CIRCULATORY CHANGES FOLLOWING OCCLUSION OF
THE MIDDLE CEREBRAL ARTERY AND THEIR
RELATION TO FUNCTION*

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The sudden onset and rapid recovery from a neurological deficit is relatively common in the course of cerebrovascular disease in man. Thereafter recurrent attacks of a similar nature may occur with a varying degree of recovery.1,3,4,7,26 Careful review of the history together with observation at the bedside show that a number of factors may precipitate these transient ischemic attacks. Commonly such attacks are preceded by impaired cardiac output or a fall in blood pressure.24 More rarely anoxia appears to have provoked an attack. A well-defined understanding of these hemodynamic crises is important in planning rational treatment but the sequence of events in the cerebral circulation during these attacks is not yet fully understood.25

Pathological studies have clarified the anatomical background but have not resolved the physiological basis for these transient ischemic attacks.7,15 In general, a patchy softening is present in the distribution of the diseased vessel which usually is found to be the internal carotid or basilar artery and, less commonly, a vessel comparable in size to the middle cerebral artery. Occasionally cerebral infarction is found without demonstrable occlusion of a cerebral vessel. The functional deficit present in life is frequently far greater than can be accounted for by the anatomical extent of the lesion and only hypothesis can be offered to explain recovery from preceding attacks. Anatomical studies have shown the rich supply of small arterial anastomoses which supply additional adjustments in the cerebral collateral circulation other than the circle of Willis.30 Presumably these vessels play a major role in supplying the circulatory demands of the compromised territory.

In order to define the nature of the neurological deficit following vascular occlusion a series of acute experiments have been made while recording

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localized changes in blood flow and oxygen tension from several areas of the brain during occlusion of cerebral vessels. Following occlusion of a cerebral vessel there is reduction of the cerebral oxygen tension within the territory of its supply, the severity of which depends on the effectiveness of the collateral circulation provided by arterial anastomoses. These arterial anastomoses may be observed in the pia with a microscope. For example, when the middle cerebral artery is occluded in the monkey the collateral circulation is provided largely from arterial anastomoses in the pia derived from the anterior and posterior cerebral arteries. These vessels measure 50–250 μm in size. The most important stimulus for increase in the collateral circulation appears to be a localized reduction in intraluminal pressure so that blood flows from high- to low-pressure areas; local reduction in pH and oxygen tension are less potent stimuli.

Cortical ischemia can proceed to the point of failure of the electroencephalogram and the production of a potential of injury caused by depolarization of nerve cells without damage to vessels, but prolongation of ischemia beyond that point causes anoxic damage to the vascular endothelium, resulting in stasis beginning in the venules. Soon after its production this stasis is reversible by such measures as increasing the blood pressure and the administration of heparin. Infarction appears to result primarily from damage to vascular endothelium with resulting edema, hemococoncentration, sludging and stasis.

Experiments in monkey and later in man demonstrate the high consumption of oxygen and small reservoir of oxygen in healthy cerebral tissue. Polarograms in monkeys and in man show that oxygen tension and oxygen metabolism are reduced in freshly infarcted cortex but in bordering zones the oxygen tension is the same or higher than in undamaged regions of the brain. In man, under local anesthesia measurements of cortical oxygen tension were correlated with the functional state of the cerebrum as judged by clinical tests and electroencephalogram as the carotid artery was occluded in the neck. Reduction of the cortical oxygen tension to low levels results in temporary impairment of cortical function and slow activity in the electroencephalogram. If the collateral circulation is adequate, compensation begins within 45 seconds of occlusion and the oxygen tension rises towards the steady state prior to release of the artery and functional impairment does not occur. After occlusion of a cerebral vessel the collateral blood flow continues to increase for many days. In the monkey, a relatively controlled degree of cerebral infarction in the Sylvian region may be produced by placing a clip on the parasellar portion of the middle cerebral artery and lowering the blood pressure to 70 mm. of mercury or lower.

Occlusion of the middle cerebral artery for periods of less than 15 minutes produces only temporary impairment of motor function. To produce a degree of impairment as severe as that associated with permanent occlusion it is necessary to occlude the vessel for at least 50 minutes; in this study,
however, a few animals with permanent occlusion of the middle cerebral artery had transient hemiplegia without severe infarction.

The scope of the present paper is to report direct microscopic observations of pial blood flow and oxygen tension in the unanesthetized chronic preparation following occlusion of the middle cerebral artery for as long as 9 weeks and to correlate these observations with the recovery from any functional disorder. In addition, attempts were made to provoke transient ischemic attacks in the convalescent phase by anemically and chemically induced hypotension and by anoxia and to observe any modification of these events by anticoagulant drugs.

