STROKE

Patient characteristics, efficacy of a stroke unit and evaluation of hemodilution therapy

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UMEÅ 1986
STROKE. Patient characteristics, efficacy of a stroke unit and evaluation of hemodilution therapy

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ABSTRACT

Stroke is a major health problem in all developed countries. These studies, performed in a stroke unit at a medical department, were designed to characterize essential clinical features of the different cerebrovascular disorders on admission to hospital, to evaluate the efficacy of admitting unselected stroke patients to a stroke unit and, to evaluate hemodilution as a therapeutical regime in patients with cerebral infarction.

A prospective registry included 409 patients admitted to the stroke unit over a five-year period. Modern diagnostic equipment (CT scan and CSF analyses) and strict diagnostic criteria revealed a diagnostic distribution of 11% hemorrhagic, 76% ischemic cerebrovascular lesions and 13% TIAs. Mean age varied between 65.8 and 77.5 years in the various diagnostic groups with the highest in patients with embolic cerebral infarctions. Concomitant disorders affecting the cardiovascular system were highly prevalent and only 14% was free of such diseases prior to the stroke.

In a comparative prospective study, over 16 months, no differences were found between patients treated in the stroke unit (n = 110) and the general medical wards (n = 183) regarding prognostic indicators on admission such as age, concomitant disorders and neurological symptoms. The stroke patients treated in the stroke unit had a statistically significant better prognosis regarding functional outcome and the need for long-term hospitalization was reduced up to one year after the stroke when compared to patients treated in general medical wards. All stroke patients seemed to benefit with the possible exception of patients in coma on admission. These results were achieved within the same or shorter length of initial hospital stay for patients in the stroke unit. Neither overall mortality, nor mortality in subgroups of prognostic importance was significantly affected by the stroke unit regime.

Rapid hemodilution in the early phase of cerebral infarction by the combination of venesection and administration of dextran 40 was evaluated in a prospective controlled trial. After randomization 52 hemodiluted and 50 control patients were comparable in prognostic variables. Signs of blood-brain-barrier breakdown and hemorrhagic admixture to the cerebrospinal fluid in the acute phase were less frequent in hemodiluted subjects. The hemodiluted patients showed a significantly higher degree of early improvement and fewer progressions. Neurological and functional disability in survivors and need for long-term hospitalization was significantly reduced at 3 months and at one year after the stroke compared to controls. Mortality was not affected.

Key words: Acute cerebrovascular disease, blood viscosity, cerebral infarction, hemodilution therapy, stroke unit
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by
TAGE STRAND

UMEÅ 1986
To Jenny, Anna and Kristoffer
ABBREVIATIONS

ADL = Activities of daily living
BBB = Blood-brain-barrier
CBF = Cerebral blood flow
CSF = Cerebrospinal fluid
CT = Computed tomography of the skull
CVD = Cerebrovascular disease
GMW = General medical ward
ICD = International classification of diseases
RIND = Reversible ischemic neurological deficit
SAH = Subarachnoid hemorrhage
SU = Stroke unit
TIA = Transient ischemic attack
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This thesis is based on the following papers, which are referred to by their Roman numerals:

I Eriksson S, Asplund K, Hägg E, Lithner F, Strand T, Wester PO. Clinical profile of the different cerebrovascular disorders: studies in a population-based patient sample admitted to a stroke unit. Submitted for publication.


INTRODUCTION

Stroke is a major health problem in all developed countries, ranks high as a cause of death and are the main cause of severe permanent disability in the last decades of life. It strikes the victim sudden and unexpectedly.

When our prospective studies were started in 1978 there was no conclusive evidence, elicited from properly designed controlled studies, showing that specialized care in stroke units during the acute phase of stroke when compared to conventional treatment, would benefit the stroke victim. Further, there was no general, effective and safe therapeutic regime to offer the majority of stroke patients, those with a completed cerebral infarction.

These studies were designed to evaluate the efficacy of admitting unselected stroke patients to a non-intensive stroke unit during the acute phase of stroke and to evaluate an acute therapeutic regime aimed to increase cerebral blood flow without unaccepted adverse effects in the majority of patients with acute ischemic stroke.

REVIEW OF THE LITERATURE

Epidemiology

Stroke, or acute cerebrovascular disease (CVD), is defined as the sudden onset of a focal neurological deficit of presumed vascular origin and without previous trauma to the head. If the neurological deficit is completely reversed within 24 hours, and the cause is presumed to be ischemic, the term transitory ischemic attack (TIA) is used (1, 2).

The annual stroke incidence rate per thousand population has been reported to be 2.9 in Söderhamn, Sweden (3), 2.35 in Kuopio, Finland (4) and 2.4 in Fredriksberg, Denmark (5) when all age classes except children are included. These figures are also valid in a world-wide perspective (6-8), and even higher figures are reported from China (14).
Each year approximately 25,000 persons in Sweden will suffer a stroke (3). Of these, approximately one third dies during the first three months after their stroke (3, 6, 9-11). Of those who survive, approximately one third will recover completely or almost completely, one third are left with minor to moderate neurological and functional deficits and one third will be heavily disabled. These figures are deduced from several population based epidemiological studies during the last decade, showing no major variations in the prognosis of acute CVD (3, 6, 10, 11).

Although a declining age-specific incidence of stroke and stroke mortality has been reported from some countries during the last years (12, 13) and further development of preventive measures is to be expected, acute CVD will remain a highly significant clinical problem. The stroke incidence increases rapidly with age (3-8) and, since the proportion of old aged people will continue to increase, one cannot expect great reductions in morbidity figures (15).

General features in a stroke population

Figure 1 shows the temporal profile of clinical stroke. Though most TIA's only will last a couple of minutes (16), the other profiles offer greater problems. The frequency of deterioration in acute stroke varies between 23 and 46% in different studies (1, 17-19), mainly depending on lack of clarity in definition and the frequency and accuracy of repeated clinical examinations during the early acute phase. In a recent Swedish study of 402 consecutive acute stroke patients, deterioration in motor function and/or speech ability after arrival at hospital was found in 42% of patients with ischemic lesions and in 61% of patients with intracerebral hemorrhage. Progression was fairly marked in 25% of the patients and half of the progressions occurred within the first 24 hours after admission. No characteristics were found that identified a risk of deterioration (17).

A stroke is arbitrarily said to be completed if no progression is shown 48 hours after symptom onset if the lesion is in the territory supplied by a carotid artery (1); a corresponding figure in the vertebro-basilar territory is postulated to be 72 hours (1). A progression of neuro-
logical deficits after these two symptom-free intervals then must be considered as development of cerebral edema (20) or a recurrent stroke. Classifications on clinical grounds, i.e. neurological symptoms, is also arbitrary and the distinction between TIA, RIND (reversible ischemic neurological deficits) and minor stroke is also a matter of accuracy in the clinical assessment. Many patients, classified as having a TIA, are showing a picture of cerebral infarction on CT-scan (21).

Fig. 1. Temporal profile of acute stroke.

The patients may be referred to hospital at any time point during the acute phase of stroke and, thus, in the individual patient, it is impossible at the time of first clinical examination to tell what the neurological deficit will turn out to be in the next couple of hours or days. The delay from onset of symptoms until admission to hospital (if admitted) may show considerable variations. Median onset-admission delay was five hours in a consecutive series of stroke patients referred to our stroke unit over a period of five years (1).

Although there are miscellaneous causes to cerebrovascular pathology (infections, arteritis, immunopathies, vascular anomalies, migraine, SAH related vasospasm, metabolic alterations and tumor complications), clinical stroke is mainly a late manifestation of atherosclerotic vascular disease. Therefore, also other atherosclerotic manifestations are common in a stroke population. Thus coexisting heart diseases, mainly of ischemic origin are highly prevalent in stroke patients (11, 22,
This is of both pathogenetic importance for the stroke per se, i.e. as a source of embolization and hemodynamic alterations, and of prognostic importance for survival and residual morbidity (24). Disorders of importance for the development of atherosclerotic vascular disease are also common in stroke populations; thus hypertension is reported in 40-60% in unselected stroke populations (9, 22, 25, 26) and coexisting diabetes mellitus in 10-15% (9, 22, 23, 25). Short- as well as long-term prognostication is not possible with accuracy if not also these factors are considered in addition to the cerebral lesion as such.

Recent studies, on well investigated stroke populations, using modern diagnostic methods (CT-scan with or without concomitant CSF-analyses), report that approximately 85-90% of all patients, presenting with a sudden onset of focal neurological dysfunction which persists for more than 24 hours, have a cerebral infarction and only 10-15% have an intracerebral hemorrhage (27-29). Previous studies on stroke epidemiology did not include well-investigated patients, which might have overestimated the frequency of intracerebral hemorrhage. The present general availability of effective antihypertensive treatments may also have contributed to a real decline in the incidence of intracerebral hemorrhages (12, 30).

**Hospital admittance**

Referrals to hospital both in the acute and/or in the subacute-chronic phase of stroke are influenced by socioeconomic factors and show great geographic variability (6). In Sweden, hospital care is free of charge, all costs are covered by the national health insurance system and, thus, hospitalization rates for severely disabled patients are not significantly influenced by economic factors. In Söderhamn, Sweden, approximately 90% of all acute CVD patients were admitted to hospital shortly after symptom onset (3). A slightly lower figure seems to be valid in the USA (70-80%) (9) whereas in the rest of the industrialized world, reports from the UK show low acute hospitalization rates (31, 32), even for severely disabled patients (32).
Obviously, disabling stroke represents a catastrophe for the affected individuals and their families and a substantial cost for society as well (33, 34). However, since there is no generally accepted effective specific medical regime to offer the acute stroke patient (35-37), hospital routines for investigation, treatment and rehabilitation vary considerably even in the same country and within the same hospital (9, 22, 27).

With the aim to optimize basic care and rehabilitative efforts, to evaluate diagnostic procedures and therapeutic interventions and to promote education and research, comprehensive stroke programs have been suggested (2, 38) and outlined (39) mainly during the last two decades. Such programs can be implemented either by organizing a multi-disciplinary team of stroke specialists providing services wherever the patient is placed or, by grouping stroke patients together in a stroke unit (39).

