Blood Coagulation and Plasma Fibrinolytic Enzyme System Pathophysiology in Stroke

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SUMMARY Plasma fibrinogen chromatography is a method for quantification of high molecular weight fibrinogen complexes (HMWFC), native fibrinogen and other fibrinogen derivatives in plasma. Enhanced formation of fibrin, intravascular coagulation, thrombus formation, etc., are reflected by elevation of plasma HMWFC, and the method distinguishes between subjects with normal and pathological rates of fibrin formation.

Serial standard blood coagulation assays, including plasma fibrinogen chromatography, and neurological studies were performed on 220 patients admitted to a stroke unit.

Findings from patients with cerebral infarction were compared against those of three control groups: (1) normals, (2) a stroke control group and (3) a stroke risk factor group. Plasma HMWFC findings were significantly (p < 0.001) higher in the stroke risk factor group than in the normals. Plasma HMWFC values were significantly higher (p < 0.001) in the cerebral infarction patients than in any of the control groups, and plasma fibrinogen, plasminogen, alpha,-antitrypsin and alpha,-macroglobulin also were significantly higher (p < 0.001) in the patients. The greater the degree of initial neurological deficit, the greater were plasma HMWFC values (p < 0.001), and high HMWFC values were associated with poor clinical outcome.

Plasma HMWFC values were significantly higher (p < 0.001) in patients with intracerebral hemorrhage, subarachnoid hemorrhage and cerebral embolism.

These findings document the fact that a high proportion of stroke patients have coagulopathy, characterized by pathological enhancement of fibrin formation.

Introduction

IT HAS BEEN SUGGESTED that alterations in blood coagulation function either could precipitate cerebral infarction and/or influence clinical outcome in patients with this or related stroke syndromes. Largely because of the difficulty in obtaining blood coagulation data just prior to the ictus, evidence in support of the first hypothesis is largely inferential. Evidence in support of the second hypothesis is also of a less than satisfactory nature for, despite the performance of serial blood coagulation studies following the ictus and agreement that characteristic blood coagulation changes may frequently develop, e.g., increase in plasma fibrinogen, shortening of the partial thromboplastin time, alteration in thromboelastograph findings, etc., interpretation of these data in pathophysiological terms has yet to be accomplished and uncertainty has been expressed as to the significance of the findings.4

A new approach to the study of the reactions of the blood coagulation and plasma fibrinolytic enzyme system following stroke has been suggested by recent work5-11 demonstrating that in the normal subject, fibrinogen displays, as a consequence of in vivo fibrinogen catabolism, marked biophysical and biochemical heterogeneity. Further, the degree of this heterogeneity is altered in characteristic fashion by pathophysiological events (intravascular coagulation, the presence of a thrombus, fibrinolysis, fibrinogenolysis, etc.) which influence fibrinogen catabolism in vivo. Plasma "fibrinogen," the thrombin clottable moieties of plasma, is composed of three main molecular entities. Monomeric fibrinogen of 340,000 daltons is the native molecule, but its derivatives may be either of higher molecular weight (complexes), or lower molecular weight than the native molecule. High molecular weight fibrinogen complexes (molecular weights 400,000 to 1 x 10^9 daltons) are referred to hereafter as HMWFC, while derivatives of fibrinogen smaller than the parent molecule of which the most abundant in normal plasma is fibrinogen first derivative of 267,000 daltons12-13 will be referred to collectively as fibrinogen first derivative.

The proportions and/or concentration of HMWFC reflect the rate of fibrinogen catabolism via fibrin formation and the proportions and/or concentrations of fibrinogen first derivative are a measure of plasma fibrinolytic (plasminogen/plasmin) enzyme system activity. A recent study14 demonstrates that the plasma of patients with acute cerebral infarction frequently contains pathological amounts (> mean +2 SD of normal values) of HMWFC for variable time periods following infarction. Pathological increase in HMWFC has been shown to be highly correlated (p < 0.001) with evidence of enhanced fibrin formation, documented by the presence of thrombotic lesions or intravascular coagulation, in patients having other thromboembolic diseases,11 and the finding of raised plasma HMWFC in the stroke patient has suggested the presence of similar pathophysiological disturbance of the blood coagulation mechanism following stroke.

The purpose of this study has been to correlate blood coagulation findings with serial clinical assessment of neurological deficit and early clinical outcome in patients admitted to our stroke intensive care unit. Patient groups studied included those with cerebral infarction, transient cerebral ischemia, cerebral embolism, intracerebral hemorrhage and subarachnoid hemorrhage secondary to bleeding cerebral aneurysm.

The results show that pathological increase in plasma HMWFC, documenting pathologically enhanced fibrinogen/fibrin conversion, is demonstrable in the majority of patients following an ictus and that the degree and probably also the duration of this anomaly are correlated with the...
patient's initial degree of neurological deficit and also are correlated, though less certainly, with disease outcome.

Methods

Patient and Control Populations

Patients admitted to the stroke service during a three-year period with diagnoses of cerebral infarction, transient cerebral ischemia or reversible neurological deficit (n = 182), intracerebral hemorrhage (n = 21) or cerebral embolism (n = 17) were studied. Patients with subarachnoid hemorrhage secondary to ruptured cerebral aneurysm (n = 11) were studied on the neurosurgical service. Investigations included routine neurological workup, routine chemistries, chest and skull films, admission ECG, brain scans and EEGs and serial blood coagulation studies for five days following hospitalization and thereafter at less-frequent intervals. Lumbar puncture and CSF examination were not routinely performed, but in practice were used frequently for diagnostic purposes. Cerebral angiographical studies were performed only when definite indications for their use were present, but rarely during the first few days following cerebral infarction. The number of patients originally entered into the study but omitted from consideration in this report totaled 75, 36 patients because of incomplete data collection, 31 patients with cerebral infarction who received urokinase therapy, and an additional eight patients with massive cerebral venous sinus thrombosis who also received urokinase therapy. The average age of the cerebral infarction group was 65 ± 11.4 years (SD). Two percent of the patients were under age 40, 7% averaged 40 to 50 years, 26% averaged 50 to 60 years, 27% averaged 60 to 70 years, 32% averaged 70 to 80 years and 7% were more than 80 years.

