LESIONS OF THE CARDIAC VALVES IN RHEUMATIC FEVER*

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The early descriptions of valvular disease dealt with the recognition of verrucae and the occurrence of gross valvular deformities. Aside from the absence of microscopic studies these descriptions were of limited value, first because of failure to recognize the importance of rheumatic fever as a cause of valvular disease and later because of confusion of valvular deformities due to rheumatic fever with those due to bacterial endocarditis, arteriosclerosis, syphilis, and so on. In the early part of the eighteenth century, Vieussens [1] gave clinical and pathological descriptions of mitral stenosis, aortic stenosis and aortic insufficiency. In the latter half of the century the thickening, whitening, loss of transparency and ossification of the semilunar valves were mentioned by various writers, including Morgagni,[2] de Senac,[3] and Baillie.[4]

Somewhat later Corvisart [5] described mitral stenosis and warty vegetations on various valves of an apparently rheumatic heart but believed the vegetations to be luetic. Laennec,[6] who termed these vegetations verrucae, and also Bertin,[7] failed to recognize their rheumatic origin but doubted the luetic theory of their formation. While Bouillaud [8] was not the first to observe the occurrence of heart disease in rheumatic fever, he most clearly recognized the association of various valvular lesions with that disease. He emphasized the thickening and stenosis of valves, the occurrence of verrucae at or near the free border rather than at the bases, and the occurrence of stages in valvular disease accompanied by organization and lime infiltration. However, there is considerable evidence that many of his cases were instances of bacterial endocarditis or of degenerative valvular disease. Watson [9] adequately depicted the most striking gross features of rheumatic valvular disease including the thickening, loss of transparency and pliancy, puckering, adhesions and vegetations.

During the latter half of the nineteenth century a number of reports dealt with the microscopic findings in rheumatic valvular disease. While the significance of bacteria in the causation of endo-

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carditis was understood, inadequate or imperfect bacteriological technique, incomplete clinical knowledge of the bacterial forms of endocarditis, uncertainty as to the bacterial etiology of rheumatic fever and the absence of rigid pathological criteria for the latter were some of the more important reasons for confusion. In the reports of Jaccoud,[10] Crocker,[11] Weichselbaum,[12] Klebs,[13] Birch-Hirshfeld,[14] and others, bacterial and rheumatic endocarditides were confused. The division of endocarditis into verrucous and ulcerative forms was not clear-cut because the former included bacterial as well as rheumatic lesions. Wyssokowitsch [15] and Orth [16] most clearly recognized that many of the cases of verrucous endocarditis showed no bacteria in the vegetations. The latter author stressed the importance of cellular proliferation in the valve and the avascularity of normal valves.

Detailed microscopic studies of valvular lesions in rheumatic endocarditis were reported by Achalme,[17] and by Königer,[18] and the formation of verrucae was discussed by Neumann,[19] and Ziegler.[20] The first mentioned reported bacterial infiltration of the valves and described what he considered to be the causative organism. Neumann conceived verrucae as being formed purely from the valve substance which had undergone fibrinoid degeneration. Ziegler, on the other hand, considered the verrucae to result from marantic thrombosis with deposition on the valve surface (thrombo-endocarditis). Königer's painstaking histological studies were based essentially on valvular disease in non-rheumatic infections. Only 2 definitely rheumatic cases were presented. The primary process was described as an endothelial necrosis. Verrucae were considered to be formed from the subendothelial tissues which proliferated, underwent coagulation necrosis and combined with thrombotic material deposited from the blood stream.

Later studies were characterized by a clearer delimitation of rheumatic endocarditis from subacute and acute bacterial endocarditis, from syphilitic disease and from arteriosclerotic valvular disease, especially of the Mönckeberg variety. This segregation resulted from the recognition of the Aschoff body as a specific criterion of rheumatic disease, from improved blood culture methods and more detailed clinical studies of bacterial endocarditis, from the discovery of the Wassermann reaction, and finally from more thorough knowledge of the histology of the normal valve. Nevertheless, there was still confusion between rheumatic and non-rheumatic cases in the

reports of Dewitzky [21] and of Felsenreich and von Wiesner.[22] The former, however, gave clear descriptions of the chronic valvular lesions in rheumatic fever and segregated them from those of Mönckeberg's ascending sclerosis of the aortic valve. The latter authors recognized some of the characteristic alterations of the elastica, and the lesions in the pockets of the valves and chordae tendineae attachments.

To Bulloch,[23] and especially to Carey Coombs,[24] we owe most of our recent knowledge of the histology of rheumatic valvular disease. Both of these authors, as well as Butterfield,[25] Thalhimer and Rothschild,[26] Gengenbach,[27] Clawson and Bell,[28] and others, described the presence of Aschoff bodies in the valves. Bulloch emphasized the occurrence of the earliest changes, not in the endothelial but in the subendothelial layers. These consisted of a coagulation necrosis with swelling and homogeneous transformation of the ground substance. Coombs drew attention to the proliferative and exudative reactions in the valves as well as in other regions of the heart. The proliferative reaction was the more marked. The deeper structures reacted before there was evidence of injury to the endothelial surface. This observation, among others, led to the concept of a deep valvulitis first and verrucous formation later. Following Poynton and Paine,[29] Coombs believed that infection came by way of the coronary branches and not superficially from the circulating blood. Like Poynton and Paine he also described what he believed were bacteria in the valve.

Similar descriptions were given in the more recent studies of Clawson, Bell and Hartzell,[30] and by Klinge [31] and his coworkers. The former authors described acute and healing lesions in rheumatic endocarditis and old valvular defects. Klinge described an acute stage of valvular inflammation with subendothelial focal and banded swellings, a later granulomatous stage with Aschoff bodies or diffuse cellular infiltrations, and finally a stage of scarring. The valvular lesion was considered primary and the verrucae secondary.

The detailed description of valvular lesions given by Ribbert [32] is essentially like that of Königer. Benedict [33] gave a differential pathological description between rheumatic and syphilitic disease of the aortic valve. He particularly emphasized that in lues there was an increase of endocardial elastica, whereas in rheumatic fever the elastica was torn and diminished in amount. Leary [34] drew attention

to palisade cell formations along the contact edges of the valves which he believed represented a specific early rheumatic reaction. Of the 3 cases which he reported, only 1 was definitely rheumatic, and that patient died of an acute infection.

Many of the more recent studies have concerned themselves with investigating grossly normal valves from patients dying of acute infections, or the grossly normal portions of valves which elsewhere showed macroscopic abnormality. Such reports were made by Baldassari,[35] Holsti,[36] Böhmig and Krückeberg,[37] de Vecchi,[38] and by Waldow.[39]

In summarizing and appraising the above mentioned reports on the pathogenesis of rheumatic valvulitis, they may be divided into two periods. During the period preceding the discovery of the Aschoff body as the specific lesion in rheumatic fever, the reports were largely confused by the failure in many cases to differentiate the valvular lesions of rheumatic fever from those occurring in other endocarditides as well as from other degenerative valvular changes. Following the discovery of the Aschoff body confusion still persisted: (1) because this lesion is not invariably present in rheumatic fever, especially during the less active stages; (2) because the unfortunate classification of endocarditis into verrucous and vegetative led to no sharp differentiation of the several types; (3) accurate descriptions of the normal structure of valves were not available, with the result that the pathological changes were seldom referred to with precision in respect to the layers of the valve involved; and (4) age period changes occurring in normal valves received practically no attention, thus adding considerably to the difficulty of discerning the lesions due essentially to the chronic rheumatic process.

In a series of studies reported by one of us (L. G.) with collaborators, attention was drawn to the pathogenesis of various rheumatic lesions occurring in the heart, *viz.*, of the myocardium [40] (Aschoff bodies), blood vessels,[41] large vessel roots,[42] auricles,[43] conduction system,[44] pericardium [45] and valve rings.[46] In these investigations a description of the normal histology and topography as well as of the age period changes in these sites was included. In following the life cycle of these lesions in indisputable cases of rheumatic fever certain stigmata of active as well as healed rheumatic lesions were demonstrated. These stigmata of healed rheumatic lesions are particularly

important in establishing the essential rheumatic nature of a given valvular lesion. On the basis of such studies it now becomes possible sharply to define rheumatic from non-rheumatic hearts, even in the absence of Aschoff bodies or a typical clinical history.

According to the definitions of Gross and Kugel,[47] the auriculoventricular valve leaflet consists of the fibro-elastic structure immediately distal to the auricular myocardial wedge, and the semilunar valve leaflet consists of the fibro-elastic structure attached to the subjacent ventricular myocardium through the intermediary of annulus interdigitations (Figs. 1 and 2). This definition includes the valve ring as the proximal portion of the leaflet.* The ring lesions in rheumatic fever recently described by the present authors, therefore, can be legitimately considered as part of the valvular lesion as a whole. These rheumatic ring lesions have been described separately for purposes of clarity, but reference should be made to the complete report in order to preserve a logical continuity with the descriptions to be given of the lesions in the remainder of the leaflet.

Briefly to recapitulate the findings in non-rheumatic and rheumatic rings, the following points should be borne in mind: Normal valve rings are practically devoid of inflammatory cells. The ring spongiosa in the semilunar cusps almost invariably consists of a gelatinous tissue and is generally sharply separated from the adjacent fibrous structure (annulus). In the auriculoventricular valves the spongiosa component is generally inconspicuous. Blood vessels with muscular walls are never seen in the normal rings. The incidence of capillaries in these rings, as determined in 100 normal hearts, is as follows: anterior mitral valve ring, 1 per cent; posterior mitral valve ring, 2 per cent; aortic valve ring, 0 per cent; tricuspid valve ring, 14 per cent; and pulmonary valve ring, 7 per cent. When present, the capillaries are generally few in number, small and circular on cross-section, and in structure easily differentiated from granulation tissue capillaries.

On the other hand, the characteristic features of the ring lesions in rheumatic fever are briefly as follows: The rings are almost invariably infiltrated with inflammatory cells, capillaries and blood vessels. The latter are sometimes of a characteristic type. The inflammatory process generally spreads into the contiguous valve leaflets

* A full description and delimitation of the valve rings were reported by Gross and Kugel.[47]

as well as along the annulus extensions of the aortic root. These contiguity extensions of the inflammatory process are present in the septum fibrosum as well as in the intervalvular fibrosa (the collagenous link between the aortic and mitral valves). The subvalvular angles show characteristic lesions, termed reduplications. These are frequently inflamed and vascularized. Scarring of the ring occurs, with obliteration of the ring spongiosa. The extent of these inflammatory phenomena is determined by the clinical course of the disease.

Bearing in mind, therefore, this intimate relation of the ring lesions to those that occur in the remainder of the valve leaflets in rheumatic fever, we are now in a position to take up the description of the gross and microscopic changes that take place in the latter and to discuss their significance with regard to the pathogenesis of rheumatic valvulitis. The description of these lesions will be preceded by a discussion of the gross and microscopic findings in normal valves, together with a consideration of their age period changes.

Material and Methods

The material consisted of 40 non-rheumatic control hearts and 97 rheumatic hearts. Seventy-one of the latter were from active rheumatic cases and showed Aschoff bodies in the myocardium, and 26 showed chronic valvular disease of the typical rheumatic variety but without evidence of activity either clinically or pathologically and with no demonstrable Aschoff bodies in the myocardium. The grouping as to activity and inactivity was based on the criteria outlined by Rothschild, Kugel and Gross.[48] Particular care was taken to avoid material that in any way indicated the possibility of a coexisting bacterial endocarditis or syphilis. A careful study of the clinical records and pathological specimens made it possible to divide the rheumatic cases into the following groups:

Group I. Active cases where death took place during the first attack (12 cases).

Group II. Active cases where one preceding attack occurred within 1 year of the fatal outcome (7 cases).

Group III. Active cases where one previous attack occurred at least 2 years previous to the fatal outcome (11 cases).

GROUP IV. Active cases with a history of repeated attacks, death occurring during an acute recurrence (13 cases).

GROUP V. Active cases where death was caused by decompensation without clinical evidence of a final acute attack. In some of these cases there was no previous history of rheumatic fever (28 cases).

GROUP VI. Inactive cases of chronic valvular disease of the typical rheumatic variety (26 cases).

The sections from which these studies were made were cut according to the standardized technique of Gross, Antopol and Sacks,[49] and the technical procedures were those previously described by Gross and Ehrlich.[40]

AGE PERIOD CHANGES IN THE GROSS APPEARANCE AND HISTOLOGICAL STRUCTURE OF NORMAL VALVES

A study of the gross appearance of normal valves revealed only such alterations as could be ascribed to increasing age and tension. In about half of the cases, particularly in the older age periods, the uniform slenderness and transparency of the valve cusps were slightly altered by the occurrence of isolated patches of whitish opaque thickening. These thickenings were generally not notable. They were situated at various portions of the valve leaflets but most frequently at the closure line and free margin. When present at the free margin, the thickening obscured the normal concave scalloping and rendered the margin either straight or convex.

Not infrequently there was broadening of the heads of the chordae tendineae that were attached to the region of valvular thickening. In addition to these, there were occasional yellowish lipoid flecks which spotted the valve ring, both aspects of the valve cusps, and especially the valve pockets.

The pocket of the normal valve generally formed a sharp narrow angle which was traversed only occasionally by an isolated bridge of fibrous tissue. Except for the lipoid flecks just mentioned, there were none of the irregularities that will be described as occurring in the pockets of the various rheumatic valves.

The histological structure and topographical relations of normal human heart valves have been described in detail by Gross and

Kugel.[47] Briefly considered, they are characterized by the following features: All valve leaflets carry as their main backbone a dense collagenous layer called the fibrosa (Figs. 1 and 2). Adjacent to the fibrosa layer and sometimes not clearly distinguished from it, there is a zone of loose connective tissue called the spongiosa layer. This is situated on the auricular aspect of the auriculoventricular valve fibrosa as well as on the ventricular aspect of the semilunar valve fibrosa. In the semilunar cusps the spongiosa layer may be so conspicuous as to constitute a sharply defined zone of loose gelatinous tissue. In the auriculoventricular cusps the spongiosa layer is frequently quite inconspicuous in its proximal two-thirds and becomes discernible and widened generally only in the presence of inflammation. The distal third, or tip of the valve, generally consists of a gelatinous expansion of the spongiosa layer. On the auricular surface of the auriculoventricular leaflets there lies a fibro-elastic mantle of various thickness, called the auricularis layer. This is covered by a flat layer of endothelial cells. The ventricular surface of these leaflets is covered by a much thinner layer of fibro-elastic tissue called the ventricularis. This, in turn, is also covered by endothelium. The ventricular aspect of the semilunar cusps is clothed by a fibro-elastic mantle somewhat more delicate than the auricularis of the auriculoventricular cusps. This is called the ventricularis of the semilunar cusps. The arterial aspect of the semilunar cusps is covered by an even more delicate elastic mantle. Inasmuch as the auricularis layer of the auriculoventricular valves and the ventricularis layer of the semilunar valves are the first to be impinged by the blood stream, these will be referred to as the "proximal layers." For similar reasons, the ventricularis layer of the auriculoventricular valves and the arterialis layer of the semilunar valves will be referred to as the "distal layers." These terms are not to be confused with the proximal and distal portions of the valves, *i.e.*, the insertions and tips, respectively.

Normal valve leaflets are poor in cells. This is particularly noticeable in the fibrosa layer. In spite of the controversial reports on the existence of blood vessels in valves, the available evidence leaves little room for doubt that, apart from the sparse capillaries mentioned above as occasionally occurring in the valve ring, blood vessels are seldom, if ever, present in normal human heart valves.[50] It may be stated in passing that the high incidence of valve vascularization,

as recently reported by Wearn *et al.*,[51] can be adequately accounted for chiefly by the inclusion into the statistics of vessels supplying the auricular myocardial wedges of the auriculoventricular valves, the occasional presence of ring capillaries, and acceptance of extinct or mild valvulitides as normal material.

With advancing age periods, the various layers of the valves become progressively poorer in cells and take on the following changes: The strata become increasingly well defined; the semilunar cusp spongiosa becomes more and more fibrous and elastified; the auriculoventricular valve ring spongiosa and the spongiosa situated opposite the chordae tendineae insertions become loose and often the seat of fat deposits; the elastic membranes become heavier and longer; the auricularis and often the ventricularis layers become appreciably denser, more collagenous and thickened; and the collagenous fibrosa undergoes degenerative lipoid changes. The point last mentioned is inevitably associated with the calcium salt deposition of the later age periods.