**Stroke units**

Stroke units may be classified according to the following principles:

- **Stroke intensive care units** admitting stroke patients shortly after symptom onset and equipped with facilities for intensive care (e.g. equipment for assisted ventilation and continuous monitoring of cardiac function) (40-46).
- **Non-intensive stroke units** without equipment for intensive care and admitting patients in the acute or subacute phase (22, 47-49).
- **Stroke rehabilitation units** devoted entirely to rehabilitation of survivors after the acute phase (50-53). These units often select the patients admitted with regard to their need for rehabilitation and potential to benefit therefrom.

During the 1970's, substantial attention was given to the value of stroke units in improving patient outcome. However, productivity of stroke units in terms of reducing mortality during the acute phase have not been observed, even in intensive care unit settings (41, 42, 44-46). Those evaluations are all non-randomized, retrospective comparisons between care provided in specialized neurovascular intensive care
units and regular ward care in the same hospital at different periods of time or at other hospitals. However, a reduction in post-stroke complications has been reported (43, 44) and in one study (45), which included no controls, almost no secondary complications at all were shown. In this study, however, the average duration of stay in the unit for stroke patients was only five days, leaving little opportunity for complications to develop. In two retrospective studies, a reduced acute stroke mortality was shown (40, 43), but in one of these studies (40) the comparability of patients has been questioned.

Early evaluation of stroke unit efficacy mainly dealt with mortality as an endpoint. Functional outcome in survivors, however, must also be considered of essential importance. Saving lives in otherwise severely disabled and old stroke victims may be a questionable goal as such (54). Several studies have stressed the importance of rehabilitation in determining final functional outcome (55-59). However, estimating the efficacy of rehabilitation offers some problems. Since the most severely disabled hospitalized patients probably are those who get the largest amount of physiotherapy over a long period of time, there will be an inverse relationship between the amount of physiotherapy given over time and final functional outcome (60, 61).

Many studies indicate that an early start of rehabilitative efforts after a stroke is important for a successful outcome (62-68). It has been suggested that the early start of rehabilitation rather than the amount or duration of treatment may be of decisive importance for success, particularly for occupational therapy (69). Also early family involvement in the rehabilitation process seems to be of importance (59). Therefore, several non-intensive stroke units have adopted these principles and, when admitting stroke patients in the acute or subacute phase try to facilitate early rehabilitation with the aid of skilled staff and family.

A basic question is whether intensive rehabilitative and diagnostic efforts in the very early stage of stroke produces enough functional improvement to be worthwhile in view of the time and cost of such procedures. Several studies have attempted to assess the effectiveness of
early intense stroke rehabilitation, but differences in the evaluation processes have made it difficult to interpret the conclusions reached by different authors (70).

In Table I, results from some recent controlled studies, concerning the productivity of different non-intensive stroke unit settings or team care, are listed. In the Swedish study, which showed no significant difference in functional outcome or mortality (22), the stroke unit had no extra resources for rehabilitation. In the Scottish study, the promising results regarding functional outcome at three months after the stroke (47) were not sustained at one year follow up. As suggested by the authors, this was possibly due to overprotection by family members during the rest of the year (71). In the American trial, which showed no difference in functional outcome, the patients were scattered throughout several departments in the hospital, without continuous supervision by the stroke team (72). In the English study, the patients were not admitted in the very acute phase, about 85% were admitted within three weeks after symptom onset (73).

All these studies used allocation procedures that somehow guaranteed a non-biased selection of patients to the various treatment regimes, but the results from these studies do not allow us to state that stroke units or specialized team care regimes affect the ultimate extent of neurological disability.

However, other factors that are hard to evaluate or control are important results as such. The overwhelming number of reports on stroke units have stressed the importance of the unit as a basis for education, for research and as a factor considerably stimulating the interest in stroke patient care (22, 41-46).

Cerebral blood flow

Neuronal activity, cerebral metabolism and regional CBF are tightly coupled, and the local CBF is a useful quantitative indicator of the regional functional state and metabolism (74).
<table>
<thead>
<tr>
<th>Ref</th>
<th>No of Allocation</th>
<th>No patients procedure</th>
<th>Onset-adm intervals</th>
<th>Bed availability</th>
<th>Follow-up</th>
<th>Outcome</th>
<th>Mor-tality Discharged</th>
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<td>von Arbin et al</td>
<td>22</td>
<td>494</td>
<td>-</td>
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<td>mean 21 days</td>
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<td>47</td>
<td>307</td>
<td>-</td>
<td>Randomization</td>
<td>0-7 days</td>
<td>mean 60 days</td>
<td>ns</td>
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<tr>
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<td>71</td>
<td>-</td>
<td>-</td>
<td>Randomization</td>
<td>0-7 days</td>
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<tr>
<td>Wood-Dauphinee et al</td>
<td>72</td>
<td>130</td>
<td>-</td>
<td>Randomization</td>
<td>0-7 days</td>
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<tr>
<td>Stevens et al</td>
<td>73</td>
<td>225</td>
<td>-</td>
<td>Randomization</td>
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(Improved)
The cerebral autoregulation, defined as the capacity of CBF to remain unchanged despite variations of the cerebral perfusion pressure, serves to maintain the vascular supply of oxygen and substrates to the brain grossly unchanged, and to control the capillary filtration by keeping the cerebral capillary pressure within normal limits. Poiseuille's formula implies that small variations in the vascular diameter are adequate to keep flow unchanged when the perfusion pressure varies. Thus, in normal circumstances, a relative normal blood flow can be maintained over a wide range of perfusion pressures by small variations in the vascular tone of precapillary cerebral arterioles.

The Hagen-Poiseuille equation

\[ Q = k \times P \times r^4/V \times L \]

- \( Q \) = blood flow
- \( P \) = perfusion pressure
- \( r \) = vessel radius
- \( V \) = blood viscosity
- \( L \) = vessel length

Metabolic factors such as CO2, lactate, pH, adenosine and bicarbonate are known regulators of regional CBF. Neurogenic and myogenic factors have also been proposed to be involved (75).

The range of autoregulation is shifted upwards in hypertensive individuals (76), in whom modest reductions in blood pressure may provoke significant falls in CBF. In man, the lower limit of autoregulation lies between a mean arterial pressure of 50-80 mm Hg and the upper limits around 150-180 mm Hg (77). It is unlikely that local changes in perfusion pressure in patients with normal autoregulation produces variations in regional CBF. However, perfusion pressure becomes particularly important in brain regions with impaired autoregulation. Autoregulation is impaired or abolished in various conditions, including acute cerebrovascular lesions (78).

CBF in ischemic regions shows a mixed picture. After occlusion of a middle cerebral artery in experimental animal models, the CBF initially decreases and then eventually recovers to normal or even hyperemic
values or persists in any state between these extremes (79). This mixed picture of rCBF is also confirmed in humans suffering acute cerebral infarction (78, 80, 81).

Pathophysiology of cerebral infarction

Focal cerebral ischemia or infarction are caused by a reduced local vascular supply of blood. This may be caused by a local thrombosis, heart-to-artery or artery-to-artery embolization, hemodynamic alterations such as rapid lowering of blood pressure and cardiac arrhythmias or, vasospasm related to migraine or surarachnoid hemorrhage. The atherosclerotic changes in the extra- and intracerebral artery supply, i.e. degree and extent of stenoses and occlusions, the availability of collaterals and some hematological variables, such as heamatocrit and plasma viscosity, will also influence the amount of ischemia induced.

Whatever the cause of the reduced regional CBF, the local ischemia per se induces a cascade of events that, depending on the degree and duration of ischemia, will result in brain infarction and brain cell death. This sequence of events, started by decreased ATP-production and disturbed cellular membrane ion fluxes, appears in a fairly constant manner and is listed below:

1. Synaptic transmission failure
2. Loss of autoregulation
3. Microcirculatory and rheological alterations
4. Development of cerebral edema
5. Intracellular events

These events and their combinations may further increase local cerebral ischemia and create a vicious cycle of increasing brain infarction.

Synaptic transmission failure. In subhuman primates, neurons maintain normal electrophysiological function as evidenced by normally evoked potentials with blood flow values above 20 ml/100 g/minute. Below this level evoked potential diminish, and at 15 ml/100 g/minute the evoked potential disappears completely (82). When flow falls below 12 ml/100 g/minute evidence of membrane Na\(^+\)-K\(^+\) transport failure and impending
cell death is seen, i.e. an increased extracellular potassium concentration (83). These critical levels of blood flow appear to be quite similar for different species. The flow necessary for neuronal survival may be higher in humans but reversible electroencephalographic changes also in man do not occur until CBF values fall below approximately 20 ml/100 g/minute (84).

There appears to be two critical thresholds for CBF, one for cessation of synaptic transmission activity, which causes the neurological deficit, and one for cell death (Fig. 2). The range between these two thresholds, known as the zone of "penumbra", is used to describe those neurons that because of decreased perfusion are neurophysiologically silent but remain viable (85, 86). The length of time that neurons may remain in this penumbral state with blood flow values between 12 and 20 ml/100 g/minute is unknown (86) and regional variability of susceptibility to ischemia may exist. However, the return of the normal function has been observed with the return of normal flow.

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**Fig. 2. Thresholds of cerebral ischemia.**

**Loss of autoregulation.** The deranged autoregulation has two clinical consequences; it makes CBF dependent on adequate perfusion pressure and it initiates increased capillary filtration and makes brain edema possible, especially if associated with a derangement of the blood brain barrier.
Microcirculatory and rheological alterations. The microcirculatory changes that have been observed in experimental ischemic regions consist of slowing of the velocity of blood, darkening of venous blood, aggregation of the formed elements of the blood with hemoconcentration elevating blood viscosity (87-89) and activation of platelets and coagulation mechanisms (88, 90, 91). This is followed by vasoconstriction, development of platelet thrombi in veins, the appearance of red venous blood, collapse of vessels, perivenous hemorrhages and cerebral edema (87). It has been postulated that following an ischemic insult, endothelial blebs, astrocytic foot swelling and capillary collapse might prevent reperfusion, i.e. the no-reflow phenomenon (92, 93). This concept has however been questioned as a possible artifact (94).

