Biochemical changes after spontaneous subarachnoid haemorrhage

Part I  The biochemical problem

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For a number of years this department has been intimately concerned with the diagnosis and treatment of spontaneous subarachnoid haemorrhage (Paterson, Hamilton, and McKissock, 1956; McKissock, Richardson, Walsh, and Owen, 1964; McKissock, Richardson, and Walsh, 1965). In the hope of getting further information of use in the management of these cases we turned our attention to the biochemical aspects. A background of the natural chemical histories of these patients against which to assess the individual figures reported in relation both to the source of the haemorrhage and the duration of the illness has been built up. While the changes to be described will be general systemic, reflecting the whole body's reaction to the situation, it must not be forgotten that it may be the local biochemistry that determines the outcome.

To what extent is a subarachnoid haemorrhage followed by the sequence of metabolic events that are initiated by injury elsewhere in the body? Are these changes modified by the site of the damage and do they have any prognostic significance? Do metabolic disorders play any part in the mortality of subarachnoid haemorrhage? What is the effect of superimposing a second, operative, stress on the initial disturbance? This information would help in the management of fluid and electrolyte balance and in the use of urea and other osmotherapeutic agents. Nutritional support in the acute and convalescent stages might be improved if we knew the extent of the catabolic phase.

No papers relating specifically to biochemical changes following subarachnoid haemorrhage were found in the literature. A few reports of biochemical surveys of cases of 'stroke' (mixed haemorrhage and thrombosis) were found. A planned attack on the body's reaction to a subarachnoid haemorrhage does not appear to have been made but a composite picture of some of the events that may follow such an ictus can be built up from reports of isolated metabolic disturbances. The relevant literature on injury will be reviewed when the similarities between subarachnoid haemorrhage and a closed head injury are considered in a later paper.

BIOCHEMICAL SURVEYS OF 'STROKES' REPORTED IN THE LITERATURE

Kirkegaard (1950) observed 10 patients in coma from cerebrovascular accidents; two of these had evidence of haemoconcentration, in seven blood sugar was over 110 mg. per 100 ml., and in six the blood urea was over 50 mg. per 100 ml. Plasma chloride varied from 92 to 120 mEq./l. and bicarbonate from 14 to 35 mEq./l. Roggia (1957), in a paper presented at the 1957 Stresa Convention on Cerebral and Coronary Vasculopathy, reports on single estimations of blood urea, cholesterol, and blood sugar in 342 cases of cerebral apoplexy, of which 13.5% had blood in the cerebrospinal fluid. The most common finding was a raised blood urea level, which was more frequent in cases showing a raised cholesterol than in those with low or normal cholesterol levels. Excluding known diabetics, hyperglycaemia immediately following the ictus was also more common in the high cholesterol group.

The Russian and Polish literature contains a number of references to biochemical investigation of 'strokes', but again, there is no clear distinction between haemorrhage and thrombosis. Borisenko (1959) determined blood sugar and sugar tolerance, total serum protein and its fractions, cholesterol, non-protein nitrogen and prothrombin in acute disorders of the cerebral circulation. A clear distinction is made between haemorrhage and thrombosis in grouping the results but the criteria of diagnosis are not given. Measurements were made in the acute phase and serially while changes lasted. Much attention is given to sugar curves and it is claimed that they differ in thrombosis and haemorrhage. Unfortunately, the paper was presented at a society meeting.
and the figures, though referred to, are not included in the text. The most marked alterations in blood sugar were found in the comatose cases, where elevations up to 218 mg. % were recorded. In the acute phase of cerebral haemorrhage levels of non-protein nitrogen and cholesterol were increased, while total protein was decreased. Wender and Wenclewsli (1961) give the most complete metabolic study of strokes, but still do not include balance data. In their experience, the cerebral stroke is often followed by generalized metabolic disturbances. In a series of 30 cases the most common disturbances were an increase in serum chloride and abnormalities in the electrophoretic pattern of plasma proteins. A decrease in serum sodium and potassium was more common than an increase. Hyperglycaemia was observed in several cases immediately following the ictus. In many cases the haematocrit was slightly raised. These authors consider that serum electrolyte determinations should be a routine procedure in all stroke cases and that decreased sodium and potassium levels call for immediate treatment.

