PATHOLOGY OF STROKE

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Large cerebral infarctions were caused by atherosclerosis with or without thrombosis in the proximal circumflex (cortical) cerebral arteries. Hypertension, hypercholesterolemia, hypoxidosis, and vasospasm were considered to induce endothelial cell injuries, which might be the primary events not only in atherosclerosis, but also in arteriosclerosis and arteritis formation. Morphogenesis of atherosclerosis and causes of associated thrombosis were also discussed.

Small cerebral infarcts were produced not only by arteriosclerosis, arteritis, and atherosclerosis, but also by arterionecrosis-derived microaneurysms occluded by thrombi in the distal penetrating (perforating) cerebral arteries. Pathogenesis and morphogenesis of the arterial lesions were discussed. Recent increase of the arterionecrosis occluded by thrombosis in the pathogenesis of small infarcts (lacunes) was noted.

The direct cause of hypertensive cerebral hemorrhage was the rupture of arterionecrosis-derived microaneurysms in the distal penetrating cerebral arteries. The primary change of the arterionecrosis was the medial muscle cell necrosis, the causes of which were considered to be hypertension, aging, poor diet low in cholesterol, vasospasm, and the congenitally poor wall structure of the arteries. The development and healing of experimental arterionecrosis in hypertensive rats were also reported.

I would like to present a paper on "Pathology of Stroke", the study of which was carried out with my associates in the Department of Pathology, School of Medicine, Gunma University, Maebashi. In 476 autopsy cases of the cerebrovascular diseases in our department from 1947 to 1967, the incidence of cerebral infarction was 50%, that of hypertensive cerebral hemorrhage 27%, that of the cerebral hemorrhage associated with infarction 14%, and that of subarachnoid hemorrhage 9%. At present, the hemorrhage cases are decreasing, while infarction cases are increasing in Japan. The following presentation will be concentrated on both the cerebral infarction and hemorrhage.

Relationship Between Cerebral Arteries, Arterial Changes, and Cerebral Lesions

Large cerebral infarctions were caused by the atherosclerosis with or without thrombosis in the proximal segments of the circumflex (cortical) cerebral arteries, for example the middle cerebral arteries (Fig. 1). On the other hand, small infarctions or lacunar softenings in the basal ganglia and thalami were induced by the arterio-
sclerosis, arteriosclerosis, or atherosclerosis of the distal penetrating (perforating) cerebral arteries, e.g. the external branches of the arteriae corporis striati mediae (the lateral striate arteries). The direct cause of hypertensive cerebral hemorrhage, however, was not the artero-arteriosclerosis but arterioembolism of the distal penetrating arteries. The arterioembolism was sometimes occluded by thrombi, becoming one of the causes of small infarcts.

Pathology of Cerebral Infarction

Autopsy cases in the Department of Pathology, School of Medicine, Gunma University from 1959 to 1964 revealed that 62% of large cerebral infarction were caused by atherosclerosis with thrombotic occlusion, 38% of large infarctions by atherosclerosis without thrombosis, 74% of small cerebral infarcts were induced by either artero-arteriosclerosis without thrombi or arteriosclerosis without thrombi, and 26% of small infarcts were produced by arterioneurosis with thrombotic occlusion.

The arterial walls observed in the direction of blood flow from the aorta to intracerebral arteries by light microscopy showed the falling gradient of fibromuscular intimal thickening due to aging (Fig. 2). This primary proliferation of myointimal cells was most marked in the aorta, less marked in the proximal intracerebral arteries, and not seen in the distal portions. Then insudation of blood plasma occurred in the intima of the aorta and proximal middle cerebral arteries, followed by both the swelling necrosis of increased collagen fibers with fatty infiltration and the secondary proliferation of myointimal cells, producing the atherosclerosis with collagen fiber disintegration-type atheroma (Fig. 3). The distal intracerebral arteries without primary intimal thickening revealed both the arteriosclerosis induced only by insudation without following proliferation and the atherosclerosis produced both by insudation and secondary proliferation, but no collagen fiber disintegration-type athero-sclerosis. The proximal intracerebral arteries exhibited the intermediate lesions. Well-known foam cell disintegration-type atherosclerosis was observed in all 4 type arteries.

