HYPONATRAEMIA AND SICK CELLS

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Hyponatraemia is very common in the ill patient. Over a 12-month period about 20% of all plasma samples analysed from the wards at the Royal Victoria Infirmary, Newcastle, were hyponatraemic (Flear and Menzies, unpublished); and others have reported even higher frequencies (table I). Hyponatraemia is so common that on the one hand it tends to be dismissed mistakenly as laboratory error (Van Peenen and Lindberg, 1965); on the other, also wrongly we believe, to be considered of no consequence in most instances. For example, Payne and Levell (1968) suggest that control values should be obtained from hospital patients, in preference to healthy persons, so that degrees of hyponatraemia which are of clinical significance can be identified. When this is done, the so-called control group contains lower concentrations of plasma sodium (Na⁺) than are seen in healthy persons.

<p>| TABLE I. Incidence of hyponatraemia reported in hospital patients. |
|--------------------------|--------------------------|</p>
<table>
<thead>
<tr>
<th>%</th>
<th>No. of patients</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>36</td>
<td>1,000</td>
<td>Bradham and Gadsden (1962)</td>
</tr>
<tr>
<td>39</td>
<td>7,695 (hospital 1)</td>
<td>Lindberg, Van Peenen and Couch (1965)</td>
</tr>
<tr>
<td>40</td>
<td>1,697 (hospital 2)</td>
<td>Owen and Campbell (1968)</td>
</tr>
<tr>
<td>50</td>
<td>5,000</td>
<td></td>
</tr>
</tbody>
</table>

The figures relating to hospital 2 are an underestimate since they include only those instances of hyponatraemia associated with K⁺, Cl⁻, and HCO₃⁻ levels in the 10 most common patterns. For example, the data of Bradham and Gadsden evaluated in this way yield an incidence of 19%; and data from hospital 1 an incidence of 30%.

Several mathematical techniques have been used for selecting controls from collections of data from hospital patients (see for example, Amador and Hsi, 1969; O’Halloran, Studley-Ruxton and Wellby, 1970). The use of any of these techniques assumes that there are two distinct subpopulations (control and abnormal) in respect of the parameter measured. In practice, they give contradictory answers when used on any one set of data (Neumann, 1968; Amador and Hsi, 1969; Gindler, 1970), and the results obtained also vary between different populations of patients. Confidence limits derived by any one method differ on successive batches of data (Owen and Campbell, 1968; O’Halloran, Studley-Ruxton and Wellby, 1970), on data from different patients in different wards in a given hospital (table II) and in different hospitals (table III).

| TABLE II. Lower 95% confidence limits for subpopulation of “controls” derived from observed plasma levels of sodium ([Na⁺]) in four sets of patients within one hospital. |
|--------------------------|--------------------------|
| No. of patients | Intensive | Surgical | Medical | Dermatology |
| | therapy | | | |
| [Na⁺] (m.equiv/L) | 129 | 129 | 132 | 136 |

Observations made over a 12-month period (Flear and Menzies, to be published).

| TABLE III. Difference between the lower 95% confidence limits of healthy persons and hospital controls. |
|--------------------------|--------------------------|
| | Difference (m.equiv/L) |
| Owen and Campbell (1968) | 4.0 to 8.0 |
| Payne and Levell (1968) | 10.0 |
| O’Halloran, Studley-Ruxton and Wellby (1970) | 4.0 |
| Flear and Menzies (to be published) | 4.3 |

These findings indicate that it is unreasonable to assume two distinct subgroups, and emphasize that it is arbitrary to designate a given low concentration of sodium as significant or insignificant according to whether it is below a mathematically defined boundary. Independent evidence is required from clinical practice and investigations of underlying pathophysiology.

It seems likely to us that a decrease in plasma Na⁺ concentration results from disturbances caused by illness, the extent of which determine the size of the reduction. The extent and frequency of hyponatraemia (judged by controls derived from observations in healthy persons) (Elveback, Guillier and Keating, 1970) in patients from separate wards in a...
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TABLE IV. Incidence of hyponatraemia ([Na]p <135 m.equiv/l.) in four sets of patients in one hospital (Flear and Menzies, to be published).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intensive therapy</th>
<th>Surgical</th>
<th>Medical</th>
<th>Dermatology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatraemia %</td>
<td>27</td>
<td>23</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>Lowest level [Na]p</td>
<td>120</td>
<td>113</td>
<td>108</td>
<td>125</td>
</tr>
</tbody>
</table>

The lower 95% confidence limits in 127 healthy persons with ages from 18 to 60 years was 135 m.equiv/l. (Singh and Flear, unpublished).

TABLE V. Patients showing hyponatraemia in association with medical conditions.

