Comparative Study of Arteriosclerosis between Brain and Heart, with Special Reference to the Cerebrovascular and Coronary Heart Disease

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The present study was undertaken to define the etiologic mechanism of CVD and coronary heart disease and to detect their relation.

In a series of 328 autopsies (37 cases of cerebral hemorrhage, 60 of cerebral infarction, 51 of myocardial infarction and 180 of miscellaneous disease), macroscopic and microscopic studies of intracerebral arteries, cerebral basilar arteries and coronary arteries were carried out.

Generally, intracerebral arterial lesions had no relation with atherosclerosis, but in the atherosclerotic lesions between brain and heart, close correlation was noted in individual cases. From these results some consideration to the pathogenesis of vascular lesions in CVD and coronary heart disease was conducted.

IT IS generally assumed that cerebrovascular disease (CVD) is the most leading cause of death in Japan, and it is attributable to an exceedingly high incidence of cerebral hemorrhage compared to that of cerebral infarction. But several reports recently based upon death certificates showed that the incidence of cerebral infarction has been gradually increased²³

While, coronary heart disease currently is the first leading cause of death in western countries, but the third in Japan, and epidemiological studies on cerebrovascular disease based on autopsies for five years in Hisayama, Kyushu Island, Japan proved that the incidence of cerebral infarction to that of myocardial infarction was the ratio 3.4 : 1²⁴

HASHIMOTO et al.¹⁴ mentioned that the incidence of myocardial infarction in various necropsy series in Japan has been gradually increased.

Therefore, it may be significant to compare arteriosclerosis of the brain with that of the heart. With respect to these problems, there were the extensive studies of several authors such as;

WINTER et al.⁶¹ ROBERT et al.⁵⁰ BAKER et al.³ OKINAKA et al.⁴⁰ MOOSSEY³³ and IKEDA¹⁹ and in these reviews, they compared cerebral atherosclerosis with coronary atherosclerosis.

However, cerebral hemorrhage could be caused by intracerebral vascular lesions^{28,44,53} and one of the etiologic factors of cerebral infarction might be related to the lesions of intracerebral arteries^{28,37,54,56} but the pathological details of intracerebral vascular changes, and the studies about the relation between intracerebral vascular lesions and atherosclerosis of the brain and heart, are deficient.

The present study was undertaken to define these relations and to detect the etiologic factors of CVD and coronary heart disease pathologically.

MATERIALS AND METHODS

In routine post mortem cases in the Department of Pathology, Faculty of Medicine, Kyushu University, 328 autopsy cases were selected (Table I).

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TABLE I AUTOPSY CASES FOR INVESTIGATION

<i>Cerebral hemorrhage</i>	37
<i>Cerebral infarction</i>	60
<i>Myocardial infarction</i>	51
<i>Control cases</i>	
<i>Malignant diseases</i>	54
<i>Diseases of the respiratory systems</i>	24
<i>Diseases of the liver</i>	22
<i>Diseases of the heart</i>	20
<i>Trauma</i>	12
<i>Diseases of the digestive systems</i>	11
<i>Diseases of the kidneys</i>	7
<i>Diseases of blood</i>	6
<i>Diseases of the nervous systems</i>	4
<i>(CVD was excluded)</i>	
<i>Diseases of metabolism and ductless glands</i>	4
<i>Others</i>	16
TOTAL	328

In this study, these cases were divided in the following large four groups and eight small sub-groups;

A-group: 37 cases of cerebral hemorrhage
a-subgroup; 29 cases of cerebral hemorrhage
b-subgroup; 8 cases of cerebral hemorrhage complicated with cerebral infarction

B-group: 60 cases of cerebral infarction
c-subgroup; 42 cases with small cerebral infarcts, the diameter of which were less than 2 cm
d-subgroup; 12 cases of large cerebral infarcts, the diameter of which were more than 2 cm, but smaller than the ones of e-subgroup

e-subgroup; 6 cases of extensive cerebral infarcts of the appropriate cerebral hemisphere

C-group: 51 cases of myocardial infarction
f-subgroup; 12 cases of myocardial infarction complicated with small cerebral infarcts
g-subgroup; 10 cases of myocardial infarction complicated with large cerebral infarcts

h-subgroup; 29 cases of myocardial infarction, on the brain of which there were no lesions

D-group: 180 cases of miscellaneous disease for controls

From these 328 autopsy cases the following arteries were selected for the present study. Regarding the intracerebral arteries, from the brain of each case, the brain tissues in the areas of basal ganglia, frontal lobe, posterior lobe, parietal

Fig.1. Sections for investigation of coronary arteries.

lobe, temporal lobe, hippocampus, mid-brain, cerebellum, pons and medulla oblongata were cut out. As fixatives, 10% formalin was used. From each tissue block, paraffin sections were prepared, and stained with Hematoxylin and eosin stain, MALLORY's collagen stain, phosphotungstic acid hematoxylin (PTAH), Elastica van Gieson's stain and periodic acid-Schiff technique (PAS).

The circle of Willis (including middle cerebral stems, anterior cerebral stems, communicating vessels, posterior cerebral stems, basilar artery, and end of vertebral and internal carotid arteries) was graded for atherosclerosis macroscopically by BAKER's method⁴⁸ and from these vessels, middle cerebral, anterior cerebral, posterior cerebral, internal carotid, basilar and vertebral arteries were cut out for paraffin sections, and stained with Hematoxylineosin and Elastica van Gieson's stain.

The left descending artery, the right coronary artery and the circumflex artery were selected from coronary arteries, and cut out as Fig.1. Each arterial tissue block was prepared for paraffin sections with Hematoxylineosin stain.

Grading the Atherosclerosis and Arteriosclerosis:

(1) Intracerebral arterial lesions

Intracerebral arterial lesions were classified histologically as follows;

- 1) intimal thickening
- 2) angioneclerosis
- 3) fibrous nodules
- 4) intimal edema
- 5) intimal fatty degeneration
- 6) medial calcification

The histological features of these changes are described as below:

1) Intimal thickening

The intima became thickened because of fibrotic proliferation, which were fibrotic cells and elastic fibers. The collagenous fibers were not noted. The intimal fibrotic proliferation with

TABLE II GRADING OF INTRACEREBRAL LESIONS

	1	2	3	4
<i>Intimal thickening</i>	<i>fibroblastic cells stenosis: less than 25%</i>	<i>1 + elastic fibers stenosis: 25–50%</i>	<i>2 + hyalinization stenosis: 51–75%</i>	<i>3. stenosis: more than 75%</i>
<i>Angionecrosis</i>	<i>1/2 of intima</i>	<i>all layers of intima</i>	<i>all walls of vessels</i>	<i>dilatation or hyalinization, with thrombus</i>
<i>Fibrous nodules</i>	—	—	—	<i>complete obstruction</i>
<i>Intimal edema</i>	<i>1/2 of intima stenosis: less than 25%</i>	<i>all layers of intima, stenosis: 25–50%</i>	<i>2. stenosis: 51–75%</i>	<i>with thrombus stenosis: more than 75%</i>
<i>Intimal fatty degeneration</i>	<i>stenosis: less than 25%</i>	<i>stenosis: 25–50%</i>	<i>stenosis: 51–75%</i>	<i>with thrombus stenosis: more than 75%</i>
<i>Calcification</i>	<i>without compli- cation stenosis: less than 25%</i>	<i>with intimal thickening stenosis: 25–50%</i>	<i>with intimal thickening & intimal edema stenosis 51–75%</i>	<i>3. stenosis: more than 75%</i>
<i>Valument</i>	1	4	8	12

