STUDIES ON THE DISTURBANCES OF THE CEREBRAL BLOOD CIRCULATION

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The studies on the disturbances of cerebral blood circulation have been made by the writer and his coworkers since 1955.⁽¹⁻⁹⁾

In this work, new findings of the cerebral vascular architecture (both arteries and veins) were obtained with the methods of acrylic resin injection into the cerebral vessels.^(3,7) From the view of the cerebral vascular architecture, a pathogenesis of cerebral hemorrhages in the cases of leukemia and aplastic anemia, mechanisms and common sites of the cerebral softening and hemorrhage due to venous circulatory disturbances will be explained. This type of hemorrhages can be called "edematous necrotic hemorrhages." In the experiment, the similar edematous necrotic hemorrhages were observed in the brains of anemic dogs with venous circulatory disturbances.^(3,8) In addition to the anatomical pathologic studies of the spontaneous hemorrhages and softenings of the human beings, the ligations of the anterior and middle cerebral arteries of dogs with either increased or decreased blood pressure were performed.^(6,9) On the bases of these observations, the followings will be discussed; the cerebral vascular architecture, arterial and venous cerebral softenings and hemorrhages and what an important role the pathologic blood vessels play in these conditions, especially angioneclerosis.

I. SOME NEW FINDINGS ON HUMAN CEREBRAL VASCULAR ARCHITECTURE BY INJECTION OF ACRYLIC RESIN

Materials and Methods

Red acrylic resin was injected into the bilateral common carotid arteries and vertebral arteries as soon after the start of a necropsy as possible. Immediately after a removal of the brain, blue acrylic resin injection was made through the superior sagittal sinus and the great cerebral vein. The

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brain substance was resolved in 10% sodium hydrate and washed in running water for study of cerebral vascular architecture.

The mixture consisting of equal amount of methylmethacrylate and ethylmethacrylate was used. The benzoi peroxide and dimethylaniline were applied as polymerization catalyser and crimson lake and prussian blue were employed as a dye (Fig. 11).

Results

A) *Arteries of the Anterior Brain Stem Including Basal Ganglia, Thalamus, Caudate Nucleus, Internal Capsula etc.*

1) Aa. corporis striati anteriores arise from the anterior cerebral artery and Aa. corporis striate mediae arise from the middle cerebral artery, running toward the opposite direction to the stem-arteries. 2) What are hither-to called A. striothalamica and Aa. lenticulothalamica can not be traced in our cases. 3) Globus pallidus is rather poorly vascularized compared with the other nuclei. 4) The rami perforantes of basilar artery as well as superior cerebellar artery are distributed over the tegmentum of the pons. 5) No anastomosis between arteries of anterior brain stem was observed.

B) *Meningeal Arterial Anastomoses in the Cerebrum* (Fig. 12).

The writer has demonstrated meningeal arterial anastomoses illustrated table 1, 2 and 3.

Table 1.

The Anastomoses Between the Middle and Anterior Cerebral Arteries

Middle Cereb. Art.	Anterior Cereb. Art.	Part of Anastomosis	Types of Anastomoses
Prerolandic branch	Posterior internal frontal branch	Precentral sulcus	end to end
Rolandic branch	Paracentral branch	Central sulcus	end to end
Anterior parietal branch	Paracentral branch	Postcentral sulcus	end to end
Posterior parietal branch	Paracentral branch	Sulcus parietalis superior	end to end *branched
Sup. orbito-frontal branch	Anterior and middle internal frontal branch	Sulcus frontalis superior and small sulci on the superior aspect of the Gyrus frontalis medius	*branched
Ascend-frontal branch	Middle internal frontal branch	Sulcus frontalis superior	*branched
Orbito-frontal branch	Fronto-polaris branch	Sulcus frontalis medius and small sulci on the inferior aspect of the Gyrus frontalis medius	*branched

End to end anastomoses measure 300 to 700 μ in diameter, while branched

anastomoses in the form of a candelabra measure 80 to 250 μ , and they are anastomosed in the cerebral sulci. The anterior artery does not demonstrate any anastomoses between its neighboring branches as do the middle and posterior cerebral arteries.

Table 2.

The Anastomoses Between the Middle and Posterior Cerebral Arteries

Middle Cereb. Art.	Post. Cereb. Art.	Part of Anastomosis	Types of Anastomoses
Angular branch	Parieto-occipital branch	Small sulci of the Gyrus angularis	*branched
Posterior temporal and Angular branch	Calcarine branch	Small sulci of the Gyrus occipitalis lateralis and Sulcus occipitalis lateralis	*branched

Table 3.

The Anastomoses Between the Anterior and Posterior Cerebral Arteries

Ant. Cereb. Art.	Post. Cereb. Art.	Part of Anastomosis	Types of Anastomoses
Posterior callosal branches	Callosal branch	Sulcus callosum	end to end
Small branch of the Posterior callosal branch	Callosal branch	Sulcus parietalis inferior	*branched
Precuneal branch	Parieto-occipital branch	Small sulci of the Precuneus	*branched

* branched anastomoses in the form of a candelabra

C) *Arteries in the Cerebral Cortex and Medulla* (Fig. 13-16).

The coronal sections through the preparation of acrylic resin specimen revealed that Aa. corticales rectangularly arising from meningeal arteries were densely placed throughout the cortical zone and rather large Aa. medullares were extending into the medulla. In addition to the A. corticalis and A. medullaris in the cerebral cortex and medulla, the writer has found a group of small vessels, which have a characteristically limited distribution in the upper portion of the medulla, these features have never been described. The writer calls them "A. subcorticalis."

