicker* than the fine collagenous fibers in the same sections that manifested no affinity for silver (Fig. 17). In addition, there can be observed, in some of the verrucae, dense, compact masses of argyrophilic fibers which were tightly apposed and obviously not produced by a separation of pre-existing collagenous fibrils. Therefore, it would appear that the view that the argyrophilic fibers of verruca arise through cleavage of collagen by serum is not supportable.

In some cases, the degeneration of valvular collagen was accompanied by a cellular reaction; in others it was not. We are unable to agree that the absence of cellular reaction precludes the fibrinoid material being degenerated collagen.[16] Witness, for example, the bland degeneration of collagen within sclerotic valvular rings, sclerotic arteries, or within the collagenous capsule of a chronic tuberculous focus. In each of these sites there is frequently no noteworthy "exudative response" to the presence of appreciable degenerated collagen.

The reason for the presence of a cellular response in some of the verrucae and not in others is not entirely clear. However, it would appear that some of the basic factors concerned are the degree of valvular sclerosis, vascularity and cellularity preceding the formation of a verruca. That is to say, if a valve is thickened by dense nodules of practically acellular and avascular collagen, significant cellular response to an irritant is not to be anticipated. In much the same sense, there is less likely to be an exudative response to an irritant in a torpid, sclerotic, acellular, and avascular scar anywhere else in the body.

The resistance of most of the verrucae to trypsin is additional evidence that the fibrinoid material of the verrucae is of a composition different from thrombi. This principle has been confirmed in a study of so-called mural thrombi of the aorta.[12] Of further interest is the presence of myocytes and lipoid histiocytes in the verrucae (Figs. 9 and 10). Anitschkow myocytes[17] are easily recognized cells found only in the heart. If myocytes are found within a verruca, it is to be presumed that the latter arose from the valve since myocytes are not known to circulate within the blood stream. To be sure, this presumption may be somewhat countered by the objection that the myocytes may have migrated into the thrombus from the valve. However, there is no evidence for such migration inasmuch as myocytes have not been found in mural thrombi located, for example, in auricular appendages or ventricles. The presence of foam cells within the body of unorganized verrucae constitutes additional evidence for the valvular genesis of the lesions. Foam cells are frequently associated with degenerated collagen in the heart as well as other organs, sometimes in striking concentrations. However, this latter bit of evidence must remain merely presumptive inasmuch as such cells are found occasionally within vascular and mural thrombi.

As a final word in the accumulation of evidence against the thrombotic concept of verrucae, it is to be pointed out again that the velocity and momentum of the blood in the heart and arteries would seem to operate against the deposition of thrombi.[7, 15] The factors of stasis, eddy currents, and a sluggish circulation with the pressure of venous

blood, more or less predispose to the deposition of thrombi. Such factors are of concern in the auricular appendages in fibrillation, in the pockets of valves, or in the ventricles following infarction; but it would appear that they are reduced to relative insignificance along the auricular surface of the mitral valve and the ventricular surface of the aortic valve—sites of verrucal formation—as the blood in the chambers cascades past these surfaces.[7]

In summary, we submit that the evidence is strongly in favor of the valvulogenic rather than the thrombogenic nature of the verrucae. This evidence is based on identification: (1) by special stains of much of the fibrinoid material as altered collagen; (2) by the relative resistance to trypsin of the fibrinoid material as contrasted with fibrin; (3) by the presence in the verrucae of myocardial Anitschkow myocytes and lipoid macrophages, the former never found in the peripheral blood or thrombi. These various contrasts between verrucae and thrombi obtain irrespective of their location, be it vein, artery, aorta, or cardiac chamber. However, there were found a few instances of verrucae composed essentially of serum, platelets and fibrin and a few blood cells, rather than primarily of altered collagen. It is our unproved impression that even these are essentially coagula which are derived from the exudate of permeable or eroded *valvular* vessels and have clotted on the surface of the valve very much as plasma clots on abraded skin, or, to use a homely simile, as albumin coagulates on and adheres to the shell of an egg that has been cracked while in boiling water.

Pathogenesis

We are not certain why a portion of a valve undergoes degeneration and forms a verruca, but in searching for the possible agents we regard it as likely that several factors may be involved and that the phenomenon is the product of the effects of one or more of the following: (1) allergy; (2) vitamin C deficiency; (3) hemodynamic trauma to the valves; and (4) the existence of abnormally thickened, sclerotic valves.

Allergy. Many investigators have repeatedly attributed the fibrinoid degeneration of collagen—especially the collagen of valves and arteries—to the effects of allergy.[18-22] The fibrinoid change in many of the verrucae in our cases appears to be identical with that attributed to altered tissue reactivity. The nature of the allergens in these cases is not known, of course, although the possibility of bacterial proteins is a distinct one. At any rate, at least the adjuvant rôle of allergy in the production of fibrinoid degeneration is to be considered. This is not to say that all fibrinoid degeneration of the valves is on the basis of allergy. In many instances, the fibrinoid alteration seems to represent a

form of degeneration of valvular collagen in which allergy plays no conceivable rôle. This is very likely true of the more markedly thickened sclerotic valves. Certainly, the following additional factors must be weighed and placed properly in the scheme as a whole.

