Symposium on Coronary Sclerosis

These papers report the results of the study assigned by the Japanese Circulation Society, and were presented at the 22nd Annual Meeting, Sendai, April 29, 30 and May 1, 1958.

From the Central Clinical Laboratory, Branch Hospital, University of Tokyo

A PATHOLOGICAL STUDY ON CORONARY SCLEROSIS

By

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I. Introduction

Coronary sclerosis is important as well as interesting, on the one hand, for it shows some characteristics which may contribute to the research for arteriosclerosis in general, and on the other hand, for it may cause grave myocardial changes. According to the intention of this symposium, the author has carried out a statistical and morphological observation on coronary sclerosis, and its histogenesis has been studied. The essential nature of coronary sclerosis, accordingly that of arteriosclerosis in general, will also be briefly referred to.

II. Statistical Investigations

The study to be reported here is based upon an examination of 1050 routine autopsy cases of all ages. The materials used have been obtained from the following organizations: The Tokyo University, School of Medicine, Department of Pathology; The Tokyo University, Branch Hospital; Yokufukai, Old People's Home; Tokyo Metropolitan, Komagome Hospital, Tsukiji Maternity Hospital, Tokyo Medical Examiner Office; Tokyo Teishin Hospital. The author wants to express his sincere thanks to these organizations for their kind cooperation.

Table I. Incidence of Coronary Sclerosis in Age and Sex.

<table>
<thead>
<tr>
<th>Age</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (%)</td>
<td>Cases (%)</td>
</tr>
<tr>
<td>0--9</td>
<td>92 (96.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>10--19</td>
<td>100 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>20--29</td>
<td>12 (12)</td>
<td>0 (0)</td>
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<tr>
<td>30--39</td>
<td>12 (12)</td>
<td>0 (0)</td>
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<tr>
<td>40--49</td>
<td>12 (12)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>50--59</td>
<td>12 (12)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>60--69</td>
<td>12 (12)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>70--79</td>
<td>12 (12)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>80--</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>176 (29.7)</td>
<td>121 (20.4)</td>
</tr>
</tbody>
</table>
support. Moreover, these materials comprise of 539 autopsy cases at Tokyo University, which the author and his collaborators have dealt with when they participated in the pathological statistics concerning the frequency of coronary sclerosis and myocardial infarction.

Methods for macroscopical observations: The major coronary arteries and their principal branches were sectioned at intervals of 1 to a few mm., and the distribution as well as grade of sclerosis was examined. The grade of sclerosis is classified into 5 degrees from none (−−−) to the most severe (+++). In the majority of cases sclerosis of the aorta and also the renal arteries and main cerebral arteries were macroscopically observed.

Results:

1. The incidence of coronary sclerosis according to age and sex (Table I) discloses its early appearance, namely, first in the second decade, and increase in frequency and intensity with age. For aged patients it can be said that it usually is very frequent and severe. Although it seems to appear somewhat earlier in males than in females for younger people, there is no remarkable difference related to sex in persons above 60 years of age.

2. The incidence of aortic sclerosis is almost the same in frequency as coronary sclerosis. But in degree the former is somewhat severer than the latter, especially for the aged.

The incidence of renal and cerebral arteriosclerosis is less frequent than that of coronary and aortic sclerosis, and besides the first appearance of the former is always much behind the latter.

3. There is a distinct correlation in frequency

![Fig. 1. Correlation between Coronary Sclerosis and Aortic Sclerosis](image1)

![Fig. 2. Correlation between Coronary Sclerosis and Blood Pressure](image2)
and degree between the coronary sclerosis and the aortic, renal and cerebral atherosclerosis (Fig. 1).

In addition, a certain correlation of the degree of coronary sclerosis with the intensity of arterial hypertension (Fig. 2), as well as with the heart weight can be recognized.

Comment: According to the results obtained some of the most important factors which cause coronary sclerosis seem to be identical with the systemic factors which cause arteriosclerosis in general. But it is supposed that there may be some local factors characteristic to the coronary circulatory system.