EVIDENCE FOR THE CLASSICAL RESPONSE TO TRAUMA IN SPONTANEOUS INTRACRANIAL BLEEDING The metabolic pattern that follows injury or operation is due to the endocrine changes evoked by the trauma and to the tissue damage itself, with contributions from any accompanying starvation and immobilization. As the normal regulatory mechanisms are disturbed, changes due to the metabolic management of the case may be superimposed.

A measure of the body’s natural tendency to conserve salt and water following a subarachnoid haemorrhage would be useful. A comatose or drowsy patient unable to respond to the sensation of thirst is especially liable to become dehydrated. In the presence of a strong antidiuretic response too vigorous correction of dehydration may lead to water intoxication.

A review of Palazzuoli (1955) deals with the non-specific humoral reactions to cerebral apoplexy. Sixty-nine references are given to papers dealing with, in order of frequency, the haematological aspects of strokes, peptic ulceration following strokes, melena neonatorum of birth injury, blood urea in apoplexy, hyperglycaemia, pathology, bilirubin levels, coagulation and the detection of incipient strokes, with single references to hypernatraemia, salt and water balance, blood polypeptides, 17-ketosteroids, and cerebral acetoanaemia. He concludes that as part of the syndrome of cerebral apoplexy some non-specific changes occur that resemble those described by Selye as being the sequel to stress. Shenkin (1964) includes six cases of subarachnoid haemorrhage in a study of the effect of pain on the diurnal pattern of plasma corticoid levels. Two of these had an increase in plasma ‘cortisol’, as measured by a modified Porter-Silber method, and three showed an abnormal diurnal variation; no clinical details are given. An appropriately placed cerebral lesion may interfere with the stress response. Crompton (1963), studying the morbid anatomy of ruptured intracranial aneurysms in this department, found evidence of hypothalamic damage and Wise, Hilf, and Pileggi (1959) noted a failure of the 17-hydroxycorticosteroid excretion to increase in one of three patients with head injuries all of whom failed to show the usual post-traumatic antidiuretic phase. There are no published figures for nitrogen metabolism in strokes but the negative balance of the catabolic phase following trauma may be reflected in the high blood urea found in all the surveys mentioned above. How soon the anabolic phase sets in is not known.

ELECTROLYTE DISTURBANCES OF CENTRAL ORIGIN Disturbances of sodium metabolism have been reported in association with a variety of intracranial lesions. Their exact mechanism is not yet clear though information is accumulating on the sites of the brain damage and the nature of the disturbances of chemical control produced. A leader in the Lancet (1962) on this form of hypernatraemia was prompted by a paper by Taylor (1962) in which he defends the existence of an encephalogenic form of hypernatraemia and summarizes the identified sites of brain damage in 27 published cases, adding three of his own. He concludes that the localization of the damage in the frontal lobes, hypothalamus, or lower brain-stem suggests a descending pathway for the control of sodium. This condition of hypernatraemia in association with a cerebral lesion and not accompanied by water deficit or renal damage has been termed ‘cerebral salt-hoarding’ (de Wardener) in contrast to the ‘cerebral salt-wasting’ described by Cort (1954) as a condition of low serum sodium accompanied by continuous urinary sodium loss, unaffected by administration of A.C.T.H. or deoxytocin and thought by him to be due to an interruption of the hypothalamic renal pathway affecting electrolyte absorption. More recently, cerebral hypotonia in association with inappropriate secretion of antidiuretic hormone (Carter, Rector, and Seldin, 1961; Rovit and Sigler, 1964; Poyart and Podidal, 1964; Haden and Knox, 1965; Joynt, Affi, and Harbison, 1965).

Hypernatraemia following subarachnoid haemorrhage was reported by Allott (1939) in a patient with a ruptured anterior cerebral aneurysm and by Gurdjian and Webster (1955) following ligation of both anterior cerebral arteries for a ruptured anterior
communicating artery aneurysm. Hyponatraemia following subarachnoid haemorrhage from an aneurysm of the right internal carotid artery was described by Goldberg and Handler (1960). The post-mortem finding of a slight compression necrosis of the pituitary, secondary to the aneurysm, and of a mild arteriomegaly puts this case in a different category to the three cases of hyponatraemia following aneurysmal rupture reported by Joynt et al. (1965). All three of their hyponatraemic patients had multiple aneurysms, with an anterior communicating artery aneurysm present in each case.

