

On Pathogenesis of So-Called "Cerebral Embolism"

— Cerebral Softening and Hemorrhage Due to Arteritis —

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A total of 21 cases diagnosed as "cerebral embolism" at autopsy (softening 9 and hemorrhage 12 cases, having endocarditis or sepsis) were studied in detail in an attempt to clarify the mechanism of softening and hemorrhage. According to the result obtained, mechanical obstruction of an artery by an embolus is not always the cause of "embolic softening", and the "embolic hemorrhage" is not diapedetic, but principally rhexis-bleeding. In both softening and hemorrhage, the chief role is played by some inflammatory agents carried from the heart to the meningeal and/or intracerebral artery and inciding a localized arteritis. When the arteritis undergoes a proliferative or thrombus-forming process, stenosis or obstruction of the vessel and softening occurs, whereas when it undergoes an exsudative or destructive process, rupture and hemorrhage occurs.

There are some reports on cerebral embolism (PONFICK³⁷), EPPINGER⁷), SIMMONDS³⁹), BENDA²), LUBARSCH²³), TERPLAN⁴²), LESCHKE²²), KIMMERSTIEL¹⁵), MELCHER²⁷), NAGAYO²⁰), HIRAZAWA¹⁰), NAKAMURA³²), NAGAI²⁸), KODA¹⁹), KOIKEGAMI²⁰), OGATA³⁴), TAKIZAWA⁴¹), HANABUSA⁹), KITAMURA¹⁸), KAGEYAMA¹³), KIKUJIMA¹⁴), etc.), but the mechanism of its development, especially the nature of the histopathological changes of the local arteries causing the softening has not been clarified and only suggestions based on assumptions have been published. In the case of embolism, it has been explained as due to tissue particles or verrucas from endocarditis or arteriosclerosis which act as mechanical stoppers and plug the arteries in the brain resulting in softening of the parts peripheral to this, and this opinion has been generally accepted without question. BÖTTGER⁴) (1951) has reported 2 cases of softening following endocarditis in which bacterial inflammatory changes in the arteries of the brain was the direct cause of the softening and he has discussed the relation between the arteritis and endocarditis.

On the other hand, autopsy of cases of sudden deaths from apoplectic attacks in young adults with endocarditis has revealed massive

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hemorrhage rather than softening at times. This has been explained as a secondary permeable hemorrhage following an initial softening due to plugging of the artery by embolus as in the cases of hemorrhagic infarction in other organs. These hemorrhagic lesions however, are often too massive and too fresh to be explained simply by permeation. Some investigators state that in hypertensive apoplexy, an encephalomalacia precedes the hemorrhage and the massive hemorrhage takes place by malacic damage of the vessel (BÖHNE³³), BÜCHNER⁵), NORDMANN³³), WESTPHAL⁴⁴), and the massive hemorrhage following plugging of the vessel may be acceptable according to their theory. However, it has been shown by MATSUOKA²⁵)²⁶), SPATZ⁴⁰), ANDERS-EICKE¹), OONEDA³⁶) that softening is not a prerequisite for hypertensive apoplexy but angioneclerosis (fibrinoid necrosis) is the direct cause of arterial rupture.

PONFICK³⁷), EPPINGER⁸) and BENDA²) have described bacterial aneurysms of various arteries secondary to ulcerative endocarditis and SIMMONDS³⁹) and TERPLAN⁴²) have found such aneurysm of the cerebral arteries and reported that hemorrhage occurred by rupture of these aneurysms. These cases are, however, too few for adequate clarification. SCHAWARTZ³⁸) (1930) gave the name "embolische Apoplexie" to the cerebral hemorrhage complicating endocarditis and suggested that this was due to functional diapedetic bleeding from the nutritional vessels. Though numerous investigators (NAGAI²⁸), NAGAYO²⁹), IMAI¹¹), ONO³⁵), KUSANAGI²¹) etc.) have studied this problem of the so-called "embolic apoplexy", the causal mechanism is not yet clear.

The present investigation was conducted with the object of clarifying the following. (1) Whether a plug could be found in the local artery of "embolic apoplexy", and if present, the manner in which the plug stops the artery (2) The cause for the embolic massive hemorrhage

MATERIALS AND METHODS

Cerebral embolism is a relatively rare condition and one of the authors, Nakagawa, has visited the various universities and hospitals (Tokyo, Tohoku, Kyoto, Osaka, Jikei, Kyushu, Tokyo inspection office) since 1949 and has been able to collect a total of 24 cases (Table 1).

Table 1. Materials

Condition	Place	Nagasaki Univ.	Tokyo Univ.	Tohoku Univ.	Kyoto Univ.	Osaka Univ.	Kyushu Univ.	Jikei Med. School	Tokyo Insp. Office	Total
Softening only		2	2	4		2		1		11
Hemorrhage only		4		2	1		1		1	9
Softening + Hemorrhage		1	1	1			1			4
Total		7	3	7	1	2	2	1	1	24

Table 2. Cases of so-called "embolic softening"

Case- No.	Name	Age	Sex	Clinical diagnosis	Endo- car- ditis	Region of softening	Size of softening	Name of artery which caused the softening	Cause of stenosis (arteritis)	Source
1	I. T.	64	♀	Encephalitis japonica	+	r. Lobus frontalis	Hazel-nut size	R. frontalis of a. cereb. med.	Fresh thromboarteritis	Kyushu Univ.
2	S. C.	33	♀	Meningitis tuberculosa (?)	+	r. Corpus striatum	Walnut size	REAC	"	Nagasaki Univ.
3	T. T.	37	♂	Encephalitis disseminata acuta	+	r. Putamen	"	"	Panarteritis	"
4	N. F.	35	♀	Cerebral embolism	+	l. Putamen	Pencil size	"	Endoarteritis productiva	Tokyo Univ.
5	H. H.	32	♂	"	+	r. Putamen & insula	Thumbapex size	A. cereb. med. & REAC	Organized thromboarteritis	Tohoku Univ.
6	I. X.	?	♂	Hemiplegia	+	r. Corpus stri- atum & insula	Hens-egg size	"	"	Tokyo Univ.
7	H. G.	25	♂	Septicemia	-*	"	"	"	Thromboarteritis septica	Tohoku Univ.
8	W. N.	26	♀	Cerebral embolism	+	l. Claustrum & insula	Fore-finger-apex size	Aa. insulae	"	Tokyo Univ.
9	N. S.	45	♂	Myocardiac degeneration	+	r. Frontocentral lobe & insula	Small finger- apex size	Local meningeal arteries & aa. insulae	Endoarteritis productiva	Nagasaki Univ.

REAC Rr. extt. of aa. corporis striati mediae branching from a. cereb. media

* Septicemia

At autopsy these cases had mostly endocarditis and were diagnosed as cerebral embolism or thrombosis, and in 4 cases the detailed examination revealed more than 2 lesions, that is both hemorrhage and softening, so that a total of 29 lesions were examined. In this paper, 9 cases of definite softening and 12 lesions of hemorrhage are presented and cases of non-inflammatory thrombosis and arteriosclerotic softening have been deleted.

The material was all fixed in formalin. In searching for the arterial change, it is necessary to know the normal distribution of cerebral vessels and their variations. The reports of ITABASHI^{1,2)}, KATO and MATSUOKA^{2,4)} were of aid as references in this respect. The arteries supplying the areas of hemorrhage or softening were studied macroscopically in detail and specimens from the areas together with regional arteries were taken and cut into 500–1000 serial sections. The sections were dyed with hematoxylin-eosin, van Gieson and Weigert's elastic fiber stain, when required, Gram stain was performed for bacterial investigation.

RESULTS CONCERNING "EMBOLIC CEREBRAL SOFTENING"

Table 2 shows the results in 9 cases determined to be so-called cerebral embolic softening (excluding non-inflammatory thrombosis and arteriosclerotic softening) at autopsy. These cases all show endocarditis (excluding sepsis) and suggest a migration of emboli from the heart to the brain, but it is not so simple when we search the clinical and pathological findings in detail in each case, especially the changes in the arteries which give rise to the softening.

Case 1 : I. T., 64-year-old female (Kyushu Univ.). On Sept. 1, 1949, there was a sudden attack of headache, fever (39°C) and vomiting. From Sept. 4, the sensorium became somewhat clouded and diplopia, incontinencia urinae and delirium became apparent. She became comatous on the 7th and there was aimless movement and marked muscular rigidity of the right arm. On Sept. 12, flaccid paralysis of the extremities became apparent, bronchitis set in and she died on Sept. 17. The clinical diagnosis was Japanese B encephalitis with bronchopneumonia.

Findings at autopsy : There were no signs of encephalitis. The chief findings were mitral verrucous thrombotic endocarditis, hemorrhage and softening of the right side of the brain, and infarction of the spleen and kidney. The cerebral parenchyma was somewhat swollen and the cut surface revealed a rather superficial hemorrhagic lesion 3.8 x 2.8 cm in size in the right temporal lobe (Fig. 1, H). A small area of softening was found in the cortex of the right frontal lobe (Fig. 1, S). The arteries in the base of the brain were sclerotic in general and the veins were congested. Bronchopneumonia was present in the left side.

Histological findings : The artery leading to the area of softening (Fig. 2, S) was the frontal branch of the a. cerebialis media and the bifurcation of this artery (Fig. 2, III) showed slight sclerosis under the microscope but there were no inflammatory or thrombotic changes. The branch leading directly to the area of softening

(Fig. 2, I) shows some contraction. An old thrombus is present in the lumen and on top of this there is a fresh thrombus composed of white cells and platelets (Fig. 3). The arterial wall reveals infiltration by leukocytes, lymphocytes and histiocytes, clearly showing the presence of thrombic arteritis. Repeated Gram stain failed to show bacteria. The thrombus in this case is composed of two layers, old and new and, though the old thrombus could be considered a plug, it is not so large as to "mechanically" block the vessel. On the other hand the cellular infiltration of the arterial wall and thrombus are both related to arteritis and it would be more logical to consider the softening as due to thrombic arteritis. This is supported by the presence of arteritic rupture in other branches of the *a. cereb. med.* (Fig. 2, II, see section on "embolic hemorrhage", described later). The arteritis may, however, be due to transportation of some small agent (f. i. bacteria, toxin, small thrombus) from the heart.

Case 2 : S. C., 33-year-old female (Nagasaki Univ. No. 3665). Since the beginning of 1955 there were sometimes headache, chill, fever etc. which increased gradually and she complained also slight hemiplegia, speech disorders and lethargy developing into coma. Patellar reflex was accelerated, especially on the left side, Kernig's sign and head retraction were positive. She died on Febr. 23. Clinically tuberculous meningitis was suspected.

Findings at autopsy : There was no sign of tuberculosis. The chief findings were ulceroverrucous endocarditis of the aortic valves and encephalomalacia involving the right caudate nucleus, putamen, external capsule and claustrum (Fig. 4, S) all of which are just supplying-area of the *rr. extt. of aa. corporis striati mediae* (i. e. "A. de l'hémorrhagie cérébrale"; REAC).

Histological findings : The *rr. extt. of aa. corporis striati medd. dex.* (retrogressing small branches from *a. cereb. med.*, Fig. 5) flowing into the softening-area show severe panarteritis with thrombosis (Fig. 5 and 6, a, b). The thrombi are only in the retrogressive branches and not in the stem of *a. cereb. med.* (Fig. 6, ACM), and they were microscopically much fresher than the verruca of the heart valves. Therefore, the thrombi, the cause of the softening, must have been locally built as a partial phenomenon of the panarteritis and can not be "mechanical plugs" from the heart. But the source of the localized panarteritis might be, indeed, some infectious material from the heart.

Case 3 : T. T., 37-year-old male (Nagasaki Univ. No. 3497). In the childhood he had suffered from rheumatism. In the beginning of Feb. 1954 there was sudden attack of fever (38°C), headache, somnolence and slight hemiplegia on the right side all of which gradually recovered once. On Feb. 19 the second attack of falling down, somnolence, left side hemiplegia, speech disorders etc. occurred. Head retraction and BABINSKI's reflex were positive. After 12 days' coma he died on March 12. Clinical diagnosis: Encephalitis disseminata.