Vitamin C Deficiency. In recent years, emphasis on the relationship of vitamin C depletion to degeneration of collagen, especially of the collagen of cardiac valves, has been revived. Briefly, this association is suggested by the following evidence (although isolated data to the contrary have been recorded): first, the degeneration of collagen in various organs of scorbutic guinea-pigs; [23, 24] second, the fibrinoid valvular changes observed in scorbutic guinea-pigs; [25-27] third, the positive relation of ascorbic acid to the formation of collagenous fibers *in vitro* and *in vivo*; [28, 29] fourth, the evidence that vitamin C deficiency affects the cohesion of endothelial cells; [30] fifth, the many observations that the collagenization of wounds is interfered with in vitamin C-deficient animals; [31] and finally, the tendency toward depletion of vitamin C in patients with fevers, intestinal diseases, neoplasms, postoperative periods, etc.[32-35] In accord with this evidence, many of our patients might be judged to have been deficient in vitamin C and to have been subject to the effect of such depletion as the evidence mentioned above might indicate. The reason for the absence of generalized collagenous alteration in our cases may have been due to the relatively minor degree of depletion of vitamins and to the selective predisposition of the valves to such alteration.[7] It is conceivable that other dietary deficiencies may play a part, but, as with vitamin C deficiency, it is likely that their damage is wrought in an important measure by abetting the degeneration of valvular collagen.

Hemodynamics and Sclerotic Valves. Probably a great factor in the predisposition of the valves to degeneration as compared with collagen elsewhere lies in their strategic situation which allows concentration of the continual hemodynamic impact by the blood stream against the valves. This selective "hemodynamic pounding" constitutes, in our opinion, the third and, as a rule, the principal factor in the degeneration of valvular collagen. The details of the dynamics are judged to be quite the same as those described previously in the explanation for the localization of vegetations of bacterial endocarditis.[7, 15] In brief, a "line of closure" of a previously thickened valve—and the valves on which verrucae are found are usually thickened by fibrosis—is particularly predisposed to the systolic impact of the blood stream because it tends to obstruct rather than to "give way" with the stream. In addition, this site offers great frictional resistance to the current in proportion to the degree of stenosis. The contact of the so-called line

of closure with the current of blood is further enhanced as the regurgitant stream returns through the incompetent valve. The generally accepted explanation for the localization of lesions at the "line of closure" is that this site is traumatized as the cusps slap shut. However, it is germane to point out that if a valve is stenotic, the cusps are simply unable to impinge against each other; rather, the blood impinges against the cusps.[7]

It is obviously hazardous in a particular case to presume to estimate which one of the four factors or what combination of factors operated to produce the lesion. However, it seems not unreasonable that a verruca which has provoked cellular exudation and proliferation at its base and occurs in a thin or only slightly thickened valve is more likely to be the result of a hyperergic reaction than a bland verruca occurring in a markedly sclerotic valve. In the latter instance, hemodynamics are much more apt to have played the principal rôle.

Nomenclature

These verrucae have hitherto been regarded as terminal endocarditis, nonbacterial thrombotic endocarditis, marantic thrombosis, etc. In the current study, it has been shown that the lesions occur during acute as well as chronic illnesses, in the young as well as the aged, in the well nourished and in the marantic. In other words, the evidence indicates that the lesion may occur in a variety of illnesses which the patient may survive for years, presumably with subsequent healing of any verrucae that may have formed during the illness. Therefore, the designations "terminal" and "marantic" are unjustified. Furthermore, it appears quite possible that bacterial proteins may play a rôle in the production of the lesion, so that the qualification "nonbacterial" may not be strictly accurate, although it is understood that the term implies the absence of bacteria within the verrucae. In addition, evidence against the thrombotic nature of the lesion has been presented herewith so that, in our opinion, the designation "thrombotic" is inapplicable. Finally, because it appears to us that valvular degeneration rather than inflammation is generally the major element in the formation of these verrucae, we should prefer to consider them as primarily degenerative rather than inflammatory.

Therefore, the term "degenerative verrucal endocardiosis" * is pro-

* Because of the prevalent misunderstanding of the complete meaning of the suffix "osis," the following definition is quoted from *Webster's New International Dictionary of the English Language*, ed. 2, unabridged. G. and C. Merriam Co., Springfield, Mass., 1938, p. 1726:

-osis; pl.-oses. [fr. Gr.-osis, as in metamorphosis] A suffix signifying:

1. a. Condition, state, process, and the like, as in hypn*osis*, psych*osis*, osm*osis*; specif.,

posed to designate a nonspecific endocardial alteration, verrucal in appearance when fully developed, and occurring in association with a great variety of diseases, both acute and chronic, including those clinical entities designated by Gross and Friedberg[5] as "nonbacterial thrombotic endocarditis." The verrucae in this latter condition are considered to be as nonspecific a component of the morphologic picture as is leukocytosis, for example, in many clinical syndromes.

Differentiation of Degenerative Verrucal Endocardiosis from Acute, Recurrent, Rheumatic Valvulitis

It is to be pointed out that inasmuch as the lesions of degenerative verrucal endocardiosis are prone to occur on valves fibroblastically thickened by rheumatic infection, the nonspecific verruca may erroneously be regarded as evidence of an acute exacerbation of a chronic rheumatic valvulitis. It may be impossible to establish the diagnosis by gross inspection. The differential diagnosis may be further complicated by the observation of palisaded histiocytes at the base of the verruca. This pattern of cellular proliferation is regarded as characteristic of the rheumatic lesion by Leary.[36] However, the observations made in the current study support those of Jaffé[37] who indicated that palisading of histiocytes may occur in nonspecific lesions. The absence of Aschoff bodies and of a diffuse interstitial valvulitis or, at the least, of a diffuse cellular reaction along much of the valvular surfaces, particularly the spongiosal surface, serves to differentiate degenerative verrucal endocardiosis from acute rheumatic valvulitis.