Data from patients with acute cerebrovascular disease were compared against those obtained from a group of 54 patients with "normal" fibrinogen metabolism with an average age of 58 and an average plasma HMWFC of 7.7 ± 0.84% (Group 1, table 1).

However, a proportion of the generally elderly population with atherothrombotic brain infarction are known to have, prior to the ictus, progressive vascular disease and other diseases (diabetes, hyperlipidemia, hypertension, etc.) recognized as stroke risk factors, diseases which possibly may influence fibrinogen metabolism.

Consequently, comparison also has been made between the data obtained from patients diagnosed as having cerebral infarction and those of two other groups, a "stroke control" group and a "stroke risk factor" group. The stroke risk factor group comprised two separate subgroups. The first had 33 subjects (average 59) who volunteered to take a medical screening examination to assess cardiovascular function. Eight of these patients, subject to the self-selection involved in seeking volunteers, were found to have hypertension, nine had hyperlipidemia, and two had diabetes. Mean plasma HMWFC in this group was 12.3 ± 1%. The second subgroup had 58 patients (average age 58) in whom there was sufficient evidence of coronary artery disease to justify the performance of a cardiac treadmill exercise test but in whom the test was negative. Mean plasma HMWFC in this group was 12.4 ± 0.9%. These subgroups, the volunteers and the cardiac patients, were combined to form the "stroke risk factor" group of 91 patients (Group 3, table 1).

However, epidemiological evidence indicates that presently recognized stroke risk factors can be detected in only 50% of patients with atherothrombotic brain infarction. Consequently, a stroke control group has been constructed by combining the data from the normals and the "stroke risk factor" group, weighted to represent 50% of normal data and 50% of stroke risk factor data. This group of 145 patients showed 10.05 ± 0.65% plasma HMWFC (Group 2, table 1).

Neurological Assessment

A standardized neurological examination suitable for numerical assessment was used with a total score of 120

### Table 1: Plasma HMWFC in Control Groups and Disease Groups (t-Test Values)

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<tr>
<th>Data in percent</th>
<th>Mean ± SE</th>
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<td>1 Normal</td>
<td>7.7 ± 0.94</td>
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<td>10.1 ± 0.59</td>
<td>2.57*</td>
<td>4.24†</td>
<td>2.55†</td>
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<td>12.4 ± 0.93</td>
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<tr>
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<td>15.09 ± 0.43</td>
<td>8.12†</td>
<td>6.72†</td>
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<tr>
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<td>17.1 ± 1.6</td>
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<td>13.3 ± 1.7</td>
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<td>Data in mg percent</td>
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<tr>
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<td>18.4 ± 3</td>
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<tr>
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<td>20.4 ± 2.5</td>
<td>2.40‡</td>
<td>4.3‡</td>
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<tr>
<td>3 Stroke risk factor</td>
<td>40.3 ± 3.5</td>
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<tr>
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<tr>
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<td>6.49‡</td>
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<td>Subarachnoid hemorrhage</td>
<td>52.5 ± 7.5</td>
<td>4.58‡</td>
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<tr>
<td>Cerebral embolism</td>
<td>58.1 ± 5.8</td>
<td>6.43‡</td>
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</table>

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* † ‡ § — Comparison not relevant.
* p < 0.05.
† p < 0.001.
‡ p < 0.02.
§ p < 0.01.
Neurological scores were obtained on the first, second, third or fourth, fifth and tenth days after hospital admission and were performed thereafter at approximately weekly intervals.

In general, a score greater than 100 points documented the presence of an incomplete hemiplegic lesion, less than 100 points a dense hemiplegia, and below 50 points the presence of a massive neurological deficit. The patient’s neurological status was interpreted as unchanged if the difference between initial and final neurological assessment varied within ±5 points, as either probably deteriorated or probably improved if there was variation between initial and discharged scores of 5 to 15 points and as definitely improved or deteriorated if the score varied by greater than 15 points. If the patient’s initial neurological score was greater than 100 points, changes in score of two-thirds of that described above were used to designate changed patient status. Because patient numbers were not always sufficient to perform meaningful analyses after data breakdown, some of the tables show probably improved and definitely improved patients all classed as improved with a similar combination of the two deteriorated groups.

Any patient dying in or out of the hospital within one month of the ictus was classed as severely deteriorated whether or not the neurological score at the end of the individual observation period agreed with this classification. More than 50% of patients dying within one month of the ictus died outside the hospital and, in such patients, the precise cause of death was seldom established, nor were laboratory data obtained between hospital discharge and death.

Laboratory Methods

Blood coagulation assays, plasma fibrinogen, one-stage prothrombin time, thrombin clotting time, plasma recalcification time, and assays for components of the plasminogen/plasmin enzyme system, plasma plasminogen, euglobulin lysis time and euglobulin precipitate lysis on the Mancini radial immunodiffusion method were performed by standard methods used in previous studies. Alpha2-macroglobulin, alpha1-antitrypsin and antithrombin III were determined immunologically by the Mancini radial immunodiffusion method using antisera purchased from Behring Diagnostics, New York, and Nyegaard, Norway. Plasma factor XIII concentration was purchased from Behring Diagnostics, New York, and were performed thereafter at approximately weekly intervals.

Results

Plasma Fibrinogen Chromatographic Findings in the “Control” Populations

In health, plasma fibrinogen chromatographic findings remain relatively constant. For example, findings in a 52-year-old physician, experiencing no clinically apparent illness, followed by weekly blood examinations for 42 weeks showed plasma HMWFC values (mean ± 1 SD) of 5.4 ± 3.8% (SE ± 0.59%) with a range of 3% to 12% HMWFC and 25.4 ± 5.7% (SE ± 0.88) fibrinogen first derivative. On a concentration basis, plasma HMWFC was 15.2 ± 10.1 mg % and 71.4 ± 16 mg % fibrinogen first derivative. Similarly, plasma fibrinogen chromatographic findings in a group of 54 preoperative patients with normal fibrinogen metabolism gave values (mean ± 1 SD) of 7.7 ± 6.2% (18.4 ± 21.9 mg %) for plasma HMWFC and values for fibrinogen first derivative of 25.8 ± 6.4% (61.7 ± 15.3 mg %). Data from this patient group served as a control to quantify “normal” fibrinogen catabolism.