Findings at autopsy : Cicatricial endocarditis with stenosis in the mitral valves, a fresh encephalomalacia extending to the right putamen, internal and external capsule and claustrum (Fig. 7, S) all of which are supplied by *rr. extt. of aa. corporis striati medd.* (REAC), another small softening in the right putamen, thromboarteritis of *a. brachialis dextra*, infarctions of the spleen and kidneys etc. were found. There was no thrombosis or another stenosis in the stem and chief branches of *a. cereb. med.*

Histological findings : *A. cereb. med.* and origins of REAC did not show any pathological change microscopically. However, the intracerebral portions of REAC

indicate severe acute panarteritis (Fig. 8), their lumina are nearly closed, but have not any plug. By investigation with serial sections it was confirmed that the softening had been caused by this acute inflammatory wall-thickening (Fig. 8, I) of the arteries.

Case 4 : N. F., 35-year-old female (Tokyo Univ.). Affected by a cardiac disease when 16 years of age. In April, 1948, she suddenly lost consciousness, left hemiplegia and aphasia became apparent. Consciousness became clear after 3 days. On Sept. 8, 1949, consciousness again became clouded and contrary to the previous attack, right-sided hemiplegia occurred. She was admitted to the Tokyo University Hospital on Sept. 13 and died 3 days later. Clinical diagnosis: Cerebral embolism of cardiac origin.

Autopsy findings : Macroscopically, there were recurrent verrucous endocarditis of the aortic valve, fibrous hypertrophy of the mitral valve and left arterial wall, old infarction of the kidney, an old area of softening in the right lentiform nucleus (Fig. omitted), a relatively fresh pencil-form area of softening between the left corpus striatum and the ext. capsule, extending backward and downward to the int. capsule (Fig. 9, S). The findings suggested that the initial attack was due to the old lesion in the right hemisphere and the fatal attack due to the fresh lesion in the left side.

Histological findings : The arterial wall in the region of the bifurcation of the a. cereb. med. sin. into REAC is strongly contracted, the elastic fibers are twisted, there is intensive production of granulation tissue with infiltration by lymphocytes and leukocytes in the intima (Fig. 10, A and Fig. 11). This is a picture of arteritis and not arteriosclerosis. The inflammation spreads further to the media where smooth muscle fibers are atrophic and also there is inflammatory hypertrophy of the adventitia. The REAC (f. i. Fig. 11, R) are completely obstructed at their origins by the presence of this productive endoarteritis of the stem. The above-mentioned softening in the left side is, therefore, clearly due to this productive arteritis of a. cereb. med. and neither thrombus nor embolus is the cause.

Case 5 : H. H. 32-year-old male (Tohoku Univ.). Endocarditis was diagnosed in Dec. 1946 at the Tohoku University Hospital. From Jan. to March of 1947, he was confined to his bed with a remitting fever 39-40°C. On March 31, he suddenly collapsed but remained fully conscious. Left sided hemiplegia became apparent with paresthesia. The blood pressure was 100/70 mmHg. On the 26th, respiratory distress suddenly set in, consciousness was lost, vomiting occurred repeatedly, he died on 27th. Clinical diagnosis : Cerebral embolism.

Autopsy findings: There were ulceroverrucous endocarditis of the mitral valve, a large massive hemorrhage in the left insula-claustral region (Fig. 12, H), thumb-tip-sized softening in the right insular part (Fig. 12, S), infarction of kidney, spleen and lung etc. The left cerebral hemisphere was swollen compared with the right side. The initial collapse is believed to be a result of the right-sided softening and the later attack due to the hemorrhage in the left side. (The left-sided hemorrhage will be described later.) The softening extended from the outer edge of the putamen to the insula-cortex and formed a triangle (3.5cm on each side), and reached downward to the base of the brain. The vessels leading to the softening area were branches of a. cereb. med. dex. which was markedly contracted in the middle part of its stem (Fig. 13, A), and this portion revealed inflammatory adhesion with the surrounding meningeal tissue. The narrowed lumen of this part was filled with thrombus or thrombus-like material and almost completely obliterated.

ted. The REAC were not remarkable.

Histological findings : The narrow part of the right a. cereb. med. also shows contraction microscopically. The elastica interna is markedly twisted and the lumen is filled with thrombus containing fibrin (Fig. 14, T) and granulation tissue composed of fibroblasts and capillaries (Fig. 14, G) combining with the wall of the artery. All the layers of the arterial wall show cellular infiltration, the muscle fibers of the media are atrophic or partially disappeared, the adventitia reveals marked inflammatory thickening (Fig. 14, Ad) and these sites are closely adhered to the leptomeninges. From these findings it can be seen that the picture is that of a chronic thrombic arteritis and not of "mechanical plug". The softening in the right hemisphere is therefore due to an old localized thromboarteritis of the a. cereb. med.

Case 6 : I. X., male of unknown age (Tokyo Univ.). Diagnosed as endocarditis, valvular disturbance with decompensation and left hemiplegia at the Tokyo Univ. Hospital.

Autopsy findings : There were chronic ulceroverrucous endocarditis of the aortic valve, infarction and hemosiderosis of the spleen, infarction of the kidneys, and an egg-sized softening-area in the right corpus striatum extending from the capsula interna to the insula region (Fig. 15, S). The autopsy diagnosis was "Encephalomalacia due to embolism".

Histological findings: The a. cereb. med. dex. shows contraction of the wall and narrowing of the lumen near the diverging point of rr. extt: of aa. corp. str. medd. (REAC). The lumen is filled with fibroblasts and connective fibers which are closely attached to the vascular wall (Fig. 16, A and 17). There is infiltration by lymphocytes and histocytes in this granulation tissue, in the media and adventitia. The muscle fibers of the media partially show destruction, parts of the elastica interna are disrupted. These findings closely coincide with organization of thrombus. The softening of the insula centering about the fissura Sylvii and its neighboring region is without doubt due to the obstruction of the a. cereb. med. The bifurcating points of the REAC are also completely obliterated by the granulation tissue of the main artery and even the rami are filled with the same granulation. The softening in the claustrum, external capsule, lentiform nucleus, internal capsule and caudate nucleus is no doubt due to obstruction of the REAC. It can thus be considered that this is a case of completely organized thrombic arteritis causing the brain softening.

Case 7 : H. G., 25-year-old male (Tohoku Univ.). Diagnosed as sepsis, pyelocystitis, tabes dorsalis at the Univ. Hospital.

Autopsy findings : Diffuse, wide white and partially brown softening in the right hemisphere, chronic, necrotic, suppurative cystitis, renal abscess of both sides, bronchopneumonia. No findings suggestive of tabes. The softening (6.0 x 5.5 x 3.0 cm) extended from the internal capsule over the corpus striatum, claustrum and insula to the cortex of the central gyrus (Fig. 18). From the manner of spread of the softening, the cause had theoretically to be in the main stem of the a. cereb. med., especially near the diverging points of the REAC. It was found that the a. cereb. med. was enlarged in spindle form at the stem and filled with thrombus-like matter completely obliterating the lumen (Fig. 19). The REAC were also obstructed at the origin fully explaining the softening in the central nuclei of the same side.

Histological findings : The enlargement of the a. cereb. med. (Fig. 19, region

of A) was examined by serial section. The lumen was found to be filled with coagula containing a large quantity of fibrin. There is invasion by granulation tissue from the intima and organization is considerably advanced (Fig. 20). All the layers of the arterial wall show infiltration by lymphocytes and histocytes, the media is atrophic and the adventitia is thickened. The REAC (Fig. 20, R) are also obliterated by thrombi and organization is noted in places. The direct cause of the softening in this case is without doubt, the presence of old thrombi, but in view of the inflammatory changes in the arteries, it is believed that the thrombi have been produced by the occurrence of localized septic arteritis, not by plugging.

Case 8 : W. N., 26-year-old female (Tokyo Univ.). In Sept. 1947, bloody sputum was noted. Systolic and diastolic murmurs audible at the apex of the heart and other signs of valvular disorder clearly observed. Cerebral signs such as headache, dim consciousness etc. became apparent on Nov. 20 and on Nov. 21, there were chills with fever, stiffness of the neck, aphasia and swelling of the liver. The sensorium became clear in Dec. but the remitting fever continued and he died on Dec. 15. Clinical diagnosis: Mitral disturbance and cerebral embolism.

Autopsy findings : The chief findings were ulcerative endocarditis of the mitral valve with stenoin sufficiency, encephalomalacia, infarction of the spleen and kidneys, hemorrhage in the liver etc. The softening in the brain was the size of the tip of the finger and extended from the insula to the claustrum and contained a focus of hemorrhage (Fig. 21, S).

Histological findings : The area of softening is supplied by a branch of the a. cereb. med. i. e. a. insulae. In all the layers of this artery there was severe inflammatory infiltration by leukocytes, lymphocytes and histocytes. The media and adventitia show spread destruction because of the inflammation and the lumen is filled with granulation tissue (Fig. 22). It is believed that there had been a severe thrombic arteritis and the granulation tissue in the lumen is due to organization of a thrombus. The cause of the softening in this case is believed to be an obliterative arteritis. A rupture due to arteritis was found at a short distance cardially from the site of the obliteration but this will be taken up in the later section.

Case 9 : N. S., 45-year-old male (Nagasaki Univ. No. 3512). From 1942 he sometimes complained of dyspnea and arrhythmia and later of edema on the face and extremities. Since Dec. 1953 cyanosis and since the beginning of May 1954 frequent vomiting appeared, he died on May 3rd. There was no motor paralysis. Clinical diagnosis : Myocardiac degeneration.

Autopsy findings : There were recurrent ulceroverrucous endocarditis of the aortic and mitral valves with aortic insufficiency, tiger heart, softening in the right frontocentral and insular region (Fig. 23, S₁ and S₂), fresh massive hemorrhage in the right frontal and left occipital regions (Fig. 23, H₁ and H₂), multiple infarctions of the kidneys, congestion of the lungs, infectious splenitis etc.

Histological findings : The arteries leading to the softening-areas in the frontocentral and insular regions were investigated by serial section. The arteries reveal remarkable intimal thickening where proliferation of fibroblasts and infiltration by leukocytes and lymphocytes are noted. The lumina are intensively narrowed or often completely obliterated and the media and adventitia show also diffuse inflammatory cell infiltration (f. i. Fig. 24). These changes which have occurred at places in the meningeal arteries in the same region are nothing but

Table 3. Cases of so-called "embolic hemorrhage"

Case- No.	Name	Age	Sex	Clinical diagnosis	Endo- car- ditis	Region of hemorrhage	Size of hemorrhage	Local arteritis
10	A. T.	17	♀	Inquest	+	l. Insula	Hens-egg size	+
11	I. S.	21	♀	Basilar meningitis	+	r. Insula & putamen	Thumb size	+
12	W. N.	26	♀	Cerebral embolism	+	l. Insula	Fore-finger apex size	+
13	O. M.	27	♂	Encephalitis	-*	l. Insula & putamen	Goose-egg size	+
14	Y. A.	32	♀	Basilar meningitis	+	l. Frontal gyrus	Pea size	+
15	H. H.	32	♂	Cerebral embolism	+	l. Insula & putamen	Over thumb size	+
16	O. S.	34	♂	Heart failure	+	r. Occipital lobe	Thumb apex size	+
17	O. A.	34	♀	Cerebral embolism	+	r. Insula	Walnut size	+
18	Y. Y.	42	♂	Heart failure	+	r. Frontal lobe	Walnut size	+
19	N. S.	45	♂	Myocardiac degeneration	+	r. Frontal lobe	Fore-finger apex size	+
20	K. X.	46	♀	Cerebral embolism	+	l. Frontal lobe	Over hens-egg size	+
21	M. S.	57	♂	Myocardiac degeneration	+	l. Central gyrus	Pigeon-egg size	(+)

* Septicemia

localized productive arteritis by which the softening are caused, nowhere "mechanical plugs" are found. The hemorrhage in the right frontal and left occipital regions (Fig. 23, H₁ and H₂) was caused by rupture due to destructive arteritis and will be described in the later section.

