Hemorrhagic Cerebral Infarction

Proceedings of the 4th annual meeting of
The Japanese Ischemic Cerebrovascular
Disease Conference, Nagasaki, March 18, 1977

CONTENTS

* invited speaker
** discusser

CHAIRMEN

Part 1 : Junichi Kawafuchi, *Department of Neurosurgery, School of Medicine, Gumma University*

Part 2 : Hajime Handa, *Department of Neurosurgery, Kyoto University Medical School*

Part 3 : Takenori Yamaguchi, *Department of Internal Medicine, School of Medicine, Kyushu University*

Part 4 : Jiro Suzuki, *Division of Neurosurgery, Institute of Brain diseases, School of Medicine, Tohoku University*

Part 5 : Keiji Sano, *Department of Neurosurgery, University of Tokyo, School of Medicine*

    edited by
    Hirohisa Ono, *Department of Neurosurgery, Nagasaki University School of Medicine*

Pathogenesis of cerebral infarction: A review

Hidekatsu Matsumura and Emanuel R. Ross

Division of Neuropathology, Department of Pathology

Loyola University Medical Center, Illinois, USA

Cerebrovascular disease and its sequelae, represents the commonest disorder of the nervous system. Within the U. S., it has been estimated that slightly over 200,000 deaths per year occur as a result of cerebrovascular disease. The morbidity of this type of disease appears to be 10 times greater, with over 2 million persons suffering its ravage.

In considering all type of cerebrovascular disease, Kurtzke[15] estimated that 62 % will be thromboembolic disease, 16% hemorrhage, 12% SAH and 10% other or illdefined cerebrovascular disorders. Older studies tend to indicate that cerebral hemorrhage is commoner than infarction. In more recent reviews by Kurtzke,[15] Kreuger, Gordon and others, the incidence of cerebral hemorrhage has decreased, whereas the incidence of cerebral trombosis has increased. This is not only true in the United States, but also in Japan, where until recently cerebral hemorrhage made up the major portion of cerebrovascular deaths. It now appears that thromboembolic disease is more common than cerebral hemorrahge. This has been confirmed by Katsuki[14] where the proportion of hemorrhage to thrombosis is similar to that of Western countries. This is also supported by the reports of Otsu[20] and Matsumoto[17]. It should be noted that a recent paper by Fukasawa[9] indicates that in Northern Japan the incidence of cerebral hemorrhage still remains greater than thromboembelic disease.

Infarction results, when the blood supply to a region of the brain falls below a critical value. As Adams[1] pointed out this may be independent of arteriosclerosis. This may be due to a thromboembolic event, increased intracranial pressure or systemic hypotension. The resulting necrosis may be ischemic, hemorrhagic or mixed. Thrombotic events generally give rise to pale or ischemic infarct whereas hemorrhagic infarcts are most commonly the result of an embolic process. It is the hemorrhagic infarction and its pathogentic mechanism that I would like to review at this time.

The macroscopic appearance of a hemorrhagic infarction is readily distinguished from the pale or ischemic lesion, in that the affected gyri appear swollen, flattened with multiple isolated or even confluent hemorrhages. The tissue is soft, and because of the

swelling the sulci in the affected area are generally obliterated. In contrast the ischemic or pale infarct is usually soft, pale, tan–yellow and is generally totally devoid of hemorrhagic discoloration.

The cut surface of the hemorrhagic infarct reveals hemorrhages which may be mild to severe and varies from area to area. The affected zone is sharply demarcated and generally limited to the cortical zone. The cortico–white junction is obliterated. Deeper white matter lesions are rarely hemorrhagic, but remain pale (Fig. 1). Involvement of the white matter by pale grey–white sharply demarcated lesions, appear to occur more commonly in hypertensive patients. Basal ganglia when affected, may likewise be hemorrhagic. The basis for this will be discussed shortly.

Microscopically, ischemic neuronal degeneration is first to occur (Fig. 2). Rapid disappearance of oligodendroglia with swelling and eventual disappearance of astrocytes follows. Microglia being most resistent persists the longest. Myelin changes are characterized by a loss of stainability, followed by degenerative changes. Axonal degeneration follows shortly after the myelin changes. Most resistant to the affects of ischemia are the blood vessels themselves. These are the last structures to undergo degeneration. One further comment, in early lesions perivascular polymorphonuclear leucocytic aggregates are found. These may be so prominent that an erroneous diagnosis of meningoencephalitis may be made by the unwary.

Despite intensive investigation and increasing knowledge, the question as to why one develops a hemorrhagic rather than ischemic infarct or vice versa is not fully understood. Globus maintained that the ischemic and hemorrhagic infarcts were different stages of the same process. The escape of blood from a ruptured vessel within the area of ischemic necrosis transforms this to a hemorrhagic infarct. This view was later supported by Bohne.

In 1932, Westphal expressed the view that hemorrhagic infarction resulted from temporary arterial occlusion brought on by prolonged angiospasm.

As a result of his studies of human autopsy material, Fazio[7] stated that the hemorrhagic infarct was unrelated to massive hemorrhage and the result of a localized vasodilatation resulting in stasis and diapedesis. The vasodilatation was possibly due to a vaso – vascular reflex from some remote stimulus or possibly due to a local secretion of a vasodilating substance produced by a previous circulatory arrest.

Meyer and Denny-Brown[18] subsequently reported experimental data revealing that occlusion of large caliber vessels led to contraction of distal segments having a diameter of 50–250μ. Shortly thereafter, as a result of a reduction in pressure, the contraction was replaced by mild dilation of some 10%.

An important factor in the development of an infarct is the status of the collateral circulation. This is demonstrated by those cases where occlusion of one or even both carotid arteries fail to give rise to any type of infarction. Vander Ecken and Adams[24] demonstrated the existence of a collateral circulation between the major vessels of the cerebrum by means of the meningeal cortical vessels. Faris and co-workers[6] considered the collateral circulation as essential to the production of a hemorrhagic infarct. Hypertension was also considered

as a significant factor contributing to the development of hemorrhagic infarction.   Both contributing factors were demonstrated in dogs who underwent both middle cerebral artery clipping and in whom surgical coarctation was performed. In the non–hypertensive controls, ischemic encephalomalacia was noted, whereas in the clipped middle cerebral artery – hypertensive dogs the lesions were hemorrhagic infarcts. The hypertension,   with its increased intravascular pressure opened existing anastomosis between the major   vessels thus confirming Vander Ecken and Adams'[24]   earlier work.   It should be noted that in these experiments hemorrhages may have occurred as a result of fibrinoid degeneration of the arterioles resulting from hypertension.

Penry and Netsky[21] observed that because of the existence of an adequate collateral circulation, embolic occlusion of a single leptomeningeal vessel failed to give rise to an infarct.   Only when a cortical penetrating branch of the artery was occluded did a grey matter infarct arise.   This extended only to the depth of sufficiently large   anastomotic channel. Hain and co–workers occluding the middle cerebral artery of dogs produced both pale and hemorrhagic lesions. Clipping of the middle cerebral artery distal to the perforating ganglionic branch leads to ischemic necrosis, on the other hand clipping done so as to leave some perforating branches in front, as well as behind the clips, leads to hemorrhagic infarction.   When the middle cerebral artery of monkeys was occluded pale infarction always occurred leading these investigators to conclude that the different response to middle cerebral artery clipping was due to a differentiation in collateral circulation distal to the clipping.   This was confirmed by the observations of other investigators.   Fazio[7], Meyer and Denny – Brown[18] and others, Hain et al[10], felt that the escape of blood in the hemorrhagic infarcts was due to diapedesis.

Fisher and Adams[8] in 1951, stated that of the 66 cases of hemorrhagic infarction all but three were due to embolic disease. Hence, the statement made earlier in this paper that essentially all hemorrhagic infarcts are embolic in origin.

In a subsequent paper, Adams[2] proposed that an embolic process also can give rise to mixed infarcts.   The embolus, either by dilation or fragmentation is propagated peripherally restoring the circulation to the damage vessels, thus permitting free passage of blood through the already damaged vessel walls. Some vessels remaining plugged contiune to show ischemic necrosis.

Cobb and Hubbard[5] state that hemorrhage into the parenchyma arise from veins and capillaries secondary to venous stasis, with no evidence of bleeding from the arterial side. Cammermeyer in studying cases of arterial occlusion, venous thrombosis, and herniation estimated to be 1–12 days, also noted hemorrhages along veins and capillaries and rarely about arteries. The veins were distended, with some showing wide rupture of the wall.   Cammermeyer believes the rupture to be due in part to the loss of support by the surrounding parenchyma.   This loss is secondary to the necrotizing process of the infarct and partially due to the high venous back flow pressure which develops.

Recently we observed a biopsy specimen of a hemorrhagic infarct of a parietal lobe. Our preliminary findings reveal attenuation of some endothelial cells within the capillary. The

endothelial surface shows prominent undulations with many pinocytotic vesicle formation (Fig. 3-A). Occasionally discontinuities in the endothelial wall of the capillary were noted which varied in size. Plasma and fibrinous material were seen in these areas of discontinuity as well as in the enlarged pericapillary spaces (Fig. 3-B). These findings have been reported as the morphological basis of increased permeability of blood vessels and the break down of the blood brain barrier in various pathological conditions.

REFERENCES

1. Adams, JH, Scot Med J 12 : 339, 1967.
2. Adams, RD et al, Annual Rev Med 4 : 213, 1953.
3. Baker, AB et al, Neurology 13 : 445, 1963.
4. Cammermeyer, J, Acta Psychiat Neurol Scan 28 : 9, 1953.
5. Cobb, S et al, Am J Med Sci 178 : 693, 1929.
6. Faris, AA et al, Arch Neurol 9 : 468, 1963.
7. Fazio, C, J Neuropath Exp Neurol 8 : 43, 1949.
8. Fisher, M et al, J Neuropath Exp Neurol 10 : 92, 1951.
9. Fukasawa, J, Tohoku J Exp Med 117 : 357, 1975.
10. Hain, RF et al, J Neuropath Exp Neurol 11 : 34, 1952.
11. Hardin, C et al, Arch Neurol 9 : 473, 1963.
12. Hicks, SP et al, A. M. S. Arch Path 52 : 403, 1951.
13. Hirano, A, In Pathology of Cerebral Microcirculation (Ed. J Cervos-Navarro) 203p, 1974.
14. Katsuki, S et al, In Transactions of the Fifth Princeton Conference 99p, 1966.
15. Kurtzke, JF, Epidermology of Cerebrovascular Disease, Springer-Verlag Berlin 4 7, 60, 69p, 1969.
16. Little, JR et al, Stroke 7 : 35, 1976.
17. Matsumoto, N et al, Stroke 4 : 20, 1973.
18. Meyer, JS et al, Neurology 7 : 447, 1957.
19. Meyer, JS et al, A. M. A. Arch Neurol & Psychiat 72 : 296, 1954.
20. Otsu, S, Jap. Circulat. J. 33 : 1459, 1969.
21. Penry, JK et al, Arch Neurol 3 : 1960.
22. Stehbens, WE, Pathology of the Cerebral Blood Vessels, C. V. Mosby Co. 13 1 p, 1972.
23. Sundt, TM et al, J Neurosurg 31 : 311, 1969.
24. Vander Ecken, HM et al, J Neuropath Exp Neurol 12 : 132, 1953.
25. Zülch, KJ, In Pathology of the Nervous System (J. Minckler), 1522p, 1971.
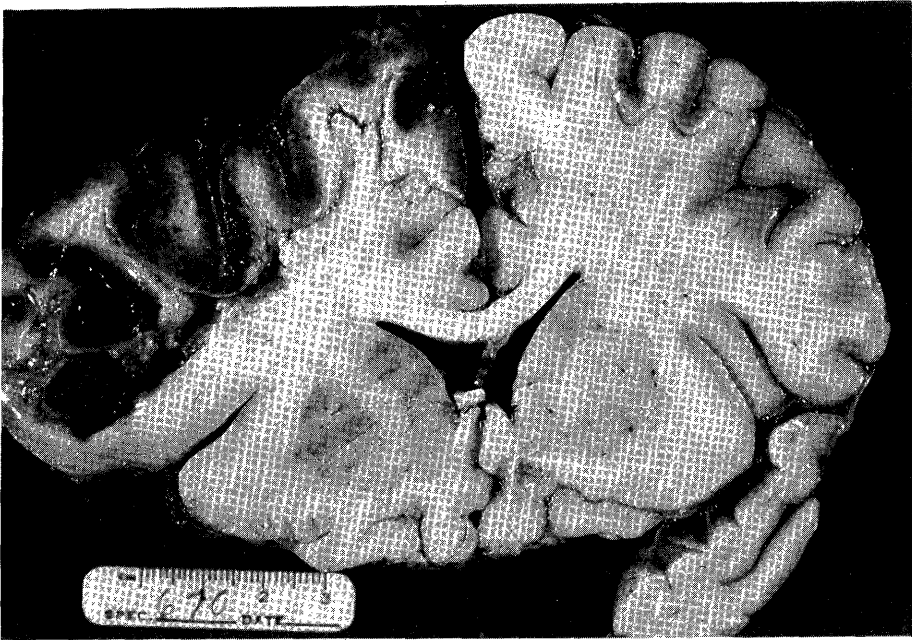
Fig. 1. Punctate and confluent hemorrhages are present thrughout most of the left cerebral cortex. A localized ischemic infarct is noted in the paramedial convexity. The subcortical white matter is pale, softened and collapsed.
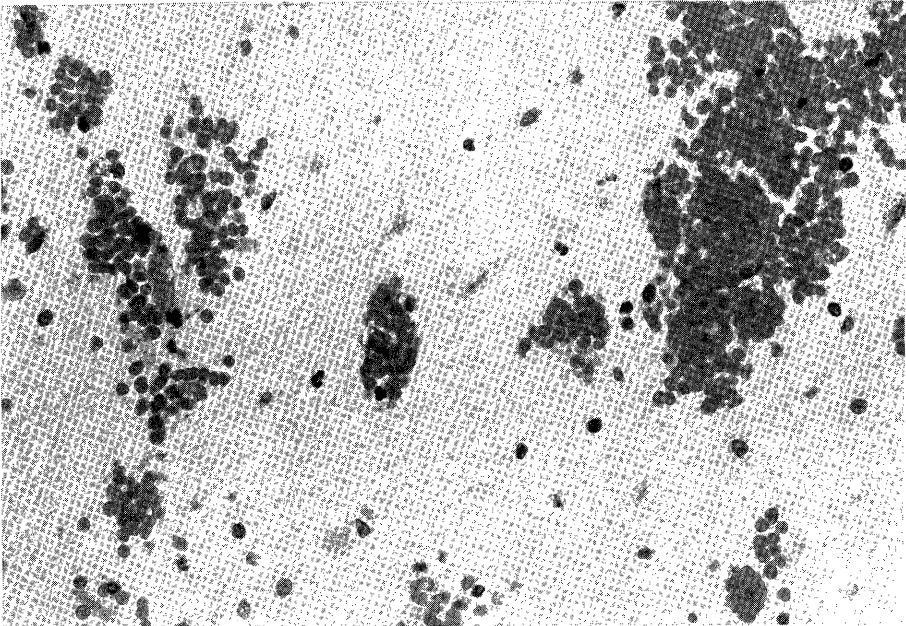
Fig. 2. Typical ischemic neurons (center) scattered focal hemorrhages with few scattered reactive microglia.