TABLE III GRADING FOR CEREBRAL ATHEROSCLEROSIS

TABLE III												
		0	I	II		III		IV		V		
Intimal changes	fibroblastic cells		+	+	+	+	+	+	+	+	+	
	elastic fibers			+	+	+	+	+	+	+	+	
	hyalinization						+	+	+	+	+	
Atheromatous materials	foam cells							+	+	+	+	
	cholesterin crystal									+	+	
Internal elastic lamella	damaged				+	+	+	+				
	disappeared								+	+	+	
Formation of thrombi											+	
Valument		0	1	3	4	6	7	8	9	10	11	12

hyalinization corresponded to intimal fibrotic, hyaline thickening of MUKAE.³⁵

2) Angionecrosis

In the vascular walls in which this degeneration were present, fibrin, neutrophil leukocytes and erythrocytes were observed intermingled with fibrinoid substance in the subendothelial layers

and vascular walls. Fibrinoid substance was shown by H-E stain as conglomeration of trabecular substance or homogeneous substance, stained intensely red with eosin. It was purple red by MALLORY's collagen stain, deep blue samely as fibrin by PTAH and yellow by van GIESON's stain.

TABLE IV GRADING FOR CORONARY ATHEROSCLEROSIS

		0	I	II		III			IV			V		
<i>Intimal changes</i>	<i>fibroblastic cells</i>		+	+	+	+	+	+	+	+	+	+	+	+
	<i>collagenous fibers</i>			+	+	+	+	+	+	+	+	+	+	+
	<i>hyalinization</i>				+	+	+	+	+	+	+	+	+	+
<i>Atheromatous materials</i>	<i>foam cells</i>				+		+	+	+	+	+	+	+	+
	<i>cholesterin crystal</i>							+	+	+	+	+	+	+
<i>Calcification</i>	<i>in minimum</i>						+		+			+		
	<i>in massive</i>							+		+	+		+	+
<i>Internal elastic lamella</i>	<i>damaged</i>				+	+	+	+	+					
	<i>disappeared</i>									+	+	+	+	+
<i>Medial muscular layers</i>	<i>fibroses</i>				+	+	+							
	<i>atrophic</i>							+	+	+	+	+	+	+
<i>Intimal hemorrhage</i>										+	+			+
<i>Formation of thrombi</i>											+	+	+	+
<i>Valument</i>		0	1	2	3	4	5	6	7	8	9	10	11	12

3) Fibrous nodules

They were nodules with proliferation of connective tissue and organization, leading to disappearance of normal vascular architecture, and to severe stenosis or obstruction of the vascular lumen. MASTUOKA²⁸ reported as "fibrous nodules", BEITZKE⁵ "bindgewebiges Granulom", or "bindgewebig verödete kleines Aneurysm".

4) Intimal edema

The deep layers of intima were permeated by serum protein and permitted to form the slit contained with protein fluid. They corresponded to SCHWARTZ's "Aufsplitterung".⁵¹

5) Intimal fatty degeneration

Of the intimal edema, some arteries had aggregation of foam cells in the intimal deep layers. These changes were regarded as atherosclerosis of small arteries.

6) Medial calcification

The arterial lesions, on the media of which the deposits of substance like calcium was noted:

The microscopic grading of intracerebral arterial lesions was on the grade 1 (minimal lesion) to grade 4 (maximal lesion)(Table II). Grades were correlated with percentage of luminal obliteration and with histologic features of arterial wall. Each grade was given 1, 4, 8, 12 for weighting.

(2) Cerebral Basilar Arteries

After the histologic sections from each of 6 cerebral basilar arteries above described, were made, each section was graded microscopically (Table III).

(3) Coronary Arteries

Of each section of the coronary arteries, as Fig. 1, the paraffin-specimens were made, and searched for atherosclerosis by microscopic grading method (Table IV).

RESULTS

A. Intracerebral Arterial Lesions

1. The Frequency of Incidence:

The results of determination of the frequency of incidence of intracerebral arterial lesions were listed in each group and in each subgroup in Table V. Of these arterial lesions, intimal thickening was found with the highest frequency, that was 93.5% in the brain of cerebral infarction, 89.1% in cerebral hemorrhage, 68.6% in myocardial infarction and 25.0% in controls.

Intimal thickening, fibrous nodules, intimal edema and intimal fatty degeneration were noted with the most frequency in the brain of cerebral infarction, and then in order: cerebral hemorrhage (59.4%) than cerebral infarction (41.6%).

Medial calcification was found about equal in

TABLE V FREQUENCY OF INCIDENCE OF INTRACEREBRAL ARTERIAL LESIONS

Subgroups	Cerebral Hemorrhage			Cerebral Infarction			Myocardial Infarction				Controls	
	a	b	subtotal	c	d	e	subtotal	f	g	h	subtotal	
Intimal thickening	25/29 (86.2)	8/8 (100.0)	33/37 (89.1)	37/41 (90.2)	13/13 (100)	6/6 (100)	56/60 (93.3)	10/12 (83.3)	7/10 (70.0)	18/29 (62.0)	35/51 (68.6)	45/180 (25.0)
Angionecrosis	17/29 (58.6)	5/8 (62.5)	22/37 (59.4)	22/41 (53.6)	2/13 (15.3)	1/6 (16.6)	25/60 (41.6)	2/12 (16.6)	1/10 (10.0)	2/29 (6.9)	5/51 (9.8)	7/180 (3.8)
Fibrous nodules	6/29 (20.6)	3/8 (37.5)	9/37 (24.3)	22/41 (53.6)	5/13 (38.4)	1/6 (16.1)	28/60 (46.6)	3/12 (25.0)	1/10 (10.0)	1/29 (3.4)	5/51 (9.8)	0/180 (0)
Intimal edema	14/29 (48.2)	6/8 (75.0)	20/37 (54.0)	33/41 (80.4)	6/13 (41.6)	3/6 (50.0)	42/60 (70.0)	5/12 (25.0)	3/10 (30.0)	3/29 (10.3)	11/51 (21.5)	14/180 (7.7)
Intimal fatty degeneration	4/29 (13.7)	1/8 (12.5)	5/37 (13.5)	19/41 (46.3)	4/13 (30.6)	0/6 (0)	23/60 (38.3)	2/12 (16.6)	1/10 (10.0)	0/29 (0)	3/51 (5.7)	0/180 (0)
Calcification	9/29 (31.0)	4/8 (50.0)	13/37 (35.1)	17/41 (41.4)	6/13 (46.1)	1/6 (16.6)	24/60 (40.0)	3/12 (25.0)	5/10 (50.0)	14/29 (48.2)	22/51 (41.3)	50/180 (27.2)
												() : %

() : %

Fig. 2-a. Mean grades for intracerebral arterial lesions by decades (to be continued).

each group.