1) *A. Corticalis*: Aa. corticales arise from rather large meningeal cerebral arteries (which are usually connected with the A. medullaris), they directly or after a short transverse trip over the cortical surface extend into the brain tissue with a right angle to the cortical surface, then many are distributed into the cortex running in a somewhat curved fashion and completely ramified before getting into the medulla. The branches from the meningeal cerebral arteries are extending into the deeper sulci, making the more dull angle to the cortical

surface. The main branches measure 40 to 60 μ in diameter (Fig. 1). The branches of cortical arteries can be clasified into 3 major forms: 1. branched, 2. tendril, 3. braiding. The structures of A. corticalis consist of mixture of previously described 3 forms and usually a combination of the tendril and branched forms is encountered. No anastomoses between branches or main branches of Aa. corticales are evident (Fig. 2).

Fig. 1 Architecture of main branches of the Aa. corticales.

Fig. 2 Branched forms of the A. corticalis.

2) *A. Medullaris*: The many small branches running over the cerebral surface arising from the anterior, middle and posterior cerebral arteries go into the brain tissue and terminally continue to the A. medullaris. The A. corticalis and sometimes A. subcorticalis give off many branches, before going in to the brain tissue, which run through the cortex parallel to the A. corticalis, then abruptly make a sharp angle toward the nearest lateral ventricle reaching into the medulla without narrowing of the lumen. The Aa. medullares are gradually reducing in diameter without interlacing each other and completely ramified terminally. The main branches measure 100 to 200 μ in diameter (Fig. 3).

There are a few anastomoses between the A. medullaris in the medulla. The anastomoses are increasing in number in the deeper part of medulla compared to the intermediate part, while the upper part (subcortical white matter) is poor in anastomoses. The branches of anastomoses measure 80 to 120 μ in diameter.

Fig. 3 Architecture of main branches of the Aa. medullares.

The Aa. medullares concentrate toward the lateral ventricle. The figure shows that one in the lateral lobe runs in vertical against the plane and toward the anterior inferior horn of the lateral ventricle.

Fig. 4 Branched forms of the A. medullaris.

a: right angle
b: backward
c: onward
d: revolving
ma: anastomotic branch

Occasionally the A. medullaris gives off branches in the cortex, showing similar ramifications to the A. corticalis.

The forms of ramification of the A. medullaris in the medulla are following; 1) branches with a right angle, 2) backward, 3) onward and 4) revolving. There are no anastomoses between their neighboring branches, though main branches show the anastomoses which has previously been described (Fig. 4).

The Aa. medullares give off branches mainly up and down, running over the same plate to the main branches along the long axes of the gyri. The branches make a dull angle at the corner of the main branches corresponding to the angles of the gyri. In the areas of near the ventricle, however, some main branches give off branches in different directions (Fig. 5).

3) *A. Subcorticalis*: A. subcorticalis are distributed in the almost similar fashion to that of the A. medullaris with exception of some differences that the former is smaller and shorter than the latter and is completely ramified in the upper portion of the medulla (subcortical white matter). The writer gives a name of Aa. subcorticales to these arterioles based upon the distributed area.

These arterioles are considered to be 2 types. 1) Long type: this measure 60 to 80 μ in diameter and 1 to 2.5 cm in length, giving off branches only in the medulla. 2) Short type: this measure 50 to 60 μ in diameter and 0.5 to 1 cm in length, giving off branches in the deeper portion of the cortex, then go into the medulla with some ramifications in the medulla.

Fig. 5 Solid delineation on the directions of branches of the Aa. medulares observed from the surfaces of the brain.

The small branches lie on the same plane to the main branches, which is in parallel to the long axes of the Gyri.

Fig. 6 Architecture of main branches of the Aa. subcorticales.

1: long type
s: short type

In this type of ramification, the branches of the cortex are corresponding to the Aa. corticales and the branches of medulla to the A. medullaris. The branches of the Aa. subcorticales make a same plate to that of the main branches in the medulla as do the A. medullaris. However, no anastomoses between these main branches are evident, comparing to the A. medullaris having anastomoses between main branches. The distribution of this artery is limited only in the upper portion of the medulla just beneath the cortex (subcortical white matter) having a clear distinction to the deeper Aa. medulares (Fig. 6, 7).

D) *Arteries in the Cerebellum*

1) *Meningeal Arterial Anastomoses of the Cerebellum*: The end to end anastomoses measure 220 to 480 μ in diameter. a) The anastomoses between the superior cerebellar and the anterior inferior cerebellar arteries lie in the horizontal sulci and anterolateral portion of the superior semilunar lobulus, b) the one between the superior cerebellar and the posterior inferior cerebellar arteries lie in the posterolateral portion of the superior semilunar lobulus and near the horizontal sulci of the superior posterior pole close to the posterior

Fig. 7 Arterial architecture in the cortex and medulla.

- A: Meningeal Artery
- C: A. corticalis
- Sl: Long type of the A. subcorticalis
- Ss: Short type of the A. subcorticalis
- m: A. medullaris
- ma: Anastomotic branch
- mt: Transverse branch

The medullar branches of the Aa. medullares and Aa. subcorticales are in vertical to this plane and overlapped with the main branches in fact. This can be shown in convenience.

cerebellar fistula, c) the one between the anterior inferior cerebellar and posterior inferior cerebellar arteries lie on the inferior medial aspects of the inferior semilunar lobulus. Neither anastomoses of each bilateral cerebellar arteries, nor anastomoses between neighboring arteries are encountered.