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of patients</th>
<th>% hypo-natraemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>397</td>
<td>62</td>
</tr>
<tr>
<td>Infant malnutrition</td>
<td>219</td>
<td>62</td>
</tr>
<tr>
<td>Hepatic cirrhosis</td>
<td>112</td>
<td>46</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>45</td>
<td>56</td>
</tr>
</tbody>
</table>

Unless otherwise stated, hyponatraemia is defined as a Na+ concentration below the lower 95% confidence limits of normals also investigated by the same authors. In the case of Garrow, Smith and Ward (1968), Na+ concentrations were less than 134 m.equiv/l. They found the lowest in 36 normal infants to be 136 m.equiv/l.; 46% is therefore an underestimate. The data of Sherlock et al. (1966) relate to Na+ below 130 m.equiv/l., the normal range not being specified.

given hospital (table IV), and in various illnesses (table V), reflect differences in the severity of disturbances. Support for this viewpoint is afforded by observations, in individual patients with heart failure, that plasma Na+ concentrations fell as the disease progressed (Flear, 1960a,b; 1967) or with development of complications (Weston et al., 1958). It was observed also that these levels rose with improvement of heart failure (Flear, 1960a,b; 1967), on recovery from respiratory failure (Flear et al., unpublished), with improvement in a wide variety of disorders involving damage to or inflammation of the central nervous system (Bartter and Schwartz, 1967), and in liver failure.

It was also observed in groups of patients that hyponatraemia is more marked and commoner in the severely ill patient with pulmonary tuberculosis (Westwater, Stiven and Garry, 1939), in congestive heart failure (Flear, 1960a,b; 1967) and in infantile malnutrition (Smith, 1963; Garrow and Pike, 1967; Garrow, Smith and Ward, 1968). Danowski, Fergus and Mateer (1955) reported that of patients who developed hyponatraemia 33–50% died. It is also known that hyponatraemia is less marked after recovery or remission from infantile malnutrition (Garrow, Smith and Ward, 1968), tuberculosis, meningitis (Harrison, Finberg and Fleishman 1952), and bronchopneumonia (Flear et al., 1973).

TABLE VI. Incidence of hyponatraemia in congestive heart failure (Flear, 1960b).

<table>
<thead>
<tr>
<th>Patient's condition</th>
<th>Incidence (%)</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>42</td>
<td>156</td>
</tr>
<tr>
<td>Moderate</td>
<td>61</td>
<td>91</td>
</tr>
<tr>
<td>Severe</td>
<td>83</td>
<td>150</td>
</tr>
</tbody>
</table>

The classification of patient's condition is arbitrary, as follows:

Mild: immediate improvement, no congestive failure after 3 weeks
Moderate: no improvement for 2 weeks, no congestive failure after a further few weeks
Severe: no reduction in oedema for at least 6 weeks, with persisting signs of congestive failure; or death.

TABLE VII. Percentage mortality in relation to hyponatraemia.

<table>
<thead>
<tr>
<th>[Na]p</th>
<th>Congestive heart failure</th>
<th>Infant malnutrition</th>
<th>Pulmonary tuberculosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>397</td>
<td>304</td>
<td>169</td>
</tr>
<tr>
<td>normal</td>
<td>11</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>low</td>
<td>35 (Flear, 1960a,b)</td>
<td>49 (Westwater,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stiven and Garry,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1939</td>
<td></td>
</tr>
</tbody>
</table>

When [Na]p was 120 m.equiv/l. or less, the mortality was 100% in congestive heart failure and 50% in infant malnutrition.

From this viewpoint, it would appear that any lowering of plasma Na+ concentration must be considered to reflect illness. This is supported by the fact that plasma Na+ concentrations do not decrease in healthy persons admitted to hospital. This was noted by Deitrick, Whedon and Shorr (1948) who studied four young healthy males in hospital for some 20 weeks (for the first 6–8 weeks they were...
TABLE VIII. Conditions in which SIADH is said to occur (Barter, 1970).

<table>
<thead>
<tr>
<th>ADH from tumour</th>
<th>CNS disorders</th>
<th>Pulmonary disease</th>
<th>Endocrine disease</th>
<th>&quot;Masked&quot; by underlying disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Oat-cell&quot; pulmonary neoplasm</td>
<td>Acute intermittent porphyria</td>
<td>Pneumonia</td>
<td>Addison's disease</td>
<td>Postoperative state</td>
</tr>
<tr>
<td>Pancreatic carcinoma</td>
<td>Guillain-Barré syndrome</td>
<td>Tuberculosis</td>
<td>Myxoedema</td>
<td>Heart failure</td>
</tr>
<tr>
<td>Duodenal carcinoma</td>
<td>Meningitis</td>
<td>Aspergillosis</td>
<td>Hypopituitarism</td>
<td>Cirrhosis with ascites</td>
</tr>
<tr>
<td>Lymphoma (?)</td>
<td>Head injury; brain abscess</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ambulant; then for 6–7 weeks they were immobilized with bilateral plaster casts from umbilicus to toes; finally they were active again for 4–6 weeks. Observations of Moore and Ball (1952) in healthy volunteers admitted to hospital and confined to bed are shown in figure 1.

One of us (C.T.G.F.) has observed, on two occasions in the same healthy person, that febrile disorders were accompanied by a fall in plasma Na⁺. Observations were made while levels were being monitored daily over a period of some 12 months. In both instances they returned to their previous values on recovery some 2–3 days later.

![Graph](image)

Fig. 1. Plasma sodium levels [Na]₀ in 5 healthy volunteers admitted to hospital for metabolic investigations. Data from Moore and Ball (1952).

What disturbances cause Na⁺ levels to fall?

