Clinicopathological Study on the Thickening of Parietal Endocardium in the Adult Heart

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Careful examination of unselected 117 autopsied hearts revealed various degrees of pathological parietal endocardial thickening in 74% of them. A new classification of the pathological thickening of parietal endocardium is proposed. From the morphological standpoint, it is divided as (1) structureless fibrosis, (2) fibroelastosis, (3) thickening of the subendothelial layer, (4) thickening of all of the 5 layers (elastomyofibrosis), (5) thickening of the subendocardial layer, and (6) false thickening. From their pathogenesis, it is divided as (I) thrombogenic, (II) hypertrophic and/or hyperplastic, (III) exudative, edematous or deposited, and (IV) congenital. Endocardial fibrosis due to mechanical stimulation consists of the jet lesion which is divided as structureless scar and endocardial pocket, and the elastomyofibrosis. The endocardial fibroelastosis is concerned partly with cardiac dilatation. The endocardial change due to metabolic disturbance exhibits subendocardial edema or fibrosis (endocardosis).

SINCE Nagayo’s study concerning the normal structure of parietal endocardium,11-23 a few systematic research on pathological endocardial thickening has been published.37-41,10 Recently, the unusual form of heart disease with a marked endocardial fibrosis, for example, endocarditis parietalis fibroplastica (Löffler41), endomyocardial fibrosis (Davies37), diffuse endomyocardial sclerosis (Lynch and Watt39), foetal endocardial fibroelastosis (Weinberg and Himelfarb40) and so on, has drawn many attentions concerning the pathogenesis of this kind of disease. The present study was undertaken on the endocardial thickening with clear pathogenesis which encountered commonly at necropsy, in order to clarify the endocardial lesion with unknown pathogenesis. From the analysis of the materials, new classification of endocardial fibrosis based on morphology and pathogenesis was proposed and some clinicopathological consideration about miscellaneous form of endocardial lesions was made with the purpose of gaining a clue to find out some of the factors playing a role in the pathogenesis of unknown endocardial fibrosis.

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**Material and Method**

The hearts from 117 consecutive, unselected autopsied cases were carefully examined. All were from the Second Department of Internal Medicine, University of Tokyo, between 1958 and 1960. They consisted of 77 males and 40 females, whose ages ranged from 13 to 81 years, with an average of 47.8 years. The materials consisted of 42 cases of cardiac disease, 11 of chronic nephritis, 17 of liver cirrhosis, 22 of malignant tumor, 9 of pulmonary disease, 6 of blood disease and 10 of others. The hearts were weighed after removal of the extracardiac tissue and the aorta above the aortic valve. The thickness of the valve leaflets were measured by micrometer. The degree of atherosclerosis of aorta and coronary arteries was described according to Gore’s grading,¹¹ and atherosclerosis index was calculated. The volume of each chambers of the heart was estimated by ballooning method* after its fixation in Formalin. The grade of parietal endocardial thickening was macroscopically classified as: none (−), slightly opaque (+), moderately white with not elevated surface (++), markedly white with elevated surface (+++), and extremely thickened scar formation (++++). The distribution of these changes was described geographically in the cardiac map¹² which had I to XIV divisions as longitude, and 1 to 3 divisions for both ventricles and 1’ to 2’ divisions for both atria as latitude, showing geographically developed endocardial surface by Goode’s method (Fig. 1). Tissue slices were taken from interventricular septum with horizontal cut at 2 cm. beneath the semilunar valves, including endocardium of the outflow tract of both ventricles, from anterior and posterior wall of both ventricles with vertical cut including papillary muscles, from posterior wall of both atria, as well as from areas with abnormal endocardial thickening. The tissue specimen was fixed in Formalin, and was embedded mostly in paraffin or partly in carbowax, and the sections were prepared in the usual manner. They were stained with hematoxylin-eosin, Mallory’s azan or Masson’s trichrome, and Weigert-van Gieson’s technique for elastica, smooth muscle and collagen. PAS and Sudan III stain were also applied whenever it was needed.

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* A method for volume estimation of the heart. Water is injected into a balloon which fulfills arbitrary cavity of the heart. The volume of the water indicates the volume of lumen of the heart.
RESULTS

(1) Normal parietal endocardium: From 27 cases with macroscopically normal endocardium without cardiac, pulmonary, hypertensive, anemic and hepatic disease, it was proved that physiological thickening of endocardium was observed at the outflow tract and papillary muscles of the left ventricle, the outflow tract and apical portion of the right ventricle and the anterior portion of atrial septum as well as posterior wall of both atria (Fig. 1). These findings have prompted the author to designate this geographical distribution of endocardial thickening as "normal or physiological pattern."

In microscopic examination of the normal endocardium, it became apparent that the thickness of mural endocardium became thicker with age and grossly paralleled the thickness of aortic valvular leaflet (Fig. 2).
normal structure of parietal endocardium has been described in detail by Nagayo. He divided it into 5 layers at the left ventricle and into 4 layers at the both atria (Fig. 3). Fig. 4 shows the thickness of endocardium and that of its individual layer measured microscopically in above mentioned cases. The mean thickness of the normal endocardium was 20 μ at the outflow tract and papillary muscles of the left ventricle, 10 μ at the antero-posterior wall of the left ventricle and the outflow tract and papillary muscles of the right ventricle, 7 to 8 μ at the antero-posterior wall of the right ventricle, 300 μ at the posterior wall of the left atrium and 100 μ at the posterior wall of the right atrium (Fig. 4). The author designated

![Diagram showing physiological distribution of parietal endocardial thickness.](image)

the endocardium which had these 5 or 4 layers and normal thickness, as "normal histological type" of the endocardium.

(2) Jet lesion: So called jet lesion appeared at the parietal endocardium where the jet stream of blood struck, as a result of abnormal intracardiac hemodynamics.

(a) Impact zone of the jet stream with vertical direction: Fig. 5 shows the endocardial scar of 2.2×6 cm. in size and 2 mm. in thickness, at the lateral wall of right ventricle where the jet stream struck with almost vertical direction to the wall through 0.7×0.7 cm. sized interventricular
(a) Endocardial scar in the right ventricle due to jet stream from the ventricular septal defect (arrow mark shows source of jet stream).

(b) Microscopical view of structureless endocardial fibrosis with overlaid thrombus. A few capillary invasion but without elastic proliferation. Azan stain. 40x

septal defect. Histological research of the lesion disclosed a homogenous and structureless fibrosis with red thrombus on its surface. This fibrosis was lost the primary structure of endocardium completely and had a few invasion of capillaries, but neither cellular infiltration nor elastic fiber.

(b) Impact zone of the jet stream with oblique direction: Many cases of valvular disease of the heart had jet streams with oblique direction to the parietal endocardium. For example, the jet stream of aortic regurgitation struck the outflow tract of left ventricle, that of aortic stenosis struck the wall of aorta, that of mitral insufficiency struck the posterior wall or vertex of left atrium, that of mitral stenosis struck somewhere in the left ventricle and that of pulmonary valvular lesions struck the pulmonary artery or the right ventricle. In some of these cases, such as aortic regurgitation and mitral insufficiency, the area of endocardium struck by the jet stream showed fibrotic thickening which had a sickle form and directed with its concavity and sharp limitation towards the source of the jet stream (Fig. 6 (b)). This fibrosis developed a pocket-form fibrosis opening towards the source of the jet stream, and finally a endocardial pocket or pseudovalve of 0.3 to 2 cm in size. Sometimes, multiple pockets were observed (Fig. 7 (a)). In histological examination, the pocket had neither vascularity nor inflammatory sign, and it consisted of looser connective tissue near the surface and denser collagen fibers at the basis in the relatively fresh pocket. In the considerably old pocket, elastic fibers were arranged only near the surface, and took fan-shaped arrangement from
both edges of the cusp. All of the pockets maintained characteristically the primary structure of endocardium beneath almost undamaged elastic layer at the basis (Fig. 7 (b)). Therefore, this type of fibrosis consisted of thickened subendothelial (inner) connective tissue layer. The other cases with relatively weak jet streams had the jet lesions which consisted of
simple subendothelial fibrosis. These lesions showed a localized or patchy thickening of the inner connective tissue layer and had almost normal endocardial structure beneath the elastic layer. The endocardial pockets or subendothelial fibrosis exhibited almost the same feature in both rheumatic and luetic heart diseases.

