The Distribution and Density of Reduced Cerebral Blood Flow Following Acute Middle Cerebral Artery Occlusion: An Experimental Study by the Technique of Hydrogen Clearance in Baboons

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Abstract: The effect of middle cerebral arterial occlusion on blood flow over the parietal aspect of the cortex and in the putamen of baboons has been assessed by the technique of hydrogen clearance. Reduction of blood flow was present over the entire lateral aspect of the cerebral hemisphere, maximal in the regions of frontal, parietal and temporal opercula where the blood flow was reduced to some 25% of control levels, and in the deep nuclei where the average flow in three animals was 20%. Reactivity to carbon dioxide was correspondingly reduced and, indeed, paradoxical reactivity or intracerebral steal was found in the most densely ischemic opercular zone. There was no evidence in the present studies of any area with increased tissue blood flow following middle cerebral occlusion.

Under control conditions, some inhomogeneity of blood flow was evident in the cortical areas studied, the parietal association areas having a significantly lower blood flow than the more anterior regions of the hemisphere.

Additional Key Words: middle cerebral occlusion, inhomogeneity of hemispheric blood flow, gradation of ischemia, intracerebral steal

Occlusion of the middle cerebral artery has been used by numerous investigators over many years, as a model for the production of an acute stroke in a wide variety of species. In the normotensive primate, acute middle cerebral occlusion produces a clinical stroke, the neurological deficit varying from a mild parietal sensory loss, joint position sense loss, and loss of finger facility in the arm and hand, often associated with inattentive hemianopia, to dense hemiparesis with virtually complete loss of function in the face and arm. The leg is much less affected and the animal is invariably mobile after the stroke. The variability of the clinical deficit produced by middle cerebral occlusion is well recognized, and it is probable that the two factors most involved in this variability are the variation in collateral potential from animal to animal — a relatively minor factor — and, more important, the variation from one experimental model to another in the degree of involvement of the perforating branches, occlusion of which produces a dense ischemic lesion in the basal ganglia and internal capsule. Perfusion studies have demonstrated that the area of ischemia produced by middle cerebral occlusion in the monkey or dog is quite similar to that produced by acute middle cerebral obstruction, thrombosis, or embolization in man. The areas most densely involved are the Sylvian opercula and, provided the perforating arteries have been occluded by insult, the putamen and lentiform nucleus in the basal ganglia. Infarction over the lateral aspect of the hemisphere in the parietal and frontal distributions of the middle cerebral artery is scarcely apparent — a demonstration of the notable collateral potential in the healthy primate.

The reliability of middle cerebral occlusion in producing an ischemic zone has resulted in the use of this model in a wide variety of metabolic and blood flow studies. However, it is by no means clear to what extent the reduction in blood flow over the lateral aspect of the hemisphere is homogenous. In recent years, regional blood flow investigations using the inert gas tracer techniques in man have shown appreciable variation in the normal cerebral hemisphere.
Methods

Thirteen baboons (*Papio cynocephalus*) of either sex in the weight range 10 to 15 kg were used in this study. The animals were tranquilized with phencyclidine intramuscularly and anesthesia was induced with a sleep dose of thiopentone IV. They were then intubated, and continuously ventilated with a Starling pump at a constant stroke volume to maintain a normal arterial PCO2 in the region of 40 mm Hg and not outside the range 38 to 43 mm Hg. Anesthesia was maintained with IV alpha chloralose (60 mg per kilogram). The animals were immobilized with gallamine triethiodide (1 mg per kilogram IV), repeated as necessary. In three prepararations, electrodes were introduced stereotactically into the putamen after fixation of the head in a Narashigi stereotactic apparatus (Model S.N.3), and electrodes also were introduced obliquely into the frontal and parietal cortex through twist drillholes in the skull. In the other ten animals, the brain was covered by a paraffin pool and multiple electrodes inserted into the cortex of the middle cerebral field in the approximate distribution shown in figure 1. The electrodes used in these preparations were constructed so that about 1 mm bared platinum with the standard diameter of 0.3 mm and tapering to a sharp point protruded from a ball of acrylic, thus preventing the electrode from transgressing the cortex. In each experiment one electrode 4 mm long was placed, the terminal 1 mm only being bare of insulation, so that a white matter recording was obtained usually from the postfrontal zone. Electrodes were allowed to stabilize for a period of one-half hour before recordings were made, according to the technique previously described.17

The middle cerebral artery was occluded by subtemporal dissection in nine experiments, and by a separate transorbital dissection in four. There was no significant difference in the pattern of ischemia produced by occlusion in these two methods of approach, and it appears, therefore, that a careful subtemporal approach does not produce significant damage to the temporal lobe.