RESULTS CONCERNING "EMBOLIC CEREBRAL HEMORRHAGE"

Table 3 shows the clinical diagnosis, site and size of the hemorrhage, presence of the arteritis, hemorrhagic globus and arterial rupture, name and size of the ruptured artery, etc. in 12 cases determined to be embolic cerebral hemorrhage by autopsy. The majority of the cases were young adults under 40 years of age. Eleven were cases with endocarditis and 1 was a case of sepsis. Clinically, 4 had been diagnosed as cerebral embolism, 4 as cardiac disorder and 3 as encephalitis or meningitis, while 1 was an inquest case in which autopsy was performed to determine cause of death.

Bleeding globe	Arterio-rhexis	Name of ruptured artery	Diameter of ruptured artery	Source
+	+	Aa. insulae (from a. cereb. med.)	1030 μ	Tokyo Inspect. Medical Office
+	+	"	1392	Nagasaki Univ.
+	+	"	792	Tokyo Univ.
+	+	"	1024	Nagasaki Univ.
+	+	A. meningea (from a. cereb. ant.)	1288	"
+	+	A. meningea (from a. cereb. med.)	1458	Tohoku Univ.
+	+	A. meningea (from a. cereb. post.)	1497	"
+	+	A. meningea (from a. cereb. med.)	1425	Kyoto Univ.
+	+	"	964	Nagasaki Univ.
+	+	"	165	"
+	+	"	905	Kyushu Univ.
+	(+)	"		Tohoku Univ.

Case 10 : A. T., 17-year-old female (Tokyo Insp. Med. Off.). Rested on Aug. 21, 1950 because of headache. The following morning, she left the house even though not feeling well and suddenly collapsed in the street and died. She had complained of a weak heart before.

Autopsy finding (Inquest) : The chief findings were verrucous endocarditis of the mitral valve; encephalomalacia and brain hemorrhage; congestion of the both lungs and kidneys; infectious spleen etc. There was a hen's egg sized massive hemorrhage extending from the outer edge of the left claustrum to the cortex of insula, most extensive in the coronal plane across the optic chiasms (Fig. 25).

Histological findings : From the normal distribution of the vessels in the area of the hemorrhage, it was assumed that the cause was in the left aa. insulae. The lesion was examined carefully by serial sections and a rupture was found in a relatively large meningeal artery (dia. = 1.030 μ) deep in the fissura Sylvii (Fig. 25, 26, 27). The media and adventitia near the site of the rupture showed cellular infiltration by lymphocytes, leukocytes and histocytes suggesting that relatively severe arteritis had occurred here some time in the past. The elastica interna, the media and the adventitia have been lost due to the inflammation in one place

with rupture (Fig. 27)* There has been a flow of blood out from this rupture into the brain tissue forming a large hemorrhagic globus** (Fig. 26, arrow). It can clearly be seen that this is a hemorrhage per rhexin resulting from the destructive process of severe arteritis. The involvement of endocarditis can be assumed but it is believed that the hemorrhage is not a result of hemorrhage per diapedesis in a softening by plugging with an embolus.

Case 11 : I. S., 21-year-old female (Nagasaki Univ. No. 3064). Afflicted with rheumatic arthritis in April 1949. Since then, there had been frequent occurrence of fever of 38°C with general malaise and headache. On July 16, general convulsion and unconsciousness occurred. Consciousness had been recovered later but anorexia and insomnia remained. At time of hospitalization there were continuous headache, marked stiffness of the neck, positive Kernig's sign, accentuation of the patellar reflex, leukocytosis and elevated spinal fluid pressure. On July 27, consciousness became clouded again, and there were vomiting, generalized seizure and incontinencia urinae. Fell into coma on the 28th and died. Clinical diagnosis: Tuberculous meningitis.

Autopsy findings : The main findings were: relatively old verrucous endocarditis of the mitral valve with myocardial hypertrophy; "embolic" brain hemorrhage; slight suppurative meningitis; hemorrhagic infarction of the lungs; anemic infarction of the kidney and spleen. The mitral valve showed diffuse fibrous thickening and there was old verruca in the free edges (Fig. 28). An elongated thumb-sized massive hemorrhagic lesion extending from the outer edge of the putamen to the insula and temporal cortex was present in the right side (Fig. 29). The surrounding tissue was somewhat soft. No signs of tuberculous meningitis were found.

Histological findings : As the area of hemorrhage was quite extensive, several specimens were taken and examined by serial sections in detail but no significant findings were obtained. The region of the bifurcation of the aa. insulae in the central gyrus was then examined and the following was observed. A relatively old suppurative arteritis was present on a meningeal artery (dia. = 1.392 μ) in the deep part of the insular fissura. A part of the wall of this artery has been destroyed and here all the layers are absent, that is ruptured. There is a flow of blood towards the cerebral parenchyma (Fig. 30) and the subarachnoideal space. No plug or thrombus is observed. The bleeding is therefore, a hemorrhagia per rhexin due to localized inflammatory damage of the artery. It can be supported that this arteritis is caused by some inflammation inducing substance transported from the endocarditis (only residual scars observed now) but the rupture is not due to a mechanical or instantaneous damage from plugging of the artery.

Case 12 : W. N., 26-year-old female (Tokyo Univ.) This is the same case as case No. 8.

Autopsy findings: The main findings were ulcerative endocarditis of the mitral valve and a finger-tip sized softening from the claustrum to the insula in the left hemisphere with central hemorrhage (Fig. 21).

Histological findings : The direct cause of the softening was an inflammatory obstruction of the deep meningeal artery in the insular sulcus as described

* Fig. 27 has been printed in order to show the inflammation of the arterial wall and the absence of the wall elements; the figure of extravasation of the blood lies in more peripheral portion.

** Coagula attached to the artery produced by rupture of the vessel. An accurate sign of arterial rupture according to MATSUOKA.²⁶⁾

previously (Fig. 22). This artery was followed further cardially and a site of rupture was found. There was severe panarteritis with infiltration by leukocytes, lymphocytes and histocytes and all the layers of the arterial wall were damaged and blood was escaping outwards from this site (Fig. 31) (dia. of the ruptured artery= 792μ). The hemorrhage was, therefore, due to rupture and the rupture was due to an inflammatory damage of the artery. This is a case having softening and hemorrhage at the same site and this type of lesion was regarded formerly as softening induced by plugging together with diapedesis. In the present case, however, it has been shown that arteritis occurred secondarily to endocarditis and during the inflammatory process obliteration of the lumen occurred in one place (resulting in softening) and damage to the wall occurred at another close-by site (resulting in rupture and hemorrhage).

Case 13 : O. M., 24-year-old male (Nagasaki Univ. No. 3144). Anorexia and general malaise had been present since July 27, 1951. On Aug. 5, a fever of 39°C . On the following day, at the hospitalization, there were marked stiffness of the neck, unconsciousness, increased spinal fluid pressure etc. but heart sounds were normal and no enlargement was noted. He fell into coma on the 7th and died. Clinical diagnosis: Suspected encephalitis.

Autopsy findings : The chief findings were : sepsis secondary to pyoderma; suppurative meningitis; cerebral hemorrhage; splenomegaly with hemorrhagic infarction; pulmonary abscess. The base of the brain was coated with pus, the left hemisphere was somewhat swollen, and there was widespread meningeal hemorrhage in the left frontal and temporal lobes. On the cut surface this hemorrhage extended from the insula to the outer edge of the putamen (Fig. 32). The main branches of the a. cereb. med. were imbedded in the lesion.

Histological findings : Serial sections, including the hemorrhagic lesion and the a. cereb. med. and its branches were carefully examined and a rupture of the a. insulae (dia.= 1.025μ) in the fissura of Sylvius was finally discovered. The arterial wall at this site showed suppurative inflammation with cellular infiltration and there is destruction and disappearance of the tunica elastica and damage of all layers of the wall with formation of a hemorrhagic globus on the outside (Fig. 33). Another branches of the aa. insulae revealed also purulent destructive arteritis without rupture. In this case, gross hemorrhage had occurred in the cerebral parenchyma and the subarachnoidal space due to damage and rupture of arteries as a result of localized arteritis occurring secondarily to sepsis and thrombus or embolus had no rôle.

Case 14: Y. A., 32-year-old female (Nagasaki Univ. No. 3115). On Sept. 25, 1950 (23 days prior to death) severe headache, low back pain, neuralgic pain of the legs, chills, fever of 39°C , anorexia and insomnia suddenly occurred. From Oct. 5, speech difficulty, clouding of consciousness and coughing became apparent. At time of hospitalization (Oct. 7), there was marked stiffness of the neck, positive Kernig's and Babinski's signs and elevated spinal pressure. She fell into coma on Oct. 16 and died the next day. Clinical diagnosis: Tuberculous meningitis.

Autopsy findings : Main findings: Ulceroverrucous endocarditis of the mitral valve; "embolic" cerebral hemorrhagia; suppurative meningitis; multiple small abscesses of the liver, kidneys and left lung; anemic infarction of the spleen. There were two pea-sized fresh reddish verruca on the mitral valve (weight of the heart 200 g). The brain revealed several hemorrhagic-suppurative lesions on the meninges of the both frontal and left temporal lobes with marked dilatation of vessels,

a horizontal cut-surface of the left hemisphere showed 3 small foci (largest : 1.4 x 1.0 cm) of hemorrhage in parenchyma of the gyr. frontalis med. and gyr. centralis ant. (Fig. 34, 1, 2 and 3). No findings of tuberculous meningitis.

Histological findings : The mitral valve showed fresh septic ulcerative endocarditis and Gram-positive staphylococcus was found. By close examination of the meningeal arteries leading to the hemorrhagic lesion in gyr. front. med. sin. (Fig. 34, 1), a rupture of a branch of the a. cereb. med. (dia. = 1.288μ) was discovered. A part of the wall is destroyed by a severe suppurative inflammation and a V-shaped defect (all layers lost) was present (Fig. 35). There is exsanguination from this defect into the cerebral parenchyma and subarachnoid tissues. Staphylococci were also found in the subarachnoid tissue and site of rupture. Thrombus-like matter was found at the site of rupture but it is believed that this is a final product of hemorrhage and neither related to the development of the arteritis nor transported from the heart.

Case 15 : H. H., 32-year-old male (Tohoku Univ.). This case is the same as No. 5. There was ulceroverrucous endocarditis (mitral), softening in the right insular region and massive hemorrhage in the left brain-stem (Fig. 12). The hemorrhage extended from the outer edge of the putamen to the insular cortex and frontal lobe and downward to the base of the temporal lobe (2.5 x 9.5 x 2.5 cm). The picture bears macroscopically some resemblance to that observed in hypertensive hemorrhage (Fig. 12. H).

Histological findings : As the site of the bleeding was believed to be near the bifurcation of the a. cereb. med., the region of the bifurcation and aa. insulae were examined by serial sections. The arteries reveal severe inflammation and in same place the tunica elastica is destroyed, atrophied and twisted (Fig. 36). Somewhat caudally to this, there is a defect of all layers of the arterial wall, from which flow of blood outward extended towards the main hemorrhagic lesion. In this case too, the bleeding was due to rupture following non-thrombic arteritis. As described previously, there were two attacks at an interval of 28 days in this case. The initial attack can be attributed to the softening caused by proliferative arteritis (Fig. 14) in the right hemisphere and the second and fatal attack to the massive hemorrhage caused by rupture following destructive arteritis in the left side.

Case 16 : O. S., 34-year-old male (Tohoku Univ.). There was a past history of rheumatic arthritis at the age of 17 years. Mitral stenosis with pulmonary infarction was diagnosed at the Sendai Hospital in July 1931 (33 years of age).

Autopsy findings : The chief findings were mitral stenosis, verrucous endocarditis of the aortic valve, cerebral hemorrhage, infarction of the right kidney, congestion of the liver, spleen and lungs. There was marked stenosis of the mitral valve and thrombus was present at this site. The aortic valve was hypertrophied and ulceration and verruca formation were found in place. In the brain, an aneurysmatic swelling of the right a. cereb. post. was noted close to the gyrus hippocampus (Fig. 37, A). There was rupture of the aneurysm with bleeding into the brain substance and the subarachnoidal space. The ventricles too, were filled with coagula. The size of the hemorrhage by horizontal section was 10.0 x 3.1 cm (Fig. 38).

