Mechanisms of Cerebral Lesions in Experimental Cerebrovascular Disease on Dogs

KЕIJI YOSHIDA
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For the practical diagnosis, therapy and prevention of cerebrovascular disease have been studied in several series of experiments on dogs. The author observed the mechanisms of cerebral lesions by their kinds and severity, and found that the most frequent sites of the both hemorrhagic and nonhemorrhagic lesions in our procedure are occurred at Nucleus caudatus. The collateral circulation in the brain is emphasized in this report, and it will prevent occurrence of cerebrovascular lesions.

CEREOVASCULAR DISEASE is one of a major unsolved medical problem, and it has recently come first mortality in Japan.

This problem has been studied over many years, and we have been progressed the knowledges on the mechanisms of cerebral lesions.

Harvey, J. and Rausmann, T. in 1951 produced hemorrhagic infarction by clips placed on the middle cerebral artery. Globus, in 1953, reported experimental cerebral hemorrhage. The experimental production of cerebral infarction in animal was reported by Whisnant, J. P. in 1954.

The mechanisms of cerebral vascular lesions revealed to be unsolved, however there are various opinions and theories.

Adams, R. D. pointed out that it may be said with reasonable certainty that the etiology of all the more common vascular lesions in the brain is either atherosclerosis or some abnormality incident to hypertension. Fisher, C. M. illustrated that the recurrent ischemic cerebral attacks cause cerebral lesions.

The one recorded recently by Denny-Brown and associates, in which a cerebral vein is distended abruptly by saline, producing a hemorrhage infarction in the area drained by that vein.

Thompson et al., Meyer et al. mentioned that hypotension induced by drugs or by bleeding has been found in several studies to affect adversely the extent of cerebral infarcts in cats, dogs and monkeys, after clips has been placed to occlude the middle cerebral artery. Millikan and Whisnant noted that actually one can find every gradient between the pale infarcted one and hemorrhagic one, but still the point remains that grossly hemorrhagic infarcts are in most instances embolic.

In order to make clear clinical problems of diagnosis, therapy, and prevention of cerebrovascular disease, our studies has been concentrated to clear by the mechanisms of cerebral lesions on their kinds and severity. Recently our experimental methods on dogs were established, and we are able to produce either frank hemorrhage, hemorrhagic infarc-
tion, or white infarction.

The author has observed several important results, which may be able to apply to the practical management of cerebrovascular patient.

**Experimental Method**

We selected dogs weighed from 8 to 15 kg. The dogs have been anesthetized by intravenous injection of penta sodium, and one side of the internal carotid artery was exposed by 10 cm long incision on the neck under the sterile technique, and the bifurcation of suprathyroidal artery and internal carotid artery was found, and then a tiny incision on the suprathyroidal artery was made. The polyethylene catheter, which is 0.7 mm in the inner diameter, was inserted into the internal carotid artery via the suprathyroidal artery, and carefully reached at the base of the skull. The fragmented homologous clots were slowly injected through the catheter. After the operation, the suprathyroidal artery was ligated, and was closed. We gave an effort for no vascular changes of the internal carotid artery. The clots were prepared as follows: about 5 cc of blood was drawn from each dog, and kept in the aseptic test tubes at room temperature for two days. The clots were fragmented by a surgical scissors.

The size of the fragmented clots are about 2 to 3 mm in the greatest dimension. When we used the fragmented clots, 0.2 cc of them were suspended in normal saline of 5 cc.

This studies were performed in seventeen groups of dogs, and the number of dogs were encountered 88.

Each group was divided into three categories: the first one uses clots injection only, the second one injects adrenalin intravenously, the third one injects intravenously adrenalin and noradrenalin. We thought that the first categorie is to be a control group, the second one is hypertensive one as well as the third one. In the experimental dogs, the blood pressure measured with a direct method, elevated up to 200 to 250 mmHg with the intravenous injection of adrenalin. The dogs, manifested the cerebrovascular attack, are observed, and were treated with several drugs such as heparin, chlorpromazine, and glucocorticoid.

Some of them died within 24 hours of the cerebrovascular damages. We omitted these dogs from this data.

Before and after the administrations of heparin, the prothrombin time was checked. The therapeutic dose has been kept until the dogs were sacrificed.

The dogs survived in average 7 days after the fragmented clots injection. The clinical manifestation of the cerebrovascular lesions on dogs are such as: hemiparesis, forced circling etc.