Differentiation of Degenerative Verrucal Endocardiosis from Bacterial Endocarditis and Atypical Verrucous Endocarditis

Grossly, a small proportion of the lesions, especially those of the multiverrucal type (Figs. 3 and 4), may simulate acute or subacute bacterial endocarditis. A clue to the diagnosis may be offered in the usually greater irregularity of the vegetations of bacterial endocarditis. The diagnosis must not rest on the culture, *e.g.*, of *Streptococcus viridans*, or of an enterococcus from the lesions, inasmuch as such organisms may be recovered incidentally from cultures of normal valves in a significantly high percentage of cases.[38] The diagnosis must be established on the basis of the histologic picture with the weight being given

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in pathology, *abnormal* or *diseased condition*, as in melan*osis*, sten*osis*, varic*osis*, etc. b. A physiological increase or formation (of something specified), as in chyl*osis*, leukocyt*osis*, etc.

2. In plant pathology, a disease of which a (specified) fungus is the causal agent; a myc*osis*; as in chytridi*osis*.

Hence, endocardiosis signifies a disease of the endocardium.

particularly to the presence of a destructive or suppurative valvulitis [14] and of *colonies* of bacteria rather than an isolated bacterium here and there.

An even more difficult problem is the differentiation of the few cases of large multiverrucal lesions of degenerative endocardiosis from those of atypical verrucous endocarditis (Libman-Sacks disease, disseminated lupus erythematosus). It may be quite impossible to establish the diagnosis grossly in these instances. Indeed, some of the verrucae of Libman-Sacks disease may be indistinguishable from those of degenerative endocardiosis. As a rule, however, the differentiation may be made by the characteristic interstitial valvulitis and the associated, practically pathognomonic changes in the collagen, especially of the kidney, heart and spleen, which have been recently described in detail.[13]

Relationship of Degenerative Verrucal Endocardiosis to Bacterial Endocarditis

We regard the lesions of degenerative verrucal valvulosis as one of the basic morphologic events in the development of bacterial endocarditis. The fibrinoid material, with certain limitations,[8] appears to be an attractive medium for the ensnaring and propagation of bacteria present in the general circulation. In principle, this is essentially the point of view of Grant, Wood and Jones,[3] who, however, hold the underlying lesion to be a simple thrombus. We feel that the same hemodynamic factors, in large measure responsible for the localization of the initial verruca, operate to bring circulating bacteria in contact with the verruca.[7, 15] It is our belief that identical principles are concerned in the superimposition of bacteria onto the verrucae of acute rheumatic endocarditis as well as atypical endocarditis (Libman-Sacks disease, disseminated lupus erythematosus). The affinity of the lesions of atypical verrucous endocarditis for bacteria is strikingly illustrated in the occurrence of bacterial endocarditis in fully one-third of the 12 cases described by Klemperer, Pollack and Baehr.[13] In other words, the verruca of both the specific and nonspecific variety is prone to become a nidus of bacterial proliferation. The details of the evidence for this concept are considered separately.[8]

Healed Lesions of Degenerative Verrucal Endocardiosis

Finally, the evidence indicates that the lesions of degenerative verrucal endocardiosis may heal by fibrosis if the patient survives the illness during which the valvular alteration occurred. As might be expected, it is impossible to distinguish the healed verruca of acute rheumatic disease from that of degenerative endocardiosis. In both instances, the

healed lesion seems to take the form of fibrous tabs such as Lamblian excrescences attached to the corpora arantii or the adjacent ridge of semilunar valves. Similar fibrous prongs may occur on the auriculoventricular valves (Fig. 12), or they may take the form of small, smooth nodules or bulbous thickening near the edges of these valves. Such focal fibrous nodules occurring on nonrheumatic valves have been hitherto regarded generally as "senile" or "tension thickenings." It would seem more reasonable, in the light of findings herein presented, to classify them as healed stages of degenerative verrucal endocardiosis.

Summary and Conclusions

1. Fifty cases of so-called "terminal endocarditis" or "nonbacterial thrombotic endocarditis" were studied.

2. The valvular lesions of "terminal endocarditis" are characteristically hillocks of degenerated, swollen, *valvular* collagen, occasionally with an admixture of varying amounts of serum, fibrin, platelets and blood cells derived from permeable or eroded vessels of the valves. They are *not* regarded as thrombi deposited onto the valves from the blood within the cardiac chambers, contrary to the generally held impression.

3. It is believed that the lesions are not necessarily "terminal" and that they may occur during the course of a variety of acute and chronic illnesses, many of which are survived with consequent healing of the valvular lesion.

4. The healed lesion, of which the Lamblian excrescence is an example, takes the form of a fibrous tab or nodule, or slight bulbous collagenous thickening near the free edge of the valve (so-called "senile" or "tension thickening"). The healed lesion, by virtue of its projection and consequent hemodynamic disadvantages, is, in turn, prone to undergo recurrent degeneration.

5. The active lesions are, as a rule, primarily degenerative rather than inflammatory.

6. It is suggested that such names as "terminal endocarditis" or "nonbacterial thrombotic endocarditis" are not applicable. The nonspecific term, "degenerative verrucal endocardiosis," is offered as being more in keeping with the available knowledge of the lesion.

7. Allergy, vitamin C deficiency, hemodynamic stresses and valvular sclerosis, alone or in combination, may be concerned in the pathogenesis of this nonspecific lesion.

8. Differentiation from acute and recurrent rheumatic valvulitis, bacterial endocarditis, and atypical verrucous endocarditis is usually possible. Gross and microscopic structure, bacterial content, and the

concomitant valvular and extravalvular cardiac lesions must be considered in establishing differentiation.

9. The lesions of degenerative verrucal endocardiosis constitute an important morphologic basis for the development of bacterial endocarditis.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 188

(Figures 1 to 4 illustrate the wide range of patterns assumed by the verrucae of degenerative verrucal endocardiosis.)

FIG. 1. The most common form of degenerative verrucal endocardiosis—the "small, univerrucal" type. The intervening small nodules are possibly the healed, fibrous residuum of verrucae.