Fig. 3-A
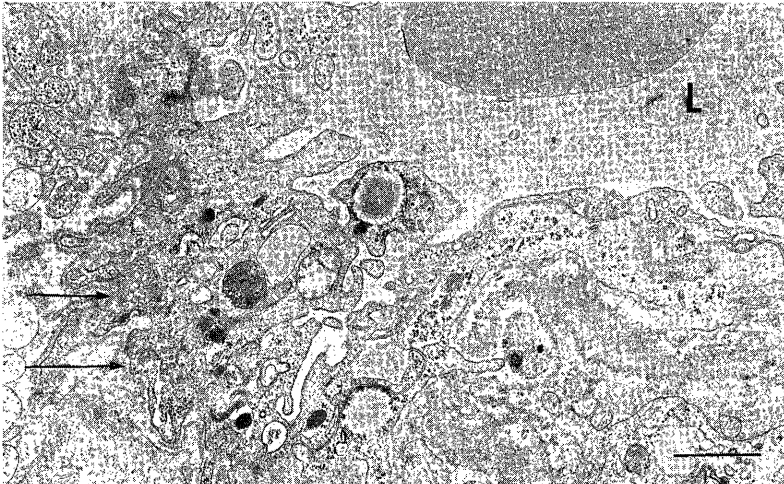
Fig. 3-B

Fig. 3 A. Surface infolding of the capillary endothelial wall with arrows indicating an
increased number of pinocytotic vesicles. X 12000.

Fig. 3 B. A discontinuity in the capillary endothelial wall is present between the
arrows. An arrow head indicates the attenuation of the endothelial wall.
Plasma and fibrinous materia are seen in the pericapillary space. X 16000.

A clinicopathologic study of hemorrhagic infarction
of the brain

Masakuni Kameyama

Department of Geriatric Medicine,
Faculty of Medicine, Kyoto University,
Kyoto, Japan.

If blood reflows into the area of encephalomalacia, red infarction may occur, which results in marked brain swelling and severely interferes the prognosis of the patients. Consequently, the pathogenetic mechanism of cerebral hemorrhagic infarction is an important problem. The purpose of this study is to clarify the following two points from a clinicopathologic point of view:

    1. frequency and distribution of hemorrhagic infarction in the brain, and

    2. clinical conditions significantly differing between the pale and red infarct.

MATERIALS AND METHODS

For this investigation, 223 subjects aged sixty year or more and having cerebral infarction were selected at random from the routine autopsy series at the Yokufukai Geriatric Hospital. All of the brains were intensively studied with neuropathologic techniques. Red or hemorrhagic infarction signifies that hemorrhage is apparent to the naked eye in the distribution of an occluded vessel, while pale softening indicates an ischemic area, even though microscopic examination of the infarcted tissue may show diapedesis of red cells around the smaller vessels.

Hypertension was defined as repeatedly measured systolic blood pressure of more than 160 mmHg or diastolic pressure of more than 90 mmHg.

If two or more arteries at the base of the brain showed narrowing of more than 50 percent of the lumen, the grade of cerebral atherosclerosis was classified as severe.

RESULTS

    1. Distribution and frequency of hemorrhagic infarcts in the brains.

Of all subjects with cerebral infarct examined, frequency and distribution of the hemorrhagic infarct were as follows (Table 1):

Table 1. Frequency of pale and red infarcts

arterial supply and location	Infarcts		Total
	pale	red	
Internal Carotid	3 (50%)	3 (50%)	6
Middle Cerebral { massive	28 (47%)	32 (53%)	60
{ localized	40 (52%)	37 (48%)	77
Anterior Cerebral	16 (53%)	14 (47%)	30
Posterior Cerebral	3 (27%)	8 (73%)	11
Basilar (massive)	3 (100%)	0	3
Internal Capsule and Basal Ganglia	18 (64%)	10(36%)	28
Cerebellum	4 (50%)	4 (50 °)	8

Hemorrhagic infarction was observed in 50% of the cases with intrenal carotid occlusion; 53% of massive and 48% of partial softenings in the area of the middle cerebral ; 47% of the anterior cerebral and 73% of the posterior cerebral arteries. In basilar thrombosis, all of the intarctions were ischemic. In the internal capsule and basal ganglia, 36%, and in the cerebellum, 50% of the cases showed red infarcts.

Among the cerebral regions, areas of the posterior cerebral arteries were most vulnerable to the hemorrhagic infarction.

2. Frequency of arterial occlusion in cases with cerebral infarction at autopsy.

Complete occlusion of the internal carotid or middle cerebral arteries was observed in 23 (46.2%) of 49 cases with compatible infarctions; in the anterior cerebral, in all 8 cases; and in the posterior cerebral in 3 (60%) of 5 cases. In total, frequency of arterial occlusions was 55% of 62 cases examined. A tendency was found that in cases with complete arterial occlusion, onset of stroke was slower and the blood pressure at the stroke was lower than in the cases without occlusion.

3. Difference of clinicopathologic features between red and pale infarctions.

Cerebral infarctions were divided according to the location of necrosis into the cortico–subcortical and the penetrating artery group.

In the cortico–subcortical group (Table 2), presense of arterial hypertension prior to stroke was significantly more frequent in the hemorrhagic than in the ischemic infarcts. Blood pressure elevation at stroke was a prominent feature in cases with red softening, while in pale infarctions blood pressure tended to be unchanged or lower. Frequency of atrial fibrillation, myocardial infarction of recent onset or malignancies of various kinds did not differ between the pale and red infarctions. Severe cerebral atherosclerosis was found in approximately equal frequency between the pale and red infarctions. However, in the penetrating artery group (Table 3), a significant defference was noted only in the frequency of severe atherosclerosis, being more frequent in the hemorrhagic infarctions.

Table 2. Infarcts in the cortico–subcortical group

	Infarcts	
	pale	red
Number of Cases	94	98
Severe Cerebral Atherosclerosis	73(77.7%)	80(81.6%)
Hypertension prior to Stroke	59(62.8%)**	75(76.5%)*
Blood Pressure at Stroke { elevated	13(13.8%)**	40(40.8%)*
unchanged	20(21.3%)	24(24.5%)
lowered	60(63.8%)*	29(29.6%)**
undetermined	1 (1.1%)	5 (5.1%)
Atrial Fibrillation	17(18.12)	18(18.42)
Myocardial Infarction of recent onset	11(11.7%)	6 (6.1%)
Malignancies	9 (9.6%)	7 (7.1%)

*>** significant (p<0.05)

Table 3. Infarcts in the penetrating arteries group

	Infarcts	
	pale	red
Number of Cases	21	10
Severe Cerebral Atherosclerosis	20(95.2%)*	7 (70%)**
Hypertension prior to Stroke	12(57.1%)	6 (60%)
Blood Pressure at Stroke { elevated	3 (14.3%)	3 (30%)
unchanged	11(52.4%)	0 (40%)
lowered	7 (33.3%)	3 (30%)
undetermined	0	0
Atrial Fibrillation	3 (14.3%)	2 (20%)
Myocardial Infarction of renent onset	3 (14.3%)	2 (20%)
Malignancies	2 (9.5%)	1 (10%)

*>** p<0.05

DISCUSSION

Pathogenetic mechanisms of hemorrhagic infarction have been repeatedly reported by many authors[1-5], in which recanalization of the thrombotic arteries or development of callateral circulation into the infarcted area was considered most important. Faris, et al[5], stressed the importance of hypertension. I pointed out a significance of hypertention prior to and at stroke in the pathogenesis of hemorrhagic infarction from a clinicopathologic standpoint. Hypertension seems to be the significant factor in two ways[5]; firstly, by increasing the changes in the vessel wall ; and secondly, by increasing the available intravascular pressure, thus rendering the collateral circulation functional. On the other hand, hypertension may promote the bleeding of diapedes type in the necrotic vessels and fragmentation of the blood clot. Atherosclerotic changes do not seem to have an importnat

role in the production of hemorrhagic infarction.   The role of a fibrinolytic action in the local or general circulation remains to be clarified.

SUMMARY

Of 223 cases with cerebral infarction, red and pale softenings were observed in approximately equal frequency in the areas perfused by the internal carotid and middle cerebral as well as by the anterior cerebral arteries. In the posterior cerebral artery region hemorrhagic infarction was more preponderant. In the penetrating arterial system, pale infarcts were more common. Arterial occlusion was found at autopsy in about half of the cases with infarcts. The most significant difference, between the red and pale infarctions, was presence of hypertension prior to and at stroke in the hemorrhagic cases. Frequency of severe atherosclerosis, atrial fibrillation and myocardial infarction of recent onset or malignancies were not significantly different between the red and pale infarcts.

The pathogenetic mechanism of arterial hypertension in the hemorrhagic infarction was discussed.

REFERENCES

1. Hain, R. F., et al. : J. Neuropath. Exp. Neurol. 11 : 34, 1952.
2. Fazio, C. et al. : Ibid., 8 : 43, 1949.
3. Fisher, C. M., et al. : Ibid., 10 : 92, 1951.
4. Globus, J. H., et al. : Ibid., 12 :107, 1953.
5. Faris, A. A., et al : Arch. Neurol., 9 : 468, 1963.

Experimental hemorrhagic cerebral infarction

Its clinical and pathological aspects
compared with those of pale infarct

Yoshinari Kamijyo,* Julio H. Garcia**
and Jonathan A. Cooper**

* *Department of Neurosurgery, Tenri Hospital, Nara, Japan.*
** *Department of Pathology, University of Maryland, U.S.A.*

Using a minimally traumatic method for occluding the middle rerebral artery (MCA) the authors have evaluated in two groups of adult cats, with permanent and temporary clipping ; (1) the occurrence, type and severity of the resulting motor deficit, (2) extravascular leakage of a protein–bound tracer, (3) patterns of microvascular filling, (4) degree and timing of tissue swelling, and (5) leakage of red blood cells into the area of the brain supplied by the occluded artery.

MATERIALS AND METHODS

Transorbital occlusion of the MCA was performed on 34 adult cats in the manner described by the authors[1]. In 18 cats the arterial clip remained in place until sacrifice (1 hour to 8 days post–occlusion), and in 16 cats the clip was removed either 1, 6 or 24 hours after occluding the vessel. Animals in the latter group were killed between one to eight days after the initial occlusion. Two to three hours prior to sacrifice, 10 ml of an Evans blue solution (1%) was injected via a forelimb vein. At the time of the sacrifice, approximately 100 ml of 1:2 dilution of carbon black in normal saline was infused through the inferior vena cava. The brains were fixed by immersion in a buffered solution of formaldehyde for a period of two weeks. The capillary filling pattern was evaluated after freezing fragments of brain and cutting slices, 200–microns thick. Other portions of the cerebral tissues were processed and embedded in paraffin for routine histologic examination.

RESULTS

Table I displays the outcome of the experiments in animals in which permanent occlusion of the artery results in observable ischemic lesions. The neurologic deficit was

characteristic and similar in all animals in whom it developed, in both the temporary and permanent groups. This consisted of hemiparesis, more severe in the forelimb, circular gait, and a late–appearing sign of forelimb flexion and hindlimb extension when the animal was lifted by the neck. This sign persisted long after the hemiparesis and circular gait disappeared, as they did in all cases within 2-3 days post–occlusion, regardless of the size of the lesion. The hemiparesis became maximal at approximately 24 hours. Animals without neurologic deficit had no demonstrable lesions in the brain. It was noted that in the temporary group there was no evidence of neurologic deterioration after removal of the clip.

Evans blue extravasation was negligible when the MCA occlusion lasted one hour, but the extravasation occurred in animals in whom the occlusion was of six hours' duration or longer. The most extensive staining by the dye was seen in animals with arterial occlusions lasting 8 days. Reperfusion into the area of ischemia made the extravasation of the dye occur much earlier and more densely than in the permanently occluded animals. The size of the lesions, however, was much smaller than in the latter.

Table II presents the outcome of the temporary occlusions. No instances of grossly visible pallor were found in this group, an observation which indicates patency of the capillary network within the territory of the temporarily occluded artery. It is to be noted that, as pallor was seen only in the animals with permanent occlusion, hemorrhagic softening developed only in the animals with temporary occlusion, increasing in frequency with the duration of the occlusion. Thus, 60% of the animals with temporary occlusions lasting 24 hours showed evidence of hemorrhagic infarction.

Table III demonstrates the distribution of the lesions in the two groups. Infarctions in the hemispheric cortex were far more common in animals with permanent occlusion, but in neither group were as common as lesions in the basal ganglia. Hemorrhagic infarction was also much more common in the basal ganglia than in the cortex.