The incidence of jet lesion is demonstrated in Table I. Among 39 hearts with valvular deformity or abnormal shunt, 87% of total cases and 100% of aortic valvular lesion had jet lesion. In the table, probable jet lesion indicates the fibrosis which may be assumed as the result of jet lesion but the possibility of endocarditis causing this lesion can not be completely ruled out.

(3) Friction zone (Elastomyofibrosis): Macroscopically, whitish thickened endocardium of the outflow tract of the left ventricle appeared in 75% of the heart with persistent hypertension (Fig. 8 (a)). This appeared most markedly at the endocardium on the shoulder of hypertrophied interventricular septum convexed towards the left ventricle. Histological finding of this lesion showed marked hypertrophy and hyperplasia of all of the 5 layers of endocardium (exaggerated normal histological type), especially of the smooth muscle layer (Elastomyofibrosis, Fig. 8 (b)). The geographical distribution of this type of endocardial thickening maintained physiological pattern. The most remarkable thickening of the friction zone was measured up to 300 μ in thickness at the outflow tract and papillary muscles of the left ventricle.

There was apparently significant correlation between the thickness of the smooth muscle layer at the outflow tract of the left ventricle and the maximal blood pressure. Especially close correlation was proved in the hypertensive group with blood pressure of more than 160/100 mm.Hg (Fig. 9).
Fig. 8.
(a) Hypertensive heart disease. Whitish thickening of endocardium at the outflow tract of left ventricle.
(b) Elastomyofibrosis of endocardium. Hypertrophied and hyperplastic smooth muscle layer.
Elastica van Gieson's stain. 100x

* These symbols are common in the following figures.

Fig. 9. Thickness of smooth muscle layer of endocardium and blood pressure.

If the thickness more than 30 μ of the smooth muscle layer was assumed as pathological, 75% of hypertensive group (21/28), 13% of aortic regurgi-
tation (2/16) and 7% of normotensive group (6/73) had the pathological elastomyofibrosis. Especially the heart of the chronic glomerulonephritis with terminal uremia showed a tendency of macroscopically diffuse, whitish and edematous appearance of endocardium. It exhibited elastomyofibrosis complicated with subendocardial edema (endocardosis) in histological finding. The degree of elastomyofibrosis was also related with the grade of hypertrophy of muscle fibers in myocardium. No abnormal finding was discovered in this lesion by PAS or Sudan III stain.

(4) Endokardose or endocardosis: In the case with the persistent general metabolic disturbance, such as liver cirrhosis and uremia, one could frequently discover myocardial degeneration which has been mentioned as Wuhrmann’s Myokardose. The parietal endocardium in such a case with metabolic disturbance characteristically showed a marked edema or invasion of a certain plasma component in the subendocardial space. The highest grade of subendocardial edema was seen in the subacute yellow liver atrophy and uremia (Fig. 10 (b)), and successively increased collagen fibers in the subendocardium were observed in the long standing portal liver cirrhosis (Fig. 10 (a), (c)). The grade of subendocardial edema or fibrosis was fairly well correlated with the lowering of serum albumin level (Fig. 11). The almost same change was observed in the endocardium of both atria in the case with metabolic disturbance, however, in such a case the edematous process was observed not only in subendocardial layer, but even

![Fig. 10. Endocardosis.](image-url)

(a) Liver cirrhosis. Macroscopical view of endocardium of left ventricle.
(b) Liver cirrhosis. Subendocardial edema. Elastica van Gieson’s stain. 100x
(c) Liver cirrhosis. Subendocardial fibrosis. Elastica van Gieson’s stain. 100x
(d) Liver cirrhosis. Marginal villi on the aortic valvular leaflets (A special type of Lambl’s excrescence).
in the inner and median layer of the endocardium itself. PAS and Sudan III stain could reveal no specific abnormality.

The subendocardial edema or fibrosis was frequently accompanied by marginal villiform processus (Lambl’s excrescence) on the noduli arantii of aortic valvular cusps which consisted of deposited or organized fibrin-like substance (Fig. 10 (d)). This type of endocardial changes should be called as “Endokardose or endocardosis”. The geographical distribution of this endocardial change had a certain tendency to be preponderant at the inflow tract of the both ventricle, which was contrary to the normal distribution (Table VI (a)). The incidence of endocardosis was demonstrated in Table II, and was high in liver cirrhosis and uremia.

Table II. Endocardosis

<table>
<thead>
<tr>
<th>Case</th>
<th>Number of cases</th>
<th>Endocardosis</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver cirrhosis</td>
<td>17</td>
<td>16</td>
<td>94%</td>
</tr>
<tr>
<td>Chronic nephritis</td>
<td>11</td>
<td>8</td>
<td>73%</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>9</td>
<td>7*</td>
<td>78%</td>
</tr>
<tr>
<td>Blood disease</td>
<td>6</td>
<td>4</td>
<td>67%</td>
</tr>
<tr>
<td>Malignant tumor</td>
<td>22</td>
<td>6</td>
<td>27%</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>42</td>
<td>7</td>
<td>17%</td>
</tr>
<tr>
<td>Collagen disease</td>
<td>2</td>
<td>(2)**</td>
<td>(100%)</td>
</tr>
<tr>
<td>Others</td>
<td>8</td>
<td>1</td>
<td>12%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>117</td>
<td>51</td>
<td>43%</td>
</tr>
</tbody>
</table>

* Only at right ventricle
** With inflammatory reaction

(5) Endocardial fibrosis resulted from reparative process: Destructed parietal endocardium in myocardial infarction was covered immediately
with thrombus. An organization of the overlaid thrombus was followed by endocardial fibrosis (Fig. 12 (a), (b)). If the overlaid thrombus was too large, a creeping overgrowth of new connective tissue along the surface of thrombus was observed (Fig. 12 (c)). This type of endocardial fibrosis had homogenous proliferation of collagen fiber and had, of course, no primary endocardial structure. An older endocardial scar had few capillaries and no cellular infiltration. In a relatively fresh endocardial

Fig. 12. Reparative fibrosis.
(a) Fresh myocardial infarction. 14 days after the last attack.
(b) Destruction of endocardium due to myocardial infarction. 1 day after the attack. Elastica van Gieson’s stain. 400×
(c) Creeping fibrous tissue on the fibrin thrombus. Elastica van Gieson’s stain. 100×

Fig. 13. Endocardial fibroelastosis.
(a) Old myocardial infarction (arrow mark).
(b) Endocardial fibroelastosis. Elastica van Gieson’s stain. 100×
fibrosis of this type, no increase in elastic fiber was found. On the contrary, in the endocardial fibrosis whose process persisted more than 6 months after the attack of myocardial infarction and was influenced by some distension due to aneurysmal change of the ventricular wall, the proliferation of elastic fibers became marked. In such a case, the elastic fibers were arranged regularly and oriented parallel to the lumen, and the homogenous fibroelastosis was completed (Fig. 13 and Fig. 14 (b)). No endocardial fibro-

![Graphical demonstration of the relationship between the thickness of the elastic layer or fibroelastosis of the parietal endocardium and the left ventricular volume (Fig. 14 (a)), indicates that no marked increase in elastic fiber was seen in the endocardium with normal structure, though a considerable dilatation of the ventricle was present, but that the fibroelastosis became marked and grossly paralleled the dilatation of the ventricle in the previously destructed endocardium.](image)

(a) Thickness of elastic layer or fibroelastosis of endocardium and cardiac dilatation.