Two other “control” populations, the “stroke control” group and the “stroke risk factor” group, are described in the Methods section. Plasma fibrinogen chromatographic findings in these two groups are shown in table 1.

Neurological Status of the Cerebral Infarction Group

A total of 182 patients with the diagnosis of cerebral infarction were studied. Fifty-seven percent of this group were admitted to the hospital within 24 hours of the ictus, 89% within 48 hours, and the remainder at times up to four days postictus. On initial neurological examination, 98 patients were scored at more than 100 points, 64 patients scored at 100 to 50 points, and 20 patients at less than 50 points. The crude “hospital” mortality rate, death within one month of ictus, was 15%.

At the end of the observation period, 98 patients with initial neurological scores of more than 100 points were classed as 34 improved, 51 unchanged and 13 deteriorated (five died). Of the 64 patients with initial neurological scores of 100 to 50 points, 23 improved, 25 were unchanged and 16 deteriorated (13 died). The 20 patients with initial neurological scores of less than 50 points showed eight improved, three unchanged and nine deteriorated (all nine died).

Plasma Fibrinogen Chromatographic Findings

Patients with cerebral infarction may show abnormal plasma fibrinogen chromatographic findings for hours, days or sometimes weeks following the ictus. Figure 1 shows plasma fibrinogen chromatographic findings in a young woman on oral contraceptive therapy who was admitted to
the hospital six hours after the development of hemiplegia (initial neurological score 105 points). Plasma HMWFC determinations made at six, eight and 11 hours after the ictus were grossly abnormal with HMWFC proportion ranging from 40% to 30% (upper limit of normal findings: 20% HMWFC). Plasma fibrinogen was 250 mg % and plasma HMWFC concentration, ranging from 100 to 75 mg %, was also in the pathological range (upper limit of normal: 71 mg %). However, by the next morning, plasma fibrinogen chromatographic findings were within the normal range and remained so for the remainder of the hospital course (five further daily blood examinations). Initially, fibrinogen first derivative was in the low normal range but rose significantly during the first five hours of hospital observation, a finding demonstrating enhancement of plasma fibrinolytic activity. Her neurological deficit improved, and on discharge the neurological score was 115 points.

Figure 2 shows findings in a 57-year-old man admitted to the hospital within eight hours after weakness developed in the right hand and leg (initial neurological score 111 points). Essentially complete clinical recovery occurred within 24 hours of hospital admission (upper part of figure). The middle panel shows that plasma fibrinogen, initially 282 mg %, peaked at 380 mg % on hospital Day 4 and three days after clinical recovery had occurred. The lower portion of the figure shows plasma fibrinogen chromatographic findings which, on admission, were within normal limits. However, at the time of neurological improvement on Day 2, plasma HMWFC rose to 22% and there was depression of fibrinogen first derivative to 17%. By Day 3, fibrinogen first derivative concentration increased to 45%, a finding indicative of increased plasma fibrinolytic activity, and plasma HMWFC fell to 12%. On Day 4, at the time when neurological recovery was complete, plasma HMWFC again rose to pathological levels (23%) but thereafter returned to, and remained within, normal limits for the rest of the hospital course (an additional four daily blood examinations). Transitory recurrence of blood coagulation dysfunction following apparent clinical stabilization of the neurological deficit has frequently been observed in our patients.

Figure 3 presents serial coagulation findings in a patient with severe posterior circulation infarction, whose initial neurological score was 23 and who was followed until death 41 days later. On Day 2, plasma fibrinogen chromatographic findings were normal, but by Day 3, plasma HMWFC had risen to 45% of total fibrinogen (171 mg %). Plasma HMWFC was still elevated on Day 7, but had returned to normal levels on Day 12 and remained so until Day 23 during which time the patient's neurological status remained unchanged. On Day 27, concomitantly with further deterioration in her condition, plasma HMWFC rose to 30% of total fibrinogen, an elevation lasting at least until Day 37, the day of the last biochemical examination. Concomitantly, with the initial peaking of plasma HMWFC concentration, plasma fibrinogen rose sharply, but fibrinogen first derivative fell from an initial value of 47% to 20%. These changes reverted toward normal values on Days 11 to 25, but thereafter the biochemical changes seen earlier recurred. Plasma factor XIII concentration fell sharply between Days 2 and 3 and again with recurrence of the abnormal plasma fibrinogen chromatographic findings noted on Day 23.
While plasminogen tended to increase during the initial days of hospitalization, there was a fall at the time of the second increase in fibrinogen complex formation. Similarly, antithrombin III concentration was also depressed at this time. Alpha2-macroglobulin concentration fell concomitantly with increase of plasma HMWFC on both occasions.

Tables 2 and 3 display serial plasma fibrinogen chromatographic data, calculated on a daily average basis for Days 1 to 10 following the ictus, for 182 patients with intracerebral infarction, 11 with subarachnoid hemorrhage secondary to bleeding cerebral aneurysm, 17 with cerebral embolism and 21 with cerebral hemorrhage. Table 2 shows these data calculated on a percentage calculation basis and table 3, the same data expressed on a concentration basis as mg %.

Of all groups on Day 1, patients with cerebral embolism showed the highest proportion and concentration of plasma HMWFC. However, in this group, plasma HMWFC proportion and concentration thereafter declined and tests of Days 1 to 3 findings of plasma HMWFC percentage against Days 4 to 7 findings, respective means of 19.7% versus 12.8%, were significant at the 5% level. Also, plasma HMWFC findings, expressed as mg %, displayed a similar decline (p < 0.05). Initially, the cerebral embolism group showed the highest proportions and concentration of fibrinogen first derivative, but subsequently there was a decline in both, concomitantly with a decrease in plasma HMWFC.

In contrast, the cerebral infarction group showed essentially normal plasma HMWFC on Day 1, but had a sharp increase by Day 2 from 9.7 to 12.8% (difference NS) and from 25.1 mg % to 47.9 mg % (p < 0.02). On succeeding days, there were nonsignificant variations in both plasma HMWFC percentage and concentration, and by the end of the ten-day observation period plasma HMWFC was still low.