Of the small subgroups, the brain with small cerebral infarcts had the most severe lesions of intracerebral arteries.

2. Relationship of Degree of Intracerebral Arterial Lesions to Age and to Brain lesions:

The numbers representing the degree of intracerebral arterial lesions in each of 11 brain sections were added separately in each arterial lesion to indicate the grade for an individual brain. Then all of the latter grades in each decade were added and the sum divided by the number of cases in that decade to determine the mean grade of intracerebral arterial changes for that decade.

Fig. 2 shows the relative severity of various

intracerebral arterial lesions at different decade in each group. The severity of intimal thickening was excessively prominent in the cases of cerebral hemorrhage and cerebral infarction at each decade. In the cases of myocardial infarction, the severity of intimal thickening showed the steepest gradient at the seventh decade, and in the control cases, it rose with increasing age, and was correlated with aging statistically ($p < 0.01$).

About the severity of angioneclerosis and intimal edema in the group of cerebral hemorrhage, and fibrous nodules in the group of cerebral infarction, there were no differences in each group at each decade.

The distribution of the degree of intracerebral

Fig.2-b. Mean grades for intracerebral arterial lesions by decades.

- Cerebral hemorrhage
- Cerebral infarction
- × Myocardial infarction
- △ Controls

Fig.3. The degree of intracerebral arterial lesions in each subgroup.

Fig.4. The degree of intracerebral arterial lesions and blood pressure.

arterial lesions in each subgroup was shown in Fig. 3.

The degree of intimal thickening was the highest in the subgroup of single cerebral hemorrhage, but generally, the most severe intracerebral arterial lesions were noted in the subgroups complicated with small cerebral infarcts, namely, in the subgroups of cerebral hemorrhage with small cerebral infarcts, small cerebral infarcts and myocardial infarction with small cerebral infarcts. This tendency was clearly demonstrable especially in angioneclerosis, fibrous nodules and intimal edema.

3. Relationship of Degree of Intracerebral Arterial Lesions to Blood Pressure:

The cases used in this study were divided into hypertensive group and normotensive group. The two criterias that were used to determine whether the patient was hypertensive, were that adopted by World Health Organization⁶⁰ and the consideration of the pathological data. Blood pressure measurements were obtained from the clinical records for autopsy. If a reliable record could not be found, the second criteria was used, that was a total heart weight of 350 gr. or more and

the existence of arteriosclerosis in kidneys.

The histogram of Fig. 4 showed the relation of the severity of intracerebral arterial lesions to hypertension or to normotension in each group.

The severity of intimal thickening, angioneclerosis, fibrous nodules and intimal edema were more exceedingly prominent in the hypertensive cases than in the normotensive cases in each group. But in the severity of intimal fatty degeneration and medial calcification, there was no significant differences between hypertensive cases and normotensive cases.

B. Cerebral Basilar Arteries

1. Relationship of Degree of Cerebral Atherosclerosis to Age:

Six numbers representing the microscopic grade of atherosclerosis in each of 6 cerebral basilar arterial branches already mentioned, were added and the sum divided by 6 to determine the mean grade of atherosclerosis for each brain. Then all of the latter grades in each decade were added and the sum divided by the number of cases in that decade to determine the mean grade of cerebral atherosclerosis for that decade.

The results of determination of the mean grade

Fig. 5. Mean grade for cerebral atherosclerosis by decades

of cerebral atherosclerosis for each decade in each group were shown in Fig. 5.

In the group of cerebral infarction, the mean grade of cerebral atherosclerotic process appeared to become more rapid after the fourth and seventh decades. The degree of cerebral atherosclerosis in the group of cerebral hemorrhage, became prominent with increasing age until the sixth decade, but it was equal at different decades over the sixth.

The degree of cerebral atherosclerosis in the group of controls was the gradual progression with increasing age. At the seventh and eighth decades, the curve for cerebral atherosclerosis was the steepest gradient, and so there was almost no difference compared to that of cerebral infarction, myocardial infarction and cerebral hemorrhage over the seventh decade.

There was statistical relation ($p < 0.01$) between the degree of atherosclerosis and age in the groups of myocardial infarction, cerebral hemorrhage and controls, but in the group of cerebral infarction, there was not any relation.

2. Differences of Degree of Cerebral Atherosclerosis based on Brain Lesions:

Between each subgroup already mentioned, the coding numbers of cerebral atherosclerosis

Fig. 6. Cerebral atherosclerosis in each subgroup

Fig. 7. Degree of atherosclerosis of main cerebral arteries

by BAKER's method of each case were plotted in Fig. 6. In the group of cerebral hemorrhage, the averaging of cerebral atherosclerosis of the subgroup of single cerebral hemorrhage was 19.2 and generally less prominent than that of subgroup of cerebral hemorrhage complicated with small cerebral infarcts, which varied extensively.

In the group of cerebral infarction, the degree of cerebral atherosclerosis of the subgroup with small infarcts revealed severe between coding-number 30 to 50, in 30 of 41 cases, and those of other two subgroups were demonstrated by same tendency.

On the other hand, the degree of cerebral atherosclerosis of the cases of myocardial infarction complicated with large cerebral infarcts was less prominent than that of cases with large cerebral infarcts in the group of cerebral infarction.

3. Mean Grade of Cerebral Atherosclerosis by Major Arterial Branches by Decades:

Since the grades of atherosclerosis on right and left side were about the same, they were averaged together and the values obtained from the internal carotid, the middle cerebral, the anterior cerebral, the posterior cerebral, the basilar and vertebral arteries in each group were shown in histogram (Fig. 7).