Cerebral edema. According to the present opinion edema is a stereotypic reaction of the brain tissue to numerous lesions disturbing the energy supply. Edema develops in two stages (20). Firstly, the failure of energy-dependent active ionic transport leads to intracellular uptake of water and a cytotoxic edema arises (electrolyte edema). Secondly, after some hours to a few days, vasogenic edema follows due to microvascular damage with subsequent escape of protein-rich fluid from the bloodstream into the extracellular space. Edema increases intracranial pressure which will decrease effective perfusion pressure in the ischemic region and possibly enlarge the ultimate extent of brain infarction. If excessive brain-stem herniation with death will occur.

Intracellular events. Among the various metabolic events induced by cerebral ischemia some seem of more pathogenetic importance than others in experimental situations. These are, intracellular accumulation of calcium, accumulation of free fatty acids especially arachidonic acid, lactic acidosis and free radical induced reactions. For review see (95).

The failure of the energy-requiring membrane pump systems causes an increase in cytosolic concentrations of sodium and calcium ions. Accumulation of calcium ions in the cytosol is a possible early step in the sequence of events leading to cell death (95, 96). Other possible mechanisms are phospholipase activation causing increased concentration of
FFA, such as arachidonic acid, which by further oxidation produces short-living and highly reactive prostaglandin-like substances, such as thromboxanes and leukotrienes, and also free radicals, all potentially harmful to the neuron and surrounding tissue (95).

Under normal conditions the high energy requirements of the brain are covered by oxidation of glucose. In incomplete ischemia, as opposite to complete ischemia, glucose supply is maintained and anaerobic glycolysis causes tissue lactacidosis which sometimes may become extreme (97). It has, therefore, been suggested that severe incomplete ischemia is even more detrimental to the brain than complete ischemia (98, 99) and that postischemic biochemical changes during the reperfusion period add to the ultimate degree of neurological deficit (95, 97, 100). Another explanation that has been suggested is that of the membrane damage by lipid peroxidation induced by free radicals which are produced during hypoxia but not when oxygen is totally absent (100, 101).

Blood viscosity and stroke
Patients with both primary and secondary polycythemias are shown to be at increased risk for thrombo-embolic vascular accidents (102-108). The critical factor underlying this relationship seems to be the height of the hematocrit with the increased platelet count assuming secondary importance (102, 108). In the Framingham study, high hematocrit, even in the normal physiological range, was associated with a twofold increased risk of stroke (109). If this was due to the elevated hematocrit per se, or secondary to smoking habits or hypertension needs, however, further investigations, as suggested by the authors (109). Other disorders, such as sickle cell disease, elevate blood viscosity considerably, and those patients often suffer strokes in the early years of life (110, 111). There are also reports on TIAs and stroke associated with leukocytosis in acute leukemias (112, 113).

Under pathological conditions plasma protein concentrations may be considerably elevated and significantly influence whole blood viscosity. Stroke is a common complication in paraproteinemias such as Waldenström's macroglobulinemia and myelomatosis (114-116). Also elevated fibrinogen levels are reported to increase the risk of both myocardial
infarction and stroke (117). On the other hand, patients with anemia, and normal patterns of plasmaproteins seem to be relatively protected from vascular complications (118).

In patients who suffer a stroke, the clinical outcome also appears to be influenced by viscosity factors. In a large Japanese autopsy series, it was found that the extent of cerebral infarction was directly proportional to the hematocrit (108). Also, the size of cerebral infarcts measured by CT scan in patients with angiographically proven carotid occlusion was found to be related to the height of the prevailing hematocrit in an English study (119). This relationship has also been confirmed in animals (120).

Cerebral blood flow and blood viscosity

Basically, as Poiseuille stated in 1842 (121), there are three factors that determine the flow of Newtonian liquids in round tubes. These are the internal tube diameter, the perfusion pressure and the viscosity of the liquid. Although blood rheology is non-Newtonian and the flow is pulsative in non-rigid tube systems, this equation would appear to be valid for application also to the cerebral circulation.

The CBF is reported to be elevated in patients with anemia (122, 123) and low in patients with high viscosity due to polycythemia (124-126) and in persons with high "normal" hematocrit (127). Thomas and coworkers have shown an inverse relationship between CBF and Hct in the normal range between 36 and 53% (127). When the hematocrit is reduced by hemodilution, CBF increases in animals (128), in normal man (129) and in patients with primary polycythemia (126) or high normal hematocrit values (127, 130).

Changes in CBF related to the hematocrit may, however, just be a physiological consequence, unrelated to viscosity, of the higher oxygen-carrying capacity of blood with high concentration of red blood cells (131-133) and is not necessarily harmful. However, the CBF in anemic patients with paraproteinemia, who have a reduced amount of oxygen carriers but elevated blood viscosity, have been shown to be significantly lower than the CBF in anemic patients without plasma protein abnormali-
ties (134). The authors conclude that viscosity factors rather than oxygen-carrying capacity determines CBF (134). Also, in psychological tests, patients have been shown to score better when hematocrit is lowered by venesection (135). The possible explanation of this increased alertness when blood viscosity is reduced is that the elevation of the CBF is in excess of that predicted on the basis of the reduction in arterial oxygen content, and thus actually increases cerebral oxygenation. An increased oxygen transport to the brain, measured as the product of CBF and arterial oxygen content, has been shown in patients with elevated hematocrit values after venesection (136).

Blood flow and arterial oxygen content are the main determinants of tissue oxygenation. However, the delivery of oxygen to the brain is also influenced by the partial pressure gradient of oxygen across the capillary wall and the position of the oxygen dissociation curve. Elevated CBF has been reported in patients with polycythemia secondary to the presence of a hemoglobin variant characterized by high oxygen affinity, although these patients probably have a high blood viscosity (137). In contrast to the conclusion of Humphrey and coworkers (134), there are also other reports that indicate that oxygen delivery capacity, rather than viscosity factors, is the dominant factor in the regulation of cerebral blood flow (138-140).

Determinants of blood viscosity
Blood is a non-Newtonian fluid in which the viscosity varies at different shear rates and there is no constant level of blood viscosity which could be valid for the entire circulation. Blood viscosity decreases as shear rates or flow velocities increase (141). The main determinants of whole blood viscosity are shown in Fig. 3.

Under normal conditions hematocrit is the main determinant of whole blood viscosity (142) and especially the magnitude of the "yield stress", the minimal force required to start flow once it has been stagnant, depends on the hematocrit level (143). As flow velocity falls, viscosity increases considerably, mainly because of the red cell aggregation that occurs at low rates of shear. At normal patterns of plasma proteins, fibrinogen is the main determinant of plasma viscos-
ity. Fibrinogen also influences the aggregation of erythrocytes and elevated levels of plasma fibrinogen will increase blood viscosity considerably at low flow states due to this enhanced red cell aggregation (144). Capillary hematocrit is reported to be approximately half of that in the systemic circulation (145). However, since the diameter of the red cells exceeds that of the vessel at the capillary level viscosity rises sharply depending on the energy required to deform the red cell (146). Red cells are reported to be more rigid in various diseases and also under conditions of anoxia and low pH (147).

Fig. 3. Important factors determining blood viscosity.

Under pathological conditions of low blood flow the viscosity factors apparently interact in a vicious cycle, which progressively increase viscosity and tend to slow blood flow even further. In ischemic situations this concept may be of clinical significance.

Therapies directed towards reducing blood viscosity
Blood viscosity can be reduced and blood flow improved by manipulating any of the above mentioned viscosity factors. Fibrinogen has been lowered acutely using Ankrod, a fibrinogen-cleaving enzyme obtained from a snake venom (157), in a small study without conclusive results regarding outcome. Red cell deformability has been enhanced by the administration of pentoxifylline (158). In patients suffering ischemic stroke, hemodilution has been applied and investigated since the 1960's (148-156). In some studies, CBF has been investigated and found to be elevated during therapy (155, 159), but as regards clinical outcome, the results from controlled studies have mostly been disappointing.
(150-152). Positive results have been reported by Gottstein et al (154) in a large retrospective study without a randomized control group and by Gilroy et al in a randomized study with comparable controls (149).

In practice, hemodilution has been most widely used of all blood viscosity lowering regimes. Hemodilution consists of phlebotomy and replacement of blood volume by low-molecular-weight dextran or other substitutes (isovolemic hemodilution) or infusion of plasma volume expanders without concomitant phlebotomy (hypervolemic hemodilution). These hemodiluting regimes reduce viscosity by reduction of the packed red cell volume and enhance CBF (160). When dextran 40 is used as a plasma volume expander also the erythrocyte-desaggregating effect (161) and the platelet anti-aggregating effect (162, 163) may account for some beneficial results obtained with this solution. Hemodilution is limited by the reduction of the net oxygen transport capacity of the blood and the patients capacity to increase cardiac output and hemodynamic monitoring may be of value (156). However, hematocrit can be reduced considerably before tissue oxygenation (i.e. blood flow multiplied by hematocrit) subsides. Optimal hematocrts for delivery of oxygen to the tissues have been estimated experimentally to be 30-33% (164-166), which is also clinically supported in postoperative patients (167). However, in older patients the optimum hematocrit for oxygen delivery may be higher (168). In Table II, some controlled studies regarding hemodilution therapy with dextran are summarized. It emerges that the results are conflicting and that in only one study is the long-term clinical outcome evaluated.
Table II. Randomized controlled studies of hypervolemic hemodilution in acute ischemic stroke.