In the group of cats having permanent MCA occlusion, the resulting lesions were all in the gray matter with the exception of one. In the animals with temporary occlusion, however, six of the ten cats developing infarctions showed them either predominantly or selectively in the white matter.

Microscopically, it was possible to follow the progressive derangement of the cortical microangioarchitecture. Two to three hours after occlusion of the MCA, it was only the deepest stratum of the cortex which showed non–filling by carbon black. After six hours all strata were involved. By three days, some dilated vasculature appeard in the area of pallor. Occlusions for 8 days resulted in complete replacement of the normal vascular structure by dilated, tortuous channels and the infarcted tissue was completely replaced by macrophages. In animals with the temporary occlusion it was possible to show patency of all capillary networks within the areas of Evans blue staining. In the areas showing hemorrhagic infarction there were severe stasis and congestion of the capillaries accompanied by extravasation of red blood cells and lack of penetration of carbon black, except in some of the long perforating vessels.

TABLE 1   MCA OCCLUSION IN CAT: PERMANENT SERIES

- - - - - NEUROLOGIC DEFICIT

— · — · — PALLOR

———— EVANS BLUE EXTRAVASATION.

4+

3+

2+

1+

6 hr   12 hr   24 hr   48 hr   72 hr   8 days

POST-OCCLUSION TIME
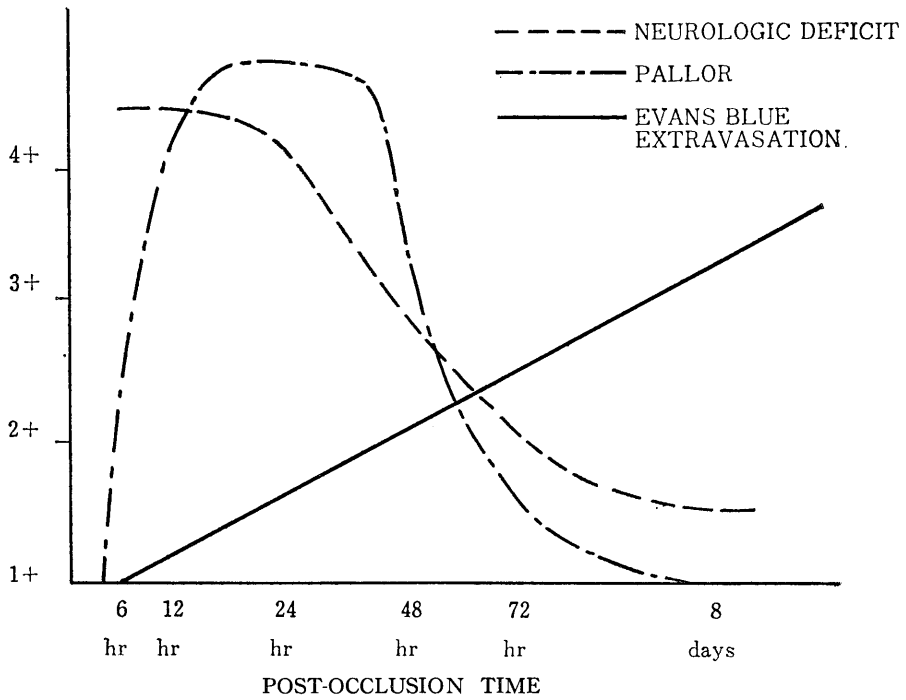
TABLE ‖   MCA OCCLUSION IN CAT: TEMPORARY SERIES

———— EVANS BLUE EXTRAVASATION

— · — · — HEMORRHAGIC INFARCTION

100

60   60

40

0   0

1 hr   6 hrs   24 hrs
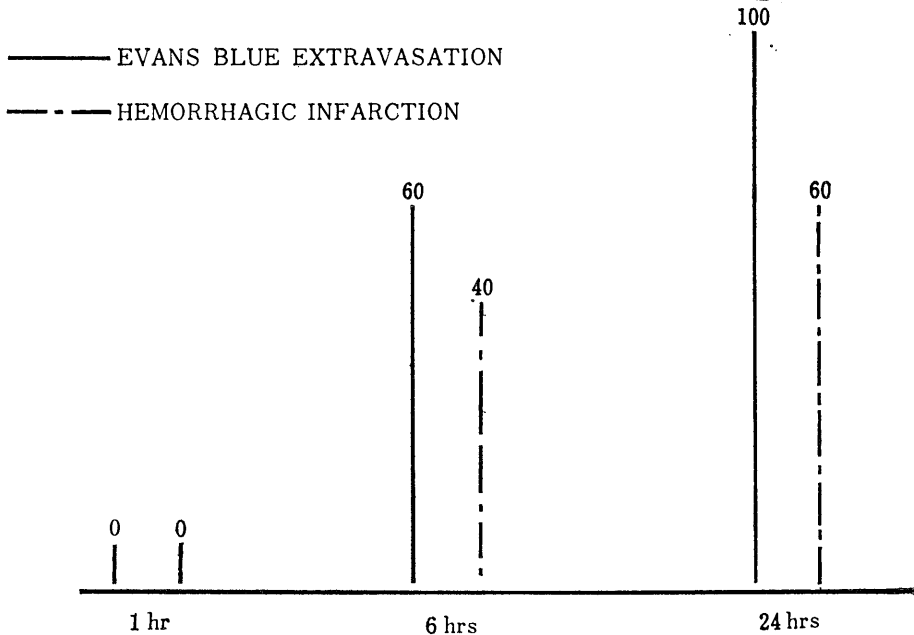
N.B: RESULTS ARE EXPRESSED AS PERCENTAGE OF TOTAL CASES.
      NO CASES SHOW PALLOR.

TABLE Ⅲ   MCA OCCLUSION IN CAT: COMPARISON OF TEMPORARY VS.
PERMANENT MCA CLIPPING (OCCLUSION OF 6 HOURS OR LONGER)
LOCATION OF LESIONS

		BASAL GANGLIA	CORTEX
TEMPORARY GROUP	EVANS BLUE	58%	25%
	HEMORRHAGIC INFARCTION	41%	25%
PERMANENT GROUP	EVANS BLUE	92%	83%
	HEMORRHAGIC INFARCTION	NONE	NONE

N.B.:   RESULTS ARE EXPRESSED AS PERCENTAGE OF TOTAL CASES.

COMMENT

Ischemic neurological deficit produced by MCA occlusion in cat appears to correspond with the human stroke known as RIND.   This would be based upon the anatomical peculiarity of the feline brain : (1) a location of the cortical motor area which sits over the border zone territory between ACA and MCA, and (2) the effective leptomeningeal anastomoses[1]. Although reperfusion of blood through ischemic areas results in hemorrhagic infarction or increased permeability to the protein tracer predominantly in the subcortical white matter, the size of the lesions is much smaller than that of permanent ischemia.

We suggest that reperfusion of ischemic brain responsible for RIND, prior to 24 hours after the arterial occlusion, may result in significant protection of the corresponding tissues and that hemorrhagic infarction proper may not be harmful.

REFERENCE

1) Kamijyo, Y. et, al Stroke 6: 361, 1975

Acute brain swelling and hemorrhagic infarction by recanalized MCA (middle cerebral artery) occlusion

—An experimental study—

Mamoru Taneda, Toru Hayakawa

* *Department of Neurosurgery, Hanwa Hospital*
** *Department of Neurosurgery, Osaka University*
Osaka, Japan

Rapid neurological deterioration after recanalization of the occluded major cerebral artery are frequently observed clinically. To elucidate its mechanism, the changes of superficial and deep cerebral microvasculatures in experimental recanalized cerebral infarction were studied by observation of cortical surface and its fluorescein angiogram through a cranial window and by post-mortem microangiograms. The MCAs of adult cats were occluded temporarily or permanently via a transorbital approach and focal cerebral ischemia was produced.

Rapid deterioration or acute death frequently occured after restoration of MCA flow. Severe brain swelling with tentorial herniation was found in almost all of them but massive hemorrhage only in some. In the observation of cortical surface through the cranial window, the ischemic area decreased in size or completely disappeared and reactive hyperemia with perivascular hemorrhage frequently appeared immediately after restoration of flow. Fluorescein in this reflowed portion extravasated remarkablly. Thereafter, development of brain swelling was apparently accelerated. On microangiograms, the vessels in deep structures in the temporarily occluded cases were usually well visualized including fine arterioles even with only few exceptions.

The data obtained indicate that the reactive hyperemia might play the most important role in causes of acute fatal outcome following recanalization of major cerebral artery, because it has an intimate relationslhip with acute brain swelling. Homorrhagic infarction itself may play a secondary or less important role as the direct cause of fatal outcome.

Experimental MCA occlusion in monkeys

Shinichi Yoshida,* Richard A. R. Fraser,
** Russel H Patterson Jr.**

* *Department of Neurosurgery, University of Tokyo hospital, Tokyo, Japan*
** *Division of Neurosurgery, The New York Hospital-Cornell Medical Center, USA.*

Following the introduction of microsurgical technique, embolectomy and thrombectomy for acute MCA occlusion have been increasingly popular without firm experimental supports. In order to find the appropriate indications for such direct vascular surgeries, the origin of the middle cerebral artery (MCA) was clipped temporarily via a transorbital route for 1 to 6 hours of duration. Clinical deficits and extents of infarction were compared with those of the group of permanent clipping. Three weeks later the surviving animals underwent a 2nd surgical procedure in which MCA on the other side was clipped for the same duration. At the termination of experiments retrograde transaortic perfusion was carried out with a mixture of carbon black and formalin. The final data were collected from 52 monkeys.

Results

1. Temporary occlusions for 1 to 3 hours produced no or mild clincal deficits and pathological changes which were significantly less extensive than those produced by permanent occlusions.

2. Temporary occlusions for 6 hours produced clinical deficits and pathological changes close to those of permanent occlusion.

3. Macroscopic hemorrhage in the brain occurred in 1/3 of animals following release of MCA occlusion in 6 hours and resulted in a high mortality.

Clinical implications

1. Six hours following the onset, MCA embolectomy or thrombectomy may not only be ineffective but also dangerous because of the possibility of producing macroscopic hemorrhage in the brain leading to a high mortality.

2. Useful adjunctives should be searched to elongate the short golden period in which surgical restoration of cerebral blood flow is meaningful.

3. Treatment for ischemic brain edema should be studied.

Experimental blood–brain barrier (BBB) change and diapedetic bleedings following temporary ischemia of relatively short duration in Mongolian Gerbils

Umeo Ito, Kikuo Ono, and Yutaka Inaba

*Department of Neurosurgery, Tokyo Medical and
Dental University, Tokyo, Japan*

The present study aims to elucidate a mechanism, especially of relation to BBB change, of the diapedetic bleedings which occur during recirculation following temporary ischemia of less than 6 hrs.   *1. Comparative studies on diapedetic bleedings and BBB change for Evans blue (EB)*: The left carotid artery of the ischemia–sensitive Gerbils was clipped for 30 mins, 1,3 and 6 hrs.   Then animal brain was recirculated for 30 secs to 20 hrs. Evans blue was injected intravenously prior to releasing the clip. Animal brain was fixed by perfusion, and examined for EB permeation and histology. Diapedetic bleedings occurred in 20-60% of animals during 1-20 hrs of recirculation.   This was not parallel in incidence of animals positive for BBB change (Table).   There was certain topographical dislocations between the areas of BBB damage and diapedetic bleedings. Diapedetic bleedings seemed to occur frequently along the veins and capillaries which drain the blood to the cerebral base and internal cerebral vein.

2. Electronmicroscopic study using horseradish peroxidase (HRP) as a tracer: HRP was injected intravenously at the end of recirculation for 1 hr,   following temporary ischemia of 30 mins, 1 and 6 hrs.   The brain was perfused with paraformaldehyde–glutalardehyde fixative in Na–caccodylate buffer, and treated for peroxidase reaction according to Reese & Karnovsky. HRP extravastion was demonstrated electronmicroscopically in all 3 animals of 6 hrs ischemia group.   The endothelial cells were well torelated the ischemic insult. Pinocytotic vesicles containing HRP in the endothelial cells are significantly increased in number.   So far as we have examined, no evidence of extravasation of HRP and red blood corpscles through the intercellular tight junction of the endothelial cells was observed. *Conclusion*: The diapedetic bleedings after temporary ischemia of relatively short duration seem to be mainly caused by the secondary circulatory disturbances especially of veins due to brain edema etc.

Duration of temporary ischemia	Duration of recirculation	No. of animals with hemorrhage *	No. of perivascular bleedings foci *	No. of confluent bleedings foci *	No. of animals with BBB damage for EB *
30 mins	30 secs	0	0	0	0
	15 mins	0	0	0	0
	1 hr	0	0	0	0
	5 hrs	0	0	0	0
	20 hrs	0	0	0	3
1 hr	30 secs	0	0	0	0
	15 mins	0	0	0	0
	1 hr	1	5	0	0
	3 hrs	0	0	0	0
	5 hrs	1	5	5	1
	20 hrs	1	11	0	5
3 hrs	30 secs	0	0	0	0
	15 mins	0	0	0	0
	30 mins	0	0	0	1
	1 hr	3	21	3	3
	2 hrs	2	14	1	4
	3 hrs	2	11	4	5
	20 hrs	3	18	11	5
6 hrs	30 secs	0	0	0	0
	15 mins	0	0	0	4
	30 mins	0	0	0	4
	3 hrs	2	5	1	5
	10 hrs	3	18	3	5
	20 hrs	2	42	32	5

* 5 animals are included in each group

Experimental hemorrhagic cerebral infarction in the dog.