Histological findings : The region of the aneurysmatic swelling of the right a. cereb. post. (dia. = 1.458μ) was examined serially. An old fibrous inflammation was found generally in the arterial wall (Fig. 39), but a portion of the wall has been destroyed by the inflammation and ruptured resulting in massive hemorrhage.

It is suggested that some inflammation-causing agent was transported to this site from the heart and incited a localized arteritis and aneurysm, resulting finally in rupture.

Case 17 : O. A., 34-year-old female (Kyoto Univ.). Cardiac disease had been diagnosed at 27 years of age. In Nov. 1943 ($\frac{1}{2}$ year before death), there were remitting fever of 39°C and general malaise. The heart was enlarged to the left, an systolic murmurs were present at all the valves. White cell count was 9,000-12,000 and streptococcus was isolated from the blood. The heart gradually enlarged and the murmurs became stronger. In March 1944, incontinentia urinae and weakness of the legs became apparent. On April 15, there were generalized seizure and unconsciousness. On the 20th, right hemiplegia appeared and death occurred on April 21. Clinical diagnosis: Cerebral embolism.

Autopsy findings : The chief findings were verrucous endocarditis of the mitral valve, myocardial degeneration, patent foramen ovale, cerebral hemorrhage, anemic infarction of the spleen and kidney etc. A walnut-sized hemorrhage (3.0 x 1.5 cm) was found extending from the right fissura Sylvii to the insula cortex (Fig. 40) and the right a. cereb. med. was embedded in the lesion.

Histological findings : There was infiltration of the mitral valve by leukocytes and a broad thrombus containing numerous bacterial globi was attached to the valve. In the deep layer there was granulation tissue composed of fibroblasts, epitheloid cells and giant cells. It is believed, therefore, that this was endocarditis lenta. Frontal plane sections (in front of the optic chiasma) were prepared so that the hemorrhagic lesion could be examined. A total of 2,000 serial sections were examined and a rupture was found in a branch (dia. = 1.425 μ) of the right a. cereb. med., namely, there was a large defect in the arterial wall and a typical hemorrhagic globus, ca. 5mm in diameter, was present outside of the defect (Fig. 41). There was cellular infiltration and granulation throughout all the layers of the remained arterial wall and giant cells were present in some places. These inflammatory changes were especially marked in the region of the rupture. Short chain streptococcus (morphologically coinciding with streptococcus viridans) was found by Gram stain in the surrounding area. The bleeding in this case is believed to have been caused by rupture of the meningeal artery which had been weakened by inflammation due to bacteria carried here from the heart.

Case 18 : Y. Y., 42-year-old male (Nagasaki Univ. No. 3045). Cardiac disturbance had been noted since birth. In the spring of 1948 (about 9 months before death), chest pain, night sweating and cough became apparent. In the summer of the same year, neuralgic pain of the left forearm and left leg occurred. In Jan. of the next year there were headache and fever and a systolic murmur was audible at all valvular orifices. On Jan. 15, he suddenly collapsed and lost consciousness. This was followed by a state of coma and he died on Jan. 17. Clinical diagnosis : Heart failure.

Autopsy findings : The chief findings were verrucous endocarditis of the aortic valve (with perforation), cerebral hemorrhage (embolic?), infarction of the spleen, congestion of the liver, kidney and spleen. There was left ventricular hypertrophy, malformation of the valve (1 of the aortic valves absent), ulceration, verruca formation and adhesion of the valves. In the horizontal plane, a large hemorrhage (3.0 x 5.0 cm) was found anterior to the right basal ganglion and coinciding with the medulla of the frontal lobe and the neighboring cortex (Fig. 42). A widespread subarachnoid bleeding was present extending upward from the

fissura Sylvii and to the meninges of the right frontal gyrus.

Histological findings : The hemorrhagic lesion in the vicinity of the fissura Sylvii containing the a. cereb. med. was examined serially first, but the cause of the bleeding could not be ascertained. Various sections of the lesion were further examined without success. Frontal sections of the posterior portion of the lesion finally revealed a rupture in the a. insulae (Fig. 43). A U-shaped defect was present in an artery (dia. = 964μ) under the meninges of the deep part of the insular sulcus and a large hemorrhagic globus was found outside the rupture, embedded in the hemorrhagic lesion. The residual walls of the artery showed severe inflammation. The bleeding in this case therefore is due to rupture following localized arteritis secondary to endocarditis.

Case 19 : N. S., 45-year-old male (Nagasaki Univ. No. 3512). This is the same case as the No. 9.

Autopsy findings : The main findings were recurrent endocarditis, softenings in the frontocentral and insular region (Fig. 23, S₁ and S₂), fresh massive hemorrhages in the right frontal and left occipital region (Fig. 23, H₁ and H₂), infarction of the kidney etc.

Histological findings : Concerning the softening the detail has been described above. The hemorrhagic lesion in the frontal region (H₁) was examined serially. A relatively small meningeal artery (dia. = 165μ) in the deep portion of the sulcus revealed a rupture and there hemorrhagic globus was built (Fig. 44, G), being embedded in the main lesion which destroyed the brain parenchyma. There was distinct inflammatory changes in the arterial wall. This case therefore, has had many localized arteritis in the meningeal arteries (probably due to endocarditis), and some of them were proliferative or obliterative (f. i. Fig. 24) and had caused softenings, and others were exsudative or destructive (f. i. Fig. 44) and had caused ruptures.

Case 20 : K. X., 46-year-old female (Kyushu Univ.). Valvular disturbance was diagnosed at 7 years of age. There had been severe headache and palpitations since Feb. 1949 (about 2 years 9 months before death). In Jan. 1950, pulmonary infiltration with valvular failure was diagnosed and walking became almost impossible. In June, cough, hemoptysis, night sweat and weakness suddenly occurred and hospitalization on June 20. At that time, there were elevation of the cardiac region, marked systolic murmur at all valves and the spleen was swollen and tender. In Oct., absolute arrhythmia became apparent. The condition gradually became worse from the middle of Sept. and the consciousness became cloudy on Nov. 3 and she died on Nov. 8. Clinical diagnosis : Mitral and aortic stenosis with insufficiency and cerebral embolism.

Autopsy findings : The main findings were cor triloculare biventriculare, slight congenital stenosis of the aortic ostium, chronic endocarditis of the mitral and pulmonary valves, cerebral hemorrhage, infarction of the kidney etc. The heart was markedly enlarged, the interatrial septum was absent, the mitral valves revealed fibrous thickening and adhesion, and old verrucous thrombi were found attached to the hypertrophied pulmonary valve. A large massive hemorrhagic lesion was present in the left hemisphere anterior to the insula and upward from the lentiform and caudate nuclei (Fig. 45).

Histological findings : The pulmonary valve was productively hypertrophied with relatively old verruca formation and bacteria could be found in parts of the verruca. Horizontal sections of the hemorrhagic lesion of the brain were prepared

with full consideration of the course of the vessels. A rupture was discovered in a meningeal artery (a branch of a. cereb. med., dia.=905 μ). There was a V-shaped defect in the arterial wall outside of which a massive hemorrhagic globe (3.5 x 3.2 mm) was present (Fig. 46, G). The hemorrhagic globe is imbedded in the hemorrhage. Signs of severe inflammation are present in the arterial wall and the bleeding is without any doubt due to rupture of the artery.

Case 21 : M. S., 57-year-old male (Tokyo Univ.). Headache, dizziness, general malaise, palpitations, increased respiratory rate suddenly occurred from about 1- $\frac{1}{2}$ years before death. An apoplectic attack took place one year later and right hemiplegia remained. Death occurred on May 9, 1935. Clinical diagnosis: Myocardial degeneration.

Autopsy findings : The chief findings were verrucous endocarditis of the mitral valve, cerebral hemorrhage arteriosclerotic renal atrophy etc. The heart was enlarged and had grayish scars in the myocardium and numerous verruca were present in the mitral valve. A pigeon-egg sized hemorrhage was present in the left hemisphere between the gyrus frontalis medius and the corpus callosum (Fig. 47).

Histological findings : Serial sections of the brain lesion were prepared in the frontal plane. A hemorrhagic globe (2.5x2.0 mm) was found in the area supplied by a branch of the left a. cereb. med. (Fig. 48). The site of rupture could not be ascertained in the sections prepared but from experience the presence of the hemorrhagic globe is a certain sign of rupture.

DISCUSSION

A. Mechanism of development of embolic softening.

The term cerebral "embolism" is commonly used since VIRCHOW⁴³⁾ and it has been accepted that this occurs when a particle of tissue or thrombus is transported from the heart, aorta, arterial aneurysm or lungs to the brain where it becomes lodged in a small artery and forms a plug obstructing the blood-flow resulting in localized necrosis or softening. In other words, a "sudden mechanical obstruction" of the artery is the most important causal factor. Therefore, not only clinical but also at autopsy, cerebral embolism was often diagnosed in the presence of endocarditis and cerebral softening (apoplectic attack), without examining the cerebral arteries. Similar reports of autopsy cases have been published in Japan (NAGAYO²⁹⁾, NAGAI²⁸⁾, KAGEYAMA¹³⁾, KIKUJIMA¹⁴⁾, KITAMURA¹⁸⁾, etc.).

The authors attempted to find out if a thrombus or a plug was always present in the arteries leading to the softening-areas in cases such as these and a careful study by serial section was made in 9 cases and unexpected findings were obtained. Namely, it was found that in the presence of endocarditis, there was severe localized acute thrombic arteritis or chronic proliferative arteritis (scar formation) in extracerebral and/or intracerebral arteries and as result, there was narrowing or obliteration of the vessel, thus softening occurred.

On the other hand, it is known that transportation of intracardial bacteria-containing thrombi to the cerebral artery results in the occurrence of localized arteritis, and/or aneurysm (PONFICK,³⁷⁾ EPPINGER,⁷⁾ BENDA,²⁾ TERPLAN,⁴²⁾ BÖTTGER⁴⁾, etc.), some of which can rupture and cause hemorrhage (see the later section). There was bacterial thrombic arteritis of the a. cereb. med. in the 2 cases of endocarditis reported by BÖTTGER⁴⁾ (1951) and this caused encephalomalacia. One of the BÖTTGER's cases had endocarditis lenta and the cerebral artery revealed

similar inflammatory granulation to that of the cardiac valve having giant cell formation. In the authors' series, endocarditis was present in 9 of 8 cases (sepsis in 1 case) and severe arteritis was found in the artery leading to the softening-area, but any material regarded as a plug from the heart could not be ascertained. A thrombus was found in the case 1, 2 and 7, but in the former 2 cases the thrombus was much fresher than that of the heart and the latter one was a case of sepsis and had no endocarditis. Therefore, it is believed that the obliteration of the vessel in all cases was due to fresh or organized thrombic arteritis or to proliferative arteritis which was chronic from the beginning. The cause of the arteritis must be, of course, some agent (bacteria, toxin, small infected material, etc.) transported from the heart or initial septic lesion but this does not necessarily have to be a large embolus which would "mechanically" obstruct the vessel. It can be said that it is the arteritis which plays the most important role in the obstruction of the vessel. It is suggested that the term "arteritic encephalacia" is more appropriate than "cerebral embolism" or "embolic softening" (Fig. 49).