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Ref no</th>
<th>Treatment regime</th>
<th>No of patients</th>
<th>Follow up</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>H  C</td>
<td></td>
<td>Mortality</td>
</tr>
<tr>
<td>Gilroy et al</td>
<td>149</td>
<td>Dextran 40</td>
<td>46  54</td>
<td>10 days</td>
<td>ns</td>
</tr>
<tr>
<td>Spudis et al</td>
<td>151</td>
<td>Dextran 40</td>
<td>30  29</td>
<td>21 days</td>
<td>ns</td>
</tr>
<tr>
<td>Matthews et al</td>
<td>150</td>
<td>Dextran 40</td>
<td>52  48</td>
<td>21 days</td>
<td>ns*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 months</td>
<td>ns</td>
</tr>
<tr>
<td>Kaste et al</td>
<td>152</td>
<td>Dextran 40</td>
<td>20  20</td>
<td>29 days</td>
<td>ns</td>
</tr>
</tbody>
</table>

Dexamethasone

*Mortality in severe hemisphere strokes (21 and 13 patients, respectively) was significantly reduced.
AIMS OF THE STUDY

The aims of the present prospective study were:

1. To characterize essential clinical features of the different cerebrovascular disorders in well investigated, unselected, acute stroke patients.
2. To evaluate the impact of a non-intensive stroke unit regime on the short and long-term clinical outcome for unselected acute stroke patients.
3. To define any particular subgroup(s) of stroke patients who benefit more than others from stroke unit care.
4. To evaluate the effect of early hemodilution therapy on the short and long-term clinical outcome in patients with acute cerebral infarctions, and of the safety of such a treatment.

PATIENTS AND METHODS

Description of methods and procedures used in these studies are presented in detail in each paper (I-V) and are summarized here. A more extensive description will be given of the organization and function of the stroke unit.

Background population

Umeå University Hospital serves a population of about 116 000 inhabitants (49.6% males) in the city of Umeå and the surrounding rural area. The population of Umeå is somewhat younger than that of the entire county; 29.4% of the population are 50 years and above, the corresponding figure for Sweden being 33.8%.

All acute stroke patients in the district of Umeå, coming to hospital are admitted to the Department of Internal Medicine (250-325 patients annually). When the diagnosis subarachnoid hemorrhage is established, however, the majority of these patients are transferred to the Department of Neurosurgery. All other acute stroke patients are without exception treated at the Department of Medicine, which has 144 beds in
five wards. After a run-in period, a non-intensive stroke unit was established at one of these wards in January 1978, with an estimated capacity to treat approximately one third of all acute stroke patients in the district of Umeå.

Patients
A total of 592 patients were prospectively included in these studies from January 1978 until December 1982. Of these, 409 patients were treated at the stroke unit and 183 at one of the other four general medical wards. The patients are listed in Table III.

Table III. Patients included in Studies I-V

<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients</th>
<th>Allocated to SU</th>
<th>Allocated to GMW</th>
<th>Study period</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>409</td>
<td>409</td>
<td></td>
<td>1978-1982</td>
</tr>
<tr>
<td>II, III</td>
<td>293</td>
<td>110</td>
<td>183</td>
<td>1979-1981</td>
</tr>
<tr>
<td>IV, V</td>
<td>102</td>
<td>102</td>
<td></td>
<td>1980-1982</td>
</tr>
</tbody>
</table>

Study I. All patients admitted to the stroke unit and fulfilling the inclusion criteria (see above) were included during a five-year period from January 1978 until December 1982. Altogether 428 patients were admitted during that period. Of these, a well-defined cerebrovascular diagnosis (ICD 8, No 431-435) was established in 409 patients.

Study II and III. All patients admitted to the Department of Internal Medicine and fulfilling the admission criteria of the stroke unit were included during a 16-month period (October 1979 to January 1981). A total of 293 patients were included, of whom 110 were treated in the stroke unit and 183 in the general medical wards.

Study IV and V. The patients were all treated at the stroke unit and recruited according to the following inclusion criteria: a) focal neurological deficits of presumed vascular origin with acute onset and persisting at the time of inclusion in the study, b) start of treatment possible within 48 hours of the onset of symptoms, c) no macroscopically hemorrhagic admixture in the cerebrospinal fluid, d) hemoglobin
levels between 120 and 180 g/l, e) no myocardial infarction during the last week, f) absence of unstable angina pectoris and overt signs of left ventricular failure, g) plasma creatinine < 300 umol/l, h) absence of concomitant severe disorders in the terminal stage, i) absence of coma not responding to pain stimuli and k) no ongoing treatment with anticoagulant agents.

From December 1979 until April 1982 a total of 102 patients were randomized to a treatment (52 patients) or to a control group (50 patients).

THE STROKE UNIT

The stroke unit is a 6-bed, non-intensive care and research unit for patients with well-defined acute cerebrovascular disease. In charge of the unit is the Head of the Department of Medicine and the Stroke Group, a group of physicians meeting weekly, to discuss and decide about management of the unit. All patients admitted are subjected to a strictly structured program of investigation, nursing, medical treatment and rehabilitation.

Admission criteria
All patients from the district of Umeå, regardless of age, who without preceeding trauma to the head present with focal neurological dysfunction with a duration not exceeding one week or patients with TIA during the last week are admitted. Patients with dizziness and/or disturbance of consciousness or orientation without concomitant focal neurological signs are not admitted. The sensitivity and specificity of such criteria has been found valid and appropriate for a standardized identification of stroke in the acute situation (169).

Admission procedure
Considerable precautions are taken to avoid a biased selection of patients to the stroke unit. Regular repeated information about the admission criteria is given to the personell admitting patients. At the emergency department, the physician on duty has to contact the stroke unit whenever a stroke patient filling the inclusion criteria is admit-
ted to the hospital. Provided a bed is available, the patient is admit­ted to the unit; otherwise he/she is admitted to a general medical ward. Once admitted, no patient is transferred between the stroke unit and the general medical wards. This mode of patient allocation has been shown to provide a patient sample representative of all those admitted for acute stroke in the Umeå hospital district (II).

Content of stroke care
The essential features of the stroke unit include (1) team work, (2) a program of staff education directed to improve knowledge and to promote a dedicated attitude to the care of stroke patients, (3) very early and determined activation, (4) active participation of family members in the rehabilitative efforts and (5) education of patient and family mem­bers.

Once a week there is a planning conference headed by the stroke unit physician where all members of the stroke team update all aspects of each patient in the unit and plan for the following weeks' care and rehabilitative activities. During hospital stay there is also one or more conference(s) where patient and family members participate and in­formation concerning the cerebrovascular diagnosis, present status of the patient and plans for the near future are given. Other activities involving family members are home visits by the patient and members of the stroke team during hospital stay to prepare discharge to the home. At discharge, a final conference with patient and family members is arranged at which all aspects of the acute stroke event are explained and discussed and the follow up is planned.

Prior to discharge from the stroke unit, social services, physicians or institutions involved in the future care of the patient are carefully informed about the patients' problems and program for further rehabil­itation.

The patients stay in the stroke unit until they are able to return home or are transferred to a long-stay hospital. All patients that are can­didates for transfer to a long-term care hospital are seen by a senior physician from the only long-term care hospital in the district. He
uses identical criteria for selection to long-term hospital care for patients from the stroke unit and from general medical wards, the main determinants being severe neurological deficit, mental impairment and inability to provide adequate nursing care at home. For patients accepted there is a waiting list for admission to the long-term care hospital. In accordance with a separate agreement, the waiting time for admission to the long-term hospital is reduced for stroke unit patients.

The patients are followed up at three months and at one year after the initial stroke event at our out-patient stroke clinic, which is staffed by a physician, a physiotherapist and an occupational therapist. Place of stay is registered and patients, family members or hospital/nursing home staff are interviewed on some selected ADL items. In addition there is a clinical examination and neurological assessment by the physician.

The stroke team
Members of the stroke team are (1) a physician working part-time in the unit, (2) a nurse (full-time) who follows a modified primary nursing approach including contacts with family members and social institutions; only occasionally is a social worker consulted, (3) a physiotherapist (part-time) and (4) an occupational therapist (part-time).

The stroke unit physician performs all clinical investigations and is responsible for and supervises the medical care. The nurse has a crucial role in the unit; she participates in and coordinates all aspects of the patients' daily treatment including education of relatives and cooperation with social authorities. The objectives of the physiotherapist and occupational therapist are mainly to assess patient performance and act as instructors for other personnel in the ward to ensure a continuous training of all patients.

Nurse's aids on the ward have particular training and experience in the care of stroke patients. There are weekly rounds in the unit where specialists in rehabilitation and physical medicine participate. A speech therapist is occasionally consulted, but the training of aphasic patients is, with few exceptions, performed by the stroke team and family members.
Diagnostic procedures

Every patient in the stroke unit is subjected to a standardized scheme of investigations. Repeated clinical assessments are performed, the first by the emergency ward physician and then by the stroke unit physician. These investigations are performed routinely at the time of admission, day 1, day 4 and at discharge. All data obtained from these investigations are registered in a 574-item protocol for computer use.

In particular, the stroke unit patients are carefully observed in order to detect signs of deterioration and secondary complications to the stroke. Repeated assessments of locomotor function, ADL capacity and perceptual function are performed by the physiotherapist and the occupational therapist.

Computed tomography of the brain (EMI Scan Mark One Head Scanner 1978-1982), is routinely performed as soon as possible on every patient not in need of general anesthesia for cooperation and is repeated, if possible if the results are inconclusive.

Lumbar puncture is performed in the lateral recumbent position in all patients on admission and repeated on the fourth to fifth day after admission if there are no contraindications. The spinal fluid is analyzed for cells, total protein content according to Lowry (170), visual xanthochromia after centrifugation, and subvisual xanthochromia by the spectrophotometric method described by Kjellin and Söderström (171). Provided red blood cell admixture from traumatic lumbar puncture is eliminated by very early centrifugation, a spectrophotometric peak oxyhemoglobin absorbance at 415 nm above 0.0030 is accepted as a pattern of hemorrhage.