(b) Time-factor in the pathogenesis of endocardial fibroelastosis.

elastosis was observed without previous destruction of the endocardium.

The graphical demonstration of the relationship between the thickness of the elastic layer or fibroelastosis of the parietal endocardium and the left ventricular volume (Fig. 14 (a)), indicates that no marked increase in elastic fiber was seen in the endocardium with normal structure, though a considerable dilatation of the ventricle was present, but that the fibroelastosis became marked and grossly paralleled the dilatation of the ventricle in the previously destructed endocardium.

(6) Endocardial fibrosis due to parietal endocarditis: The most popular parietal endocarditis having some possibility to develope endocardial fibrosis was of rheumatic origin. The initial histologic picture was focal mononuclear infiltration or appearance of Ashoff's nodule in the swollen endocardium (Fig. 15). A chance to catch the early stage of this change was so rare, as seen in the present study, that only one case of such was found among 14 cases of rheumatic heart disease. Localized proliferation of the subendothelial connective tissue (Fig. 16) (6/14), the subendocardial fibrosis (5/14), the structureless fibrosis (3/14) and the fibrinoid degeneration or necrosis of the endocardium (3/14) were frequently observed in rheumatic heart disease (Table III). A case with structureless endocardial fibrosis
Fig. 15. Rheumatic endocarditis.

(a) Combined valvular disease. Irregular patchy endocardial thickening of the left ventricle.

(b) Fresh rheumatic parietal endocarditis.
H. E. stain. 400×

Fig. 16. Rhumatic endocarditis.

(a) Mitral stenosis. Diffuse irregular endocardial thickening of the left atrium.

(b) Markedly thickened subendothelial layer with capillary invasion and mononuclear cell infiltration in the deeper layer.
Elastica van Gieson’s stain. 40×

(c) Focal thickening of the subendothelial layer with sparse remnant of the normal structure of endocardium.
Elastica van Gieson’s stain. 100×

that showed a characteristic feature of rheumatic change is demonstrated (Fig. 17 (a)). The endocardium of such a case consisted of a dense
avascular scar with irregularly arranged delicate elastic fibers in the superficial layer and increased capillaries with infiltration of monocytes and hemosiderin-laden histiocytes in the deeper layer (Fig. 17 (a)). This complicated lesion might exhibit a chronic and recurrent nature of rheumatic endocarditis. Above mentioned miscellaneous and complicated types of the endocardial fibrosis of rheumatic origin were commonly seen as localized or patchy fibrosis at the posterior wall of left atrium (Fig. 16) or in the left ventricle (Table III).

In the luetic heart disease, subendothelial fibrosis of the endocardium was frequently observed at the outflow tract of the left ventricle, but it was very difficult to differentiate this change from the jet lesion since the aortic regurgitation was most frequently found in the luetic valvular disease. In 4 cases of such, the endocardial lesions were scattered even beneath the trabeculae carneae or behind the papillary muscles. A few subendocardial fibrosis or structureless fibrosis might also be related with luetic heart disease (Table III).

Diffuse and loose proliferation of the subendothelial connective tissue with scattered lymphocytes in the left ventricular endocardium was observed in 2 cases of subacute bacterial endocarditis (Fig. 17 (b)). Almost similar
but more localized lesion was also found in rheumatic heart disease.

A case with suspected congenital aortic stenosis showed a non-specific parietal endocarditis with diffuse lymphocytic, monocytic and plasma cellular infiltration in the irregularly arranged collagen fibers in the left ventricle (Fig. 17 (c)). A case of acute bacterial endocarditis had several mural vegetations which consisted of localized abscess in the endocardium.

Generally speaking, endocardial thickening due to endocarditis had no significant relationship with myocarditis but rather had some relationship with valvular lesion. If the endocardial fibrosis was a remnant of endocarditis, the fibrosis had to have commonly localized or patchy distribution and miscellaneous histological type with irregularly arranged collagen fibers or elastic fibers. Diagnosis of this type of fibrosis became more rational if there were some chronic or recurrent inflammatory signs in the endocardial fibrosis.

(7) Endocardial fibrosis of miscellaneous origin:

(a) Parietal endocardium of collagen disease other than rheumatic fever frequently appeared whitish. A heart with periarteritis nodosa showed subendocardial cellular infiltration as well as perivascular infiltration. A successive subendocardial fibrosis distributed rather predominantly at the
inflow tract of the left ventricle (Fig. 18 (a)). Almost same process was observed in endocardium of a case with lupus erythematoses.

Fig. 18. Subendocardial fibrosis of miscellaneous origin.
(a) Periarteritis nodosa. Subendocardial cellular infiltration. Elastica van Gieson’s stain. 100×
(b) Interstitial myocarditis. Subendocardial fibrosis with remnant of elastic layer. (This case was from the Medical Examiner’s Office of Tokyo.) Elastica van Gieson’s stain. 400×
(c) Amyloidosis. Subendocardial deposition of PAS positive substance. PAS stain. 400× (This case was from the 3rd Dept. of Int. Med., Univ. of Tokyo.)
(d) Gargoyleism. Subendocardial deposition of special substance. PAS stain. 400× (This case was from the Mitsukosei Hospital.)

(b) A case of giant cellular myocarditis with diffuse subendocardial fibrosis which was assumed as a result of subendocardial inflammation was also observed (Fig. 18 (b)).
(c) Amyloidosis (Fig. 18 (c)) and gargoyleism (Fig. 18 (d)) had some special substance deposited in the subendocardial connective tissue and caused successive fibrosis. In these hearts, the parietal endocardium appeared macroscopically whitish.
(d) Leukemic infiltration into the parietal endocardium was accompanied by a diffuse fibroplastic process, and occasionally it might resemble endocarditis parietalis fibroplastica (Löffler) (Fig. 19 (a), (b)).
(e) Subendocardial bleeding was seen in cases of aplastic anemia (Fig. 19 (c)), leukemia (2/6), malignacy (5/22), liver cirrhosis (2/17) and heart disease (1/25), up to 8.5% of the total cases studied.
(f) A specific heart disease with marked diffuse endocardial fibrosis such as endocardial fibroelastosis', endocarditis parietalis fibroplastica, endomyocardial fibrosis and endomyocardial sclerosis will be discussed in the next report.
Fig. 19. Heart of blood disease.
(a) Monocytic leukemia. Whitish irregular thickening of endocardium of the left ventricle.
(b) Diffuse leukemic infiltration in the endocardium with increased collagen fibers. Elastica van Gieson’s stain. 100× (This case was from the Dept. of Int. Med. and Physiotherapy, Univ. of Tokyo.)
(c) Aplastic anemia. Bleeding into the endocardium. Elastica van Gieson’s stain. 40×

(8) False thickening of the parietal endocardium: Marked atrophy of the myocardium brought about a waving of endocardium, selectively of

Fig. 20. False thickening of endocardium.
(a) Sarcoma. Whitish discoloration of the outflow tract of left ventricle.
(b) Marked waving of elastic layer of the endocardium. Elastica van Gieson’s stain. 100×
the elastic layer (Fig. 20 (b)). The endocardium appeared relatively thickened up to 100 μ, but it was not a real thickening. The geographical distribution of the false thickening of the endocardium showed the normal pattern, and this type of endocardial change could be recognized even macroscopically by the feature of the fine wrinkles on the endocardial surface (Fig. 20 (a)). The weight of the hearts with the false thickening of the endocardium (231 Gm.) was statistically smaller than that of the hearts with the normal endocardium (268 Gm.). As a matter of fact, this phenomenon was most frequently observed in the hearts of malignant tumor with cachexia (55%, 12/22).