Salt depletion and acute water intoxication were the earliest recognized causes, but neither state is very common. In 1957, Schwartz et al. suggested that hyponatraemia in two patients with carcinoma of the bronchus might have been provoked by overproduction of antidiuretic hormone (ADH), persisting as a result of continued but inappropriate secretion. Since then, they and others have suggested that the syndrome of inappropriate secretion of ADH (SIADH) is responsible for a wide variety of conditions (table VIII). Indeed, the prevailing assumption now seems to be that almost all hyponatraemia has this same underlying pathophysiology. The criteria for making such a diagnosis (table IX) are hardly stringent (table X). In fact, this pathophysiology has never been demonstrated clearly, except in some instances of carcinoma of the bronchus, tumours from which have been shown to secrete ADH substantially in vitro. We believe that in very many diseases hyponatraemia arises not as a result of abnormal secretion of ADH but because of widespread disturbances at the cell level. Thus, we consider that hyponatraemia is a consequence of "sick cells".

TABLE IX. Criteria used for diagnosis of syndrome of inappropriate secretion of antidiuretic hormone (SIADH) (Barter and Schwartz, 1967; Barter, 1970).

<table>
<thead>
<tr>
<th>Type</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitive</td>
<td>(1) Measurable level of ADH in serum</td>
</tr>
<tr>
<td></td>
<td>(2) Hyponatraemia</td>
</tr>
<tr>
<td></td>
<td>(3) Low plasma osmolality</td>
</tr>
<tr>
<td>Supportive</td>
<td>(4) Urine less than maximally dilute</td>
</tr>
<tr>
<td></td>
<td>(5) Urine Na⁺ greater than intake</td>
</tr>
<tr>
<td></td>
<td>(6) Blood urea nitrogen less than 10 mg/100 ml</td>
</tr>
</tbody>
</table>

Infrequently sought, more rarely found (Gupta, 1971); can be present without SIADH (see table XII).

Criteria 2, 3, 4, 5 "may all be absent in a patient with the syndrome" (Barter, 1970).

What is meant by "sick cells"?

Body fluids are in osmotic equilibrium. The osmo-
lality of fluids inside cells is the same as that of fluids outside (Conway and McCormack, 1953; Appleboom et al., 1958; Maffly and Leaf, 1959). The osmolarity of the external fluids is very largely determined by solutes which can diffuse into cells. In contrast, a substantial contribution to the osmolarity of cell fluids is made by solutes that are constrained within the cell by virtue of their size and physical characteristics, and by the permeability limits of the cell membranes. Prominent among these solutes are compounds such as adenosine triphosphate, creatine phosphate, amino-acids, and metabolic intermediates including the hexose and trinose phosphates (Conway, 1957). Most of the non-diffusible solutes in cells are negatively charged, but some have positive charges also. The net residual negative charges on the compounds are largely balanced by potassium ions, a small number of sodium ions also serving as counter-ions. Their number is small, as sodium ions are normally actively pumped out from cells as fast as they leak in from extracellular fluids (ECF) by a metabolically “driven” sodium pump, of which there may be different types.

The molar quantity of non-diffusible solutes is normally fairly constant. It is the outcome of a dynamic balance between metabolic production and utilization, and in some cases perhaps also of slow escape from cells. Its constancy is one of the features of self-regulation of metabolism (Atkinson, 1969) and, although it is often thought to derive merely as a product of other metabolic activities, we consider that its achievement is of prime consideration. This balance also substantially assures a constant residual quantity of anions requiring to be balanced by cationic counter-ions, and is therefore responsible for the constant quantity of cations (Na⁺ and K⁺ combined) which are present in cells as counter-ions. An additional factor is the pH of cell fluids, a change in which will alter the dissociation of some solutes and so influence the net residual negative charges on non-diffusible solutes.

Conway (1945) and Brown and Stein (1960) have pointed out that the osmolality of ECF and its Na⁺ concentration (Na⁺ and its accompanying anions are the major solutes) is determined by the intracellular osmolality. As indicated, this is a result of the self-regulation of cell metabolism. Regulation of the total solute content of cells is the primary event in fixing the osmolality of body fluids. Disturbance at this level can cause hyponatraemia, and because it has arisen as a result of illness or trauma, affected cells can be regarded as “sick cells”.

Osmoregulation and the excretion of water and sodium.

Modulation of excretion of water and sodium by the kidney, and the attendant neuro-humoral servo-mechanisms, normally play a secondary part in osmoregulation. The primary role is taken by cells throughout the body in controlling their content of solutes; this determines the osmolality of body fluids. As long as cells are successful in this, regulation of urinary losses of water and sodium will limit the variability in osmolality which is imposed by fluctuations in dietary gains and extrarenal losses, and at the same time will limit fluctuation in the volumes of fluid both inside and outside cells. This oversimplification ignores the contributory role of thirst and its regulation of fluid intake (Fitzsimmons, 1972).

Net gains of water by the body lead to a water diuresis; net losses of water cause the kidney to excrete a concentrated urine. A concentrated urine is elaborated in response to an increase in the plasma level of ADH, triggered by shrinkage of cells in osmoreceptors, and of other cells in the body when water is lost. When osmoreceptor cells gain water and swell, secretion of ADH is inhibited and dilute urine is formed. A loss of water increases the osmolality of body fluids; a gain decreases osmolality. Changes in the osmolality of body fluids which do not alter the water content of osmoreceptor cells are without effect on ADH secretion. Normally Na⁺ is effectively restricted to the ECF. An increase in the ECF Na⁺ content would raise its osmolality above that in intracellular fluid, and as a result provoke a shift of water from cells including osmoreceptor cells. Consequently, the secretion of ADH would increase, causing the body to retain water. Therefore, uncorrected gains of Na⁺ would result in expansion of the ECF; a loss of sodium would contract the ECF. Expansion of the ECF causes a decreased secretion of aldosterone and an increase in the “third factor” (Schrier and de Wardener, 1971). This results in an increased excretion of Na⁺. Contraction of the ECF has the opposite effect.