Fig. 8. Mean grades for cerebral atherosclerosis of the 6 main branches by decades (control group)

TABLE VI STENOTIC LESIONS OF CEREBRAL BASILAR ARTERIES AND BRAIN LESIONS

	Ant. cereb.	Int. carotid.	Mid. cereb.	Post. cereb.	Basil.	Vert.	Total case numbers
Cerebral Hemorrhage	2/29 (6.8)	0/29 (0)	3/29 (10.3)	5/29 (17.2)	0/29 (0)	0/29 (0)	6/29 (20.5)
Cereb. Hemor. + Cereb. Infarct	3/8 (37.5)	0/8 (0)	3/8 (37.5)	2/8 (25.0)	0/8 (0)	1/8 (13.5)	5/8 (62.5)
Small Cerebral Infarct	9/41 (21.9)	0/41 (0)	6/41 (14.6)	5/41 (12.1)	0/41 (0)	1/41 (2.4)	17/41 (41.4)
Large Cerebral Infarct	1/13 (7.6)	0/13 (0)	6/13 (46.1)	3/13 (22.8)	0/13 (0)	0/13 (0)	10/13 (76.9)
Extensive Cereb. Infarct	0/6 (0)	1/6 (16.1)	1/6 (16.1)	2/6 (33.3)	0/6 (0)	0/6 (0)	3/6 (50.0)
Small Cerebral Infarct	0/12 (0)	0/12 (0)	5/12 (41.6)	3/12 (25.0)	0/12 (0)	1/12 (8.2)	7/12 (58.3)
Large Cerebral Infarct	1/10 (10.0)	0/10 (0)	1/10 (10.0)	1/10 (10.0)	1/10 (10.0)	1/10 (10.0)	3/10 (30.0)
No Brain Lesions	2/29 (6.8)	0/29 (0)	4/29 (13.7)	3/29 (10.3)	1/29 (3.4)	0/29 (0)	5/29 (17.2)
Control Group	2/180 (1.0)	0/180 (0)	2/180 (1.0)	3/180 (1.5)	1/180 (0.5)	2/180 (1.0)	4/180 (2.2)
						() : %	

In the group of cerebral hemorrhage and cerebral infarction, the average of the grade for cerebral atherosclerosis was the highest in the middle cerebral arteries, and then in order, the posterior cerebral, the anterior cerebral arteries. While, in the groups of myocardial infarction and controls, the severe atherosclerosis was found in the middle cerebral, internal carotid and vertebral arteries.

Then, the average of the microscopic grade for cerebral atherosclerosis in each of 6 arterial branches in the group of controls were plotted by decade (Fig. 8).

There was some increase in atherosclerosis from decade to decade in each of the 6 pairs of arteries. After the third decade, the middle cerebral artery tended to show the highest grade of atherosclerosis, and the difference between this and other arteries became more eminent at old ages. The internal carotid atherosclerosis revealed higher grades than that of other arteries except the middle cerebral arteries at the sixth and seventh decades. But over the eighth decade, the posterior cerebral atherosclerosis was more prominent than the internal carotid.

4. Stenosis and Occlusion of the Cerebral Basilar Main Branches:

Table VI summarized the distribution of severe stenosis (luminal narrowing more than 80%, more than grade 4 for narrowing) of cerebral basilar arteries in each subgroup. Histologically, the arteries of which the diameter was relatively small, such as anterior cerebral or posterior cerebral arteries, showed the augment of elastic fibers mingled with collagenous fibers, and these elastic lamina were reduplicated. In these arteries atheromatous material was absent or in lesser amount. On the other hand, in the arteries with larger diameter such as internal carotid, vertebral and basilar cerebral arteries, a lot of collagenous fibers, hyalinization of these, accumulation of gruel materials in the intimal deep layers, disappearance of elastic lamina, atrophy of medial muscle fibers, were observed.

Of the group of cerebral hemorrhage, the incidence of these arterial luminal stenosis with high degree was found more frequently in the subgroup of cerebral hemorrhage with small cerebral infarcts than in the subgroup without. About the half of the all cases with small cerebral infarcts were accompanied with the severe stenosis of cerebral arteries, that was in the subgroup of cerebral hemorrhage with small cerebral infarcts in 62.5%, the subgroup of single

small infarcts in 41.4%, and the subgroup of myocardial infarction with small cerebral infarcts in 58.3%.

Compared with the incidence of severe stenosis of cerebral arteries found in the cases of large cerebral infarcts, that of the group of cerebral infarction was more frequent (76.9%) than that of myocardial infarction (30.0%).

In the cases without brain lesions, the severe stenosis of cerebral arteries was seen in 17.2% in the group of myocardial infarction, and in 2.2% in the controls. While, they distributed almost equally in each six cerebral basilar branches in the cases with small cerebral infarcts, but localized upon the middle cerebral arteries in the cases with larger cerebral infarcts.

The complete occlusion in 5 cases, and occlusion of 6 vessels (3 middle cerebral arteries, 1 internal carotid, 1 vertebral and 1 cerebral basilar artery) were noted. The 4 vessels of these were due to organized thrombi based on severe atherosclerosis, and 2 were accompanied with relatively fresh thrombi. The 3 obstructions in the middle cerebral arteries, one of which was fresh thrombus laid at the origin of the middle cerebral artery to the end of internal carotid, were leading to cause extensive infarction in its territory. In the cases of the vertebral occlusion and the cerebral basilar occlusion, there were small old infarcts on the bilateral sides of basal ganglia and pons, and the question arose whether it was related to the occlusion.

C. Coronary Arteries

1. Relationship of Coronary Atherosclerosis to Age:

Twelve numbers representing the microscopic grading for atherosclerosis of 12 portions in coronary arteries, were added and the sum divided by 12 to indicate the average of coronary atherosclerosis for each heart. Then all of the latter values in each decade were summation and divided by the number of cases in that decade to determine the mean value of coronary atherosclerosis for that decade.

The results of investigation was demonstrable for each group separately in Fig. 9.

The average of coronary atherosclerosis for each decade was the most eminent in the group of myocardial infarction than in other groups. Between the group of cerebral hemorrhage, cerebral infarction, and controls, at the younger decades, coronary atherosclerosis was more severe in the group of cerebral infarction, but at the

Fig. 9. Mean grades for coronary atherosclerosis by decades

older decades, there was no differences at these three groups, and rather at the eighth decade and more over, coronary atherosclerosis was noted more prominently in the group of controls than in cerebral infarction. The statistical relation of coronary atherosclerosis to age was significant in the group of controls ($p < 0.01$), and in the group of cerebral hemorrhage ($p < 0.05$).

2. Mean Grade of Coronary Atherosclerosis by Three Coronary Arterial Branches by Decades: The average numbers of coronary atheros-

Fig. 10. Degree of atherosclerosis of 3 main coronary arteries (controls)

clerosis obtained separately from left descending artery, circumflex artery and right coronary artery for each decade in the group of controls were plotted in Fig. 10.

They were progressively prominent with increasing age, in order of left descending, circumflex and right coronary arteries.