Routine blood tests on admission include hemoglobin, hematocrit, red and white blood cell counts, platelets, fibrinogen, sedimentation rate, protrombin-complex, fibrinogen degradation products, APTT (partial thromboplastin time), circulating concentrations of glucose, sodium, potassium, chloride, bicarbonate, albumin, calcium, phosphorus, creatinine, aminotransferases (ASAT, ALAT), lactic dehydrogenase (LD), and creatine kinase (CK). On the following two days blood tests for amino-
transferases are repeated. At the end of the hospitalization period blood tests for cholesterol and triglycerides are drawn.

Routine urine tests for albumin, glucose and red and white cells are performed on the first day after admission.

Every patient is subjected to repeated, routine 12-lead ECG investigations during the first three days after admission. Chest x-rays are routinely performed in every patient once during stay in the stroke unit, including an estimation of the relative cardiac volume in patients able to stand unaided.

If cerebral embolism of possible cardiac origin is suspected, echocardiography and pulmonary-artery cineangiocardiography (172) are performed.

Angiographic examinations of intracerebral and neck vessels are performed in younger subjects with minor neurological deficits and in patients with TIA if they are considered as candidates for carotid thrombendarterectomy.

Diagnostic criteria
Findings at CT-scan, spinal fluid spectrophotometry, clinical examination and, when applicable, at autopsy are all considered when establishing a final cerebrovascular diagnosis. Conclusive findings at CT-scan and at autopsy take predominance over CSF-spectrophotometry. Controversial diagnoses are discussed by the stroke group. Minimal diagnostic criteria for the different cerebrovascular diagnoses are listed below:

TIA: focal neurological deficits of presumed ischemic origin and with a duration of less than 24 hours (ICD 8, No 435).

Cerebral infarction: neurological deficits persisting more than 24 hours or until death without signs of bleeding by CT-scan and/or spinal fluid spectrophotometry.
Embolic cerebral infarction: non-documented or sudden symptom onset and with a potential source of embolism (atrial fibrillation or flutter, recent myocardial infarction, left ventricular aneurysm, rheumatic and non-rheumatic valvular disorders) (ICD 8, No 434).

Non-embolic cerebral infarction: no potential source of embolism and/or a documented non-sudden symptom onset (ICD 8, No 433).

Intracerebral hemorrhage: hematoma on CT-scan and/or conclusive hemorrhagic pattern at CSF-spectrophotometry (ICD 8, No 431).

Ill defined acute cerebrovascular disease: neurological deficits of presumed vascular origin when no diagnostic procedures have been performed or when the results are inconclusive (ICD 8, No 436).

Basic care and medical therapy
The stroke unit has no facilities for intensive care, i.e. no capacity for assisted ventilation and continuous cardiac monitoring. A cornerstone in the stroke unit regime is very early mobilization of every patient and start of activation often within the first 24 hours, if the patient's clinical status permits.

Electrolyte and fluid balance. In patients unable to self-feed, intravenous infusions of electrolytes and carbohydrates are given to maintain balance during the acute phase. The fluid is restricted in order to avoid overload and possible aggravation of cerebral edema.

Nutrition. Great attention is given to oral feeding. Complete parenteral nutrition is started in patients unable to self-feed on the fourth day after admission. As soon as possible the intravenous route is changed to enteral tube feeding.

Bowel and bladder function. Bulk laxative or lactulose are routinely used in order to maintain regular bowel function and to avoid constipation in bed-ridden patients. Urinary catheters are seldom used and mainly on the indication of urinary retention. Incontinent patients use napkins and are trained in their bladder function.
Pressure sores and contractures. A scheme of repeated changes of position for bed-ridden patients is strictly followed with passive movements in paralysed extremities supervised by the physiotherapist.

Airways. Attention to mucous stagnation in lower airways. Removal of mucous by suction if necessary. Cleaning of mouth and upper respiratory tract.

Deep venous thrombosis. Repeated examinations for clinical signs of deep venous thrombosis in the lower limbs. If a thrombus is documented or suspected, treatment with heparin and oral anticoagulation is started when there are no contraindications. In patients highly suspected or at risk for developing DVT, subcutaneous heparin is prophylactically given during hospital stay until full mobilization. Pulmonary embolism is vigourously treated with full dose heparin.

Infections. Sustained fever, pulmonary and urinary findings suggesting airway or urinary tract infections are promptly treated with appropriate antibiotics. Body temperature is followed twice daily during the first week in every patient, thereafter only in high risk patients.

Cardiac complications. Disturbances in cardiac rhythm and contractility are followed and treated in order to sustain a hemodynamically optimal state of cerebral perfusion. Routine ECG is performed daily during the first three days and thereafter on specific ordination. Concomitant myocardial infarction and unstable angina pectoris are conventionally treated.

Hypertension. Blood pressure levels are measured every 6th hour during the first three days and once daily thereafter. Patients previously on antihypertensive treatment are maintained on their medication. Extremely high blood pressures (no fixed limits) are treated by careful lowering of pressure to about 180/110 mm Hg. Moderately elevated blood pressure is regularly not treated unless the patient has an intracranial hemorrhage. After the acute phase, all patients found to be hypertensive are treated.
Diabetes mellitus. Careful monitoring of blood and urinary glucose, electrolyte and fluid balance during the acute phase. Non-insulin dependent diabetics are temporarily given insulin.

Other concomitant disorders. The patients keep their regular drug regimes if appropriate.

Seizures. General or partial epileptic seizures are immediately treated with benzodiazepines intravenously or other appropriate drugs. If repeated seizures during hospital stay occur, prophylactic antiepileptic therapy is instituted.

Increased intracranial pressure. Decreasing level of consciousness, development of pupillary anisokoria, rising blood pressure and reduction of pulse rate are signs indicating increased intracranial pressure caused by either massive cerebral edema formation or ongoing intracranial bleeding. These patients are treated with intermittent intravenous infusions of hyperosmolar mannitol, thus minimizing the risk of rebound cerebral swelling by extravasation of mannitol into the cerebral parenchyma.

TIA. Patients with repeated TIAs during the last week or more than one TIA during 48 hours receive heparin intravenously for five days followed by oral anticoagulants. Patients with a single TIA receive acetyl salicylic acid 1-1.5 g daily. If the patient assents to and is suitable for carotid surgery, neck vessel angiography is performed.

Progressing stroke. Significant deterioration of focal neurological deficits after hospital admission is treated with heparin intravenously for five days if intracranial hemorrhage is excluded.

Cerebral infarction. In patients without deterioration, no specific treatment directed towards the cerebral lesion as such is instituted during the acute phase. During a two-year period a randomized trial of hemodilution was performed (IV, V). Patients with embolic infarctions of presumed cardiac origin usually start oral anticoagulant therapy approximately one week after symptom onset.
**Intracerebral hemorrhage.** Neurosurgeons are always consulted for evaluating the possibility of acute surgery.

**Subarachnoid hemorrhage.** Usually, transfer to the Department of Neurosurgery when the diagnosis is established. Some old patients, however, remain in the stroke unit and are treated with protracted bed rest during the acute phase.

**Hemodilution therapy (IV, V)**

The patients randomized to treatment underwent as soon as possible (day 0) a 250 ml venesection during which approximately 150-200 ml of 10% dextran 40-saline (Rheomacrodex R) was infused, making the initial phase of the procedure isovolemic (173). Another 300-350 ml of the dextran solution was given over the next 2-4 hours, the rate being adjusted according to the patient's cardiac status. On the following day, patients with hemoglobin levels above 120 g/l were subjected to another 250-400 ml venesection, the volume being dependent on the hemoglobin level. The equivalent volume of dextran 40 was given during the venesection (150-350 ml) in order to keep the initial procedure isovolemic, followed by dextran to a total volume of 500 ml. In patients with hemoglobin below 120 g/l no venesection was performed but 500 ml of dextran was infused over 2-4 hours. On day 2, 4 and 6 after randomization dextran 40 infusions were given without concomitant venesections (500, 250 and 250 ml, respectively).

**Evaluation of stroke unit care (II, III)**

A protocol including neurological signs, functional capacity and previous medical history in each patient was filled in at the emergency department whenever a stroke patient fulfilling the inclusion criteria of the stroke unit was admitted. At discharge, a corresponding record of the present status of the patient was completed. The patients were followed up at three months and at one year after admission. Place of stay and mortality were registered and patients, family members or hospital/nursing home staff were interviewed by a nurse on certain selected ADL items (ambulatory capacity, feeding, personal hygiene and dressing). The nurse was not affiliated with the stroke unit.
Evaluation of hemodilution treatment (IV, V)

Neurological assessment was performed by the Frithz & Werner modification (174) of a scoring system developed by Mathew (175). The scoring was done before randomization, on day 3 and on day 9. These assessments were performed blindly by a physician who did not know to which group the patient had been assigned.

Deaths, recurrent strokes and other major vascular events were registered during the first year after the stroke. All surviving patients were seen in our out-patient stroke clinic at three months and at one year. These examinations were open, and included an assessment of the ADL, a physical examination and a registration of whether the patient was institutionalized or not. Hemoglobin and hematocrit values were registered daily during the first ten days and were also determined at three months after the stroke.

In a subsample of seven hemodiluted patients, whole blood viscosity was determined at different shear rates on day 0, 1, 2 and 7, using a Brookfield viscosimeter.

Statistical analyses

The chi-square test was used for testing the significance of differences in proportions of patients (I, II, III, IV and V). To estimate mortality and need for hospital care, also the lift-table technique and log-rank tests according to Peto et al (176) were used (III). Multiple regression was calculated as described by Snedecor and Cochran (177) (III). Means were calculated with their 95% confidence intervals (I, IV). For comparisons of groups of data we used Student's t-test (for paired when applicable), chi-square test, Wilcoxon's rank sum test and log rank test (IV).
RESULTS

The results of each study are briefly summarized here. Detailed information is given in the separate papers (I-V).