**Table 2** Plasma Fibrinogen Chromatographic Findings (% Age) by Day in the Neurological Disease Groups

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<td>Intracerebral hemorrhage</td>
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<td>Complexes</td>
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Table 3: Plasma Fibrinogen Chromatographic Findings (mg %) by Day in the Neurological Disease Groups

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<td>25.1</td>
<td>47.9</td>
<td>31.1</td>
<td>52.8</td>
<td>53.7</td>
<td>57.9</td>
<td>72.3</td>
<td>46.6</td>
<td>93.4</td>
<td>66.4</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>158.4</td>
<td>192</td>
<td>182.4</td>
<td>180.7</td>
<td>181.6</td>
<td>174.9</td>
<td>198.2</td>
<td>196.8</td>
<td>180.8</td>
<td>188.8</td>
</tr>
<tr>
<td>Fibrinogen first der.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>100.1</td>
<td>109.7</td>
<td>114</td>
<td>103.4</td>
<td>109.3</td>
<td>133.5</td>
<td>94.4</td>
<td>155.9</td>
<td>141.8</td>
<td>133</td>
</tr>
</tbody>
</table>

Substantially higher than the Day 1 findings.

Patients with subarachnoid hemorrhage secondary to bleeding cerebral aneurysm also showed values of plasma HMWFC within the normal range on Day 1 of hospitalization, followed by subsequent increase, while those with cerebral hemorrhage showed high plasma HMWFC values initially with a decline by Day 2 followed by a gradual return of plasma HMWFC to Day 1 values. In this group, plasma fibrinogen chromatographic data are not listed beyond Day 3, as the data become unrepresentative of the group as a whole by this time because of the high patient mortality (15 out of 21 died within one week).

Table 1 displays means and standard errors for the combined Days 1 to 10 plasma HMWFC data shown in tables 2 and 3. Data for percentage HMWFC are shown in the upper portion of the table and data for concentration, mg %, in the bottom portion.

Data from the three control groups (Group 1: normals, Group 2: "stroke controls," and Group 3: "stroke risk") are given for both HMWFC percentage and concentration. The "t" test value is given for each comparison between controls and for controls versus disease groups. Because the stroke risk factor concept has been validated only for atherothrombotic brain infarction, only the data from the cerebral infarction group have been compared against those of all three groups. The cerebral hemorrhage data have been compared with control groups 1 and 2, while the cerebral embolism and subarachnoid hemorrhage data have been compared with only the "normal" control data.

Comparison of the disease group findings with those of the normals (Control Group 1) demonstrates that both the proportions and concentrations of plasma HMWFC were substantially increased over control values for all disease groups. Excepting only the percentage plasma HMWFC increase in patients with subarachnoid hemorrhage, significant at the 1% level, all other comparisons between the disease groups and the normals were significant at the 0.1% level.

Table 1 shows that both the percentage and concentration of plasma HMWFC are substantially higher in the stroke risk factor group than in the normals (p < 0.001 in each instance). Similarly, as would be expected from the group composition, plasma HMWFC percentage and concentration are significantly higher (p < 0.05 and p < 0.01, respectively) in the stroke control group than in the normals.

Comparison between the cerebral infarction group and the three control groups shows that plasma HMWFC concentration is significantly greater in the cerebral infarction group (p < 0.001 in all instances) and that plasma HMWFC percentage also is increased over control values (p varies from 0.001 to 0.01).

Cerebral Infarction

Tables 2 and 3 show plasma fibrinogen chromatographic data for Days 1 to 10 for all patients with cerebrovascular disease. Table 4 shows a breakdown of the data for those with cerebral infarction by initial neurological score for those with scores of ≤50, 50 to 100 and ≥100; means and standard errors for each group also are shown.

Findings for plasma HMWFC are on the left side of the table and those for fibrinogen first derivative on the right side, with statistical tests between the groups shown at the bottom of the table. Daily average figures for plasma HMWFC and fibrinogen first derivative for each cerebral
infarction disease severity group are shown in figure 4 (as component percentages) and in figure 5 (as concentration, mg %).

Table 4 demonstrates that patients with an initial neurological score of <50 points subsequently showed the highest percentage in concentration of plasma HMWFC with similar findings for fibrinogen first derivative. Patients scoring 100 to 50 points showed lesser elevation in these parameters, while those scoring >100 points showed lower plasma HMWFC and lower fibrinogen first derivative than the other groups. The results of "t" testing are shown below and demonstrate that the differences between the cerebral infarction group and Groups 1 and 3 are significant at either the 0.1 or 1% level with statistical significance in all other comparisons except for HMWFC component proportions between Groups 2 and 3. In all cases, differences between groups are of higher significance for plasma HMWFC and fibrinogen first derivative expressed as concentrations as mg % than as proportions expressed as percentage of total "fibrinogen." Comparison between the plasma HMWFC and fibrinogen first derivative data shown in figure 4 (plotted as percentage) and figure 5 (plotted as mg %) also shows that on a daily average basis, differences between groups are greater when the data are plotted in concentration format.

As mentioned in the Methods section, these data are incomplete, since more than 50% of the patients classed as deteriorated either deteriorated or died after hospital discharge. Moreover, the series is of insufficient size to allow additional breakdown by initial neurological status, a factor already shown to be related to disease outcome (table 4).

The data in table 5, to be interpreted in the light of the limitations described above, show that significant difference in plasma HMWFC percentage was not observed between the deteriorated, unchanged, or improved groups (p > 0.1 in all instances). However, patients who deteriorated showed significantly higher concentrations of plasma HMWFC (mg %) than those classed as unchanged (p < 0.05) or improved (p < 0.1). Similarly, while significant differences in plasma HMWFC percentage fibrinogen first derivative between the two groups were not observed (p < 0.1 in both instances), deteriorated patients had higher plasma fibrinogen first derivative concentrations than the unchanged or improved groups (p < 0.01 and p < 0.02, respectively). Consequently, the table 5 data indicated that differences in disease outcome were manifested by group differences in plasma fibrinogen chromatographic findings expressed on a concentration basis but not on a percentage component basis.