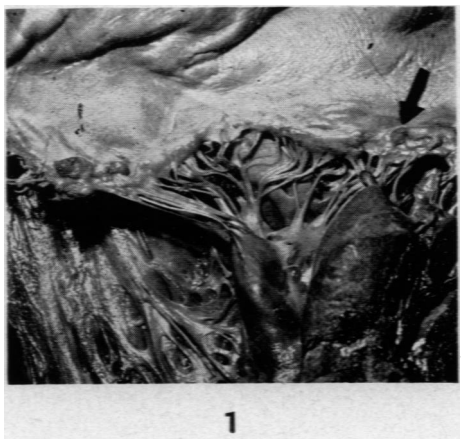
FIG. 2. The "large, univerrucal" type of degenerative verrucal endocardiosis occurring in aortic valves showing evidence of old rheumatic inflammation. This lesion is to be differentiated from bacterial endocarditis by histologic examination.

FIG. 3. "Large, multiverrucal" form of degenerative verrucal endocardiosis. From the eroded area of endocardium a verruca had been removed manually. (See Fig. 7 for histologic section.)

FIG. 4. An unusual example of the "large, multiverrucal" type. This and the preceding form require study of histologic sections for definite differentiation from bacterial endocarditis.

FIG. 5. Lamblian excrescences of aortic valves. These projections from the region of the corpora arantii are regarded as the healed, fibrous stage of verrucae of either degenerative endocardiosis or acute rheumatic valvulitis. The lesions are particularly prone to recurrent degenerative changes because of their exposure to the impact of the blood stream. Very small dentate verrucae may be seen along the valvular ridge. Similar excrescences occur on the mitral and tricuspid valves (see Fig. 12).

FIG. 6. Lamblian excrescences of aortic valves.



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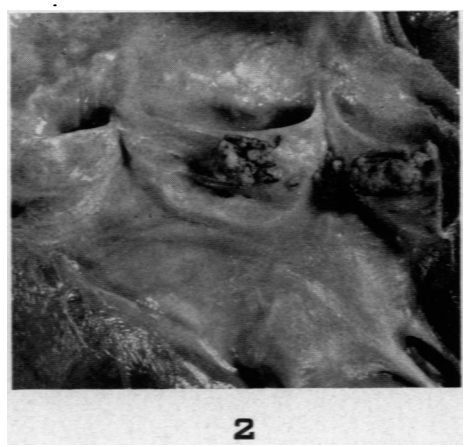

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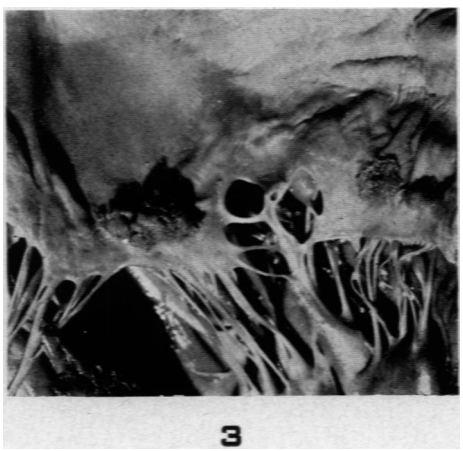

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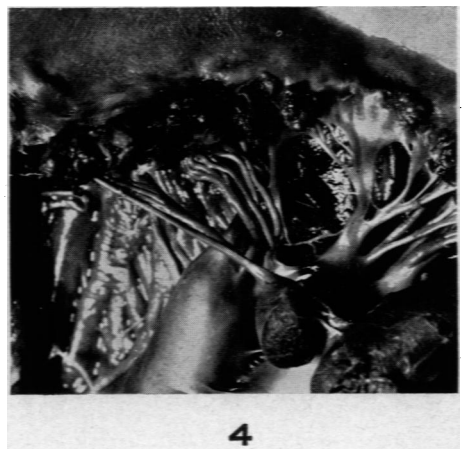

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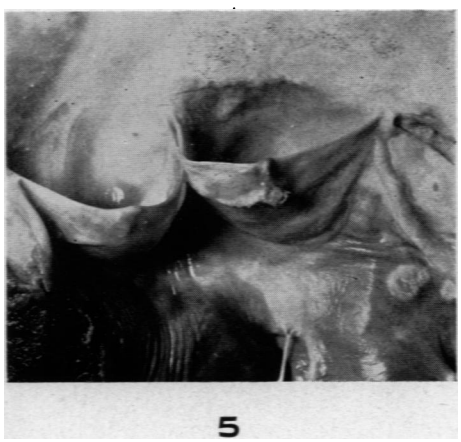

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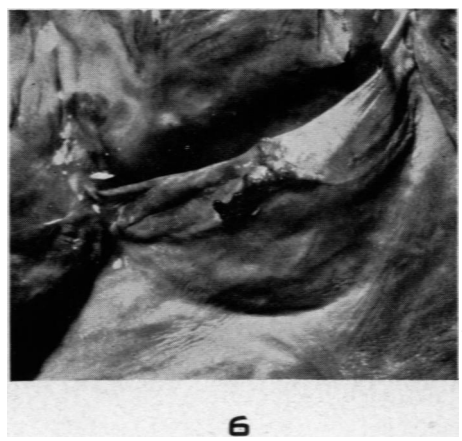

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Allen and Sirota Degenerative Verrucal Endocardiosis

PLATE 189

FIG. 7. Section of the "exudative" type of degenerative verrucal endocardiosis illustrating the moderate increase in swollen, hyperchromatic histiocytes at the base of the lesion. Section taken from heart illustrated in Figure 3. Hematoxylin and eosin stain. × 100.