Clinical profiles of the different cerebrovascular disorders (I)
During five years (January 1978 to December 1982) 428 consecutive patients representative of all cases admitted for acute stroke within a well-defined population were admitted to the stroke unit. In 409 of these unselected patients, mean age 71.9 years, a well-defined acute cerebrovascular diagnosis, according to our diagnostic criteria, was established (ICD 8, No 431-435) and clinical features on admission were investigated.

In people 50-79 years of age the men:women risk for stroke was established to be 1.40:1, above the age of 80 a similar risk for the two sexes was observed. The cerebrovascular diagnoses were distributed as follows: Intracerebral hemorrhage 11%, TIA 13%, non-embolic cerebral infarction 51% and embolic cerebral infarction 25%. Of all 409 patients, 54% had a prior medical history of hypertension, 21% atrial fibrillation or flutter, 35% congestive heart failure, 27% angina pectoris, 13% myocardial infarction and 17% diabetes mellitus. Only 14% of the patients were free of previous concomitant disorders affecting the cardiovascular system. Similar proportions of patients in all diagnostic categories had a previous medical history of hypertension (48-59%) and previous stroke (27-33%). TIA preceeded intracerebral hemorrhage in 11%, embolic cerebral infarction in 15% and non-embolic cerebral infarction in 20%. Diastolic blood pressure level and routine blood chemistry on admission were not grossly different among the diagnostic groups.

As opposed to patients with cerebral infarctions, subjects with intracerebral hemorrhage had no male preponderance, and fewer had a history of cardiac disorders, diabetes and smoking, but they had higher systolic blood pressure levels and more severe symptoms on admission to hospital.
Effects of a non-intensive stroke unit regime on functional disability and need for long-term hospitalization (II)

In a prospective controlled trial of 16 months (October 1979 to January 1981) the clinical outcome for 110 acute stroke patients treated in the stroke unit was compared to 183 patients treated in the general medical wards. These 293 patients represented all acute CVD patients admitted to the Department of Medicine and filling the admission criteria of the stroke unit (see above) during that period of time. The patients were allocated to the stroke unit if a bed was available, otherwise to one of the general medical wards.

Patients admitted to the stroke unit did not differ from stroke patients admitted to general medical wards in age (mean age 72 and 73 years, respectively) or sex distribution. A history of cardiac disorders was somewhat more commonly observed among the stroke unit patients (65 vs 52%), otherwise the prevalence of concomitant disorders were comparable in the two groups. Only 11% of SU patients and 20% of GMW patients had no previous history of disorders affecting the cardiovascular system. Mean interval from the onset of symptoms to admission was 12 hours for both SU and GMW patients. The neurological symptoms presented in the emergency room did not differ in the two groups.

Mortality rates over the first year after the stroke were similar in the two groups. One year after the stroke, 39% of SU and 41% of GMW patients were dead. At discharge walking ability was significantly better (p < 0.01) among the stroke unit patients and fewer were discharged to a long stay hospital (p < 0.05) when compared to patients treated in the general medical wards. At three months after the stroke, 15% of the survivors initially admitted to the stroke unit and 39% of those admitted to general medical wards remained hospitalized (p < 0.001). The corresponding figures at one year after the cerebrovascular accident were 12 and 28%, respectively (p < 0.05). One year after the stroke a greater proportion of surviving stroke patients was independent in walking (0.10 > p > 0.05), personal hygiene (p < 0.05) and dressing (p < 0.001).
Mean length of stay was similar for patients initially treated in the stroke unit and general medical wards who died (14 vs 15 days) or who were discharged to their homes (15 vs 18 days).

Is there any subgroup of stroke patients who benefit more than others from a stroke unit regime? (III)

In this extension of study II another statistical technique, log-rank testing, confirmed that the reduction in long-term hospitalization for surviving patients treated in the stroke unit was of high statistical significance (p = 0.0001). Further, in a multiple regression analysis three major determinants for long-term hospital care after discharge from the Department of Medicine were recognized. These were (i) presence of hemiparesis on admission (p < 0.0001), (ii) high age of the patient (p = 0.004) and (iii) care in the general medical wards (as opposed to the stroke unit) (p = 0.007). Other variables analyzed in the multiple regression model were marital status, side of neurological deficit and presence/absence of concomitant cardiovascular disorders. These variables had no predictive value in determining the need for long-term hospitalization.

When the patients were subclassified with regard to age, neurological deficits on admission, marital status and coexisting disorders no important differences between SU and GMW patients regarding mortality emerged in any subgroup. However, the proportion of patients discharged home was larger for all categories if the patients had been treated in the SU; log-rank analysis showed that the differences were statistically significant in most subgroups.

At one year follow up the difference in hospitalization in favour of the SU regimen was marked in patients > 75 years old (7% vs 20% in GMW patients; p < 0.02), and in patients with hemiparesis on admission (9% vs 21%; p < 0.05). In patients < 75 years old and in patients without hemiparesis on admission, the effect of initial care in the SU vs the GMWs on the need for hospital care at one year after the stroke was not statistically significant.
Effect of hemodilution therapy in acute brain infarction (IV)
The clinical effect of rapid hemodilution, by the combination of venectomy and administration of low molecular weight dextran in the early phase of ischemic stroke, was evaluated in a prospective controlled trial. From November 1979 until September 1982, 52 patients were randomized to hemodilution therapy and 50 to a control group. The two groups were comparable in all important prognostic variables such as age, concomitant disorders and neurological deficit on admission.

In the treated group mean hematocrit level fell from an initial 43% to 37% over the first two days, corresponding figures in the control group were 43% and 42%, respectively. The reduction in hematocrit in the treated group was paralleled by a reduced whole-blood viscosity when tested in a subsample of seven hemodiluted patients. Blood pressure recordings over the first ten days and at three months' follow-up were very similar in the two groups. Cardiac and other circulatory events appeared less frequent during the treatment period in the hemodiluted when compared to the non-hemodiluted group.

Median neurological score on inclusion was 64 points in patients randomized to hemodilution therapy and 69.5 points in control patients; the difference was not statistically significant. The improvement in neurological score points over the first 10 days was significantly greater in the hemodiluted group \(p < 0.002\) and the improvement seemed to encompass all the neurological variables assessed in the score. In the treated group 44 patients (85%) improved in neurological score points compared to 32 patients (64%) in the control group \(p < 0.025\). A deterioration in neurological score (including deaths) occurred in 4 hemodiluted (8%) and in 13 (26%) non-hemodiluted during the first ten days \(p < 0.02\). Two control patients received heparin therapy because of rapidly progressing symptoms.

By three months after the stroke, the case fatality rate was similar in hemodiluted and control group: 13 (25%) and 14 (28%) patients, respectively, were dead. Among survivors 5 (13%) of the hemodiluted and 14 of the control patients (39%) remained hospitalized at three months after
the stroke (p < 0.05). Inability to walk was noted in 3 hemodiluted (8%) and in 13 control patients (36%) at three months follow up (p < 0.005).

Two patients randomized to hemodilution therapy developed dextran induced anaphylactoid reactions shortly after start of the treatment. These patients were not hemodiluted but are included in the treatment group when evaluating the clinical outcome adhering to the intention-to-treat principle.

**Effect of hemodilution therapy on long-term outcome after brain infarction and evaluation of safety (V)**

In this extension of study IV the long-term outcome and the potential risk of the combined venesection/dextran 40 therapy were evaluated in the 52 treated and 50 control patients.

One year after the stroke, 16 patients (31%) initially randomized to hemodilution therapy and 20 patients (40%) in the control group were dead. Survival curves revealed no significant difference in the mortality rates. Of those patients who were severely disabled and hospitalized at three months after the stroke (5 hemodiluted and 14 non-hemodiluted), 6 patients died during the remainder of the year, 2 of them belonged to the hemodiluted group and 4 to the control group.

Thirty-six hemodiluted and 30 non-hemodiluted patients survived the first year following stroke. Among these, 4 hemodiluted and 2 control patients suffered a recurrent stroke. At clinical examination one year after the stroke, disturbances of orientation, speech and motor function were less frequent among hemodiluted patients and a statistically significant larger proportion of initially hemodiluted patients could walk independently, 92 vs 73% (p < 0.05). Total dependence in performance of ADL was noted in 6% of hemodiluted and in 30% of non-hemodiluted patients (p < 0.05). The proportion of surviving patients still hospitalized at one year after the stroke was 8% and 27% in the hemodiluted and control group, respectively (p < 0.05).
Prior to randomization, the CSF concentration of total protein and findings at CSF-spectrophotometry were closely similar in the two groups. However, when lumbar puncture was repeated at four days after the stroke, signs of blood-brain-barrier breakdown, measured as CSF-total protein content, and hemorrhagic admixture to the CSF at spectrophotometry were less pronounced and less frequent in hemodiluted subjects compared to controls.

Subset analysis revealed a tendency towards improved outcome for hemodiluted patients in all clinically important subgroups, except in those patients with a prior medical history of congestive heart failure. Because of small numbers of patients in each group, statistical significances were not to be expected.

DISCUSSION

Paper I
Most epidemiological data on acute cerebrovascular disease are derived from old studies without the aid of modern diagnostic technology. The distribution of the different cerebrovascular diagnoses in these studies must therefore be considered uncertain. Especially, recognition of intracerebral hemorrhages is poor without the use of CT scan (27, 178-180), and the diagnostic accuracy may be further strengthened if spinal fluid spectrophotometry is added (27, 179, 181). Since a correct diagnosis is a prerequisite for adequate decisions about therapy and for evaluation of therapeutical effects, reliable epidemiological data upon the distributions of the different cerebrovascular diagnoses are needed.

In 428 consecutive, unselected patients, presenting with focal neurological deficits, admitted to the single acute hospital in an epidemiological well-defined region of Northern Sweden, a definite acute cerebrovascular diagnosis was established in 409. The diagnoses were based on repeated clinical examinations, CT scan, spinal fluid spectrophotometry and, occasionally autopsy. When uniform diagnostic criteria were used (see Methods), the distribution of ischemic (89%) and hemorrhagic
(11%) cerebrovascular lesions was in accordance with the results reported by other investigators during recent years, showing a frequency of hemorrhages between 10-20% in most epidemiological studies (27-29).