III. PHYSIOLOGICAL DEVELOPMENT OF THE CORONARY ARTERIAL WALL

Materials and methods for histological observation: More than 220 cases were examined microscopically. Several pieces of tissue were removed from the left anterior, the left circumflex and the right coronary arteries, and from the myocardium mainly of the left ventricle. These pieces were fixed in Zenker-formalin fluid, neutral formalin and alcohol-formalin, and embedded respectively in colloidal-paraffin, hard and soft paraffin melting at 60°C and 54°C. Then the sections were stained and examined histochemically as follows; hematoxylin and eosin, azan, aldehyde-fuchsin for elastica combined with Goldner trichrome, periodic acid-Schiff reagent (PAS), toluidine blue and so on. Besides these pieces fixed in neutral formalin were taken for frozen sections and stained with sudan III.

As already described, coronary sclerosis appears in very young individuals, and for the aged its occurrence is common. Many authors have pointed out that the intima of the coronary artery is much thicker than that of other arteries even in infancy. Therefore, in order to reveal the histogenesis of coronary sclerosis, the physiological development of the coronary arterial wall must be investigated. For this study about 30 cases ranging from newborn to persons aged nearly 20 years of age were used.

Results: 1. In general, there is no intimal tissue in the coronary artery of the newborn. However, tiny edematous cleavages can be recognized between the endothelium and the internal elastic lamina at several portions. There also are peculiar cell groups, accompanied by duplication or separa-

tion of the internal elastic lamina. These cell groups are considered to be muscle bundles lying parallel to the axis of the vessel. They are usually located in the intima, but sometimes presumably outside the internal elastic lamina according to the mode of separation of the latter. These longitudinal muscle bundles are better developed at the bifurcations of the vessels, where they are seen even in the newborn. These probably correspond to the so-called “polster”-formations which consist of muscle fibers and intermuscular edematous loosening (Fig. 3). The latter is usually followed by production of collagen as well as elastic fibers. In this manner the intima increases in thickness relatively rapidly. However, the intimal thickening is much variable in degree in each individual, and even at each portion of the same circumference of a vessel.

Fig. 3. BSN 16. Elderly. 9. Proximal segment of the left anterior descending coronary (adjacent to a branching), showing thickening of the intima, so-called “polster” which consist of well developed longitudinal muscle bundles and interstitial edematous loosening. En.—endothelium. El.—internal elastic lamina. X.—edematous loosening or cleavage. Elastica-Goldner. 10×30. (*Tokyo University, Branch Hospital, Autopsy Case No.)

2. In parallel with the intimal thickening, the media also increases gradually in thickness. Even in infants some minute foci of edematous loosening or fibrosis are present in the media, especially in its intermediate zone. The internal elastic membrane may be frequently degenerated beneath the fibrous plaques. In the media beneath these areas focal edema or fibrosis which appears at the internal zone, progresses outwards, accompanied by damage of muscle fibers. One can recognize even in some cases of infants only several months after birth changes similar to those of arteriosclerosis (Fig. 4).

3. The intima in full growth may be divided
into the outer layer, “elastisch-musculöse Schicht”, the intermediate one, “elastisch-hyperelastische Schicht”, and the inner one, “bindegewebige Schicht” (Jores) (Fig. 10). But the development of the intima shows a marked individual as well as local variation. Sometimes the intima consists of only two layers, and sometimes shows no tendency to separate into layers. These facts are in particular noteworthy.

4. The intima, in parallel to the media, usually increases in thickness rapidly until one year after birth, then slowly until nearly fifteen years of age (Fig. 5). In the cases older than 15 years there is much individual difference, several cases showing marked intimal thickening. In these cases the intima is often thicker than the media. From almost the same age the coronary sclerosis may be initiated into macroscopic appearance. The interesting fact that the absolute value of intimal thickness and its ratio to that of the media are far greater than those at other arteries seems to be one of the most important characteristics of the coronary artery.