The tips (distal portions) of the valve leaflets become somewhat thickened with advancing age periods. In the auriculoventricular valves, particularly the mitral, this thickening is due to two processes, *viz.*, fibro-elastification of the auricularis layer at the closure line, and absorption of thickened chordae tendineae insertions into the fibrosa. The fibro-elastified thickening at the site of the closure line is generally quite dense, somewhat oval on cross-section and never contains inflammatory cells or blood vessels. The chordae tendineae insertions beneath the tips of the leaflets show reduplications of their endocardial covering. These may become so exaggerated and agglutinated to one another as to thicken appreciably the tip of the cusp. As will be shown subsequently, however, thickening at the tips of rheumatic valves is due to an entirely different process.

Other age period changes in the auriculoventricular cusps are the formation of delicate crescentic reduplications of the ventricularis layer around the insertions of the chordae tendineae of the second and third order. In the semilunar cusps advancing age produces a more gradual and more delicate elastification of the ventricularis layer, particularly near the semilunar folds. The noduli Arantii and Morgagni become markedly elastified and hyalinized. Here again inflammatory phenomena are absent.

Gross Appearance of Rheumatic Valves in Group I

(*12 Active Cases Where Death Took Place During the First Attack*)

The most frequent gross alteration of the valve leaflets observed in this group was a definite diffuse thickening. This was invariably present in the mitral and aortic valves and in eight of the twelve tricuspid valves, but the pulmonic valves, with one exception, appeared normal. In general, the thickening was uniform throughout the cusp, but in the mitral valve this change was accentuated at the closure line by the formation of a fine ridge.

The normally concave, scalloped, sharp margins of the auriculoventricular valves were almost invariably thickened and straight. In about one-third of the mitral valves the peripheral portion of the leaflet became slightly protuberant to form an overhanging shelf.* In a few of the tricuspid valves the scalloped concavity of the free margin was likewise obliterated, but in no instance was there shelf formation.

The auricular surface of the auriculoventricular valves occasionally showed an irregular corrugation. In 3 cases moderate gross vascularization was noted on the superficial aspects of the auricular surface of the mitral valve and once on the tricuspid valve.

In the aortic valve the sharp margin of the cusps frequently became thickened and rounded, and in about one-third of the cases this rolled margin was slightly inverted toward the sinus pocket. In 2 cases the semilunar folds were elevated toward the free margin, and once the free margin showed a distinct notch at about the site of the nodulus.

Verrucae were present on all of the mitral valves, on eight of the aortic and on seven of the tricuspid. The verrucae were fine, pinhead-sized, yellowish and gray elevations which usually fused with each other. Many of them were fresh; some showed evidences of healing. The verrucae were situated at the closure line, free margin, or at both sites. Extension of the verrucae from the mitral leaflets to the insertions of the chordae tendineae was frequent. They occasionally extended around the free margin to the ventricular aspect of the

* The term "shelf" is employed to indicate the projection of valve tissue over the first order chordae tendineae insertions in such a manner as to overhang the latter. In contradistinction to the "shelf," prominence of the closure line is referred to as a "ridge."

valve. In 1 case there was a fresh verrucous deposit in the pocket of the posterior mitral cusp. The verrucae tended to form conglomerate mounds on the noduli Arantii of the aortic valve and from there extended in rows along the semilunar folds. Frequently the verrucae occurred in isolated fashion, affecting only a single cusp of a valve or even only part of a cusp. In one instance the verrucae on the tricuspid valve extended onto a papillary muscle.

The pockets of the valves in this group were generally normal. In 1 case, as has been mentioned, there were fresh verrucae in the posterior mitral pocket. In 2 cases there were a few irregular folds and ridges in the sinus pocket of the aortic valves.

In about one-third of the cases in this group there were distinct abnormalities of the chordae tendineae. The occurrence of verrucae at their attachments to the valve has already been mentioned. In 1 case there were organizing verrucae extending halfway down the chordae. Not infrequently the chordae tendineae were distinctly thickened at their attachments to the valves (ham shaped), particularly where these attachments were close to confluent verrucae on the valve. Sometimes they were shortened and rarely was there fusion of isolated chordae. In 1 case the chordae tendineae of the septal leaflet of the tricuspid valve were agglutinated to the underlying endocardium (Fig. 3).

Microscopic Appearance of Rheumatic Valves in Group I

The thickening of the valve leaflets in this group was due to inflammation, edema and hypercapillarization of the proximal layers of the valve (auricularis layer of the auriculoventricular valves and the ventricularis layer of the semilunar valves) together with similar involvement of the spongiosa layer (Figs. 4 and 5). The lesions obviously represented a contiguity process from the ring and generally extended along the entire length of the leaflets. The vascularization of these layers, as well as the others to be described, consisted almost entirely of capillaries. Occasionally vessels with muscular walls were noted. These were sometimes of the intimal musculo-elastic hyperplastic type. The inflammatory cells were chiefly lymphocytes. In some cases, however, polymorphonuclear leukocytes predominated. Plasma cells, fibroblasts, macrophages and other mononuclear cells were occasionally seen.

Besides edema, hypercapillarization and exudate, the spongiosa

layer sometimes showed elastica condensation and disruption. Eosinophilic swelling of the collagen was not infrequently seen. This generally involved the spongiosa layer in its main body as well as at the tip of the leaflets. The tip was rarely scarred.

A prominent feature of this group was inflammatory involvement of the fibrosa layer (Figs. 4 and 5). This was greatest in the aortic valve and occurred chiefly in the zone that is adjacent to the spongiosa. It consisted of capillarization, inflammatory cell involvement and sometimes elastic tissue formation. In a number of cases the fibrosa layer contained large swollen cells with basophilic cytoplasm between the collagen bundles. These cells not infrequently bore a resemblance to those that form the Aschoff body. Indeed, in a number of instances, typical Aschoff bodies were seen in the fibrosa layer. This occurred most frequently in the tricuspid and pulmonic valves.

In most of the auriculoventricular valves the ventricularis layer was thickened, inflamed and vascularized. The arterialis layer of the semilunar cusps was also frequently thickened and somewhat inflamed. Vascularization of this layer, however, was infrequent.

The tips or distal portions of the valves in this group generally retained some of their normal spongy structure, even though many of them were the seat of inflammatory lesions including Aschoff bodies. By contrast it will be shown that in the groups to be described, the mitral, aortic and tricuspid valve tips showed increased fibrosis.

In discussing the incidence of verrucous lesions in all the clinical groups studied, as determined by microscopic examination, reference will be made only to those that were fresh, *i.e.*, still possessed eosinophilic hyaline material with or without evidence of organization. The sections cut were generally selected with a view toward including such lesions. Furthermore, as is to be expected, verrucous lesions were sometimes noted microscopically when they were overlooked on gross examination. As a consequence, there will be a discrepancy in the incidence of these lesions as listed under the gross and histological findings, respectively. The latter undoubtedly present a more accurate picture of the actual incidence of those lesions that still contained unorganized verrucous material.

Histological studies on the nature of these verrucous lesions suggest that neither platelets nor fibrin are concerned in their formation. They appear to be due to a disintegration and fusion of proliferating

cells on the superficial layers of the valve leaflets, generally at their most exposed portions, or at sites that form a cul-de-sac in which blood eddies or stasis may occur. Together with this fusion of proliferated cells (endothelium, fibroblasts and other cellular constituents), swelling and eosinophilic changes take place. Whether or not constituents from the plasma are deposited within this material, it is as yet impossible to determine. It appears that the verrucous material is extruded from the valve leaflet because of its swelling and because of cicatrization and contraction of the underlying tissues. Another contributing factor leading to the extrusion of the verrucous material may be the accumulation of inflammatory exudate and the proliferation of swollen basophilic endothelial cells at the base of the verrucae. The fresh verrucae are seldom covered by endothelial cells. The healing stages consist of fibroblastic invasion of the verrucous material with, eventually, complete replacement by scar tissue. Typical granulation tissue capillaries may invade the verrucae (Fig. 6).

The verrucae as a whole in this group were quite extensive and fresh. Moreover, their incidence was high. In 9 of the 12 cases these lesions were present at the closure line of the anterior mitral leaflet. In 3 of the 9 cases they were extensive and spread completely around the tip of the cusp on the ventricularis surface. In 3 additional cases verrucae were observed on the chordae tendineae attachments to the leaflets. Thus, verrucae were observed in every case of this group on the anterior mitral cusp or its chordae tendineae insertions. In 9 cases there were verrucae on the posterior mitral leaflet. Some of these were at the extreme tip of the cusp. Most of them, however, were on the closure line. One additional case showed verrucae on the chordae tendineae insertions (Fig. 5), and another in the posterior mitral pocket. In 9 cases verrucae were present on the closure line of the aortic cusps, and an additional case showed verrucae in the aortic pocket. In 4 cases verrucae were present on the tricuspid valve. An additional 4 cases, however, showed verrucae in the tricuspid pocket. In 2 cases these were seen on the chordae tendineae insertions. Including the pocket and the chordae tendineae insertions, verrucae were present on some part of the tricuspid leaflet in 8 of the 12 cases in this group. Only one pulmonic valve showed verrucae on the closure line. In 2 additional cases, however, verrucae were present in the pulmonic pocket. It is of considerable interest to

note that when the inflammatory lesion did not extend beyond the ring or the base of the pulmonic valve, verrucae tended to occur either in the pocket or in the subvalvular angle. Thus, there appeared to be a tendency for verrucae to localize at a level corresponding to the distal extension of the inflammatory process within the leaflet. This point will be discussed more fully.

As mentioned above, verrucae were noted once in the aortic pocket, once in the posterior mitral, four times in the tricuspid and twice in the pulmonic. Apart from these lesions, most of the valve pockets in this group showed endocardial reduplications, often with mild inflammatory cell infiltrations. These were most notable in the semilunar pockets. At times, the reduplication showed eosinophilic degeneration. This occasionally involved the elastic limiting lamellae, chiefly in the semilunar pockets. Another even more characteristic pocket lesion is polypoid formation (Fig. 8). On cross-section this consists generally of inflamed, finger-like processes, giving the impression of minute polypi. Whether, indeed, these are polypi or whether the spaces between the finger-like processes represent merely dipping down of the endocardium to form vascular channels, it is difficult to determine. The early stages in their formation apparently consist of the extrusion of tiny endocardial hillocks into the valve pocket, *i.e.*, toward the cardiac lumen. These hillocks become elongated and their bases may undergo eosinophilic swelling and fusion. These polypoid lesions were noted in the aortic pocket four times, in the tricuspid once, and in the pulmonic three times.

The incidence of verrucae on the chordae tendineae insertions has already been mentioned. In addition, the chordae tendineae of the anterior mitral cusp showed inflamed reduplications in half the cases. Three of these were vascularized. Four of the cases showed vascularized inflamed reduplications around the insertions of the chordae tendineae in the posterior mitral cusp (Fig. 6). Only 1 case showed reduplications on the tricuspid valve chordae tendineae. Not infrequently the chordae tendineae insertions were agglutinated to one another through the intermediary of verrucous material. Cross-sections of these chordae tendineae often showed swollen basophilic cells scattered between the collagenous bundles. These cells were similar to those described in the inflamed fibrosa layer of the valve.

Although gross vascularization of the valves was inconspicuous in

this group, its incidence microscopically was extraordinarily high. Thus, in the single sections which generally represented each cusp studied, 11 cases of this group of 12 showed blood vessels (generally capillaries) in the anterior mitral cusp, 12 in the posterior mitral, 9 in the aortic, 8 in the tricuspid and 6 in the pulmonic. Moreover, in almost every section blood vessels were present in the valve ring. Thus, if the ring is considered, as it should be, the proximal portion of each cusp, it may be said that almost invariably every cusp of the heart showed blood vessels in this group.

Considered as a whole, the mitral and aortic valves generally showed the widest involvement. However, the leaflets of the tricuspid valve were quite frequently more intensely inflamed than were those of the other valves. In this respect, there was a similarity to the very flagrant involvement of the tricuspid ring. Furthermore, the inflammation seemed to be most severe toward the root of the valve, and edematous widening and hypercapillarization of the auricularis layer were occasionally present. The pulmonic valve generally showed milder lesions. Both the exudative phenomena as well as capillarization were subdued. The most extensive lesions were found in the spongiosa layer.

Summarizing the conspicuous features of the valvular lesions as a whole in Group I, the following points should be noted: The ring lesions * were extensive, consisting of pronounced capillarization and infiltration with inflammatory cells, sometimes with edema. Blood vessels of the muscular type were infrequent. Aschoff bodies were present in about 10 per cent of the rings. There was little scarring. Practically all the rings and subaortic angles showed lesions. In the latter site, reduplications, when present, were generally not multiple. Approximately half the cases showed involvement of the intervalvular fibrosa.

The lesions in the remainder of the valves generally consisted of intense inflammation, edema and hypercapillarization which involved all portions of the leaflets about equally. There was considerable involvement of the spongiosa and fibrosa layers. Aschoff bodies and eosinophilic swelling of collagen were present in these layers in some cases. The tips of the valves were seldom scarred. The incidence of verrucae was high. These lesions were extensive, fresh, and

* The descriptions of the ring lesions given in the summary of each group are abstracted from the detailed report by Gross and Friedberg.[46]

showed little organization. Lesions in the pocket and chordae tendineae were frequent. Capillarization of valve leaflets was almost universal.

Gross Appearance of Rheumatic Valves in Group II

(7 Active Cases Where One Preceding Attack Occurred Within 1 Year of the Fatal Outcome)

The most constant gross alteration in this group was a thickening of the valve cusps. Compared with Group I, the thickening was somewhat greater. In no case was the mitral, aortic or tricuspid valve of normal slenderness and translucency. The pulmonic valves, which in Group I were generally normal, revealed in the cases of this group a juicy, succulent consistence with occasional thickening and opacity. Gross vascularization was observed in every case and occurred chiefly in the mitral valve.

Ridge formation at the closure line of the mitral valve, as well as the presence of an overhanging shelf, was quite frequent and much more advanced than in Group I. Corrugation of the auricular surface occurred to the same degree as in the first group.

The aortic valve showed alterations similar to those in the first group, but these were much farther advanced. The thickening was greater and verrucae were present in all cases. The semilunar folds of the aortic cusps were invariably elevated toward the free margins or were completely obliterated (Fig. 10). Rolling and inversion of the free margin and notching at its center were present in 4 of the 7 cases. The notching was due to inversion of the nodulus Arantii into the sinus pocket. Occasionally the nodulus was greatly hypertrophied, forming a knob near the middle of the free border. In 2 cases there was adhesion of the commissures.

Fresh, healing or healed verrucae were invariably present in this group. The location of the verrucae was the same as in Group I except that they were often superimposed upon the ridge on the mitral valve. Furthermore, a double row of verrucae was present on a few valves, one representing healed and one fresh lesions. In addition to the thickening of its cusps, the tricuspid valve invariably revealed verrucae, isolated or in a row.

Abnormalities in the pockets of one or more valves were present in every case. In 4 of the 7 cases there were fresh or healing verrucae in one or more of the valve pockets. These appeared either as tiny,

pinhead-sized yellowish deposits, or as small, yellowish smooth mounds. Occasionally there were other irregularities forming tiny nodular ridges or folds which distorted the normal sharpness of the pocket angle. The alterations of the chordae tendineae were similar to those in the previous group, but the changes appeared more frequently and were more advanced.

Microscopic Appearance of Rheumatic Valves in Group II

As noted above, the cusps in this group were somewhat more thickened than in Group I. The thickening was due to the following factors: The proximal layers of the valves generally showed one or more reduplications (Figs. 7, 8 and 9). These were frequently fibroelastic and occasionally fused with the underlying, generally widened spongiosa. These layers contained numerous inflammatory cells as well as muscular blood vessels, many of which showed typical intimal musculo-elastic hyperplastic changes.* Indeed, the high incidence of the latter is one of the most conspicuous features of this group. The inflammatory involvement of the valve leaflets showed definite contiguity with the increased ring lesions present in this group. The spongiosa participated notably in these changes. In all the cusps this layer was generally considerably widened with inflammatory exudate and profusely vascularized. The exudative phenomena were even more prominent in this group than in the previous one. As in the latter, the inflammatory cells were chiefly lymphocytes. Occasionally the polymorphonuclear leukocytes predominated. Fibroblasts, plasma cells and macrophages also occurred.