The biochemical picture of the patient following a spontaneous subarachnoid haemorrhage is incomplete. In primary cerebral haemorrhage a raised blood urea level, sometimes accompanied by an increase in cholesterol and/or blood sugar, has been reported, while the sodium and potassium levels have been lowered with chloride and bicarbonate levels varying widely in either direction. Severe disturbances of sodium metabolism have been reported following aneurysmal rupture, especially in association with anterior communicating artery aneurysms. There is a lack of information on the incidence of these abnormalities and the time sequence in which they arise or the effect of operative interference. Part II which follows describes the incidence of biochemical abnormality in 134 patients with recent spontaneous subarachnoid haemorrhage on admission to hospital. Subsequent articles will deal with the pattern of metabolic response in both conservatively and surgically treated cases.

Part II  The patient on admission

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To help to assess the patient on arrival at the neurosurgical centre, we obtained a blood sample from all patients admitted with a diagnosis of recent subarachnoid haemorrhage. All specimens were take soon after arrival in the ward and before any food, drink, or intravenous fluid had been given or other investigations performed.

CASE MATERIAL

All patients came from a referring hospital where a lumbar puncture had confirmed the presence of blood in the cerebrospinal fluid. At first we were particularly interested in patients too ill to look after their own fluid intake and studied all patients admitted within seven days of a spontaneous subarachnoid haemorrhage, who were either in coma or very drowsy. Subsequently all cases of recent spontaneous subarachnoid haemorrhage were included. In this way 79 alert patients (41 men and 38 women) and 55 comatose cases (28 men and 27 women) were sampled. The patients referred to as 'comatose' were either in coma or too drowsy to be responsive to thirst. The day of the haemorrhage is referred to as 'day 0'.

Bilateral carotid angiography, according to our usual scheme (McKissock, Walsh, and Richardson, 1960), was carried out in all but three cases. Where carotid examination was negative, vertebral angiography was done two days later, except in the cases of one 64-year-old woman and a 68-year-old man, each presenting with a non-coma-producing subarachnoid haemorrhage who were not subjected to vertebral angiography on account of their age. Of the three patients not examined angiographically, one died before investigation and the diagnosis was obtained at necropsy. In a further case the diagnosis of intracerebral haemorrhage was accepted on the basis of clinical signs and ultrasonography, and in the last case the diagnosis of pontine haemorrhage was assumed from ventriculography. Table I gives details of the lesions found; six cases with bilateral aneurysms are included among the named aneurysms.

**TABLE I**

<table>
<thead>
<tr>
<th>Source of Haemorrhage</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior communicating artery aneurysm</td>
<td>24</td>
</tr>
<tr>
<td>Middle cerebral artery aneurysm</td>
<td>15</td>
</tr>
<tr>
<td>Posterior communicating artery aneurysm</td>
<td>20</td>
</tr>
<tr>
<td>Multiple aneurysms, with source of haemorrhage not known</td>
<td>8</td>
</tr>
<tr>
<td>Angioma</td>
<td>10</td>
</tr>
<tr>
<td>Primary intracerebral haemorrhage</td>
<td>29</td>
</tr>
<tr>
<td>No abnormality demonstrated on angiography</td>
<td>28</td>
</tr>
<tr>
<td>Total</td>
<td>134</td>
</tr>
</tbody>
</table>

LABORATORY METHODS

Blood was taken into E.D.T.A. for determination of the sedimentation rate and packed cell volume (Wintrobe method) and haemoglobin as oxyhaemoglobin (Dacie, 1956).

Heparinized plasma was used for determinations of sodium and potassium (EEL flame photometer), chloride (Schales, 1953), bicarbonate by titration (Varley, 1962a), urea (Varley, 1962b), total protein (King and Wootton, 1956), glutamic-oxaloacetic transaminase (Varley, 1962c). Plasma osmolality was measured by depression of freezing point using an osmometer. Blood sugar was

1 Advanced Instruments Inc., model H.
Biochemical changes after spontaneous subarachnoid haemorrhage. I. The biochemical problem.
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*J Neurol Neurosurg Psychiatry* 1966 29: 291-3
doi: 10.1136/jnnp.29.4.291

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