Frequency of Coagulopathy in Cerebral Infarction

Of 182 study patients with cerebral infarction, four or more serial blood samples were examined in 107. In 25 of these patients (23% of the series), plasma HMWFC values were all within the range of mean ± 2 SD of normal. This finding does not exclude the development of coagulopathy in these patients, for plasma HMWFC elevation sometimes may be of short duration (fig. 1). Indeed, in 10 of these 25

---

**TABLE 4 Chromatographic Analysis in Relation to Neurological Score on Admission**

<table>
<thead>
<tr>
<th>Group</th>
<th>Complexes</th>
<th>mg %</th>
<th>Fibrinogen first der.</th>
<th>%</th>
<th>mg %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 &lt;50</td>
<td>18.43 ± 1.40</td>
<td>80.35 ± 8.09</td>
<td>38.44 ± 2.03</td>
<td>156.1 ± 10.32</td>
<td></td>
</tr>
<tr>
<td>2 50-100</td>
<td>15.23 ± 0.71</td>
<td>53.15 ± 2.84</td>
<td>34.10 ± 0.86</td>
<td>128.54 ± 3.91</td>
<td></td>
</tr>
<tr>
<td>3 ≥100</td>
<td>14.30 ± 1.51</td>
<td>46.76 ± 1.95</td>
<td>32.08 ± 0.72</td>
<td>106.2 ± 2.88</td>
<td></td>
</tr>
<tr>
<td>1 versus 3</td>
<td>t = 2.67*</td>
<td>5.82$</td>
<td>t = 2.03$</td>
<td>6.1$</td>
<td></td>
</tr>
<tr>
<td>1 versus 2</td>
<td>t = 2.03$</td>
<td>3.88$</td>
<td>t = 2.18$</td>
<td>2.42$</td>
<td></td>
</tr>
<tr>
<td>2 versus 3</td>
<td>NS</td>
<td>1.91</td>
<td>t = 2.81*</td>
<td>4.72$</td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.01.
† p < 0.001.
‡ p < 0.05.
§ p < 0.02.

---

**FIGURE 4.** Mean daily values for HMWFC percentage (• --- •) and for fibrinogen first derivative percentage (○ --- ○) in patients with cerebral infarction. On the left are the findings in those with initial neurological scores of <50 points; in the middle, those with scores of 100 to 50 points; and on the right, findings for those with scores of >100 points. For discussion, see text.

**FIGURE 5.** Constructed in identical fashion to figure 4, but the data are expressed as concentration, mg %, instead of percentage. Note that differences between the various patient groups are greater when expressed on a concentration basis.
patients, plasma fibrinogen rose 20% or more following ictus and average plasma HMWFC in the group was 10.9 ± 1.35%. This value for HMWFC is significantly greater than that in the normal controls (p < 0.05).

In the other 82 patients in whom four or more plasma samples were examined, the frequency of samples containing >20% HMWFC was: in 25 patients, <25% of samples examined, in 28 patients, 25% to 50% of samples examined, in 17 patients, 50% to 75% of samples, and in the remaining 12, 75% to 100% of samples examined.

Breakdown of these data into improved, unchanged or deteriorated classes did not show significant differences among the class frequencies.

Duration of Coagulopathy

Patients with initial neurological scores of >100 points were observed in a hospital for a median period of eight days if they were in the improved group or a median period of 9.2 days if they were unimproved. In these two groups of patients, one-third of the last samples obtained prior to discharge showed pathological concentrations of plasma HMWFC. Consequently, the duration of the coagulopathy cannot be estimated in these patient groups because of hospital discharge prior to resolution of abnormality.

Observations were available on 15 patients between the eleventh and forty-fifth hospitalization day. One patient showed persistently abnormal plasma HMWFC findings until Day 35 and died one week later, five others showed intermittent abnormality on Days 12 to 19 before reverting to normal, and the remainder had normal findings during this observation period.

Other Coagulation Studies

Table 6 shows the means and standard errors for Days 1 to 10 values of plasma fibrinogen mg %, plasminogen CTA units per milliliter, and immunological assays for plasma antithrombin III, alpha-antitrypsin, and alpha-antitrypsin for patients classed by initial neurological score groups of <50, 50 to 100 and >100 points. Values for each neurological class are shown in the top half of the table and the significance for the differences in the bottom half of the table.

Patients originally classed in the <50 neurological group showed the highest fibrinogen values (389.6 ± 10.3 mg %), those who scored 100 to 50 points had lower fibrinogen levels (366.8 ± 7.4 mg %), and those who were initially classed as >100 points, the lowest fibrinogen value (332.7 ± 1.6 mg %). With the exception of the difference between Group 1 and Group 2, which did not quite reach the conventional 5% significant level, all other fibrinogen differences between the groups were statistically significant at the 0.1% level.

Plasminogen assays between the three patient groups did not differ significantly, but antithrombin III concentration was substantially higher in Group 3 as compared to Group 2 (p < 0.02). Group 1 had higher alpha-antitrypsin levels than Group 2 (p < 0.002), while alpha-antitrypsin concentration increased significantly with increased disease severity as assessed by initial neurological score.

Table 7 shows the same data as those of table 6, except it is classified on the basis of disease outcome rather than initial neurological score. The patient groups in this instance were the deteriorated, the unchanged and the improved. Fibrinogen values were significantly higher in the deteriorated patients (p < 0.02 and p < 0.001, respectively, compared to the other groups). Plasminogen tended to be lower in the deteriorated groups, but the difference did not reach statistical significance. However, antithrombin III levels tended to be higher in the improved patients and when this difference was tested in the patient group with scores of >100, the improved patients showed average antithrombin III levels of 28.11 mm², while the deteriorated unchanged

<table>
<thead>
<tr>
<th>Group</th>
<th>Fibrinogen (mg %)</th>
<th>Plasminogen (CTA U/ml)</th>
<th>Antithrombin III (nmol²)</th>
<th>α2-Macro. (nmol²)</th>
<th>α1-Antitrypsin (nmol²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 &lt;50</td>
<td>389.6 ± 10.3</td>
<td>2.454 ± 0.102</td>
<td>25.05 ± 0.8</td>
<td>31.43 ± 1.22</td>
<td>32.3 ± 1.16</td>
</tr>
<tr>
<td>2 50–100</td>
<td>366.8 ± 7.4</td>
<td>2.418 ± 0.046</td>
<td>24.3 ± 0.41</td>
<td>28.58 ± 0.62</td>
<td>29.08 ± 0.76</td>
</tr>
<tr>
<td>3 &gt;100</td>
<td>332.2 ± 1.6</td>
<td>2.492 ± 0.043</td>
<td>25.67 ± 0.38</td>
<td>29.52 ± 0.64</td>
<td>28.47 ± 0.63</td>
</tr>
</tbody>
</table>

Table 6 Assay Values in Cerebral Infarction Patients as a Function of Admission Neurological Score

* p < 0.02. t p < 0.05. t p < 0.001. t p < 0.001.
group showed average values of 24.77 mm², a difference significant at the 0.1% level.