Cellular disturbances causing hyponatraemia.

Since cells throughout the body play the primary role in establishing the osmolality of body fluids, osmolality must fall if they fail to sustain their normal quantities of non-diffusible solutes. In considering this, Maffly and Edelman (1961) pointed out that a loss of organic phosphate compounds and
proteins from cells would also entail a loss of potassium since cells would then contain fewer non-diffusible anions. It is apparent from Conway's writings that the outcome will depend on which solutes diminish, and whether or not the $\text{pH}$ of cell fluids changes also (Conway, 1957).

The way in which a primary decrease in cellular osmolality would reduce osmolality overall was adumbrated by Orloff and colleagues (1959). Initially, the osmolality in cell fluids would fall below that in the ECF, with the result that water would shift from the cells. The consequent shrinking of cells would provoke an increased secretion of ADH, with retention of water and re-expansion of cells. They pointed out that this would entail residual expansion of ECF. It is probable, however, that this would be corrected by neurohormone-induced saline loss. In 1950, Sims and colleagues suggested that a primary reduction by neurohormone-induced saline loss. In 1950, Sims and colleagues suggested that a primary reduction in the osmolality of cell fluids could explain the sustained hyponatraemia which they noted in patients with pulmonary tuberculosis. They suggested that it was brought about by "osmotic inactivation" of intracellular cations. However, this is unacceptable.

A decrease in the molar quantity of non-diffusible solute in cells can be envisaged as a result of metabolic disturbance, cellular undernutrition, or alterations in membrane permeability. Normally, cells are rather poorly permeable. Zierler (1961) has calculated and Robinson has written that "instead of speaking of cell membranes as 'freely permeable to water' we should marvel that so thin a layer can be so nearly waterproof. It should be added in fairness that permeabilities to solutes are often thousands of millions of times smaller" (Robinson, 1965). It has been pointed out elsewhere (Flear, 1970, 1973) that an abrupt increase in the permeability of a substantial mass of the body's cells, if sufficiently marked, would cause a rapid redistribution of solutes and water, resulting in hyponatraemia. The influx of sodium would be faster, leading to an intracellular accumulation of sodium and anions such as chloride, unless active efflux of Na$^+$ were to increase also. By itself an accumulation of sodium and chloride in the cells will not reduce the concentration of Na$^+$ throughout the ECF. (In due course this is succeeded by a new balanced state in which cells contain excess Na$^+$.

By then, most of the chloride which entered with Na$^+$ has left, together with an equal amount of K$^+$, and cells will also have lost the water initially gained. Water, K$^+$ and Cl$^-$ will all largely have been lost from the body, and the level of Na$^+$ throughout ECF will remain unchanged.)

Together with sodium and chloride, water also moves into cells which gain an isosmotic saline. When, at the same time, there is a leak from cells of normally non-diffusible solutes, then the net gain of solute by cells is correspondingly reduced and so is the gain of water. In this situation, cells effectively gain a saline which is richer in Na$^+$ and Cl$^-$ than is ECF and this lowers the level of these ions in the residual ECF. (Hyponatraemia here is very similar to that provoked by the intravenous infusion of mannitol (Dagher et al., 1966; Aviram et al., 1967) which cannot penetrate into cells and so withdraws water from them.)

In this situation, hyponatraemia exists without dilution of the body fluids, so that secretion of ADH remains unaffected on this account. During the early stages of its onset, the secretion of ADH may be actually increased because of shrinkage of the ECF, also resulting from the cellular events (Flear, 1970, 1973). Hyponatraemia persists so long as the solutes which escape from cells remain within the ECF. The situation is far from static. Some of these solutes will be excreted in the urine, when they may provoke a solute diuresis. At the same time they may leak continuously from cells fed by a continuing metabolic production; this results in substrate depletion. A reversal of the membrane changes will plug the leak of solutes from cells, and will be followed by a return of plasma Na$^+$ to normal concentrations, as what is left of the escaped solutes is excreted. Involvement of more of the body's cells will protract or exacerbate hyponatraemia. In clinically labile situations with fluctuations in the mass of cells disturbed in this way, the plasma concentrations of Na$^+$ will oscillate markedly.

Evidence that hyponatraemia is caused by sick cells.

1) A sustained primary reduction in cell osmolality. Figure 2 presents observations in three groups of patients. In chronic heart disease, and a miscellaneous group, there was a striking correlation between the reduction of plasma Na$^+$ concentration and the extent of cellular depletion of K$^+$. These data support and extend the suggestion made by Edelman in 1956 that K$^+$ depletion might be the cause of hyponatraemia. A gain of cellular K$^+$ in patients in heart failure was associated with a rise in plasma Na$^+$; a loss of K$^+$, with a fall in Na$^+$ (Flear,

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Fig. 2. Serum levels of Na+ and cell losses of K+ coexisting in patients with congestive heart failure; with miscellaneous conditions including pulmonary tuberculosis, bronchiectasis, bronchial carcinoma, hepatic cirrhosis, undernutrition, nephrotic syndrome, hypoprothrombinaemia, and duodenal ulcer; and with steatorrhoea.