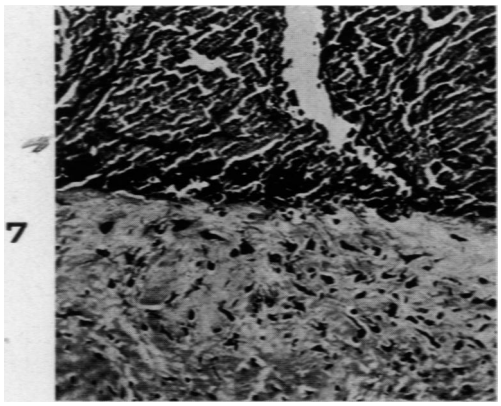
FIG. 8. Section of "exudative" type of degenerative verrucal endocardiosis illustrating the extreme degree of reaction observed. This extensive reaction is seen rarely and only in the "exudative" type of lesions, as shown in Figures 3 and 4. The lesion simulates rheumatic valvulitis but is distinguished by the absence of interstitial valvulitis and of Aschoff bodies. Hematoxylin and eosin stain. × 100.

FIG. 9. Section of a verruca of degenerative endocardiosis illustrating Anitschkow myocytes (see arrows) in the midst of the fibrinoid material. These cells are not found in cardiac mural or vascular thrombi. Hematoxylin and eosin stain. × 500.

FIG. 10. Section of a verruca of degenerative endocardiosis illustrating the large foam cells. Hematoxylin and eosin stain. × 600.

FIG. 11. Low-power view of Figure 10. Foam cells are seen throughout the verruca. Hematoxylin and eosin stain. × 16.

FIG. 12. Section of fibrous tabs on mitral valve. These are analogous to the Lamblian excrescences of the aortic valves and are regarded as the healed lesion of degenerative verrucal endocardiosis. Hematoxylin and eosin stain. × 30.



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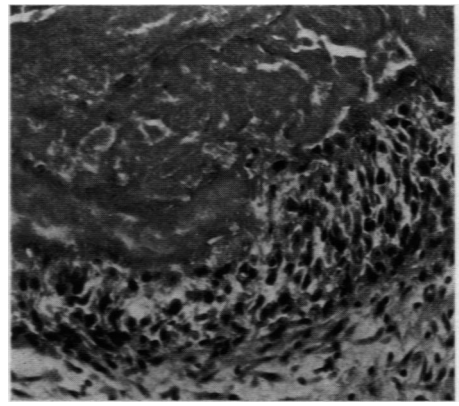

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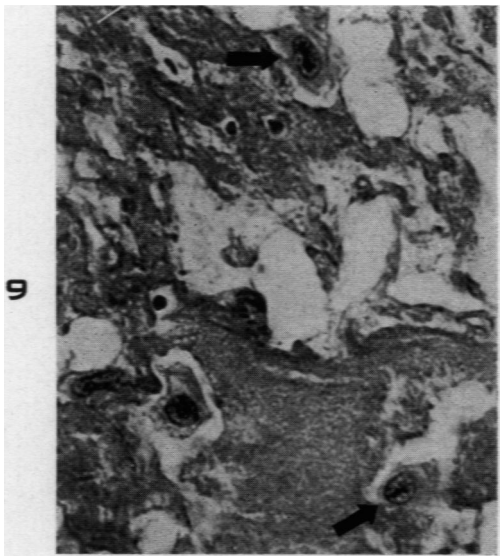

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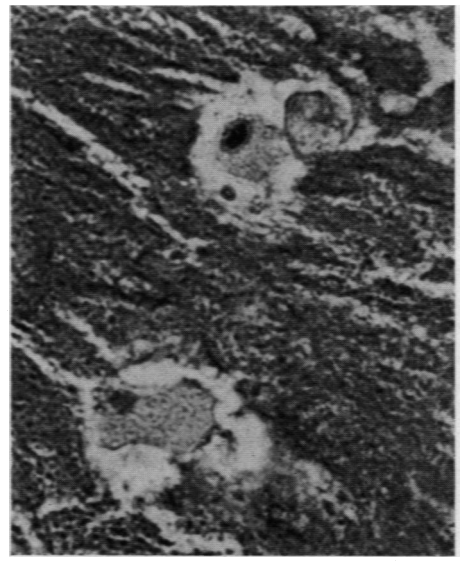

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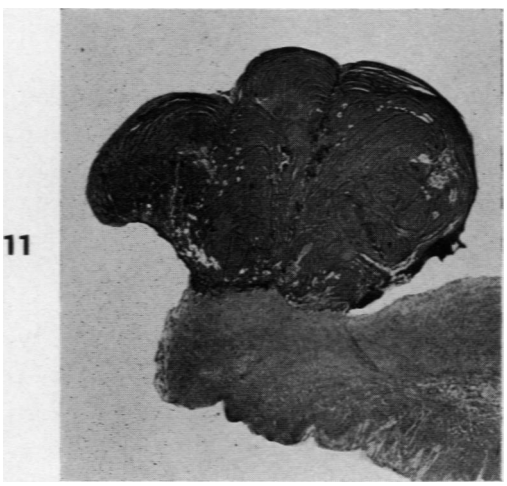

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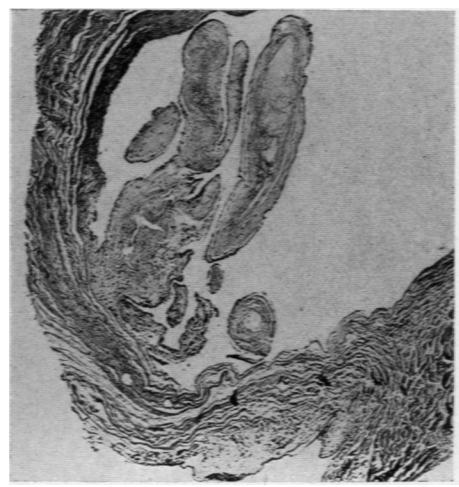

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PLATE 190

FIG. 13. Section illustrating the pre-verrucal stage of degenerative endocardiosis. The lesion is obviously a valvular degeneration although the left half of it superficially simulates a thrombotic deposit. Hematoxylin and eosin stain. × 125.