Comment: In order to explain the above mentioned facts and to reveal the histogenesis of arteriosclerosis one must contemplate the blood or liquid circulation in the arterial wall. As is well known the larger arteries receive a distribution of so-called “vasa vasorum”, but only over the outer half of the media and the adventitia. Therefore, the inner half of the media and the intima have no blood vessel, as well as the whole wall of the smaller arteries. These tissues without blood vessel, so-called “bradytroph” tissues, are nourished by a serous fluid insuated from blood through the endothelium. This fluid probably flows slowly towards the outside and pours itself into veins in the surrounding tissue. This liquid flow may be disturbed by several variations of conditions; namely, injuries of endothelium and elevation of arterial blood pressure presumably resulting in increased insudation, regressive changes of the arterial wall tissue, especially of its ground substance, disturbance of fluid outflow due to elevated venal blood pressure, and so on. Under these conditions a stagnation of
the fluid in the arterial wall seems to be caused. Then it may be accompanied by shortage of oxygen and other nutritives, especially in the media which is located farthest from the lumina in spite of a large nutritive need for its function. The above mentioned loosening or fibrous foci which appear early in the intermediate zone of the media are formed under such relative nutritive or oxygen shortage. Therefore, elevated function as constriction seems to be one of the factors for changes of the media. Moreover, the above described loosening as well as thickening of the intima in the physiological development may be due to increase of fluid flow in the arterial wall.

The fact that the intramural fluid flow and its disorder may differ from part to part, from time to time and from person to person seems to play a part for the variable structure and thickness of the intima, although irregular development of the "elastisch-muskulöse Schicht" may play another part. The morphological characteristics of the coronary arteries are realized through this peculiar physiological development. And in this physiological process one can already recognize changes simulating arteriosclerosis. This fact accounts for that the development of arteriosclerosis may have an intimate relation to the physiological growth of the arterial wall.

IV. MORPHOLOGY AND DISTRIBUTION OF CORONARY SCLEROSIS

After the observations relating to the physiological development of the coronary artery, the histogenesis and microscopic appearance of coronary sclerosis, mainly at the coronary stem will be pursued. Atherosclerosis occurring most frequently shall be dealt with chiefly.

Results:

1. Morphological findings: a) The possible primary or earliest change of the sclerosis is focal edematous swelling in the intima and the media, which seems to be essentially similar to the physiological edematous loosening (Fig. 6). As there often are some injuries of the endothelium at the same time, the so-called increased "insudation" or "Plasmaphorese" (W. W. Meyer) may be assumed to have played a significant role in this process. In general, this process involves only a small part of the circumference and is frequently localized at the bifurcation (so-called "polster", etc.), bending por-

Fig. 6. TN 20176.* Female, aged 27. (Diag.: Lupus erythematosus). Proximal segment of the left anterior descending coronary. Disturbance of the endothelium and marked edematous swelling in the intima as well as in the media with degenerated (dark stained or edematous) muscle fibers. Azan. 10×20.
(*Tokyo University, Dept. of Path., Autopsy Case No.)

Fig. 7. Schema showing Location Predisposed to Sclerotic Plaques at the Branching.

tion and so on (Fig. 7). This process can be accompanied by several histologic changes, which seem to occur simultaneously or secondarily. These are: (1) appearance of increased amounts of mucoid ground substance in the intima and the media; (2) degeneration and disappearance of elastic tissue and muscle fibers; (3) slight proliferation of fibroblasts and infiltration of leucocytes in the intima; (4) small areas of intramural hemorrhages; (5) minute mural thrombosis; (6) appearance of foam cells and deposition of lipid mainly in the intima.

Although there are marked individual variations, this process does not usually show such a marked cellular reaction (3) making it impossible to designate it as an inflammatory process (Fig. 6). Therefore, it is presumed that the onset of a arteriosclerosis is not initiated by an inflammatory process in a narrow sense. According to toluuid blue technics increased amounts of metachromatic substances (1) are present even in the early lesions of edematous swelling both in the intima and the me-
dia. Concomitant with the increase in metachromatic substances there are occasionally focal areas of degeneration of the internal elastic membrane (2). It is suggested that these lesions are followed by fibrous or hyaline thickening of various degrees, occasionally under fibroblastic proliferation. Moreover, these changes tend to occur in preformed sclerotic foci and their adjacent area (Fig. 8).