Presentation of a New Classification of the Abnormally Thickened Parietal Endocardium—

Classification of the abnormal endocardium can be made from the morphological standpoint and the causal-genetic standpoint.

A. The classification of parietal endocardial thickening on the morphological basis (Fig. 21):

1. structureless fibrosis.
   (a) homogenous type.
   (b) irregular type.
2. fibroelastosis.
   (a) homogenous type.
   (b) irregular type.
3. thickening of subendothelial layer.
4. thickening of all of the 5 layers...elastomyofibrosis.
5. thickening of subendocardial layer.
6. false thickening.

B. The classification on the causal-genetic basis:
1. thrombogenic type.
(i) postnecrotic.
(ii) inflammatory.
(iii) miscellaneous.

(II) hypertrophic and/or hyperplastic type.
(i) mechanically stimulated.
(ii) abnormally reacted.

(III) exudative, edematous or deposited type.
(i) inflammatory.
(ii) due to altered membrane permeability.
(iii) related to metabolic disturbance.
(iv) due to deposition of some special substance.

(IV) congenital type.

Table IV. Correlation between Morphological and Genetic Classification of Endocardial Fibrosis

<table>
<thead>
<tr>
<th>Morphological classification</th>
<th>Causal-genetic classification</th>
<th>Process to fibrosis</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibroclastosis</td>
<td></td>
<td>Induced from any type of fibrosis by dilatation of chamber or distension of endocardium.</td>
<td>Endocarditis. Leukemic infiltration.</td>
</tr>
<tr>
<td>Subendothelial fibrosis</td>
<td>altered reactivity</td>
<td>Altered sensitivity and reactivity of endothelium and subendothelial layer.</td>
<td>Cardiac dilatation. Ventricular aneurysm.</td>
</tr>
<tr>
<td>Subendocardial fibrosis</td>
<td>mechanical stimulation</td>
<td>Acellular slowly progressive fibrosis successive from edema or deposition of special substance. Subendocardial inflammation.</td>
<td>Allergic endocarditis. SBE. Rheumatic endocarditis.</td>
</tr>
</tbody>
</table>

Correlation between these 2 types of classification is shown in Table IV. When these 2 types of classification were applied to the endocardial thickening, many clinico-pathological problems on the previously described intracardiac lesion might be resolved.

(1) The structureless endocardial fibrosis might usually be resulted from
organization of mural thrombus on destructed endocardium. Myocardial
infarction (postnecrotic), endocarditis (inflammatory) and impact of strong
jet stream (miscellaneous) destructed normal endocardium, and thereafter
the thrombogenic fibrosis of the endocardium occurred. Therefore, the
structureless endocardial fibrosis was considered to exhibit the terminal
stage of reparative process of destructed endocardium. In the initial stage,
the fibrosis had vascular invasion and cellular infiltration, but in the later
stage, it transformed to the homogenous fibrosis without vascularisation or
cellular infiltration. About the fibrosis resulted from endocarditis, the
diagnosis could be made easily in the initial stage due to its marked
irregularity of arrangement of collagen fibers, but it became difficult to
make diagnosis in the later stage since the irregular collagenosis was taken
place by homogenous non-specific structureless fibrosis. The same tendency
was observed in the case of myocardial infarction. Extremely complicated
endocardial fibrosis was observed frequently in the case with chronic re-
current endocarditis such as rheumatic fever. In such a case, as demon-
strated in Fig. 17 (a), regularly arranged collagen fibers were mingled with
irregularly arranged ones with inflammatory sign.

The structureless fibrosis might be partly resulted from other causes
than the thrombogenic origin. When the apparently normal superficial
layer of subendocardial fibrosis degenerated and disappeared, the structure-
less endocardial fibrosis might be completed from the subendocardial
fibrosis. The structureless type of fibrosis might be resulted from mis-
cellaneous types of endocardial lesions in the terminal stage. The author
had, however, no experience that subendothelial fibrosis or elastomyofibrosis
transformed to the structureless fibrosis.

(2) Typical endocardial fibroelastosis was seen in the foetal endocardial
fibroelastosis which was assumed to be of congenital origin. Acquired
fibroelastosis was considered to have developed from the structureless
fibrosis under certain special condition. When rhythmical distention
has been acting on the endocardial scar tissue for sufficiently long time
such as more than 6 months, increased elastic fibers were found in the
endocardial fibrosis (Fig. 13 (b), Fig. 14). In fact, this type of fibroelastosis
appeared remarkably in the wall of ventricular aneurysm or in the wall
of markedly dilated ventricle. Much attention should be paid to the
fact that the fibroelastosis was established when the normal structure of
endocardium was lost. But a few exception was observed, too. The increase
in elastic fiber was sometimes recognized in the subendocardial fibrosis if
it persisted for a sufficiently long time. Whether the fibroelastosis was
homogenous or not could be determined by the presence or absence of
recurrent distortion or destruction of the established fibroelastosis. Much
of the fibroelastosis showed homogenous type with regular arrangement of
elastic fibers oriented parallel to the lumen, but a few instances with chronic
recurrent endocarditis such as rheumatic fever (Fig. 17 (a)) had the distorted
or split elastic fibers. If sufficiently long term elapsed from the establish-
ment of fibroelastosis, irregular type of the fibroelastosis might transform
to homogenous and regular type. The time factor to establish the fibro-
elastosis is indicated in Fig. 14 (b). It needed more than 6 months to
establish the fibroelastosis either from the case of myocardial infarction or
from the case of endocarditis. As a special instance, some elastic fibers
increased only in the superficial layer of the endocardial pocket. It was
considered that the site where elastic fiber increased received the strongest
strain from jet stream.

(3) The subendothelial fibrosis consisted of 2 types; the localized type
and diffuse type. The endocardial pocket (Fig. 7) and endocardial fibrosis
due to localized endocarditis belonged to the former (Fig. 16). In the case
of subacute bacterial endocarditis, the diffuse type of subendothelial fibrosis
was observed (Fig. 17 (b)). The pathogenesis of the subendothelial fibrosis
was usually considered to be thrombogenic. The thrombus deposited on the
slightly damaged endocardium which maintained the normal structure at
the basis beneath the elastic layer, then, the thrombus was organized and
the thrombogenic fibrosis appeared. The trivial damage of superficial
endocardium would be due to the impact of jet stream with oblique direc-
tion to the wall, endocarditis of slight degree and hypersensitive state of
endothelium resulted from allergy or other chemical stimulation. Fig. 6 (a)
showed fibrin deposition on the apparently normal endocardium. In such
cases, the abnormal coagulability of blood might also play a role to build
up the subendothelial fibrosis.