**METHODS**

Twenty-three monkeys (Macacus mulatta and Rhesus cynomologus) were studied in the present series of experiments. The middle cerebral artery was occluded in 11 experiments without the use of anticoagulant drugs; in an additional 12 experiments anticoagulant drugs (heparin or Dicumarol) were administered prior to the time of occlusion and were continued throughout the period of observation. Heparin was administered by intramuscular injection in doses of 200–500 U.S.P. units per kg. of body weight at 12-hour intervals. The clotting time was consistently found to range between 40 and 90 minutes. Dicumarol (3,3-methylenebis-4-hydroxycoumarin) was administered daily by gastric tube in doses of 0.3–3 mg. per kg.; with this dosage the prothrombin time varied between 40 and 80 seconds, compared to control readings of 15 seconds.

The animals were anesthetized with Nembutal, 0.5 mg. per kg. of body weight, and in some instances chlorpromazine, 2 mg. per kg., was also given to aid in lowering the blood pressure. The head was held firmly in a McGill head holder after shaving the scalp. A hemispherical skin flap was turned down over the zygoma followed by a temporal muscle and periosteal flap using aseptic technique (Fig. 1D).

A trephine hole was made overlying the frontal or parietal operculum of the Sylvian fissure. The trephine hole was tapped and a tight-fitting window, measuring 15 mm. in diameter, was screwed into the skull (Figs. 1D and 2C). The window in the skull was machined according to my specifications by the Harvard workshop and was modified after that described by Sohler et al. in 1941.* The glass window was recessed in its brass frame so that the window-glass could be irrigated externally with saline at 98°F. in order to prevent heating of the brain by the source of light (Fig. 2C). Photographs and observations were made through a pool of saline in the glass window as this was found to minimize reflections of light. Two water-tight screws could be removed temporarily from the frame of the window in order to insert polarographic electrodes for making measurements of oxygen and for irrigating the brain.

With the window screwed firmly in place, a large osteoplastic bone flap was fashioned with the window remaining in its center. The bone flap was made by means of a small trephine and a Gigli saw. The dura mater was removed widely and the endosteum of the bone flap was scraped away to prevent growth of fibrous tissue

* Dr. Herbert Jasper of the Montreal Neurological Institute kindly loaned us a window of his own design for use with cortical electrodes. This model was also helpful in designing the window used in these studies.
Fig. 1. (A) To show rapid recovery of an animal treated with heparin 24 hrs. after occlusion of middle cerebral artery. (B) The hopping and placing reactions are absent in the left forelimb. (C) A left homonymous hemianopia is present. (D) Close-up view of same animal to show window in place and scalp incision used to permit occlusion of middle cerebral artery. The lateral portion of brain beneath window shows periventricular hemorrhages.

at the edge of the window. The Sylvian fissure was exposed and the frontal lobe was elevated gently with a small malleable retractor. A spot-light was focused on the middle cerebral artery and it was occluded by two or three silver clips. Lowering the blood pressure at the time of surgery was accomplished by the administration of chlorpromazine in doses of 2-5 mg. by lowering the feet on a tilt-table and by the removal of blood. In 3 experiments the vessel was sectioned after the clips had been put in place, in 2 experiments four or five anastomotic branches were occluded on the cortex and in 2 experiments the anterior cerebral artery was occluded in addition to the middle cerebral artery. The tip of the temporal lobe was removed by subpial resection in order to provide internal decompression.

The bone-flap with the window in the center was wired into place so that the window overlay the ischemic cortex in the distribution of the middle cerebral artery. The periosteum, the temporal muscle and the scalp were then closed in layers with
interrupted sutures and the window was exposed through a tightly fitting circular incision made in the scalp. The brain under the window could be irrigated with warm saline. Penicillin, 300,000 units, and streptomycin, 0.2 mg., were given by intramuscular injection after surgery. With practice the whole procedure was completed in 3 hours.

The systolic blood pressure was estimated approximately with a sphygmomanometer and a narrow cuff placed around the lower abdomen with a pad compressing the abdominal aorta. The systolic pressure was taken to be the point at which the femoral pulse was obliterated. This method of sampling the systolic blood pressure obviated puncture of the femoral artery.

Measurements of cortical oxygen tension were made by the polarographic method, using sterile electrodes described in previous communications. The anode (silver-silver chloride) was insulated with Teflon except for its last 1 cm. which was freshly chlorided prior to use. The anode was inserted into the muscle of the scalp through the skin flap. The cathodes, or active electrodes, consisted of finely tapered and exposed tips of 0.01-inch platinum wires insulated with Teflon. They were inserted into the cortex through screw holes built into the skull window for that purpose. The exposed portion of wire (1–2 mm. in length) was carefully scraped clean with a scalpel before use but care was taken so that the portion of exposed wire remained unchanged. In this way calibrated readings in electrical units could be compared at different times. It has been found that electrodes insulated with Teflon give readings that are uniform from day to day providing the surface

FIG. 2. (A) To show stereoscopic microscope and camera arranged for high-power macrophotography. With this arrangement the image is magnified 180X. (B) To show camera in use at operation. The window is in place within the skull below the drapes. The polarograph and the stereoscopic microscope are to the left of the picture. The electronic flash attachment is to the right behind the camera. (C) To show trephine, tap and modified Forbes window. The glass is recessed so that the window may be cooled externally. The screws have been removed from the window on the right to show how electrodes may be inserted and the brain beneath the window irrigated.
area of the exposed wire is not altered and the metal is kept scrupulously clean.