FIG. 14. Section illustrating a more advanced stage of verrucal formation. The altered valvular fibrous tissue has swelled to form the irregular knobs of verrucae. There is absence of cellular reaction. This is the "degenerative" type and represents the usual picture of degenerative endocardiosis. Hematoxylin and eosin stain. × 100.

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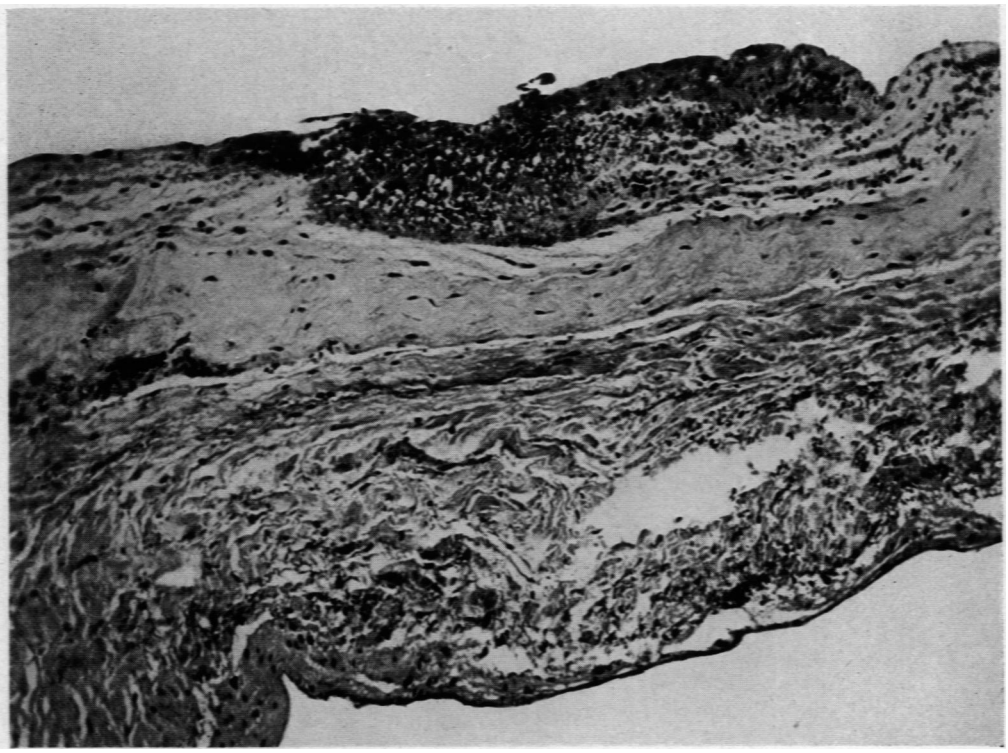

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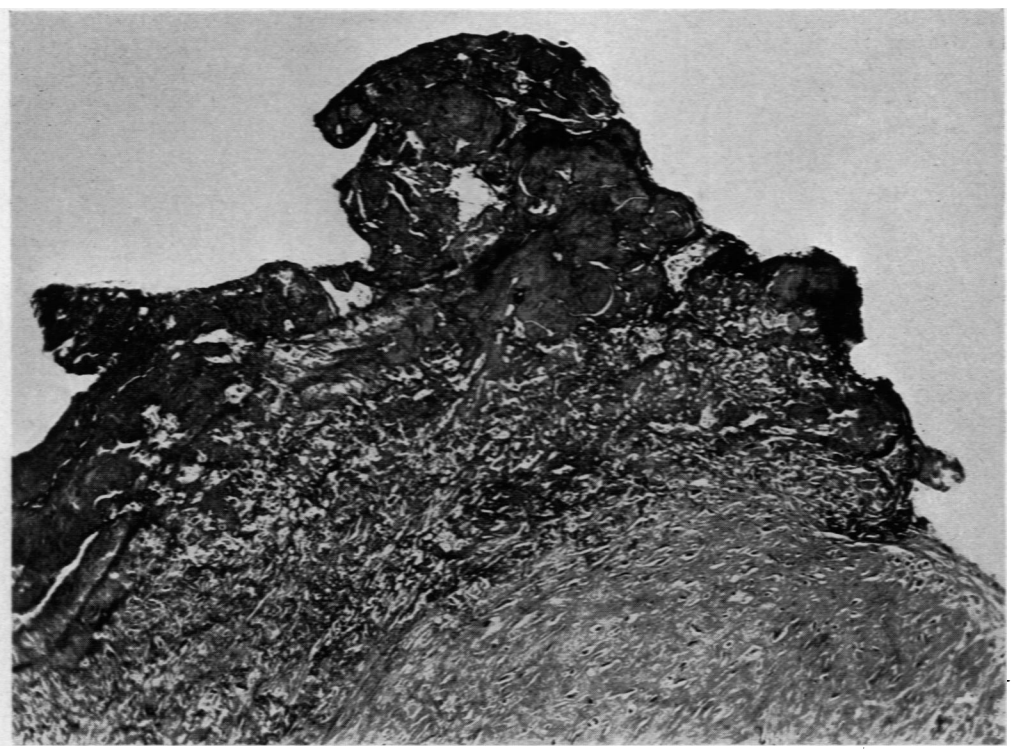