An attention should be given to primary overgrowth of subendothelial
connective tissue due to slight mechanical stimulation to the subendothe-
lial mesenchymal cells or hypersensitive reaction of them, as a part of
pathogenesis of this type of endocardial fibrosis.

(4) The endocardial elastomyofibrosis maintained the 5 layers of the
normal endocardium, but they were markedly hypertrophic or hyperplastic.
Among them, the smooth muscle layer was thickened most remarkably,
and its thickness had a correlation with previous hypertension (Fig. 9).
The pathogenesis of this type of endocardial thickening might be concerned
with an increased intracardiac pressure and a friction effect of ejecting blood
stream from the left ventricle. But it appeared that the elastomyofibrosis
was neither related to previous endocardial destruction nor to thrombogenic
origin in its pathogenesis. The friction effect of blood stream might cause a
strain in the endocardium, and brought about hypertrophy and hyperplasia
of smooth muscle layer as well as other layers. Anemic state might promote
this change. These findings have prompted the author to designate this
elastomyofibrosis as “friction zone”.

The mechanical stimulation of blood stream might cause several types
of endocardial fibrosis. The impact of strong jet stream with vertical direction to the wall was considered as a cause of the structureless endocardial fibrosis. That with oblique direction caused the endocardial pocket and the simple subendothelial fibrosis. These 2 types of mechanical lesion were mentioned as "jet lesion." The friction effect of jet stream with parallel direction to the wall caused "friction zone."

(5) The subendocardial fibrosis was assumed as a terminal form resulted from miscellaneous changes in the subendocardial space. Inflammation, exudative process, edema or invasion of a plasma component and deposition of some special substance might be main causes of subendocardial fibrosis. The subendocardial inflammation was observed usually in rheumatic heart disease and periarteritis nodosa. Abnormal membrane permeability due to anoxia of endocardium might be responsible to a subendocardial exudative process without cellular reaction. Cases with general metabolic disturbance, such as liver cirrhosis and uremia, had marked subendocardial edema. Amyloidosis, gargoylism and other disease with metabolic abnormality exhibited subendocardial deposition of special substance or metabolite, respectively. The successive fibrosis from these miscellaneous changes except that due to endocarditis, was considered as "endocardosis."

Whether subendocardial myocardial degeneration or necrosis was responsible for subendocardial fibrosis or not, was difficult to determine. So-called subendocardial infarction usually preserved several layers of muscle fibers right beneath the endocardium, and in this case, overlaid endocardium commonly maintained the normal structure. When the destruction of myocardium involved overlaid endocardium, the structureless endocardial fibrosis or fibroelastosis appeared. On the other hand, myocardial degeneration due to metabolic disturbance had no special preponderance in the myocardium just beneath the endocardium. Therefore, subendocardial fibrosis which maintained normal endocardial structure in the superficial layer, would be rarely compatible with subendocardial myocardial fibrosis. Generally speaking, the subendocardial myocardial fibrosis was usually accompanied by the structureless fibrosis or fibroelastosis of endocardium.

**Considerations about Several Factors Concerning the Degree of the Endocardial Thickening**

Above mentioned consideration was limited to the qualitative aspect of 5 types of endocardial thickening. The quantitative appraisal of endocardial thickening is tried in this chapter.

(1) The role of anemia to endocardial thickening was disclosed in Fig. 22. Simple anemia was not always incompatible with normal endocardium. There were 9 cases with normal endocardium in the severe anemic group with hemoglobin index of less than 60%. However, the thickening of pathological endocardium was more remarkable in the anemic group. Therefore,
Blood Hemoglobin (Sahli-Index)

* These symbols are common in the following figures.

Fig. 22. Endocardial thickening and anemia, excluding endocardial thickening due to endocarditis, postnecrotic fibrosis and jet lesion.

It might be assumed that anemia was a factor to accelerate the thickening process of pathological endocardium, above all, in the endocardiosis and elastomyofibrosis. But, it was difficult to determine which was effective on the endocardial thickening, anemia or metabolic disturbance, since the grade of anemia might be a reflection of the severity of metabolic disease.

(2) No apparent correlation between heart weight and thickness of endocardium was proved in general, but the hypertrophied heart of more than 500 Gm. never had normal endocardium. A gross relationship between heart weight and the grade of elastomyofibrosis was recognized among the heart of the hypertensive group, in the range of 300 Gm. to 600 Gm. (Fig. 23 (a)).

(3) Cardiac dilatation, estimated as the volume of left ventricle, had no significant relationship with thickening of endocardium. On the other
hand, the left ventricular dilatation of more than 40 ml. was incompatible
with normal endocardium (Fig. 23 (b)). The endocardial elastomyofibrosis
and fibroelastosis was proved frequently in the dilatation group.

(4) Fig. 24 (a), indicates relationship between coronary sclerosis index
and thickness of left ventricular endocardium. The coronary sclerosis
showing more than 30 in the sclerosis index was incompatible with normal
endocardium, and the same evidence between endocardial thickening and
the aortic sclerosis index of more than 40 was recognized. It was suggested
that endocardial fibrosis was related with myocardial insufficiency resulted
from coronary sclerosis as well as with myocardial infarction.

(5) Apparently significant relationship between myocardial fibrosis and
endocardial thickening is shown in Fig. 24 (b). The degree of myocardial
fibrosis was divided as: none (−), mild (+), moderate (++), severe (+++), or
extremely severe (+++). The degree of myocardial fibrosis was significantly
parallel with endocardial thickening. Moreover, no normal endocardium
was present in the group of myocardial fibrosis of more than grade (++),
and the structureless endocardial fibrosis or fibroelastosis was frequently
observed in the extremely severe myocardial fibrosis.

(6) The thickness of pathological endocardium commonly had no marked
correlation with thickness of the aortic valvular leaflet except the thickness
of elastomyofibrosis.

(7) Thrombogenic type was most frequently observed in the pathogenesis
of endocardial fibrosis. The author examined macroscopically thrombus
formation on the parietal and valvar endocardium. The thrombosis was
Table V. Incidence of Thrombus Formation on the Endocardium

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of cases</th>
<th>Endocardial thrombosis</th>
<th>Incidence of thrombosis</th>
<th>Site of thrombosis*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sclerotic heart disease</td>
<td>17</td>
<td>6</td>
<td>35%</td>
<td>Left Vent. 6 Right Vent. 0 Left Atr. 1 Right Atr. 0 Valve M: Mitral A: Aortic T: Tricuspid M + A 3* T 1</td>
</tr>
<tr>
<td>Hypertensive b. d.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valvular heart d.</td>
<td>25</td>
<td>12*</td>
<td>48</td>
<td>5* 1* 4 1</td>
</tr>
<tr>
<td>Chronic nephritis</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>9</td>
<td>3</td>
<td>33</td>
<td>1 0 0 0 2</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>17</td>
<td>2**</td>
<td>12</td>
<td>1** 1 1 1</td>
</tr>
<tr>
<td>Malignant tumor</td>
<td>22</td>
<td>6</td>
<td>27</td>
<td>2 1 3 4 A 1</td>
</tr>
<tr>
<td>Blood disease</td>
<td>6</td>
<td>1</td>
<td>17</td>
<td>1 0 1 1 0</td>
</tr>
<tr>
<td>Others</td>
<td>10</td>
<td>2</td>
<td>20</td>
<td>2 1 0 0 0</td>
</tr>
<tr>
<td>Total</td>
<td>117</td>
<td>32</td>
<td>27%</td>
<td>18 4 10 9 11</td>
</tr>
</tbody>
</table>

* Including 2 cases of subacute bacterial endocarditis.
** Including 1 case of acute bacterial endocarditis due to Klebsiella-septicemia.

observed in 27% of a total of 117 cases. Among them, there were 12 cases of valvular heart disease including 2 cases of subacute bacterial endocarditis, 4 with coronary sclerosis, 1 with atypical verrucous endocarditis and 14 with non-bacterial thrombotic endocarditis. The non-bacterial thrombotic endocarditis was observed chiefly in the malignant tumor group and other wasting diseases (Table V), and 12 out of 14 cases of this group had thrombus-formation on the parietal endocardium.