Measured amounts of exchangeable body K+(K+e) were first compared with standard values for healthy persons of the same sex and height (Flear et al., 1966). Body weights (oedema-free) were also compared with standard values. In calculating the cellular K+ depletion, it was assumed that half of any weight loss was caused by loss of cell mass. Details of calculation are presented elsewhere (Flear, 1967). Values for per cent depletion in the heart disease group are averages of the two estimates detailed there.

Measured values of K+e providing data in the miscellaneous group are largely unpublished; those in the steatorrhoea group were mostly presented by Flear et al. (1958) and Cooke and Flear (1965).

The stippled band depicts the 95% confidence limits of serum levels of Na+ in healthy persons (Flear and Hughes, 1963).

Table XI. The types of evidence to support the conclusion that K+ depletion in patients in congestive heart failure is caused by a primary fall in non-diffusible anions within cells.

1. Tissue analysis: calculations of non-diffusible anions (Flear, 1960); scrutiny of variability in composition (Flear, 1969)
2. Cell loss of K+ in excess of cell gain of Na+: calculated from K+e and Na+e (Flear, 1967)
3. Urinary anion gap increases when K+ excretion is increased (Flear, unpublished)
4. Supplements of K+ do not always prevent, nor always replete (Flear, 1965)
5. Repletion without supplementing diet occurs when patients recover (Flear, 1965)
6. Depletion cannot be explained as simple complication of diuretic therapy (unpublished, see Flear, 1972)

1967). Table XI summarizes the reasons for our belief that potassium depletion in patients in heart failure is caused by a failure to sustain normal levels of non-diffusible intracellular organic anions.

Adult patients with steatorrhoea with comparable cellular depletion of K+ were often not hyponatraemic (fig. 2). When present, hyponatraemia bore no relation to depletion of K+. Analysis of skeletal muscle biopsies discounted water gain as the cause of hyponatraemia in patients with steatorrhoea (Flear et al., 1965). The combined concentrations of Na+ and K+ in tissue water does not correlate with plasma sodium in these patients. The findings suggest that their cells contain subnormal molar quantities of non-diffusible solutes without parallel falls in K+. A similar conclusion must be drawn from observations of Clowdus and associates (1961) in patients with liver failure. They noted that the ratio of exchangeable body Na+ and exchangeable body K+ per kg of total body water was about the same in subjects with the most marked hyponatraemia as in those with more normal Na+ levels. Balance studies (Na+, K+, water) during development and recovery from hyponatraemia in congestive heart failure (Jaenike and Waterhouse, 1959) also suggest that a fall in the molar quantity of non-diffusible solutes in cells plays a role in the onset of hyponatraemia and that an increase in these solutes contributes to its reversal.

(2) Abrupt and widespread increase in membrane permeability. Deterioration in patients in severe congestive heart failure is accompanied by a decrease in plasma Na+ concentration. Weston and associates (1958) observed such episodes in patients on low sodium diets, and concluded that abrupt falls in plasma Na+ were caused by gains of water. However, Flear (1966) was aware of many such instances unaccompanied by weight gain, which could not have resulted from the accumulation of water. Three
instances of a fall in Na\(^+\) level, unaccompanied either by significant gain of water or by loss of body Na\(^+\) and K\(^+\), are shown in figure 3. A further two examples in a patient with Whipple's disease and a patient with liver failure, are shown in figure 4. In these patients the rapidity with which Na\(^+\) concentrations decreased and increased is noteworthy; such oscillations cannot have arisen from changes in body water content. The serum concentration of K\(^+\) increased in patient B, while that of Na\(^+\) decreased. This is also the case commonly in heart failure (Flear, 1960b).

![Graphs showing changes in serum Na+ and K+ concentrations](image)

**Fig. 3.** Examples of a fall in serum Na\(^+\) in patients in chronic congestive heart failure, unaccompanied by loss of body (Na\(^+\)+K\(^+\)), or by significant gain of water as reflected in body weight. Measurements were of K\(_e\) and Na\(_e\), or daily balances.

**Fig. 4.** Further examples of falls in serum Na\(^+\) unaccompanied by loss of body (Na\(^+\)+K\(^+\)), or gain of water. Note also the striking fluctuation in serum levels. Both patients were very ill, patient A being fed exclusively by intragastric milk.
These findings are consistent with an abrupt and widespread increase in cell membrane permeability. When this happens, the concentrations of Na⁺ should decrease without a decline in plasma osmolality; or with less of a reduction than would occur if the fall in Na⁺ simply reflected dilution of body fluids. We have investigated this possibility in a number of experimental and clinical situations by making serial observations of the relationship between plasma sodium and osmolality (water content of plasma was measured and plasma Na⁺ expressed as m.equiv per kg plasma water). The way in which observations are examined is shown in figure 5. An instance of a fall in plasma sodium caused by water retention is shown also. Figure 6 shows the findings to be expected following an abrupt and widespread increase in membrane permeability, and the actual measurements during the onset of endotoxic shock in dogs. Shock caused by bleeding dogs was also attended by reductions in plasma Na⁺ without dilution (Singh and Flear, 1969; Flear, 1970).