Each episode of hydrogen clearance was measured after a period of 4 to 7 minutes' inhalation of 7% to 10% hydrogen, and the clearance was pursued over 15 minutes after inhalation had stopped. The first 40 seconds of each postinhalation period was discarded to eliminate arterial recirculation problems.17 Two control clearances were taken at the start of each experiment, followed by an assessment of the reactivity of the circulation to CO2, arterial PCO2 being raised from control levels by the inhalation of 7% CO2. The middle cerebral artery then was occluded during a period of hydrogen saturation, and an immediate postocclusion flow recorded. Further flows were taken at one-half hour and one hour following occlusion, and CO2 reactivity then was assessed by further flow during the inhalation of 7% CO2. The basic CO2 reactivity was regarded as an essential check on the functional integrity of the cerebral circulation in the preparation.

The output of the electrodes was carried through the amplifier system previously described19 and displayed on a Rikadenki four-channel pen recorder catering for eight electrodes by a channel-sharing multiplex technique. Systemic blood pressure was recorded from a femoro-aortic catheter by means of a Statham P23 G arterial gauge, central venous pressure was recorded from the right atrium by means of a catheter introduced from the femoral vein connected to a Statham P23 BB or P23 V venous gauge, and end-tidal CO2 was continuously monitored from the endotracheal tube via
DISTRIBUTION AND DENSITY OF REDUCED CBF

an infrared gas analyzer (Beckman Model LBI). The output from these transducers was displayed on a Beckman Type R chart recorder. Linked event markers permitted synchronization of data on the two recorders.

TECHNIQUES OF CLEARANCE ANALYSIS

The basic characteristics of the hydrogen clearances obtained by our technique have been described. In the present group of experiments, no attempt was made to fractionate fast and slow components; instead, a two-minute initial clearance was taken from the first 40 seconds onward. In previous experiments, about 40% of cortical electrodes in normally perfused cortex showed monoexponential clearance, while in the remainder, clearance was biexponential. The fast component of the biexponential curve, when extracted, corresponded to the figures obtained from those electrodes recording monoexponentially. In the current experiments, however, possibly because of a change in electrode design so that the electrodes could more confidently be regarded as entirely within cortex, we found that the proportion of electrodes recording monoexponentially rose to 36% under conditions of normal perfusion. Further, following the establishment of an ischemic zone, even electrodes which had previously recorded biexponentially tended to revert to a monoexponential clearance. Thus, in the region of the opercula (Zone A of fig. 2), in the electrodes which had cleared biexponentially under control conditions, some 38% of the total, two-thirds cleared monoexponentially following middle cerebral clip. In the intermediate zone (Zone B of fig. 2), of 44% which had recorded biexponentially, three-quarters became monoexponential after clipping and only one electrode changed in the reverse direction. We therefore found it impossible to compare a biexponential clearance before occlusion with the single postocclusive monoexponential, and considered it theoretically more valid, therefore, to use the "flow initial" technique of Lassen.

The analysis of postocclusive flows presented a further problem in that saturation recorded from electrodes in an ischemic zone was a great deal slower than under normal circumstances. Indeed, those areas where the ischemia was dense would continue to saturate for some time after the inhalation had been discontinued, while normal areas in the periphery of the hemisphere had already established a rapid clearance. The explanation of this may be, in part, the arrival of delayed flow in the areas of ischemia from the anterior and posterior cerebral collaterals, as demonstrated by Symon using a technique of radioactive red cell injection after middle cerebral occlusion. Figure 3, which is reproduced from this earlier work, clearly displays the late arrival of counts in an ischemic zone which, under the circumstances of hydrogen clearance, would result in continued saturation in the area of ischemia, while the normally perfused cortex had already established a rapid clearance. The establishment of a clearance, therefore, in the slowly saturating areas of the infarct had to be judged by eye, and this was made considerably easier by the fact that these electrodes invariably showed a monoexponential clearance. Under these circumstances, therefore, flow was assessed in the infarct by awaiting the establishment of a monoexponential slope, although this might be several minutes after the discontinuance of hydrogen inhalation. Curves demonstrating this phenomenon are shown in figure 4.