(8) Table VI (a) showed that the geographical distribution of thickened endocardium was characteristically concerned with the histological type of endocardial fibrosis. Most types of fibrosis had a preponderant site of thickening at the outflow tract of both ventricles. However, the subendocardial fibrosis that consisted chiefly of endocardosis, exhibited frequently preponderance of inflow tract or equality of inflow and outflow tract of both ventricles (50% in the left ventricle, and 80% in the right ventricle). Endocardial fibroelastosis and structureless fibrosis had essentially no preponderant site.

(9) The incidence of pathological endocardial thickening was 74% among
Table VI. (a) Relationship between Histological Type and Geographical Distribution of Endocardial Thickening

<table>
<thead>
<tr>
<th>Endocardial thickening:</th>
<th>0 &gt; I*</th>
<th>0 = I</th>
<th>0 &lt; I</th>
<th>0 &gt; I</th>
<th>0 = I</th>
<th>0 &lt; I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal or Border line case</td>
<td>32</td>
<td>5</td>
<td>0</td>
<td>17</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Subendocardial fibrosis</td>
<td>47</td>
<td>18</td>
<td>4</td>
<td>10</td>
<td>25</td>
<td>12</td>
</tr>
<tr>
<td>Elastomyofibrosis</td>
<td>28</td>
<td>0</td>
<td>0</td>
<td>21</td>
<td>53</td>
<td>26</td>
</tr>
<tr>
<td>Subendothelial fibrosis</td>
<td>16</td>
<td>1</td>
<td>1</td>
<td>88</td>
<td>100</td>
<td>6</td>
</tr>
<tr>
<td>Structureless fibrosis</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>67</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Fibroelastosis</td>
<td>7</td>
<td>0</td>
<td>3</td>
<td>57</td>
<td>100</td>
<td>43</td>
</tr>
</tbody>
</table>

* 0 > I; predominant at outflow tract.
  0 = I; equal at outflow and inflow tract.
  0 < I; predominant at inflow tract.

(b) Pathological Thickening of Parietal Endocardium
Its Standard and Incidence

<table>
<thead>
<tr>
<th>Case</th>
<th>Number of cases</th>
<th>Pathological thickening of endocardium</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive, sclerotic heart d.</td>
<td>17</td>
<td>16</td>
<td>94%</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>25</td>
<td>24</td>
<td>96%</td>
</tr>
<tr>
<td>Chronic nephritis</td>
<td>11</td>
<td>9</td>
<td>82%</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>17</td>
<td>12</td>
<td>70%</td>
</tr>
<tr>
<td>Malignant tumors</td>
<td>22</td>
<td>10</td>
<td>46%</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>9</td>
<td>9</td>
<td>100%</td>
</tr>
<tr>
<td>Blood disease</td>
<td>6</td>
<td>2</td>
<td>33%</td>
</tr>
<tr>
<td>Others</td>
<td>10</td>
<td>6</td>
<td>60%</td>
</tr>
<tr>
<td>Total</td>
<td>117</td>
<td>88</td>
<td>74%</td>
</tr>
</tbody>
</table>

the total of 117 examined hearts with various diseases, if the thickness more than 100 µ at the left ventricle, more than 50 µ at the right ventricle, more than 1,000 µ at the left atrium and more than 500 µ at the right atrium in the parietal endocardium were assumed as standard of pathological thickening of endocardium (Table VI (b)).
COMMENT

It is generally considered that endocardial fibrosis may occur from miscellaneous origin. It has been classically divided to be thrombogenic, functional-elastic and inflammatory by Hertel\(^1\),\(^2\) or to be functional and non-functional as well as to be reparative and compensatory by Fisher and Davis.\(^3\) From another standpoint, primary and secondary endocardial sclerosis has been classified.\(^4\) However, most of these classic classifications were too incomplete to analyse endocardial thickenings resulted from various causes.

The author proposed a new classification on the basis of morphology and pathogenesis, and discussed the relationship between these 2 types of classification.

(1) The jet lesion has been classically described by Saphir,\(^1\) Hellerstein\(^5\) and Edward\(^6\) as "endocardial pocket" or "pseudocusp". The pathogenesis of the endocardial pocket has been considered as primary proliferation of subendothelial connective tissue. Mechanical stimulation such as the impact of the jet stream irritated the surface of endocardium, and caused proliferation of collagen fibers followed by increased elastic fibers or even smooth muscles probably developed from mesenchymal cells in the subendothelial layer.\(^7\) The pocket-form of this lesion was dependent on the direction of the jet stream. Therefore, the systolic and diastolic type of pocket was described by Saphir.\(^8\) Less attention has been paid to the jet lesion other than the endocardial pocket.

The author observed the structureless endocardial scar with overlaid organizing thrombus as a jet lesion (Fig. 5). It was sometimes very difficult to differentiate this lesion from the remnant of endocarditis, especially in luetic heart disease. The pathogenesis of this endocardial scar might be thrombogenic. The organization of the thrombus which deposited on the endocardium damaged by the impact of the jet stream, might develop to the homogenous endocardial scar. The endocardial pocket could be found only in the case of aortic regurgitation and mitral insufficiency. This exhibited that the endocardial pocket needed not only the oblique direction of the jet stream but a considerable pressure gradient between two chambers for its pathogenesis. In the initial stage of this lesion, organizing fibrin thrombus was observed on the apparently normal endocardium, with sharp limitation towards the source of jet stream (Fig. 6). In the later stage, the superficial layer of the endocardial pocket consisted of looser connective tissue and the basal layer had dense collagen tissue, and sometimes fibrin thrombus on the surface of the pocket was also observed (Fig. 7). In the terminal stage, the endocardial pocket consisted of homogeneous collagen fibers and increased elastic fibers appeared in the superficial layer. The normal elastic layer was always present at the basal layer of
the pocket in all of the examined cases. These findings prompted the author to consider the pathogenesis of this lesion is due to thrombogenic origin. Neither vascular invasion nor cellular infiltration in this lesion was compatible with thrombogenic origin if the pocket was sufficiently old. Even the fibrosis of inflammatory origin showed sometimes homogenous structureless scar, if it persisted sufficiently long time. The increase in elastic fibers in the superficial layer of the pocket exhibited a new formation of elastic fibers in the area receiving the strongest strain, and was compatible with thrombogenic origin. Therefore, the author considered that thrombogenic origin might be playing main role in establishing the endocardial pocket, but the simple overgrowth of the connective tissue might also play a role occasionally. The simple hyperplasia of the subendothelial connective tissue layer was observed as a jet lesion in the area where the weak jet stream struck with either vertical or oblique direction. Usually this lesion was not limited so sharply but showed rather diffuse fibrosis. The pathogenesis of this lesion was considered as thrombogenic origin or simple overgrowth of subendothelial layer.