2) *Arteries in the Cerebellar Cortex and Medulla:* It is possible to distinguish the cortical and medullar zones with arterial distribution which are rather obscured to that of the cerebrum. Branches of all cerebellar arteries running over the superficial areas of cerebellum are distributed mainly in the cortex, while in the most parts of the medulla two rather large deeper branches of the superior cerebellar artery are encountered (Fig. 8).

Fig. 8 Arterial architecture in the cerebellar white matter.

The cerebellar arteries running over the superficial areas give off many branches extending deeper into the sulci, then these branches are more ramified symmetrically and with right angle in the cerebellar cortex, and deeper extending branches anastomose with deeper branches of the medulla. Two deeper branches of the superior cerebellar arteries are arized, making a right angle, from the branches on the superior lateral aspects of the quadrangular lobe and medial aspects close to the vermis cerebelli, going into the cerebellar substance and partly anastomose with branches in the medulla after running through the

previously mentioned cortex. The vermis cerebelli is divided into the left and right in the midline and is supplied by branches from the superior cerebellar arteries without their bilateral arterial anastomoses (Fig. 8).

E) Venous System of the Brain

1) *Veins of Anterior Brain Stem:* Venules are collected into many veins running in parallel each other and making some curves and reach to the lateral ventricular wall, then at this point they change their directions along the wall, going into the V. terminalis and thereafter they, through the Vv. cerebri internae and V. cerebri magna, reach to the sinus rectus.

Some of them pour into the Vv. anastomoticae sagittales without making a usual structure of main venous branches and form many anastomoses with V. terminalis. The venules in the anterior brain stem are collected to 3 or 4 rather large venous branches to descend and terminate into the V. basalis. These rather large venous branches are anastomosed with V. terminalis and Vv. anastomoticae sagittales in the upper portion without decreasing in diameter. These are many anastomosed branches between the inferior and superior venous system and no clear distinction between them is demonstrated in the peripheral branches (Fig.9).

Fig. 9 Venous architecture of the cerebrum.

Horizontal Section

Coronal Section

a: V. cerebri magna
b: Vv. cerebri internae
c: V. septi pellucidi
d: V. striata superior
e: V. chorioidea
f: V. terminalis

g: Vv. anastomoticae sagittales
h: V. thalamica
i: V. hippocampi
j: V. basalis
Vs: Vv. subcorticales
Vm: Vv. medullares

2) *Veins in the Cerebral Cortex and Medulla:* The Vv. corticales in the

cortex and the Vv. subcorticales in the upper portion of the medulla (subcortical white matter) are collected to the meningeal veins over the surface of the brain, passing through the superior cerebral vein and lead to the sinus sagittalis superior. The main and small branches of the V. subcorticalis run over the almost same dimension which is parallel to the cortico-medullary junction in the cortex with forming of curves. This manner is similar to the one in the A. subcorticalis.

F) *The Ways of Blood Circulation in the Cerebrum*

a) *Anterior Brain Stem*:—The blood supplied from “perforating arteries” mostly passes through the ascending vein reaching to the ventricular wall and partly pours down to the V. basalis. There are large and increased numbers of anastomoses between the ascending and descending veins and direct and strong anastomoses are also encountered between the ventricular veins and descending veins. The main blood flow owes to the ascending venous system, while the descending veins presumably play a role of anastomoses between the V. cerebri magna and the V. basalis (Fig. 10).

b) *Cerebral Cortex and Medulla*:—Blood flows supplied by the Aa. corticales, subcorticales and medullares in the cortex and the upper portion of the medulla (subcortical white matter) are collected to the corresponding veins (Vv. corticales

and subcorticales) each and return to the superior, middle and posterior cerebral veins over the brain surface, while blood flows by Aa. medullares in the deep medulla probably return to the lateral ventricular plexus through veins (Vv. medullares).

II. STUDIES ON THE STATISTICS AND PATHOGENESIS OF INTRACRANIAL HEMORRHAGES OCCURED IN CASES OF LEUKEMIA AND APLASTIC ANEMIA

Materials and Methods

The material was obtained from brains of 39 cases of leukemia and 13 cases of aplastic anemia who died at the [REDACTED] and 6 cases of leukemia at the [REDACTED] in the years of 1953 to 1956. The material from the [REDACTED] is excluded in statistic studies. A 10% formalin fixed brain tissue was embeded in paraffin and celloidin, making H-E and other special stains.

Results

1. *Frequency of the Intracranial Hemorrhages:* 1) In leukemia, age incidence of intracranial hemorrhages is shown in table 4 and the relation between the types of leukemia and intracranial hemorrhages is shown in table 5. 2) In aplastic anemia, age incidence of intracranial hemorrhages is shown in table 6.

Table 4.

Age	Numbers of autopsy in leukemia	Cases of intracranial hemorrhages	
0~10	6	1	16.6%
11~20	11	2	18.2%
21~30	9	5	55.5%
31~40	5	3	60.0%
41~50	5	4	80.0%
51 over	3	0	0%
Total	39	15	38.5%

Table 5.

	Numbers of autopsy	Cases of intracranial hemorrhages		
Myeloid Leukemia {	acute	21	8	38.1%
	subacute	3	2	66.6%
	chronic	14	5	35.1%
Lymphatic Leukemia	1	0	0	0%

Table 6.

Age	Numbers of autopsy in Aplastic anemia	Cases of intracranial hemorrhages	
0~10	1	0	0%
11~20	3	2	66.6%
21~30	2	2	100.0%
31~40	3	1	33.3%
41~50	2	1	50.0%
51 over	2	1	50.0%
Total	13	7	53.8%

2. *The Localization of Hemorrhages:* The table 7 shows the localization of intracranial hemorrhages in leukemia and aplastic anemia.