Fibrinoid swelling of the collagen fibers in the intima may be another change resulting in sclerotic thickening of the intima. It often appears alone or accompanied with interstitial edematous swelling. It is frequently encountered in the advanced sclerotic lesions.

Both swelling of ground substance and that of collagen fibers can occur repeatedly. And when they are of a mild degree, they will result in diffuse thickening of the intima, while the edematous swelling of a severer degree can cause marked sclerotic plaques.

b) Intramural hemorrhages(4) and minute mural thrombosis (5) are present only in a few cases, and usually accompanied by marked edematous swelling of the intima (Fig. 9 and 10). Therefore, they cannot be the common first step of the arteriosclerosis.

c) Lipid deposition (6), as well known, is one of the most important findings in arteriosclerosis, and has been suggested by many authors as an essential evidence in the course of arteriosclerosis. In areas of edematous changes the fat is frequently deposited within the cytoplasm of the connective tissue cells or in the intercellular ground substance.
(Fig. 11). The cells containing much lipid are called “foam cells”. However, no intimate relationship of lipid to the early lesions can be demonstrated, especially in younger individuals. There are many cases showing early lesions in which lipid is absent. Although the frequency and grade of lipid deposition show marked individual variation, there is a greater degree of lipid deposition in the older age group. It is suggested that the amount of lipid deposition in the arterial wall depends chiefly upon the fat content in the blood serum. These results will support the concept that the lipid deposition is a subordinate occurrence to the principal one; edematous or mucoid swelling.

d) When the intima is divided into the layers mentioned above, the borders between each layer as well as the internal elastic membrane can inhibit the intramural fluid flow to some extent, consequently the spread of edematous swelling as well as lipid deposition over other layers. Accordingly the fat may be only in some layers of the intima or in the media. Especially, in many cases showing early sclerosis the fat is absent in the deepest layer of the intima, “elastisch-musculöse Schicht” (Fig. 11). But in the course of the arteriosclerosis this layer becomes fibrous, as the disappearance of muscle fibers get more conspicuous. Concomitant with this process, lipid deposition in this layer may increase in frequency and degree. Therefore, lipid deposition of a high degree is usually encountered in the deep area of the intima, especially, inside the “elastisch-musculöse Schicht” (Fig. 12). Marked lipid deposition is frequently accompanied by disintegration of the tissue there, resulting in atherosclerotic foci. It is well known that crystalline cholesterol and deposited calcium are often present in these areas.

e) In the media, as already described, there are also interstitial edematous foci frequently with disintegration of muscle fibers which begin in its intermediate zone, then appear just outside of the internal elastic membrane. These foci can finally fall into minute fibrosis and gradually increase in extent. Fibrosis in the media is usually most extensive just outside the marked intimal thickening, and frequently so diffuse and severe that the media at these portions is far thinner than that at other portions (Fig. 12). These disintegrations of the media also show marked individual variations. Moreover, muscle fibers of the media often demonstrate obvious hypertrophy. It is noteworthy that whether the muscular hypertrophy of the media exists or not seems to be characteristic to each individual.

f) According to the toluidin blue technic for mucopolysaccharide used in many cases of all ages, as already mentioned, some metachromatic substances are often found just beneath the endothe-
lium or near the internal elastic lamina even in infants. The more advanced the age, the more abundant are they present both in the intima and the media. They are usually greatest in the areas near the internal elastic lamina which is occasionally degenerated or fragmented (Fig. 13). In the media distribution of these substances often becomes irregular in cases above fifty years of age, and then tend to decrease in quantity in individuals above seventy. In the intima, however, they do not obviously decrease in quantity in the older age group, although the distribution gets usually irregular. As a result it is supposed that the metachromatic substances are located in the edematous swollen or fibrous thickened portions both in the intima and in the media. As toluidine blue technics in pH 7.0 and in pH 2.5 produce approximately the same results, it is suggested that the metachromatic substances consist mainly of chondroitin sulforic acid. However, enzymic reaction to confirm this concept has not been performed. Attention must be paid to the fact that they usually seem to appear prior to lipid deposition. These results support the present author’s opinion concerning the morphogenesis of arteriosclerosis.