The principle of the polarographic method requires a potential of 0.6 volt supplied to the anode by a potentiometer. The platinum electrode was connected to the positive pole of the potentiometer through a resistance of 1.2 million ohms. On either side of this resistance leads were taken to the input of an Offner 8-channel Type D8 polygraph. The output from the polarograph was wired directly to the Type 9138 Input Coupler of the inkwriter after calibration with a microammeter.\textsuperscript{19,22,23} The electroencephalogram was recorded from the scalp by bipolar needle electrodes placed in both frontal and occipital positions.

Observations of the pial circulation were made with either a Spencer stereoscopic microscope having various magnifications from 18 to 144 times (Fig. 2A) or a monocular Bausch and Lomb microscope permitting magnification up to 480 times. Either microscope was mounted on an adjustable arm. When high-power observations were made a Nicholas illuminator with a blue filter and condenser was used. The illuminator was mounted on an adjustable hinged arm and the light beam was focused on the cortex. In order to avoid heating of the brain the window was irrigated externally with saline.

Macrophotographs (no ocular lens used) were taken with a Praktina camera (VEB Kamera—Werke Niedersedlitz, Dresden, Edgar-André Strasse 56) modified for this purpose.\textsuperscript{*} The camera was mounted on an adjustable hinged arm in such a way that an extension bellows was used for fine adjustment of the focus in a manner similar to that used with a microscope (Fig. 2A, B). Extension tubes were added so that the length of the tubes could be adjusted from 30 to 45 cm. Four lenses were used, each fitted with an adjustable diaphragm. The focal length of the lenses was 50 mm., 25 mm. and 15 mm., and in addition a Bausch and Lomb 10× objective was used. With this arrangement direct magnification from 18× to 180× could be obtained on the ground-glass focusing screen. Anscochrome 35 mm. daylight film was used in the camera and the color transparencies were enlarged on a 31/2"×41/2" contrast process Panchromatic intermediate negative. Positive prints at various enlargements were made from this. By this means a macrophotograph 180× could be printed satisfactorily on a 5×7" print with a resulting magnification of 720×. All macrophotographs were taken with an electronic, high-speed stroboscope unit having a flash duration of 1/1000 of a second and producing a daylight color flash of 5,600 K\textsuperscript{1} temperature.\textsuperscript{†} The stroboscope unit was focused on the window from a distance of 10 cm. and provided intense illumination of such short duration that the brain was not heated. The camera was fitted with a reflex view-finder and ground-glass focusing screen adjusted to eye-level so that the photographic field could be viewed as the exposure was made. The animals were examined daily and notes were made of their degree of alertness, respiratory rate, size and reaction of the pupils, visual fields and tendon jerks together with their motor and sensory performance (Fig. 1A, B, C).

With these methods daily observations and photographs of the pial circulation were correlated with the electroencephalogram, cortical oxygen tension and any functional deficit in the restrained but unanesthetized animal. In one animal 8 ml. of a saturated solution of trypan blue was injected intravenously 48 hours after occlusion in order to estimate any increased vascular permeability. The brains were

\textsuperscript{*} Mr. Leo Goodman, Medical Photographer, The Mallory Institute of Pathology, Boston City Hospital, assisted in modifying this camera for high-power macrophotographs.

\textsuperscript{†} Dejur-Ansco Corp., 45-01 Northern Blvd., Long Island City 1, N.Y.
removed immediately after death or sacrifice, photographed, fixed in 10 per cent formalin and embedded and stained for microscopic study. Details of the nature of changes in local hemodynamics from day to day as well as histological studies of the brain will be presented in subsequent papers.\textsuperscript{17,18}