**Group 1:** Two dogs were injected 0.2 cc of the fresh homologous clots only.

**Group 2:** Within one year prior to the operation, allylamine was injected intravenously two to three times, then homologous clots and 125 mg of allylamine were injected into the internal carotid artery of each two dog.

**Group 3:** The mixture of 0.2 cc of the fresh homologous clots and 125 mg of allylamine were injected into the internal carotid artery of each four dog.

**Group 4:** 0.2 cc of 48 to 72 hours old homologous clots were injected into the internal carotid artery of each seven dog.

**Group 5:** After 0.2 cc of 48 hours old homologous clots injection into the internal carotid artery, 1 cc of homologous blood extract was injected intravenously. The homologous blood extract made from the mixture of grinded homologous blood clot and serum. Six dogs were used.

**Group 6:** After 0.2 cc of 48 hours old homologous clots were injected into the internal artery, 5 cc of the extract was intravenously injected to each eight dog.

**Group 7:** 48 hours old homologous clots were injected into the internal carotid artery, and then adrenalin was injected intravenously every 48 hours three times. Seven dogs were used.

**Group 8:** After 0.2 cc of 48 hours old homologous clots were injected into the internal carotid artery, the jugular vein of the dog was compresses several times, and venous congestion of head was induced. Also adrenalin was injected intravenously every 48 hours three times. Six dogs were used.

**Group 9:** 1 mm in greatest dimension clots were injected into the internal carotid artery, and then adrenalin, noradrenalin were intravenously administered to each four dog.

**Group 10:** 0.2 cc of 3 to 5 mm in greatest dimension clots were injected into the internal carotid artery, and then adrenalin, noradrenalin were intravenously administered to each three dog.

**Group 11:** 0.2 cc of 48 hours old homologous clots were injected into the internal carotid artery, and then adrenalin, noradrenalin were intravenously administered to each nine dog.

**Group 12:** 0.2 cc of 48 hours old homologous clots were injected into the internal carotid artery, and then adrenalin, noradrenalin, and heparin were intravenously administered to each seven dog.

**Group 13:** 0.2 cc of 48 hours old homologous clots were injected into the internal carotid artery,
and then heparin (25 mg) was intravenously administered several times. Five dogs were used.

Group 14: 0.2 cc of 48 hours old homologous clots were injected into the internal carotid artery, and then predonine (glucocorticoid) was intramuscularly administered to each five dog.

Group 15: 0.2 cc of 48 hours old homologous clots were injected into the internal carotid artery, and then adrenalin, noradrenalin were intravenously administered. One day after clots injection, predonine was intramuscularly administered every day. Four dogs were used.

Group 16: 0.2 cc of 48 hours old homologous clots were injected into the internal carotid artery, and then chlorpromazine (Wintermin 25 mg) was intramuscularly administered every day. Six dogs were used.

Group 17: 0.2 cc of 48 hours old homologous clots were injected into the internal carotid artery, and then adrenalin, noradrenalin were intravenously administered. Chlorpromazine (Wintermin 25 mg) was intramuscularly administered one day after the operation, and it was repeated until the dog sacrificed. Five dogs were used.

Kinds of drugs administered are illustrated in Table I.

Results

The brain was examined carefully. The coronal sections were made, each slice were measured 5 mm in thickness.

Experimental cerebrovascular disease produced with these methods gave many kinds of cerebral lesions in various locations. The cerebral lesions were of various size and number. Hemorrhagic infarction, nonhemorrhagic infarction and frank cerebral hemorrhage were the results.

Table I Kinds of Drugs Administered

<table>
<thead>
<tr>
<th>Clots Injection</th>
<th>Hypertension Induced by Adrenalin</th>
<th>Hypertension Induced by Adrenalin &amp; Noradrenalin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>2 Allyamine (I.V.)</td>
<td>8 Jugular Compression</td>
<td>10</td>
</tr>
<tr>
<td>3 mixed with Allyamine</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>4 (48-72hrs, old clots)</td>
<td>12 Heparin (I.V.)</td>
<td>12</td>
</tr>
<tr>
<td>5 Extract 1 cc (I.V.)</td>
<td>15 Predonine (I.M.)</td>
<td>15</td>
</tr>
<tr>
<td>6 Extract 5 cc (I.V.)</td>
<td>17 Wintermin (I.M.)</td>
<td>17</td>
</tr>
<tr>
<td>13 Heparin (I.V.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 Predonine (I.M.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 Wintermin (I.M.)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Number shows group.
I.V.: intravenously administered
I.M.: intramuscularly administered

The frank cerebral hemorrhage were observed in 27 out of 88 cases (31%). Lesions consisted of cerebral hemorrhage and hemorrhagic infarction in 15 out of 88 cases (17%), frank cerebral hemorrhage and white infarction in 10, frank cerebral hemorrhage, hemorrhagic infarction and white infarction in 4, hemorrhagic infarction only in 18, hemorrhagic infarction and white infarction in 6, white infarction only in 8 out of 88 cases (Table II).