Shobu Shibata, Akio Yasunaga, Hirohisa Ono and Kazuo Mori

Department of Neurosurgery, Nagasaki Universiry
School of Medicine, Nagasaki, Japan

The middle cerebral artery (MCA) of dogs was occluded by a clip and the collateral blood supply was compromised by subjecting to hemorrhagic hypotension for 1 hour. Following restoration of the systemic blood pressure by infusion of the shed blood, an area

of ischemia in the territory normally supplied by the clipped artery could be easily demarcated by fluorescein angiography (FAG) through the lingual artery and the femoral vein and by carbon perfusion (CP) through the heart.

The involved cerebral tissue showed marked hemorrhagic infarction 24 hours after restoration of the blood pressure which localized in the boundary zone between the deep cortical layer and the subcortical white matter.

These findings correlated well with extent of the leptomeningeal circulation and were interpreted as due to rough capillary networks in the region which anastomose with those of the deep cortical layer and the subcortical white matter.

Sizes of the hemorrhagic infarction, demonstrated by FAG and CP, were smaller in a group of dogs in which the MCA clip was removed and the involved area was reperfused, than those of a group with the artery remained clipped. Severity of hemorrhage, postulated from amount of extravasated carbon particles, however, was more extensive in the former group.

# Experimental MCA occlusion and extra-intracranial arterial shunt.

Akira Nishimoto, Kazushi Kinugasa, Yuji Yamamoto, Hiroyuki Fujisawa, Yasunori Yagyu and Takashi Ohmoto

*Department of Neurological Surgery, Okayama
University Medical School. Okayama, Japan.*

Occlusion of the middle cerebral artery (MCA) was experimentally produced by a transorbital route in 25 dogs. In 20 of these dogs, microangiography was performed with a 60% solution of barium sulfate (Micropaque) on the 2nd day to 16th day following the occlusion. Extravasation of Micropaque and hypervascularity were observed in 5 of 8 animals in which microangiography was done from 4 to 7days after the MCA occlusion. However, other 12 animals demonstrated no extravasation microangiographically (Fig. 1). In addition, extracranial (maxillary) artery-middle cerebral artery by-pass formations were performed 4 hrs., 1 week and 3 weeks after the occlusion in 19 dogs. Histopathological study demonstrated that the size of infarct following a prompt by-pass at 4 hours after the occlusion was much smaller than that of control, but the size in late by-passes (1 week and 3 weeks) appeared to be almost the same as that of control. Some hemorrhagic parts were seen in the infarction area only in three of 7 cases of 1 week by-pass formation.

These results indicate that the vascular vulnerability to the hemorrhagic infarction in the territory of occlusive vessel may be increased 1 week after the occlusion.

Fig. 1 MICROANGIOGRAPHICAL FINDINGS FOLLOWING
M.C.A. OCCLUSION

● : extravasation
＊ : hypervascularity
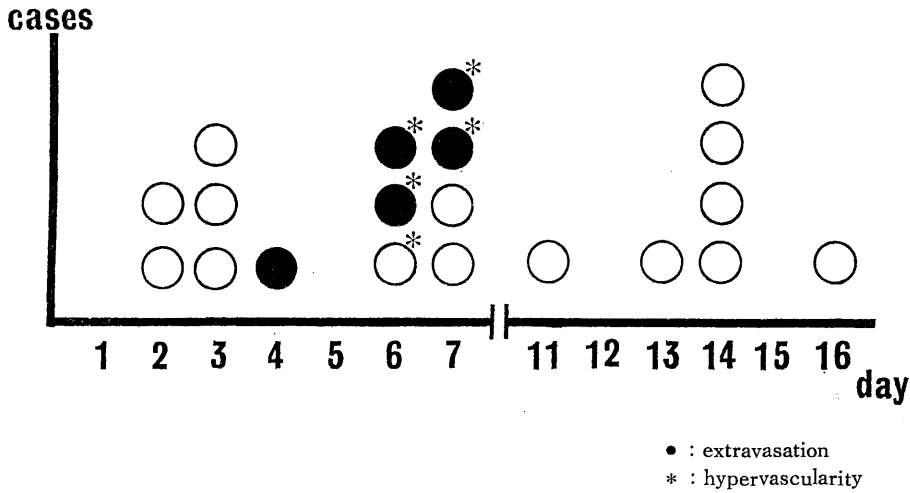
Pharmacological study for regional ischemic infarction of the anterior thalamus in the dog

Jiro Suzuki., Takashi Yoshimoto and Tetsuya Sakamoto

Division of Neurosurgery, Institute of Brain Diseases,
Tohoku University School of Medicine, Sendai, Japan.

Consequences of occluding a cerebral artery in experimental animals differed significantly in nature, extent and location of pathological changes of the brain. The authors developed a new experimental method in dogs which resulted in a high incidence (more than 70%) of localized ischemic infarction of the anterior thalamus as described elsewhere. This report concerns with functional alteration of the ischemic anterior thalamus after perfusion of the tissue with pharmacological solutions.

Methods and results: Under Nembutal ansesthesia, the internal carotid, posterior communicating, anterior cerebral and middle cerebral artery of a dog were occluded temporarily through a temporal craniotomy.

Under electrical monitoring of the ischemic anterior thalamus and the brain cortex, two types of experiments, 20% mannitol perfusion for short term and 7 days administration of CDP–choline, were designed and changes in power spectrum of EEG were compared after the administration with that of a control group of dogs without the treatment. The authors confirmed significant effects of these pharmacological solutions on a functional improvement of the ishemic tissue by noting a less extensive decrease in fast components of EEGs during occlusion of the arteries and earlier recovery as well after release of the occlusion.

Clinical aspects of internal carotid artery embolism with blood-stained cerebrospinal fluid

Tadayoshi Irino

Division of Cerebrovascular Diseases, Hanwa Hospital,
Osaka, Japan

A large number of pathological and experimental studies have suggested that cerebral infarction in the acute stage often results in hemorrhagic infarction.[1,2] However, there has been no sufficient clinical report regarding this pathological condition as yet. In this study, in order to clarify the clinical aspects of infarcted patients accompanying hemorrhagic infarction, acute stroke patients with internal carotid arterial embolism were observed clinically and comparisons were made between those with and without sanguinous or xanthochromic cerebrospinal fluid.

MATERIALS AND METHODS

Among the stroke patients who had an apoplectiform onset of symptoms and were diagnosed following both physical and angiographical findings within 24 hours after ictus, 18 patients had cerebral embolism caused by acute internal carotid artery occlusion and were given consecutive cerebrospinal fluid (CSF) examination at one to three-day intervals within a week after the onset. They were not treated with fibrinolytic agents or anticoagulants. Ten cases had colored CSF (sanguinous or xanthochromic) and the remaining eight cases did not. The former group was classified as Group I and the latter as Group II; clinical observations for the two groups were compared below.

(1) Clinical findings

Clinical findings included the frequency of atrial fibrillation, hypertension (systolic pressure higher than 150 mmHg within a week) and outcomes estimated one month after onset.

(2) Follow-up cerebral angiographies

Follow-up cerebral angiographies were performed on the 18 patients to inspect alterations of the occluded artery because some previous reports suggested that recirculation of occluded arteries was closely related with the development of hemorrhagic infarction.[1] The occurence ratios of spontaneous recanalization were compared between those two groups.

Table. Case Summary

		Atrial Fibrillation	Recanalization	Hypertension
Group I	No. 1		○	○
	2	○	○	○
	3		○	
	4	○	○	
	5	○		○
	6 *		○	
	7			
	8 *	○	○	○
	9 *	○	○	○
	10		○	
Group II	11			
	12			○
	13	○		
	14	○		
	15	○		
	16	○		
	17			
	18*			

* fatal case within a month after onset

RESULTS

The Table summarized the results.
(1) Clinical findings
  i. Atrial fibrillation
    Five cases of Group I (50%) and four of Group II (50%) showed atrial fibrillation on ECG.
  ii. Outcomes within a month
    All cases had poor prognosis, i. e., the degree of himparesis did not improve enough to allow the patients to leave the bed without assistance. Three cases of Group I died within a month but one in Group II did.
  iii. Hypertension
    Five cases (50%) of Group I, but only one (13%) in Group II, were judged as hypertensive.
(2) Follow-up cerebral angiographies
    Of the 18 cases, eight (44%) showed angiographical recanalization of the occluded points within a few days; all were in Group I. Group II had no recanalized cases.

DISCUSSION

According to the previous reports on animals, experimental hemorrhagic infarction can be observed either when the occluded cerebral arteries are recanalized after ligation[2] or when the animals with occluded cerebral arteries were made hypertensive.[3] These reports explain well the present results of patients with recanalization and hypertension showing blood-stained CSF to indicate development of hemorrhagic infarction. This study suggests that recanalization of the occluded arteries is more closely related with the development of hemorrhagic infarction than hypertension as for the human beings.

On the other hand, pathological studies by Fisher suggested that hemorrhagic infarction could be observed in the autopsied brain where occluded cerebral artery had not been found pathologically.[1] He said that hemorrhagic infarction could be caused by blood flow through recanalization, which, however, had not been confirmed angiographically during life. We have previously reported that angiographically demonstrated recirculation did not contribute to recovery of infarcted patients and that sanguinous CSF frequently occurred in recanalized cerebral infarction.[5][6] In addition, we have shown that several pathological findings such as capillary blush or space taking signs were not infrequently observed on the postrecanalized angiograms, which suggested the development of hemorrhagic infarction in recanalized embolism.[7]

CONCLUSION

The present findings summarized are:

(1) The presence of atrial fibrillation did not run parallel with the occurrence of colored CSF.

(2) Elevated blood pressure was observed in half of the patients with sanguinous CSF.

(3) Patients with colored CSF had poorer prognosis than those without CSF abnormality.

(4) Angiographically demonstrated recanalization was closely related with development of sanguinous CSF.

REFERENCES

1) Fisher M, Adams RD: Observations on brain embolism with special reference to the mechanism of hemorrhagic infarction. J Neuropath Exp Neurol 10 : 92-94, 1951

2) Harvey J, Rasmussen T: Occlusion of the middle cerebral artery. An experimental study. Arch Neurol Psychiat 66 : 20-29, 1951

3) Zulch KJ: Hemorrhage, thrombosis, embolism. In Minckler J (ed) : Pathology of the Nervous System. New York, McGraw-Hill, vol 2, 1971

4) Irino T, Taneda M, Minami T : Positive scans in angiographically proved cases of

recanalized cerebral infarction. Stroke 6 : 132–135, 1975

5) Irino T, Taneda M, Minami T et al : Angiographical extravasation of contrast medium in hemorrhagic infarction. Case report. Stroke 7 : 641–617, 1976

6) Irino T, Taneda M, Minami T : Sanguinous cerebrospinal fluid in recanalized cerebral infarction. Stroke, in press

7) Irino T, Taneda M, Minami T : Angiographic manifestations in postrecanalized cerebral infarction, Neurology, in press

Hemorrhagic cerebral infarction

Goro Araki

Institute of Brain and Blood Vessels
Mihara Memorial Hospital, Gumma, Japan

INTRODUCTION

Although the pathogenesis of hemorrhagic infarction which may occur during the coruse of cerebral infarction is still not quite certain, moving embolus in an occlusive process has been recognized as a cause of the hemorrhagic infarction.[1] The author reports autopsied cases of cerebral infarction in the authors hospital which were analized clinico-pathologically and evaluates the possibility of making diagnosis of hemorrhagic infarction by computed tomography (CT) or angiographical study. By elucidation of several important clinical factors, the author discusses causes of the hemorrhagic infarction, such as moving embolus.

MATERIAL AND METHOD

1. Materials

Twenty – five autopsied cases of cerebral infarction including 15 cases of cerebral thrombosis and 10 cases of cerebral embolism are studied. The author found no hemorrhagic infarction in the autopsied cases of cerebral thrombosis while hemorrhagic infarctions were found in 7 cases out of 10 cases of cerebral embolism. The average age of the cases of cerebral embolism (3 males and 7 females) was 62.8.

2. Diagonstic criteria of cerebral embolism.[1]

The angiographical delineation of an abrupt round edged occlusion in a vessel leading to an avascular region and of retrograde flow of the contrast material in collateral vessels

to the deprived area were taken as criteria of an embolic occlusion. Additional diagnostic sings of cerebral embolism, such as early filling of cerebral veins, early positive brain scanning and early appearance of low density in CT study were also used. The movement or disappearance of an occlusive process on subsequent angiographical studies was considered to be a more definite sign of an embolic phenomenon. Clinical examinations were performed carefully to evaluate whether or not the patients were suffered from auricular fibrillation.

RESULTS

1. Angiographic findings.[2]
  Carotid angiograms were performed on 10 patients of cerebral embolism, within 2 days after the onset in 7 cases, 7, 10, and 14 days after the onset in other cases. The angiographic findings of these 10 cases are summarised in Table 1. Three cases in this group of the patients had no mass sign angiographically. One of 2 cases of middle cerebral artery branch occlusion without mass sign died of a re-attack of cerebral embolism in the contralateral hemisphere. Another case, whose angiography was performed five hours after the attack, was found to have hemorrhagic infarction at necropsy, 2 days after the onset. The exact time of occurance of the hemorrhagic infarction was not determined in this case. Seven cases with angiographic mass signs consisted of 1 case of internal carotid occlusion, 1 case without apparent occlusion, 4 cases with moving embolus or with recanalization and 1 case with the abrupt round edged occlusion in the basilar artery. In 4 case with the moving embolus or with recanalization the time interval between the onset of the clinical symptoms and angiograpic examination was less than 24 hours in 1 case, 2 days in 2 cases, 7 days in 1 case and 21 days in 1 case.

2. CT study
  CT studies were performed on 3 cases. A high density area observed in 2 cases enlarged gradually during the course up to death. The high density in the CT study of these 2 cases were found in accordance with the foci of hemorrhagic infarction at necropsy. However, another case, which was found to have a middle cerebral artery branch occlusion

Table 1 Angiographic findings of 10 patients of cerebral embolism

		mass sign (+)	mass sign (−)
MCA occlusion	M$_1$	0	1
	Branch	0	2
ICA occlusion		1	0
Occlusion (−)		1	0
Moving embolus or Recanarization		4	0
Round edged ociclusion		1	0

without angiographical mass sign, also had cerebral infarction of hemorrhagic type in autopsy.   It was difficult to correlate angiographical findings of the vessel occlusion to presence of the high density area in CT study,   because the moving embouls was seen in the subsequent angiograms in the cases of cerebral embolism.