Fig. 49

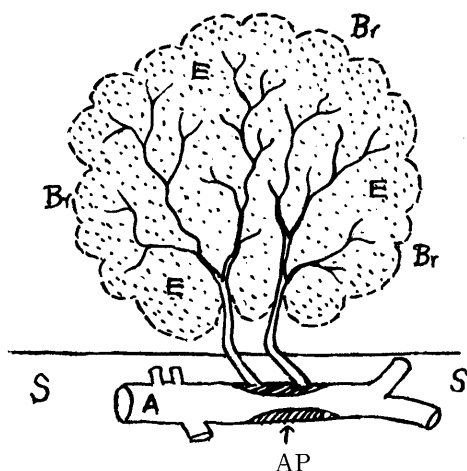
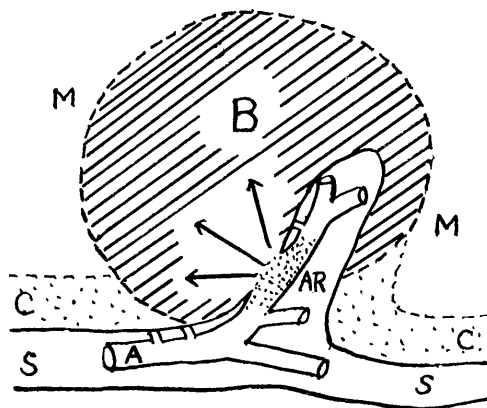


Fig. 50



B. Mechanism of development of embolic cerebral hemorrhage.

As stated previously, there are numerous theories as to how embolic cerebral hemorrhage occurs and most of the investigators suggest that this is a diapedesis (capillary) bleeding resulting from plugging of the vessel by an embolus as in the case of ordinary hemorrhagic infarction, or a venous hemorrhage following necrosis of cerebral parenchyma. In the authors' series of 12 cases however, it was found that the hemorrhage was a result of arterial rupture and neither capillary nor venous. The mechanism of the rupture differed totally from hypertensive cerebral hemorrhage. The characteristics of the hemorrhage are as follows:

1) The hemorrhage is macroscopically, fresh in general, massive, and sharply demarcated and these characters are similar to hypertensive bleeding, but whereas hypertensive bleeding occurs most frequently in the gray matter of the basal ganglia, this hemorrhage is found in or close to the cortex. Hypertensive bleeding occurs always by rupture (due to angioneurosis) of small intracerebral arteries (f. i. aa. corp. striati), while in this case, the rupture occurs always in meningeal artery, i. e. relatively large branch of a. cereb. med., ant., post., etc.

2) Detailed examination of the hemorrhage by serial sections reveals the presence of 1 or more so-called "hemorrhagic globe". This is composed of layers of fibrin net, white cells and red cells and surrounds the ruptured portion of the artery. This is constructed of blood which has flown out of the rupture and its presence has been shown to be definite sign of arterial rupture (MATSUOKA). According to MATSUOKA, in the case of hypertensive hemorrhage the globe is about 1.0 mm in size, whereas in the present cases the globe ranged from 2.0 mm to 5.0 mm in size suggesting that the ruptured arteries were of a greater size.

3) A V-shaped or U-shaped defect was always found in the arterial wall and the ruptured artery was always fairly constant size, usually, being larger than 1.0 mm in diameter and 5-10 times larger than in hypertensive bleeding (average 50-200 μ in diameter). The strong blood flow out of the rupture damaged the cerebral parenchyma forming a massive hemorrhage.

4) Detailed examinations of the ruptured arteries usually fails to disclose the presence of a thrombus or embolus but there is always severe inflammatory signs in the arterial walls and it can clearly be seen that the rupture was due to destruction of the walls by inflammation (Fig. 50). It is also of interest that Gram positive streptococci or staphylococci are sometimes present not only in the heart but also in the walls of the ruptured artery.

5) Causal agent: As shown, the bleeding is due to a rupture and not to obstruction and the rupture takes place when the wall of the artery is damaged and weakened by an inflammatory process. As in the case of the "arteritic softening" the cause of the inflammation must be some agent (bacteria, toxin, small thrombus etc.) transported from the heart or initial septic lesion (f. i. No. 13).

C. Arteritic cerebral apoplexy

As mentioned above, even at autopsy, cerebral hemorrhage accompanied by endocarditis has been explained as diapedesis bleeding following softening. but the authors have conducted a painstaking examination of the hemorrhagic area and have been able to verify rupture of the artery. Therefore, even if there is some permeation, this is not important. The theory of SCHWARTZ³⁸⁾ that this is a functional bleeding of the nutritional vessels following embolism, cannot be denied.

BÖHNE³⁹⁾, BÜCHNER⁴⁰⁾, NORDMANN³³⁾, WESPETHAL⁴⁴⁾, etc. have suggested that a softening is present prior to occurrence of hypertensive cerebral hemorrhage. As it has also been suggested that embolic bleeding occurs as a permeation following embolic softening, utmost care was taken in the investigation in order to verify the presence together with or prior to the hemorrhage. Not one case which could be attributed to prior softening was observed. In one case, softening and hemorrhage were found together in the same place, but close examination revealed an obstruction in one place and a rupture close by in the same artery (No. 8). In other word, softening was not a prerequisite for hemorrhage.

PONFICK³⁷⁾ has explained the hemorrhage as being due to mechanical damage of the arterial wall resulting from a plugging by an embolus but this is too fantastic idea. It is well known that an aneurysm develops in local artery when a bacteria-containing embolus is transported there from endocarditis (EPPINGER⁷⁾, BENDA²⁾) and there may be cases of cerebral hemorrhage due to rupture of such aneurysm (SIMMONDS³⁹⁾). In the authors' series of cases, only 1 showed visible aneurysm and its rupture (No. 16).

As shown, the so-called embolic softening is due to "localized arteritis" coming

from endocarditis and the non-hypertensive massive cerebral hemorrhage accompanied by endocarditis is caused by arterial rupture which is due to "the same origin (localized arteritis)". In other word, localized arteritis coming secondary to endocarditis (or sepsis without endocarditis) may result in softening in some cases and hemorrhage in others and both softening and hemorrhage can be present in defferent parts of the same brain (f. i. cases No. 1, 5, 8, 9). When the arteritis undergoes a proliferative process, stenosis or obstruction of the vessel and hence softening occurs, whereas when it undergoes a destructive process, rupture and hemorrhage occurs.

On the basis of these findings, it is suggested that the term "cerebral softening due to arteritis" is preferable to embolic softening, and "cerebral hemorrhage due to arteritis" is preferable to embolic hemorrhage. It is also suggested that the term "arteritic cerebral apoplexy" may be used to cover both.

SUMMARY

A total of 21 cases diagnosed as "cerebral embolism" at autopsy were studied. Nine of 21 case were softening and 12 were massive hemorrhage. The lesions and the arteries leading into the lesions were examined in detail by sections in an attempt to clarify the mechanism of softening and hemorrhage. The following are observed.

1) The cause of so-called "embolic cerebral softening" is not always "mechanical obstruction" of an artery by an embolus, and so-called "embolic hemorrhage" is not diapedetic, but principally rhexisbleeding.

2) In both embolic softening and hemorrhage, the chief role is played by some inflammatory agents (bacteria, toxin, small thrombi, etc.) carried from the heart (endocarditis) or other sites to the meningeal and/or intracerebral artery and inciting first a localized arteritis, and it is the arteritis which is the direct cause of the obstruction or rupture.

3) When the localized arteritis undergoes a proliferative or thrombus-forming process, a stenosis or obstruction of the vessel and hence softening occurs. When it undergoes a destructive process, a rupture and hemorrhage occurs. Sometimes both softening and hemorrhage occur together in different parts of the same brain.

It suggests that the term "cerebral apoplexy due to arteritis" may be preferable to cover both embolic softening and hemorrhage. The arteritis causing obstruction or rupture appears most frequently in a. cereb. med. and its branches.

4) The theory that cerebral softening and hemorrhage acompanied by endocarditis is caused by mechanical plugging of artery by emboli should be revised, and thrombi, and emboli or aneurysm produced by bacterial infection are not essential factors in development of hemorrhage.

5) As both "embolic hemorrhage" and "hypertensive cerebral hemorrhage" are due to arterial rupture, the gross findings of lesions at autopsy are quite similar but the two can be differentiated even macroscopically on the basis of predilection for different areas.

6) The rupture in cases of embolic hemorrhage occurs usually in meningeal arteries larger than 1.0 mm in average diameter. It is essentially different from arterial rupture in hypertensive cerebral hemorrhage in which the rupture is caused by angionecrosis (fibrinoid necrosis) of intracerebral small arteries measuring 200 μ or less in diameter.

Remarks: A part of this investigation was published in *Igaku-Kenkyu* (Japanese) by NAKAGAWA^{30) 31)}.

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Explanation of plates

- Fig. 1. Case No. 1, 64 year old female; endocarditis (+). Horizontal section of the right hemisphere. Softening (S) in cortex of the frontal lobe, superficial hemorrhage (H) in posterior part of the temporal lobe.
- Fig. 2. Same as above. Distribution of the right a. cereb. med. And parts (broken line I, II, III) excised and examined. Anterior branch (a) leads to the softening (frontal lobe) and posterior branch (b) to the hemorrhage (temporal lobe).
- Fig. 3. Same as above. Section (through Fig. 2, I) of the arterial branch (Fig. 2, a) leading to the softening (Fig. 1, S). Fresh thrombus present in lumen, marked cellular infiltration of walls (thrombic arteritis). H-E stain.
- Fig. 4. Case No. 2, 33 year old female; endocarditis (+). Horizontal section of the brain showing a large softening (S) in the left corpus striatum.
- Fig. 5. Same as above. Rr. extt. of aa. corporis striati medd. (REAC) branching from a. cereb. med. (ACM) and leading to the softening area. Section through A (containing ACM and branch a and b) is shown in Fig. 6.
- Fig. 6. Same as above. Branch a and b show severe thrombic arteritis, their lumina are obliterated (cause of the softening), while ACM is intact. H-E stain.
- Fig. 7. Case No. 3, 37 year old male; endocarditis (+). Horizontal section of the brain showing a large softening (S) in the right putamen and internal capsule.
- Fig. 8. Same as above. Severe suppurative panarteritis of an intracerebral branch of REAC which caused the softening. M. Media damaged by inflammation. I Thickened intima with accumulation of numerous wander cells. L Lumen narrowed. v. Gieson stain.
- Fig. 9. Case No. 4, 35 year old female, endocarditis (+). Cross section of frontal lobe. Fresh pencil-shaped softening (S) between outer edge of the left putamen and claustrum.
- Fig. 10. Same as above. Arteries leading to the softening. Section through A (bifurcation of the left a. cereb. med. and REAC) is shown in Fig. 11.
- Fig. 11. Same as above. Excised section of Fig. 10, A. Main stem (a. cereb. med.) shows severe proliferative endoarteritis and though not completely obliterated, the sites of bifurcation of REAC (f. i. R) are obliterated by intimal thickening of the stem resulting in the softening (Fig. 9, S). H-E stain.
- Fig. 12. Case No. 5, 32 year old male; endocarditis (+). Horizontal section of the cerebrum. Triangular area of softening (S) extending from the putamen to insula on right, massive hemorrhage (H) extending from outer edge of the putamen to the temporal and frontal lobes on left side.
- Fig. 13. Same as above. Distribution of the right and left a. cereb. med. and parts excised (broken line A and B). A is shown in Fig. 14 and B in Fig. 36.
- Fig. 14. Same as above. Section of the right a. cereb. med. (Fig. 13, A). The vessel contains organized (G) and fresh (T) thrombi, marked cellular infiltration in the media and adventitia (Ad). i, e, it reveals chronic obliterative thrombo-panarteritis which was the cause of the softening. H-E stain.
- Fig. 15. Case No. 6, male of unknown age; endocarditis (+). Horizontal section of the cerebrum. Large area of softening (S) from the right corpus striatum and cap. int. to insula.
- Fig. 16. Same as above. Schema of the right a. cereb. med. and REAC, leading to the