In a previous report it was shown that one of the characteristic features of the ring lesions in Group II is the formation of multiple vascularized elastified reduplications at the subvalvular angles (Figs. 8 and 9). A somewhat similar process takes place in the auricularis layer over the ring region of the auriculoventricular valves (Fig. 7). Not infrequently a prolongation of these multiple vascularized elastified reduplications produces considerable thickening of the cusps.

Another notable feature in this group was the definite involvement of the fibrosa layer. This was generally vascularized or capillarized along the zone that is contiguous with the spongiosa layer.

* For a detailed description of these vascular lesions see Gross, Kugel and Epstein.[41]

The fibrosa sometimes showed edema, elastica condensation and disruption. Inflammatory cells were numerous. Not infrequently one could trace the vascularization and inflammation of the fibrosa layer along the intervalvular fibrosa. This in turn showed a contiguity process from the aortic ring. In two instances the fibrosa lesion in the mitral leaflet showed such distinct whorling and inflammatory infiltration as to resemble a syphilitic contiguity process from the root of the aorta.

Aschoff bodies were present either in the fibrosa or spongiosa layer in several of the cases. These occurred with approximately the same frequency in all four valves. In addition, the annulus, particularly of the semilunar cusps, occasionally showed eosinophilic swelling of the collagen. Intercryptic cells resembling those seen in Aschoff bodies were also noted in the fibrosa layer, chiefly of the semilunar cusps.

Delicate reduplications of the distal layers of the valves (ventricularis layer of the auriculoventricular cusps and arterialis layer of the semilunar cusps) were frequently present. These reduplications were often inflamed and, in about one-third of the cases, showed vascularization.

A distinct difference from the previous group is the fact that the tips of the cusps almost invariably showed considerable fibrosis and some elastification. Thus, the normally gelatinous tip, which can be considered as forming an extension of the spongiosa layer, was almost always converted into a dense, fibrotic or fibro-elastic, often vascularized, inflamed structure. When the tip becomes collagenous (and, to a lesser degree, elastified), it fuses with a similarly altered auricularis layer to form a thickened ridge. Elastic lamellae from the auricularis and spongiosa layers, together with smooth muscle bundles, may be seen curving beneath this thickened ridge. The tips of the pulmonic cusps, however, rarely showed this collagenous transformation.

The incidence of verrucae still possessing a hyaline structure was highest in this group. Furthermore, the verrucae were generally quite broad and often extended from the closure line around the tip of the leaflet to the ventricularis surface on the auriculoventricular cusps. Verrucae were present on the anterior mitral leaflet in 6 cases. In 2 cases verrucae were noted on the chordae tendineae attachments to this leaflet. Every case showed verrucae on the pos-

terior mitral cusp, two in the posterior mitral pocket, and two on the chordae tendineae insertions. Verrucae were present on all the aortic valves. These lesions were also generally broad and extended around the tip of the cusp, sometimes reaching the arterialis layer. In 1 case verrucae were noted in the aortic pocket. Verrucae were present on the tricuspid leaflets, pockets or chordae tendineae insertions in every case. In only 3 of these were they situated on the closure line or at the tip; in 3 they were present in the pocket, and in 1 on the chordae tendineae insertions. In 1 case verrucae were present on the closure line of the pulmonic valve, and in another they were situated on the auricularis surface at about the middle of the septal leaflet. This case also showed pocket verrucae. In a 3rd case verrucae were present in the pulmonic pocket only.

As mentioned above, verrucae were noted in the aortic pocket once, in the posterior mitral pocket twice, in the tricuspid pocket three times and in the pulmonic pocket twice. Apart from these, other lesions were frequently present at this site. Thus, the great majority of cases showed a knob-like, elastified endocardial reduplication. This generally consisted of a whorled collagenous mass permeated by numerous transverse, discontinuous elastic fibers. The superficial layers of the knob were sometimes intensely elastified and were often the seat of mild or severe inflammation. Occasionally the reduplications were vascularized. An important feature was the tendency for these reduplications to involve the arterialis layer of the semilunar cusps where they shared in the thickening of the valve. In addition, polypoid formations were present in the aortic pocket in 2 cases (Fig. 8), and in the tricuspid in 1 case. The latter sometimes showed agglutination of the chordae tendineae insertions.

The chordae tendineae insertions of the anterior mitral cusp presented considerable agglutinations, with absorption into the valve tip in many instances. They also frequently possessed collagenous, sometimes inflamed vascularized reduplications. These lesions were perhaps more conspicuous in the posterior mitral cusp, where they were occasionally multiple. In one instance an Aschoff body was seen in these reduplications. Chordae tendineae absorption was not as frequently noted in the tip of the tricuspid valve. The reduplications were more delicate and less frequent. However, inflamed vascularized reduplications were noted in two instances.

As stated above, gross vascularization of the valves was frequently

observed in this group. Microscopically, vascularization or capillarization of all the valves was almost invariable. In contrast to Group I, intimal musculo-elastic hyperplastic vascular lesions were conspicuous. Inasmuch as Group I represents a clinical course whose average duration was 6 weeks, it would appear that this lesion generally requires more than 6 weeks for its development. Other observations suggest that the intimal musculo-elastic hyperplastic lesions undergo metamorphosis into intimal fibro-elastification with medial hypertrophy in less than 1 year.

Considered as a whole, the intensity and extent of the inflammatory involvement of the various valves in Group II was similar to that noted in Group I. Perhaps the most extensive involvement occurred in the aortic valve, and in this the contiguity process from the flagrant aortic ring lesion was noticeable. The thickening of the aortic cusps was often largely determined by a prolongation of thick subaortic reduplications on the ventricularis aspect of the valve and, to a lesser extent, by prolongation of aortic pocket reduplications on the arterialis side. The tricuspid lesions were severe, particularly at the root where they merged with similarly severe ring lesions. The pulmonic lesions were the least severe.

Summarizing the conspicuous features of the valvular lesions as a whole in Group II, the following points should be noted: The ring lesions were most extensive and consisted of considerable infiltration and vascularization. The blood vessels were frequently of the intimal musculo-elastic hyperplastic type. The inflammation spread in all directions. The incidence of Aschoff bodies was approximately the same as in Group I. There was considerable scarring. Practically all rings showed involvement. The highly characteristic, multiple subaortic vascularized reduplications occurred in practically every case. The intervalvular fibrosa was invariably involved.

The remainder of the valve leaflets generally showed extreme inflammation and vascularization. Many of the vessels were of the intimal musculo-elastic hyperplastic type. The valves were thicker than in Group I. This was largely due to the more conspicuous reduplications of the proximal layers which were continuous with reduplications at the valvular angles. An important contributing factor to the valve thickening was the widened, inflamed and vascularized spongiosa layer. Involvement of the fibrosa was pronounced. Aschoff bodies were present in some cases. The tips of the

valves were frequently scarred. The incidence of verrucae was higher in this group than in any other of this series. These lesions were extensive and broad; some showed beginning organization. Lesions in the pockets and on the chordae tendineae insertions were similar to Group I. Vascularization of the leaflets was practically universal.

Gross Appearance of Rheumatic Valves in Group III

(11 Active Cases Where One Previous Attack Occurred at Least 2 Years Previous to the Fatal Outcome)

In this group moderate or great thickening of the valve cusps was universally present in the mitral, aortic and tricuspid valves and in the majority of the pulmonic valves. Compared to the preceding groups this thickening was not only more frequent but definitely greater. Furthermore, it was less uniform, the change tending to become intensely exaggerated in the distal third of the valve cusps, particularly from the closure line to the free margin. In the latter locations, especially in the mitral valve, the cusps were enlarged to form either an exaggerated ridge or plaque. Gross vascularization was frequent.

The surface of the auriculoventricular valves showed greater deformity than in the other groups. These changes were due to rugosities, puckerings and, in 2 cases, to lime deposited diffusely throughout the mitral valve. The cusps of the auriculoventricular valves, particularly the anterior mitral, showed a definite tendency to elongation. This elongation seemed to be due essentially to the formation of new material at the free margins of the cusp, supplemented by absorption of thickened, fused chordae tendineae. The formation of a well marked shelf (overhanging the chordae tendineae of the first order) was quite frequent in these cases. The result of the chordae tendineae absorption was to make them appear definitely shortened, thus bringing the papillary muscles much closer to the margins of the cusps. The characteristic auriculoventricular valve in this group showed greatly thickened cusps with irregular surface, shelf formation and elongation with incorporation of thickened shortened chordae. Chordae tendineae of the second and third order also showed thickening of their insertions. There was stenosis of the mitral valve in 2 cases and of the tricuspid valve in 1.

In addition to thickening, the aortic valves showed notching and considerable shortening. This was due to rolling and inversion of the free margin of the cusps toward the sinus pocket (entropion). Entropion of various degrees was found in approximately half of the cases. In the majority of cases the semilunar folds either approximated the free margin or were completely invisible. Adhesion of the commissures occurred in one-third of the cases. These generally showed the fused margins separated by a delicate slit, characteristic of the rheumatic commissural lesion.

Verrucae in various stages of healing were less frequent than in either of the preceding groups, occurring in about half the cases on the auriculoventricular valves, in 3 of the 8 cases on the aortic valves, and on one pulmonic cusp. There was less tendency for the verrucae to extend onto the chordae tendineae. In the aortic valves, in addition to the previous sites mentioned, the verrucae showed a tendency to extend from one cusp to another across the commissures (Fig. 10). Double rows of verrucae were encountered somewhat more frequently than in the previous group.

Abnormalities in valve pockets were present in all cases. In 1 (tricuspid) there were yellowish masses suggestive of healed verrucae. Whitish nodules, ridges and folds were frequently present. The lining endocardium was often whitened and thickened. In 1 case there was lime in the pocket of the posterior mitral cusp. Occasionally there appeared to be healed agglutinations in the pocket of the auriculoventricular valves.

Microscopic Appearance of Rheumatic Valves in Group III

This group presented qualitative as well as quantitative differences from those previously described. As mentioned in the gross description, not infrequently most of the inflammatory processes apparently occurred with predilection toward the distal part of the cusp, generally within an area relatively confined to the closure line and tip of the valve. The inflammatory process appeared on the whole to be somewhat subdued in comparison with the findings in the first two groups. Reduplications of the auricularis layer of the mitral valve, although still frequently seen and sometimes multiple, were generally notable only at the distal end of the valve. They occurred in only one-third of the cases in the tricuspid valve. Multiple vascularized ventricularis reduplications were almost invariably

present on the aortic cusps but occurred only once in the pulmonic. They consisted of fibro-elastic strata with a tendency toward elastic-collagenous transformation. These reduplications of the proximal layers of the valves frequently fused with the spongiosa layer which was almost invariably involved. As in the previous groups, the spongiosa layer was generally considerably widened, vascularized and elastified and contained inflammatory cells, chiefly lymphocytes. Many of the vessels showed distinct hypertrophy of the media. A few cases showed hypercapillarization. Intimal musculo-elastic hyperplastic lesions were scarce.

The spongiosa layer was occasionally compressed toward the basal portion of the valves and contained distorted capillaries. While the fibrosa layer almost invariably showed involvement with capillaries or muscular vessels within the zone adjacent to the spongiosa, the inflammatory phenomena were on the whole milder than those found in the two previous groups. Elastica changes such as condensations and disruptions were quite frequent. Aschoff bodies and eosinophilic changes were rarely present. One case showed intense whorling of the intervalvular fibrosa collagen and considerable vascularization and inflammation. This showed contiguity with the aortic ring as well as with the mitral valve fibrosa.

The distal layers of the valves presented mildly inflamed reduplications in approximately half the cases. They were on the whole delicate and occasionally vascularized. The mildest lesions of the arterialis layer were found in the pulmonic cusps.

With the exception of the pulmonic cusps, the valve tips were almost invariably converted into collagenous ridges or plaques. As previously described, this was due to fusion of the proximal layers with the spongiosa layer which had undergone collagenous transformation. In the auriculoventricular valves, elastic lamellae from the fused auricularis and spongiosa layers, together with blood vessels and smooth muscle bundles, frequently curved underneath these elastic-collagenous thickenings. The tips of the anterior and posterior mitral leaflets were invariably vascularized. In some instances they were hypercapillarized.

In the gross description it was mentioned that the auriculoventricular valves, particularly the mitral, often showed considerable elongation. This was due to a fusion of the auricularis and spongiosa layers at the tip of the valve with excessive formation of elastic-

collagenous tissue. The collagenous tissue envelops or absorbs the enlarged and fused chordae tendineae insertions, in this manner prolonging the extent of the leaflets.

The tip of the aortic cusps was frequently converted into a collagenous, thickened and rounded edge which represents fusion of the spongiosa and ventricularis layers. On cross-section this formed a knob which occupied almost the entire width of the valve tip and compressed the arterialis layer. The knob itself consisted of radiating fan shaped collagenous bundles whose focal point was situated just below the tip of the valve on its arterial aspect. This focal point not infrequently showed wide, delicate walled vascular channels, probably veins.

In the tricuspid valve ridge formations were inconspicuous, even though the tip was almost invariably collagenous. Knob formation was seen only once in the pulmonic cusp tips.

The verrucae still showing eosinophilic material presented on the whole considerably less reaction at the base than those previously described. Furthermore, their incidence was lower in this group. Thus, the anterior mitral leaflet showed verrucae in 5 cases; in 4 of these they were at the closure line and showed some organization. In 1 additional case they were present on the chordae tendineae insertions. In 5 cases verrucae were noted on the closure line of the posterior mitral leaflet. In most instances these were undergoing organization. An additional case showed verrucae in the valve pocket and one on the chordae tendineae insertions. Four cases showed verrucae on the aortic valve. These were situated on the closure line and presented various stages of organization. In 2 of these cases fresh verrucae were also present in the aortic pocket. Flat organizing verrucae were present on the closure line of the tricuspid valve in 3 cases. In 2 additional cases there were verrucae in the tricuspid pocket, and in 2 others on the chordae tendineae insertions. Thus, the tricuspid valve (leaflets, pockets or chordae tendineae insertions) showed verrucae more frequently than any other valve in this group. In 2 cases verrucae were present on the closure line of the pulmonic cusps and in 2 additional cases in the pulmonic pockets.

As mentioned above, verrucae were found in the valve pockets in this group with the following frequency: in the aortic, twice; posterior mitral, once; tricuspid, twice; and pulmonic, twice. In addi-

tion 5 cases showed polypoid formations in the aortic pocket, 1 in the posterior mitral and 2 in the pulmonic. Practically every pocket showed an elastified reduplication. In some instances these reduplications formed elastified knobs such as described in Group II. In several cases the pocket reduplications were vascularized and mildly inflamed.

The incidence of verrucae on the chordae tendineae insertions has already been mentioned. Reduplications around these insertions were not infrequently seen, particularly in the mitral valve. The reduplications were occasionally vascularized or showed eosinophilic degeneration. In the anterior mitral leaflet, as noted above, the chordae tendineae were occasionally absorbed into the excessively collagenized tip. This absorption was somewhat less frequent in the posterior mitral leaflet and still less in the tricuspid. A point of interest is the fact that in this group, as well as in those subsequently to be described, the spongiosa layer of the valve leaflet opposite the chordae tendineae insertions was not infrequently widened into triangular areas containing many blood vessels.

Vascularization of the valves was invariably present in the anterior and posterior mitral leaflets, as well as in the tricuspid valve. It occurred somewhat less frequently (8 out of the 11 cases) in the aortic valve and only twice in the pulmonic. However, in this group as in those previously described, the rings showed vascularization almost invariably.

This group is the first of the series in which the clinical phenomena were of a more protracted type and the inflammatory processes, therefore, somewhat more indolent. Under such circumstances, as will be more clearly seen in the groups subsequently to be described, contiguity lesions from the ring were not as obvious as in Groups I and II. With a diminution in the intensity of the ring lesions, the inflammatory process either remained confined to the base of the valve or involved chiefly the distal third of the valve, leaving the intervening portions relatively less affected. Thus, while the inflammatory lesion in the tricuspid valve still showed contiguity from the ring and was at times quite intense, it was generally confined to the basal portion. In the pulmonic cusp the lesions were least pronounced and even more frequently confined to the ring. On the other hand, in the mitral and aortic valves the most notable lesions

were at their distal extremities. The significance of these findings will be discussed subsequently.