(c) In general, coronary sclerosis is characterized by many varieties of its features. This fact may be caused (1) by marked variation of the intramural fluid flow, (2) by varied structures of the coronary artery, and (3) by various changes secondary to the essential course of the sclerosis. (1) The intramural fluid flow may vary to some extent from case to case as well as from portion to portion. These variations will influence the extent and features of edematous swelling. (2) As already described, varied physiological development and structure of the coronary artery, especially of the intima, can modify the occurrence of edematous swelling and lipid deposition there. (3) Various secondary changes will also modify the appearance of coronary sclerosis. First of all, deposited fat, one of the most important features of sclerosis, probably makes a new barrier against intramural fluid flow, and will give grave influence on the subsequence of the sclerosis. Therefore, varied appearance of fat deposition can dominate features of sclerotic foci. Secondly, in the sclerotic intima, especially in the surrounding of the atherosclerotic foci, there are frequently vascularization of various degrees. They are often accompanied by marked cellular reaction or production of granulation tissue. Lipid-filled macrophages are encountered frequently there. There are sometimes fresh hemorrhages of varied size. The hemorrhages often occur in patients with cerebral hemorrhage. However, in only a few cases are there macrophages laden with hemosiderin which show old hemorrhage. These secondary changes are encountered in far advanced sclerotic areas in general.

2. Classification of coronary sclerosis: According to whether muscular hypertrophy of the media is present or not, one can classify the coronary sclerosis in a majority of cases into two types: the first type (I) showing no media hypertrophy and the

<table>
<thead>
<tr>
<th>Types of Coronary Sclerosis</th>
<th>Media Hypertrophy</th>
<th>Intima</th>
<th>Circumferential Atheromatosis</th>
<th>Lumina</th>
<th>Schema</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I a</td>
<td>(-)</td>
<td>(+)</td>
<td>(+)</td>
<td>Dilat. (+)</td>
<td>(+)</td>
</tr>
<tr>
<td>I b</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>Dilat. (+)</td>
<td>(+)</td>
</tr>
<tr>
<td>I c</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>Dilat. (+)</td>
<td>(+)</td>
</tr>
<tr>
<td>II a</td>
<td>(-)</td>
<td>(+)</td>
<td>(-)</td>
<td>Dilat. (+)</td>
<td>(+)</td>
</tr>
<tr>
<td>II b</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
<td>Stenosis (+)</td>
<td>(+)</td>
</tr>
<tr>
<td>II c</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>Stenosis (+)</td>
<td>(+)</td>
</tr>
<tr>
<td>III</td>
<td>Marked sclerotic plaque formation. These can be combined with any type mentioned above. When they are of severe degree, marked stenosis of the lumina may occur.</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
</tr>
</tbody>
</table>

Fig. 14. Types of Coronary Sclerosis and their Findings.
second type (II) with media hypertrophy. Each type can be divided into three subtypes as shown in fig. 14: subtype (a) with diffuse thickening of the intima only of slight degree, subtype (b) with that of marked degree, and subtype (c) showing conspicuous lipid deposition or atheromatosis occupying the whole circumference. Moreover, the third type (III) characterized by marked sclerotic plaque formation can be combined with any type. Accordingly, one can classify the coronary sclerosis of each case as II (b), I(a)+III, etc. The type I(a) of the aged corresponds to the comparatively pure senile change of the coronary artery, that is to say, possibly defined as the case without sclerosis. There are, of course, all possible intermediate or transient forms between every type and others, showing that such classification is unreasonable. Therefore, this attempt has never been done for the complete classification of coronary sclerosis, but only for disclosing some factors related to its peculiar appearance.