Clearance curves taken from hydrogen clearance initiated immediately following middle cerebral clip by the transorbital route. Clearance curves 4 and 2 show an early increase in the flow within a few minutes of middle cerebral occlusion, curve 4 increasing from an immediate post-clip flow of 14 ml/100 gm per minute to one of 49.5 ml/100 gm per minute, and curve 2 from 3.0 ml/100 gm per minute to 11.0 ml/100 gm per minute. Flows in curves 1 and 3 are 10 and 12 ml/100 gm per minute, respectively.

FIGURE 2

Traces of radioactivity from a Geiger counter located within the cortex of the middle cerebral arterial field in a macaque monkey. (a) A direct carotid injection of radioactive labeled red cells was made with the circulation intact. (b) The injection was made after the middle cerebral artery had been occluded. (c) A n injection of twice the activity and twice the volume of radioactive red cells was made into the vertebrobasilar system. The time marker is five seconds. It will be seen that the arrival of the counts is spread out after vertebrobasilar injection and counts continue to arrive up to 20 to 30 seconds after the injection. (Reproduced with permission from The Journal of Physiology, 159, 1961.)
A total of 81 placements in the 13 animals was analyzed. As Leniger-Follert and Lubbers have shown, the fine resolution of the hydrogen electrode methodology carries the disadvantage that there is appreciable variability between the basal blood flow recordings from one electrode and another in its immediate vicinity. This relates to variation in capillary blood flow within an area of brain. Such variation is evened out by the use of larger electrodes than those of Lubbers, which were used in the present study, or by a regionalization of a less exact nature, as in the techniques of Xenon flow by lithium drift semiconductor detectors. In the analysis of the present results, however, the cortical electrode placements were combined into four major zones. The position of these zones is shown in figure 2. Zone A comprised electrodes in the immediate region of the lips of the Sylvian fissure, in frontal, parietal and temporal opercula; Zone B those in an intermediate zone in the hemisphere; Zone C those in the parasagittal region, that is, the territory which would be expected to be more commonly supplied by the anterior cerebral artery or to be in the immediate watershed zone between anterior and middle cerebrials; and Zone D those in the parieto-occipital region in the watershed between middle and posterior cerebral arterial distributions.

Basal blood flow in Zones A, B and C were approximately the same (fig. 5a). Thus, Zone A had a basal blood flow (two-minute clearance) of 48.2 ml/100 gm per minute (SD ± 12.0). The blood flow in Zone B under basal conditions was 54.4 ml/100 gm per minute (SD ± 19.0), and in Zone C the basal blood flow was 52.5 ml/100 gm per minute (SD ± 16.5). These figures were not significantly different from one another. Zone D, however, comprising the parieto-occipital association cortex, had a basal blood flow of 40.1 ml/100 gm per minute (SD ± 14.0), this figure being significantly different from the flows in Zone B at the level of P < 0.01 or Zone C (P < 0.02). Therefore, it is apparent, using this fairly crude technique of regionalization, that the inhomogeneity of basal flows, characteristic of the inhomogeneity of basal flows, characteristic of human regional cerebral blood flow investigations, applies also to the anesthetized experimental primate. The data distribution for basal blood flows in the animals studied is shown in table 1.

### Table 1

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Zone A</th>
<th>Zone B</th>
<th>Zone C</th>
<th>Zone D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (N = 10)</td>
<td>54.4 ± 19.0</td>
<td>52.5 ± 16.5</td>
<td>40.1 ± 14.0</td>
<td>35.3 ± 12.0</td>
</tr>
<tr>
<td>SD</td>
<td>12.0</td>
<td>19.0</td>
<td>16.5</td>
<td>14.0</td>
</tr>
<tr>
<td>Level of significance (P)</td>
<td>&gt; 0.6</td>
<td>&lt; 0.02</td>
<td>&lt; 0.01</td>
<td>&gt; 0.1</td>
</tr>
</tbody>
</table>

Each figure in this and subsequent tables is a mean value for the electrodes in that zone in one particular experiment.