Summarizing the conspicuous features of the valvular lesions as a whole in Group III, the following points should be noted: The ring lesions were somewhat milder than those in the preceding groups. The vascular lesions consisted of capillaries and muscular vessels in about equal proportions. In some cases vascularization was by means of capillaries only. The incidence of Aschoff bodies was lower than in the previous groups. Intimal musculo-elastic hyperplastic lesions were infrequent. Practically all rings showed involvement. The subaortic angle invariably presented reduplications. In most instances these were multiple vascularized but less conspicuous than in Group II. Group III possessed the highest incidence of subpulmonic lesions, *i.e.*, in approximately half the cases. The intervalvular fibrosa was invariably involved.

The remainder of the valve leaflets generally showed inflammatory infiltration and vascularization of the type found in the ring. Intimal musculo-elastic hyperplastic lesions were severe. Capillaries were sometimes distorted, due to scarring. Auricularis reduplications at the base of the auriculo-ventricular valves were thinner than in Group II. The thickening of the valve was frequently confined to the tip and produced knob formation in the aortic valve. Chiefly in the mitral valve the fibrotic thickened tip was prolonged over the chordae tendineae insertions. The fibrosa layer was invariably involved, but the lesions were generally milder than in the previous groups. Aschoff bodies were infrequent. The verrucae showed a somewhat less reactive base, and many were organizing. Their incidence was lower than in the first two groups. The incidence of pocket lesions as a whole was also somewhat lower than in the previous groups. However, the incidence of aortic pocket polypi was higher than in any of the six groups in this series. This occurred in 5 of the 11 cases. The chordae tendineae insertions frequently showed considerable thickening and absorption into the valve tips. Vascularization of the leaflets exclusive of the ring was invariable in the mitral and tricuspid valves. It occurred in the aortic valve in 8 cases and in the pulmonic in 2. Several cases in this group showed lime formation at the base of the valve.

Gross Appearance of Rheumatic Valves in Group IV

(*13 Active Cases Where Repeated Attacks Took Place, Death Occurring During an Acute Recurrence*)

Diffuse thickening of the cusps of approximately the same degree as in Group III was universally present in this group. The presence of a pronounced overhanging shelf was observed on the mitral and tricuspid valves in about two-thirds of the cases. Elongation of the auriculoventricular valves, irregularity of the valve surface, and absorption of thickened chordae were present to about the same degree as in the preceding group. The shortening, thickening and fusion of ham shaped chordae tendineae insertions (Fig. 11) were more advanced than in the preceding group. There were occasional agglutinations in the pockets formed by the chordae attachments. Lime was present only in one mitral valve.

The alterations of the aortic valve (Fig. 10) were quite similar to those in the preceding group, being characterized by thickening and shortening of the cusps, approximation of the semilunar folds to the free margin, or their disappearance, rolling, inversion and notching of the free margin, and commissural agglutination.

Fresh and healing verrucae were present in the great majority of all of the valves. Their occurrence, particularly in the tricuspid and pulmonic valves, was much more frequent than in Group III, being present in almost every case. Double rows were seen in a few instances.

Vascularization, chiefly of the mitral valve, occurred with considerable frequency.

Pocket lesions were present in all cases. The pocket angles were generally widened and irregular. The endocardial lining was white or gray and thickened. Yellowish and whitish smooth nodular elevations were often present. Transverse and radial ridges and folds occasionally occurred. Agglutinated verrucae were found in the pocket of one posterior mitral cusp.

Microscopic Appearance of Rheumatic Valves in Group IV

The microscopic lesions of the valves in this group were, on the whole, somewhat similar to those described in Group III. There were, however, several interesting differences which were undoubtedly a reflection of the clinical course (repeated attacks). It was

previously shown that vascular lesions of the intimal musculo-elastic hyperplastic type probably require more than 6 weeks for their development. Their scarcity in Group III indicates that these lesions undergo fibro-elastic metamorphosis after 2 years. (Other observations suggest that such involution may occur in less than 1 year.) Inasmuch as Group IV represents repeated attacks, one of which might have occurred within 1 year before death (thus simulating Group II), it is not surprising that many of the vascular lesions in Group IV were of the intimal musculo-elastic hyperplastic type. However, these were not nearly as conspicuous or as frequently present as in Group II, capillaries and muscular vessels being the predominant type of vascularization. Another interesting feature was the much more frequent occurrence of the collagenous thickening of the valve tips. This will be discussed in greater detail later.

Reduplications of the proximal layers of the valves were generally present. These were frequently delicate in the proximal two-thirds of the leaflets, particularly in the auriculoventricular valves. In this thinner portion of the valve leaflet, vascularization was frequent and often quite superficial. The spongiosa was widened, vascularized, elastified and in general moderately inflamed, particularly in the anterior and posterior mitral leaflets. In the mitral valve the widened spongiosa layer frequently contained large smooth muscle bundles in apposition to the auricularis layer. In the tricuspid valve the spongiosa showed its widening chiefly in the triangular zones above the chordae tendineae insertions.

The fibrosa layer of the auriculoventricular valves almost invariably showed moderate inflammation with some elastification and elastica distortion. The fibrosa layer of the aortic valve showed little involvement. Most of the cases presented intercryptic swollen cells in the fibrosa of the pulmonic cusps. These cells were generally less abundant in cytoplasm than were those found in the previous groups. In 1 case there were whorling and vascular permeation of the fibrosa collagen in the anterior mitral leaflet. This inflammatory lesion could be traced through the intervalvular fibrosa to the aortic annulus. Aschoff bodies were observed in only one valve. This was in the aortic fibrosa. On the whole it may be said that the fibrosa lesions in this group were the mildest of those thus far described, but they were still present in the majority of instances, except in the aortic cusps.

The ventricularis layer of the auriculoventricular cusps showed delicate collagenous reduplications. In a few instances these were vascularized and presented mild inflammatory changes. Similar changes occurred in the arterialis layer of the semilunar cusps. Inflamed arterialis reduplications occurred more frequently in the aortic than in the pulmonic cusps.

In almost every case each valve tip, except the pulmonic, showed fibrosis. The tips of the anterior and posterior mitral leaflets were thickened, elastified, collagenous and vascularized. As in previous groups, this was due to fusion of the collagenous spongiosa and auricularis layers. Redundant collagen from these fused and thickened valve tips frequently spread for a considerable distance over the chordae tendineae insertions and produced elongation of the cusps. Deviation of the auricularis and spongiosa elastic lamellae, blood vessels and smooth muscle bundles were generally noted beneath the thickened fused mass at the tip. On cross-section the tips of the aortic valves were represented by large collagenous knobs in every case (Fig. 12). Histologically these were similar to those described in Group III. The pulmonic cusps were the least involved and showed knobs only occasionally. The tricuspid valve tips were generally collagenous and sometimes showed extension over the chordae tendineae, but extensive thickening was infrequent.

The verrucae present in this group were generally of a more indolent type than those found in the previous groups. Many of these were flat, on a broad base and with little reaction in the underlying tissue. A number of them showed considerable organization and absorption within the leaflet. In a few cases the verrucae appeared to represent merely an eosinophilic degeneration of the superficial collagenous layer of the valve leaflet, chiefly at the closure line or around the tip of the valve.

The anterior mitral cusp showed fresh verrucae in 6 cases. These were generally situated at the closure line or near the tip. Some were undergoing organization. In 1 of these cases verrucae were also found on the chordae tendineae insertions. In 9 cases the posterior mitral cusp showed verrucae. Most of them were organizing. Verrucous lesions were present in one of the posterior mitral pockets. No verrucae were found on the chordae tendineae insertions of this cusp. In 7 cases verrucae were present on the aortic cusp. These were situated either on the closure line or around the tip. They were

generally broad and showed relatively little reaction. In 1 case verrucae were also present in the aortic pocket. Ten of the cases showed verrucae on the tricuspid valve, an unexpectedly high incidence, and the highest in this group. These were generally broad also, many resembling eosinophilic change. Some were undergoing organization. Three of the cases showed verrucae in the tricuspid pocket and 3 on the chordae tendineae insertions. Thus, in 12 of the 13 cases in this group, fresh verrucae were present on some portion of the tricuspid valve. Chordae tendineae agglutinations in the tricuspid pocket were also sometimes seen. Obviously, therefore, the tricuspid valve lesion, although leading to less fibrosis than the other cusps, maintains activity in an extraordinarily high percentage of cases. In 5 of the cases verrucae were present on the pulmonic cusps. These also were generally flat or organizing. Two cases showed verrucae in the pocket. In 6 of the 13 cases in this group verrucae were present on some portion of the pulmonic valve. This represents the highest incidence of pulmonic valve verrucae of any group and is, undoubtedly, a reflection of the multiple attacks.

As mentioned above, verrucous lesions were found in the valve pockets with the following frequency: once in the posterior mitral, once in the aortic, three times in the tricuspid and twice in the pulmonic. In addition, the aortic pocket contained polypoid lesions in 3 cases, the posterior mitral in 2, and the pulmonic in 1. Most of the cases showed elastified distorted pocket reduplications, some of which formed large knobs. In a few cases vascularized reduplications were present in the pockets.

The incidence of verrucae on the chordae tendineae insertions has already been referred to. As noted, absorption within the mitral leaflet tip was almost invariably present. Multiple vascularized inflamed reduplications were present on some chordae tendineae insertions of the mitral valve. In a number of cases many of the chordae tendineae insertions of the tricuspid valve also showed absorption.

Vascularization was present grossly and microscopically in almost all the cusps except the pulmonic, where it was noted in 6 of the 13 cases in this group. Ring lesions with vascularization were almost invariably present.

Even though the inflammatory lesions on the whole were not as varied in Group IV as in the other groups described, there were

present other manifestations of continued damage which placed this group after the first two in order of activity. On the other hand, because of the somewhat prolonged course and repeated attacks, there were present also evidences of chronicity which approximated the changes present in the groups subsequently to be described. It is, therefore, this combination of fairly active lesions and extensive healing which characterizes this group. The greatest distortion and thickening of the valve leaflets occurred in the posterior mitral cusp. Of interest was the fact that the tricuspid valve was still consistent in showing notable exudative lesions. Inflammatory involvement of the pulmonic valve was not infrequently most pronounced in the middle portion of the cusps. This is of considerable interest as indicating the tendency for lesions in this valve to be arrested before spreading to the tip.

Summarizing the conspicuous features of the valvular lesions as a whole in Group IV, the following points should be noted: The ring lesions consisted only of distorted capillaries caused by the scarring process. The occurrence of inflammatory cells was less frequent than in the previous groups. Aschoff bodies were most infrequent. All the rings were involved. All the subaortic angles showed lesions that were almost invariably of the multiple elastified variety. These, however, were not as great as in the first two groups. The intravalvular fibrosa showed a high incidence of lesions (11 of 13 cases).

The remainder of the valve leaflets generally showed somewhat milder exudative phenomena than in Group III. Vascularization was similar to Group III but, in addition, intimal musculo-elastic hyperplastic vessels were more frequent. Because of more definite scarring, distorted capillaries were frequently seen. In some instances the proximal two-thirds of the valve leaflets were fairly thin and showed superficial vascularization with thick vessels. In others the valve was diffusely thickened. Marked fibrosis and thickening of the tips of the mitral, aortic and tricuspid valves were noted more frequently in this group than in the others thus far described. The most notable thickening was that in the posterior mitral leaflet. This thickening of the tips of the auriculoventricular valves, together with elongation of the leaflets, was due to the same process as previously described. The fibrosa of the auriculoventricular valves almost invariably showed a mild degree of inflammatory involvement.

The aortic fibrosa was generally intact. That of the pulmonic valve showed intercryptic cells with basophilic cytoplasm. Aschoff bodies were found in the fibrosa only once.

The verrucae in this group showed even more indolence than in Group III. A number of them consisted of eosinophilic, swollen and degenerated collagen with little reaction at the base. On the other hand, the incidence of verrucae in this group was higher than in Group III, though somewhat lower than in the first two groups. The incidence of polypoid and verrucous pocket lesions also placed this group third in order of frequency. The incidence of verrucae on the chordae tendineae insertions and the absorption of the latter into the valve tip were somewhat similar to Group III. Vascularization of the valves was extremely frequent, occurring almost invariably in every valve except the pulmonic, where it was noted in 6 of the 13 cases in this group.

Gross Appearance of Rheumatic Valves in Group V

(28 Active Cases Where Death Was Caused by Decompensation Without Clinical Evidence of a Final Acute Attack. Some of These Cases Had No Previous History of Rheumatic Fever)

The cases in this group showed the most advanced alterations of any group. Definite diffuse thickening of the cusps was universally present in the mitral, aortic and tricuspid valves, and there was moderate thickening of the pulmonic valve. The formation of a ridge or thickening in the peripheral portion of the mitral cusps was more frequent than in the preceding group, being present in half the cases. A pronounced overhanging shelf also was present on the mitral valve in half the cases. In 9 cases the valve was diffusely infiltrated with lime which notably distorted the cusps by its projection through the auricular and ventricular surfaces. In a number of instances vertical cracks appeared through the lime at the commissural regions. Buttonhole stenosis of the mitral valve was present in 4 cases.

As in the preceding group, the aortic valves were greatly thickened, shortened, and their edges rolled and inverted. Notching was most frequent. There was a much greater tendency to the deposition of lime in the cusps themselves, in the region of the noduli, and in the commissures. Adhesions of the cusps at the commissural margins was much more frequent than in the preceding group. The

valves in general appeared much more distorted and were rigid, a characteristic not found in the preceding group.

Fresh and organized verrucae were less frequent than in the preceding group, being present in 6 cases on the mitral valve, in 10 on the aortic, in 12 on the tricuspid and once on the pulmonic valve. Double rows of verrucae were observed in several cases. Thickening, fusion, absorption and shortening of the chordae tendineae were more pronounced than in the preceding groups. Generally, only the valvular attachments of the chordae tendineae of the third order were still present. Not infrequently the papillary muscles were almost in contact with the valve margins.

Gross vascularization occurred with considerable frequency and was found chiefly in the mitral, aortic and tricuspid valves.

The pockets were characterized chiefly by a whitening and thickening of the endocardium; there was a tendency for the auriculoventricular valve leaflets to form agglutinations with the ventricular wall and thus obliterate the sharp pocket angle. Further irregularities and obliteration of the auriculoventricular pocket angles were due to the frequent presence of fibrous bands and muscular bridges at this site. The pockets of the aortic cusps and, to a less extent, of the pulmonic cusps, frequently contained nodules, ridges and folds.

Microscopic Appearance of Rheumatic Valves in Group V

The auricularis layer of the auriculoventricular valves as well as the ventricularis layer of the aortic valve showed multiple elastified reduplications in approximately half the cases. These were frequently quite thick and contained sparse scatterings of lymphocytes. Fusion of the elastic-collagenous terminations of these layers with the similarly transformed tip of the spongiosa layer produced considerable thickening. The reduplications on the proximal valvular surfaces were all vascularized in the tricuspid valve, and generally in the posterior mitral leaflet and aortic valve. Only a few cases showed vascularization of the auricularis layer in the anterior mitral leaflet. In the pulmonic cusps the ventricularis layer was either intact or showed more delicate reduplications, only a few of which were vascularized. The spongiosa layer of the valves was almost invariably thickened and vascularized, and generally mildly inflamed. The vascularization, particularly in the spongiosa layer, consisted of greatly hypertrophied muscular vessels, sometimes of the intimal

musculo-elastic hyperplastic type. In a few instances the collagenous transformation of the auricularis layer produced compression of the spongiosa layer.

Although 1 case showed definite whorling and vascularization of the fibrosa collagen, this layer was much less frequently involved than in the previous groups. In this respect Group V differed greatly from the preceding groups. Furthermore, in this group lipoid and calcific deposits involving the spongiosa as well as the fibrosa layers occurred considerably more frequently. It is to be noted, however, that the average age period of this group was somewhat older than the preceding. Aschoff bodies were seen only once. These were present in the anterior mitral leaflet. The fibrosa layer of the pulmonic valve generally showed intercryptic cells.

Most of the auriculoventricular valves showed delicate collagenous ventricularis reduplications. These were considerably exaggerated in width at the site of the chordae tendineae insertions, and on microscopic section presented the appearance of conspicuous crescents. In many instances, particularly on the mitral valve, the ventricularis reduplications were vascularized. In several instances the arterialis layer of the aortic valve consisted of widened collagenous extensions of pocket reduplications. These showed moderate inflammation, sometimes vascularization, and extended as far as the tip of the cusp, thus increasing the thickness of the leaflet. In several cases the arterialis reduplications were enormously thick and were associated with entropion of the aortic valve tip. The arterialis and ventricularis layers of the pulmonic valves were either uninvolved or showed delicate reduplications.