(2) Fisher and Davis has considered that the endocardial elastomyofibrosis might exhibit a functional or compensatory endocardial thickening due to mechanical stimulation and it might be related to cardiac hypertrophy or dilatation. The pathogenesis of this lesion was assumed to be due to a persistent hypertension, mechanical irritation or friction effect of ejecting blood steam as well as sclerosing process similar to the intimal sclerosis of vessels.

The correlation between the degree of elastomyofibrosis and the degree of previous hypertension was more strict than that between the elastomyofibrosis and cardiac hypertrophy or dilatation (Fig. 9). The heart weight and ventricular volume which indicated a gross correlation with the elastomyofibrosis, might be a sort of parameters of hypertension (Fig. 24). The elastic layers in the endocardial elastomyofibrosis exhibited some thickening as well as the smooth muscle layer, but the degree of the former was less closely related to the hypertension than the latter. The pathogenesis of this lesion might be concerned with increased intracardiac pressure and friction effect of ejecting blood. The friction effect was most markedly exhibited at the outflow tract of left ventricle when the interventricular septum was hypertrophied. The “friction zone” has been sometimes applied to the jet lesion, but the author proposed that the “friction zone” should be limitedly applied to the endocardial elastomyofibrosis.

(3) “Endokardose” has been used at first by Lange. He has described Endokardose as subendocardial edema, but has not clarified its pathogenesis. On the other hand, myocardial change due to metabolic disturbance chiefly related to dysproteinemia has been described by Wuhrmann, and it was mentioned as Myokardose. Endocardial change due to general
metabolic disturbance consisted of subendocardial edema or successive fibrosis with peculiar type of Lambl's excrescence on aortic valvular leaflets. The author considers that this endocardial change should be called as "Endokardose or endocardosis". The evidence that there was apparent relationship between subendocardial thickening and serum albumin level (Fig. 11), exhibited that the pathogenesis of endocardosis was related to the disturbance of protein metabolism. The subendocardial edema was more marked in the case with short clinical course such as uremia and the subendocardial fibrosis was more pronounced in cases with long clinical course such as portal liver cirrhosis. The endocardosis had some relation with myocardial degeneration, but no apparent relationship with subendocardial necrosis described by Still and Boulet or with mucopolysaccharide degeneration of myocardium. There was no specific PAS positive substance in the subendocardial space or endocardium itself of the hearts in liver cirrhosis or uremia.

In pulmonary disease such as pulmonary tuberculosis, the subendocardial edema was observed in the right side of the heart. However, it was difficult to decide whether this change was related to metabolic disturbance through pH change of the blood or anoxemia due to dyspnea, or not.

Moderate subendocardial fibrosis appeared in amyloidosis and gargoylism (Fig. 18). Case reports about gargoylism, glycogen storage disease and epiloia with endocardial fibroelastosis have been published. It was suspected that some of them might start with subendocardial deposition of a special substance, developing into successive subendocardial fibrosis, and then the endocardial fibroelastosis was completed by degeneration of the superficial layer which preserved the normal endocardial structure.

A special type of subendocardial fibrosis, moreover, might be established from inflammatory process related to collagen disease (Fig. 18 (a)). It was interesting that the abnormal serum protein fraction appeared in these cases, as well as liver cirrhosis. Miscellaneous inflammatory process in the subendocardial space was frequently followed by subendocardial fibrosis (Table III). In large part of these groups, they were resulted from inflammatory process, but in small part, they might be resulted from endocardosis due to a persistent or repeated decompensated state of original heart disease.

(4) Reparative endocardial fibrosis was most frequently observed by myocardial infarction (postnecrotic). About 50% of myocardial infarction has been reported to have endocardial involvement (Blumer) and hyalinization and calcification in the endocardial fibrosis has been also described (Edmondson and Hoxie). Moreover, a case of diffuse endocardial fibrosis with myocardial infarction had been reported, too. The author recognized that all cases of myocardial infarction involving endocardium had structure-
less endocardial fibrosis and had partly endocardial fibroelastosis.

(5) The typical fibroelastosis was recognized in the foetal endocardial fibroelastosis\(^8\),\(^{31}\) which was called as primary endocardial sclerosis,\(^{32}\) endocardial dysplasia\(^{33}\) and so on. The pathogenesis has been considered mostly as congenital developmental anomaly\(^{31}\) or simple hyperlasia of endocardium\(^8\) but partly as due to anoxia of endocardium,\(^{34}\)\(^{35}\) intrauterine infection, collagen disease\(^{35}\),\(^{36}\) and so on. The discussion in detail on the congenital fibroelastosis will be commented in the next report. The acquired type of fibroelastosis is discussed here. The adult or adolescent form of endocardial fibroelastosis has been reported by Auld,\(^{37}\) Horley,\(^{38}\) Panke\(^{39}\) and Dyson.\(^{40}\) Most of them were accompanied by myocardial fibrosis and some of them were considered as secondary or acquired fibroelastosis. The pathogenesis of them has been asserted as thrombogenic,\(^{40}\) as sclerosing process analogous to the vascular sclerosis\(^{46}\) or as intoxication through lung,\(^{41}\) and other various factors have been considered to be related to the acquired endocardial fibroelastosis. The dilatation factor and time factor were admitted generally as factors to increase elastic fibers in the endocardium, as has already been mentioned in this report (Fig. 14). It was evident that the dilatation of the cavity promoted establishment of the fibroelastosis in the previously destructed endocardium (Fig. 14). A marked dilatation of the cavity might split the normal elastic layer and might establish the fibroelastosis through the structureless endocardial fibrosis. The author indicated that cardiac dilatation was incompatible with normal endocardium, if it increased more than a certain limit (Fig. 23), but in such a case, the pathological endocardium was not always the fibroelastosis. Therefore, it was concluded that the endocardial fibroelastosis was concerned with cardiac dilatation in the pathogenesis, but that the cardiac dilatation did not always bring about the endocardial fibroelastosis.

(6) Rheumatic parietal endocarditis was observed most frequently at the posterior wall of left atrium, as has already been mentioned by von Glahn,\(^{43}\) Thayer\(^{44}\) and Gross.\(^{45}\) Marked fibrous thickening of endocardium with irregular arrangement of collagen fibers and with partly inflammatory signs, has been considered to be characteristic in the chronic recurrent rheumatic endocarditis.\(^{14}\) The author observed various histological types and various geographical patterns of distribution of the endocardial fibrosis in rheumatic heart disease. Among them, localized subendothelial hyperplasia and subendocardial fibrosis were most frequently recognized. The subendothelial hyperplasia might be of thrombogenic origin concerned with slight inflammation in the endothelial layer, and the subendocardial fibrosis might be mostly resulted from subendocardial inflammation such as Aschoff's nodule, granulomatous infiltration or non-specific cellular infiltration,\(^{44}\) but partly from the endocardiosis due to chronic recurrent decompensated state.
The parietal endocarditis of luetic origin has been doubtful in its presence, but a sort of hypersensitive type of luetic endocarditis has been accepted partly. However, it was extremely difficult to differentiate this type of lesion from the jet lesion or the secondary endocardial involvement due to myocardial damage of luetic origin. The diffuse loose subendothelial fibrosis with relatively rich cellular component in the case of subacute bacterial endocarditis might be resulted from thrombogenic origin or simple overgrowth of connective tissue due to hypersensitive or allergic state of the superficial layer of the endocardium. It is interesting to compare it with the Löfler's second case of endocarditis parietalis fibroplastica which was accompanied by a subacute bacterial endocarditis and was assumed to be an allergic nature in the pathogenesis.