**RESULTS**

*General Observations.* In the experiments reported here occlusion of the middle cerebral artery near the circle of Willis produced regularly a functional deficit which varied in severity from a transient (4–5 days) faciobrachial monoparesis with loss of hopping and placing reactions and depressed tendon jerks to severe flaccid hemiplegia, with hemianopia and hemianesthesia. The forelimb was consistently weaker than the hindlimb. In those animals with a severe defect there was steady functional improvement after the first week, at which time the hemiparetic limbs became spastic and the reflexes increased. Some mild weakness and absence of hopping and placing reactions in the forelimb persisted for 9 weeks. In some experiments the hemiplegia progressed to stupor and death within the first 72 hours because of brain swelling with herniation and brain-stem compression. In 2 animals in whom brain swelling was severe and whose respirations were slowed the inhalation of 100 per cent oxygen by nasal catheter appeared to reduce brain swelling and the animals survived. In general, the group of animals with severe functional defect were those in whom the systolic blood pressure fell to 70 mm. of mercury or lower. Reduction of the systolic blood pressure below 60–70 mm. of mercury at the time of occlusion produced regularly infarction of the pre- and postcentral cortex adjacent to the Sylvian fissure visible through the skull window. If the blood pressure was maintained above 90 mm. of mercury a mild, transient hemiparesis with complete recovery occurred usually but not invariably. In 1 animal in whom severe infarction occurred without a fall in blood pressure there was an anomaly of the anterior cerebral artery which was derived solely from the occluded middle cerebral vessel with consequent reduction of collateral vessels. The severity of the neurological defect could be increased regularly by occlusion of the anterior cerebral or opposite middle cerebral artery in addition to the middle cerebral artery, or by occluding four or five of the major cortical anastomoses at the cortex.

Using magnifications above 100X of either the microscope or the camera it was possible in the unanesthetized animal to observe capillaries in the pia and immediately subjacent cortex and to identify individual red and white blood cells in zones of stagnant flow.

*Circulatory Changes Accompanying Transient Hemiplegia Without Infarction.* In those animals in which the blood pressure was well maintained and a mild transient hemiparesis was present for 4–5 days followed by complete recovery there was a critical slowing of the pial circulation without significant stasis but with a marked change in the color of the terminal arterioles and veins. The veins became dark blue and the arterioles a brown-
blue instead of their normal orange-red color. The large arteries did not change in color. The capillaries were less prominent and the terminal venules appeared dark at the points where deep perforating cortical branches joined them at the surface (Figs. 3A and 4B, D). The difference in arterial and venous color was increased compared to the normal appearance of the cortex before occlusion of the middle cerebral artery. The normal axial flow of red and white blood cells was altered in venules and there was margination of white cells with a granular appearance of the arterioles. Many of the capillaries were filled with plasma flowing slowly with periodic resumption of flow of red cells through them. The marked cyanosis of the cortex persisted for the first 4–8 hours and was then followed by progressive

![Fig. 3. Serial macrophotographs to show changes in collateral circulation accompanying transient hemiplegia produced by lowering the systolic blood pressure in a monkey recovering from occlusion of right middle cerebral artery.](image)

(A) Macrophotograph (15X) of right pre- and postcentral gyri made 2 hrs. after occlusion. The systolic blood pressure was 110 mm. Hg and collateral circulation was well established. There is some perivascular hemorrhage.

(B) 24 hrs. later hemorrhages have been absorbed and circulation is restored. Mild left hemiparesis was present; systolic blood pressure was 104 mm. Hg. Blood pressure was lowered to 60 mm. Hg for 2 hrs. by administration of hexamethonium, resulting in failure of collateral circulation and development of complete left hemiplegia.

(C) 24 hrs. after administration of hexamethonium (48 hrs. after vascular occlusion) ball-hemorrhages have occurred because of restoration of collateral flow to vessels damaged by ischemic anoxia. Severe left hemiplegia and hemisensory defect were present.

(D) 4 days later (5 days after vascular occlusion) hemorrhagic zone is being invaded by clouds of white blood cells and there is recovery from hemiparesis except for absent hopping and placing reactions.
restoration of blood flow by way of the collateral circulation derived from arterial connections with the anterior and posterior cerebral arteries (Figs. 3B, 4A, and 5A, B, C, D). Hyperemia of the cortex occurred 8–72 hours after occlusion with dilatation of arterioles and venules and rapid flow in the capillary network. Restoration of flow to vessels damaged by ischemic anoxia produced perivascular hemorrhages and diapedesis which usually were absorbed by white cells or washed away by cerebrospinal fluid within 3–5 days (Fig. 3A, B, C, D.) The pia and cortex then appeared normal save for scattered brown pigment within perivascular white cells. During the stage of cyanosis the cortical oxygen tension measured 40–75 per cent of readings prior to occlusion. The oxygen tension returned to normal 8–72 hours later and supernormal levels caused by visible reactive hyperemia were common. The electroencephalogram follows the state of the circulation closely. During the first 8 hours reduction in amplitude and slowing was recorded commonly from the ischemic zone with a rapid return to normal if there was good compensation of the collateral circulation (Fig. 6H). Functional recovery, however, lagged consistently behind restoration of cortical blood flow, oxygen tension and the electroencephalogram for 1 to 4 days.