The relation between the classification and arterial hypertension (Table II): Cases classified as type (II) are found more frequently in the group of marked hypertension than in the group of less marked hypertension, concerning both maximum and minimum blood pressure. Cases belonging to subtype (b) are also more frequent in the group of marked hypertension. It is suggested that arterial hypertension will urge muscular hypertrophy of the media due to increase of its functional responsibility, and thickening of the intima, too.

3. Distribution of coronary sclerosis: a) So far as the location predisposed to sclerotic plaques is concerned they show the same characteristics as those reported by many investigators (Fig. 7). They resemble the peculiarity of the physiological thickening of the intima. This fact has been explained by a number of authors from a hydrodynamic standpoint concerning the branching or bending of the coronary artery.

b) Comparative observation regarding the severity of sclerosis at each of the three principal stems of the coronary arteries: In many cases the sclerosis is severest at the left anterior descending branch, that at the right coronary artery comes next and least at the left circumflex branch. According to Schlesinger's classification as to the distribution of the coronary arteries, it is found that the majority of cases belongs to the type showing predominance of the right coronary, while only far less cases are

### Table III. Incidence of Coronary Types (Schlesinger's Classification).

<table>
<thead>
<tr>
<th>Coronary Types</th>
<th>Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (1&lt;1)</td>
<td>890</td>
<td>86.7%</td>
</tr>
<tr>
<td>Group II (1=1)</td>
<td>88</td>
<td>8.5%</td>
</tr>
<tr>
<td>Group III (1&gt;1)</td>
<td>49</td>
<td>4.8%</td>
</tr>
<tr>
<td>Total</td>
<td>1027</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Notice: Group I (1<1) Group II (1=1) Group III (1>1)

1. Sulcus interventricularis post.

### Table II. Correlation Between Hypertension and Types of Coronary Sclerosis. (Above 20 Years of Age)

<table>
<thead>
<tr>
<th>Types of Coronary Sclerosis</th>
<th>Grade of Maximum Blood Pressure</th>
<th>Grade of Minimum Blood Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>1</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
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<tr>
<td>7</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>75</td>
<td>11</td>
</tr>
<tr>
<td>Combined with III*</td>
<td>35</td>
<td>9</td>
</tr>
</tbody>
</table>

* Cases combined with the Type III.
attached to the other types (Table III). It is noteworthy that in any case belonging to the type showing predominance of the left coronary, sclerosis of the right coronary is less marked than that of the left coronary (Table IV). This fact suggests the existence of some factors promoting coronary sclerosis which are confined to the cardiac region.

**Table IV. Schlesinger's Coronary Types and Coronary Sclerosis**

<table>
<thead>
<tr>
<th>Coronary Scleroses</th>
<th>$1 &gt; r$</th>
<th>$1 = r$</th>
<th>$1 &lt; r$</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>$1 &gt; r$</td>
<td>32</td>
<td>9</td>
<td>0</td>
<td>41</td>
</tr>
<tr>
<td>(28.08)</td>
<td>(22.08)</td>
<td>(0.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$1 = r$</td>
<td>27</td>
<td>34</td>
<td>1</td>
<td>62</td>
</tr>
<tr>
<td>(43.69)</td>
<td>(54.89)</td>
<td>(1.68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$1 &lt; r$</td>
<td>180</td>
<td>285</td>
<td>77</td>
<td>563</td>
</tr>
<tr>
<td>(20.98)</td>
<td>(25.98)</td>
<td>(11.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>237</td>
<td>369</td>
<td>78</td>
<td>696</td>
</tr>
<tr>
<td>(24.09)</td>
<td>(53.09)</td>
<td>(11.49)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Compared in both sides.

c) One must pay attention to the peculiar attitude of sclerosis of the coronary branches penetrating into the papillary muscles, especially of the left ventricle. The subepicardial branch, which probably sends smaller branches to the anterior papillary muscle frequently shows more extensive sclerosis than other coronary branches. The branch belonging to the papillary muscle is often markedly sclerotic even in younger age group. Sclerosis of this branch is histologically characterized by an extensive loss of muscle fibers in the media, by prominent edematous loosening or fibrous thickening, by severe stenosis of its lumina and so forth (Fig. 15). This fact seems to be intimately related to the anatomical as well as functional peculiarity of the papillary muscle.