3.   Relationship between cerebral embolism and hemorrhagic infarction (Table 2). Two of 4 cases with demonstrated moving embolus on angiograms showed hemorrhagic infarction pathologically, but the other two cases were found to have anemic infarction. Therefore it was apparent that the movement or disappearnce of embolus did not always lead to hemorrhagic infarction.   The case with the abrupt round edged occlusion of the basilar artery and the other case without apparent occlusion of the vessels were also found to have hemorrhagic infarction pathologically.   No explanation could be made at this time with regard to the absence of the angiographical mass signs of recanalization in two cases of hemorrhagic infarction associated with middle cerebral artery occlusion.   Two cases of moved embolus with a high density area in CT study were noted to have relatively favorable prognosis.

Table 2   CAG findings and types of cerebral infarction

	Moving embolus or Recanarization	Round edged occlusion	Occlusion (−) Mass sign (+)	Occlusion (+)		
				Mass sign (+)	Mass sign (−)	
				ICA	MCA	
					M₁	Branch
Hemorrhagic infarction	2	1	1	1	1	1
Anemic infarction	2	0	0	0	0	1
Total	4	1	1	1	1	2

CONCLUSION

1.   No obvious hemorrhagic infarction was found in autopsied cases of cerebral thrombosis while the hemorrhagic infarctions were apparent in 7 of 10 autopsied cases of cerebral embolism.   Two of these 7 cases had moving embolus or recanalization angiographically.

2.   It was noteworthy that 2 autopsied cases of moving embolus or recanalization showed the anemic infarction.   It appaered that the movement or disappearance of an occlusive process does not always lead to the hemorrhagic infarction.

3.   CT study is a useful examination to diagnose presence of hemorrhagic infarction. The author experienced 4 cases of hemorrhagic infarction (2 autopsied cases and 2 clinical cases) diagnosed by CT study.

4.   Two patients with hemorrhagic infarction diagnosed clinically by CT study were

relatively benign in the clinical course.

The significance of the hemorrhagic infarction with regard to patients prognosis must be further investigated especially with CT and angiographical study.

REFERENCES

1) Arie Liebeskind et al : Stroke, 2 : 440, 1971.
2) Irino, T et al : Brain and Nerve, 27 : 1089, 1975.

Hemorrhagic cerebral infarction; its neuroradiological findings and pathogenesis

Kazuo Uemura*
Toshio Okudera*
Kiyoshi Ishii* and
Hitoshi Fukasawa**

Division of Radiology and Pathology***
Research Institute of Brain and Blood Vessels, Akita, Japan

INTRODUCTION

Hemorrhagic infarction is thought to be an established entity in the neuropathology.[1] However, it has not been fully exploited clinically because of its diagnostic difficulty. This report describes results of analysis of the hemorrhagic infarction cases, with findings of cerebral angiography, computed tomography and autopsy.

MATERIALS

During 7 year period from 1969 to 1976, autopsies were performed on a total of 62 cases with cerebral infarction. Hemorrhagic infarction was found in 13 cases. Cerebral angiography was done on 12 cases of them (Group 1, Table 1). Group 2 (Table 2) consisted of 32 cases with cerebral infarction studied by CT (computed touography) and cerebral angiography. Of 21 cases showed revascularization of occluded arteries. We have had no case who had suspected hemorrhagic infarction by CT and verified by autopsy.

RESULTS

1) Prognosis of the case of hemorrhagic infarction : Mean survival time of the group I was approximately 14 days (Table 1). However, in the group 2 only one case out of 6 cases diagnosed as hemorrhagic infarction died at the day of onset and the other case have survived with some neurological dificits. As a result, prognosis of patients with hemorrhagic infarction could not be said absolutely pessimistic.

2) Findings of cerebral angiography and RI brain scan on group 1 : Angiographic findings of group 1 were summarized in Table 1. Trunkal occlusion of cerebral arteries, poor collateral circulation and brain swelling were observed. Revascularization of occluded arteries in various degree was noted in all of the cases. However, differential diagnosis of the hemorrhagic infarction from ischemic infarction with brain edema is thought to be difficult to make by a cerebral angiography only.

Marked abnormal uptake in RI brain scan was noted within 24h after onset in 2 cases of group 1. The finding is quite unusual for cerebral infarction.[2]

Table 1.   Group 1 : 12 cases of hemorrhagic infarction (autopsy cases)

Duration from onset	1 week	3
	2 weeks	5
	3 weeks	2
	4 weeks	2
Site of hemorrhagic infarction	Supratentorial	10
	Infratentorial	2
Angiographic findings		
Occlusion of cerebral arteries*	Occlusion (−)	2
	ICA	3
	MCA	4
	MCA + ICA	2
	SCA	1
Space taking sign	(−)	0
	Mild	3
	Severe	9
Collateral circulation	Good	3
	Poor	7
Revascularization	(−)	0
	Parietal	6
	Almost complete	3
	STA–MCA anastomosis	2
RI Brain scanning	Positive scan	2
	(within 24h from onset)	

* A case who had proved hemorrhagic infarction of the left cerebellar cortex and ischemic infarction of the right MCA distribution was not studied with vertebral angiography.

3) CT Findings of hemorrhagic infarction : Patchy high absorption areas within low absorption zone of infarcted brain accompanying with space taking sign seemed to be diagnostic as hemorrhagic infarction, and 6 in group 2 showed these findings. Spontaneous revascularizations in various degrees were also found angiographically in all of them (Table 2). The high absorption areas were observed on 2 days or 3-5 weeks after the onset following revascularization, and were noted more frequently in hypertensive patients.

4) Some consideration in pathogenesis of hemorrhagic infarction: Because cerebral edema due to infarction is most prominent in a few days after onset,[3,4] destruction of BBB must be most severe in this time. Spontaneous reascularization of infarcted brain is most frequently observed also within a week of ictus.[4,5] As a result, reopening of blood flow into infarcted brain is thought to be the most important factor of the pathogenesis of hemorrhagic infarction.[4] Existence of hypertension may accelerate the bleeding into the damaged brain.

Group 2. Diagnosed by Computed Tomography

Time after onset	Permanent occlusion (follow-up cases)						Revascularization of occluded arteries					
	N	Low density area		High density area (+)	Space taking sign (+)	Contrast Enhancement (+)	N	Low density area		High density area (+)	Space taking sign (+)	Contrast Enhancement (+)
		(+)	Transient obscuring					(+)	Transient obscuring			
1-2d	4	2	0	0	2	0/2	3	3	0	1	3	0/3
3-7d	7	6	0	0	3	1/6	8	6	0	0	6	1/6
2w	7	7	2	0	3	3/4	5	3	3	0	3	4/4
3-4w	5	4	3	0	2	5/6	11	7	7	5	7	10/11
5-6w	4	4	1	0	0	3/3	6	3	3	4	4	6/6
Over 7w	2	2	0	0	0	0/1	20	20	0	0	1	4/11

REFERENCES

1) Stehbens, W. E. : Pathology of the cerebrovascular disease. Mosby, Co. 1972.

2) Uemura, K. et al: Nippon Acta Radiol. 32 : 149, 1972.

3) Yamaguchi, K. et al: Jap. J. clinic. Radiol. 21 : 127, 1976.

4) Uemura, K. : Jap. J. Geriat. to be published.

5) Wataria, J. et al: Brain and Nerve 28 : 769, 1976.

Pathogenesis of hemorrhagic cerebral infarction

—A study with computed tomography, rCBF and fluorescein cortical angiography—

Takeshi Kawase, Masahiro Mizukami, Hiroshi Kin,
Michiharu Nishijima and Goro Araki

Institute of Brain and Blood vessels
Mihara Memorial Hospital, Gumma, Japan

The pathogenesis of hemorrhagic infarction is still unknown. The most obvious is that the recanalization of occluded artery may play an important role.[1][2][3] The purpose of this presentation is to clarify the mechanisms of hemorrhage, by means of computed tomography (CT), rCBF study, and fluorescein angiography, based on our surgical cases. All four cases were examined by serial CT, and rCBF was measured in two cases. Fluorescein angiography was carried out in one case at operation. Hemorrhage was confirmed by spinal tap or operation.

[Case 1.] This 71-year-old male suffered from a left hemiplegia with slight disturbance of the consciousness. Carotid angiograms demonstrated an occlusion of the right internal carotid artery (ICA). From third day to 10th day of stroke, CT demonstrated a low density area with a shift of central structures. On 13th day of the stroke, a part of the low density area changed into relative high density, and after contrast infusion, there was marked enhancement of the density in its surrounding area. Brain scintigram also showed positive RI accumulation in the area. Xantochromic CSF was obtained and hemorrhagic infarction was confirmed. On the second carotid angiogram, performed four days later, resolution of the occlusion and capillary blush in the temporal region were clearly demonstrated. A rCBF study showed focal dysautoregulation in the same area.

[Case 2.] This 63-year-old male had an embolus in the left cervical ICA with a slight low density area in the parietal region on CT study. One week after stroke, a small high density area in the periphery of the lucent area was noted, but the affected area was not enhanced after contrast infusion. A second angiogram demonstrated disappearance of the neck embolus, and a rCBF study showed global dysautoregulation in reperfused area. Hemorrhagic infarction was confirmed by a spinal tap.

Neurological deficit was slightly aggravated in above two cases after recanalization.

[Case 3.] This 69-year-old female suffered from a right hemiparesis, and on carotid angiograms, performed on the 9th day of the stroke, abnormal early venous filling and

tumor like stain in the left frontal region were noted. CT demonstrated a low density area with marked contrast enhancement in the region. Brain tumor was suspected, and a craniotomy was performed. At operation, no neoplasm was noted, and pathological findings indicated the tissue to be cerebral softening containing hemosiderin. After the operation, the right hemiparesis improved gradually, and she was discharged from the hospital without any neurological deficit.

[Case 4.] This 39-year-old male developed a left hemiplegia with slight distur-bance of the consciousness. Carotid angiograms, performed on the first day of the stroke, showed occlusion of the middle cerebral artery, and a CT study demonstrated a lucent area in the right hemisphere. On CTs, which was repeated from the 10th day to 20th day of the stroke, a marked cortical enhancement was noted. STA-MCA anastomosis was performed on the 20th day of stroke. Brain was edematous and apparent hemorrhage was not found macroscopically. After anastomosis, fluorescein cortical angiography (FCA), which was performed during the operation, showed marked extravasations of fluorescein dye and petechial hemorrhages around venules were noted.

Discussion

It has reported that the contrast enhancement on CT depends to a significant extent on extravasation at the blood brain barrier.[4] That was also mentioned on brain scinti-gram.[5] These facts imply the existence of hyperpermeability to contrast medium,[99]m Tc-pertechnetate, or to fluorescein sodium as in three of our cases. However, we could not observed contrast enhancement in one case (case 2.), and this case only showed marked dysautoregulation in rCBF studies. All of the four cases had the same features in respect of recanalization (naturally or artificially revascularized). From these observations, both an abrupt increase of perfusion pressure and hyperpermeability of vessels may play an important role in the genesis of hemorrhagic infarction. As seen in case 2, hemorragic infarction also ocurred without significant increase in vascular permeability, when marked dysauto-regulation was combined with recanalization. We have odserved on FCA that hemorrhagic infarction was due to extravasated red blood cells from the venules. This fact corresponds to the pathological aspects, that hemorrhagic infarction is made up, in most cases, spotted forms of hemorrhage.[6]

REFERENCES

1) Fisher, M. et al. J. Neuropath. & Exper. Neurol., 10 : 92-94, 1951.

2) Hicks, S. P. et al. Arch. Path., 52 : 403-412, 1951.

3) Irino, T. et al. Brain & Nerve, 27 : 1289-1295, 1975.

4) Gado, M. H. et al. Radiology, 117 : 595-597, 1975.

5) Quinn & J. L. Cerebral Vascular Diseases, 6th conf. 179-194, 1968.

6) Zulch, K. J. In "Pathology of the nervous system" (Minckler, J.) 1971.

Three cases of postoperative hemorrhagic infarction of the brain

Hirohisa Ono and Kazuo Mori

Department of Neurosurgery, Nagasaki University,
Sohool of Medicine, Nagasaki, Japan

Postoperative hemorrhagic infarctions of the brain have been reported in a limited number of literatures. Carotid endarterectomy and cardiac surgery were most frequently found in these literatures either as sources of emboli or causes of decreased blood flow to the brain. We are reporting 3 cases of cerebral hemorrhagic infarction (HI) which occured after neurosurgical procedures. [Case 1] A 72 year-old-male, who underwent a right carotid endarterectomy for an asymptomatic carotid bruit, never recovered from anesthesia and remained comatous. A postoperative CAG demonstrated occlusion of bilateral perica-losal arteries while the operated area was satisfactorily repaired. The occluded arteries had been perfused through the right anterior cerebral artery preoperatively. Autopsy disclosed foci of HI in the median aspects of the bilateral frontal lobes. [Case 2] A 56 year-old-male with a history of a left hemiparesis due to occlusion of the right middle cerebral artery (MCA) 20 months prior to present admission, developed a right subdural hematoma after removal of a pituitary tumor. The patient was recovering from the left hemiparesis when aggravation of the left hemiparesis were noted again 6 days after the operation. The patient expired subsequently of a perforated duodenal ulcer and was found to have HI. [Case 3] A 50 year-old-male had a thromboendarterectomy of the right MCA, 47 days after onset of a left hemiparalysis. At the end of the operation, a portion of the frontal lobe cortex started swelling and turned red underneath a brain retractor. The area was suctioned away and it was found that hemorrhagic tissue was confined in the cortical layer.