The tips of the mitral (Fig. 13), aortic and tricuspid valves were practically all converted into elastic-collagenous masses. These thickened tips were almost invariably vascularized and showed elastic bands and smooth muscle curving under the fused auricularis and spongiosa terminations. Excessive collagen formation with absorption of fused chordae tendineae insertions and elongation of the cusps was frequent in the auriculoventricular valves (Figs. 14 and 15). Some leaflets showed a moderate degree of inflammatory reaction. The tip of the pulmonic valve frequently showed fibrosis but the formation of knob-like thickening was seen in only one instance.

In spite of the fact that in the cases in this group death took place from decompensation without clinical evidence of a final acute at-

tack of rheumatic fever, and that some of these had no previous history of this condition, approximately 20 per cent of all the valve leaflets showed verrucae. This, together with the invariable presence of Aschoff bodies in the myocardium of these cases, as well as the mild inflammatory lesions in the cusps and elsewhere, indicates that decompensation in rheumatic valvular disease is frequently an evidence of activity of the rheumatic process, as contended by Rothschild, Kugel and Gross,[48] and others.

In the majority of instances the verrucae in this group were broad, flat, extremely indolent, showed little or no reaction at the base and presented the appearance of eosinophilic collagen degeneration of the superficial layers of the valve. A number of verrucae showed advanced organization. Completely organized verrucae were represented by ridges of proliferated fibroblasts at various levels on the valve tips. In 5 cases fresh or organized verrucae were situated either on the closure line or at the tip of the anterior mitral leaflet. In 2 of these the lesions resembled eosinophilic collagenous degeneration. An additional case showed a similar process involving the insertions of the chordae tendineae. In 6 cases organizing verrucae were present on the closure line or at the tip of the posterior mitral cusp. In 1 case these were also present on the chordae tendineae insertions. In 6 cases the aortic cusp showed fresh or organizing verrucae on the closure line or tip. Most of these were of the nature of an eosinophilic swelling and degeneration. In 7 cases flat verrucae or eosinophilic collagenous degeneration were present on the closure line of the tricuspid valve. One of these cases also showed verrucae on the chordae tendineae insertions. In 2 cases there were indolent verrucae on the closure line of the pulmonic cusps.

None of the valve pockets in this group showed verrucae. On the other hand, scarring of the underlying annulus and delicate elastified reduplications were present in all the valve pockets. The reduplications were inflamed and vascularized in the posterior mitral pocket in 4 cases and in the tricuspid valve pocket in 6 cases. Occasionally the pocket reduplications were multiple. The pulmonic pocket was the least involved. Besides these lesions, one aortic pocket showed a polypoid structure. Deposition of lipoid crystals in the pockets, especially toward the later age periods, was occasionally seen.

As mentioned above, the chordae tendineae insertions of the mitral and tricuspid leaflets showed verrucae in a few cases. In

several instances the reduplications were multiple and vascularized. In many cases the chordae tendineae insertions were absorbed into the elastic-collagenous valve tip and incorporated into the collagenous extension of this structure with resulting elongation of the cusps. Agglutination of the chordae tendineae to the endocardium was frequently noted in the tricuspid pocket.

Gross and microscopic vascularization was almost invariably noted in the mitral and tricuspid valves. Only 17 of the 28 cases in this group showed vascularization of the aortic valve. Vascularization of the ring was present in these and in 4 additional cases. In 13 cases the pulmonic valve showed vascularization. Vascularization of the ring was present in these and in 6 additional cases. Thus far, therefore, in the five groups described, universal vascularization of either valve leaflets or rings was found in the great majority of cases.

Inflammatory phenomena were extremely indolent in this group. However, when activity was present it still appeared to be most noticeable in the tricuspid leaflet. In a number of cases the exudative phenomena seemed to stop at the rings. Although vascularization was not present in the various valve leaflets of a number of cases, the proximal valve layer and the spongiosa layer not infrequently showed considerable thickening with transformation into collagenous ridges. Indeed, some of these cases showed indolent verrucae and one presented Aschoff bodies. This suggests the possibility that a low grade toxic process proceeding from the ring was able to elicit this gradual inflammatory transformation of the valve leaflet, chiefly at its distal portion, but was insufficient to stimulate the formation of blood vessels.

Not infrequently the posterior mitral valve was the one to show the greatest thickening process. This was often confined to the tip of the valve, the proximal part showing little more than superficial vascularization involving only the auricularis layer.

A number of the valve leaflets which were intact in other respects showed elastica condensations and ruptures in the spongiosa layer. In many cases the pulmonic cusps were notable for the complete absence of inflammatory cells. However, the relatively high incidence of vascularization in this valve indicated a previous inflammatory process.

Summarizing the conspicuous features of the valvular lesions as a

whole in Group V, the following points should be noted: The ring lesions showed considerable diminution in their extent, intensity and incidence. The blood vessels were generally thick walled arterioles or arteries, or distorted capillaries. The rings showed scarring and elastica distortion. Cellularity was sparse and Aschoff bodies rare. Subaortic lesions occurred in approximately half the cases. These were generally of the multiple vascularized variety. The incidence of the intervalvular fibrosa lesion was approximately 50 per cent. This was generally mild. In contrast with the previous four groups, universal ring lesions occurred in approximately half the cases. Ring lesions were found in three rings in another 25 per cent of the cases. Every case showed involvement of at least two rings.

The remainder of the valve lesions generally showed extremely mild exudative phenomena. Vascularization consisted of thick walled vessels and of capillaries, often distorted by scar tissue. Intimal musculo-elastic hyperplastic vessels were scarce. Thickening of the valve leaflet as a whole, due to somewhat heavier reduplications, was more frequently seen than in the last group. Thickening and elastification of the valve tips was also more frequent. On the other hand, the incidence of relatively intact leaflets was higher in this group than in the preceding one. As in Group III, the posterior mitral leaflet frequently showed the greatest thickening, and the tricuspid valve the greatest activity. Deformity of the aortic valve was often due to enormously thickened ventricularis and arterialis layers. The fibrosa layer was much less frequently involved than in the preceding groups. On the other hand, lime deposits in this as well as in the spongiosa layer occurred with considerable frequency. Aschoff bodies were found in 1 case. Verrucae occurred in approximately 20 per cent of the cases, the lowest incidence of any of the groups thus far described. These lesions appeared most frequently in the tricuspid valve and, in most instances, consisted of eosinophilic swelling and degeneration of the superficial layers of the leaflet at the tip. Polypoid lesions were found in only 1 case. This was in the aortic pocket. No pocket verrucae were present in this group. The chordae tendineae insertions showed crescentic reduplications in many cases and were often greatly thickened. Even though vascularization of the mitral and tricuspid valves was almost invariable, the incidence of vascularization of the

aortic valve decreased considerably (17 of 28 cases). The pulmonic valve was vascularized in 13 cases.

Gross Appearance of Rheumatic Valves in Group VI

(26 Inactive Cases of Chronic Valvular Disease of the Typical Rheumatic Variety)

The changes in this group varied considerably in severity. Some of the cases showed the extreme valvular deformities that have been described in Group V. There were many instances, however, in which one or more of the valves was either entirely normal or showed only a mild or moderate thickening. In selecting the cases for this group there were excluded those that presented the generally large secondary thrombotic verrucous lesions which have been separately described by Gross and Friedberg [52] under the classification of non-bacterial thrombotic endocarditis.

The mitral valve generally showed distinct thickening. Healed verrucae were present in only 4 cases out of the 26. Vascularization was visible in 14 cases. In 9 the terminal portion of the valve was converted into a collagenous mass. Lime was present in 6 cases, and in 2 there was definite stenosis of the valvular surface. In only one-fifth of the cases was there extreme deformity of the valve with elongation and absorption of thickened, shortened chordae tendineae.

Half of the cases showed only a mild or moderate thickening of the aortic valve. Healed verrucae were present in 1 case. In 4 cases there was a shortening of the cusp with notching, rolling and inversion of the margin, as previously described. In about one-fourth of the cases the semilunar folds approximated the free edge, or were obliterated. In 3 cases the cusps were rigid, chiefly because of infiltration of lime. Adhesion of the cusps at their commissures was present in 8 cases.

Most of the tricuspid valves showed only a mild or moderate diffuse thickening. Healed verrucae were present on three of the valves. Occasionally there was a loss of normal scalloping or an early shelf formation. In a few cases there was shortening and thickening of the chordae tendineae. The pulmonic cusps showed a mild degree of thickening in about two-thirds of the cases. In the remaining cases the valve was normal.

Abnormalities in the valvular pockets were present in about two-thirds of the cases. These abnormalities were qualitatively similar

to those in the preceding group, consisting of whitening and thickening of the endocardial lining, the presence of ridges, tiny nodules, folds and muscular and fibrous bridges which distorted the regularity of the pocket angle.

Microscopic Changes of Rheumatic Valves in Group VI

Practically all the mitral valves in this group showed collagenous auricularis reduplications which were generally quite flat in the proximal two-thirds of the valve, and possessed superficial vascularization with muscular vessels. In many cases the tip of the valve was converted into a collagenous mass. About half of these thickened tips were vascularized. Practically every case showed reduplications of the aortic valve ventricularis. In one-third of the cases these were multiple, and in one-half the cases they possessed enormously thick vessels with narrowed lumens. The lesions of the tricuspid valve were generally much less striking. The pulmonic valve generally showed either a delicate collagenous reduplication of the ventricularis layer or no discernible lesion.

The only consistent spongiosa lesion found in this group was in the posterior mitral cusp. In half the cases this layer was widened, elastified and vascularized. The widening was particularly noticeable over the chordae tendineae insertions. The blood vessels in the spongiosa layer were generally greatly hypertrophied and often showed intimal narrowing. Sparse scatterings of mast cells and lymphocytes were occasionally noted. In the tricuspid and aortic valves, vascularization of the spongiosa layer was infrequent. In the pulmonic valve it was rare. Chiefly in the mitral valve, the spongiosa sometimes showed considerable compression by the collagenous auricularis.

Apart from degenerative changes (hyaline transformation or lipoid or calcific deposition), the fibrosa layer was practically uninvolved in these cases. Occasionally it was thinned. In 1 case this layer showed whorling of the collagen and vascularization.

In 3 cases the ventricularis layer of the anterior mitral leaflet showed multiple reduplications. In 4 they were vascularized and richly elastic-collagenous. Apart from these, about half the cases showed crescentic reduplications of the chordae tendineae insertions. In the posterior mitral leaflet and in the tricuspid valves the ventricularis layer showed little else than crescentic thickenings of

the chordae tendineae insertions. In half the cases the aortic valve arterialis showed collagenous reduplications. The arterialis of the pulmonic valve was practically intact.

The tips of the mitral valve were invariably converted into elastic-collagenous thickenings. In two-thirds of the cases these thickened tips were vascularized. The tricuspid valve showed considerably less thickening of the tip. On the other hand, two-thirds of the cases showed extreme collagenous thickening of the aortic valve tips. These were less frequently vascularized than the mitral and generally consisted of the fan shaped collagenous knob structure described above. The tips of the pulmonic cusps showed no collagenous thickenings or other changes.

The only lesions in any way resembling verrucae found in this group were eosinophilic swelling and degeneration occurring generally on the closure line and showing practically no reaction of the underlying structure. These lesions were, on the whole, delicate and were found once on the anterior mitral leaflet, once on the posterior mitral, three times on the aortic and once on the tricuspid.

No verrucae or polypoid lesions were found in the valve pockets. On the other hand, all the valve pockets showed elastified reduplications. These were generally quite delicate and, in a few instances, vascularized. No verrucae were found on the chordae tendineae insertions. These frequently showed absorption into the mitral valve tip. In about half the cases the chordae tendineae insertions into the mitral and tricuspid valves showed crescentic reduplications. In 1 case the reduplications were vascularized.

The incidence of vascularization of the valves as a whole showed a conspicuous difference from the previous groups. Thus, while the anterior mitral leaflet was almost invariably vascularized, capillaries or muscular vessels were present in 20 of the 26 cases in the posterior mitral leaflet, in 12 cases in the aortic, in 8 cases in the tricuspid and only in 4 cases in the pulmonic. In 9 additional cases vascularization was present in the aortic ring, in 9 in the tricuspid ring and in 11 in the pulmonic ring.

Considered as a whole, this group showed a considerably lower incidence and severity of valvular deformities. Reduplications of the proximal valve layers were either delicate or not present. The mitral valve showed the most advanced lesions. Vascularization, when present, was frequently quite superficial on the proximal two-thirds

of the leaflets. Angle lesions, both over the auriculoventricular and semilunar rings were inconspicuous. Although the tricuspid valve was practically free from exudative phenomena, capillaries were still conspicuous. The pulmonic valve was notable for the frequency with which it was intact and for the slight extent of the deformity when it was involved.

Summarizing the conspicuous features of the valvular lesions as a whole in Group VI, the following points should be noted: The ring lesions showed practically no exudative phenomena. Aschoff bodies were not present. Inflammatory cells were extraordinarily sparse, scarring was appreciable and vascularization consisted of capillaries, hyaline arterioles or hypertrophied vessels. Subaortic lesions occurred in approximately half the cases. Half of these were multiple elastified reduplications and only half of these again were vascularized. Only 1 case of the 26 in this group showed a subpulmonic lesion. Intervalvular fibrosa lesions were found in only 5 of the cases. These were extremely mild. Only 6 cases showed universal ring involvement and in another 7, three rings were involved. Every case showed involvement of at least one ring.

The remainder of the valve leaflets was equally free of exudative phenomena. Vascularization was by means of capillaries and extremely thick walled vessels with greatly narrowed lumens. These were usually found in the superficial layers of the valve. Many valves were completely intact or showed some elastification of the fibrosa layer. Thickening of the leaflets occurred chiefly in the mitral valve and usually affected the tip in a manner similar to that described for the previous two groups. The only fibrosa lesion present was deposition of lime, which occurred in several cases. No Aschoff bodies were present. The only changes approximating verrucae were found in but few valves. These consisted of eosinophilic degeneration of a completely bland type. The pockets generally showed delicate reduplications and were free from verrucae or polypoid lesions. When involved, the chordae tendineae insertions showed reduplications generally of the crescentic variety. The anterior mitral leaflet was the only one which was almost universally vascularized. Blood vessels were found in 20 of the 26 cases in the posterior mitral leaflet, in 12 in the aortic, and in 4 in the pulmonic.

Discussion

In a previous report [46] it was shown that the rings are likely to be the first parts of the valves involved in a rheumatic affection. Briefly considered, the observations which support this view are as follows: (1) the valve rings almost invariably show inflammatory changes even when the remainder of the valve leaflets is relatively free from disease; (2) the lesions in the rings are generally more flagrant than those in the rest of the leaflets; and (3) particularly in the active cases, a definite contiguity inflammatory process can usually be seen extending from the valve ring into the body of the leaflet.

In the same report a discussion was given of the mechanisms concerned with the localization of the inflammatory process in the valve rings and with the spread of these lesions to and from the several rings. It appears that three mechanisms may play a rôle in this connection: (1) the simultaneous involvement of all the valve rings by the spread of infection from the adjacent myocardium; (2) involvement of the aortic and pulmonic rings by spread from the roots of the great vessels; and (3) involvement of the mitral ring from the inflamed left auricle with contiguity spread to the other rings, chiefly by way of the annulus extensions, but also through the pericardial wedges. It was shown that blood vessels do not exist in most normal rings and that they are probably not concerned with the initial localization of the rheumatic lesions in these sites.

The observations incorporated in the present report afford an excellent opportunity to study the pathogenesis of the valvular lesions and their life cycles. Assuming that the initial valvular lesion is in the ring, it appears that spread of the infection takes place by a contiguity process chiefly through the spongiosa layer, as well as the proximal layers of the valves (auricularis layer of the auriculoventricular valves and ventricularis layer of the semilunar valves). The spongiosa layer undergoes considerable widening, with edema and inflammatory infiltration. The proximal layers of the auriculoventricular and semilunar valves are prone to the formation of reduplications whose structure is somewhat similar to that previously described in the left auricle (Gross [43]). Thus, the generalized valvular thickening which occurs during an initial attack or an acute exacerbation is due partly to extensive exudation and partly to the formation of these reduplications of the proximal layer of the valves. It

appears further that verrucae result from certain exudative and degenerative processes which occur on the proximal surface of the inflamed valves, chiefly at the closure line. These processes are frequently associated with proliferation of the local fixed cells. These often arrange themselves at right angles to the surface and form the so-called palisades. This, therefore, is not a primary lesion as believed by Leary,[34] but occurs subsequent to the valvulitis. The secondary rôle in the thickening process played by the formation of verrucae will be considered separately.