Incidence of hemorrhagic cerebral lesions were 63.7%. The rest of cerebral lesions were examined as nonhemorrhagic (36.3%).

The location of these cerebral lesions were examined in each cases, and classified. Total of 127 lesions were encountered, 95 are hemorrhagic, 32 are nonhemorrhagic.

Concerning the hemorrhagic lesion, the basal ganglia shows 68 lesions out of 95 (53.5%). Lesions located at both in cortical
Table II: Character of Cerebral Lesions

<table>
<thead>
<tr>
<th>Character of Lesions</th>
<th>Number of Cases</th>
<th>Incidence %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frank Hemorrhage</td>
<td>27</td>
<td>31</td>
</tr>
<tr>
<td>Hemorrhage &amp; Hemorrhagic Infarction</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Hemorrhage &amp; White Infarction</td>
<td>10</td>
<td>11.3</td>
</tr>
<tr>
<td>Hemorrhage, Hemorrhagic Infarction &amp; White Infarction</td>
<td>4</td>
<td>4.4</td>
</tr>
<tr>
<td>Hemorrhagic Infarction</td>
<td>18</td>
<td>20.4</td>
</tr>
<tr>
<td>Hemorrhagic Infarction &amp; White Infarction</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>White Infarction</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td><strong>Total Number of Cases</strong></td>
<td><strong>88</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

Fig. 2. Coronal section of brain, showing hemorrhagic infarction at the cortical gray matter and white infarction at the left Nucleus Caudatus.

Fig. 3. Coronal section of brain, showing hemorrhagic and white infarction at the left Nucleus Caudatus.

Gray matter and white matter were 14 lesions. Gray matter showed 3 lesions (2.4%), white matter revealed 10 lesions (7.8%).

Nonhemorrhagic lesions located also at basal ganglia are 26 (20.4%). Lesions located at both in cortical gray matter and white matter showed 4 lesions, gray matter showed 1 lesion, and white matter exhibited 1 lesion.

The basal ganglia is divided in three portions: Nucleus caudatus, Thalamus and Nucleus lentiformis.

Nucleus caudatus showed 45 hemorrhagic lesions out of 68 (66%), Thalamus 17 (25%), Nucleus lentiformis 6 (9%).

Concerning nonhemorrhagic lesions, 19 out of 26 (73%), were observed in Nucleus caudatus, 4 in Thalamus (15%), 3 in Nucleus lentiformis (12%). The most frequent sites of the both hemorrhagic and nonhemorrhagic lesions in our procedure are occurred at Nucleus caudatus (Table III).

Hemorrhagic tendency was studied by each group.

Group 1, fresh homologous clot injection, revealed one case of 74-50% incidence of hemorrhagic tendency, but one case showed 24-0% incidence of it.

Group 2, allylamine intravenously administered, exhibited only 24-0% incidence of hemorrhagic tendency.

Group 3, allylamine administered into the internal carotid artery revealed an increase of hemorrhagic tendency.

Group 4, 48-72 hours old homologous clots injection, revealed some hemorrhagic tendency, however two cases showed 24-0% incidence of hemorrhagic tendency.

Group 5, extract (1cc) intravenously administered, showed 100-75% incidence of hemorrhagic tendency.
### Table III  Site and Number of Intracerebral Lesions Hemorrhagic and Nonhemorrhagic

<table>
<thead>
<tr>
<th>Location</th>
<th>Character</th>
<th>Hemorrhagic</th>
<th>Nonhemorrhagic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>68 (53.5%)</td>
<td>26 (20.4%)</td>
</tr>
<tr>
<td>Basal Ganglia</td>
<td>Nucl. Caud.</td>
<td>45 (66%)</td>
<td>19 (73%)</td>
</tr>
<tr>
<td></td>
<td>Thalamus</td>
<td>17 (25%)</td>
<td>4 (15%)</td>
</tr>
<tr>
<td></td>
<td>Nucl. Lent.</td>
<td>6 (9%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>White Matter &amp; Gray Matter</td>
<td></td>
<td>14 (11%)</td>
<td>4 (3.1%)</td>
</tr>
<tr>
<td>Cortical Gray Matter</td>
<td></td>
<td>3 (2.4%)</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>White Matter</td>
<td></td>
<td>10 (7.8%)</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Total Number of Lesions</td>
<td></td>
<td>95 (75%)</td>
<td>32 (25%)</td>
</tr>
</tbody>
</table>

hemorrhagic tendency.