- softening-area. Brokenline (A) designates area excised and shown in Fig. 17.
- Fig. 17. Same as above. Main stem of the right a. cereb. med. Lumen completely obliterated by granulation tissue, all layers of the wall reveal severe inflammatory changes (organized thrombic arteritis). (REAC were also blocked). H-E stain.
- Fig. 18. Case No. 7, 25 year old male, case of sepsis; endocarditis (-). Horizontal section of the cerebrum. Wide softening (S) from the right cap. int. to corpus striatum and insula.
- Fig. 19. Same as above. Main stem of the right a. cereb. med. and REAC leading to the softening. Marked swelling in middle part where REAC bifurcate. Section through broken line (A) is shown Fig. 20.
- Fig. 20. Same as above. Dilated part of the right a. cereb. med. Partially organized thrombus in lumen, severe cellular infiltration in walls (thromboarteritis). Small branches (R) are rr. extt of aa. corp. stri. medd. (REAC) and thrombic arteritis can be seen here too. These changes of the stem and branches are the cause of the softening. Elastic fiber stain.
- Fig. 21. Case No. 8, 26 year old female; endocarditis (+). Horizontal section of the cerebrum. Softening (S) extending from the left claustrum to insula. Hemorrhagic area included in the softening.
- Fig. 22. Same as above. Branch of aa. insulae leading to the softening is shown. Severe inflammatory destruction and cellular infiltration of the wall, granulation tissue in lumen. This arterial obliteration is the direct cause of the softening. In other part of the same artery there was rupture (cf. Fig. 31). H-E stain.
- Fig. 23. Case No. 9, 45 year old male; endocarditis (+). Horizontal section of the brain. Two softenings (S₁, S₂) in right frontocentral region and insula, two hemorrhages in right frontal and left occipital region (H₁, H₂).
- Fig. 24. Same as above. A meningeal artery leading to the softening (Fig. 23, S₁) reveals productive endoarteritis and the lumen is almost obliterated. Branches of this artery (f. i. b) are completely obliterated in sites of bifurcation. These are the cause of the softening. H-E stain.
- Fig. 25. Case No. 10, 17 year old female; endocarditis (+). Cross section of the left cerebral hemisphere (across optic chiasma) Massive hemorrhage extending from outer edge of left claustrum to insular cortex. P Site of arterial rupture.
- Fig. 26. Same as above. Area of rupture of a. insulae (a branch of the left a. cereb. med.). Site of rupture (upper part) and hemorrhagic globe (arrow). Elastic collagenous fiber stain.
- Fig. 27. Same as above. Site of rupture. Relatively old but severe arteritis can be seen, destruction of tunica elastica shown (dia. of art. = 1,030 μ). Elastic fiber stain.
- Fig. 28. Case No. 11, 21 year old male. Old endocarditis of the mitral vale.
- Fig. 29. Same as above. Horizontal section of the cerebrum. Elongated hemorrhage extending from outer edge of the right putamen to insula.
- Fig. 30. Same as above. Site of rupture of a. insulae. Severe arteritis and V-shaped defect of the wall can be seen. Massive hemorrhage is continuous with site of break in wall (dia. of art. = 1,392 μ). Elastic collagenous fiber stain.
- Fig. 31. Case No. 12, 26 year old female (same case as Fig. 21); endocarditis (+). Site of rupture of a. insulae branching from the left a. cereb. med. There is severe arteritis and defect in the wall (dia. of art. = 792 μ). Elastic fiber stain.
- Fig. 32. Case No. 13, 21 year old male; case of sepsis, endocarditis (-). Horizontal section of the cerebrum. Massive hemorrhage extending from outer edge of the left putamen to insula.
- Fig. 33. Same case as above. Site of rupture of a. insulae (dia. of art. = 1,014 μ). Elastic fiber stain.
- Fig. 34. Case No. 14, 32 year old female; endocarditis (+). Horizontal section of the left cerebral hemisphere. Three suppurative hemorrhagic lesions (1, 2, 3) in gyrus frontalis medius and gyr. centralis anterior.

- Fig. 35. Same as above. Site of rupture of meningeal artery, a branch of the a. cereb. ant. (Fig. 34, 1). Severe inflammation of the arterial wall and V-shaped defect and destruction of the cerebral parenchyma by blood flow can be seen. Elastic fiber stain.
- Fig. 36. Case No. 15, 32 year old male (same case as Fig. 12); endocarditis (+). A branch of the left a. cereb. med. leading to the hemorrhagic area (section through B in Fig. 13). The media and tunica elastica interna are destroyed by severe arteritis with incipient rupture. A rupture has been discovered a short distant cardially to this portion but photography unsuccessful (dia. of art. = 1,458). (See Figs. 12, 13, 14). Elastic fiber stain.
- Fig. 37. Case No. 16, 34 year old male; endocarditis (+). Base of the brain. Globe-shaped aneurysm (A) in region where the right a. cereb. post. attaches to the gyrus hippocampi.
- Fig. 38. Same as above. Horizontal section of the cerebrum. Massive hemorrhage from right temporal medulla into the lateral and IIIrd ventricle.
- Fig. 39. Same as above. A part of cross section of the aneurysm (Fig. 37, A). Inflammatory changes already old. Elastic membrane destroyed, invasion of connective tissue from the wall into lumen. Rupture has been confirmed but cannot be seen in this picture. Elastic fiber stain.
- Fig. 40. Case No. 17, 34 year old female; endocarditis (+). Cross section of the brain across the optic chiasma. Massive hemorrhage extending from the right fissura Sylvii to insular cortex.
- Fig. 41. Same as above. Site of rupture of meningeal artery, a branch of the right a. cerebri media. U-shaped defect of the wall, cellular infiltration and formation of granulation tissue in the remnant parts of the wall. Giant cells present close to site of rupture. Distance between both ruptured edges is about 2,398 , the ruptured artery measures 1,425 in diameter. Circular structure in upper part is a part of the hemorrhagic globe (G) (dia. = 5.0 mm). Elastic fiber stain.
- Fig. 42. Case No. 18, 42 year old male; endocarditis (+). Horizontal section of the cerebrum. Massive hemorrhage in the right frontal lobe under the cortex.
- Fig. 43. Same as above. Site of rupture in a. insulae, branch of the right a. cereb. med. (imbedded in the hemorrhagic lesion shown in Fig. 42). About one half of the wall missing due to severe arteritis forming a U-shaped defect (dia. of art. = 964). Large hemorrhagic globe (G) present. Elastic fiber stain.
- Fig. 44. Case No. 19, 45 year old male (same case as Fig. 23); endocarditis (+). Site of rupture of a relatively small meningeal artery (A) (dia. = 165), branch of the right a. cereb. ant. embedded in the hemorrhagic lesion (Fig. 23, H₁). Cellular infiltration in the arterial wall and V-shaped defect of the wall. G shows a part of the hemorrhagic globe. H-E stain.
- Fig. 45. Case No. 20, 46 year old female; endocarditis (+). Horizontal section of the cerebrum. Large massive hemorrhage extending from anterior part of the left insula to the upper part of the nucl. lentif. and nucl. caud.
- Fig. 46. Same as above. Site of rupture of a meningeal artery (dia. = 905) branching from the left a. cereb. med. V-shaped defect in the arterial wall forming large hemorrhagic globe (G) (3.2 x 3.5 mm). H-E stain.
- Fig. 47. Case No. 21, 57 year old male; endocarditis (+). Massive hemorrhage in gyrus frontalis medius of the left hemisphere extending from the cortex to the corpus callosum and anterior horn of the lateral ventricle.
- Fig. 48. Same as above. Hemorrhagic globe (3.0 x 2.5 mm) formed by rupture of a meningeal artery branching from the left a. cereb. med. H-E stain.
- Fig. 49. One of schemata of the softening due to arteritis. AP...localized proliferative arteritis causing obliteration of lumina of branches. S...subarachnoid space, A...meningeal artery, E...softening area, Br...brain substance.
- Fig. 50. Schema of development of the massive hemorrhage due to arteritis. AR...localized destructive arteritis causing rupture, B...hemorrhagic area, C...cortex, M...medulla.