Discussions were made with regard to significant factors related to pathogenesis of the HIs.

The authors postulated that compression of the ischemic brain tissue by either subdural hematoma or brain retractors in case 2 and 3 resulted in a further decrease in the critical closing pressure of vessels, probably more in that of venules as indicated by histological findings, thus added a significant effect on development of HI.

Microneurosurgical anastomosis: A biochemical
basis for improvement

George M. Austin, Gary Haugen, E.Lichter and William Hayward

Section of Neurosurgery
Loma Linda University School of Medicine
Loma Linda, California, USA

Introduction

In a series of over 100 microanastomoses performed by the senior author, significant clinical improvement has been reported in the severity of transient ischemic attacks (TIA's) and from neurological deficit after minor strokes.[1,2] Patients were selected for surgery who had TIA's or minor stroke with a decrease in regional cerebral blood flow (rCBF), as well as an angiographically visible obstructing lesion. In the published literature, somewhere between 10% to 80% of untreated patients with TIA's subsequently had a stroke,[3] within 5 years. The wide range experienced here is probably due to the broad definition for TIA's.[3] The majority of authors have included only focal TIA's, while in our study we have also included diffuse TIA's such as confusion, dizziness, recent memory loss, black-out attacks, and emotional instability. It is assumed that the cause for TIA's is on the basis of hemodynamic factors or microemboli (fibrino–platelet) breaking off from atherosclerotic plaques. The cause of the hemodynamic TIA's is thought to be due to background factors plus triggering factors that together produce a critical reduction in CBF to the point that brain PO_2 (bPO_2) is dropped to a level that reduces brain oxygen utilization ($b\dot{P}O_2$) and mitochondrial respiration. The latter results in inadequate oxidative phosphorylation and failure of the metabollically controlled ion pumps with subsequent brief episodes of neuronal depolarization. The latter is associated with the clinical phenomena known as TIA's. Background factors consist of obstructive lesions of the principle extracranial arteries leading to the brain or of major branches of the Circle of Willis (C. O. W.). Triggering factors include transient decreases in cardiac output which drop the mean blood pressure and cause a further decrease in CBF. Previously, evidence has been published showing that the majority of patients with TIA's ($> 90\%$) show a serious decrease in measured autoregulation.[4] Presumably the neuronal ambient bPO_2 is decreased to a very low level if one is to postulate a decrease in $b\dot{P}O_2$ at the mitochondrial level. At least the published evidence based on isolated liver mitochondria, suggests that in vitro oxygen utilization remains constant down to 0.5 mmHg.[5,6] In this paper we present the results of measuring

cortical CBF before and after microanastomosis. In addition, are described the results of some intraoperative measurements of relative bPO_2, $b\dot{P}O_2$, and the mitochondrial redox level of cytochrome a, a_3 before and after microanastomosis. Because these are relatively new noninvasive technigues, they are described in some detail in the Appendices.

Methods :

Patients were admitted to the Loma Linda University Hospital with a history of TIA's or minor strokes. They were worked-up according to a protocol which evaluated rCBF, cardio-pulmonary function, and numerous laboratory chemical studies. A selective cerebral angiogram was done on all patients. Finally, the decision on whether or not to offer a microanastomosis was based on the patient being a fairly good operative risk and not having any of the following contradictions :

1) Severe cardiac disease
   a) History of multiple cardiac infarctions with frequent angina
   b) Severe cardica decompensation
   c) Chronic hypotension, with mean blood pressure < 75 mm Hg
   d) Severe and poorly controlled hypertension with grade III or IV arteriosclerotic retinopathy
   e) Severe paroxysmal cardiac irregularity with severe drops in cardiac output.
2) Severe and poorly controlled, chronic obstructive pulmonary disease with aPO_2 < 70 mmH$_2$O.
3) Severe and poorly controlled diabetes
4) Abnormal blood coagulation factors resulting in hypercoagulability (as for exmple Polycythemia Vera)
5) Severe psychosis
6) Multiple major occlusive lesions demonstrable by cerebral angiography ; severe tandem lesions ; internal carotid occlusion on one side with greater that 95% stenosis on opposite side at the carotid syhon, and when the opposite side contributes to the cross filling of the occluded side
7) Defective or hypoplastic superficial temporal arteries
8) Significant cerebral infarct in distribution of the middle cerebral artery (MCA)

rCBF Measurement :

This was done by the noninvasive I.V. ^{133}Xenon injection method. A small bolus of ^{133}Xenon injection (usually 15-20 mci) was mixed with 0.5 ml. of saline and injected rapidly into an arm vein. The gamma activity was counted with 4 to 6 scintillation detection probes per hemisphere. In addition the gamma activity in the end expired air was measured, since this is proportional to the arterial concentration. The arterial time varying Fick equation is assumed to hold for each of three compartments in parallel (gray, white, and extracerebral). In this way extracerebral contamination and recirculation are accounted for. Further details are given in Appendix A.

Intraoperative studies of bPO$_2$ and cytochrome a, a$_3$:

Relative bPO$_2$ was measured by the polarographic technique. Teflon coated platinum microelectrodes were used with a 25 μ diameter. A single electrode was inserted into the cortex, near the site of the anastomosis. This technique actually measures O$_2$ availability at the electrode tip and under most conditions is proportional to bPO$_2$. A measure of relative O$_2$ utilization (b$\dot{P}$O$_2$) can be obtained by temporarily occluding an end artery near electrode and recording the rate of fall of the bPO$_2$ recording. The principle reason for decrease in bPO$_2$ when the blood supply to the area is occluded, is mitochondrail O$_2$ utilization. This method of observing relative O$_2$ utilization was first noted by Brink and Bronk[7]. It has also been used for a similar purpose by Fein in the cortex of the cat[8], and by Austin et al[9] under conditions of ischemia produced by carotid occlusion. Relative bPO$_2$ and b$\dot{P}$O$_2$ are measured before and after anastomosis by first completing the anastomosis, and then placing a temporary clip across the superficial temporal artery (STA) to create a situation similar to that prior to anastomosis. Also, measurements were made in response to changes in FiO$_2$, varying from 15% to 80%.

Redox level of cytochrome a,a$_3$:

This was accomplished by a noninvasive optical method using a dual beam spectro-photometric technique originally developed by Chance[10] and modified by Jöbsis[11] for in vivo recording[12]. The method is based on the observation that the cytochromes in their reduced level absorb light at a wavelength which is specific for that cytochrome.

The dual beam, dual wavelength reflectance spectrophotometer is focused on the cortex by means of an epi-illuminator and the signal from reduced cytochrome a,a$_3$ (Cyt. a,a$_3$) is recorded. Further details are given in Appendix B.

Results of Intraoperative Measurements :

Ⅰ. **Relative bPO$_2$:**

Release of the temporary clip on the STA following microanastomosis, always resulted in a marked increase in bPO$_2$ (Fig. 1). Reapplying the clip again resulted in a prompt fall. Changing the FiO$_2$ from its resting level of 30%, down to 15% and then up to 60% always produced a change in bPO$_2$. This was usually more marked after the microanastomosis (temporary clip off), as seen in Fig. 2a and b.

Ⅱ. **Relative b$\dot{P}$O$_2$:**

As described under methods, the relative slope of the fall in bPO$_2$ with occlusion of an artery supplying the cortical recording territory, is a measure of b$\dot{P}$O$_2$. This is shown in Fig. 3a and b before and after clip removal. The response of b$\dot{P}$O$_2$ with changes in FiO$_2$ is shown in Fig. 3c, d, and e.

Ⅲ. **Redox Level of Cyt. a,a$_3$:**

Following removal of the temporary clip on the STA, there was a significant change in the redox level of Cyt. a,a$_3$ to a more oxidized level. This is shown in Fig. 4a, which graphically portrays the change obtained in 11 patients. In response to an altered FiO$_2$, there was a significant change in the redox level of Cyt. a,a$_3$. This was usually more
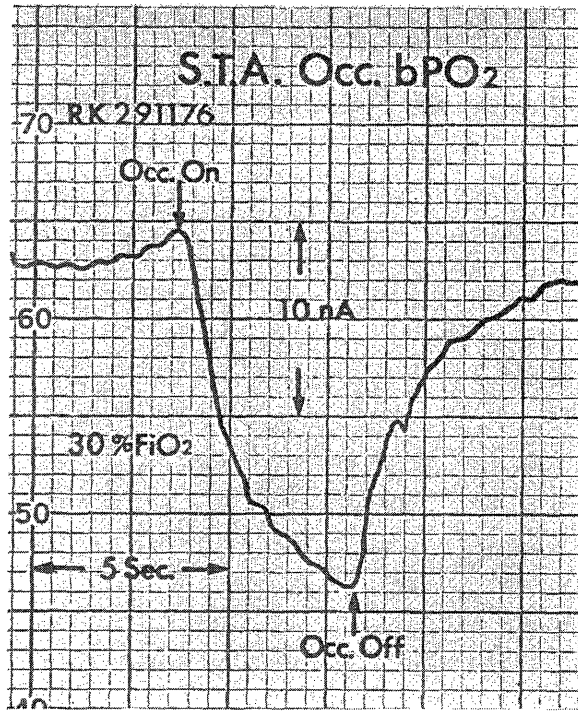
Fig. 1 Shows change in relative bPO₂ (in nA.) with clip on and off the STA, i. e. simulating before and after microanastomosis.
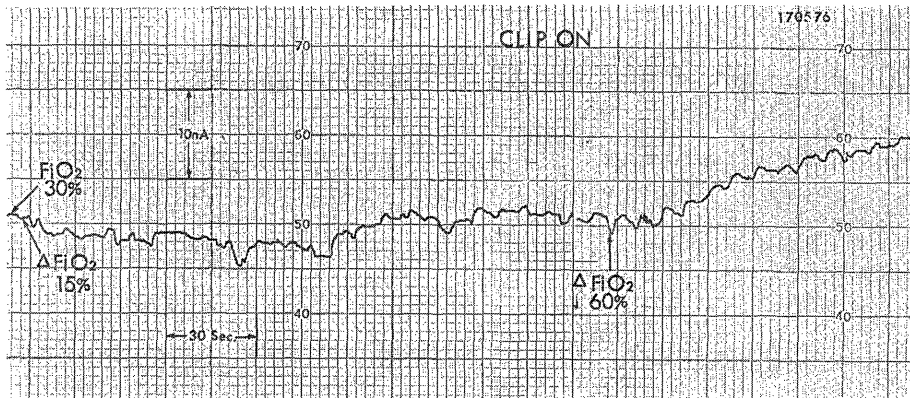

Fig. 2a Shows change in relative bPO₂ before microanastomosis (temporary clip "ON" STA) in response to altered FiO₂. Patient anesthestized with N₂O and O₂ with supplemental drugs for immobilization.
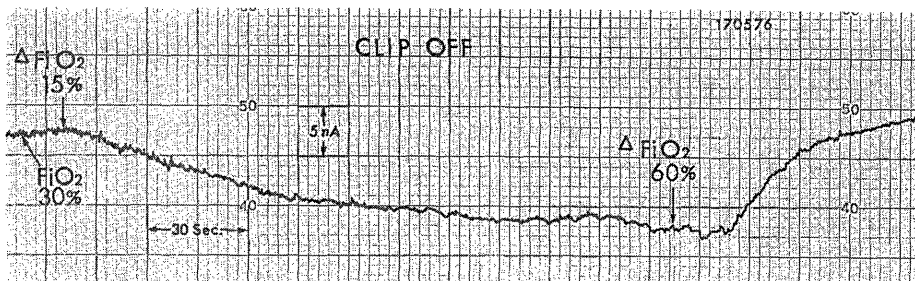

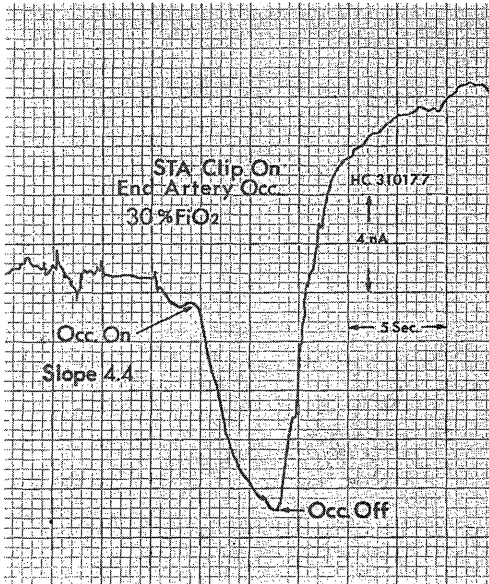Fig. 2b Changes in relative bPO₂ after microanastomosis (Temporary clip "OFF" STA) in response to altered FiO₂.