### BASIC CO₂ REACTIVITY

Basic CO₂ reactivity (fig. 5b) was used as a test of the functional integrity of the circulation, and defined as the percent change from basal flow in response to a CO₂ elevation of 27 mm Hg (SD ± 4.5). It was substantially similar in all areas studied, although Zone A, as table 2 demonstrates,

### Table 2

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Zone A</th>
<th>Zone B</th>
<th>Zone C</th>
<th>Zone D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (N = 7)</td>
<td>153.3</td>
<td>120.5</td>
<td>108.3</td>
<td>177.6</td>
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<tr>
<td>SD</td>
<td>109.8</td>
<td>133.0</td>
<td>102.9</td>
<td>132.1</td>
</tr>
<tr>
<td>Level of significance (P)</td>
<td>&gt; 0.8</td>
<td>&gt; 0.7</td>
<td>&gt; 0.01</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

The clearance curves from three electrodes after middle cerebral occlusion. Clearance curve 3 is from an electrode in Zone C substantially unaffected by occlusion, the flow being 35 ml/100 gm per minute. Electrodes 1 and 2 are in zones affected appreciably by occlusion, the delayed saturation is evident in both curves and the final flow clearances (two minutes) are 8 and 11.5 ml/100 gm per minute, respectively.
DISTRIBUTION AND DENSITY OF REDUCED CBF

had a significantly greater reactivity (156% ± 46.3) than Zone B where the reactivity was 116.5% (± 26.9) at the P < 0.05 level. Zone A also was significantly different from Zone C where the reactivity was 119.5% (SD ± 33.6) at the P < 0.02 level. The other areas were not significantly different from one another. Thus, there was an increase of

FIGURE 5

These panels show: (a) basal flows in milliliters per 100 gm per minute, (b) CO₂ reactivity in percent increase over basal flow at the time of the first CO₂ reactivity test, (c) blood flow immediately following middle cerebral occlusion expressed as percent of basal preocclusive flow, (d) the alteration in immediate postocclusive flow over the subsequent one hour, expressed as percent change of immediate postocclusive flow, and (e) CO₂ reactivity following middle cerebral occlusion, expressed as percent increase of the one hour postocclusive flow. In each of the panels standard deviations are given. N represents the number of animals in each observation, n the number of electrodes from which the data were derived.
over 100% of basal flow in the four zones in the seven animals studied, and CO₂ reactivity per millimeter. P<.005, change was 5.8% in Zone A, 4.3% in Zone B, 4.4% in Zone C, and 4.7% in Zone D.

**THE EFFECT OF MIDDLE CEREBRAL ARTERIAL OCCLUSION — CORTICAL ELECTRODES**

In the ten animals in which multiple recordings of cortical electrode placements were made, a total of 77 electrodes gave satisfactory recording in the four zones over controlled periods at the time of middle cerebral occlusion. Middle cerebral occlusion was performed during full saturation with hydrogen, and flow determined within a few minutes of the application of the middle cerebral clip. There was an immediate decline in flow after occlusion, and reduction in blood flow was detectable over the entire exposed hemispheric surface. The data for the experiments are given in table 3 and the topographical distribution of the reduction in blood flow shown in figure 5c.

Blood flow was found to be reduced maximally in the immediate ipsilateral to the Sylvian fissure, where some electrodes recorded levels of down to 10% basal flow. Zone A as a whole showed a decline in blood flow to 26.1% basal (SD ± 10.9). In Zone B, the middle zone of the middle cerebral arterial field on the lateral hemispheric surface, there was a variable decline in blood flow from zone levels to the Zone A border to near basal values in the upper part of Zone B, the area as a whole having an average blood flow of 41.9% basal (SD ± 20.4). This was significantly different from the opercular Zone A at a level of P < 0.05. In Zone C, the high collateral region of the hemisphere, a number of electrode placements gave flow values after middle cerebral occlusion which were greater than basal, although none of the increases from basal level were significant. The mean flow in this area did, in fact, show a reduction following arterial occlusion, the level reached being 84.6% basal flow (SD ± 28.2). Flows in Zone C were significantly different from Zones A and B at the P < 0.001 level, and from Zone D at the P < 0.03 level. The parieto-occipital association areas in the border zone between middle and posterior cerebral territories (Zone D) also showed a decline in tissue flow, the variation here being between 45% and 94% of basal flow. Zone D's average being 56.2 (SD ± 19.3). This was significantly different from Zone A (P < 0.005) and from Zone C (P < 0.03) but not significantly different from Zone B (P < 0.15).