The coronary arterial lesions caused myocardial infarcts were investigated, and these frequency of incidence and distribution were listed in Table VII. Generally myocardial infarction may be the

TABLE VII CORONARY ARTERIAL LESIONS OF MYOCARDIAL INFARCTION

	Left descending artery	Right artery	Circumflex artery	Total
Severe stenosis	13	12	10	35 (20.2)
Intimal hemorrhage	7	5	2	14 (9.1)
Thrombosis	5	2	5	12 (7.8)
Intimal hemorrhage + Thrombosis	12	4	12	28 (18.3)
Moderate stenosis	14	28	22	64 (41.8)
Total	51	51	51	153

TABLE VIII CORRELATION BETWEEN INTIMAL THICKENING AND CEREBRAL ATHEROSCLEROSIS

Cerebral Hemorrhage								Cerebral Infarction							
	-	+	+	+	+	+	total		-	+	+	+	+	+	total
0-9	2		1				3	0-9							
10-19		2	6	2	3		13	10-19		1					1
20-29	1	1	5	4	2	1	14	20-29		4	2	3		2	11
30-39		2		1			3	30-39	2	8	8	7	1	1	26
40-49			2		2		4	40-49		2	7	5	3	1	18
50-59								50-59		1	2				3
60-								60-			1				1
Total	3	5	14	7	7	1	37	Total	2	16	20	15	3	4	60
$r = 0.2854$								$r = 0.0622$							

Myocardial Infarction								Controls							
	-	+	+	+	+	+	total		-	+	+	+	+	+	total
0-9	1	3	1				5	0-9	55	14	2				71
10-19	1	3	2		1		7	10-19	29	23	5	2			59
20-29	2	7	3	1	2		15	20-29	18	10	3	1			32
30-39	2	8	4	2			16	30-39	4	8	4				16
40-49		3	1	1		1	6	40-49			1				1
50-59		1					1	50-		1					1
60-				1			1	Total	106	56	15	3			180
Total	6	25	11	5	3	1	51	$r = 0.3195 \quad p < 0.01$							
$r = 0.1014$															

results of one of the following coronary arterial lesions or a combination of several of them: (1) thrombosis, (2) intramural coronary arterial hemorrhage, (3) severe atherosclerosis with stenosis. Of all the coronary arteries in the group of myocardial infarction, these lesions were observed in 72.5% of left descending arteries, in 56.8% of right coronary arteries and in 45.0% of circumflex arteries. In 51 cases of myocardial infarction, and 153 vessels examined, there were severe atherosclerosis with stenosis in 20.2%, intramural coronary arterial hemorrhage in 9.1% and thrombosis in 26.1%.

D. Comparison of Grades of Intracerebral Arterial Lesions and Atherosclerosis in Individual Case

Compared the degree of intracerebral arterial lesions with atherosclerosis, the summation of

valument of intracerebral arterial lesions was divided to following six classes.

- (-): valument 0
- (+): valument 1-19
- (+): valument 20-39
- (+): valument 40-59
- (+): valument 60-79
- (+): valument 80-

Since angioneurosis, fibrous nodule and intimal edema might belong to the same origin of vascular lesions, these lesions were used in the lump for comparison of atherosclerosis, that was angioneurosis group. Intimal fatty degeneration and medial calcification were not compared with atherosclerosis in this study, because the former was in lesser frequency, and the latter may be the different vascular lesion from arteriosclerosis.

1. Comparison of Grade of intimal Thickening

TABLE IX CORRELATION BETWEEN INTIMAL THICKENING AND CORONARY ATHEROSCLEROSIS

Cerebral Hemorrhage								Cerebral Infarction							
	—	+	++	+++	++++	total		—	+	++	+++	++++	total		
0.0-0.9							0.0-0.9								
1.0-1.9			3	1	3	7	1.0-1.9				4		1	5	
2.0-2.9	2	2	1	3		9	2.0-2.9		5	5	1			11	
3.0-3.9	1	3	3	1	3	12	3.0-3.9	3	4	2	3	1	1	14	
4.0-4.9		1	3	1		6	4.0-4.9		9	3	6	2	1	21	
5.0-			2		1	3	5.0-5.9		3	4	1			8	
Total	3	6	12	6	7	37	6.0-				1			1	
$r = -0.0334$								Total	3	21	14	16	3	3	60
								$r = -0.2588$							
Myocardial Infarction								Controls							
	—	+	++	+++	++++	total		—	+	++	+++	++++	total		
0.0-0.9							0.0-0.9	30	1				31		
1.0-1.9							1.0-1.9	42	18	2			62		
2.0-2.9	1	2				3	2.0-2.9	18	8	6	3		35		
3.0-3.9	1	1	1	1		5	3.0-3.9	8	16	2			26		
4.0-4.9	1	4	4	3	3	15	4.0-4.9	6	6	4			16		
5.0-5.9	3	2	2	3	3	14	5.0-5.9	2	4	1			7		
6.0-6.9	2	3	2	3		11	6.0-	1	2				3		
7.0-7.9		2				2	Total	107	55	15	3		180		
8.0-	1					1	$r = 0.4781 \quad p < 0.01$								
Total	9	14	9	10	6	51									
$r = 0.9254 \quad p < 0.01$															

and Cerebral Basilar Atherosclerosis (Table VIII):

In the group of cerebral hemorrhage, 32.4% of the cases had close correlation between the grade of intimal thickening and cerebral atherosclerosis; in other words, 32.4% of the cases had no evidence of either intimal thickening or cerebral atherosclerosis, and had clear evidence of both arterial lesions, reversely.

The close correlation between these two arterial lesions was found in 21.6% of the cases of cerebral infarction, 19.6% of myocardial infarction, and 54.0% of controls.

It was only in the control group that close correlation was found statistically ($p < 0.01$).

2. Comparison of Grade of Intimal Thickening and Coronary Atherosclerosis (Table IX):

The cases with close correlation between the grade of intimal thickening and coronary atherosclerosis were found in 5.4% of the group of cerebral hemorrhage, in 18.4% of cerebral infarction, in 7.8% of myocardial infarction and 30.0% of controls.

It was in the groups of control and myocardial infarction that these correlation were noted statistically.

3. Comparison of Grade of Vascular Lesions in Angionecrosis-Group and Cerebral Basilar Atherosclerosis (Table X):

The cases with close correlation between these two vascular lesions were found in 18.9% of cerebral hemorrhage, in 13.3% of cerebral infarction, in 21.5% of myocardial infarction and in 42.2% of controls.

TABLE X CORRELATION BETWEEN ANGIONECROSIS GROUP AND CEREBRAL ATHEROSCLEROSIS

Cerebral Hemorrhage								Cerebral Infarction							
	-	+	++	+++	++++	-----	total		-	+	++	+++	++++	-----	total
0-9	2	1					3	0-9							
10-19	4	2	1	3	1	2	13	10-19		1					1
20-29	2	5	2	4		1	14	20-29	3	3	3			3	12
30-39	1	1			1		3	30-39	7	7	6	1	3	2	26
40-	1				1	2	4	40-49	1	3	4	2	2	5	17
Total	10	9	3	7	3	5	37	50-59	1		2				3
$r = 0.2863$								60-	1						1
								Total	13	14	15	3	5	10	60
								$r = 0.0445$							
Myocardial Infarction								Controls							
	-	+	++	+++	++++	-----	total		-	+	++	+++	++++	-----	total
0-9	5						5	0-9	68	2					70
10-19	6	1					7	10-19	49	8	1				68
20-29	12		2				14	20-29	30	2					32
30-39	9	2	3	2	1		19	30-39	10	4	2				16
40-49	3	1	2				6	40-49	2						2
50-59	1						1	50-	2						2
60-	1						1	Total	161	16	3				180
Total	37	4	7	2	1		51	$r = 0.2033 \quad p < 0.01$							
$r = 0.2512$															

It was only in the group of controls that the high correlation of these vascular lesions were noted statistically.