When distinguishing embolic from non-embolic cerebral infarctions the definitions become operational, relying on reasonable diagnostic criteria such as sudden symptom onset and potential source of embolism. Since timing of onset of symptoms often (for instance during sleep) cannot be documented and a potential source of embolism also can exist in patients suffering other types of stroke the distinction of pathogenic mechanisms underlying cerebral infarctions will remain obscure and explains the variable figures in several recent studies. The diagnostic accuracy could somehow be strengthened if early angiography is performed (28, 182) or if an intracardial thrombosis is detected (172), investigations that hardly, however, can be performed in every stroke subject.

The frequencies of coexisting disorders affecting the cardiovascular system in the 409 acute stroke patients were in good agreement with other recent reports (9, 11, 22-26) and only 14% had no previous medical history of such diseases. Although a history of hypertension was equally frequent among patients with hemorrhagic and ischemic cerebral lesions, manifestations of atherosclerotic cardiac disease were less prominent in patients with intracerebral hemorrhages.

On admission to hospital, the patients with intracerebral hemorrhage showed the most severe neurological deficits followed by, in descending order of magnitude, patients with embolic infarctions, non-embolic infarctions and TIA.

Papers II and III
Despite the importance of stroke as a major cause of death and permanent disability, hospitals treating acute stroke patients usually lack a firm policy of management in the acute phase (9, 22, 27). The historical reasons explaining these facts are, firstly, prior lack of adequate diagnostic technology and, secondly, lack of proven effective therapeutical regimes.
During the late 1960's intensive care stroke units were introduced in the USA with the aim to reduce mortality and residual disability in the acute stroke patient. Results regarding mortality were, however, disappointing (41, 42, 44-46) while some units reported a decreasing incidence of secondary complications (43, 44).

Reducing disability in surviving stroke patients was the main goal set up for non-intensive stroke units. Evaluations of the efficacy of such units, performed in agreement with modern scientific methods are, however, sparse and the results divergent (70). It has been suggested that functional gains experienced by stroke patients are primarily attributable to spontaneous recovery (183). In the majority of stroke patients this potential for spontaneous recovery seems to extend for up to six months after the stroke with most of the recovery occurring within the first three months (184, 189). When setting up stroke units it therefore seems appropriate to include a scheme of assessing its value. The admission criteria to our stroke unit (unselected acute CVD patients) and the principle to allocate every such patient to the unit provided a bed is available, involves two advantages. Firstly, it offers the possibility for a continuous prospective evaluation of outcome variables in random samples of patients and, secondly, it allows for comparisons with patients allocated to treatment in general medical wards. Thus, comparable populations of acute CVD patients will be created together with the possibility to fully utilize the capacity of the stroke unit.

When comparing the clinical outcome in SU and GMW patients the conclusions rest on the comparability of the patients admitted to either of these wards. Our mode of random allocation created two populations of stroke patients that were comparable prognostically. The prognostic variables recorded - age, previous medical history, level of consciousness, extent of neurological deficits (185) and ability to walk on admission (186) - gave no indications of a predilection of milder cases to the stroke unit. Indeed, a history of heart disorders was more commonly observed among stroke unit patients - this could somehow have affected mortality rates disadvantageously to the SU patients - if it was not the result of a more determined search for heart disorders in the SU.
There is a short-term prognostic hierarchy quo ad vitam concerning the different cerebrovascular diagnoses intracerebral hemorrhage, embolic infarction, non-embolic infarction and TIA, in that order. The diagnostic classifications were very accurate in the SU with only 5% ill-defined acute cerebrovascular disorders as opposed to 25% in the GMWs due to lack of diagnostic investigations. However, nothing indicates that the proportion of intracerebral hemorrhages with presumed unfavourable prognosis (185) within this group should exceed the expected 10-20 percent (27-29). Also, the extent of neurological deficits has a more decisive prognostic importance than the specific cerebrovascular diagnoses (185, 186). Therefore, it seems highly unlikely that an unequal distribution of hemorrhagic intracerebral lesions in the two groups explains the differences in outcome.

The overall mortality rates over the first year after the stroke were closely similar for SU and GMW patients. However, when evaluating long-term neurological and functional outcome, possible differences in mortality rates among prognostically important subpopulations are important. An uneven distribution of deaths among severely disabled patients would bias the results concerning need for hospitalization in favour of this group. However, subset analyses revealed no unequal distribution of mortality over the first year following stroke.

Different statistical approaches were used: chi square test regarding proportion of patients hospitalized at three months and at one year after the stroke and life table analyses regarding the probability of being hospitalized after the stroke. Both methods showed statistically significant differences and this strongly support that the SU regime indeed is efficacious in reducing the need for long-term institutional care. One could possibly argue that the larger proportion of SU patients being able to be in their homes was mainly due to a possible influence on attitudes in relatives during stay in the SU (187) and not related to a better functional capacity. There was, however, no significant differences between married and not-married (divorced, widowed, unmarried) patients regarding the relative reduction in further hospitalization. Although marital state probably is an insufficient parameter in assessing the complete social network around patients in these
high age groups, it offers some information. When evaluating the ADL-capacity one year after the stroke, SU patients were found to perform significantly better in most variables when compared to GMW patients (II). Thus, it seems that the reduced need for hospitalization for patients initially treated at the SU was mainly due to a better ADL performance.

Baseline data on admission, such as neurological deficits and age, are more important than any therapeutic intervention in determining outcome (185). This generally accepted order of poor prognostic signs as to functional capacity and discharges to home was confirmed in a regression analysis (III). Of the listed factors hemiparesis on admission and old age were the strongest determinants for further hospitalization. As third determinant, treatment in the GMWs as opposed to treatment in the SU emerged, confirming the results by a third statistical approach. When the SU and GMW patients were subgrouped with regard to age, concomitant disorders and severity of neurological deficits on admission, a reduction in further hospitalization was noted for SU patients in all these subsets and the difference to the GMW patients was significant in most subgroups (III). Thus, it seems important that stroke units should be designed to admit all acute stroke patients without selection.

This study was performed in a university hospital setting with the different wards all subspecialized in the field of internal medicine. It is possible that more attention is given to the stroke patients in other hospital settings and that our results are not reproducible there or, at least, that the magnitude of difference in favour of the SU regime reached in this study may not be achieved in other hospital settings.

There are three major controlled studies on the efficacy of non-intensive SUs (22, 47, 73). One from Sweden, using the same allocation procedure as ours (bed availability, unselected patients) but the results did not favour the stroke unit regime. The mortality figure for patients treated in this SU during initial hospital stay was 18% and need for further hospitalization was 38% (22). However, this SU had no extra resources for rehabilitation and the main goal was directed towards
diagnostic and therapeutic studies (188). Also no later follow up was made on potential long-term benefits (22). In another randomized study, performed in an English rehabilitation hospital setting (73), approximately 85% of the patients were allocated within three weeks after symptom onset. The results regarding functional outcome were determined every month during the first year following stroke and no overall significant results in favour of the early rehabilitation regime were found. Finally, a randomized study from Scotland, including geriatric patients suffering from stroke, showed that early but limited amounts of mainly occupational therapy significantly affected the speed of recovery (47) but not its ultimate extent (71). This is in agreement with the present study (III) showing that the speed of recovery obviously was affected in younger patients (< 75 years) and in those with less severe neurological deficits (not hemiparesis), but proportion of patients hospitalized at one year after the stroke was little reduced. In the majority of stroke patients the full potential for spontaneous recovery of neurological function seems to be reached at six months after the stroke (184, 189). This seems to be valid for patients in whom the spontaneous prognosis is fair or good (III). However, in older patients (> 75 years) and those with more severe disability (hemiparesis on admission) more decisive evidences on the reduced need for hospital care late after the stroke were documented (III).

Explanations of the discrepancies between the present studies (II, III) and other recent studies is a matter of speculation. However, it is plausible that the extra resources and the orientation of staff towards early mobilization and start of activation, often within the first 24 hours, affected outcome, since this is the difference from the other Swedish study (22). Our SU is located in a department of internal medicine, where the staff is skilled in care of advanced ill patients. The stroke patients often suffer severe secondary complications to the stroke, which if not lethal will prolong immobilization and delay the start of rehabilitation. It is possible that this special competence of the staff benefits the stroke patient by early detection and treatment of such complications. The English study (73), was performed in a rehabilitation hospital setting and they did not admit their patients
very acutely and the Scottish study (47), was performed in a geriatric hospital setting.

In these studies (II, III) the amount and content of physiotherapy and occupational therapy given each patient by our therapists was not registered. However, our SU has created an atmosphere directed towards very early activation and mobilization of all patients, a process in which all personnel take part under supervision of the physiotherapist and occupational therapist. The average daily amount of time a stroke patient in a rehabilitation unit spends with a physiotherapist and occupational therapist is reported to be remarkably short (60). The process of rehabilitation can, therefore, not be reduced to only physical therapy and occupational therapy performed by a physiotherapist and occupational therapist. There are many other components such as (a) knowledge and attitudes in staff, patient and family, (b) management of medical complications and (c) diagnosis, interacting in the process of rehabilitation of the acute stroke victim. It is reasonable to suggest that the interaction of these necessary components can be optimized in a stroke unit and explain the beneficial results achieved in this study.

Papers IV and V

The different blood flow thresholds, one for altered neuronal function but sustained neuron viability and a second for development of infarction (85, 86), implies that even a marginal increase in flow to the ischemic region may prolong survivability of ischemic cells and perhaps decrease the ultimate extent of brain infarction.