The fibromuscular intimal thickening in the
Fig. 3. Atherosclerosis of the basilar artery with collagen fiber disintegration-type atheroma and associated thrombosis caused by the cleavage of the multilamined intimal tissue. Hypertensive 71-year-old male with cerebral infarction. Mallory's collagen fiber stain. x 30.

stems of the circumflex cerebral arteries was increased with advancing age, and was accelerated about twofold by hypertension4,8 (Fig. 4). The marked fibromuscular intimal thickening was a prerequisite for atherogenesis, and provided sites of predilection for the development of more marked atherosclerosis9.

Cause of Large Cerebral Infarction

As mentioned above, large infarcts were caused by atherosclerosis in the stems of the circumflex cerebral arteries with marked fibro-

Fig. 4. Fibromuscular intimal thickening in the proximal segments of human cerebral arteries (bifurcation pads between the internal carotid and anterior cerebral arteries) was increased by advancing age and associated hypertension.

Fig. 5. Multilaminated intimal thickening in the stem of the right anterior cerebral arteries occluded by an organized thrombus containing hemosiderin pigments. Arrow indicates a cleavage of the laminated intimal tissue. Hypertensive 73-year-old female with a large cerebral infarct in the right frontal lobe and diabetic nephropathy. Weigert's resorcin-fuchs in stain for elastic fibers. x 30.

Fig. 6. Multilaminated intimal thickening of the middle cerebral artery. Collagen fiber disintegration-type atheromas (A) were formed in the two intimal layers. The inner atheroma extended to the junction (arrow) between the inner two layers. Weigert's resorcin-fuchsin stain for elastic fibers. x 33.

Japanese Circulation Journal Vol. 50, December 1986
muscular intimal thickening induced by aging and hypertension. The atheroma was usually formed by disintegration of increased collagen fibers with fatty swelling. Thrombosis formed on the atherosclerotic lesions was caused by the break of the superficial intimal tissue by enlarged atheroma and/or by the cleavage of the multilaminated intimal tissue resembling overlapping roofing tiles (Figs. 3, 5 and 6), which is a characteristic finding of the cerebral arteries, in association with intimal injuries by hemodynamic stresses. The inner intima of the proximal cerebral arteries occasionally exhibited disintegrated foam cells, suggesting that released lysosomal enzymes from the cells might induce the intimal tissue destruction, becoming another cause of the secondary thrombogenesis.

**Cause of Small Cerebral Infarction**

Fifty-two out of 66 small infarcts (lacunar softenings) in the basal ganglia and thalami studied by light microscopy of tetrahydroxynaphthalene (tetrahydroxynaphthalene)-cleared slices of the brains injected intraarterially with a gelatin-barium sulfate mixture and of their serial paraffin sections were apparently caused by obstructive or stenotic lesions of the intracerebral arteries. The arterial lesions in order of their frequency were as follows: 1) Arterionecrosis (intracerebral microaneurysms) with thrombotic occlusion...
including fibronodular arterial lesions regarded as the organized arterionecrosis with thrombi;\textsuperscript{2,13} (33.3%; figures will be shown in the following paragraph), 2) fibrocellular intimal thickening (30.9%), 3) intimal lipoidosis (foam cell accumulation and deposition of ceroid-like substance, that is, membranocytic lipids\textsuperscript{14} in the intima, 16.0%, Figs. 7 and 8), 4) atherosclerosis (11.1%, Fig. 9), 5) intimal thickening associated with medial pseudocalcification (6.2%), and 6) arterionecrosis with the greatly narrowed lumen caused by intimal fibrinoid deposit (2.5%). The fibrocellular intimal thickening (arteriosclerosis) was induced by insudation followed by secondary proliferation in the distal intracerebral arteries without primary intimal thickening (Fig. 2). The intimal lipoidosis was a representative arteriosclerosis? the foam cells of which might be the insudated blood monocytes in the intima\textsuperscript{15} The atherosclerosis of the distal intracerebral arteries was exclusively the foam cell disintegration-type atherosclerosis (Figs. 2 and 9). The foam cells were also considered to be derived from insudated blood monocytes. Secondary proliferation following the atheroma formation was seen in the inner intima (Fig. 9).

Pathology of Cerebral Hemorrhage

The direct cause of hypertensive intracerebral hemorrhage was not the athero-arteriosclerosis\textsuperscript{16} but arterionecrosis of the intracerebral small arteries\textsuperscript{1}. Atheroma in the intracerebral arteries of aged hypertensive patients occasionally broke through the internal elastic lamina. Nevertheless, the arteries were considered not to be ruptured, because a neointimal tissue with newly formed elastic fibers was seen in the subendothelial tissue.