Group 6, extract (5cc) intravenously administered, showed 100-50% incidence of hemorrhagic tendency.

Group 7, hypertension induced by adrenalin, showed an increase in hemorrhagic tendency (Table IV).

Group 8, hypertension induced by adrenalin and jugular compression, revealed moderately increase in hemorrhagic tendency.

Group 9, 10, 11, hypertension induced by adrenalin and noradrenalin showed an increase in hemorrhagic tendency.

Group 12, hypertension induced by adrenalin and noradrenalin, treated with heparin revealed remarkable increase in hemorrhagic tendency, compared with group 9.

Group 13, normotensive cases treated with heparin, revealed markedly decreased hemorrhagic tendency, and nonhemorrhagic lesions occurred (Table V).

Group 14, normotensive cases treated with predonine showed slight decrease in hemorrhagic tendency.

### Table IV  Hemorrhagic Tendency in Each Group

<table>
<thead>
<tr>
<th>Hemorrhagic Tendency</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>100-75%</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>74-50%</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>49-25%</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>24-0%</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

### Table V  Hemorrhagic Tendency in Each Group

<table>
<thead>
<tr>
<th>Hemorrhagic Tendency</th>
<th>Group 8</th>
<th>Group 9</th>
<th>Group 10</th>
<th>Group 11</th>
<th>Group 12</th>
<th>Group 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>100-75%</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>74-50%</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>49-25%</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>24-0%</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>

### Table VI  Hemorrhagic Tendency in Each Group

<table>
<thead>
<tr>
<th>Hemorrhagic Tendency</th>
<th>Group 14</th>
<th>Group 15</th>
<th>Group 16</th>
<th>Group 17</th>
</tr>
</thead>
<tbody>
<tr>
<td>100-75%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>74-50%</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>49-25%</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>24-0%</td>
<td>3</td>
<td>4</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

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Group 15, hypertension induced by adrenalin and noradrenalin, treated with predonine exhibited an decrease in hemorrhagic tendency.

Group 16, normotensive cases treated with chlorpromazine, revealed also decrease in hemorrhagic tendency.

Group 17, hypertension induced by adrenalin and noradrenalin, treated with chlorpromazine, revealed some hemorrhagic tendency (Table VI).

**Histological Findings**

After 10% formalin fixation for seven days, all the cerebral lesions were made in paraffin blocks, which were cut 6 micron in thickness. Harris Hematoxylin-Eosin stain, Azan stain, Mallory stain, Sudan III stain were applied.

Each slides were examined, and they revealed nonspecific lesions. Group 16 and 17 were examined in the continuous sections.

Frank cerebral hemorrhage consists of mainly numerous erythrocytes, showing no peripheral zone of the softening in the surrounding cerebral tissue. Hemorrhagic infarction reveals many erythrocytes escaping from the blood vessels, degeneration of ganglionic cells, and fat granulated cells in the surrounding cerebral tissue.

![Fig. 4. Hemorrhagic infarction, showing many erythrocytes and degeneration of ganglionic cells.](image)

There are a few dilated arteries filled with erythrocytes, and these vascular wall reveals structureless. White infarction exhibits proliferation of glia cells, edema of cerebral tissue and proliferation of fat granulated cells. New capillaries, collaterals are present in the surrounding cerebral tissue.

![Fig. 5. White infarction, showing proliferation of fat granulated cells and glia cells.](image)

The vascular wall of artery shows the waved lamina elastica, and the lumen usually filled with erythrocytes. The angionecrosis of cerebral artery is found in all cases of hemorrhagic lesions, except white infarction. The most occurrence of angionecrosis are found in group 5, 6, 7, 8, 9, 10, 11. The author

![Fig. 6. Angionecrosis, with Mallory stain.](image)

![Fig. 7. Perivascular hemorrhage extend to cerebral tissue damage.](image)

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considered that Extract, Adrenalin, Noradrenerglin are as increase factors, these drugs and extract affect directly vascular wall of cerebrum, and we could recognize angioneerosis.