The data, therefore, indicated a highly significant fall in flow from basal values after occlusion in Zones A, B and D (P < 0.001). The fall in Zone C, however, was not statistically significant as compared with basal values (P > 0.1).

**DEEP ELECTRODES**

In this present group of experiments there were only three putaminal electrode placements. They showed an immediate reduction in flow following middle cerebral occlusion, the values in the three experiments being 26%, 12%, and 16% of basal flow. The average level of blood flow over the group therefore was 19% of basal flow, which compares closely with the levels reached in the area of maximum ischemia in the opercular zones, where the level was 26.1% of basal.

**THE BEHAVIOR OF FLOW PATTERNS IN THE PERIOD FOLLOWING OCCLUSION**

One of the advantages of the hydrogen clearance technique is that where monoexponential flows have been established, a sudden change in flow (particularly in the direction of an increased flow) may be confidently detected from an alteration in the slope of an already established clearance curve. This advantage of the method permitted the detection of an increase in flow recorded by electrodes inside the fairly densely ischemic Zone A, within a few minutes of middle cerebral occlusion, in several instances in the present series, as shown in figure 2. This phenomenon, which was not common, was not thereafter progressive, and flow values at 30 minutes and one hour following occlusion showed no significant change from those closely subsequent to the clip (fig. 5d). The detailed data used for the construction of this figure are shown in table 4. In Zones A, B and C, mean flow values were within 5% of the immediate postocclusion level, although slightly higher in each case. In Zone D, the mean change from the immediate postocclusion level was a slight decline, but once again this was not significant. Thus, there was no evidence in the present experiments of significant change from flow levels immediately following the occlusion, although in a number of instances there was a suggestion that an increase in the very low postocclusive blood flow might occur within a few minutes of occlusion and thereafter remain unchanged over a period of one hour.

**CHANGES IN CO₂ REACTIVITY INDUCED BY THE ESTABLISHMENT OF A FRESH ISCHEMIC LESION**

At the end of one and one-half hours following the establishment of an acute ischemic zone from application of the middle cerebral clip, the CO₂ reactivity was again tested to an elevation of P<.001, of similar extent to that of the control CO₂ reactivity test. The CO₂ change in the second test was 26.4 mm Hg (SD ± 5.6). CO₂ reactivity was found to be appreciably reduced in all areas (fig. 5c). Zone C (the collateral zone of the hemisphere close to the anterior cerebral...
TABLE 4
Change in Local Cerebral Blood Flow Values at the End of One Hour After Middle Cerebral Occlusion

<table>
<thead>
<tr>
<th>Experiment no.</th>
<th>Zone</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
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<tbody>
<tr>
<td>1</td>
<td>22.0</td>
<td>1.3</td>
<td>13.2</td>
<td>24.1</td>
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</tr>
<tr>
<td>2</td>
<td>7.1</td>
<td>7.4</td>
<td>-9.6</td>
<td>-1.6</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2.2</td>
<td>-0.9</td>
<td>-1.8</td>
<td>-17.2</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4.3</td>
<td>2.9</td>
<td>22.1</td>
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<td></td>
</tr>
<tr>
<td>6</td>
<td>9.3</td>
<td>8.5</td>
<td>18.8</td>
<td>6.3</td>
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</tr>
<tr>
<td>7</td>
<td>0.6</td>
<td>4.7</td>
<td>0.0</td>
<td>4.9</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>-2.2</td>
<td>6.8</td>
<td>11.7</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>-10.7</td>
<td>5.4</td>
<td>-25.5</td>
<td>-30.2</td>
<td></td>
</tr>
<tr>
<td>Mean (N = 8)</td>
<td>4.1</td>
<td>3.2</td>
<td>3.6</td>
<td>-0.3</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>8.9</td>
<td>4.4</td>
<td>15.0</td>
<td>15.5</td>
<td></td>
</tr>
</tbody>
</table>

Each figure is the difference between one hour postocclusive flow values and those immediately after clip, both expressed as a percentage of basal flow.