Cause of Cerebral Hemorrhage

In a hypertensive hemorrhage case forming a massive hematoma in the basal ganglia, the origin of the bleeding was investigated. The lateral striate arteries branching off the middle cerebral artery at a right angle and then running in a retrograde direction against the blood flow in the latter merged their distal portions in the hematoma. Serial paraffin section study of the hematoma containing the distal lateral striate arteries disclosed a ruptured arterionecrosis\textsuperscript{8,17,18}

Postmortem arteriography\textsuperscript{17,18,19} at autopsy of a putaminal hemorrhage case exhibited an interrupted portion of the lateral striate artery adjacent to the hematoma. Serial paraffin section study of this portion disclosed histologically the arterionecrosis and its rupture\textsuperscript{1,17,18}.

Postmortem arteriography of a right thalamic hemorrhage case revealed a microaneurysm in the left lateral striate artery. This microaneurysm observed in a tissue slice cleared in tetralin was seen in a branch of the striate artery. Light microscopy of the aneurysm showed a microaneu-
A tetralin-cleared slice of the left putamen in a left thalamic hemorrhage case disclosed multiple formation of microaneurysms including an aneurysm occluded by thrombi and surrounded by hemosiderin pigments in the lateral striate arteries. Maximum 49 intracerebral microaneurysms were found in one case (64-year-old case with cerebral hemorrhage), averaging approximately 20 aneurysms per one cerebral hemorrhage case (10) (Fig. 10).

The arterionecrosis (Figs. 10 and 11), that is, the direct cause of hypertensive cerebral hemorrhage was found in the intracerebral arteries approximately 150 μ in outer diameter, especially in the lateral striate arteries. In the tunica media of the affected arteries, smooth muscle cells had already been lost, and the intima showed some fibrous thickening. In the intima, blood plasma insudation took place, and collagen fibers in the deep intima were swollen, being decreased in their blue staining with Mallory's collagen fiber stain. The internal elastic lamina was dissolved (Fig. 11). Fibrin (fibrinoid substance) deposition was seen in the intima. Neutrophil leukocytes and a few foam cells were observed in the intima. The arterial lumen was dilated, and the arterial wall and its surrounding tissue were sometimes infiltrated with red blood cells. A few lymphocytes, large mononuclear cells with or without hemosiderin pigments, and plasma cells were occasionally seen infiltrating the periarterial tissue.

Microaneurysms formed by the arterionecrosis having no internal elastic lamina being about to rupture were frequently found in the putamen of hypertensive patients (17,18) (Fig. 12).

Microaneurysms derived from the arterionecrosis without fibrin deposition in the intima, but showing marked dissolution of the internal elastic lamina were occasionally seen and supposed to be most liable to rupture, because the fibrin deposition can be considered, like mural thrombi, to have a biological significance of tentatively reinforcing the arterial wall affected with marked histolysis. (17,18)

Tetralin-cleared slices disclosed intracerebral microaneurysms in all of 30 cerebral hemorrhage cases, 4 out of 20 hypertensives without cerebral hemorrhage, and one out of 10 normotensives. The 4 hypertensive cases with aneurysms were over 56 years of age, and the normotensive case with aneurysms was a 64-year-old subarachnoid hemorrhage case (17,18).

The macroaneurysms were predominantly found in the putamen (36%) and cerebral cortex (34%), followed by the thalamus (13%), caudate nucleus (9%), and others (8%) (Fig. 13). They were rarely seen in the pallium (1%), which is supplied by the medial striate arteries, whose lumina are smaller than those of the lateral striate arteries and whose tunicae mediae are often affected with pseudocalcification (Fig. 11, P), which inhibits luminal dilatation and induces secondary fibrocellular intimal thickening (18).

The outer diameters of the majority of the microaneurysms were ranging from 300 to 700 μ, and the largest one was 2,550 μ (10). The outer diameters of most of the intracerebral arteries, in which the aneurysms were formed were ranging.
TABLE I COMPARISON BETWEEN THE ARTERIONECROSIS AND ATHEROSCLEROSIS IN THE INTRACEREBRAL SMALL ARTERIES

<table>
<thead>
<tr>
<th>Arterionecrosis</th>
<th>Atherosclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of medial SMC</td>
<td>+</td>
</tr>
<tr>
<td>Fibromuscular intima</td>
<td>±</td>
</tr>
<tr>
<td>Intima</td>
<td>Blood plasma ~ Fibrin</td>
</tr>
<tr>
<td>Lysis of IEL</td>
<td>+</td>
</tr>
<tr>
<td>Lumen</td>
<td>Dilated</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>+</td>
</tr>
<tr>
<td>Effect</td>
<td>Rupture</td>
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</tbody>
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IEL = Internal elastic lamina; SMC = Smooth muscle cell