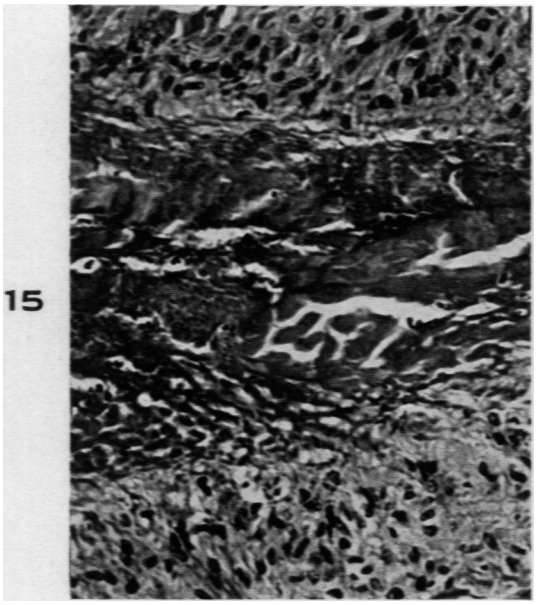
Allen and Sirota Degenerative Verrucal Endocardiosis

PLATE 191

FIG. 15. Section of granuloma annulare of the skin showing the characteristic periphery of palisaded histiocytes about a core of fibrinoid material that is, without question, altered collagen. Hematoxylin and eosin stain. × 260.

FIG. 16. Section illustrating reticulin in an organizing, mural thrombus. The orderly tracery of argyrophilic fibers contrasts with the irregular pattern in the verruca shown in Figure 17. Silver stain. × 200.

FIG. 17. Section of a verruca of degenerative endocardiosis. The haphazard arrangement of disrupted, anuclear argyrophilic fibers obviously indicates destruction of collagen rather than the organization of a thrombus. There is continuity of the fibers into the homogeneous, platelet-like mass, the latter representing for the most part the more markedly altered collagen. The thickness of the argyrophilic fibers contrasts with the fine reticulin of organizing thrombi (Fig. 16). There is an absence of associated fibroblasts. Silver stain. × 200.



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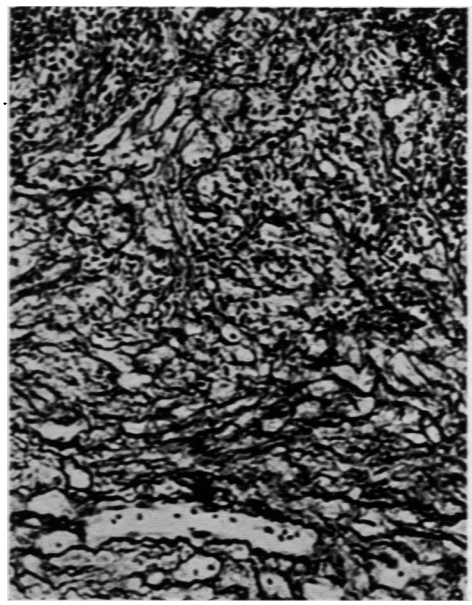
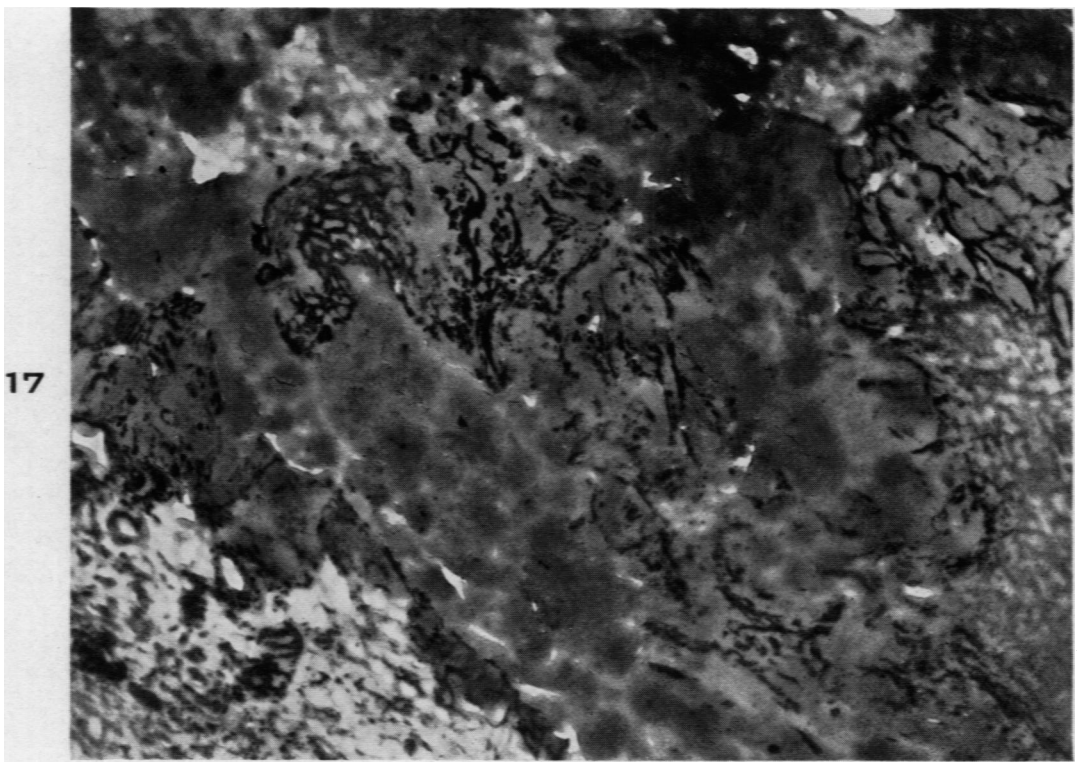