In the more chronic stages, deformity of the auriculoventricular valves is produced by thickening of these reduplications, formation of multiple reduplications, elastic-collagenous transformation of the tips of the leaflets and, in some cases, lipoid and calcific deposition in the annulus around the pocket, the fibrosa layer and the thickened tip. If the lesion is of long duration there may be added to these, thick reduplications on the ventricularis layer. Together with these processes other changes generally occur. Thus, fibrosis of the auriculoventricular valve tips is frequently associated with excessive collagen formation, part of which results from organization of verrucae. In the auriculoventricular valves this collagen spreads over and fuses with the chordae tendineae insertions, which are thickened by fibro-elastic reduplications, with resulting elongation of the valve leaflet. These elongated leaflets, with their incorporated chordae tendineae, are molded together by redundant cicatrizing connective tissue as a result of which there is eventually created a rigid, flattened or rounded, funnel shaped structure — the typical valvular stenosis. A similar process, in the absence of redundant connective tissue, leads to a less marked stenosis without lengthening of the valve leaflets — indeed, at times with shortening due to cicatrization. Thus, the formation of auricularis, ventricularis and chordae tendineae reduplications, the profuse collagenization of the valve tips and the fusion of the thickened chordae tendineae insertions with the thickened valve tips are responsible for the characteristic deformities of the auriculoventricular valves in chronic valvular disease. To these may be added the secondary lipoid and calcific changes and, in some cases, secondary thrombotic deposits on the closure line with organization (Gross and Friedberg [52]).

Deformity of the semilunar cusps occurring in the chronic cases is due to a somewhat similar process, modified, however, by the to-

pography of the commissures and by the absence of chordae tendineae. The close approximation of the inflamed semilunar folds between two cusps frequently leads to their agglutination. This produces the characteristic rheumatic commissural lesion in which a delicate groove persists between the agglutinated cusps. Eventually, thickening of the cusps and commissures leads to stenosis. The redundant collagen formation at the tip of the ventricularis layer, which is partly due to organization of verrucae, causes the semilunar cusps to fold over or become fused with a thickened arterialis layer (entropion). The latter, as has been shown, rarely undergoes the excessive collagen transformation seen in the ventricularis layer. In some instances the tips of the cusps fold over toward the lumen of the heart, producing ectropion. It is seen, therefore, that in contrast to the auriculoventricular valves the semilunar cusps are shortened by the infolding (or outfolding) of the tip. As a consequence, the semilunar folds on these cusps approximate the newly formed free edge and may eventually disappear completely. Furthermore, the infolding of the nodulus Arantii produces a distinct notching at the center of the free edge of each cusp.

It is clear from the above that the presence of chordae tendineae permits the redundant collagenous tissue to fuse with them and produce elongation of the auriculoventricular valves. On the other hand, their absence on the semilunar cusps causes the same inflammatory process to produce shortening and generally entropion of the semilunar valves with notching and approximation of the semilunar folds to the free edge or their disappearance. Obviously, the degree to which deformity will take place depends on the acuity of the inflammatory processes, on their repetition, on the valve affected, as well as on the type of reaction elicited in the given case. The latter plays a prominent rôle in determining the extent of the secondary lipoid and calcific changes which occur. As has been emphasized by Libman,[53] there are undoubtedly definite individual differences in the propensity for the deposition of calcific material in blood vessels, pericardial exudate, valve rings and valve leaflets.

The deposit of lime in the cusps in turn leads to characteristic gross and histological changes. It has been shown above that the fibrosa layer of the cusps becomes hyaline and relatively acellular with advancing age periods and that, simultaneously with these changes, lime deposition takes place. Apparently the same process

occurs in the definitely collagenous, hyaline and relatively acellular structure found in the scarred ring annulus, fibrosa layer at the base of the valve, and thickened valve tips. As has been shown for certain blood vessel lesions, rheumatic fever may greatly hasten a normally occurring degenerative process. It has been indicated before that these changes are apt to occur with predilection at the commissural regions. Secondary to the lime deposition, granulation tissue capillaries and inflammatory cells may surround the foreign material and lead to agglutination of the cusps. At times the calcific material in the commissures, particularly of the mitral valve, shows characteristic vertical cracks. These sites may be covered with thrombotic material and become infected with bacteria, thus producing a bacterial endocarditis. Metaplasia with bone and bone marrow formation may occur in the areas of lime deposition.

It was previously shown that the lesions in Group I (cases with death during a first attack) are characterized by the acuity and extent of the exudative phenomena and by the fact that the vascularization of the valves is mainly of the capillary type. Reasons were given which indicate that 6 weeks are generally insufficient for the production of muscular wall vessels by the rheumatic process. In the Group II cases the patients had suffered one previous attack within 1 year of the fatal outcome. In these the exudative phenomena were even more distinct. In addition, characteristic reduplications were present at the valve angles and on their surfaces, and the vessels present in the inflamed valves were frequently of the intimal musculo-elastic hyperplastic type. It appears that this type of vessel lesion, therefore, apparently generally requires more than 6 weeks for its production. In Groups III, IV and V the active exudative phenomena became increasingly indolent and were absent in Group VI. The vasculature in the valves of these more chronic groups consisted of capillaries, often distorted by scar tissue, and of vessels with muscular walls, and sometimes intimal fibrosis (particularly in Groups V and VI).

Of great interest is a consideration of the verrucous lesions found in these cases. Their incidence was unexpectedly high and apparently closely paralleled the clinical course of the disease. Thus, verrucae were almost invariably present on the mitral, aortic and tricuspid valves (including the pockets and chordae tendineae insertions) in Group II, and occurred with high frequency in these

valves in Group I. Group IV was the next in order of frequency as regards the incidence of these lesions. This was not unexpected in view of the fact that this group represents cases with repeated attacks. Furthermore, inasmuch as one of these rheumatic bouts occurred within 1 year of the fatal outcome in a number of cases (thus simulating Group II), the incidence of intimal musculo-elastic hyperplastic vascular lesions was also somewhat high in this group. Verrucae occurred in approximately 50 per cent of the valves in Group III. Their incidence fell considerably in Group V, occurring in approximately 20 per cent of the valves. In Group VI they were rare and consisted entirely of degenerated eosinophilic material resulting from collagen necrosis. The relation of these lesions to nonbacterial thrombotic endocarditis (Gross and Friedberg [52]) will be subsequently discussed. Verrucae were present on the pulmonic valve in over 40 per cent of the cases in Groups IV and II. Their incidence was somewhat lower in the pulmonic valves in Groups III and I. They were rare in Group V and not present in Group VI.

The histological structure of the verrucae suggests that they are made up of hyaline eosinophilic material resulting from necrosis and fusion of inflammatory exudate as well as of the superficial layers of the valve. Their appearance is apparently greatly influenced by the clinical course of the disease. Thus, they were fresh and showed considerable reaction at the base in Group I. In Group II they were broad and presented evidence of some organization and considerable reaction at the base. In Group III they were broad, showed increasing incidence of organization with, however, reaction still present at the base. In Group IV some verrucae appeared to consist of eosinophilic degeneration of the superficial layers of the valve with somewhat milder reaction at the base. In Group V the great majority of verrucous lesions consisted of extremely indolent lesions of the eosinophilic degeneration type, and in Group VI, apart from their rarity, they were completely bland and were obviously of the eosinophilic degeneration type. There may be some question as to whether or not lesions of this type should be properly considered verrucae. However, all gradations may be found between the typical extrusion lesions with pronounced inflammatory base seen in active rheumatic fever cases and those consisting solely of degenerating collagen. It does not seem advisable, therefore, to make a sharp differentiation between these lesions. In the healed cases (Group VI) these lesions

may become the seat of a secondary non-bacterial thrombotic deposit which may reach considerable size. Such secondary thrombotic verrucae have been included in the purely descriptive classification of non-bacterial thrombotic endocarditis (Gross and Friedberg [52]). Obviously, therefore, the latter designation does not exclude a rheumatic origin for the underlying condition. When definite evidence of rheumatic stigmata are present in the valves and elsewhere (auricle, rings, pericardium, and so on) the condition should be termed a rheumatic lesion, healed (Group VI) with or without superimposed non-bacterial thrombotic endocarditis.

As already shown, the proliferative and necrotic processes which are concerned with the formation of verrucae occur with predilection at the most exposed portions of the valve (closure line) as well as within culs-de-sac in which eddies or blood stasis may be present, *e.g.*, in the valve pockets and chordae tendineae insertions. It was further shown that verrucae tend to localize at the most distal portion of the valve that still presents inflammatory changes. This was best exemplified in the pulmonic cusps. As deformity of the valve tip takes place, different portions of this structure become the most conspicuous edge presented to the blood stream. As a consequence, fresh rows of verrucae are found on the newly exposed portions. Thus, in the chronic cases it was not unusual to find several distinct rows of verrucae. The oldest and generally completely organized row represented the original closure line. The other rows showed various grades of organization, the most recent and freshest verrucae being situated on what would correspond to the new closure line of the altered valve, even though no actual apposition of these parts may take place because of the stiffening and deformity. This observation immediately throws out of account any consideration which assumes that anatomical and architectural factors in the vascularization of the valve determine the site of formation of these verrucae. Indeed, as was shown particularly in Groups V and VI, such verrucous transformation may take place in valves that are completely devoid of blood vessels but which show evidence that a toxic or irritative process extended from the ring through the valve leaflet into the tip. Furthermore, the mechanism described explains the occurrence of verrucae in the valve pockets and on the chordae tendineae insertions, areas that are unquestionably free from blood vessels normally.

On comparing the incidence of verrucae in the several valves and including in these figures verrucae occurring in the pockets and on the chordae tendineae insertions, it is seen that the highest incidence was in the tricuspid valve and posterior mitral leaflet. The incidence of these lesions on the aortic valve and anterior mitral leaflet, however, was so close to this that the differences could be accounted for on a statistical basis. Clearly, however, the pulmonic valve showed the lowest incidence of verrucae. It is of interest to note that the incidence of ring and valve lesions was also decidedly lower in the pulmonic valve.

The extent of the deformity varied considerably in the several valves, being greatest in the mitral and next in the aortic, tricuspid and pulmonic, in this order. These differences occurred in spite of the fact that the acuity of the initial lesion (ring lesion) and the continued activity (incidence of verrucae) appear to be approximately the same in each of these three valves. It is interesting to speculate on the determining factors that lead to these marked differences in the subsequent development of the valvular lesion. That vascularization of the valves plays no rôle in this, is obvious for the following reasons: (1) valvulitis may occur in totally non-vascularized valves; (2) observations by Gross and Kugel,[47] which have been recently extended[50], indicate that normal valves rarely, if ever, possess blood vessels distal to the rings; (3) recent workers who have claimed a high incidence of vascularization in normal valves could show no parallel between their figures and the incidence of valvular lesions [51]; and (4) once a rheumatic process has set in, the incidence of valve vascularization is practically universal, certainly in the first five clinical groups discussed. Nevertheless, the extent of valvular damage, as is well known, differs in the several valves of the heart. On the other hand, many observations indicate that the pressure to which the valve leaflet is exposed may be an important factor in determining the extent of the valvular deformity produced. The additional trauma component of intracardiac pressure, in the presence of the rheumatic infection, can account for the considerably greater extent of the valvular deformities that occur in the left heart. The trauma of valvular apposition may explain the predilection of the valve tips as opposed to the proximal two-thirds of the leaflet for the localization of the continued fibroblastic proliferative process. Of considerable interest in this connection is the frequency

with which the tricuspid valve is the seat of verrucae in the presence of hypertension of the lesser circulation (pulmonary emphysema, mitral stenosis, and so on), even in the absence of fresh lesions on the mitral valve. The fact that the tricuspid valvular lesion is generally far more severe than the pulmonic may be accounted for by the continued infection of the tricuspid ring through the annulus extensions from the aortic root and from the mitral valve. As already shown, the pulmonic ring is not linked to these annulus extensions.

In further support of the view that intracardiac tension probably plays an important rôle in determining the progress of an initial rheumatic lesion are the figures reported by Gross and Ehrlich [40] on the incidence of Aschoff bodies in the several chambers of the heart. They showed that Aschoff bodies occurred with greatest frequency in the left ventricle, and with decreasing frequency in the right ventricle, left auricle and right auricle, in that order. This incidence of Aschoff bodies is strikingly paralleled by the tension within the respective chambers. These authors also showed that there may be differences in the incidence of Aschoff bodies within various parts of the same chamber. This suggests that there are additional factors determining local predisposition, of which we have at present no knowledge. It is not necessary to assume that the epithelium covering valve tips has especial phagocytic properties since the pressure factors discussed above can adequately explain the localization of particles (bacteria) at these sites. Finally, differences in the oxygen tension of the blood bathing the valves in the right and left hearts may also have some bearing on the progress of the lesions.

The striking differences in the inflammatory reactions within the valves as influenced by the clinical course of the disease bring up the question as to what rôle general or local tissue immunity may play in this connection. It was shown that if a patient dies during a first attack or if he suffered from only one previous attack within 1 year previous to the fatal outcome, the lesions are flagrant and differ chiefly in the nature of the blood vessels, the latter in turn being determined by the duration of the rheumatic bout. However, in the more chronic cases the inflammatory reaction is considerably subdued. It may be argued that the severity of the disease which is sufficient to lead to a fatal outcome during the first or second attack

occurring within 1 year, may be so intense that flagrant exudative phenomena are to be expected. Similarly, the fact that a patient can survive a series of rheumatic attacks or present a chronic course, may be indicative of less severe infection, *i.e.*, one that would lead to a more indolent type of reactivity in the valve. On the other hand, these differences in the severity of the reaction may indicate differences in the relative immunity of the patient to the disease. Indeed, the clinical groups into which the rheumatic cases were divided may be considered as representing various degrees of resistance to the infection. Group I represents a fulminating infection with little or no resistance. In Group II, one attack was successfully resisted for a short time only, the patient dying of either a second attack or a second exacerbation. In Group III, the first attack was even more successfully resisted; however, after a period of 2 or more years, a second attack encountered insufficient resistance and led to death. Group IV can be construed as representing partial immunity to the disease, the patient successively showing temporary phases of greater or lesser resistance to the infection. In Group V, immunity is great enough to permit of a chronic drawn-out course, without, however, complete healing. Group VI represents complete immunity to the infection with cessation of all activity. Considered in this light, the qualitative and quantitative differences in the inflammatory phenomena as observed in the various groups may well depend, at least to some extent, on such differences in immunity or reactivity. In previous reports it was shown that similar differences, corresponding to the clinical course of the disease, may be observed in the response to the rheumatic infection of the myocardial interstitium (Aschoff bodies [40]), coronary tree,[41] left auricle [43] and pericardium.[45]

The comparison of the valvular lesions occurring in the different clinical groups has already been presented in the summaries given at the end of each of these chapters. It need only be repeated that the first two groups are notable for the exudative phenomena, and the last four groups for the productive changes. Group IV occupies an intermediary position in that it represents at the same time the chronicity of the latter groups, as well as the acute exacerbations of the former. Group VI represents complete healing of the rheumatic process or cessation of the rheumatic lesions. As such, the findings in this latter group are of extreme importance in that they disclose

the stigmata of the completely involuted rheumatic processes in the valve leaflets.

In conclusion, attention should be drawn to the additional gross lesions described in this report. Until comparatively recently the only gross rheumatic lesions known to occur in the heart were those due to the acute and healing stages of pericardial inflammation, the fresh and healed verrucae on the closure line and chordae tendineae insertions of the valves, the valvular deformities with the characteristic commissural agglutinations of the aortic cusps, the thickening of the chordae tendineae, the regurgitant endocardial pockets (also occurring in other conditions), the auricular endocardial lesions and, rarely, the macroscopic Aschoff bodies. To these there have been recently added the lesions at the roots of the great vessels (Gross [42]) which produce dimpling in the sinus pockets (Fig. 10) and the thickening and prominence of the subvalvular angles and ring regions (Gross and Friedberg [46]). In the present communication, descriptions are given of the more minute topographical changes found in the valves, including elongation of the auriculoventricular leaflets, with obliteration of their normal scalloping, the ham shaped chordae tendineae insertions, the approximation of the semilunar folds of the semilunar cusps to the free edges and their disappearance, the notching, entropion and ectropion of the semilunar cusps, the characteristic pocket lesions consisting of verrucous, polypoid and nodular formations, and the agglutinations and rounding of the auriculoventricular valve pockets with obliteration of their sharp angle. A description of the pathogenesis of these lesions, their life cycles and their incidence in the various clinical subdivisions of rheumatic fever is given.