Fig. 14. Medial smooth muscle cell (SMC) damage in the development of arterionecrosis and atherosclerosis in the intracerebral arteries.

from 100 to 300μm

Histological study confirmed all of the microaneurysms to have been resulted from the arterionecrosis. As for their histological pictures, 77% of 269 microaneurysms in 35 cases exhibited the arterionecrosis with intimal fibrin deposition, 21% the fibronodular arterial lesions, that is, the organized arterionecrosis with its obliterating thrombus, and 2% the arterionecrosis without intimal fibrin.

At the beginning of the morphogenesis of the arterionecrosis, medial muscle cells were injured and then the lumen became somewhat dilated, followed by some intimal thickening with fibrous tissue. In such intima occurred blood plasma insudation, which induced histolysis and subsequently intimal deposition of fibrin (fibrinoid substance). Finally the arterionecrosis associated with hypertension caused intracerebral microaneurysms and their rupture. The arterial hemorrhage was followed by the secondary capillary and venous bleeding in the territory supplied by the ruptured arterial system, leading to the massive hematoma formation. As for the cause of the histolysis of arterial wall, blood plasma infiltration was considered essential. Elastase and collagenase, both derived from neutrophil leukocytes in the intima were also expected to participate in the histolysis.

Electron microscopy of the intracerebral artery of a hypertensive case without cerebral hemorrhage revealed a preceding change of the arterionecrosis, that is, marked muscle cell necrosis of the tunica media. Electron microscopy of the arterionecrosis demonstrated the very thin tunica media without muscle cells. The internal elastic lamina was fragmented and lost. Frayed and fragmented collagen fibers due to blood plasma infiltration were seen in the intima.

Comparison between the arterionecrosis and atherosclerosis of the intracerebral small arteries revealed that loss of medial muscle cells was marked in the former and less marked in the latter; fibromuscular intimal thickening of the former was less marked having blood plasma infiltration including fibrin deposition, while that of the latter was marked with atheroma; the internal elastic lamina was dissolved in the former and relatively well preserved in the latter; the lumen was dilated in the former and narrowed in the latter; and thrombosis occurred frequently in the former and was not seen in the latter (Table I).

The causes of the medial muscle cell damage, which was the primary change of the arterionecrosis were considered to be hypertension, aging, poor diet low in cholesterol, vasospasm, and the primarily thin media poor in muscle cells. The earliest change of the arterionecrosis was marked medial muscle cell necrosis. On the other hand, the intracerebral athero-arteriosclerosis responsible for small cerebral infarction retained relatively well-preserved medial muscle cells. The turning point deciding the development of the two types of arterial lesions may be the grade of the preceding medial muscle cell damage in the intracerebral arteries (Fig. 14).
Experimental Study on Hypertensive Arterionecrosis

We induced hypertension in male Wistar rats, 60–85 g, by constricting both the renal arteries with silver clamps of 0.24–0.28 mm inside diameter. The arterionecrosis-like lesions were induced in these hypertensive rats. Electron microscopy of the cerebral arteries demonstrated intimal fibrin deposits and the fragmented and dissolved internal elastic lamina, and both of them were preceded by medial muscle cell necrosis and loss. Granular cell debris were seen in the media instead of muscle cells. Massive intracerebral hemorrhage was occasionally seen in these rats. Light microscopy of the hematoma disclosed the ruptured arterionecrosis.

Healing of hypertensive arterial lesions was studied in rats. The renal arteries of rats were bilaterally constricted with clamps to induce hypertension over 200 mmHg. Five weeks latter an exploratory laparotomy was performed in the rats. After confirming the intimal fibrin deposits, that is, marked blood plasma insudation by biopsy of the mesenteric arteries, the bilateral clamps were removed. Blood pressure fell to 150 mmHg level in most animals. Two to five weeks after the removal, the animals were sacrificed to study the arteries of the whole body. Intimal fibrin deposits were not seen, but fibromuscular intimal thickening was evident in some arteries. The progression of medial muscle cell necrosis was stopped and fibrosis was noted in the media.