The above mentioned features concerning the distribution of the coronary sclerosis will possibly support that the development of the sclerosis depends not only upon systemic but also local factors related to hemodynamic conditions.

d) In general, the sclerotic changes are less severe in the smaller arteries. But the prearterioles and arterioles tend again to get more sclerotic. They sometimes show prominent hyalinosis of the intima (Fig. 16). After all, in the intermediate segments between the main stems or branches and distal finer branches (especially in the proximal segments of the intramyocardial branches), sclerosis is usually least prominent (Fig. 17). These segments often show remarkable muscular hypertrophy of the media, which tends to be more conspicuous in the hypertensive group (Fig. 18) as well as in the cases of the type II coronary sclerosis. The more marked is the muscular hypertrophy of the media in the intermediate arteries, the more extensive sclerosis in both proximal and distal segments. These relations which are more evident in the renal arteries

![Fig. 16. YN 1864. Female, aged 69. (Diag.: Hypertension + Cardiac Insufficiency). Arteriolar sclerosis (hyalinosis) in the myocardium of the left ventricle. Azan. 10 × 40.](image1)

![Fig. 17. YN 1578. Female, aged 73. (Diag.: Cerebral Hemorrhage). Intermediate segment of the coronary (proximal segment of the intramyocardial branch), showing no sclerosis. Marked muscular hypertrophy of the media is seen. Azan. 10 × 40.](image2)
support the opinion that the pathogenesis of arteriolosclerosis should be different from that of atherosclerosis in the large arteries like aorta. Arteriolosclerosis, as claimed by Suwa, is initiated by some circulatory disturbances of the arterioles due to constriction at the proximal segments of the arteries.

e) In the cases without marked hypertension, coronary sclerosis tends to be restricted to the stems and less in grade, while in those with marked hypertension it is often far extensive in distribution as well as severer in grade, and the media often shows evident hypertrophy of muscle fibers simultaneously.

V. HISTOGENESIS AND SOME RELATED FACTORS.

Based on morphological findings the histogenesis of coronary sclerosis and some factors which possibly promote this process will be discussed.

1. Histogenesis: Several opinions concerning the histogenesis of arteriosclerosis have been expressed by many authors. They are in the order as follows, although this classification is quite imperfect.

The views that the arteriosclerosis will originate from metabolic disturbances (Marchand, Rinehart, Lansing, etc.).

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lipid deposition (Anitschkow, Leary, Altschul, Hueper, Duff, Katz, etc.), intramural hemorrhages (Winternitz, etc.), mural thrombosis (Duguid, Morgan, etc.), inflammatory process (Schulz und Klinge, Hueck, Bredt, v. Albertini, etc.), edematous swelling of the intima (W. W. Meyer, E. Müller, W. Rotter, Holle, etc.).

However, as already described, the present author is of the opinion that the arteriosclerotic changes originate from intramural edematous swelling (Fig. 19). Therefore, as to the onset of sclerotic changes, the author agrees with W. W. Meyer, etc. This initial change is, on the one hand, due to the increase in insudation based on disturbances of the endothelium. On the other hand, it is also due to disturbances of the intramural fluid flow originated from disintegration of the media as well as from changes of the ground substance like senile change, lipid deposition, etc. As already described, the disintegration of the media possibly is caused by absolute and/or relative shortage of nutrition. It is suggested that the edematous or mucoid swelling will result in fibrous or hyaline thickening, that is to say, in arteriosclerosis. This process may be essentially the same as the physiological thickening of the intima. In general, as this process advances slowly and mildly, it tends to appear as metabolic changes, without proving itself as inflammatory changes. Therefore, the inflammatory changes, the intramural hemorrhages, mural thrombosis, etc. are not the principal process of the arteriosclerosis, but occurrences subsidiary to the principal one.