Table 7.

		Leukemia (15 Cases)		Aplastic Anemia (7 Cases)	
Cerebrum hemisphere	both	3	8 53.3%	2	4 57.1%
	left	3		0	
	right	2		2	
Brain stem	left	3	4 26.6%	0	2 28.5%
	right	1		2	
Meninges		12	80.0%	4	57.1%
Cerebral peduncles		1	6.6%	0	0%
Pons		1	6.6%	0	0%
Medulla		1	6.6%	0	0%
Cerebellum		5	33.3%	2	28.5%
Hypopysis		0	0%	1	12.2%

3. *Histopathological Findings and Clacifications:* The types and clacifications of intracranial hemorrhages in leukemia and aplastic anemia are shown in table 8.

The isolated and localized hemorrhages in leukemia consist of focal infiltrates of leukemic cells based upon heterotopic extra medullary hematopoiesis mainly due to damages of capillaries, venules and occasionally arterioles. These are so-called ring hemorrhages or white hemorrhages (Fig. 22, 23). The former is composed of inner layer of chiefly leukemic cells and the outer layer of chiefly erythrocytes around capillaries, while the latter only leukemic cells around minute vessels. In both types, the cerebral edema is frequently accompanied in the visinities of the lesions. The aggregated hemorrhages are formed secondary to the aggregation of isolated and localized hemorrhages (Fig. 17, 24, 25).

In aplastic anemia, the hemorrhages are mainly based upon increased per-

Table 8.

Forms of Intracranial Hemorrhages in Leukemia and Aplastic Anemia.

- I. Hemorrhages due to increased permeability of capillary and venule walls and breakdown of vascular wall.
 1. Subarachnoid Hemorrhage
 - 1) diffuse
 - 2) hematomatous
 - 3) mixture
 2. Cerebral Hemorrhage
 - 1) Isolated and localized Hemorrhage
 - 2) Aggregated Hemorrhage
 3. Intraventricular Hemorrhage
- II. Hemorrhages due to a breakdown of arterial wall (Only in cases of leukemia)
- III. Edematous Necrotic Hemorrhage
 - 1) Subcortical white matter type
 - 2) Deep white matter type
 - 3) Mixture type
- IV. Cortical hemorrhage secondary to extension of subarachnoid Hemorrhage.

meability of capillaries and venous walls due to changes of blood components, mainly erythrocytes and edema around the blood vessels as well as in the brain substance. In many occasions, the fibrin exudation and swelling of endothelial cells of the blood vessels are encountered. These isolated hemorrhages are fused together, resulting the massive aggregated hemorrhages (Fig. 26).

The subarachnoid hemorrhages are classified as diffuse, hematomatous and mixture types.

The intraventricular hemorrhages are caused by bleeding from venous plexus or capillaries of the ventricular wall or direct extension of the intracerebral hemorrhages.

The hemorrhages due to a breakdown of arterial walls caused by leukemic cell infiltration with destruction and loss of the lamina elastica interna often produce massive hemorrhages (Fig. 27).

The cortical hemorrhages secondary to extension of subarachnoid hemorrhages disclose the continuous relation of hemorrhages around intracortical arteries and veins from that of the subarachnoid in filling of perivascular spaces and produce localized or aggregated rather massive hemorrhages.

The edematous necrotic cerebral hemorrhages are observed in both cases of leukemia and aplastic anemia which are considered to be caused by both factors of local circulatory disturbance of the cerebral venous system and of generalized anemia. Only in the upper portion of the medulla (subcortical white matter), the specific type of hemorrhage occurred parallel with a distinction between cortex and medulla is encountered. Microscopic examination of this

lesion shows no leukemic cell infiltration but hemorrhage accompanied by cerebral edema, necrosis and small hemorrhages in its vicinity (Fig. 18, 28). In the cases of aplastic anemia, the localized massive hemorrhage with extensive cerebral edema and necrosis similar to that of leukemia is noted only in the subcortical white matter or deep white matter excluding the cortex and the subcortical white matter (Fig. 19, 20, 21).

The lesions of necrosis and hemorrhages in both cases occur in different areas which are thought to be explained by specific characters of blood circulation in the subcortical white matter and deep white matter.

The writer clarifies this as the edematous necrotic cerebral hemorrhages on the basis which will be discussed later.

III. EXPERIMENTAL STUDIES OF CEREBRAL HEMORRHAGES AND SOFTENINGS DUE TO CIRCULATORY DISTURBANCE OF CEREBRAL VENOUS SYSTEM IN ANEMIC DOGS

Materials and Methods

One hundred mature dogs, weighing 10–15 kg each, were used and 22 dogs of which were tolerated in the operation. Approximately 5 cc of 8% phenylhydrazine hydrochloride solution was injected intravenously per a day or so for producing 30–50% hemoglobin in Sahli method. With these anemic dogs under ravonal anesthesia, the superior sagittal sinuses were ligated at the point of distal end just before going into the confluence of sinuses and melted paraffin with 40°C melting point was injected into the superior sagittal sinus to be filled in the rather large main branches of superior cerebral veins. Postoperatively, 20 to 50 cc of 1% trypan blue saline solutions were injected intravenously in several occasions for the examination of permeability of blood vessel walls in the brain. The autopsy was performed in the animals died or killed 3 hours to 7 days after the operation. The brain was fixed in 10% formalin solution and embedded in the celloidin etc. for many different stainings.

Results

Twenty two dogs out of 100 were satisfied in the operation. The figure 29–34 shows the cases having hemorrhages or softenings: a case of massive hemorrhage within the large area of softening; 4 cases of moderate softenings, 3 of which having moderate hemorrhages within them and one case having only softening; 2 cases of petechial or small hemorrhages within the minimal softenings; 4 cases of petechial hemorrhages without softening and 11 cases of normal

findings without hemorrhages or softenings.