territory) most closely approximated normal; but, although control CO₂ reactivity had been more than 100% increase in flow, the flow increase following middle cerebral occlusion to a similar elevation of Pco₂ was only 84.7% (SD ± 36.7) compared with the one-hour postocclusive flow values, as detailed in table 5. All other areas showed a very much lower CO₂ reactivity, varying from 8.5% in Zone B to 9.7% in Zone D. In Zone A, indeed, there was a decrease in flow of 20.8% (SD ± 10.9) compared with flow levels during occlusion, the flow increase following middle cerebral occlusion, although individual detectors in Zone C might show an increase not outside the variability of the method. This is in contrast to the demonstration by Wilkinson et al.13 and by Herrschaft and his colleagues23 of inhomogeneity of regional cerebral blood flow over the surface of the primate hemisphere. This, most evident in Wilkinson's work in unanesthetized patients, also was evident24 to a lesser extent in studies under anesthesia. It is by no means clear why experimental baboons anesthetized with alpha chloralose should show a significantly lower blood flow in the parieto-occipital association areas than in the remainder of the hemispherical surface, and it would be particularly interesting to study the distribution of these inhomogeneities in animals under different types of anesthesia. It also is of interest that there was a gradient of flow under basal conditions between areas A, B and C, although these did not reach significant levels, higher flows being present in the parasagittal zone than in the temporal region. This again parallels the findings in humans; for example, Ingvar25 reported low blood flow in the temporal zone, as did Wilkinson et al.13.

The effect of middle cerebral occlusion on blood flow over the convexity of the cerebral hemisphere, in the current experiments, showed a gradation of reduction in flow, maximal in the immediate lips of the Sylvian fissure, that is, the frontal parietal and temporal opercula, and decreasing in intensity as the midline was approached. In these experiments, however, even the immediate parasagittal zone — an area normally supplied by the anterior cerebral artery in the baboon — showed a reduction in tissue flow, although this did not reach significant levels. None of the four zones showed an increase in tissue flow following middle cerebral occlusion, although individual detectors in Zone C might show an increase not outside the variability of the method. This is in contrast to the demonstration by Wilkinson et al.13 and by Herrschaft and his colleagues23 of inhomogeneity of regional cerebral blood flow over the surface of the primate hemisphere. This, most evident in Wilkinson's work in unanesthetized patients, also was evident24 to a lesser extent in studies under anesthesia.

The capacity of the hydrogen method to make multipoint recordings of flow in the relatively small brain of the experimental primate has in current experiments yielded information of interest which is in many ways comparable to that obtained by the technique of Xenon clearance in the much larger brain of the human subject. The current demonstration, for example, that flow under basal conditions in these experimental animals was not homogenous, has a parallel in the demonstration by Wilkinson et al.13 and by Herrschaft and his colleagues23 of inhomogeneity of regional cerebral blood flow over the surface of the primate hemisphere. This, most evident in Wilkinson's work in unanesthetized patients, also was evident24 to a lesser extent in studies under anesthesia.
establishment of an ischemic zone producing a rapid redistribution of blood by the pial network, and a slower seepage of blood into the ischemic zone by direct capillary continuity resulting, therefore, in an overall gradient of ischemia from the most dense to the less affected regions. Although assessment of flow in the deep nuclei was made in only a few experiments in the current series, these indicated that the sensitivity of the deep nuclei in the middle cerebral field to middle cerebral occlusion was comparable to that of the cortex in the most densely ischemic zones. Thus, flow declined to somewhere about 20% of basal levels compared to 25% of basal levels reached after occlusion in the most densely ischemic zone, Zone A.

There was no significant increase in blood flow from the immediate posts ischemic levels over the period of one hour following occlusion. It seems clear that the ischemic zone established by such occlusion is only slowly modified in experimental primates. This observation is in keeping with changes noted in intraarterial pressure in the pial network observed some years ago27 in monkeys, in which no recovery of intravascular pressure could be detected up to one hour following middle cerebral occlusion. It is of note, however, that detectable recovery of such pressure was evident in the dog under similar circumstances. It also is of interest that in a few recordings in the present series, where saturation was continued up to the moment of the application of a clip after which desaturation was started, there was some evidence of an early increase in flow. This increase occurred about three to four minutes after the ischemia (fig. 2) and was detected, as described earlier, from alteration in the slope of an already established monoexponential clearance. The time course of this slight but definite increase in flow in the most densely ischemic zone parallels closely the recovery of middle cerebral arterial pressure which was noted in the dog, and it may well be that this represents the opening up of collateral flow with a corresponding slight modification of clearance in the area of some electrodes, at least in the densely ischemic zone.