Fig. 1

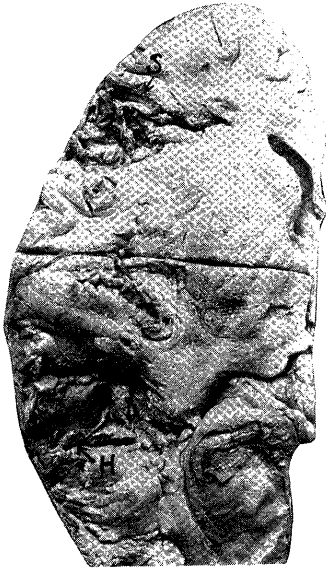


Fig. 4

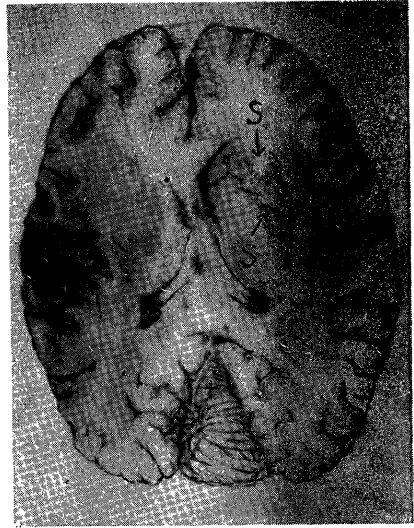


Fig. 2

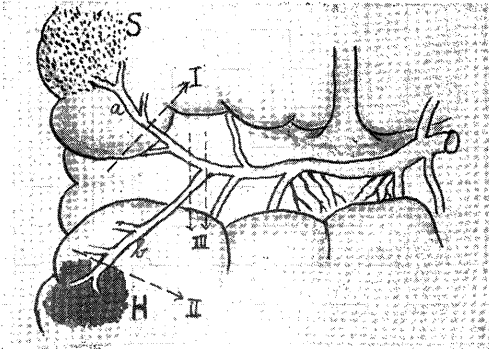


Fig. 5

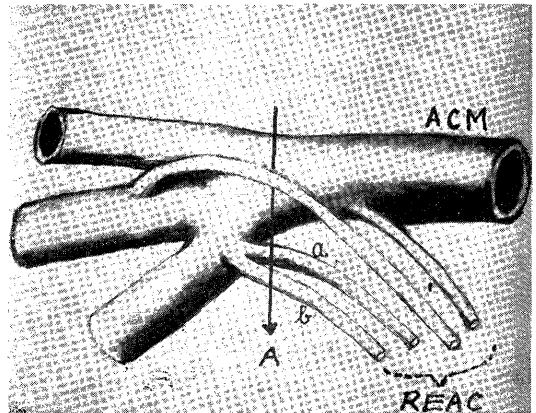


Fig. 3

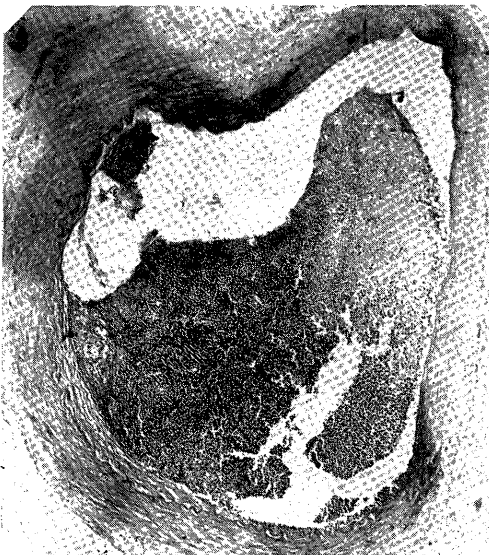


Fig. 6

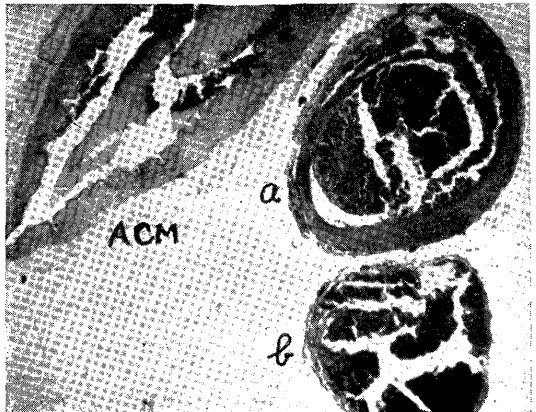


Fig. 7

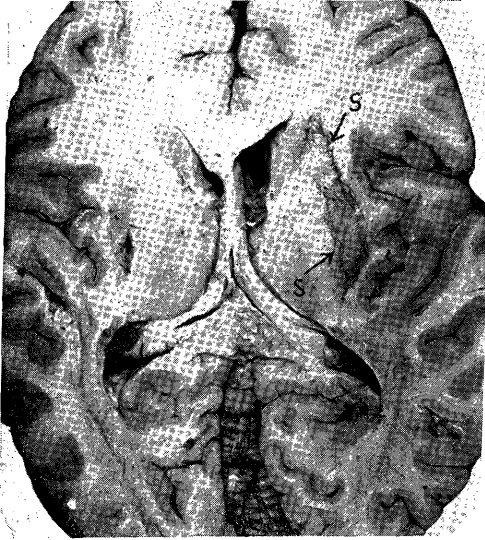


Fig. 10

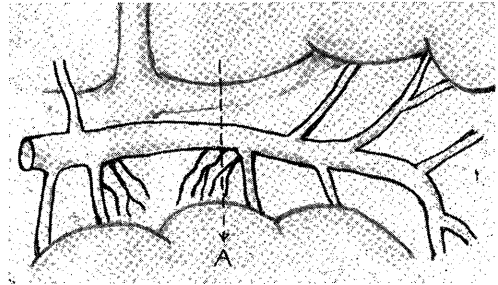


Fig. 8

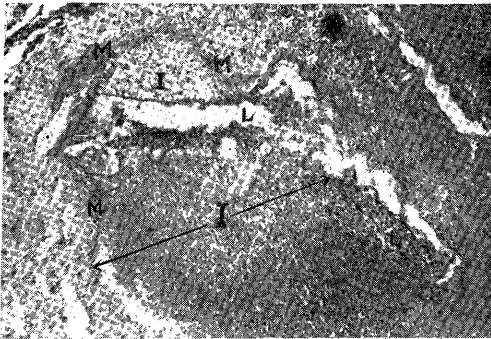


Fig. 11

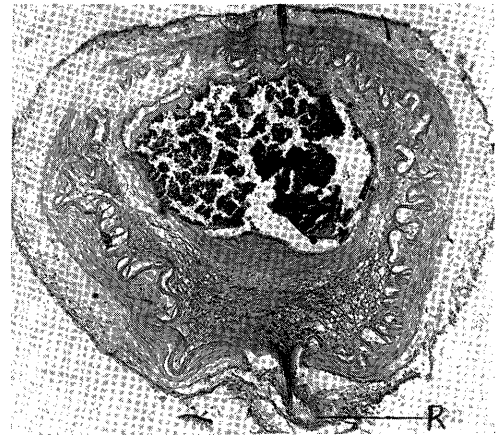


Fig. 9

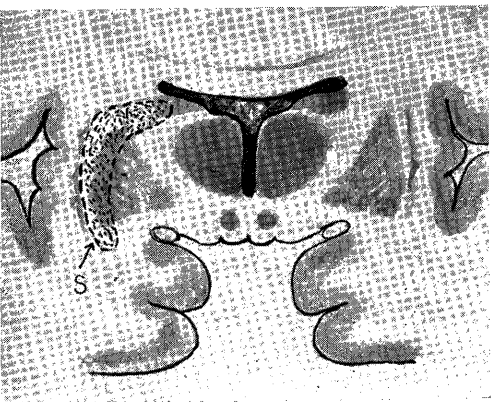


Fig. 12

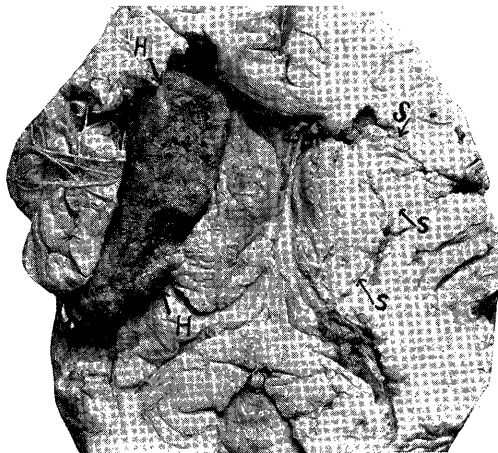


Fig. 13

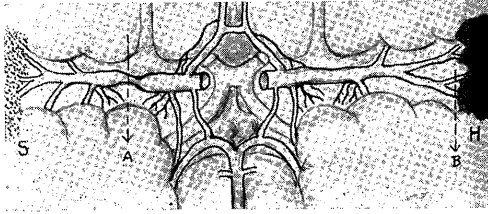


Fig. 16

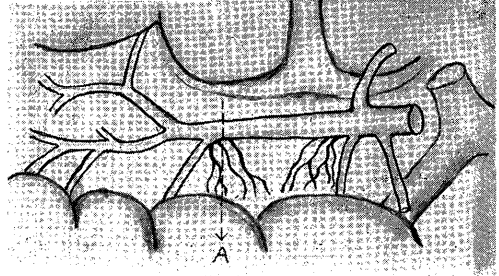


Fig. 14

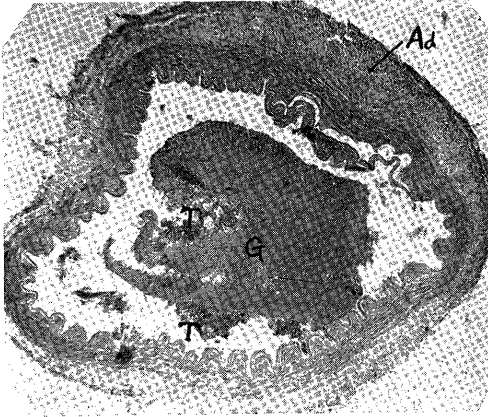


Fig. 17

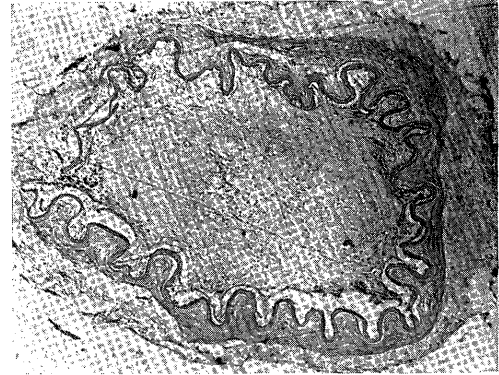


Fig. 15

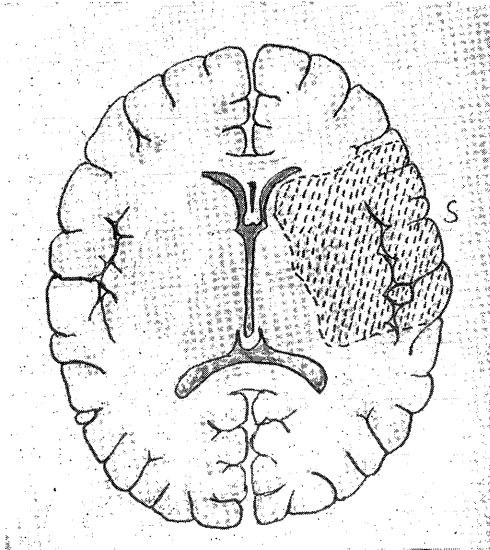


Fig. 18

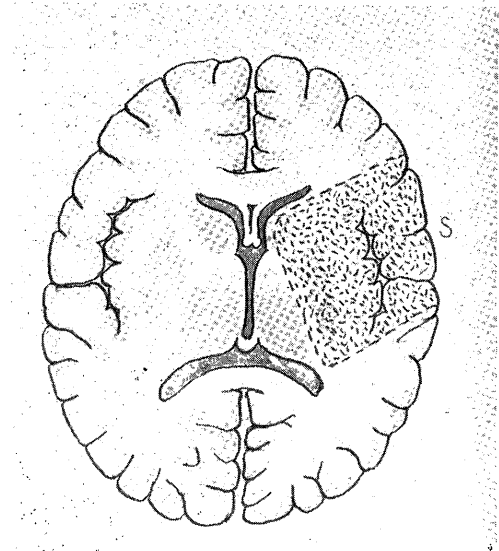


Fig. 19

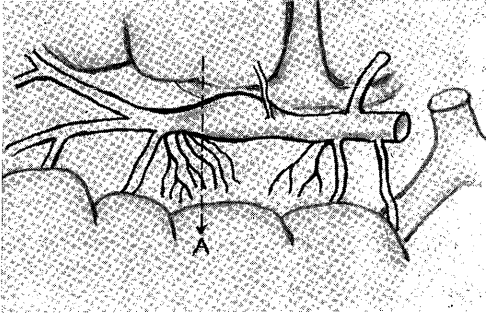


Fig. 22

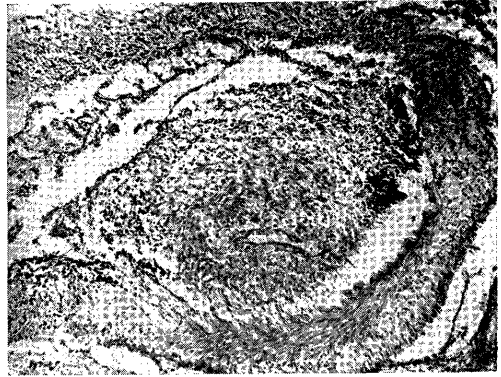


Fig. 20

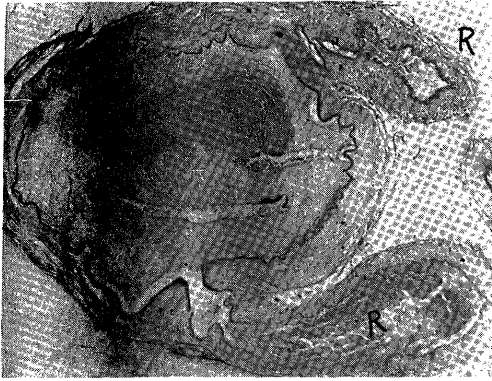


Fig. 23