On the gross examination, the case no. 39 sacrificed 3 hours after paraffin injection disclosed severe congestion of the leptomeninges and subarachnoid hemorrhages around the venules and on cut surfaces are encountered blood vessel congestion and pinpoint to miliar hemorrhages in the white matter. The case No. 31 sacrificed 6 hours postoperatively disclosed foci of hemorrhages having some blood clots measuring 0.3–1.0 cm in diameter in the white as well as gray matter. The case sacrificed 48 hours postoperatively revealed the softening in the cerebral white matter on the aspect of either one hemisphere or both, having a tendency to be localized in the frontal and parietal lobes. In the softening were pinpoint hemorrhages, rather large hemorrhages (resulting from aggregation of pinpoint hemorrhages) and hemorrhages with blood clots. The case No. 42 subjected by trypan blue disclosed the softenings with pinpoint hemorrhages and rather large aggregated pinpoint hemorrhages in the subcortical white matter as well as deep white matter, and these areas took trypan blue dye, showing increased permeability of blood vessel walls (Fig. 29–34).

Histologic examinations through the lesions revealed the softenings in the white matter, having rather clear distinction to the cortex, in which were no abnormalities with exception of blood vessel distention and cortical pinpoint hemorrhages in some cases. The softening in the white matter and in its vicinity contained pinpoint hemorrhages and rather large hemorrhages were formed by their aggregation around capillaries or veins. There were edema, fat granule cells and minimal infiltrates of neutrophiles and small round cells in the stroma of the lesions. A necrosis of blood vessel walls (Angionecrosis), demyelination and swelling of the myeline sheath in the foci of softenings, hemorrhages and in their visinities were encountered. In the leptomeninges were hemorrhages, edema and infiltrates of neutrophiles and small round cells in some cases (Fig. 35–39).

DISCUSSIONS ON THE EDEMATOUS NECROTIC HEMORRHAGES

The mechanism of the edematous necrotic hemorrhages will be discussed, since the writer observed the edematous necrotic hemorrhages in the subcortical white matter or the deep white matter of the patients with leukemia and aplastic anemia and they were also induced experimentally which have previously been described (Table 9).

Three types of the edematous necrotic hemorrhages are clacified, showing Table 8: 1) subcortical white matter type; the hemorrhages, softenings and edema being localized in the subcortical white matter and running parallel to the distinction between the cortex and medulla. 2) deep white matter type; the

Table 9. Pathogenesis of Intracranial Hemorrhages in Leukemia and Aplastic Anemia

one in the deep white matter including anterior brain stem with exception of the cortex and subcortical white matter. 3) combined type; the one with combination of the 1st and 2nd type. The writer has noted a close relation between the localizations of hemorrhages and cerebral blood pathways.

The arterial system in the cerebral gray and the white matter with even the deep medulla is originated from the anterior, middle and posterior arteries running cerebral surfaces which has previously been mentioned in the chapter I. The venous system assumedly returns in two ways; the one in the subcortical white matter and the cortex returns to the cerebral surface and the other in the deep white matter reaches to the ventricular wall. In details, the blood flow in the subcortical white matter supplied by A. subcorticalis returns to the corresponding veins (V. subcorticalis) in the subcortical white matter and reaches to the cerebral surfaces, while the subcortical veins are rather poor in the anastomoses than the V. corticalis, which have strong anastomoses and innumerable openings to the meningeal veins, and pour into the small numbers of the main branches of the veins. Therefore, when an inhibitant factor against the blood circulation occurs locally, the following effects will be observed easily. The mechanical pressure to the veins due to the subarachnoid hemorrhages with a certain extension, thromboses of venous sinuses and main branches or leukemic cell thrombosis in the cases of leukemia produces slight passive congestion in the cortex, while in the subcortical white matter it produces severe one. Moreover, marked differences in the numbers of the arterial distribution between the cortex and medulla are encountered. In addition to the localized venous blood circulatory disturbances in the brain, the effect of generalized hypoxemia appears markedly in the poorly vascularized medulla. Then, the generalized hypoxemia due to leukemia or aplastic anemia with the localized blood circulatory disturbances in the cerebral veins, having changes of blood components and the increased blood vessel permeability produce congestive edema, necrosis and softening in the brain substance due to venous circulatory disturbances. Finally small to large hemorrhages followed by degenerative necrosis and damages of vessels selectively in the distributed areas of the veins of the subcortical white matter are encountered. In the cases of leukemia and aplastic anemia having edematous necrotic hemorrhages, are encountered severe anemia, subarachnoid hemorrhages, thromboses or leukemic cell thromboses in the corresponding areas of venous returns. These findings insist on writer's hypothesis. The pathogenesis of edematous necrotic hemorrhages in the deep white matter will be similar to that of the subcortical white matter. The establishment of the local blood circulatory disturbances, the circulatory disturbances reaching to the ventricular

walls, probably is based upon wheather leukemic cell infiltration or leukemic cell thrombosis in the veins of the deep white matter, ventricular walls and their visinities. In the cases of aplastic anemia, minimal hemorrhages or thromboses due to hemorrhagic diathesis strongly suggest factors of circulatory disturbances in the deep white matter which is supplied by terminal branches of the cerebral arteries and poorly vascularized, therefore hypoxemia will play a most important role.