Predonine (glucocorticoid) administered group 14, 15, revealed less occurrence of angioneerosis.

Angioneerosis is confirmed by using Azan and Mallory stain, and appeared to be bluish purple staining with Azan, and red staining with Mallory stain in each intima, media, and adventitia.

Occasionally entire vascular wall as well as into the perivascular cerebral tissue stained with these methods.

**Discussion**

In 1954, Whisnant\(^6\) reported first the introduction into one internal carotid artery of dogs, of 0.2 to 0.3 cc Liquid vinyl acetate. This rather promptly hardened on contact with the blood and occludes the internal carotid and usually the middle cerebral and sometimes other cerebral arteries. This is usually in a continuous strand within the arterial tree.

Second their method has been a similar injection from syringe of 0.2 cc of 48 hours old homologous clot.

We compared this method with ours. Our method uses internal carotid artery via suprathyroidal artery, and the carotid arterial wall is intact. We found the best clot for the experimental cerebral lesion was 48 hours old homologous clot, and the clot should be 2 to 3 mm in the greatest dimension.

After a few months of experiments, we were able to let survive these dogs for average period of seven days after clots injection.

Studies by each group were performed. Group 1 and 2, none of hypertensive drugs were given, exhibited a little hemorrhagic tendency, however the groups treated with allylamine, extract of clot, adrenalin, and noradrenalin & adrenalin, and jugular compression after the administration of adrenalin, showed an increase in hemorrhagic tendency (Group 3, 5, 6, 7, 8, 9, 10, 11).

Hypertension, induced by drugs, following cerebral infarction in dogs, has been found to the extent of hemorrhagic infarction.

The reports have been made by Meyer et al.\(^7\) and Endo.

Hypertensive factor could be an increasing factor of angioneerosis, and its hemodynamic action will increase hemorrhage from the weak point of cerebrovascular lesion directly.

The effect of the anticoagulants in experimental cerebral infarction has been demonstrated by Whisnant, J. P.\(^7\) in 1959, who stated that frank cerebral hemorrhage has been demonstrated within the infarct, by giving anticoagulants following cerebral infarction. The author considered that the frank cerebral hemorrhage must be the results of rupture of vascular walls. The fact explains that, if heparin is injected to the normotensive dogs, which are unable to reveal hemorrhagic lesions, but nonhemorrhagic lesions are produced.

Mechanisms of collateral circulation has been proved by Adams and Ecken\(^1\), illustrated the anatomy functional significance of the meningeal anastomosis of the human brain, in which stated no collaterals on the penetrating vessels of the middle, anterior cerebral arteries.

When the coronal sections of brain in this studies were examined, the most cerebral lesions are located in basal ganglia. We know this area is getting blood supply from the anterior cerebral artery as pathologists describe. Why nonhemorrhagic lesions were occurred in cerebrum? Our studies show about 36% of nonhemorrhagic lesions. Adams emphasized that nearly all hemorrhagic infarctions are embolic, whereas anemic infarctions may be embolic or thrombotic. Our results show 36% of white infarction by injection of homologous clots. These cerebral lesions are considered to be embolic. Histologically the lumen of the vessel is occluded completely by clot, and the distal end of the vessel does not contain any cell elements of blood. The circulatory and metabolic disturbances affect cerebral tissue, and the local area become white infarction. If collateral circulation
compensates immediately after the occlusion of cerebral vessels, the white infarction will remain.

The lumen of vessel is occluded incompletely by clot, the distal end of vessel contains cell elements of blood. The circulatory and metabolic disturbance occur in the local area, where the pathological changes of vessels increase.

Angioneurotic appears in such a place. The wall of the vessels may be in anoxic state, the erythrocytes and serum escape from the vascular lumen through the cerebral vascular wall, then hemorrhagic infarction may be observed.

Fazio, C. and Sacchi, V.\textsuperscript{17} reported that the occlusion, when embolus migrates to the other place, results hemorrhage.

Predonine (Glucocorticoid) group without hypertensive drugs revealed only nonhemorrhagic lesions in all cases.

Stefanini, M. et al.\textsuperscript{10} reported the effect of steroid hormone in the case of disseminated prostatic carcinoma, and they found the decrease of plasmin activity and hemorrhagic tendency.

We know that the glucocorticoid has been administered in Henoch-Schönlein purpura case, and it is effective.

Glucocorticoid group reveals nonhemorrhagic lesions in all cases of this experimental cerebrovascular disease, this is probably due to the effect on vascular walls.