Table 8 compares the findings in tables 6 and 7 with those of the stroke risk factor group. In all comparisons, plasma fibrinogen was significantly elevated in the cerebral infarction groups (p varied from <0.01 to <0.001). Plasminogen values were significantly higher in the infarcted patients than in the controls, while antithrombin III values tended to be higher in the disease groups, though in no single group was formal statistical significance reached. Alpha₁-macro-globulin levels were substantially increased in the cerebrovascular disease groups as compared to the control values, the significance of this difference in all instances exceeding the 0.1% level. Similarly, alpha₂-antitrypsin concentration in the cerebrovascular disease groups was substantially increased over that observed in the controls, the differences being significant at the 0.1% level in all instances.

Discussion

Our data indicate that disturbed fibrinogen catabolism resulting from increased fibrinogen/fibrin formation and documented by increase in plasma HMWFC is frequently demonstrable in patients with cerebral infarction, cerebral embolism, intracerebral hemorrhage and subarachnoid hemorrhage. Both percentage and concentration plasma HMWFC were significantly elevated in all cerebrovascular disease groups when compared with control. All comparisons were significant at the 0.1% level excepting only for percentage plasma HMWFC in those with subarachnoid hemorrhage, which was significant at the 1% level.

Our findings in the subarachnoid hemorrhage patients support Ettinger's hypothesis

order demonstrate increased coagulability of venous blood shortly after the onset of hemorrhage. Our findings in the cerebral embolism group with rapid early increase in plasma HMWFC followed by rapid decrease are in line with the pathological concept that embolization of an artery incites secondary thrombotic extension, but that the plasma plasminogen/plasmin enzyme system (plasma fibrinolytic enzyme system) may restore vascular continuity.

Patients with intracerebral hemorrhage also showed pathologically enhanced plasma HMWFC, a finding suggesting that intracerebral blood may activate the coagulation system, but in this instance adsorption of fibrin fragments from the clotted intracerebral blood with subsequent complexing of these fragments with plasma fibrinogen cannot be excluded as an alternative mechanism resulting in plasma HMWFC elevation.

Since cerebral infarction frequently develops in patients with stroke risk factors, the data from patients with cerebral infarction have been compared not only against findings from a normal control group but also against those of two other groups, a "stroke control" group and a "stroke risk factor" group (see Methods).

Both plasma HMWFC percentage and concentration were significantly higher in the stroke control group and in the stroke risk factor group than in the normal controls (normals versus stroke controls, p < 0.01 and p < 0.02, respectively) and normals versus stroke risk factor group (p < 0.001 in both instances). These findings suggest that elevated plasma HMWFC may reflect the presence of stroke risk factors, possibly the presence of atherosclerosis; further, that in a proportion of patients, abnormality of fibrinogen catabolism may precede the ictus, an hypothesis supported by the studies of Pilgeram et al. Moreover, it has been demonstrated that in women receiving oral contraceptive

**Table 7** Assay Va vs. in Cerebral Infarction Patients as a Function of Clinical Outcome

<table>
<thead>
<tr>
<th>Group</th>
<th>Fibrinogen (mg%)</th>
<th>Plasminogen (CTA U/ml)</th>
<th>Antithrombin III (mm²)</th>
<th>α-Macro. (mm²)</th>
<th>α-Antitrypsin (mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deteriorated</td>
<td>374.4 ± 9.5</td>
<td>2.377 ± 0.060</td>
<td>25.27 ± 0.54</td>
<td>29.72 ± 0.89</td>
<td>31.53 ± 0.97</td>
</tr>
<tr>
<td>Unchanged</td>
<td>349.2 ± 5.3</td>
<td>2.514 ± 0.039</td>
<td>25.01 ± 0.34</td>
<td>28.96 ± 0.59</td>
<td>27.13 ± 0.54</td>
</tr>
<tr>
<td>Improved</td>
<td>344.8 ± 3.6</td>
<td>2.470 ± 0.045</td>
<td>26.00 ± 0.42</td>
<td>29.57 ± 0.55</td>
<td>28.72 ± 0.51</td>
</tr>
<tr>
<td>1 versus 2</td>
<td>2.43*</td>
<td>1.82</td>
<td>4.09†</td>
<td>2.76†</td>
<td></td>
</tr>
<tr>
<td>1 versus 3</td>
<td>3.77†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 versus 3</td>
<td>0.71</td>
<td></td>
<td>1.85</td>
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</tbody>
</table>

*p < 0.02.

**Table 8** Differences (t Values*) Between Cerebral Infarction Groups and Stroke Risk Factor Group

<table>
<thead>
<tr>
<th>Group</th>
<th>Fibrinogen (mg%)</th>
<th>Plasminogen (CTA U/ml)</th>
<th>Antithrombin III (mm²)</th>
<th>α-Macro. (mm²)</th>
<th>α-Antitrypsin (mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke risk factor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>317.8 ± 8.5</td>
<td>2.25 ± 0.046</td>
<td>24.70 ± 0.53</td>
<td>22.77 ± 0.53</td>
<td>23.36 ± 0.30</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 50</td>
<td>5.22†</td>
<td>2.10†</td>
<td>0.37</td>
<td>7.56†</td>
<td>9.64†</td>
</tr>
<tr>
<td>50 to 100</td>
<td>3.25†</td>
<td>2.38‡</td>
<td>-0.59</td>
<td>6.24†</td>
<td>5.54†</td>
</tr>
<tr>
<td>≥ 100</td>
<td>2.69†</td>
<td>3.52†</td>
<td>1.48</td>
<td>6.82†</td>
<td>5.571</td>
</tr>
<tr>
<td>Deteriorated</td>
<td>5.32†</td>
<td>1.70</td>
<td>0.75</td>
<td>6.76†</td>
<td>8.19†</td>
</tr>
<tr>
<td>Unchanged</td>
<td>2.93†</td>
<td>3.77‡</td>
<td>1.31</td>
<td>6.00†</td>
<td>4.14†</td>
</tr>
<tr>
<td>Improved</td>
<td>4.45†</td>
<td>3.09†</td>
<td>1.83</td>
<td>7.82†</td>
<td>7.12†</td>
</tr>
</tbody>
</table>

*In all instances except that marked (*), assay values are greater in the cerebral infarction groups than in the stroke risk factor group.