Circulatory Changes Accompanying Severe Hemiplegia with Infarction.
Severe or prolonged hemiplegia was associated regularly with some degree of infarction visible in the living cortex in spite of eventual functional recovery. In this group of experiments the oxygen tension in the infarcted zone was reduced to 5–20 per cent of normal within the first 24 hours and the cortex presented a pale, cyanotic appearance because of collapse of the vascular network. Severe ischemic anoxia of this degree was accompanied regularly by brain swelling, and clumping, segmentation and stasis of red cells in venules which occasionally progressed within the next 4 days to involve small arteries (Figs. 7 and 8). White thrombi caused by clumping of platelets were seen but their appearance changed commonly with local alterations of flow (Fig. 7C, D). Arteriolar stasis resulted commonly in progressive brain ischemia and swelling, occasionally producing a vicious cycle which terminated in death from brain edema (Fig. 9A, B). Rarely
Fig. 6. A, B and C are 3 records from same animal made 7 wks. after occlusion of right middle cerebral artery to show production of transient hemiplegia by breathing 100 per cent nitrogen. (A) shows slow gradient of fall in oxygen tension (EPG) recorded from zone of infarction (see diagram of brain at bottom of figure). EEG from ischemic hemisphere (2–4) shows progressive slowing while EEG from left hemisphere (1–3) shows little change. (B) shows EEG and EPG after breathing nitrogen for 1 min. Left hemiplegia was now present. EPG was reduced from initial readings of 6 to 5.4x10^-8 Amp. (C) 3 min. later EPG shows a rise with improvement in both EEG and degree of paralysis.

D, E, F and G are 4 samples of a continuous record from a monkey treated with heparin and Dicumarol whose right middle cerebral artery was occluded 2 days before, to show production of transient hemiplegia following a spontaneous localized left-sided seizure. Initial EPG reading was 6x10^-8 Amp. but rapidly fell to 2x10^-8 Amp. in record E at which time the seizure ceased. Oxygen tension remained low and postictal hemiplegia persisted when record F was made 4 min. later. Record G was made 10 min. later as animal recovered from hemiplegia.

H, I and J are 3 EEG records from another animal to show spontaneous fluctuation in functional defect caused by changes in collateral circulation. (H) 20 hrs. after occlusion; mild left hemiplegia was present. (I) 3 days after occlusion severe hemiplegia was present. (J) On the 4th day recovery was beginning.

brain swelling was so severe that the cortex became flattened against the window and cut off its own blood supply by compression of the pial vessels (Fig. 9B). If death resulted from brain swelling it occurred within the first 4 days when increased vascular permeability was at a maximum. The substance of the brain was seen to increase in volume beneath the window, resulting in flattening of the gyri and obliteration of the sulci. Diapedesis of red cells through the walls of vessels was pronounced and if trypan blue was injected intravenously 24–28 hours after the production of infarction the staining of the ischemic zone was greater than reported within the first 8 hours.

Severe anemic infarction after occlusion of the middle cerebral artery
Fig. 7. Series of macrophotographs from the same animal.

(A) Macrophotograph taken at magnification of 18X to show collapse of pial vessels with segmentation, stasis and diapedesis in small venules 5 hrs. after occlusion of middle cerebral artery. Animal was stuporous at this time.

(B) High-power macrophotograph (54X) to show detail of collapsed pial artery. There is stasis in terminal arteriole, capillary and venule. The artery nicks the vein at point of crossing because of decreased intraluminal pressure. Capillary and venular networks are outlined by perivascular hemorrhages. Granular appearance of terminal venules is caused by clumping of red cells.

(C) Appearance of pial vessels 20 hrs. after occlusion to show stasis in terminal venules (X18). The animal showed severe flaccid hemiplegia.

(D) Appearance of pial vessels 24 hrs. after occlusion to show progressive stasis in some vessels and return of flow in others and an increase in perivascular hemorrhages. There are white thrombi in two of the veins (X18). The animal was drowsy with complete hemiplegia and hemisensory defect.
was produced regularly in the normotensive animal by placing clips on major anastomotic cortical vessels or by occluding the anterior cerebral or opposite middle cerebral artery (Fig. 8).

Delayed Resolution of Stasis. Stasis present in small vessels for periods up to 4 days regressed if the collateral blood flow improved after delay (Figs. 7 and 8). Such delayed increases in the collateral flow resulted in movement of the static clumps of blood into bordering zones of normal circulation where the clumps disintegrated and normal flow was resumed in the damaged vessel. The collateral flow may vary from day to day with intermittent stasis and resumption of flow in small vessels. Intermittent restoration of flow in static vessels resulted in progressive diapedesis and hemorrhage which produced extensive hemorrhagic infarction consequent upon anoxic damage to the walls of the vessels (Figs. 9 and 10B). Varying degrees of hemorrhagic infarction reflect the pattern of development of the collateral

Fig. 8. Series of 5 macrophotographs (15X) of same area of cortex in a normotensive animal taken at different times following occlusion of right middle cerebral artery, the opposite middle cerebral artery having been occluded 7 days before.