4. Comparison of Grade of Vascular Lesions in Angionecrosis Group and Coronary Atherosclerosis (Table XI):

The cases with close correlation between these two vascular lesions were obtained in 16.2% of cerebral hemorrhage, in 10.0% of cerebral infarction, in 3.9% of myocardial infarction and in 22.7% of controls. Between these two vascular lesions, there was no statistical relation in any group.

In summary, in the groups of cerebral hemorrhage, cerebral infarction and myocardial infarction, there was little correlation between the degree of intracerebral arterial lesions and atherosclerosis. On the other hand, in the group of controls, there were very close correlations between the degree of intimal thickening and atherosclerosis.

sclerosis.

E. Comparison of Cerebral Atherosclerosis and Coronary Atherosclerosis

1. Comparison of Grades of Cerebral and Coronary Atherosclerosis in Individual Cases:

The scattergrams that compared cerebral with coronary atherosclerosis in each case, was demonstrated in Fig. 11.

In the group of cerebral hemorrhage, the majority of the cases had evidence of coronary atherosclerosis with insignificant cerebral atherosclerosis. Thus in individual cases there was very little correlation between degrees of atherosclerosis in the 2 systems.

In the group of cerebral infarction, the degree of cerebral atherosclerosis of the major cases were parallel with that of coronary atherosclerosis, but statistically, there might not be close correlation in the 2 arterial systems.

TABLE XI CORRELATION BETWEEN ANGIONECROSIS GROUP AND CORONARY ATHEROSCLEROSIS

Cerebral Hemorrhage								Cerebral Infarction							
—	+	++	+++	++++	-----	total		—	+	++	+++	++++	-----	total	
0.0-0.9								0.0-0.9							
1.0-1.9	3		1	1	1	1	7	1.0-1.9	1	1			1	2	5
2.0-2.9	4		1	4			9	2.0-2.9	3	1	2		2		8
3.0-3.9	3	4	1	1	1	2	12	3.0-3.9	3	7	3			1	14
4.0-4.9		2		1	1	2	6	4.0-4.9	6	1	8	2	2	5	24
5.0-5.9		3					3	5.0-5.9		4	2	1		1	8
6.0-								6.0-						1	1
Total	10	9	3	7	3	5	37	Total	13	14	15	3	5	10	60
$r = 0.0464$								$r = 0.0431$							
Myocardial Infarction								Controls							
—	+	++	+++	++++	-----	total		—	+	++	+++	++++	-----	total	
0.0-0.9								0.0-0.9	35						35
1.0-1.9								1.0-1.9	63	3					66
2.0-2.9	3						3	2.0-2.9	32	6	1				39
3.0-3.9	2	2	1				5	3.0-3.9	14	3	1				18
4.0-4.9	8	3	3	1			15	4.0-4.9	10	2	1				13
5.0-5.9	7	1	1	1	1		11	5.0-5.9	4	2					6
6.0-6.9	7					1	8	6.0-	3						3
7.0-7.9	2	3	1	3			8	Total	161	16	3				180
8.0-	1						1	$r = 0.2482$							
Total	30	9	6	5	1	1	51								
$r = -0.0914$															

In the group of myocardial infarction, it was observed that the degrees of coronary atherosclerosis were more prominent than that of cerebral atherosclerosis in the greater parts of the cases. Statistically there was not any correlation in these 2 arterial systems.

In the 180 cases of controls, there was a very close correlation between the degrees of cerebral atherosclerosis and that of coronary atherosclerosis, statistically (Table XII).

2. Comparison of Severity and Rates of Progression of Cerebral and Coronary Atherosclerosis with Age in Control Cases:

According to the methods used, the average of coronary atherosclerosis of 180 cases of controls progressed steadily and was more severe than cerebral atherosclerosis in the same decade

until fifth decade (Fig. 12). While the curve for cerebral atherosclerosis tended to follow the same rate of climb as the curve for coronary atherosclerosis until sixth decade, its rate of progression markedly increased over the seventh decade and became beyond the curve for coronary atherosclerosis.

This tendency was the same in both male and female.

DISCUSSION

1. Intracerebral Vascular Lesions

MATSUOKA²⁸ classified the intracerebral vascular lesions into angioneclerosis, calcification, intimal edema, intimal fibrotic thickening, intimal fibrotic hyaline thickening and perivascular necrosis.

Fig.11. Correlation between cerebral and coronary atherosclerosis

TABLE XII CORRELATION BETWEEN CEREBRAL AND CORONARY ATHEROSCLEROSIS (CONTROL GROUP)

	0.0	0.6	1.1	1.6	2.1	2.6	3.1	3.6	4.1	4.6	5.1	5.6	
	-0.5	-1.0	-1.5	-2.0	-2.5	-3.0	-3.5	-4.0	-4.5	-5.0	-5.5	-6.0	
0- 5	13	9	2	4	1	1	1	1		1			33
6-10	3	6	7	3	4	2		1	1				27
11-15	2	3	9	5	5	2	2		1				29
16-20	1	2	3	6	6	2	4	2					26
21-25			2	3	7	4	5		1				21
26-30						5	2	3					10
31-35							6	4					10
36-40								4	2		1		7
41-45									3	2			5
46-50										4	1		5
51-									1		5	1	7
Total	19	20	23	21	22	16	20	15	9	7	7	1	180

$$r = 0.6718 \quad p < 0.01$$

In the light of our own observation, we divided these lesions into intimal thickening, angionecrosis, fibrous nodules, intimal fatty degeneration and calcification.

The hyaline mingled with fibrotic elements in the arteriolar intima, noted in normotensive per-

sons, may differ from hyalinosis related to hypertension. One can observe swelling of individual smooth muscle fibers of the media adjacent to a focus of hyaline deposition, and MONTGOMERY and MUIRHEAD²⁹ considered this as an additional link indicated muscular origin of the hyaline sub-

Fig.12. Sex differences of cerebral and coronary atherosclerosis

stance. On these views, intimal hyaline thickening may be included in the category of intimal thickening, especially as these lesions makes the marked narrowing of the vessels, these two arterial lesions have the functional similarity.

The various observers postulated that angioneclerosis, fibrous nodules and intimal edema were different phases of intracerebral vascular lesions.

HAUST and MORE¹⁵ believed that the intimal edema was due to the permeation of blood plasma into the intima, and the splitting intima was also due to it. OONEDA⁴⁴ considered the intimal edema was sometimes associated with the deposition of fibrin or fibrinoid substance in the intima, and accordingly, the fibrinoid degeneration (angioneclerosis) could be regarded as a severe type of intimal edema.