Fig. 3a Change in relative b$\dot{P}$O$_2$ slope following temporary occlusion of small cortical end arterey with STA clip removed.
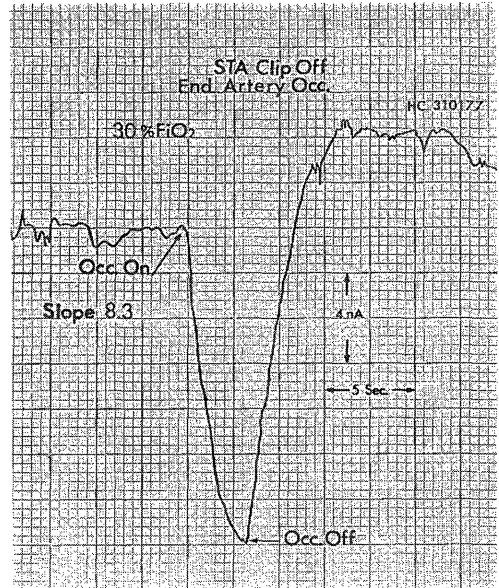
Fig. 3b Change in relative slope (increased) in b$\dot{P}$O$_2$ following temporary occlusion of small cortical end artery with STA clip removed.
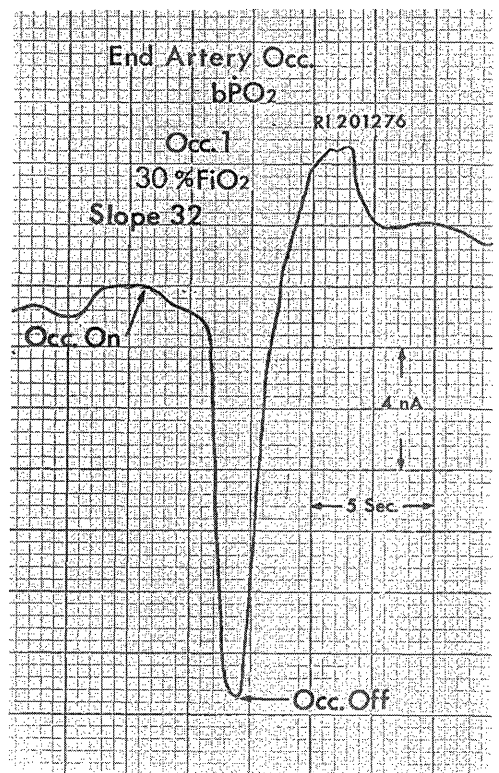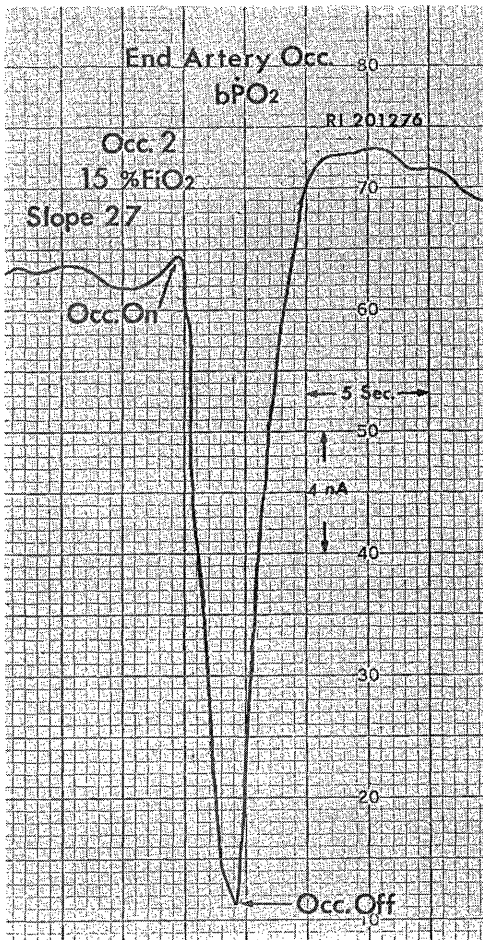
Fig. 3d Relative b$\dot{P}$O$_2$ at 30%FiO$_2$.

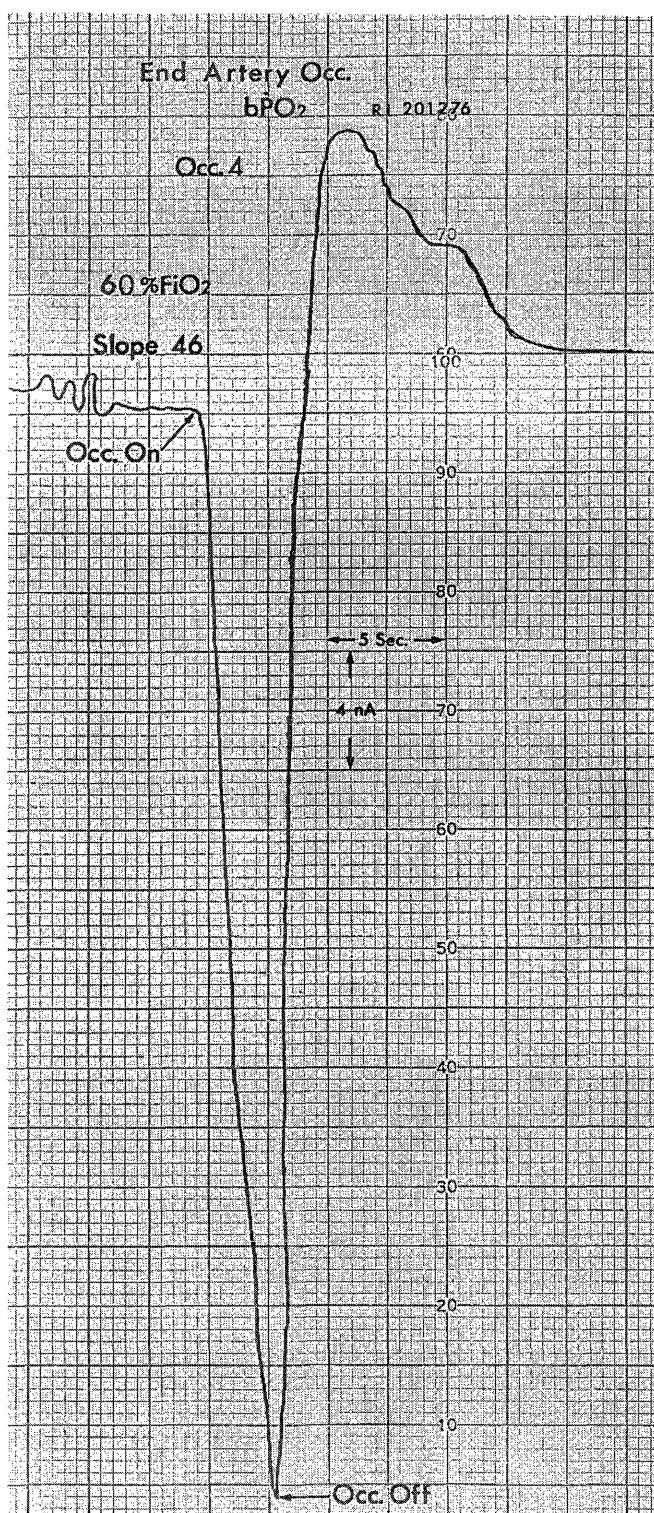← Fig. 3c Relative b$\dot{P}$O$_2$ (slope of fall in bPO$_2$ with temporary end artery occlusion) at 15% FiO$_2$.

Fig. 3e   Relative bṖO₂ at 60% FiO₂.

pronounced following clip removal as seen in Fig. 4 b.

Resuts of rCBF Measurement :

Preoperative rCBF studies show that the majority of patients with TIA's have a significant reduction in rCBF. Some apparently do not, and the cause for this is not clear. Possible explanations include the following :

1) Insufficient number of recording probes used over the head

2) Recording probes too large to detect small focal abnormalities

3) There exists no significant region of depressed rCBF, but with loss of autoregulation, transient drops in cardiac output are sufficient to lower the CBF to a critical level

4) There is no significant region of depressed rCBF, but transient release of fibrino-platelet microemboli cause the TIA's.

Shown in Table I, is the reduction of rCBF preoperatively including all cases, i. e. even those with normal rCBF. In Table II is shown the change in rCBF which was measured postoperatively. Only those patients who had a significant (i. e. > 2 S. D.) reduction of rCBF preoperatively are included in this Table.
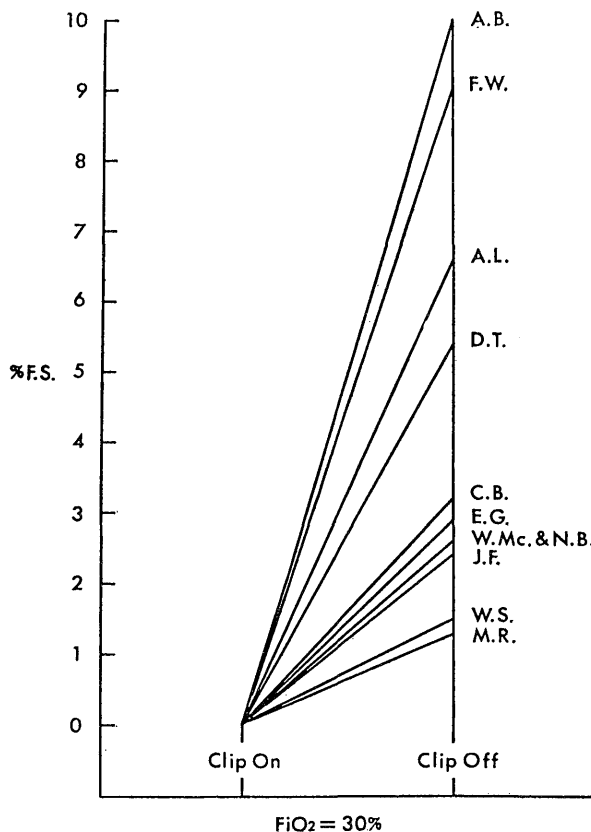

Fig. 4a   Increase in amount of oxidized Cyt. a, a_3 (ordinate) following microanastomosis.
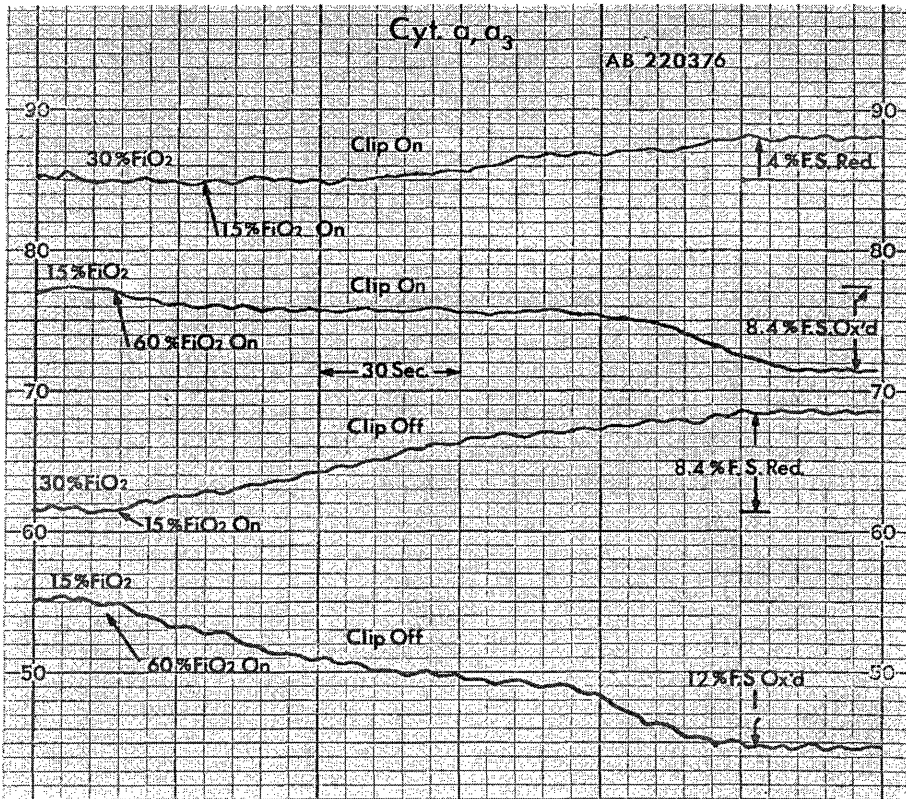
Fig. 4b Changes in level of Cyt. a, a_3 in response to altered FiO_2 before and after microanastomosis (temporary clip "ON" and "OFF" the STA).

Table I   Changes of CBF in patient with arterial obstructions. P = probability as determined by the t test. α = probability as determined by the Mann-Whitney U test.

	n	MEAN	S.D.	%	P
LEFT I.C. OCCLUSION	15	62.07	15.55	-17.33	<0.015
RIGHT I.C. OCCLUSION	12	57.62	11.59	-23.17	<0.001
MIDDLE CEREBRAL STENOSIS	8	53.94	17.16	-28.1	<0.005
BBILATERL I.C. OCCLUSION	6	57.77	20.83	-23.0	<0.92
HIGH I.C. STENOSIS	6	51.87	12.91	-30.84	<0.11

Table II   Changes in CBF pre and post-operatively (gray matter only). Significance calculated using student's paired t test.

GROUP I

No.	REGION	FLOW PRE-OPERATIVE	FLOW POST-OPERATIVE	P-VAUE
16	Operated Frontal	47±10	55±18	0.16
13	Operated Parietal	46±9	57±13	0.04
11	Opposite Frontal	47±8	58±19	0.19

DISCUSSION :

The authors have only given the results of rCBF measured in gray matter. This was because the two compartment model was used, which only provides gray matter flow values. Also, it has been shown that white matter flow values are much less susceptible to change. Schmiedek and Gratzl have shown significant increases in rCBF following micro-anastomosis[13,14]. It remained to investigate whether this flow serves a useful metabolic purpose. Conceivably, one might say that any increase in collateral flow, should enable the patient with TIA's to better withstand transient drops in cardiac output. What has been attempted by the present intraoperative measurements, has been to examine the effect of a surgically produced collateral blood flow on cortical mitochonrial respiration. Measuring the relative cortical $b\dot{P}O_2$ together with the relative redox level of the terminal Cyt. a,a_3, provides an approximation of the mitochondrial metabolic activity before and after the microanastomosis. Values of relative bPO_2 before and after anastomosis show a marked increase with the new collateral flow. At the higher bPO_2 there is usually an increase in the response to altered FiO_2 (Fig. 2 b, 3 c, d, and e) and a more rapid decline following temporary end-artery occlusion. This suggests an increase in O_2 utilization, which is further substantiated by the increased level of oxidized Cyt. a,a_3 following microanastomosis (Fig. 4 b). These results suggest the following conclusions regarding cortical mitochondrial function following microanastomosis :

1) There is a significant increase in the mean rCBF on the side of the anastomsosis and to a lesser extent on the contralateral side.

2) The increase in rCBF is mainly in the distribution of the MCA.

3) With the increase in collateral blood flow, there is a significant increase in the level of the relative bPO_2 and in the oxidized level of Cyt a,a_3.