(A) 2 hrs. after occlusion there is widespread segmentation and stasis in veins and venules. Animal was stuporous at this time.

(B) 1 day later. There is return of flow to many vessels with perivascular hemorrhages. Bilateral hemiparesis and left homonymous hemianopia were present and animal was drowsy.

(C) 2 days later. Flow continues to return to zones of stasis with further hemorrhage. Animal showed partial recovery from bilateral hemiplegia.

(D) 4 days later. Further return of circulation with more extensive perivascular hemorrhages. Bilateral hemiparesis continued to improve.

(E) 5 days later. Little stasis remains. Some of the old perivascular hemorrhages have been removed but fresh perivascular hemorrhages have also occurred. Vision had returned to left visual field and moderate spastic left hemiparesis persisted.
FIG. 9. Macrophotographs taken at magnification of 13X. (A) Massive ischemic infarct 45 min. after occlusion of middle cerebral artery, showing brain swelling and collapse of capillary network. The brain is pale and cyanotic and stasis is beginning in lower portion of field. (B) Massive hemorrhagic infarct 4 hrs. after rupture and occlusion of middle cerebral artery. Brain swelling is so severe that the pial vessels became collapsed and empty because of pressure against glass window. Animal remained in stupor, with dilated pupils and periodic respiration and died 18 hrs. later.

Restoration of flow commonly resulted in recovery from the functional defect in spite of perivascular hemorrhage. Thus, commonly the hemorrhagic component of infarction progressed while function was improving. If the hemorrhagic infarction was severe enough, however, secondary worsening of the hemiplegia resulted because of brain hemorrhage and edema. Spontaneous fluctuations in the collateral blood flow were common within the first 5 days and were closely correlated with intermittent changes in the hemiplegia (Figs. 6H, I, J, 7 and 8). After 14 days the collateral circulation became more stable, functional improvement was steady.
and hemorrhages were gradually absorbed. Areas of necrosis were phagocy-
tosed by white cells and the collateral circulation was supplemented by the
regeneration of new vessels from the edge of the infarcted zone.

**Provocation of Transient Ischemic Attacks.** During the stage of recovery
from the hemiparesis and for the longest period of observation in these
experiments (9 weeks) the collateral circulation was barely able to supply
the metabolic requirements of the ischemic zone in spite of any reduced
metabolism resulting from ischemic damage. Factors that temporarily de-

![Fig. 10](image.png)

**Fig. 10.** To show absence of stasis and segmentation following occlusion of middle cerebral artery
in 2 heparinized monkeys.

(A) Macrophotograph (135X) made 4 hrs. after occlusion of middle cerebral artery with blood
pressure of 70 mm. Hg. There is cyanosis of terminal venule and capillary network is collapsed but there
is not clumping or stasis of red blood cells. Severe hemiplegia was present. Clotting time 40 sec.

(B) Macrophotograph (56X) made 24 hrs. after occlusion of middle cerebral artery. Clotting time
45 sec. At time of occlusion systolic blood pressure fell to 65 mm. Hg, but when this photograph was
made blood pressure had risen to 100 mm. Hg. In spite of marked perivenous hemorrhages no stasis
occurred.
creased the collateral circulation or increased the local metabolic demand resulted in worsening of the functional defect. For example, repeated episodes of hemiplegia of 1–3 days’ duration were induced by reduction of the blood pressure to 50–70 mm. of mercury for 10–20 minutes in animals that had recovered from occlusion of the middle cerebral artery. During these attacks, the pial circulation slowed with cyanosis of the veins and collapse of the vascular network, with prompt return of collateral flow as the blood pressure increased. The longer the hypotension was maintained (20 to 80 minutes) the more severe were the resultant functional defect and stasis of the pial vessels. For example, prolonged reduction in blood pressure below 65 mm. of mercury by the injection of 10 mg./kg. of hexamethonium or reduction of circulating blood volume produced regularly a severe hemiplegia associated with visible infarction of the cortex in the territory supplied by the occluded vessel (Figs. 3 and 4).

Anoxic anoxia produced by brief breathing of nitrogen or carbon monoxide also provoked a transient hemiplegia of 12–72 hours’ duration in animals recovered from occlusion of the middle cerebral artery (Fig. 6A, B, C). Recording of oxygen tension from the infarcted zone during breathing of nitrogen showed a slower gradient of fall than is seen in normal cortex when 100 per cent nitrogen is breathed. In some instances reinfarction was produced by the anoxia. This was particularly true of healed infarcts of 2 to 5 weeks’ duration when newly regenerated vessels are particularly prone to anoxic damage.