(7) There was apparent relationship between endocardial thickening and myocardial fibrosis (Fig. 24 (b)). There were possible 3 courses through which the former and the latter interacted injuriously each other. In the first course, the myocardial insufficiency, which was represented by the degree of myocardial fibrosis, brought about cardiac dilatation, which might cause the secondary endocardial thickening. Fig. 23 (b) showed the evidence that the cardiac dilatation more than a certain limit was incompatible with normal endocardium. By the way, the structureless endocardial fibrosis might develop the endocardial fibroleastosis which had gross correlation with cardiac dilatation. So, at least a part of endocardial thickening such as a secondary or compensatory type might be related to the myocardial insufficiency through cardiac dilatation. In the second course, the same factor that caused myocardial fibrosis, might act upon the endocardium simultaneously, and it might result in the endomyocardial fibrosis. When the myocardial infarction involved the endocardium, the reparative process might establish the structureless endocardial scar. In the third course, the primary endocardial thickening especially due to thrombogenic origin, might cause occlusion or stenosis of the vascular system communicating between myocardium and cardiac lumen, such as thebesian vein and arterioluminal anastomosis. Such a case that showed this evidence, has been reported by Flynn. The primary endocardial changes might cause subendocardial ischemia and successive fibrosis, because subendocardial muscle fibers received blood supply from cardiac lumen. However, in the most cases with endocardial thickening myocardial damage was not always localized in subendocardium, but was scattered in median or outer layer of myocardium. Therefore, the most cases of endocardial thickening were related to myocardial damage as the compensatory (secondary) and reparative process. The case with primary endocardial sclerosis and secondary myocardial fibrosis, was supposed to be rare. The author showed the evidence that the heart weight, cardiac dilatation and coronary sclerosis were incompatible with normal
endocardium if they increased more than a certain limit (Fig. 23, 24). This evidence might mean a secondary endocardial damage through myocardial insufficiency due to anoxia or hypertrophy of muscle fibers.

(8) Though anoxia of endocardium has been repeatedly insisted as a factor of pathogenesis of endocardial fibrosis, yet severe anemia might be compatible with normal endocardium (Fig. 22). The degree of pathological thickening of endocardium, on the other hand, appeared to be promoted by anemia. Therefore, the anemia might be a promoting factor of pathological endocardial thickening, but not a essential factor to establish endocardial fibrosis.

(9) On the pathogenesis of various types of endocardial fibrosis including a specific endocardial disease (Löffler,4 Fossel,6 Davies7 et al.), the thrombogenic origin was most frequently observed. But few attention has been paid to the thrombus formation on the parietal endocardium. The author observed 14 cases with non-bacterial endocardial thrombosis among a total of 117 cases. About this type of thrombosis which has been considered as a terminal phenomenon of wasting disease,5 previous description4 was limited only to valvular thrombosis. The author recognized mural thrombosis in 12 out of 14 cases of non-bacterial endocardial thrombosis. But, it is not clear, whether this type of thrombosis plays a certain role in establishing the parietal endocardial thickening or not.

(10) The geographical distribution of the parietal endocardial fibrosis had a characteristic feature by its histological type. Most of the endocardial fibrosis in left ventricle had a preponderant site at the outflow tract, but the endocardial fibrosis due to endocardosis had, on the contrary, almost equal grade of thickening at the outflow tract and at the inflow tract, or in part, somewhat preponderance of the inflow tract (Table VI (a)). The same tendency was observed at the right ventricle. It was very interesting to remember Davies' description that the strict limitation of endocardial thickening was seen at the inflow tract of both ventricles in his endomyocardial fibrosis in Uganda which was assumed to be concerned with nutritional disturbance in the pathogenesis.

As far as the pathological endocardial thickening is concerned, one must show exactly its localization or distribution and the type of the structural changes in its components, because there is the physiological endocardial thickening, which varies considerably in each case.

(11) The incidence of the pathological parietal endocardial thickening has been reported to be extremely low such as 0.2% among 11,045 autopsied cases4 or 4 among 115 cases with chronic endocarditis,2 on the other hand, the other author has reported its considerably high incidence up to 60% among 109 autopsied hearts.3 In the present study, the pathological thickening of parietal endocardium was found at a very high incidence up to 74% among 117 unselected autopsied hearts.
Severe and diffuse endocardial thickening might show a peculiar clinical syndrome mentioned as “parietal endocardial thickening syndrome” and the author will discuss the clinical problems in cases with markedly thickened endocardium in the next report.

**SUMMARY**

Macroscopical and microscopical examination of 117 unselected autopsied hearts revealed various degrees of pathological parietal endocardial thickening in 74% of them. The physiological thickening of the normal parietal endocardium was determined as 20 μ at the outflow tract and papillary muscles of the left ventricle, as 10 μ at the inflow tract of the left ventricle, the outflow tract and papillary muscles of the right ventricle, as 7 μ at the inflow tract of the right ventricle, as 300 μ at the posterior wall of the left atrium and as 100 μ at the posterior wall of the right atrium. The parietal endocardium had a tendency to increase its thickness with age.

A new classification of the pathological thickening of parietal endocardium which was made on the morphological and causal-genetic basis was proposed:

A. Morphological classification.
   1. structureless fibrosis.
   2. fibroelstosis.
   3. thickening of subendothelial layer.
   4. thickening of all of the 5 layers.
   5. thickening of subendocardial layer.
   6. (false thickening.)

B. Causal-genetic classification.
   I. thrombogenic type.
   II. hypertrophic and/or hyperplastic type.
   III. exudative, edematous or deposited type.
   IV. congenital type.

The correlation between these 2 types of classification revealed the following evidences:

(1) The endocardial fibrosis resulted from mechanical stimulation of the blood stream consisted of the jet lesion and the friction zone. The former was divided into 2 types and was commonly of thrombogenic origin. The impact of strong jet stream with vertical direction to the wall caused the structureless endocardial scar. On the other hand, the impact of jet stream with oblique direction caused the endocardial pocket or subendothelial fibrosis. The friction zone preserved all of the 5 layers of endocardium, but they were markedly hypertrophied and hyperplastic (Elastomyofibrosis). The pathogenesis of the friction zone was concerned with friction effect of
the blood stream directed parallel to the wall and was related strictly with the persistent hypertension.

(2) The endocardial change due to general metabolic disturbance, exhibited the subendocardial edema or fibrosis (endocardosis), and the degree of this change correlated with the lowering of serum albumin level.

(3) The endocardial fibrosis due to endocarditis showed various histological types, and was mainly circumscribed fibrosis. Subendothelial fibrosis, subendocardial fibrosis or structureless fibrosis were frequently observed. They showed characteristically the irregular arrangement of collagen fibers with chronic inflammatory process.

(4) The myocardial infarction was frequently accompanied with the structureless endocardial scar (reparative fibrosis).

(5) The acquired endocardial fibroelastosis was developed from the fibrosis which lost the primary structure under a certain condition that consisted of mechanical distention and sufficiently long clinical course of more than 6 months.

(6) There was apparent relationship between the grade of endocardial thickening and that of myocardial fibrosis.

(7) The geographical distribution of the endocardial thickening showed commonly the preponderance at the outflow tract of both ventricles. However, some of the endocardosis had a tendency to be preponderant to the inflow tract of both ventricles.

(8) Increase in the heart weight, the grade of cardiac dilatation and the grade of coronary sclerosis was incompatible with the normal endocardium, if they increased more than a certain limit.

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References

   ——: Arch. Path. 16: 315, 1933.