4) There also appears to be an increase ın relative $b\dot{P}O_2$ following microanastomosis, with an increase in bPO_2.

5) These observations made in the acute intraoperative phase following anatomosis, suggest that a major cause of post-operative improvement in TIA's and neurological deficit, is the provision of an increase in cortical bPO_2 and mitochondrial respiration. In the absence of uncoupling of oxidative phosphorylation it is postulated that this results in an augmented ATP synthesis and utilization at the neuronal level.

REFERENCES

1) Austin, G. M. et al, Surgery 75 : No. 6, 861, 1974.

2) Austin, G. M. et al, "Microvascular Anastomosis for Cerebral Ischemia" . 1976. IN PRESS

3) Cartlidge, N. E. F. et al, Mayo Clinic Proceedings 52 : No. 2, 117, 1977.

4) Schuler, W. et al, Presented at the Sixth Annual Meeting, Society for Neuroscience, Toronto, Canada, 1976.

5) Chance, B. et al, I. U. B. Symposium Series 31 : 367.

6) Jobsis, F. F. , Fed. Proc. 36, 1404, 1972.

7) Davies, P. et al, Fed. Proc. 16 : No. 3, 689, 1957.

8) Fein, J. M., In : "Blood Flow and Metabolism in the Brain" . Churchill Livingstone, Edinburgh, Scotland, 1975.

9) Austin, G. M. et al, "Contemporary Aspects of Cerebrovascular Disease" 46, 1976.

10) Chance, B., Rev. Sci. Inst. 22 : 634, 1951.

11) Jöbsis, F. F. et al, In vivo reflectance spectrophotometry of cytochrome a. a_3 in the cerebral cortex of the cat, 1976. IN PRESS

12) Rosenthal, M. et al, Exp. Neurol. 50 : 477, 1976.

13) Schmeidek, P. et al, Europ. Neurol. 6 : 354, 1971–1972.

14) Schmeidek, P. et al, J. Neurosurg. 44 : 303, 1976.

APPENDIX A
DERIVATION OF DIGITAL COMPUTER ANALYSIS

Assume that cerebral blood flow following an intravenous (I. V.) isotope injection, is measured through three compartments in parallel. These consist of a fast (gray matter), slow (white matter), and slowest (extra cerebral). Assume also that extra cerebral flow occurs in a single slow compartment.

Let C_i = concentration of isotope in the ith compartment, and from the
Fick equation

$$\frac{dC_i}{dt} = f_i \left(A - \frac{C_i}{\lambda_i} \right) \tag{1}$$

where,

A = arterial concentration of isotope as a function of time

f_i = perfusion flow through the ith compartment in ml/100g/min.

λ_i = tissue to blood partition coefficient of isotope (^{133}Xe) for the ith

compartment

t = time in minutes

$K_i = f_i / \lambda_i$

(1) is a first order linear differential equation. Transposing and multiplying by the integrating factor e^{Kt}, integration then yields

$$C = W\lambda K e^{-Kt} \int_o^t A(\tau) e^{K\tau} \, d\tau$$

where τ = a dummy variable
or

$$C_i = W_i \, \lambda_i \, K_i e^{-K_i t} \int_o^t A(\tau) e^{K_i \tau} \, d\tau = f(t, K_i, W_i) \tag{2}$$

W_i = relative weight of the ith compartment combined with a proportionality factor

Now express as a Taylor series the function $f(t, K_i, W_i)$ as it takes on the values of $f(t, K_i + \varepsilon K_i, \; W_i + \varepsilon W_i)$ when,[32]

i) K_i has a value $K_i + \varepsilon K_i$ near to a given fixed value K_i, and

ii) W_i has a value $W_i + \varepsilon W_i$ near to a given fixed value W_i. Then omitting the subscript i and dropping terms of second and higher order,

$$T = f(t, K + \varepsilon K, W + \varepsilon W) = f(t, K, W) + \varepsilon K \frac{\partial f}{\partial K} + \varepsilon W \frac{\partial f}{\partial W} \tag{3}$$

Expanding (3), one obtains

$$\frac{\partial f}{\partial K} = \lambda W e^{-Kt} \int A e^{K\tau} d\tau - W\lambda K t e^{-Kt} \int A e^{K\tau} d\tau +$$

$$W\lambda K e^{-Kt} \int \tau A e^{K\tau} d\tau = \text{``B''}$$

$$\frac{\partial f}{\partial W} = \lambda K e^{-Kt} \int A e^{K\tau} d\tau = \text{``D''}$$

and

$$f(t, K, W) = C$$

Then the difference between the theoretical and observed values at each point becomes :

$$T - \left[C + \varepsilon KB + \varepsilon WD \right]$$

In order to minimize the differences between the observed and calculated results, we proceed as follows. Assume that the most likely values of the small constant εK and εW are those for which the sum of the squares of the difference between the observed and calculated results are minimal. Proceeding with the least squares formula, [32]

$$S = \left[T - (C + \varepsilon KB + \varepsilon WD) \right]^2 \tag{4}$$

Then

$$S = T^2 + C^2 - 2CT - 2\varepsilon KBT + 2\varepsilon KBC - 2\varepsilon WDT + 2\varepsilon WCD + 2\varepsilon K\varepsilon WBD + (\varepsilon KB)^2 + (\varepsilon WD)^2 \tag{5}$$

Minimizing (4) by equating the partial derivatives of (5) with respect to εK and εW, to zero gives [32,33]

$$\frac{\partial s}{\partial \varepsilon k} = -2BT + 2BC + 2\varepsilon WBD + 2\varepsilon KB^2 = 0 \tag{6}$$

$$\frac{\partial s}{\partial \varepsilon W} = -2DT + 2CD - 2\varepsilon KBD + 2\varepsilon WD^2 = 0 \tag{7}$$

or,

$$BB\varepsilon K + BD\varepsilon W = B(T-C) \tag{8}$$

$$BD\varepsilon K + DD\varepsilon W = D(T-C) \tag{9}$$

and in martrix formulation (8) and (9) can be written,

$$\begin{bmatrix} BB & BD \\ BD & DD \end{bmatrix} \begin{bmatrix} \varepsilon K \\ \varepsilon W \end{bmatrix} = \begin{bmatrix} B(T-C) \\ D(T-C) \end{bmatrix}$$

or,

$$Aij \cdot Xi = Yj$$

$$X = A^{-1}Y$$

Similar equations to (6) and (7) are formulated for each of the three compartments giving 6 equations in the 6 unknown error terms. In practice, initial values for Ki and Wi are selected in the middle of the expected range of each parameter. Since second and higher order terms have been dropped in the Taylor series expansion, the initial values obtained for the error terms are only approximations. The computation procedure

is, therefore, reiterated using updated values of Ki and Wi until no further significant improvement is obtained. The digital computer program for this was written by one of the authors (D. Laffin) and is one component of a software system that is obtainable on request. In a subsequent paper, the effects of number of counts per minute, duration of recording, added noise and significance of the expired air curve envelope, are discussed. The programs were written in Fortran and are run on a PDP 11/10 Computer. Analysis of the 3 compartment, 40 minute recording curve requires 120 seconds per curve, whereas analysis of the 2 compartment, 12 minute recorded curves, takes only 20 seconds per curve.

Table IB   List of useful absorption wavelengths for spectrophotometry.

Mitochondrial	Components
	Useful Peak Absorbtion λ in nm
Cytochrome b	564
Cytochrome c	550
Cytochrome c_1	553
Cytochrome a	605
Cytochrome a_3	600
flavoprotein	450

Hemoglobin	Derivatives
	Useful Peak Absorbtion λ in nm
Red. Hemoglobin Hb	555
Ox. Hemoglobin HbO_2	576–578
Isosbestic point $Hb+HbO_2$	584.5
Methemoglobin	578
Cyanomethemoglobin	580–590
Alkaline hematin	550–580
Heme	575

APPENDIX B

OPERATION OF DUAL BEAM, DUAL WAVELENGTH, REFLECTANCE, SPECTROPHOTOMETER

A tungsten light source is used to illuminate two monochromators which are adjusted to different wavelengths, one for the sample wavelength and the other for the reference wavelength. The sample wavelength used is 605 nm because this is a peak absorption wavelength for reduced Cyt. a, a_3. The reference wavelenght chosen must meet several conditions so that an algebraic sum relationship with respect to the sample wavelength can be maintained. These conditions are:

1) The reference wavelength must not contain any spectral activity with respect to either oxidized or reduced Cyt. a, a_3.

2) Because there is some hemoglobin component (both HbO_2 and Hb) at the sample wavelength, the reference wavelength must be an equibestic point, i. e. it must have the same relative absorption for HbO_2 and Hb, are found at the sample wavelength.

3) It must be close enough to the isosbestic point for total hemoglobin (that point where both HbO_2 and Hb have the same absorption) so that a relative indication of total hemoglobin concentration can be recorded as a measure of relative blood volume.

The reference wavelength chosen which best meets the above conditions for Cyt. a, a_3 (605 nm) is found at 590 nm. Once the monochromators are set for 605 and 590 nm, the light is chopped at a rate of 60 Hz, and 180° out of phase with each other. The light is transmitted to the microscope barrel and epi–illuminator assembly by means of a fiber optical bundle. The light (605 and 590 nm) is then focused on a 3 mm diameter area of the cortex by the epi–illuminator. That light which is reflected from the cortex is again focused by the epi–illuminator on a photomultiplier tube which converts the light energy into electrical energy. This resulting electrical energy is then fed back and processed in the amplifier.

Electronic processing is as follows. In the Cyt. a, a_3 channel electrical energy resulting from both 605 and 590 nm light (180° out of phase and of opposite polarity) is algebraically summed by a differential amplifier. Since an equibestic point is used for a reference wavelength, there will be no resulting voltage due to hemoglobin in the field as the sum of the voltages at 605 and 590 nm for hemoglobin will always equal zero and the only voltage present will be the result of the redox state of Cyt. a, a_3. An increase in the ratio of 605 to 590 nm reflected light due to a relative increase in the amount of reduced Cyt. a, a_3, results in a more negative voltage; whereas a decrease in the ratio of reflected light due to a relative decrease in the amount of reduced Cyt. a, a_3 results in a more positive voltage at the stripchart recorder. In the blood volume channel, electrical energy resulting from only the 590 nm signal (total hemoglobin component) is amplified and fed to the stripchart recorder, where an incrase in 590 nm signal equals an increase in positive voltage representing a decrease in relative blood volume. This is true because 590 nm is close enough to 584.5 nm, the so–called isosbestic point for Hb, i. e. that point where oxygenated (HbO_2) and disoxygenated (Hb) have equal absorption. See Table IB.
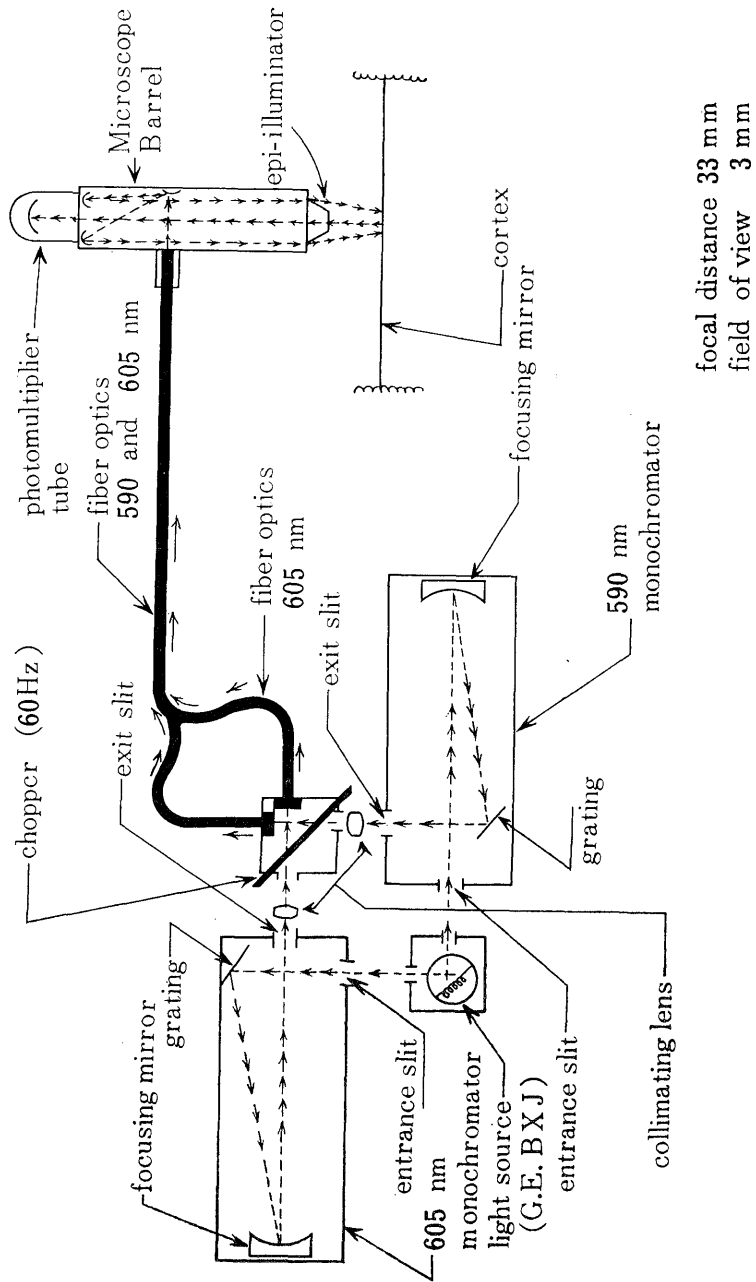
Fig. IB DIFFEHTIAL DUAL WAVELENGTH REFLECTANCE SPECTROPHOTOMETER

Fig. IB Diagram of dual beamreflectance spectrophotometer used for in vivo recording from cortex. (Jobsis–Chance modification)