Under normal conditions it is unclear if viscosity factors influence CBF (190). At low flow states, however, vasoregulatory mechanisms are exhausted and blood flow is passively dependant on the perfusion pressure and viscosity factors. In animals, the ultimate extent of brain infarction has been reduced and CBF improved by hemodilution when compared to controls (191, 192). Reports on clinical improvement by hemodilution therapy in patients with ischemic stroke are, however, so far sparse (149, 153, 154).
The combined venesection/dextran 40 therapy used in these studies gave a rapid and persistent reduction of hematocrit and blood viscosity and reduces the risk of hemodynamic fluctuations. Also, by the use of dextran 40 as a plasma volume expander the platelet activation induced by venesection (193) may be counteracted as well as other unfavourable thrombo-embolic processes activated by the stroke per se (90, 91, 194).

Patients with spontaneously very low blood viscosity - such as anemic patients and the very rare patients with hemoglobinopathias who need a high Hct for sufficient tissue oxygenation (shifted dissociation curve) are not likely to benefit. Anemic patients were therefore not included in the study protocol but the affinity of hemoglobin to oxygen, was not tested. Patients in obvious unstable cardiac conditions were also excluded from the study protocol. Severe heart failure diminishes the potential to increase the cardiac output. In such patients a reduced peripheral resistance, induced by hemodilution, will not compensate for the reduced myocardial performance. A reduction in hematocrit without concomitant rise in cardiac output will result in a decreased tissue oxygenation. A plasma volume expansion in decompensated patients will also increase central venous pressure and subsequently elevate intracranial pressure, thus reducing the effective cerebral perfusion pressure.

There was a close parallelism in mortality, even in subgroups of prognostic importance, sustained up to one year after the stroke. However, among survivors, the hemodiluted subjects improved faster, showed fewer progressions in the acute phase, and were left with less functional impairment at three months and at one year after the stroke when compared with control patients. Thus, it seems possible that early hemodilution therapy may reduce the ultimate extent of cerebral infarction.

The comparability of hemodiluted and control patients is a crucial factor in evaluating therapeutical effects in a relatively small study like this. In particular, when evaluating effects on stroke patients in whom the clinical outcome is unpredictable in the acute phase the results must be interpreted with caution (195). Considering the prognostic variables recorded prior to randomization, such as age, degree of
neurological deficits and prior medical history (185) nothing suggests that the patients randomized to hemodilution therapy should have a more favourable spontaneous prognosis. If anything, concomitant cardiac disease appeared to be slightly more common and the initial neurological deficits somewhat more severe in patients allotted to hemodilution therapy. The mean concentration of CSF total-protein, indicating disturbed blood-brain-barrier, was equal in both groups prior to randomization. Further, the CT scans revealed more visible lesions during the acute phase in the hemodiluted group which may imply a worse prognosis (196). It therefore seems highly unlikely that differences in clinical outcome between the two groups are the result of an unequal distribution of prognostic variables in favour of the hemodilution group. Also, as deduced from the literature, between 20 and 40% of patients with cerebral infarction should show a deterioration in their neurological symptoms after arrival at hospital (17-19). In the control group this rule was fulfilled (26% deteriorations). In the hemodiluted group only 8% progressed.

Recently, measurements of CBF in 12 patients during hemodilution therapy showed a significant increase in flow to the ischemic region in only 3 patients and this increase was correlated to clinical improvement (197). Also, interim results from a large Scandinavian multicenter trial of hemodilution therapy in acute ischemic stroke do not show significant results in favour of the hemodilution regime (198). It is not immediately evident why our positive results from hemodilution therapy (IV, V) were not reproduced in this larger trial. However, because of the mixed CBF flow patterns in acute cerebral infarction (199), it is not reasonable to believe that all patients benefit from a hemodiluting regime. From a theoretical point of view, benefit from a hemodiluting regime is expected in ischemic conditions where the neurons are neurophysiologically silent but still viable. Cerebral infarctions located in regions well supplied by collaterals are more likely to benefit than infarctions supplied by occluded end arteries. Beneficial effects may also be expected in those patients who, while on hemodilution therapy, occasionally suffer a recurrent or progressing ischemic stroke. In the acute situation there is unfortunately no reliable method available to predict which patient would benefit and who would not. Therefore, it
seems more appropriate to answer the question if there are any risks with hemodilution in acute ischemic stroke. If some subgroups of patients would deteriorate by hemodilution, this would be an unacceptable price for the benefit of some other patients. In addition to patients in very unstable cardiac condition and anemic patients not included in this study (IV, V) the hemodiluting regime applied seemed to improve outcome or, at least not worsen outcome in all important subgroups of stroke patients when compared to controls. Although statistical significances were not to be expected because of the small number of patients in the subgroups overt risks seem unlikely.

The apparent risk with immediate anticoagulant therapy, thrombolytic therapy or surgical revascularization in ischemic stroke, is to convert an ischemic lesion to a hemorrhage. It cannot be ruled out that also hemodilution therapy implies such risks. However, in the hemodiluted group, hemorrhagic admixture to the CSF was less frequent and less prominent when compared to controls as judged by the CSF spectrophotometry (171). It thus seems unlikely that hemodilution therapy increases the risk of converting infarctions to hemorrhages.

Hypervolemic hemodilution has experimentally been shown to increase intracranial pressure (191, 192). Possible explanations are that a general increase in CBF also increases the intracranial blood volume with subsequent elevation of intracranial pressure, or that improved blood flow through ischemically damaged vessels would possibly increase cerebral edema. Further, if cardiac decompensation exists, the increased venous return cannot be managed and backward stasis with increased intracranial venous pressure will occur. In this study (IV, V), the hemodilution procedure was approximately isovolemic during the initial phase. The amount of blood drawn was substituted by an equivalent amount of dextran 40 (173) followed by further infusion of 250-300 ml of dextran. The second phase thus was slightly hypervolemic. Intracranial pressure was not monitored in this study. However, signs of blood-brain-barrier breakdown, as judged from the elevation in CSF total-protein content at second lumbar puncture, were more frequent in the control group when compared to the hemodiluted. This suggests that the possible improvement in CBF induced by hemodilution did not in-
crease the extravasation of plasma protein through a damaged BBB or, that the BBB damage became less extensive in hemodiluted subjects.

The results of these studies (IV, V) suggest that modest hypervolemic hemodilution, performed by skilled personell in a stroke unit, is a clinically safe and effective therapeutical regime in the acute phase of ischemic stroke. In cerebral infarction, therapy can be directed either at minimizing the ischemia itself or to increase the brains tolerance to ischemia. The complex, multifaceted pathophysiology of acute cerebral infarction, makes it highly probable that a combination of therapies, rather than a single agent, will result in a maximal recovery (200). The results of these studies (IV, V) also suggest that early hemodilution should be one of the possible therapeutic components in such future regimes.

GENERAL SUMMARY AND CONCLUSIONS

These studies, performed in a stroke unit at a medical department, were designed to characterize essential clinical features of the different cerebrovascular disorders on admission to hospital, to evaluate the efficacy of admitting unselected stroke patients to a stroke unit, and to evaluate hemodilution as a therapeutical regime in patients with cerebral infarction.

I A prospective registry included 409 patients admitted to the stroke unit over a five-year period. Modern diagnostic equipment (CT scan and CSF analyses) and strict diagnostic criteria revealed a diagnostic distribution of 11% hemorrhagic, 76% ischemic cerebrovascular lesions and 13% TIs. Mean age varied between 65.8 and 77.5 years in the various diagnostic groups with the highest in patients with embolic cerebral infarctions. Patients with intracerebral hemorrhage presented with the most severe symptoms on admission followed by patients with embolic infarction, non-embolic infarction and TIA. Concomitant disorders affecting the cardiovascular system were highly prevalent and only 14% of the patients were free of such diseases prior to the stroke. Diagnostic distribution, concomitant disorders, age and symptoms on admis-
sion in patients treated in the stroke unit was in accordance with other recent reports on unselected stroke populations.

II A comparative prospective study over 16 months included all patients filling the admission criteria to the stroke unit who were admitted to the hospital. No difference was found between patients treated in the stroke unit (n = 110) and the general medical wards (n = 183) regarding prognostic indicators on admission such as age, concomitant disorders and neurological symptoms. The stroke patients treated in the stroke unit had a statistically significantly better prognosis regarding functional outcome and the need for long-term hospitalization was significantly reduced up to one year after the stroke when compared to patients treated in the general medical wards. All stroke patients seemed to benefit with the possible exception of patients in coma on admission. These results were achieved within the same or shorter length of initial hospital stay for patients in the stroke unit. Neither overall mortality, nor mortality in subgroups of prognostic importance was significantly affected by the stroke unit regime. It is concluded that a non-intensive stroke unit regime does not affect mortality but reduces short- as well as long- term functional disability and reduces the number of days needed to be spent in hospital. This refers to all subgroups of stroke patients and, in particular, old and hemiparetic patients.

III Rapid hemodilution in the early phase of cerebral infarction by the combination of venesection and administration of dextran 40 was evaluated in a prospective controlled trial. After randomization 52 hemodiluted and 50 control patients were comparable in prognostic variables. Signs of blood-brain-barrier breakdown and hemorrhagic admixture to the cerebrospinal fluid in the acute phase were less frequent in hemodiluted subjects. The hemodiluted patients showed a significantly higher degree of early improvement and fewer progressions. Neurological and functional disability in survivors and need for long-term hospitalization were significantly reduced at three months and at one year after the stroke compared to controls. Mortality was not affected. Hemodilution therapy by the combination venesection/dextran 40 administered in a stroke unit appears clinically safe and improves short-term
as well as long-term outcome in the majority of acute ischemic stroke patients.

FINAL CONCLUSIONS

A stroke unit admitting acute CVD patients provided a bed is available will create random samples of representative stroke patients well fitted for the purpose of epidemiologic, prognostic and comparable studies of efficacy in stroke care. The multifaceted regime followed in the unit, performed by skilled staff and directed towards early activation of every patient, improves short-term as well as long-term outcome in surviving stroke patients and reduces the need for long-term hospitalization. Mortality, however, is not affected neither as a whole nor in subgroups. When applied in the stroke unit, early hemodilution therapy with combined venesectio/dextran 40 is clinically safe and improves the clinical course in patients with acute cerebral infarctions.
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