While, in the extensive reviews, MATSUOKA²⁸ SPATZ⁵³ and NORDMANN⁴⁰ conclude the walls of arteries previously damaged by fibrinoid degeneration may be healed by fibrous replacement and hyalinization, and be leading to fibrous nodules.

The hyaline material is greatest interest because it has a region of lipid substance, like the atheroma of large vessels. The lesions of the vacant spaces in the intima and space between duplicated internal elastic membrane, in which contains lipids and foam cells, are described as intimal fatty degeneration by OONEDA,⁴⁴ MATSUOKA²⁸ and INOSE²⁰ BAKER and KENT² mentioned the arteriolar lipid usually exhibited no tendency to be phagocytosed as did the athero-

matous lipid, nor it usually exhibited calcification.

Medial calcification are considered as deposits of carbonic and calcium or phosphoric and calcium. While, because MÖNCKERBERG's sclerosis³⁰ of femoral arteries was due to hypoxia and mal-nutritional state,¹⁷ the medial calcification may differ from other intracerebral arterial lesions on its origin.

In the results of our own investigation, angioneclerosis, fibrous nodules and intimal edema closely related to hypertension, while intimal thickening had no significant differences of incidence between hypertensive and normotensive group. Moreover, the degree of intimal thickening became gradual progression with increasing age.

On the other hand, the grades of angioneclerosis, fibrous nodules and intimal edema were not correlated with that of atherosclerosis, but the intimal thickening was severe in the cases with severe atherosclerosis.

Some believe that the arteriosclerosis is the first changes and a cause of hypertension, and some believe that hypertension is the first change and a cause of arteriosclerosis. Others suggest that arteriosclerosis and hypertension are an independent process. Intimal hyalinosis were observed in both hypertensive and normotensive group equally by MORITZ and OLDT,³⁶ and in the normotensive cases of old ages by SCRIBA⁵² and IKEDA!¹⁹ The hyaline substance noted in the intimal thickening of arterioles may be derived from medial smooth muscle fibers (MONTGOMERY)²⁹ or from hyaline thrombus of the origin of blood component (DUGID),¹¹ or a result of infiltration, deposition and concentration of blood plasma in vessel wall (KOIDE)²⁶

OONEDA⁴⁴ concluded arteriosclerosis advanced generally through a slow and mild course, but sometimes showed acute exacerbation or relapse. Namely, sudden appearance of arteriosclerosis might be intimal edema and also subendothelial deposition of fibrin. Therefore, one of etiologic factors of arteriosclerosis might be blood pressure.

By our observation, we believe that of the intracerebral vascular lesions, aging process of arteriosclerosis may play an important part in the progression of intimal thickening, and hypertension may be a secondary effect on its severe development. On the other hand, angioneclerosis and intimal edema may initially be influenced by hypertension.

It is of considerable interest that these hyper-

tensive vascular lesions are limited to the brain. It is known that the cerebral arteries, differ anatomically from these in other organs, being thinner, and containing less elastic tissue, concentrated in the internal lamella. Additionally, it should be considered that intracerebral arteries are larger in the size than capillaries, and some of them, especially, the perforating arteries through basal ganglia, have the special architecture²¹ of reverse bifurcation to the main branches.

2. Cerebral and Coronary Atherosclerosis

The concept that atherosclerosis steadily progress with age is defined by several authors. WOLKOFF⁶² noted that in the cerebral arteries, lipid plaques first began to occur in the fourth decade and were present in all cases by the sixth decade. Many investigators^{13,48,50} in the western countries, indicated that cerebral atherosclerosis continued to progress to a certain level until the sixth decade and then increased rapidly throughout the remaining decades. In Japan, NAKANO³⁹ demonstrated that in necropsy cases in HISAYAMA, Kyushu Island, cerebral atherosclerosis progressed rapidly through the end of fifth decade and the beginning of the sixth decade. The comparative study of cerebral atherosclerosis between Japan (Kyushu University) and America (Minnesota population)^{22,49} revealed that cerebral atherosclerosis in both countries increased promptly after sixth decade, and it was with great interest that the degree of cerebral atherosclerosis in Japan was beyond that in America in all decades. Findings of cerebral atherosclerosis in the present study corresponded to the works of these authors.

The commonly accepted belief is that coronary atherosclerosis arise in relatively young life and progresses steadily to a certain level with age and then tends to level off (ACKERMAN,¹ LOBER,⁴⁶ WHITE et al.,⁵⁹ WINTER et al.⁶¹). In the great statistical reviews based on 1,150 autopsies of Japanese, SCHOZAWA⁵⁵ found coronary atherosclerosis progressed through the sixth decade, but its severity had no linear progression throughout the remaining decades. It does not mean that the coronary atherosclerotic process continues to increase to a certain age and then slows down. In our observation, coronary atherosclerosis started occurring at the third decade and its rate showed a moderate progression through the seventh decade, but over this, it revealed rather the steepest gradient.

The general opinion of investigators^{1,46,50,55}

is that coronary arterial disease is remarkably more frequent in males than in females, and females under the age of 50 with coronary disease are unusual. Findings in the present study indicated that severity of coronary atherosclerosis showed male preponderance until seventh decade. These facts may confirm the results of previous studies. The reason for the preponderance of males with severe coronary atherosclerosis is still not clear. Various possibilities have been suggested. Hormonal differences^{43,47} have been considered, and some experimental work has been done. Others have suggested^{10,31} that there was a structural difference between the coronary arteries of males and females observable even in the newborn.

WINTER,⁶¹ MOOSSY,³² and ROBERT et al.⁵⁰ confirmed that coronary atherosclerosis in each decade was more severe than cerebral atherosclerosis in the same decade. But in the results of our investigation, the occurring of coronary atherosclerosis started in earlier life than of cerebral atherosclerosis, and the curve of cerebral atherosclerosis tended to follow the same rate of climb as the curve for coronary atherosclerosis from the fourth to the sixth decade, but it increased steadily up through the seventh decade when it became more severe than that of coronary atherosclerosis.

It is of great interest for this result to coincide with the report mentioned above of comparison of cerebral atherosclerosis between the Japanese and American. But these facts may not mean the high incidence of CVD in Japan. The reason is that, in control group, cerebral atherosclerosis has the close correlation with coronary atherosclerosis. While, it is natural that cerebral atherosclerosis in the cases of cerebral infarction is severe, the same as coronary atherosclerosis in the cases of myocardial infarction.

In our observation, the middle cerebral artery tended to show the highest grade for atherosclerosis of the six main branches of the cerebral arteries, and internal carotid atherosclerosis revealed a higher grade than that of other arteries at the sixth and seventh decades, but over the eighth decade, the posterior cerebral atherosclerosis was more prominent than the internal carotid. Therefore, some attention to cerebral atherosclerosis of the territory of cerebral infarcts should be paid, with respect to the pathogenesis of cerebral infarction, and the lesions of stenosis or obstruction of cerebral arteries might be important.