16



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Allen and Sirota Degenerative Verrucal Endocardiosis

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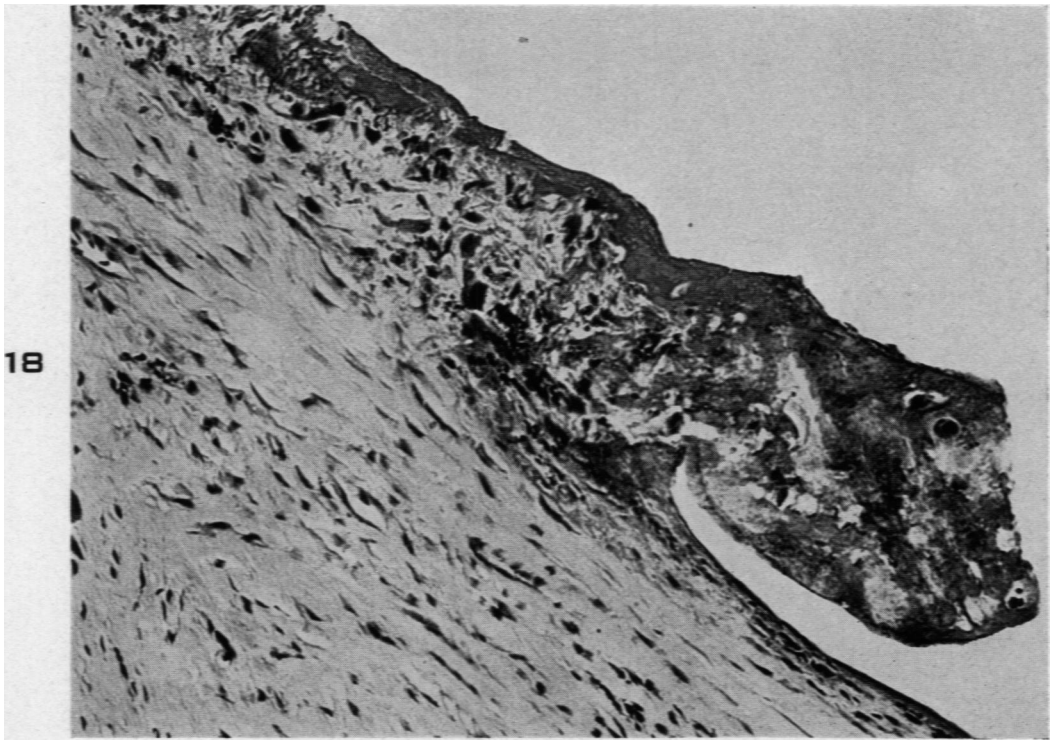
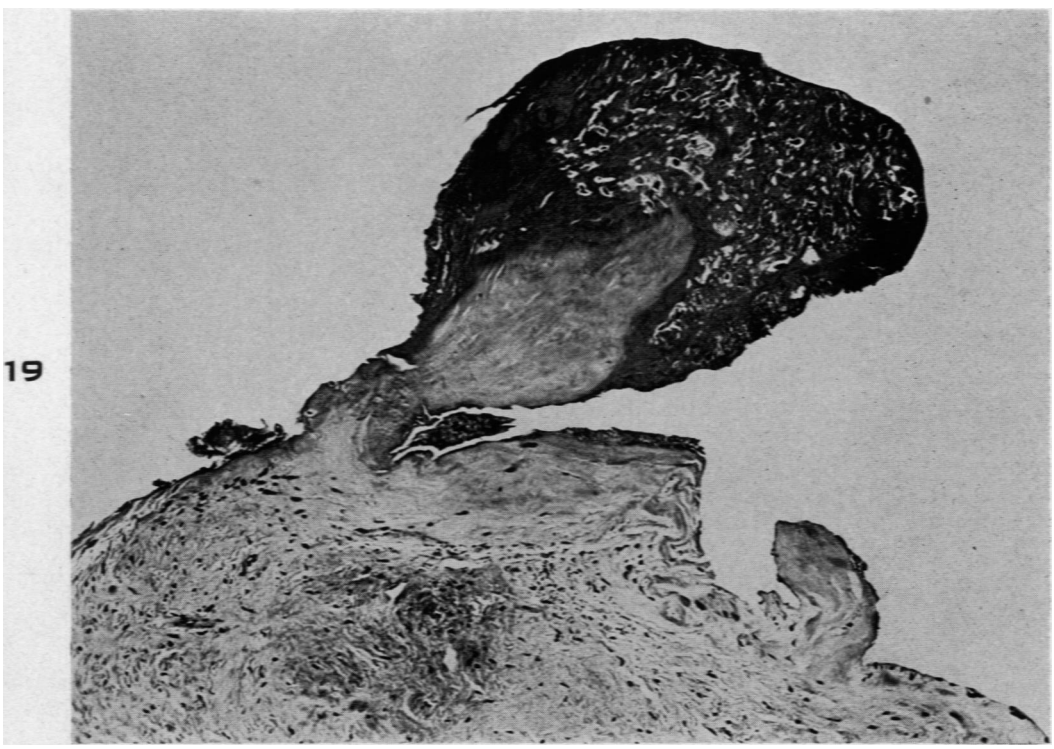
FIG. 18. Section of a verruca of acute rheumatic valvulitis to illustrate the similarity in morphogenesis of the verrucae of degenerative endocardiosis and of acute rheumatic valvulitis. The outpouching of the verruca from the valve is well shown and is strongly suggestive evidence against the view that verrucae are thrombotic deposits. × 200.

FIG. 19. Section illustrating recurrent degenerative endocardiosis within a healed verruca. The darker periphery is degenerated collagen—not a thrombotic deposit. Hematoxylin and eosin stain. × 100.



18



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