In conclusions, the blood circulatory disturbance in the series of the V. subcorticalis through the superior cerebral vein to the superior sagittal sinuses produces edematous necrotic hemorrhages of the subcortical white matter type, while the one in the series of the V. medullaris through the V. terminalis, Vv. anastomoticae sagittales and Vv. cerebri internae to the V. cerebri magna probably produces edematous necrotic hemorrhages of the deep white matter type. This hypothesis was proved by the experiments that necroses and hemorrhages were observed in the white matter of the anemic dogs with paraffin injection into their sinus sagittalis superior. One might consider that in the observation of the acrylic resin injection into the dog's veins, their V. subcorticalis were rather longer than that of the human being and they reach to the rather deep white matter which might cause large areas of softenings and hemorrhages.

IV. EXPERIMENTAL MASSIVE CEREBRAL HEMORRHAGE IN DOGS

Materials and Methods

Two groups of dogs were used for the materials. Ligation of both anterior and middle cerebral artery at their roots with silver clips was performed in each group.

1) First group (group of increased blood pressure, 26 dogs). Each dog was given 5 mg of neosynalin intravenously 1 to 3 days after ligation of arteries. 2) Second group (group of decreased blood pressure, 10 dogs). Each dog received subcutaneous injection of 10 mg of hethaclon-P every twelve hours preoperatively, and was sacrificed or died on the 2nd to 7th day of operation. The brain was fixed in 10% formalin solution and embedded in paraffin, making H & E and other special stains.

Results

In the first group 6 cases showed massive cerebral hemorrhage, 8 submassive, and 11 a little (petechial). One case was observed to have only cerebral softening.

In the second group no massive hemorrhage. One case showed submassive and five a little. Four cases showed only cerebral softening. Fourteen cases (53.9%) of massive or submassive hemorrhage were observed in the first group and 1 (10%) in the second. In other words, higher incidence of cerebral hemorrhage was observed in the first group than in the second with the ratio of 14 to 1 (Fig. 40-45).

Furthermore, dogs with increased blood pressure had smaller lesions of softening and milder sensory disturbances and hemiplegia than those with decreased blood pressure. These findings suggest a close relationship between the blood pressure and formation of collaterals (probably by capillaries or arterioles).

"Angionecrosis" was divided into 2 types according to the staining properties (Table 10).

Table 10.

	Type I	Type II
H-E	eosinophilic	eosinophilic
Van Gieson	yellowish brown	yellowish brown
Mallory	red	red
Azan	blue-bluish violet	red
PTAH	negative for fibrin	positive for fibrin
PAS	positive	positive
Alcian Blue	negative	negative

Type II stained with Azan staining was positive for fibrin. With other kinds of staining it showed the same staining reaction as Type I. Type I seems to be made up by the infiltration of serum components without fibrinogen into the vascular wall as well as into the perivascular tissue, and Type II serum components with fibrinogen. Type I is observed in a relatively early period after the operation and Type II late in general (Fig. 46 and 47).

No acid-mucopolysaccharides (Alcian blue negative) were noted in the angionecrotic lesion.

"Angionecrosis" appears to be induced by the increased blood flow in the degenerated or necrotic arteries in the lesion of cerebral softening due to arterial ligation, followed by the rupture of arteries resulting in hemorrhage, or by the infiltration of serum components into the vascular wall. Therefore, "angionecrosis" appears to be an accompanying phenomenon with cerebral hemorrhage, representing modified arterial degeneration or necrosis in cerebral softening by the imbibition of serum.

In conclusion, a close relationship was observed among cerebral hemorrhage, blood pressure and cerebral softening caused by arterial ligation.

Table 11. *Pathogenesis of Cerebral Hemorrhages and Softenings*

DISCUSSIONS ON THE SPONTANEOUS CEREBRAL HEMORRHAGES

The writer has studied histologic examinations about cerebral hemorrhages and softenings on the autopsy cases and attempted to explain the pathogenesis of cerebral hemorrhages. The writer seemed to reach the following understandings of the pathogenises on cerebral hemorrhages on the basis of experimental studies of the dogs as well as the histologic examination of the human materials (Table 11).

1) Decreased amount of blood circulation in the brain, namely anoxic or hypoxic conditions, if it is severe, produces necroses or softenings in the cerebral substance. In addition to this, with increased blood pressure and following increased circulatory blood volume in the lumens lined by the degenerated and necrotic vessel walls in the areas of softenings and their visinities, the vessels are breakdown and so-called spontaneous cerebral hemorrhages or hemorrhagia per diapedesin occur. In the "angionecrosis (fibrionide Wandnekrose—STÄMMLER, Hyalinose—SCHOLZ, Plasmatische Zerstörung—Wolff)," plasma components infiltrate into the degenerated and necrotic blood vessel walls. This "angionecrosis" is a phenomenon occurred simultaneously or secondarily with the cerebral hemorrhages. On this basis, huge hemorrhages into the areas of softening due to blood vessel breakdowns are spontaneous cerebral hemorrhages and multiple hemorrhagia per diapedesin into the areas of softening are of "red cerebral softening." In the cases of cerebral softenings having no increased blood pressure, it is of "white cerebral softening." In the spontaneous cerebral hemorrhages, red and white cerebral softenings, the basic mechanism is the same. However, they reach to the different conditions up to what important roles play during their courses; factors of either increased or decreased blood pressure, either blood vessel breakdowns or extravasation with whole blood through the vessel walls or only plasma components into the vessel walls.

2) Decreased amount of blood circulation, hypoxic conditions, if it is mild and longstanding, makes degeneration of the vessel walls, chiefly endothels, then the permeability of the vessel walls is increasing. Futhermore, with the factor of increased blood pressure, the plasma components infiltrate into the vessel walls and their neighborhoods, producing "angionecrosis." This angionecrosis is a primary and causative factor, forming secondarily spontaneous cerebral hemorrhages which are observed when the blood vesseles are breakdown or something happens after forming of the milialy aneurysms.