We also found that plasma Na⁺ concentrations decrease during and following surgery (Singh, 1971). In some cases there was a reduction in osmolality, indicating that dilution had contributed. Our investigations were made without altering treatment, which was entirely determined by our clinical colleagues. It is well known that hyponatraemia can be provoked by intravenous dextrose (Wynn and Rob, 1954). Data of Wright and Gann (1962), who induced marked reductions in plasma Na⁺ in this way, are shown in figure 7. Considerable dilution resulted some time after operation in patient App. (fig. 7).

Consistently we have found that the extent to which the Na⁺ concentration is reduced without the expected fall in “corrected” osmolality (measured...
Fig. 6. Expected consequences of (1) intracellular gain of NaCl associated with leak of some normally non-diffusible solutes; (2) as (1), plus production (and leak) of additional solutes within cells (from breakdown of adenosine triphosphate, creatine phosphate, glycogen etc.).

Findings in: a dog shocked by infusing a suspension of killed E. coli (Singh and Flear, 1969); 11 and 14, two patients during and after surgery (resections of abdominal aortic aneurysm, and prosthetic graft) (Singh and Flear, 1968).

Open circles represent observation before surgery or shock; lines connect consecutive observations during 6 hours of sustained shock in dog 5, during and after surgery for some days in cases 11 and 14.

Confidence limits represent ±3 SD of methodological errors in the dog; ± twice the average SD of normal day-to-day variation seen in nine fit subjects (Singh and Flear, unpublished).

value minus osmolality attributable to plasma urea and glucose) is more marked after major operations, and is exaggerated during complications (for example, infection and blood loss). This is illustrated in figure 8, which presents observations made in 3 patients following severe crushing injury of the lower limbs with irreparable vascular damage, after a massive burn injury, and during complications arising after an operation for acute pancreatitis.

We have made similar observations in several non-surgical situations, during respiratory failure (Flear et al., 1973), liver failure, heart failure, after acute myocardial infarction, and during renal failure. Some of these are shown in figure 9. The general findings in all situations are similar. Hyponatraemia is usually present in the severely ill, and osmolality is higher than would be expected from simple dilution of body fluids, although it may be lower than normal. While the patient’s condition is unstable there is a considerable and largely unrelated variation in both plasma Na⁺ and corrected osmolality. The situation usually progresses in those who are dying; conversely, it settles with clinical improvement, and levels of Na⁺ and osmolality return to normal on recovery.

Similar changes occur in dogs with uraemia when an autologous transplant of a perfused kidney is accompanied by immediate or delayed contralateral nephrectomy (fig. 10). Hyponatraemia develops without dilution. The disparity between plasma Na⁺ and corrected osmolality worsens in severe uraemia, and returns to normal on resumption of good renal
Fig. 7. (Right) Plots of ([Osm]_w/[Na]_w) calculated from data of Wright and Gann (1962). Six slopes (●——●) represent in-vivo total body dilutions with 2.0 l. of (5% w/v) dextrose in six patients. Two slopes (O——O) represent in-vivo total body dilutions with 1.5 l. of (13.3% w/v) dextrose in two patients.

Oblique parallel lines on this and subsequent figures (figs. 8, 9, 13) define the area in which may be expected to lie values resulting from dilution of body fluids. They are projections from the highest and lowest values of [Osm]_w seen by us in 56 healthy persons (see fig. 13). They are projected with the same gradient as the mean observed slope of dilution-concentration (see fig. 5,3). The area in which fell undiluted values seen in the same 56 healthy persons is delineated by vertical lines within the oblique parallels.

(Left) Observations on patient App. show episode of postoperative dilution.

Fig. 8. Observations on [Osm]_w and [Na]_w in three very ill patients. Initial values are marked "I", and the last observation "L". The shaded bands in this and figs. 7, 9 define the expected daily variation in values of [Na]_w and [Osm]_w for healthy persons. They span twice the average observed SD on either side of the initial observation, and are projected from this observation along the mean slope of dilution-concentration (fig. 5,3). Oblique and vertical lines define the normal range of values with and without dilution (see fig. 7).
function by the transplanted kidney. Similar changes were noted also (fig. 11) during perfusion in vitro of dog kidneys (Johnson et al., 1972).

Observations in 28 patients with advanced carcinoma are presented in figure 12, and compared with those in healthy persons. Considerable dilution is present in most cases, but the findings suggest that some redistribution of water has taken place in response to the escape of normally non-diffusible solute through leaky cell membranes.

Support for the view that an abrupt and widespread increase in permeability of cell membranes results in hyponatraemia is provided by the observations of Haddow and Klein (1970), and of Williams, Withrow and Woodbury (1971), that toxic doses of ouabain given to rats provoke marked falls in plasma Na⁺ (fig. 13). There is evidence that ouabain, at the levels calculated to occur throughout ECF in these animals, increases the membrane permeability of skeletal muscle fibres (Flear, Greener and Bhattacharya, 1973). Ouabain also decreased the resting membrane potential in skeletal muscle in these rats, as would be expected if permeability had increased. Low resting membrane potentials have been measured in skeletal muscle in rats (Campion et al., 1969; Shires et al., 1972) and in patients (Cunningham et al., 1971) in situations in which hyponatraemia is common. They have also been noted in liver perfused in vitro (Lambotte, 1970).