Summary and Conclusions

There have been described in this report the incidence and gross and microscopic appearance of lesions in the valves, valve pockets and chordae tendineae occurring in 97 cases of rheumatic fever. These cases have been divided into six clinical groups which represent various courses taken by this disease. It has been shown that each group presents certain gross and microscopic features that bear a relation to the clinical grouping. Anatomical evidence is presented which suggests that the course taken by the disease as well as the response of the tissue may be determined by the relative state of

immunity. This does not, however, imply that rheumatic fever is primarily an allergic disease. New macroscopic and microscopic data are presented on the development of the rheumatic lesions in the valves, and a discussion is given of the factors which determine the spread of infection, the localization of the verrucous and other lesions, the extent of the valvular damage and the pathogenesis of the characteristic deformities of the valvular apparatus. Certain stigmata of the rheumatic process occurring in completely healed valves are described. These supply additional data which are of value in elucidating the pathogenesis of other cardiac lesions. A description is also given of the changes that take place in non-rheumatic valves during the first eight decades of life.

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DESCRIPTION OF PLATES

PLATE 146

FIG. 1. Cross-section of normal posterior mitral leaflet. Age 8 years. Low power. Weigert's elastic and Van Gieson's connective tissue stain.

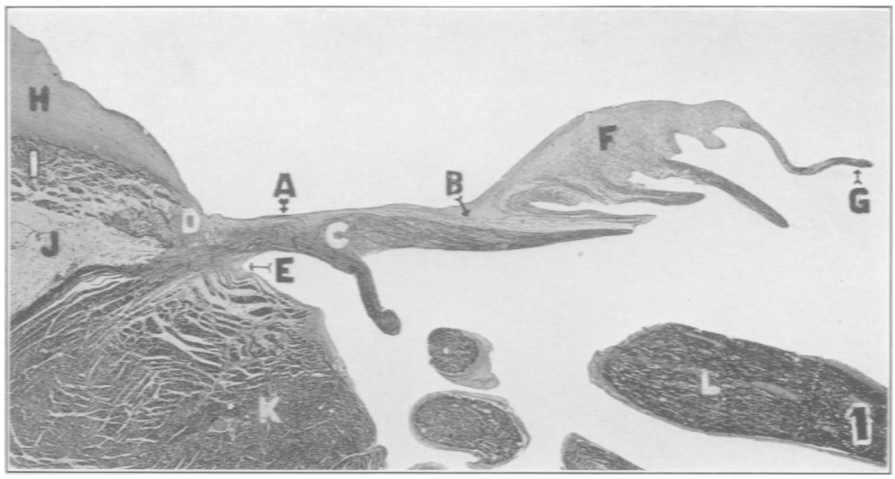
A = auricularis layer discernible only as a delicate elastic lamella; B = spongiosa layer; C = fibrosa layer; D = valve ring; E = valve pocket; F = gelatinous valve tip; G = first order chorda tendinea insertion; H = left auricular endocardium; I = left auricular myocardial wedge; J = left auricular pericardial wedge; K = left ventricular myocardium; L = columna carnea.

FIG. 2. Cross-section of normal posterior aortic cusp (to the right of the lower arrow point) and normal anterior mitral leaflet (to the left of the upper arrow point). Age 8 years. Low power. Weigert's elastic and Van Gieson's connective tissue stain.

A = proximal layer of valve; B = spongiosa layer; C = fibrosa layer; D = valve ring; E = aortic valve pocket; F = valve tip; G = second order chorda tendinea insertion; H = left auricular endocardium; I = left auricular myocardial wedge; J = left auricular pericardial wedge; K = aortic root; L = intervalvular fibrosa.

FIG. 3. Gross photograph of tricuspid valve from a case of active rheumatic fever (Group I), showing chordae tendineae agglutinations to underlying endocardium. Age 9 years.

A = right auricle; B = anterior tricuspid leaflet; C = retracted septal tricuspid leaflet; D = chordae tendineae agglutinated to ventricular wall; E = outflow tract of right ventricle.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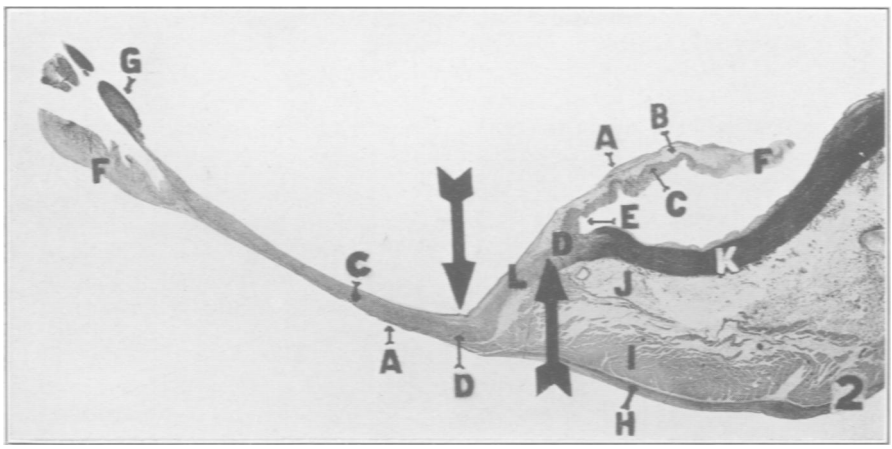
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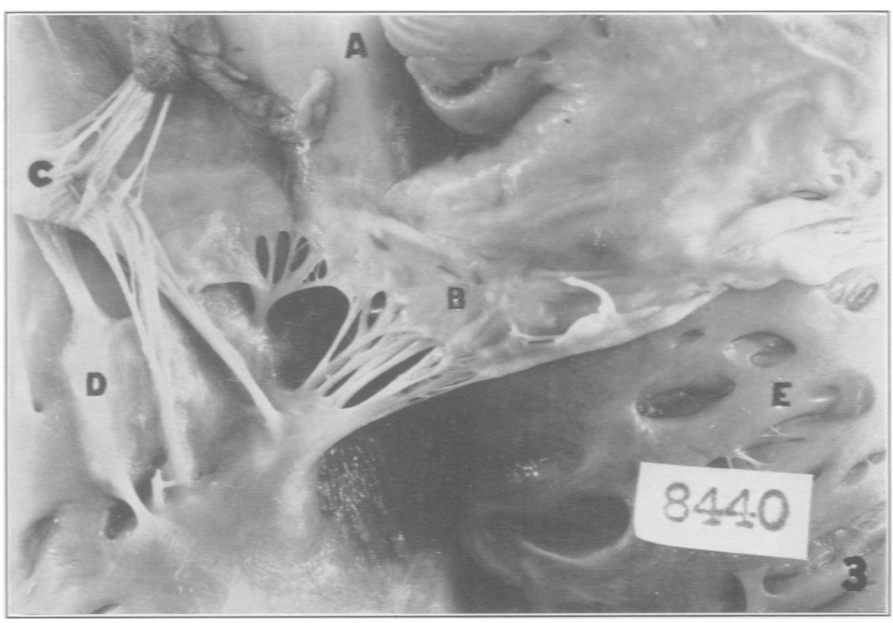
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PLATE 147

FIG. 4. Cross-section of posterior mitral leaflet from a case of active rheumatic fever (Group I). Age 17 months. Low power. Hematoxylin and eosin stain.

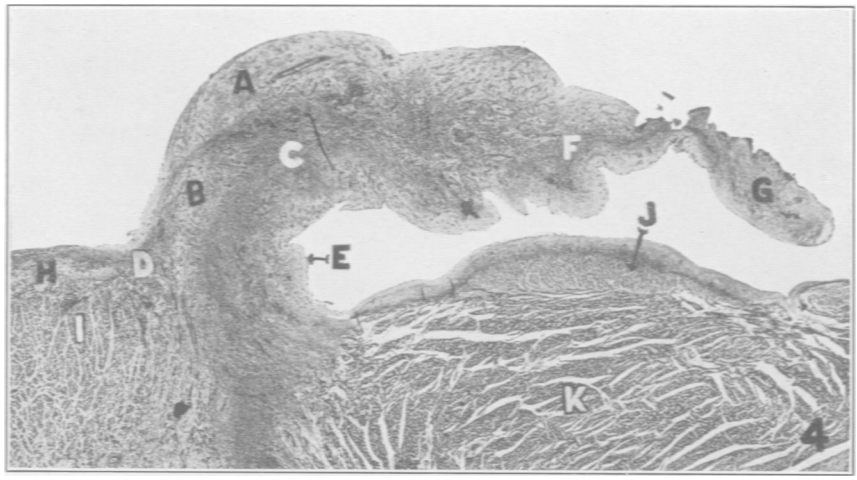
A = edematous inflamed hypercapillarized auricularis layer; B = inflamed hypercapillarized spongiosa layer; C = inflamed capillarized fibrosa layer; D = inflamed valve ring; E = inflamed capillarized pocket reduplication becoming continuous with inflamed capillarized arterialis reduplication; F = inflamed valve tip; G = inflamed, capillarized, thickened first order chorda tendinea insertion; H = inflamed left auricular endocardium (note inflamed subendocardium); I = left auricular myocardial wedge; J = left ventricular endocardial thickening; K = left ventricular myocardium.

FIG. 5. Cross-section of posterior mitral leaflet from a case of active rheumatic fever (Group I). Age $2\frac{1}{2}$ years. Low power. Hematoxylin and eosin stain.

A = edematous inflamed hypercapillarized auricularis layer; B = inflamed capillarized spongiosa layer; C = inflamed capillarized fibrosa layer; D = inflamed valve ring; E = inflamed capillarized valve pocket; F = inflamed fibrotic valve tip with verrucous change; G = inflamed chordae tendineae agglutinated by verrucous material; H = inflamed left auricular endocardium (note inflamed subendocardium); I = left auricular myocardial wedge; J = inflamed thickened left ventricular endocardium; K = left ventricular myocardium.

FIG. 6. Cross-section of posterior mitral leaflet from a case of active rheumatic fever (Group I). Age $6\frac{1}{2}$ years. Low power. Weigert's elastic and Van Gieson's connective tissue stain.

A = inflamed widened auricularis layer; B = edematous spongiosa layer; C = fibrosa layer; D = valve ring; E = inflamed reduplication in valve pocket; F = inflamed valve tip; G = cross-section of chorda tendinea showing reduplication of the endocardial covering; H = verrucous material with granulation tissue base situated on closure line (note delicate layer of fibrin attached to the surface of the verrucae); I = very delicate ventricularis reduplication; J = left ventricular myocardium.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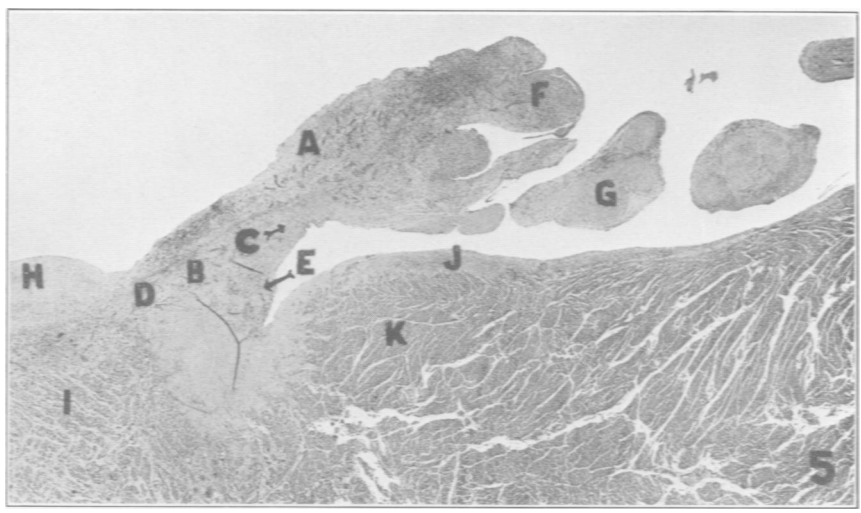
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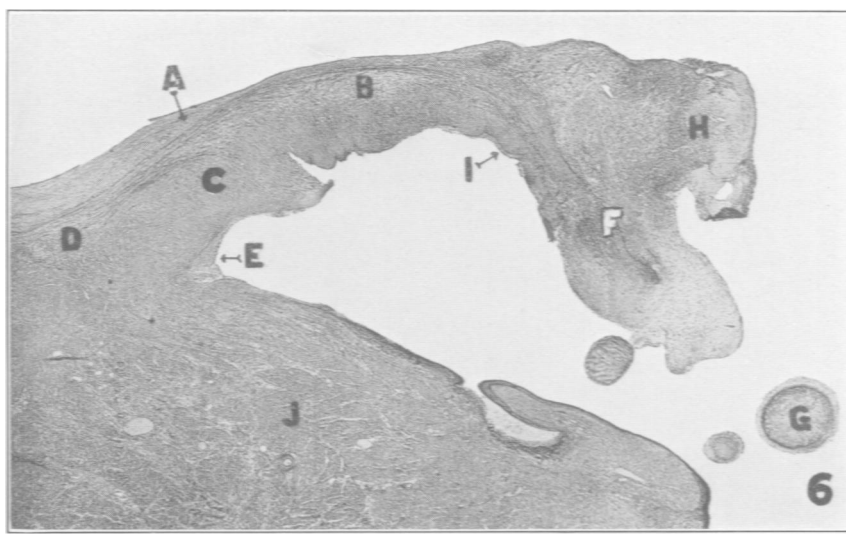
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PLATE 148

FIG. 7. Cross-section of tricuspid leaflet from a case of active rheumatic fever (Group II). Age 13 years. Low power. Hematoxylin and eosin stain.

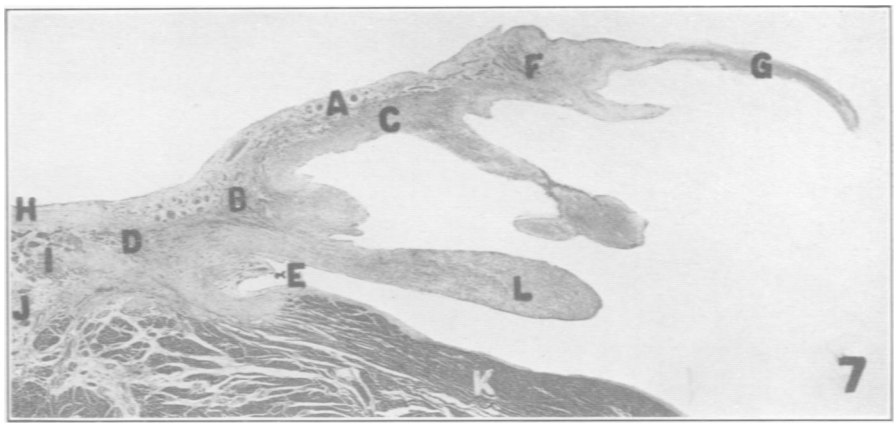
A = widened vascularized auricularis layer (note numerous intimal musculo-elastic hyperplastic vessels); B = vascularized spongiosa layer; C = fibrosa layer; D = vascularized valve ring; E = vascularized fibrotic reduplication in tricuspid pocket; F = fibrotic vascularized valve tip; G = first order chorda tendinea insertion (note fibrotic reduplication); H = left auricular endocardium; I = left auricular myocardial wedge; J = left auricular pericardial wedge; K = left ventricular myocardium; L = thickened third order chorda tendinea insertion.

FIG. 8. Cross-section of right aortic cusp from a case of active rheumatic fever (Group II). Age 18 years. Low power. Weigert's elastic and Van Gieson's connective tissue stain.

A = elastified ventricularis reduplications; B = widened fibrotic vascularized spongiosa layer; C = fibrosa layer; D = fibrotic valve ring (note multiple elastified subaortic reduplications with intimal musculo-elastic hyperplastic vessels); E = aortic valve pocket showing polypoid formation; F = fibro-elastic transformation of valve tip with approximation of greatly thickened ventricularis layers to fibrosa and compression of spongiosa; G = fibrotic arterialis reduplication; H = verrucous lesion on closure line; I = aortic root; J = ventricular myocardium; K = considerably thickened blood vessel showing intimal musculo-elastic hyperplastic lesion.