Postictal Paralysis. Four of the animals in this series of experiments were observed to have repeated localized seizures limited to the paretic side 2–21 days after occlusion of the middle cerebral artery. After the seizures subsided the degree of paralysis was worsened temporarily. In all instances there was some degree of hemorrhagic infarction visible beneath the window. Harvey and Rasmussen13,14 reported similar spontaneous seizures in several of their animals recovering from occlusion of the middle cerebral artery. In 2 animals with a mild hemiparesis caused by occlusion of the middle cerebral artery spontaneous localized seizures occurred while recording the electroencephalogram and cortical oxygen tension from the ischemic zone. Fig. 6D is a record from one of these animals showing the onset of the seizure with the appearance of high voltage spikes in the electroencephalogram and clonic twitching of the left face and limbs. There was a rapid fall of cortical oxygen tension to near zero levels (εX10–8 Amp.).2 When the seizure subsided there developed complete flaccid hemiplegia of the left side and the electroencephalogram showed high voltage slowing. The cortical oxygen tension gradually increased over the ensuing 10 minutes, the electroencephalogram became more nearly normal, and strength of the left side was equal to that present prior to the seizure. In an additional animal focal seizures with consequent worsening of the hemiparesis were provoked by the administration of Metrazol by injection.

Effect of Administration of Anticoagulant Drugs. The administration of
heparin or Dicumarol prior to occlusion of the middle cerebral artery prevented the development of stasis or clumping of red cells within the ischemic zone in every instance (Fig. 10A, B). In one instance the systolic blood pressure was lowered to 20 mm. Hg without producing stasis. There was not any significant difference in the size of the infarcts in either the anticoagulated or control group but the survival rate was greater in the anticoagulated group and if recovery occurred it was frequently more rapid than in the control group. The infarcts in the anticoagulated group were more hemorrhagic than in the control group, similar to the observations reported by Whysnant in 1957.

The production of transient ischemic attacks after recovery from the hemiplegia by anemically and chemically induced hypotension or by breathing of nitrogen was rendered more difficult in the anticoagulated group and the duration of the functional defect, if it could be provoked, was significantly shorter (1/2–3 hours) than in the control group (1–3 days). Furthermore, in none of the anticoagulated group was stasis or infarction produced by hypotension or anoxia.

**DISCUSSION**

Occlusion of the main trunk of the middle cerebral artery in the monkey produces regularly a contralateral motor and sensory defect because of ischemic anoxia, the severity of which depends upon the functional adequacy of the collateral circulation derived principally from arterio-arterial anastomoses in the cortex. As observed by others the severity of the hemiplegia bears a close relationship to the level of the systolic blood pressure at the time of occlusion; if it falls below 70 mm. Hg a severe hemiplegia with a persistent neurological defect follows regularly. Daily observations of the cortical vessels reveal that the collateral circulation fails if the blood pressure is not maintained, with resulting infarction of the cortex visible in the living animal.

If the blood pressure is well maintained the collateral circulation is barely sufficient to meet the metabolic demands necessary for survival of tissue within the first 8 hours and is not sufficient to maintain normal neuronal function, resulting in contralateral motor and sensory paralysis of variable degree. During this phase there is inadequate supply of oxygen as shown by the blue-black appearance of the veins and the low cortical oxygen tension, but the ischemic anoxia usually is not sufficient in degree to produce damage to the vascular endothelium with consequent intravascular clumping of red blood cells. This state of impaired circulation persists for 4 to 8 hours; thereafter, during the ensuing 24–48 hours there is a striking hyperemia of the previously ischemic zone caused by increased rate of flow in the cortical capillaries, many of which become visible for the first time. The entire vascular network is congested and the arterio-arterial anastomoses are widely dilated. At this stage, the dilated vessels can be caused to narrow in response to increase of blood pressure, for example by the intra-
venous injection of adrenalin (Fig. 5). This confirms the important role played by reduced intraluminal pressure in the dilatation of these arterial anastomoses. The consequent rise in blood pressure results in rapid localized constriction of the dilated arterio-arterial communications, later followed by dilatation again as the blood pressure returns to normal levels.

If the collateral circulation fails because of a fall in blood pressure or the application of clips to important collateral vessels, the ischemic anoxia is of sufficient degree to damage the endothelium of vessels, resulting in intravascular stasis beginning at small points in the capillary network with consequent increase in local cerebrovascular resistance. At this time the cortical oxygen is near zero levels. The endothelial damage results in the extravasation of the fluid constituents of the blood resulting in edema of the brain visible through the window. The increased vascular permeability reaches a maximum 48–72 hours after occlusion and the intravenous injection of trypan blue at this time results in a localized, intense blue staining of the brain substance with the dye. The increased vascular permeability also results in diapedesis of red cells and if the vascular damage is severe enough rupture occurs with the development of perivascular ball-hemorrhages (Fig. SC). Stasis frequently continues to progress until the fourth day, although the process may be intermittent because of fluctuations in an unstable collateral circulation. Improved collateral blood flow results in slow movement of previously static clumps of red cells to zones of normal flow where the clumps disintegrate and normal flow is restored, frequently resulting in vascular rupture and hemorrhage. If stasis persists beyond the fourth day the vessel and its static content of red cells are phagocytosed by white cells.