**Comparison of SIADH and “sick cells” as mechanisms of hyponatraemia.**

Persistent secretion of ADH and the cellular disturbances outlined both cause hyponatraemia. Table XII compares the findings to be expected in each case.

The earlier preference for SIADH, as a simpler hypothesis than a primary reduction of cell fluid osmolality (Fuisz, 1963), is no longer valid. Not only is it simple to understand that cell disturbances could arise in disease, but findings during the unprovoked onset of clinical hyponatraemia and during spontaneous remission are consistent with predictions of a primary cause. Apart from ectopic production by tumours, the reason for an inappropriate increase in ADH secretion is unclear. It is still less
HYPONATRAEMIA AND SICK CELLS

Fig. 10. Measurements in two dogs (Johnson and Flear, unpublished). One kidney from each animal was removed, preserved for 24 hr, and then transplanted back homologously into the dogs. The contralateral kidneys were removed immediately (A) or 17 days after the autologous transplant (B).

In B, the first observations (open circle) were made immediately before the first nephrectomy. The plasma levels of urea and creatinine were 26 and 1.2 mg/100 ml. This dog died in uraemia 3 days after transplant. Levels of urea and creatinine were then 320 and 9.9 mg/100 ml.

The first observations of $[\text{Osm}]_w$ and $[\text{Na}]_w$ in A were made 24 hr after transplantation (open circle). Levels of urea and creatinine were then 123 and 4.9 mg/100 ml. Six days after transplant, they had risen to 270 and 7.8 mg/100 ml. When the final observations were made, the levels were 67 and 1.4 mg/100 ml. Both transplanted kidneys were preserved for 24 hr by Collins method (Collins, Bravo-Shugarman and Terasaki, 1969) after 30 min of warm ischaemia. Details of technique and results are given in Johnson (1972, 1973).

Oblique lines are projected from the first A and last B observations. The slope of both lines is the mean gradient observed on dilution of plasma from 22 dogs (Singh and Flear, 1969; Singh, 1971). During onset of uraemia, plasma sodium level falls without corresponding fall in $[\text{Osm}]_w$. With recovery, sodium level rises without rise in $[\text{Osm}]_w$.

An estimate of the variation normally to be expected in the relationship between $[\text{Osm}]_w$ and $[\text{Na}]_w$ is shown, based on observations in healthy humans.

<table>
<thead>
<tr>
<th>TABLE XII. Comparison of findings expected in SIADH and when hyponatraemia is a result of “sick cells”.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SIADH</strong></td>
</tr>
<tr>
<td>Total water, intra- and extracellular fluid</td>
</tr>
<tr>
<td>$K_e$</td>
</tr>
<tr>
<td>Body weight (during abrupt fall in plasma Na$^+$)</td>
</tr>
<tr>
<td>Plasma levels</td>
</tr>
<tr>
<td>ADH</td>
</tr>
<tr>
<td>Osmolality (corrected) (see fig. 5)</td>
</tr>
<tr>
<td>K$^+$</td>
</tr>
<tr>
<td>Urea</td>
</tr>
<tr>
<td>Urine</td>
</tr>
<tr>
<td>Osmolality</td>
</tr>
<tr>
<td>Na$^+$</td>
</tr>
</tbody>
</table>

Prolonged administration of pitressin to man (Jaenike and Waterhouse, 1961) and to dog (Davis, Howell and Hyatt, 1954; Levinsky, Davidson and Berliner, 1959) eventually leads to a state of Na$^+$ balance at a given state of hydration.

$^1$To the level predicted from observed concentration of Na$^+$.

$^4$Always higher than the level predicted from observed plasma concentration of Na$^+$. 

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Fig. 11. Observations during continuous perfusion of three isolated dog kidneys. All were perfused for 24 hr with plasma protein fraction (PPF). Details of perfusion are described elsewhere (Johnson et al., 1972).

Kidney A was perfused after 30 min of warm ischaemia. Kidney C was removed from the donor dog after a period of 4 hr profound circulatory collapse (systolic blood pressure <60 mm Hg) induced by blood loss. Kidney B was subjected to neither insult. It was perfused immediately after excision. The first two kidneys were washed out with saline prior to perfusion; B was washed out with Collins solution (Collins, Bravo-Shugarman and Terasaki, 1969).

Oblique lines are projected from the first observation made shortly after onset of perfusion. Parallel lines on either side enclose 6 standard deviations based on replicate analyses. They are projected with the same gradient as the mean observed slope of dilution obtained by diluting samples from 18 batches of PPF.

Sodium levels fell in all instances; and without fall in \([\text{Osm}]_{c_w}\). At the point indicated by arrow on C plot, about 4.5 ml of 8.4 g/100 ml NaHCO₃ was added to the perfusate. There was an immediate rise in levels of \([\text{Na}]_{w}\) and \([\text{Osm}]_{c_w}\). The correspondence between the rise in both levels agreed with expectation.

Fig. 12. (Left) Values for \([\text{Osm}]_{c_w}\) and \([\text{Na}]_{w}\) in 58 healthy persons. The slope of the oblique lines enclosing data is the same as that of the average functional relationship between the variables defined by in-vitro dilutions of blood from 25 persons.