**p < 0.001.

**p < 0.01.
therapy, a group at approximately tenfold greater than normal risk of having cerebral infarction, pathological elevation of plasma HMWFC occurs with approximately fivefold greater frequency than in unmedicated women. Particularly since women who have cerebral infarction while receiving oral contraceptive medication are in the younger age groups and infrequently exhibit conventionally recognized stroke factors, it is probable that pathologically raised HMWFC not only might precede the ictus in a proportion of cases, but possibly act as a precipitating cause.

Whether or not plasma HMWFC is significantly raised preictus in a proportion of patients, the table 1 data demonstrate that following ictus, plasma HMWFC is significantly increased in cerebral infarction patients as compared to all three control groups (p < 0.001 in five comparisons and p < 0.02 in one comparison). Moreover, the data shown in table 7 show that the cerebral infarction patients had significantly increased values (p < 0.001 in all instances) for plasma fibrinogen, plasminogen, alpha_2-macroglobulin and alpha_2-antitrypsin over those of the stroke risk group. These findings demonstrate that disturbed fibrinogen catabolism, demonstrated postictus in the cerebral infarction group, is of postictal origin.

Other findings supporting this concept include (a) the statistically significant correlation between increase in plasma HMWFC and initial disease severity, (b) the finding that plasma fibrinogen chromatographic group values differ significantly when analyzed on the basis of disease clinical outcome, (c) the finding that in patients with cerebral infarction scoring >100 points, antithrombin III was significantly elevated in the improved group, as compared to the unchanged and deteriorated groups, and (d) other evidence indicating that depression of plasma factor XIII, usually within the normal range shortly after the ictus, was statistically related to disease severity.

While the data demonstrate that in the cerebrovascular disease groups studied enhanced fibrinogen catabolism via fibrin formation developed postictus, they do not establish the pathological basis for enhanced fibrinogen formation. Enhanced fibrinogen catabolism via fibrin formation in the cerebrovascular disease patients could be due to causes consequent upon disease-primary pathology or due to extracranial causes.

Causes secondary to disease-primary pathology could include (a) the release of thromboplastin material from ischemic or necrotic cerebral tissue with activation of the blood coagulation system in blood flowing through the infarct area, (b) adherence of red cells or platelets passing through the infarct or other afflicted areas might similarly produce activation of the coagulation system, (c) blood flow stasis occurring at the site of the affected cerebral area or that produced by vascular spasm, a phenomenon of frequent occurrence in subarachnoid hemorrhage, might predispose to activation of the coagulation system, and finally, (d) the presence of a cerebral thrombus or embolus could induce changes in fibrin formation through secondary thrombotic extension. Moreover, changes in plasma HMWFC could result from extracranial causes such as the presence of a clinically silent lower limb venous thrombosis. Warlow, Ogston and Douglas** studied 30 stroke patients with paralysis of at least one leg by the ^126I-labeled fibrinogen uptake method for detection of lower limb deep venous thrombosis. They described the presence of a thrombus in the paralyzed limb in 60% of their series at the end of a ten-day observation period with detection of bilateral leg thrombi in two patients. Pulmonary embolism was considered to be the primary cause of death in two patients and was also diagnosed in two others on the basis of clinical findings. Sixty percent of the group in whom a leg thrombus was diagnosed by the ^125I-labeled fibrinogen method showed physical signs diagnostic of this condition.

The relevance of these findings to our data is unclear. While Warlow et al. discussed neither stroke pathology nor the severity of the neurological deficit in their series, their ten-day mortality rate of 37% suggests that they studied patients with massive neurological deficits comparable to those classed as <50 points in our present investigation. The major portion of the data in our series were obtained from less severely affected patients (89% of the series had initial neurological scores of >50 points and 54% had scores of >100 points). Moreover, our previous studies on the correlation between the presence of an isotopically detected thrombus and plasma fibrinogen chromatographic findings** demonstrate that the presence of deep vein thrombosis induced persistent elevation of plasma HMWFC, which did not remit until thrombus disappearance. Thus, either of the two prolonged episodes of HMWFC elevation, particularly the second, shown in figure 3 (findings in a patient with a severe neurological deficit resulting in death) could be interpreted as consistent with development of a deep venous thrombotic lesion. However, as documented by the analysis of relative frequency with which abnormal and normal plasma fibrinogen chromatographic findings were observed in our patient studies (see text), the findings shown in figure 3 are highly atypical of the series. By far the most frequent pattern of chromatographic abnormality observed was that shown in figure 2, a pattern of abnormality inconsistent with the presence of a lower limb thrombus. Moreover, our clinical experience differed from that of Warlow et al., for diagnoses of deep venous thrombosis and/or pulmonary embolism were made only infrequently in our series, as compared with a high frequency of these diagnoses in their series.

While our data suggest that the degree and duration of plasma HMWFC elevation (demonstrative of enhanced fibrin formation) may be associated with clinical outcome, this conclusion is subject to uncertainty resulting from less than ideal data collection methods and a degree of data confounding. Data collection, due to the complex clinical/economic factors governing hospitalization duration, was less than ideal, since the majority of patients were discharged prior to the obtaining of adequate evidence that blood coagulation system anomalies had remitted and since half the patients classed as deteriorated died outside the hospital and laboratory data could not be obtained after the patient's hospital discharge. Data confounding was the inevitable result of the finding that the degree and duration of the coagulation anomaly were significantly associated with the patients' initial neurological score. It has long been recognized and has also been confirmed by our data on clinical outcome that prognosis in patients with cerebral infarction is greatly influenced by the degree of initial neuro-
logical deficit. For instance, our data show that death within one month of the ictus occurred in 5% of those patients with an initial neurological score of >100 points, in 20% of those with an initial neurological score of 100 to 50 points, and in 45% of those with an initial neurological score of <50 points. This substantial degree of confounding between initial neurological score and disease outcome makes it unlikely that other than a very large study would provide evidence that disease outcome and plasma fibrinogen chromatographic studies were correlated independently of initial neurological score. Nevertheless, it is significant that data (table 5) from our relatively small study demonstrate limited correlation between plasma HMWFC, expressed as concentration (mg %), and clinical outcome in cerebral infarction.