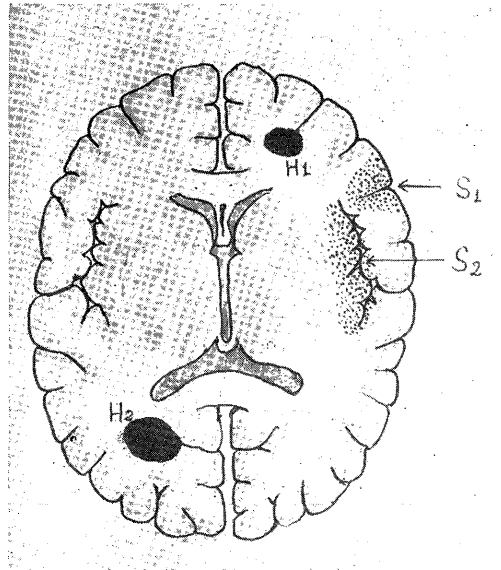


Fig. 21

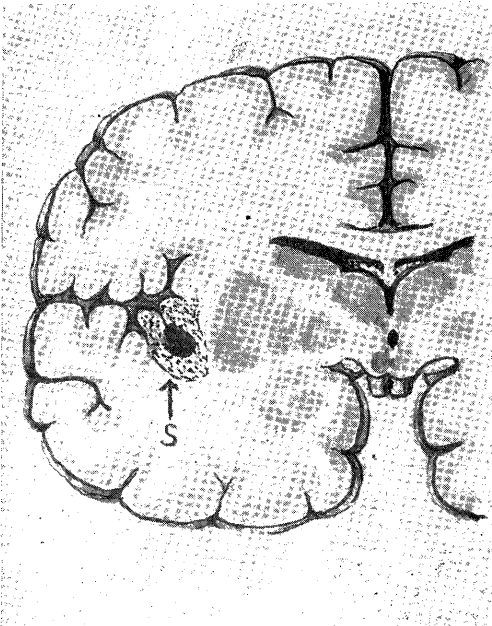


Fig. 24



Fig. 25



Fig. 28

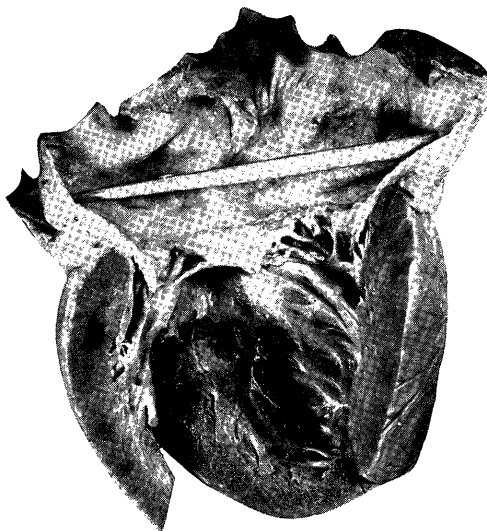


Fig. 26



Fig. 29



Fig. 27

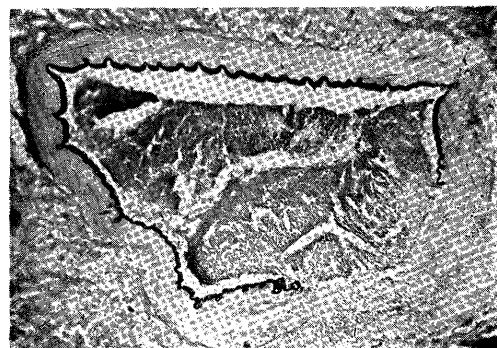


Fig. 30

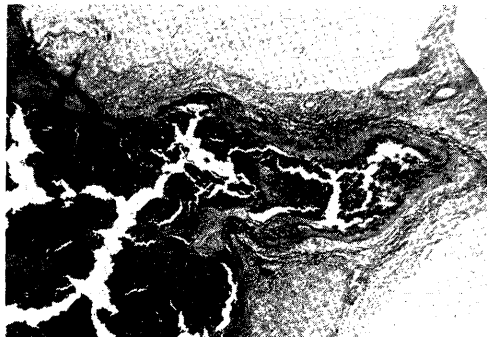


Fig. 31

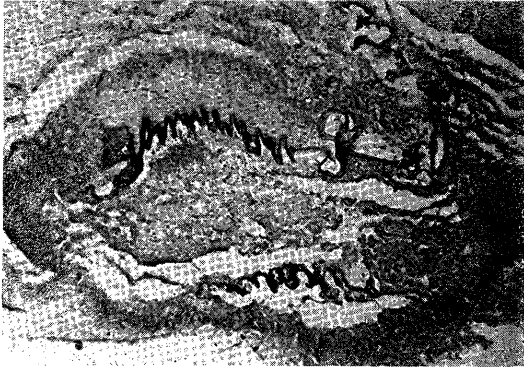


Fig. 34

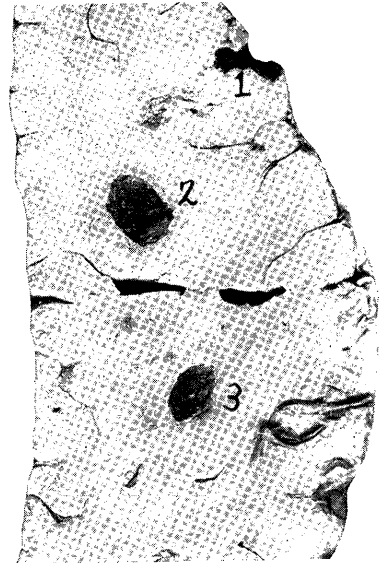


Fig. 32



Fig. 35



Fig. 33

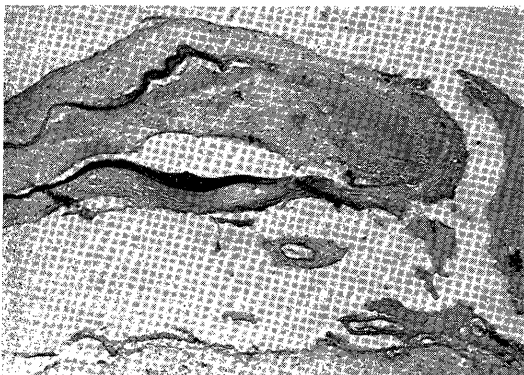


Fig. 36

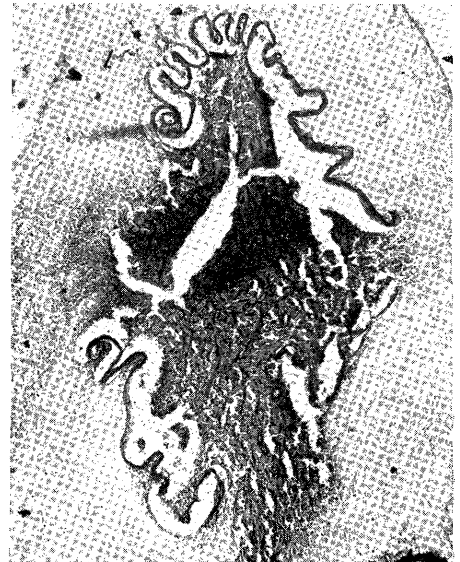


Fig. 37

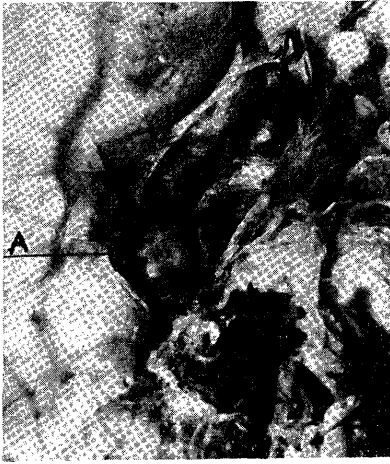


Fig. 40

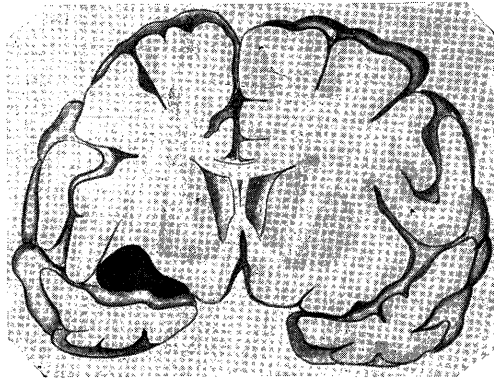


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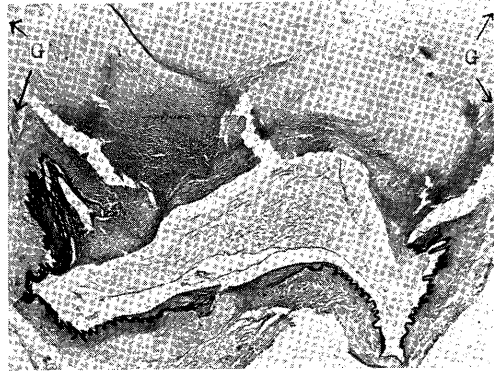


Fig. 38



Fig. 42

Fig. 39

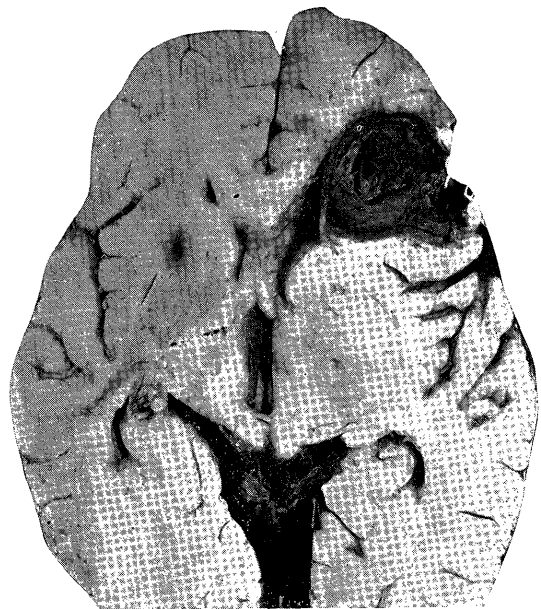
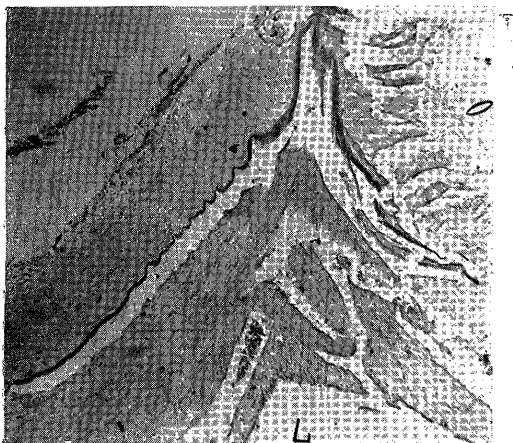


Fig. 43

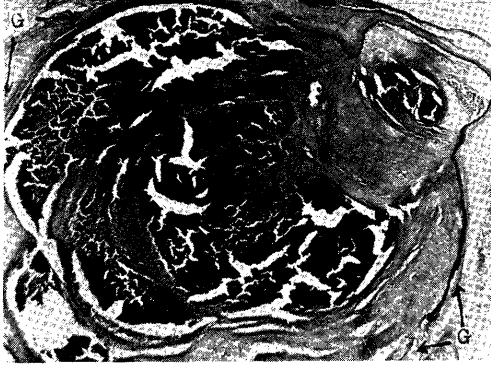


Fig. 46

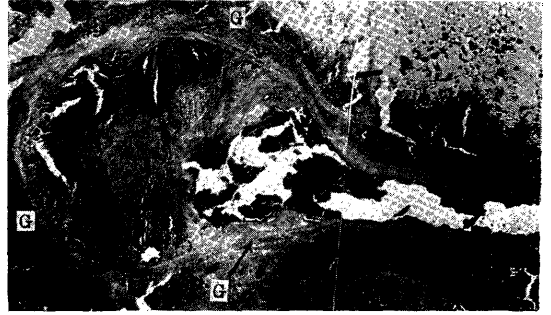


Fig. 44

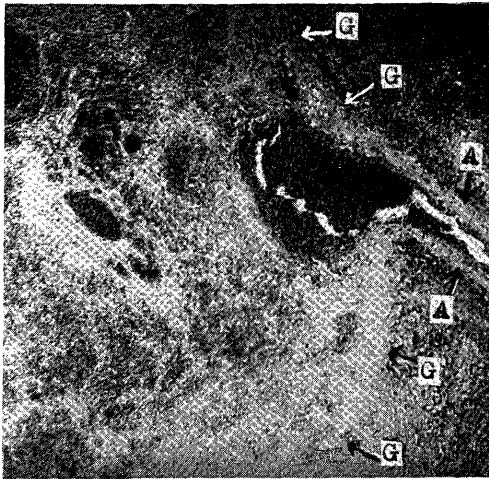


Fig. 47

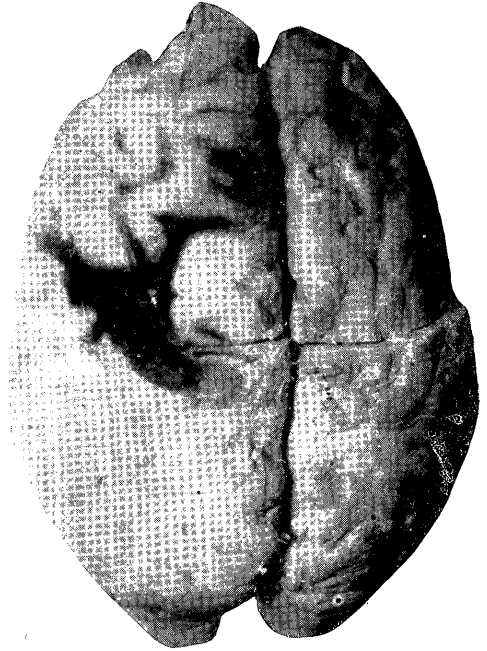


Fig. 45

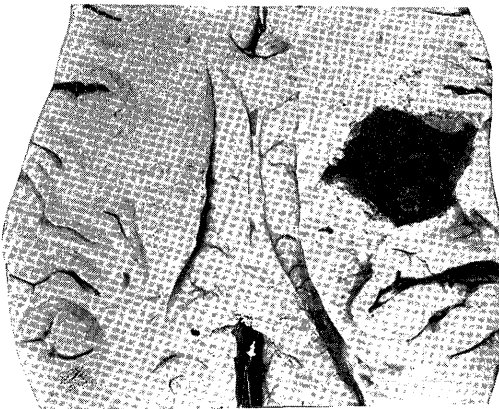


Fig. 48