In the pathogenesis of the decreasing amount of blood circulation, the narrowing of the lumen due to arteriosclerosis, repeated drops of blood pressure,

blood vessel spasms, embolism and others should be considered.

The writer believes the following factors as the causes of cerebral hemorrhages most commonly occurred in the anterior brain stem.

1. The pathologic changes of the cerebral blood vessels are most severe in the anterior brain stem, while minimal in the leptomeninges, cerebral gray matter and white matter. Therefore decreased circulatory blood volume, circulatory disturbance, due to the narrowing of blood vessel lumens easily occurs in the anterior brain stem.

2. *Aa. corporis striati anteriores* and *media* ramified into the anterior brain stem arise from the anterior and middle cerebral arteries and run toward the opposite direction. These arterial branches having previously described uncommon hemodynamic characters easily produce a circulatory disturbance, mainly in the area of the anterior brain stem.

3. There are relatively large anastomoses between the leptomeningeal arteries and in the consideration of *A. corticalis* and *A. medullaris* ramifying from the leptomeningeal arteries, the former shows dense arterioles and capillary distributions and the latter discloses anastomoses to the main branches in the white matter. No anastomoses between the arteries supplying the anterior brain stem are evident. Therefore, on the circulatory disturbances in the cerebral gray and white matter, the collateral circulations are easily formed and the damages rarely occur. While in the anterior brain stem severe damages secondarily to the circulatory disturbances readily happen, because of no arterial anastomoses.

4. In the *globus pallidus*, the arterial distribution are rather loose than that of another nuclei in the anterior brain stem, so that hypoxia and anoxia play an important role.

5. In the cases of cerebral hemorrhages, the narrowing of vessel lumens due to arteriosclerosis is encountered in the basilar arteries, Vessels of Circle of Willis, anterior, middle and posterior cerebral arteries.

On these bases, the writer considers that in the anterior brain stem, decreased circulatory blood volume and circulatory disturbances appear first which produce softenings and sometimes following cerebral hemorrhages. The most common site of softening and hemorrhages observed in the anterior brain stem can be explained by this mechanism.

In conclusion, 1) the cerebral hemorrhages occur in the following conditions; (a) proceeding cerebral softenings, (b) rupture of primary angioneurosis or the miliary aneurysm produced secondarily to the angioneurosis. 2) The angioneurosis observed in the cases of cerebral hemorrhages consists of primary one

formed before hemorrhages which is a direct factor to the cerebral hemorrhages and secondary one accompanied by the cerebral hemorrhages.

CONCLUSION

1. Some new findings of the human cerebral vascular architecture (both arteries and veins) by employing acrylic resin injection were obtained.

2. The pathologic and statistic studies of 52 cases of leukemia and aplastic anemia obtained at the department of pathology, [REDACTED] through 1953 to 1956 were made.

3. On the observations of the pathogenesis of cerebral hemorrhages in the cases of leukemia and aplastic anemia, it seems that the venous circulatory disturbances play an important role in the cerebral hemorrhages which are given a term of edematous necrotic hemorrhages.

4. The cerebral hemorrhages and softenings were observed in dogs with experimentally produced anemia and venous cerebral circulatory disturbances.

5. The pathogenesis of cerebral hemorrhages and edematous necrotic hemorrhages due to venous circulatory disturbances, and a close relationship between common sites of hemorrhages and the cerebral vascular architecture are discussed.

6. The pathogenesis of hither-to called spontaneous cerebral hemorrhages of the human beings was described on the observations of the experimentally induced cerebral hemorrhages in dogs.

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Fig. 11. Whole view of the specimen prepared with injection of acrylic resin. The black area shows a distribution of blue acrylic resin i. v. through the superior cerebral veins.

Fig. 12. End to end anastomoses between the middle and anterior cerebral arteries in the sulcus centralis.

Fig. 13.

A: Meningeal Artery

c: Aa. corticales

s: Aa. subcorticales

m: A. medullaris

Fig. 14.

A: Meningeal Artery

c: Aa. corticales

s: Aa. subcorticales

m: A. medullaris

Fig 15.

c : Aa. corticales

s : Aa. subcorticales

m : Aa. medullares

ma: Anastomotic branch of the A. medullaris

v : V. subcorticalis

Fig. 16.

Transverse section through the gyrus with injection of acrylic resin.

c : Aa. & Vv. corticales

s : Aa. subcorticales

ma: Aa. medullares

mv: Vv. subcorticales (in the pictures they are black in color and dotted lines in the other figure)

Fig. 17.
Aggregated hemorrhages composed of aggregations of ring hemorrhages from 23 year old male with acute myelogenous leukemia.

Fig. 18.
Subcortical hemorrhages from 17 year old female with acute myelogenous leukemia. This is a subcortical white matter type of edematous necrotic hemorrhages.

Fig. 19.
Subarachnoid hemorrhages over the right hemisphere with the subcortical edema, softening and hemorrhages from 34 year old male with aplastic anemia.
This is a subcortical white matter type of edematous necrotic hemorrhages corresponding with the distribution of the Vv. Subcorticales.

Fig. 20.
Continuous picture of the figure 19 on serial sections, showing hemorrhages throughout the subcortical white matter and partial extension to the cortex and deep white matter.

Fig. 21.