Reliance on clinical criteria, supported by brain scanning in those patients who were positive by this technique, for the diagnosis of cerebral infarction has precluded other than relatively crude analysis of the data from patients with this condition. Had cerebral angiography been performed, it is possible that analysis by presumed cause of infarction might have partially explained certain data anomalies. For instance, it is conceivable that those patients, 22% of those with cerebral infarction, in whom pathological increase in plasma HMWFC was not unequivocally demonstrated in any sample could fall in that ~30% of patients with this disorder in whom vascular disease is not demonstrable by cerebral angiography performed shortly after the ictus. However, the hazard involved in cerebral angiographical examination at this time precluded use of this procedure, except in the presence of specific indications.

A major reason for undertaking the present study has been to determine whether a biochemical rationale could be established for the use of antithrombotic agents (anticoagulants, thrombolytic agents, and antiplatelet agents) in selected patients with acute cerebrovascular disease. The results demonstrate that enhanced fibrin formation/deposition develops in the substantial majority of the patients studied and that, within the limits of the present data, the degree of this abnormality would appear to be associated with clinical outcome. While proof of association is not necessarily proof of causation, the findings would suggest that the therapeutic use of antithrombotic agents in patients with cerebral infarction could be supported on biochemical, but not necessarily on clinical, grounds.

Therapeutic trial of antithrombotic agents in patients with cerebral infarction has been undertaken previously on the assumption that the pathology underlying infarction was thromboembolic, an assumption now known to be only partly true. The present findings indicate that whatever the precise primary pathology, evidence of enhanced fibrin formation/deposition develops in the majority of patients. The apparently paradoxical finding that plasma fibrinogen rose in patients in whom fibrinogen/fibrin formation was found to be increased is explicable on the basis of animal experimental studies. In these studies, it was shown that while infusion of relatively large doses of thromboplastic materials produced depression of plasma fibrinogen concentration, the infusion of smaller doses induced substantial increase of plasma fibrinogen.

Clinical results of previous trials of antithrombotic agents in acute cerebral infarction have been of a generally inconclusive nature, have been conducted under the handicap that blood action and blood dosage could be measured only by depression of blood coagulation function and not by action upon the disease process itself. This difficulty has led to drug dosage uncertainty and possibly the toxic effects of drug "overdose" may have been prominent. The development of plasma fibrinogen chromatography allows adjustment of drug dosage to be made according to whether or not pathological enhancement of fibrin formation/deposition is persistent and demonstrable. It is presently uncertain whether this is a clinically valuable method for controlling drug dosage but, especially in view of the widely acknowledged inadequacies of present monitoring tests used for this purpose, it is certainly worthy of trial. Our studies with urokinase therapy demonstrated the feasibility of determining appropriate drug dosage in this manner.

References
Intracranial Neurosurgical Treatment of Occlusive Cerebrovascular Disease

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SUMMARY. Anastomosis of the extracranial superficial temporal artery to the intracranial middle cerebral artery offers an additional source of blood to the cerebral circulation in patients with transient ischemic episodes. Fourteen cases are reported. Two representative cases with three anastomoses demonstrate the use of this technique in occlusion of the internal carotid artery, occlusion of the middle cerebral artery and stenosis of the middle cerebral artery. Indications and contraindications of the procedure are discussed.

SURGICAL TREATMENT of arteriosclerotic occlusive disease of coronary, aortic, and extremity vessels is well known. Until recently, only a few investigators have applied microsurgical techniques to deal with severe cerebral arteriosclerotic disease, hitherto considered inaccessible or technically out of reach of usual vascular surgical techniques. In 1967, Donaghy and Yasargil proposed a new bypass operation to provide additional blood supply to the ischemic brain in patients with carotid occlusion or middle cerebral artery stenosis or occlusion. This procedure entails an anastomosis of the superficial temporal artery (STA) to a cortical branch of the middle cerebral artery (MCA) by way of a 4-cm craniotomy above the ear (fig. 1). We have carried out such a procedure in 13 cases; in another, the anastomosis was made between the occipital branch of the external carotid artery and the middle cerebral artery (table 1). Another shunting procedure (which we have not yet carried out) was designed by Lougheed using a saphenous vein graft to carry blood from the common carotid artery in the neck through a craniotomy into the intracranial portion of the internal carotid artery in cases of internal carotid occlusion in the neck, when the superficial temporal artery is too small to permit an effective anastomosis with the middle cerebral branches. In the two patients presented here, transient ischemic attacks (TIAs) led to angiography which disclosed occlusive disease; one patient had stenosis of the right MCA and occlusion of the left MCA; and the other had occlusion of the right internal carotid artery.

Report of Cases

Case 1

A 50-year-old man was admitted to the University of Illinois Hospital because of episodes of transient numbness and weakness of the left face, arm, hand, and leg and associated speech difficulty lasting three to four minutes, occurring five times during the month prior to admission. He was not receiving treatment for arterial hypertension known for about one or two years. Examination showed blood pressure of 160/110 mm Hg; the left nasolabial fold was flattened; and the carotid pulses were somewhat decreased. Chemical tests indicated borderline diabetes, and a Frederickson type IV hyperlipoproteinemia. The EEG and brain scan were normal. Carotid and vertebral angiography showed stenosis of the right MCA (fig. 2) and occlusion of the left MCA, with retrograde flow into the distribution of this artery by way of the left posterior cerebral artery (fig. 3).

The patient had an uneventful recovery from a right STA-
Blood coagulation and plasma fibrinolytic enzyme system pathophysiology in stroke.
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