FIG. 9. Cross-section of right aortic cusp from a case of active rheumatic fever (Group II). Age 14 years. Low power. Weigert's elastic and Van Gieson's connective tissue stain.

A = multiple elastified ventricularis reduplications continuous with subaortic reduplications; B = fibrotic vascularized spongiosa layer; C = fibrosa layer; D = fibrotic valve ring (note multiple elastified subaortic reduplications with numerous intimal musculo-elastic hyperplastic vessels); E = aortic ring annulus permeated with intimal musculo-elastic hyperplastic vessels; F = fibro-elastic transformation of valve tip showing earliest stages of entropion; G = aortic valve pocket; H = verrucous lesion surrounding valve tip; I = aortic root; J = retroaortic pericardial mantle (note intimal musculo-elastic hyperplastic vessels); K = left auricular myocardial wedge. L = left auricular endocardium.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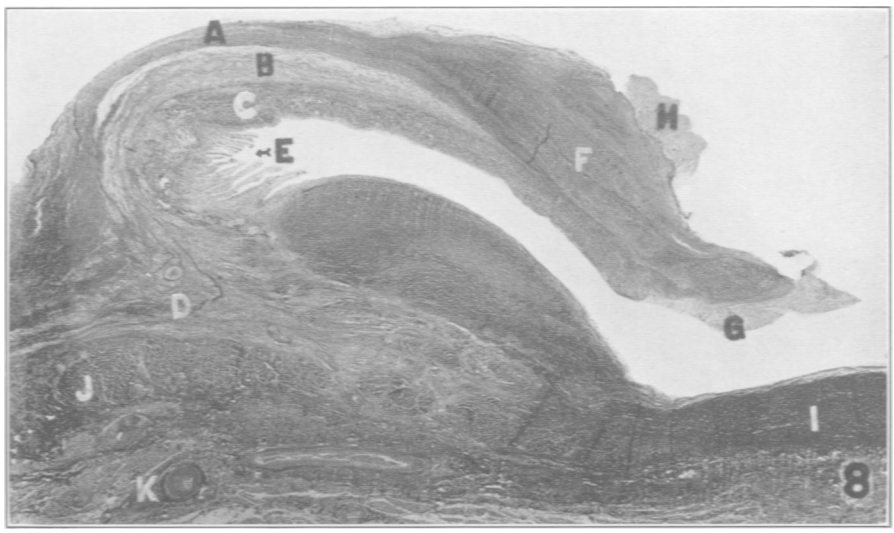
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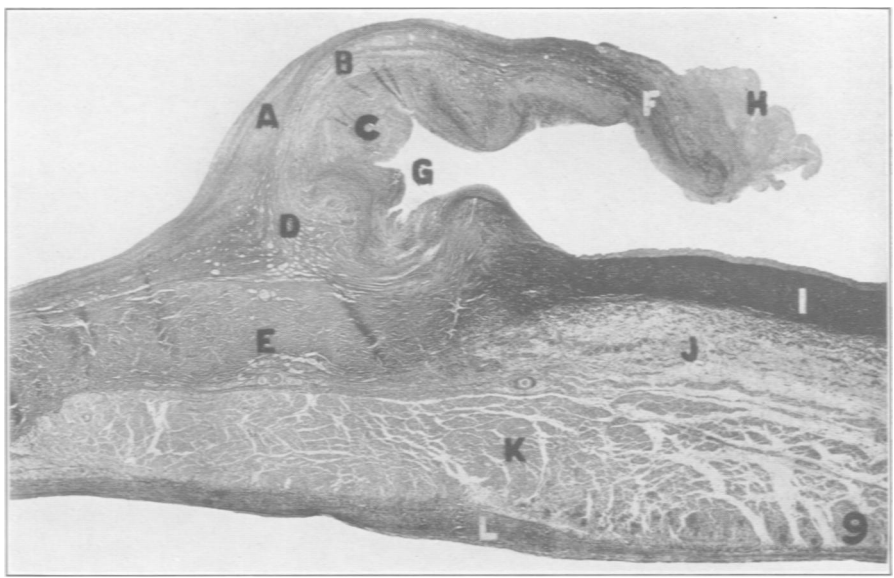
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PLATE 149

FIG. 10. Gross photograph of aortic valve from a case of active rheumatic fever (Group IV). Age 12 years.

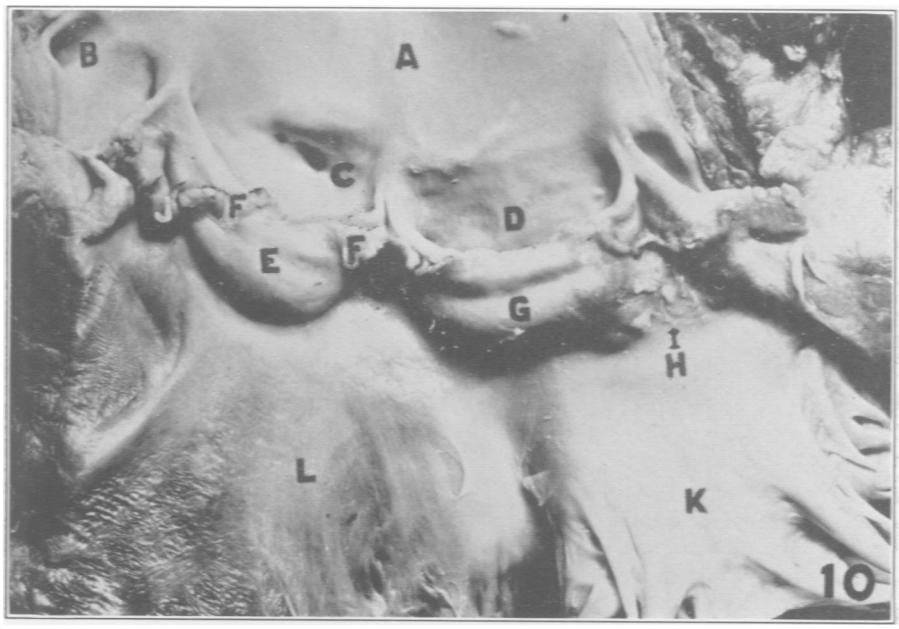
A = aorta; B = left coronary ostium; C = right coronary ostium; D = posterior sinus pocket (note dimpling of annulus); E = right aortic cusp (note notching at center of free margin and approximation of (F) semilunar folds to free margin); G = posterior aortic cusp (note rolling and thickening of free edge, beginning entropion and approximation of semilunar folds to free margin); H = irregularity of subaortic angle due to formation of subaortic angle lesions; J = bridges of verrucous material agglutinating commissure; K = ventricular aspect of anterior mitral leaflet; L = outflow tract of left ventricle.

FIG. 11. Gross photograph of mitral valve from a case of active rheumatic fever (Group IV). Age 49 years.

A = left auricle; B = anterior mitral leaflet (note gross vascularization of body of leaflet, also fresh verrucae along closure line); C = verrucae situated on chordae tendineae insertions (note ham shaped terminations of latter); D = posterior mitral leaflet with marked straightening of scalloped edge (note verrucae on closure line); E = posterior papillary muscle; F = anterior papillary muscle.

FIG. 12. Cross-section of right aortic cusp from a case of active rheumatic fever (Group IV). Age 13 years. Low power. Weigert's elastic and Van Gieson's connective tissue stain.

A = thick fibrotic vascularized ventricularis reduplications; B = elastified compressed spongiosa layer; C = fibrosa layer; D = fibrotic valve ring (note distorted compressed capillaries); E = fibro-elastified reduplication in aortic pocket; F = ectropion of fibro-elastified valve tip; G = verrucae on new closure line; H = verrucae in cul-de-sac; I = aortic root; J = ventricular myocardium showing considerable scarring.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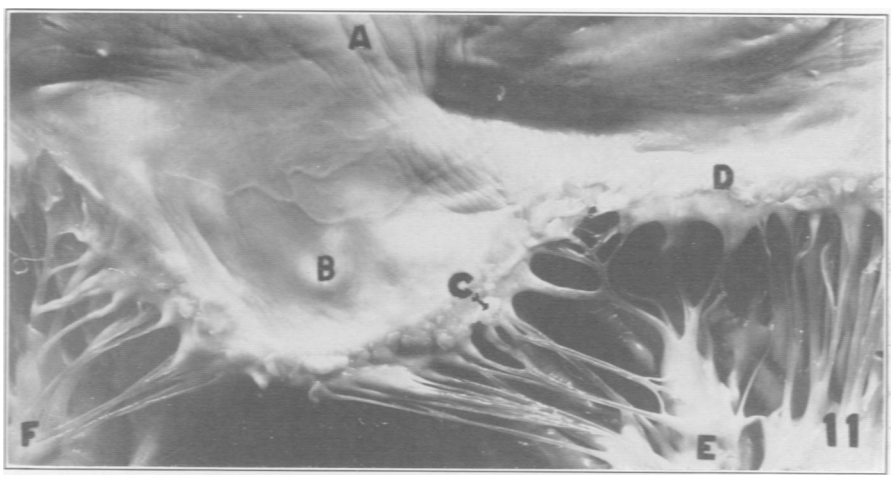
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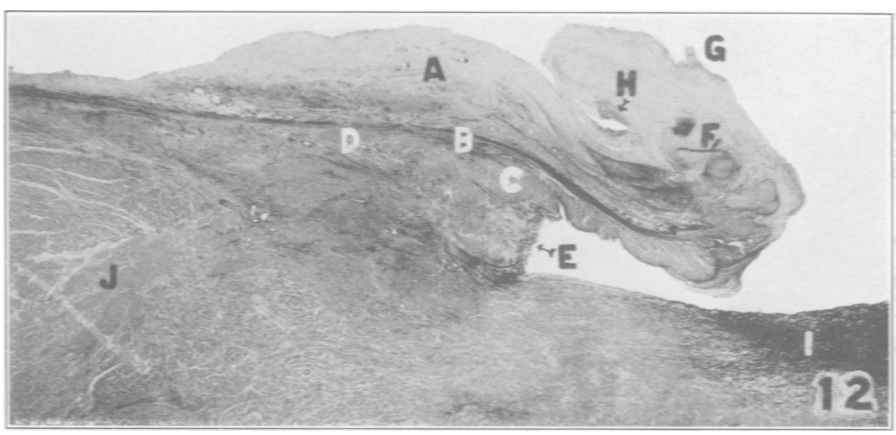
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PLATE 150

FIG. 13. Cross-section of anterior mitral leaflet from a case of active rheumatic fever (Group V). Age 33 years. Low power. Weigert's elastic and Van Gieson's connective tissue stain.

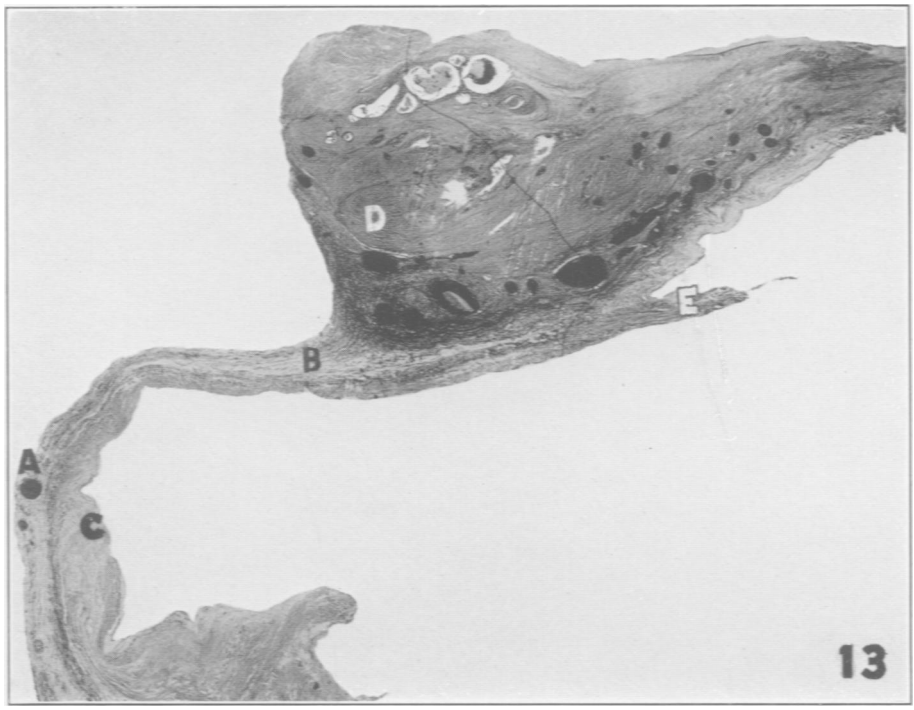
A = superficial vascularization (injected) of auricularis layer in the proximal two-thirds of the valve leaflet; B = moderately widened spongiosa layer; C = fibrosa layer; D = enormously thickened distal third of the valve leaflet. The thickening is due to fibro-elastification and fusion of auricularis and spongiosa layers together with the production of redundant elastic collagenous tissue. Note extensive vascularization of thickened tip. E = chorda tendinea insertion.

FIG. 14. Cross-section of posterior mitral leaflet from a case of active rheumatic fever (Group V). Age 50 years. Low power. Weigert's elastic and Van Gieson's connective tissue stain.

A = fused auricularis and spongiosa layers; B = chordae tendineae insertions marking the original site of the valve tip; C = enormously redundant fibrotic tissue from fused auricularis and spongiosa layers spreading over chordae tendineae and producing elongation of the valve leaflet (note absorption of chordae tendineae into this mass); D = left auricular myocardial wedge; E = left auricular pericardial wedge; F = left ventricular myocardium.

FIG. 15. Cross-section of tip of anterior mitral leaflet showing absorption of chordae tendineae and the mechanism of elongation of the leaflet. Case of active rheumatic fever (Group V). Age 66 years. Medium power. Weigert's elastic and Van Gieson's connective tissue stain.

A = tip of leaflet; B = absorbed chordae tendineae insertions; C = redundant fibro-elastic tissue from fused auricularis and spongiosa layers enveloping chordae tendineae.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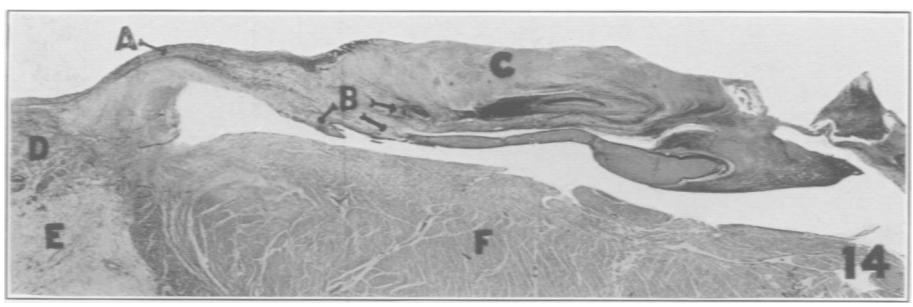
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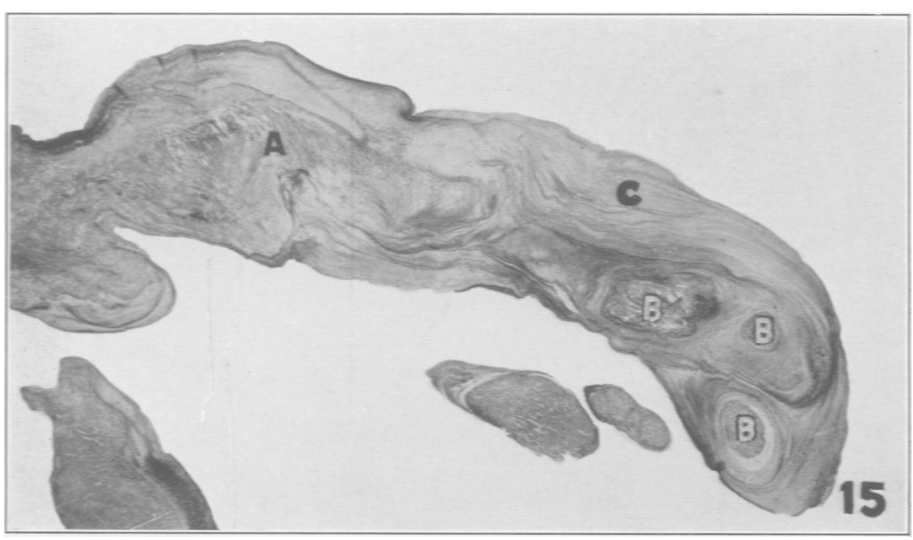
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