An effect of steroid hormone in aplastic anemia and acute leukemia could decrease hemorrhagic tendency. It could be due to the increase of number of platelets and capillary tolerance to pathological changes in the vascular wall. The cause of decrease hemorrhagic tendency in aplastic anemia and acute leukemia has been reported as above, but if we count megakaryocytes in the bone marrow and platelets in the peripheral blood, we will find there is no significant changes with the administration of steroid hormone. The effect of the steroid hormone as to decrease hemorrhagic tendency could be illustrated with capillary tolerance to pathological changes in the vascular wall. Angioneurotic is observed in all cases of hemorrhagic lesions, except white infarction.

Chlorpromazine group exhibited a decrease of hemorrhagic tendency, and it showed an inhibiting effect on pathological changes of blood vessels. Chlorpromazine also inhibits collateral circulation. Angioneurotic induced by adrenalin and cerebral hemorrhage could not be prevent with administration of chlorpromazine.

The mechanisms of cerebrovascular disease in our experiments could be started with the stenosis or obstruction of cerebral vessels.

In human being arteriosclerosis, embolism, thrombosis, tumor, syphilis and angiospasm may cause stenosis or obstruction of cerebral vessels. The lumen of local cerebral vessels are narrowed or obstructed, and then circulatory and metabolic disturbances will occur in the brain.

It seemed probable that neither decreased oxygen nor increased carbon dioxide tissue concentrations. The circulatory and metabolic disturbances such as, metabolite and carbon dioxide accumulation, pH shifts etc. may also play a role in maintaining or developing these collateral circulation. Angiospasm may reveal none of pathological changes of cerebral vascular wall and cerebral tissue.

Arteriosclerosis, embolism, thrombosis, tumor and syphilis will develop pathological changes of vessels in the brain, after that the circulatory and metabolic disturbances will increase. The collateral circulation may compensate such disturbances. If compensation by the collateral is not sufficient, pathological changes of vascular walls will become angioneurotic.

Angioneurotic followed by infiltration of serum components into the vascular wall results rupture of vascular wall.

Cerebral hemorrhage can be seen after rupture of vascular wall, and also develop cerebral tissue damage (Table VII).

**Summary**

Studies on mechanisms of cerebral lesions in experimental cerebrovascular disease, using 88 dogs were presented.

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13 cases received adrenalin, 32 cases received noradrenalin and adrenalin intravenously after the homologous clots injection into unilateral carotid artery.

Every gradient between the white infarction, hemorrhagic one, and frank cerebral hemorrhage were found. The classification of the lesions revealed 63.7% of hemorrhagic cerebral lesions, and the rest of them were nonhemorrhagic.

1) Difference of experimental cerebral vascular disease between our methods and Millikan & et al. are discussed.

2) Influences of hypertension to cerebrovascular disease are reconfirmed. Hypertension, induced by drugs, following cerebral infarcts in dogs has been found to increase the hemorrhagic tendency. The frank cerebral hemorrhage is observed in this study 27 out of 88 cases (31%).

3) The reason, why the cerebral lesions are located often in the basal ganglia, is discussed. Our studies reveal 74% of lesions in the basal ganglia.

4) The collateral circulation is emphasized in this report. The collateral circulation is very important for the prevention of cerebral vascular disease.

5) Nonhemorrhagic lesions were found, even though hypertension was induced by drugs. The mechanisms of nonhemorrhagic lesion is discussed. The author supports that the theory of the cause of nonhemorrhagic lesion is embolic.

6) Anticoagulant, heparin is administered to the clots injected dogs. The dogs, if hypertension is induced by drugs, were treated with heparin, exhibited frank cerebral hemorrhage.

The dogs, if hypertension is not induced by drugs, were treated with heparin, exhibited less hemorrhagic cerebral lesions.

The effect of heparin may be an accelerator on collateral circulation, and remove circulatory and metabolic disturbances.

7) The glucocorticoid group revealed to decrease hemorrhagic tendency. The glucocorticoid seems to prevent the occurrence of pathological changes of cerebral vascular wall.

8) Chlorpromazine seems to inhibit pathological changes of cerebral vessels, and also inhibit collateral circulation.

The author greatly acknowledges his indebtedness to Professor Toyozo Aita and for kind guidance in conducting this study. The author wishes to thank Dr. Y. Goto, Dr. T. Hasegawa, Dr. H. Takizuka for technical advices.

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REFERENCES