CO₂ reactivity in basal circumstances in the present experiments was high, between 4% and 5% per mm Hg CO₂ change in all areas. This is no doubt a reflection of the excellent condition of the superficial circulation in the primate cortex covered with warm mineral oil. Despite differences in the four areas in basal flow, there was little evidence of significantly different reactivity; indeed, flows under the influence of a CO₂ stimulus showed a tendency toward homogenization, although the reactivity was significantly higher in the relatively lower flow Zone A than in Zones B and C.

The pattern of CO₂ reactivity following occlusion also was of interest, particularly in the occurrence and distribution of steal phenomena. Although it appeared at the time of the Lund Conference (1968) that this phenomenon had reached universal acceptance, considerable debate has continued as to the significance of the phenomenon, and its occurrence in various reports has varied widely. Thus, Yamamoto and colleagues28 in experiments on the dog claimed that steals did not occur, while evidence suggesting steal has been presented by numerous other workers.29-31 It has always seemed likely30 that the steal phenomenon was characteristic of a fairly densely ischemic zone, and such a contention has been borne out by the results of the present group of experiments. Although CO₂ reactivity was markedly reduced over the entire hemisphere following the establishment of the acute ischemic zone following middle cerebral occlusion, the reduction of CO₂ reactivity showed a gradation similar to that of the reduction in basal blood flow. Thus, CO₂ reactivity was reduced to its greatest extent in the region of the opercula, and least in the areas which preserved blood flow most nearly approximating normal. Only in Zone A did steal occur at all frequently. It still seems likely, therefore, that the explanation for steal is the competition for a finite input flow among areas of peripheral resistance which have lost their CO₂ reactivity in varying degrees. The hydrodynamic analogy is one of a finite fluid flow into a number of variable peripheral resistances connected in parallel with one another. The flow input cannot be increased, because of maximal afferent vessel dilatation, and so resistance changes in the areas distal to this fixed afferent input must result in a volume redistribution of blood which will be unfavorable to that area of the peripheral circulation which cannot decrease its resistance pari passu with its neighbors. The area of maximal ischemia, therefore, completely vasodilated and without CO₂ reactivity, will bleed into the neighboring areas where CO₂ reactivity has been retained. The electrical analogy, frequently adduced to refute the theoretical basis of steal phenomena, is that in which two electrical resistances in parallel are placed within a circuit and current measured through either, with its fellow in or out of the circuit. Under these particular circumstances, of course, the presence of the second resistance parallel in the circuit makes no difference to the current flowing through the primary resistance. The analogy is inapplicable in the hydrodynamic situation since it assumes an input flow (or voltage source) capable of infinite increase, unlikely in the circumstances of the stressed cerebral circulation. The steal phenomenon in the present experiments was observed only in electrodes where the reduction in blood flow was to less than 40% of basal levels.

Experiments carried out in parallel with those reported here, in which evoked responses were obtained at various points in the somatosensory cortex as a result of sensory stimulation, demonstrated that the steal phenomenon could be associated with abolition of an evoked response which had gradually
DISTRIBUTION AND DENSITY OF REDUCED CBF

recovered after ischemia. These experiments, which will be reported in detail elsewhere, demonstrate that the phenomenon of steal may have an important functional correlate.

The implications of the present experiments for experimental cerebrovascular research are clear. The distribution of pathological change following middle cerebral occlusion could be predicted as most likely in the basal ganglia and in the opercular zones, and such is indeed the case in identical animals maintained for a period of up to three years following experimental middle cerebral occlusion. Also, it is clear that where surface electrodes are used to assess the function of tissue or of metabolic fractions following middle cerebral occlusion, detailed focal blood flow recordings must be made in relation to such electrodes, since the degrees of ischemia produced at various points over the lateral aspect of the hemisphere cannot be assumed to be similar. The occurrence of steal following vasodilatation emphasizes once more the inad-

visability of vasodilator therapy in the acute phase of stroke, and the occurrence of this phenomenon only in fairly dense areas of ischemia probably explains the failure of certain experimental designs to demonstrate the phenomenon. If a sufficiently dense ischemic zone is not produced by the experiment in question, steal will not occur. Further, if the blood flow is effectively averaged over a very wide area as, for example, in the techniques using large Xenon detectors in the small experimental animal brain, then the steal phenomenon will be averaged out and is unlikely to be seen.

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