Cerebral edema, degeneration, necrosis and hemorrhages in the deep white matter excluding areas of the cortex and subcortical white matter from 20 year old female with aplastic anemia. This is a deep white matter type of edematous necrotic hemorrhages corresponding with distributions of the Vv. medullares.

Fig. 22.

Histologic picture of the figure 17 showing an inner layer of leukemic cells and an outer layer of red cells around capillaries. This is a so called ring hemorrhage. (Van Gieson).

Fig. 23.

White hemorrhages in the cerebellar white matter from a case of acute myelogenous leukemia revealing almost leukemic cells around capillaries. (H & E).

Fig. 24.

Histologic picture of the figure 17 showing intermediate form from "isolated, localized ring hemorrhages" to aggregated massive hemorrhages. (H & E).

Fig. 25.
High power view of the figure 24.

Fig. 26.
Histologic picture of the figure 21 showing hemorrhages, edema and fibrin exudation around the blood vessels as well as in the brain substance.

Fig. 27.
"Arterial breakdown hemorrhages" observed in the case of acute myelogenous leukemia disclosing a partial destruction and loss of the lamina elastica interna. (H & E).

Fig. 28.
Histologic picture of the figure 18 showing edema, necrosis and hemorrhages in the subcortical white matter without a leukemic cell infiltration or hemorrhages in the cortex. (H & E).

Fig. 29.

■■■■ died 48 hrs. postoperatively showing a massive necrosis in the white matter of the left parietal lobe. In this necrosis are a massive hemorrhage with a coagulated blood measuring approximately 2×1 cm and diffuse small hemorrhages in the vicinity of the massive hemorrhages.

Fig. 30.

■■■■ died 6 hrs. postoperatively showing a massive hemorrhage with an ellipse of coagulated blood measuring approximately 0.8×0.3 cm in the subcortical white matter of the right Gyrus ento et lateralis.

Fig. 31.

■■■■ died 3hrs. postoperatively showing vascular engorgement in the white and gray matter and multiple pinpoint to millitary hemorrhages in the white matter.

Fig. 32.

■■■■ sacrificed 48 hrs. postoperatively with 1% of trypan blue injection, showing the softening in the white matter of the right parietal lobe and many pinpoint hemorrhages within it. This is blue in color with trypan blue.

Fig. 33.

■■■■■ sacrificed 48 hrs. postoperatively showing hemorrhages with approximately 0.5 cm diameter of coagulated blood in the subcortical white matter of the right Gyrus centralis anterior and multiple pinpoint to rice-grain sized hemorrhages in other areas of the white matter.

Fig. 34.

■■■■■ sacrificed 48 hrs. postoperatively showing the softening in the white matter of bilateral frontal lobes and some hemorrhages with 0.1 to 0.5 cm diameter of coagulated blood in the subcortical white matter and the gray matter.

Fig. 35.

■■■■■ The softening and hemorrhage in the white matter of the left parietal lobe closed to the gray matter. No specific findings with exception of capillary and venous engorgement are noted in the gray matter. (H & E).

Fig. 36.

■■■■■ The arrow points out edema and demyelination in the subcortical white matter. (H & E).

Fig 37 (left).

Edema and demyelination and pinpoint hemorrhages around veins in the white matter of the right temporal lobe. (H & E)

Fig. 39.

"Angionecrosis" showing tarnish red and homogenous venous walls in the area of the softening. (H & E).

Fig. 38 (right).

Marked edema and multiple fat granular cells in the subcortical white matter. (Oil-red O).

Fig. 40.

of a group of an experimental increased blood pressure with 5 mg of Neosynsin i. v. and sacrificed 3 days postoperatively. The massive hemorrhage over the right frontal and temporal lobes, having a 2 cm diameter of coagulated blood.

Fig. 41.

of a group of an experimental increased blood pressure with 5 mg of Neosynsin i. v. and died 5 days postoperatively. The massive hemorrhage in the right anterior brain stem.

Fig. 42.

of a group of an experimental increased blood pressure with 5 mg of Neosynsin, sacrificed 3 days postoperatively. The massive softening and multiple pinpoint hemorrhages within it in the right lateral lobe, nucleus lentiformis, nucleus caudatus and capsula interna.

Fig. 43.

of a group of an experimental decreased blood pressure with 10 mg of hethaclon-P i. m. every 12 hrs., sacrificed 6 days postoperatively. The white softening in the left temporal lobe, a part of parietal lobe, capsula interna, nucleus lentiformis and caudatus.

Fig. 44.

of a group of an experimental decreased blood pressure with 10 mg of hethaclon-P i. m. every 12 hrs., died 3 days postoperatively. The white softening in the temporal and parietal lobes, capsula interna, nucleus lentiformis and caudatus.

Fig. 45.

of a group of an experimental decreased blood pressure with 10 mg of hethaclon-P i. m. every 12 hrs., sacrificed 3 days postoperatively. The softening, pinpoint hemorrhages within it and a moderate degree of hemorrhages following their aggregation in the left temporal lobe, a part of parietal lobe, capsula interna, nucleus lentiformis and caudatus.

Fig. 46.

"Angioneclerosis" type II, disclosing red homogeneous, non structure or fine granular vascular wall and its surrounding tissue. (H & E).

Fig. 47.

The same lesion to the figure 46 in PTAH stain showing fine granular or elongated bluish violet fibrin substance in the area of the tunica media. This area is of bright red in Azan stain.

Fig. 48.

No. 18 a group of an experimental decreased blood pressure. The angioneurosis pointed out by an arrow in the area of hemorrhages with a thickening of the lamina interna next to it.

Fig. 49.

High power view of the area of the thickening lamina interna in figure 48 showing only connective tissue cells and fibers without elastic fibers.