The wide variation in the degree of athero-

sclerosis between the cerebral and coronary blood vessels in any one case may be striking. Accordingly, the degree of atherosclerosis in different arterial systems, at least in some instances, may be determined by different factors. As one of these factors, there are many studies^{4,12,57} of association between atherosclerosis and malignant diseases. The results of a large majority of these studies showed that in malignant diseases, the incidence and severity of atherosclerotic lesions were significantly less than in controls. In our present study, of these problems, this special consideration was not given.

3. *Some Consideration to the Pathogenesis of CVD and Myocardial Infarction*

The hypothesis that cerebral hemorrhage is due to rupture of intracerebral arterial aneurysm is not new. Both hemorrhage and infarcts may frequently occur together in the same brain. These infarcts are small and old. While, we suggested that the fibrinoid form of hyaline might be transformed into collagen form of hyaline as a part of healing process in the previous study,^{5,6} the marked narrowing of such vessels, and of many with fibrinoid alternation, would be expected to lead to local ischemia. The basic hypertensive arteriopathy may, therefore, injure the brain by including hemorrhage when fresh, and by small focal infarcts when old. The form of cerebral hemorrhage accompanied with small cerebral infarcts are frequently the mesial type of MUTLU³⁸ and not combined with intraventricular bleeding. When the extravasation of blood into an infarct is severe, it is difficult for such hemorrhagic infarct to be distinguished from cerebral hemorrhage. But the necrosis of brain tissue at the periphery of the hemorrhage should be discriminated whether it is secondary to compression of the tissues, or of the associated vessels.

The most common conceptions are those still widely taught, that infarcts of the brain are usually caused by thrombosis. CONSTANTINIDES⁹ found that cerebral arterial thrombi were attached to breaks in atherosclerotic or fibrosed arterial wall and that in most of his cases these breaks were overlaid and filled by the white nuclei of the thrombi. The frequency of thrombi noted in the cerebral basilar arteries, in western countries, was reported in 18% of cerebral infarction by FISHER et al.,¹³ in 33% by HICKS et al.¹⁶ and in 61% by BERRY.⁷ MOOSSY^{33,34} found that cerebral thrombi caused ischemic lesions in 13% of old cerebral infarcts, but in 55% of fresh

cerebral infarcts. In our present study, 5 cases of cerebral infarction of 60 cases (8.2%) were due to thrombi in the cerebral arteries of their territory.

On the other hand, the commonest cause of myocardial infarction is thrombosis of coronary arteries. Some investigators discovered that all thrombi had been caused by breaks in the atherosclerotic arterial lining and that most of accompanying plaque hemorrhage had originated from lesion through the same fractures in the lining (BENSON⁶, KOCH and KONG,²⁵ CONSTANTINIDES⁸). Other authors confirmed that hemorrhagic lesions within the intima from vascularization by discrete capillaries was a common finding in association with atherosclerosis, and attention was called to the probable importance of intramural arterial hemorrhage in the pathogenesis of coronary thrombosis (LEARY,²⁷ PATERSON,⁴⁵ HORN,¹⁸ WARTMAN⁵⁸). HASHIMOTO et al.¹⁴ mentioned that the incidence of coronary thrombosis of myocardial infarction was found in 50–85% in western countries, but in 8.4–56.4% in Japan from literatures. We consider that the cerebral thrombosis in Japan may be less frequently than in western countries the same as coronary thrombosis, and this may be one of reasons for less incidence of cerebral infarction compared with cerebral hemorrhage.

OTSHU⁴² believed myocardial infarcts without coronary thrombi were given rise by recurrent coronary insufficiency due to severe coronary atherosclerosis, leading to the fusion of small myocardial necrosis, or by acute intimal edema due to hypoxia, or by coronary spasmus caused by inflammation. While, the pathogenesis of cerebral infarction without cerebral thrombosis should be devoted attention to the importance of cerebral vascular spasm or vasoconstriction and to cardiocirculatory insufficiency. When cerebral infarction is accompanied by myocardial infarction, cerebral arterial embolus from intramyocardial thrombi must be considered. As a matter of fact, in our observation, cerebral atherosclerosis in the cases of cerebral infarction with myocardial infarcts was less prominent than in ones without.

However, in the light of our investigation, we will suggest that one of the most important etiology of cerebral infarction in Japan, may be associated with intracerebral arteriosclerosis affected greatly by hypertension.

SUMMARY

In a series of 328 autopsies (37 cases of cere-

bral hemorrhage, 60 of cerebral infarction, 51 of myocardial infarction and 180 of miscellaneous disease), macroscopic and microscopic studies of intracerebral arterial lesions, cerebral basilar arteries and coronary arteries were carried out.

Results obtained are summarized as follows.

1. The intracerebral arterial lesions consisted of intimal thickening, angioneclerosis, fibrous nodules, intimal edema ("Aufsplitterung"), intimal fatty degeneration (atherosclerosis of small arteries) and medial calcification. Of these changes, intimal thickening was found more frequently than the others. Angioneclerosis was frequently observed in the cases of cerebral hemorrhage. The prominent changes of fibrous nodules, intimal edema and intimal fatty degeneration were noted in the cases with small cerebral infarct, the diameter of which was less than 2 cm. In controls (cases of miscellaneous disease), intimal thickening was seen in relation to aging. Intimal thickening, angioneclerosis, fibrous nodules, and intimal edema were more frequently seen in the hypertensive group than non-hypertensive group.
2. Atherosclerosis of cerebral basilar arteries became prominent with increasing age in the group of cerebral hemorrhage, myocardial infarction and controls. But in the group of cerebral infarction it was about equal at different ages. In the cases of CVD, the most severe cerebral basilar atherosclerosis was seen in the middle cerebral arteries and followed in order, in the posterior and anterior cerebral arteries. On the contrary, in the cases of non-CVD, it was found in the middle cerebral arteries and then in lesser amount in the carotid and vertebral arteries. In the middle cerebral arteries, atherosclerosis was already seen in the third decade and became more prominent with increasing age. The degree of atherosclerosis in the carotid and vertebral arteries showed the steepest gradient at the sixth and seventh decades. In the posterior arteries it was about the same at the higher decades than seventh.
3. Atherosclerosis of coronary arteries was prominently observed in the groups of cerebral infarction and controls with increasing age.
4. In the group of controls the degree of intimal thickening was correlated with atherosclerosis of cerebral and coronary arteries, and also the degree of atherosclerosis was very close correlation between cerebral basilar arteries and coronary arteries.

In conclusion, the lesions of intracerebral arteries which are etiologic factors of CVD are

greatly affected by hypertension, and may occur more abruptly than atherosclerosis, which develops slowly with aging. Thus CVD is more closely relation to hypertension than coronary heart disease, and this may contribute to the high incidence of CVD in Japan.

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