After the second day patchy infarction of the cortex with softening becomes recognizable in the living animal. Microscopic examination of cortex shows that clouds of white cells derived from remaining intact vessels invade the area of necrosis (Fig. 3D). The clouds of white cells rapidly ingest necrotic brain and extravasated red cells and assume a granular yellow or golden-brown appearance. The stuffed histiocytes then migrate back to vessels and re-enter the blood stream. Detailed descriptions of changes in the properties of circulating elements in the blood occurring in the ischemic zone have been published recently and neuropathological studies will be reported subsequently. Commonly fluctuations in the severity of the hemiparesis and the degree of slow activity present in the electroencephalogram correspond to variations in the collateral circulation.

Proliferation of capillaries at the edge of the infarct progresses rapidly and their differentiation into arterioles and venules provide additional collateral circulation. For the first week after their appearance these new vessels are friable and rupture easily with consequent hemorrhage. The revascularized edge of the infarct has a high oxygen tension whereas the necrotic center usually has a low oxygen tension.

After the second week the collateral circulation becomes more stable. Up to this point it is clear from the appearance of the brain, the measure-
ments of oxygen tension and the recovery of the electroencephalogram that much of the functional improvement is the result of restoration of neuronal function temporarily impaired but not destroyed by ischemia. Thereafter, any further slow improvement is presumably ascribable to reorganization of function within a permanently damaged nervous system.

The transient ischemic attacks provoked in the recovered animal by anoxic anoxia, by reduction of blood pressure and by epileptic attacks appear to have a common mechanism in that they all tend to decompensate a tenuous balance between the supply of oxygen derived from the collateral circulation and the metabolic requirement of the ischemic area. Any measure that temporarily decreases the collateral blood flow or increases the local metabolic requirement results in failure of the local supply to meet the demand of the tissue, with resulting temporary functional impairment. These data amplify and confirm the experiments of Corday et al. concerning the role of hypotension in the production of transient ischemic attacks.

These authors produced electroencephalographic changes in the distribution of an occluded internal carotid artery in the monkey by lowering the blood pressure.

The Nature and Significance of Hemorrhagic Infarction. Direct observations reported here show that hemorrhagic infarction is the result of re-establishment of blood flow in vessels damaged by ischemic anoxia and that this process of hemorrhagic infarction may progress while function improves. Thus, hemorrhagic infarction indicates that at some time there has been improvement in the collateral circulation whereas a “pale” infarct represents failure of the collateral circulation. Microscopic observation in the living brain emphasizes that the division between “pale” and hemorrhagic infarcts is an arbitrary one since microscopic hemorrhages are common in “pale” infarcts.

Thus, anticoagulant drugs that prevent stasis increase the return of blood to ischemic zones via the collateral circulation. If the zone is already infarcted there results a greater degree of hemorrhagic infarction without functional improvement. If the ischemia is less severe, for example, in the experimental production of transient ischemic attacks by hypotension or anoxia, the prevention of stasis by anticoagulant drugs improves collateral circulation. As a result, transient failure of the collateral circulation is harder to provoke in the anticoagulated preparation but, once provoked, recovery is more rapid than in similar preparations not treated with anticoagulant drugs.

SUMMARY

Occlusion of the middle cerebral artery in the monkey results in a functional deficit ranging from transient hemiparesis with recovery to severe and persistent hemiplegia. Lowering the systolic blood pressure below 70 mm. Hg or occlusion of principal collateral vessels in addition to occluding the middle cerebral artery consistently produces severe hemiplegia. Ac-
companying vascular changes are visible through a skull window placed in the distribution of the middle cerebral artery. Transient hemiplegia is accompanied by cyanosis of the pial vessels with slowing of flow but rapid restoration of pial circulation by collateral vessels. Severe hemiplegia results when the collateral circulation fails and there develop clumping, segmentation and stasis of red cells within vessels. Ischemic anoxia produces damage to the endothelium of the vessels and edema. Restoration of blood flow to damaged vessels results in perivascular hemorrhages. Heparin and Dicumarol prevent stasis in the collateral vessels.

In the animal recovered from occlusion of the middle cerebral artery transient hemiplegia may be provoked either by reduction of the systolic blood pressure, resulting in temporary collapse of the collateral circulation, or by anoxic anoxia or by increased neuronal consumption of oxygen consequent upon convulsive activity originating in the ischemic zone. Heparin and Dicumarol render production of transient hemiplegia by these methods more difficult.

REFERENCES
EFFECTS OF OCCLUSION OF MIDDLE CEREBRAL ARTERY