Healing of hypertensive medial muscle cell necrosis was studied in rats. The renal arteries were bilaterally constricted by clamps, and several weeks later the constricting clamps were removed. The clamp-removal was carried out 4 or 6 weeks after the constriction, and after that the rats were allowed to survive for 4 weeks. Control groups without clamp-removal were also prepared. The medial areas occupied by muscle cell bodies as seen in electron micrographs of the cross-sectioned middle cerebral arteries were measured by an electric planimeter. The mean medial areas occupied by muscle cell bodies in the rats with clamp-removal were significantly larger than those of the hypertensive controls without clamp-removal of the comparable experimental weeks (p < 0.03), suggesting that the medial muscle cell necrosis, that is, the earliest and leading lesion of the arterionecrosis was healed by the removal of the cause of hypertension.

The cerebral hemorrhage frequently occurred in thin Japanese people ingesting a diet low in cholesterol. Therefore we examined the effect of a cholesterol-rich diet on the medial muscle cells in the cerebral arteries of hypertensive rats. Male Wistar rats were divided into two groups: The first group rats were fed a high lipid diet with the supplement of cholesterol and lard, and the second group rats fed a diet without the supplement. After one week on the diets, both
the renal arteries of all the rats were constricted with clamps to induce hypertension, and sacrificed 9 weeks later. The medial areas occupied by muscle cell bodies as seen in electron micrographs of the cross-sectioned middle cerebral arteries were determined. The hypertensive medial muscle cell necrosis was significantly inhibited by the high lipid diet (p < 0.01)\textsuperscript{13,30} The reason why the cerebral hemorrhage occurs less frequently among the Japanese may be the high lipid diet consumed by the Americans. Cholesterol and lipoproteins are believed to be important materials for the reproduction of cell membranes of muscular muscle cells injured by hypertension. Overeating of lipids, however, is a well-known cause of atherosclerosis. There is a happy medium in everything.

Healed Arterionecrosis as Another Cause of Small Cerebral Infarction

Fibronodular arterial lesions resulting from organization of microaneurysms (arterionecrosis) occluded by thrombi were frequently found in the basal ganglia and other regions of hypertensive patients\textsuperscript{2,13} (Figs. 15 and 16). In such a way, microaneurysms caused by arterionecrosis were sometimes healed and saved from rupture. The occluded ones, however, were one of the causes of small infarcts (lacunes) in the basal ganglia and others\textsuperscript{2,3,12,13}

Autopsy study suggested that the ratio of the arterionecrosis-derived microaneurysms occluded by thrombi to all the arterial changes responsible for small infarcts (lacunes) in the basal ganglia and thalamus has increased recently as compared with that of 15 years ago\textsuperscript{13} The ratio was 22 to 84 (26.2\%) in the materials of 1959–1964, while 108 to 255 (42.4\%) in those of 1976–1977. The difference was significant (p < 0.01). The reason for the recent increase of occluded arterionecrosis may be the increased thrombosis caused by high fat diets, which are brought about by the modernization of dietary life of the Japanese. The increase of occluded arterionecrosis with thrombosis may also be one of the reasons of the decreased incidence of the hypertensive cerebral hemorrhage in Japan in recent years.

Figure 17 was presented as the conclusion. Hypertension, hypercholesterolemia, hypoxidosis induced by heavy smoking, and vasospasm were considered to cause endothelial cell injuries, which might be the primary events of atherosclerosis, arteriosclerosis and arteriosis formation, as the cause of large or small cerebral infarction. The cause of hypertensive intracerebral hemorrhage is arterionecrosis-derived microaneurysm of the intracerebral arteries. The primary change of the arterionecrosis was medial smooth muscle
cell necrosis, the causes of which are considered to be hypertension, aging, poor diet low in cholesterol, vasospasm, and the congenitally poor wall structure of the arteries. The reasons for the decreased incidence of the cerebral hemorrhage in Japan in recent years might be not only the effective control of hypertension, but also the prevention of the hypertensive medial smooth muscle cell necrosis and the increase of occluded arterioles, and the thrombosis. Both of these phenomena might be induced by high lipid diets. Although the diets are a well-known cause of athero-arteriosclerosis leading to cerebral infarction, there is a happy medium in everything.

Acknowledgments
This study was carried out with my associates, Dr. Yoji Yoshida, Masayasu Kojimahara, Keiji Suzuki, Hiroko Shinkai, Morie Sekiguchi, Yasuo Takayama, Sadao Hori, Kiyohisa Kobori, Tatsuru Miura, Toshio Fukuda, Nobuhide Masawa, Ichiro Mori, Toshinobu Nishimura, and Shinobu Murata in Gunma University.

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