2. Factors promoting the arteriosclerotic process and causing characteristics of the coronary sclerosis: Although it is preferable to refer to these factors inclusively, discussion will not be extended over the etiology of the sclerosis. It will be confined to some pathogenetic questions, mainly from a morphological viewpoint.

a) Elevated function of the arteries, for example spasm, that will urge nutritive need of the media, followed by changes of the latter. These changes can often result in arteriosclerotic lesions. The early changes thus formed in the media are nothing but interstitial loosening following fibrosis, often accompanied by the appearance of metachromatic substances. In cases with renal or essential hypertension the function of the media tends to be urged, resulting in muscular hypertrophy of the media which may extend from the stems to the intermediate segments. As already mentioned, it is suggested that the pathogenesis of arteriolosclerosis probably differ from that of the atherosclerosis of the stems. This surmise will support the view that elevated function of arteries is one of the important factors for the development of arteriosclerosis. Moreover, the portions exposed to marked mechanical stimuli likely fall into disintegration of the media in consequence of elevated function of the latter.

Therefore, one must estimate the primary changes of the media for the histogenesis of arteriosclerosis more seriously than heretofore. According to this view, so-called secondary sclerosis subsequent to mesoartitis luetcia, periarteritis nodosa, etc. can be formed principally in the same course as that of the arteriosclerosis in general. The theory that changes of the media should be the primary event of the arteriosclerosis may be approved itself reasonable.

b) Factors concerning hemodynamics: First of all, the high blood pressure is apparently one of the most important factors according to the literatures and to the author's studies. In cases with hypertension elevated mechanical stimuli must be given to the coronary arteries, following rise of their function. This relation, as a result, will urge arteriosclerosis as well as media hypertrophy.

Secondly, some hemodynamic characteristics localized in the cardiac region are the most important factors which will cause peculiarities as to structure and distribution of the coronary sclerosis. These factors will be brought from the following situations: (1) The coronary arteries originate from the Valsalva's sinus as the first branch of the aorta. Accordingly they are expected to be under peculiar conditions concerning the blood flow into them. (2) The coronary arteries have a peculiar bending or branching in accordance with the form of the heart. This fact will explain the relation that mechanical stimuli usually vary from portion to portion. (3) The distal segments of the coronary arteries are exposed to mechanical influences due to periodic constriction of the cardiac musculature. This relation will account for the fact that the branches penetrating into the papillary muscles show especially marked sclerosis.
nary arteries seem to depend upon factors related to the peculiar coronary circulation. As already described, the structure of the coronary arteries can vary physiologically to a certain extent, and moreover, a structure similar to the coronary sclerosis can be formed even in the physiological process. These conditions may influence the onset and form of the coronary sclerosis. That is to say, the characteristic structure of the coronary arteries is another important factor which will cause peculiar form and distribution of the coronary sclerosis.

d) Lipid metabolism, especially increased lipid content in the blood plasma may influence the grade of lipid deposition in the sclerotic lesions to a great extent. Marked lipid deposition will be one of the factors which can alter the tempo and/or form of the sclerosis. Therefore, disturbances of lipid metabolism are suspected to be one of the most important systemic factors concerning sclerotic process.

VI. Conclusion.

Coronary sclerosis obtained from routine autopsy cases have been observed statistically and morphologically, and the histogenesis as well as some related factors have also been discussed. Although a satisfactory solution could not be obtained, the present observation seems to support the concept summarized as follows: (a) coronary sclerosis is formed under systemic as well as local influences concerning metabolism, hemodynamics, etc. (b) Characteristics as to appearance of coronary sclerosis are much related both to the local hemodynamic factors and to the peculiar development and/or structure of the coronary arteries occurring mainly under local hemodynamic factors. (c) Namely, coronary sclerosis is a pathological process which is essentially the same as the structural variation of the coronary arteries in the physiological development.

Finally, for the arteriosclerosis in general, of course the matter is the same. Arteriosclerosis may be understood as a pathological process, which is essentially the same as the physiological one, and is so influenced by varied factors regarding function as well as structure of the artery, as the physiological process at the artery is.

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