(Right) Observations of \([\text{Osm}]_{c_w}\) and \([\text{Na}]_{w}\) in 28 patients admitted to hospital with advanced carcinoma (of bronchus, stomach, colon, rectum, neck, breast, prostate) (Singh and Flear, unpublished observations).
Hyponatraemia and Sick Cells

Fig. 13. Fall in plasma Na⁺, and rise in K⁺ shortly after ouabain is injected into rats. Concentration of ouabain in ECF was calculated to be around 10⁻⁵M. Data from Haddow and Klein (1970) (---) and Williams, Withrow and Woodbury (1971) (-----).

obvious why it should remit with improvement of the underlying disease situation.

Cell membranes are known to possess a dynamic structure (Zierler, 1958) and permeability is known to be increased by hypoxia, substrate depletion, various metabolic inhibitors, and endotoxin including that from E. coli (Batey et al., 1970; Singh, 1971). Disturbance of membranes provoked by disease will lessen with improvement in the disease. A primary reduction of cell fluid osmolality is seen as a result of metabolic disturbances. For example, ischaemia reduces the creatine phosphate present in cells. Metcoff and colleagues (1966) report a substantial reduction in the amounts of phosphoenolpyruvate, α-ketoglutarate, oxaloacetate and pyruvate in the skeletal muscle of malnourished children.

Gupta (1971) reported his failure to find increased plasma concentrations of ADH in 20 patients in whom SIADH had been diagnosed. He observed also that plasma ADH can vary substantially without any change in plasma Na⁺ concentration, and he suggested that ADH may not be related aetiologically to hyponatraemia. Moreover, it has been found, when patients with a diagnosis of SIADH are given large amounts of fluid, that the further dilution of body fluids cannot be explained by water gain. Bartter and Schwartz (1967) were forced to invoke a decrease in cell solutes in addition. They also invoke a gain of cell solutes when fluid intake is restricted. De Souza and colleagues (1964) have drawn similar conclusions in both situations and reference may be made also to Dudley and colleagues (1954), and to Starmont and Waterhouse (1961). Furthermore, Schwartz and colleagues (1957), when proposing the pathophysiology of increased ADH secretion, noted that one of their patients showed 25% depletion of body K⁺ (measured by exchangeable body K⁺). A cell depletion of this amount could itself account for the hyponatraemia (plasma Na⁺ 112 m.equiv/1.) noted in the patient at that time (fig. 2). Finally, it should be noted that data presented by Kaye (1966) for the muscle composition in 5 patients with a diagnosis of SIADH suggest a considerable loss of non-diffusible solutes.

Clinical significance.

Hyponatraemia is an indication of disease, but unless it directly worsens the situation in which it arises, there is no need to try to influence it directly. In a wide variety of situations, attempts to do so by giving NaCl by mouth or vein have been largely unsuccessful in the past. They have often provoked accumulation of oedema and sometimes have been disastrous, particularly in heart and liver failure. There is evidence that hyponatraemia caused by an abrupt accumulation of water can be harmful. It should be treated by water restriction, or by intravenous hypertonic saline if severe symptoms such as convulsions are present. In some situations, NaCl by mouth has proved helpful (Flear and Hill, 1957). The difficulty, of course, is in establishing the reality of water gain. In its absence, restricting fluids will still elevate plasma Na⁺, but to no real purpose and at some discomfort. Other than in this situation, it is difficult to ascribe symptoms or harm to the reduction of the plasma Na⁺ concentration. Indeed, Wright and Gunn (1962) found that reducing plasma Na⁺ acutely by about 20 m.equiv/l. without reducing osmolality (fig. 7) had no demonstrable effect. Moreover, there is evidence which suggests that hyponatraemia is more appropriate to the circumstances which provoke it than is a so-called normal level (table XIII).

Treatment should be directed not at a low sodium
TABLE XIII. Consequences of low extracellular level of Na+ which may be beneficial. Both 3 and 4 have minimized harmful cell gains of Na+, and cellular swelling.

<table>
<thead>
<tr>
<th>Consequences</th>
<th>Description</th>
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<tbody>
<tr>
<td>(1) Helps the heart to withstand anoxia in vitro</td>
<td></td>
</tr>
<tr>
<td>(2) Positive inotropic effects</td>
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<tr>
<td>(3) Lessens Na+ influx into cells, thus reducing the amount to be pumped out again</td>
<td></td>
</tr>
<tr>
<td>(4) Lessens electrochemical gradient across cell membranes against which Na+ has to be pumped</td>
<td></td>
</tr>
</tbody>
</table>

concentration but at the underlying disease. When treatment is successful, the sodium concentration returns to normal. Where hyponatraemia is a result of "sick cells", it is likely that measures which lessen cell membrane permeability and which increase sodium pumping will help. As Elkinton (1956) stated, "this calls for a tonic". Insulin and glucose have been used with benefit in a variety of situations: congestive heart failure (Flear, 1960a; Brenner, 1960; Allison, Morley and Burns-Cox, 1972; Editorial, 1972); severe burns (Hinton et al., 1973); terminal carcinoma (Neufeld, 1962); and in uraemia (Flear and Scott, unpublished observations). Some situations provoking hyponatraemia (the postoperative period, for example) are normally so brief that such treatment is unnecessary. However, hyponatraemia is aggravated and protracted if complications arise such as blood loss into the wound, sepsis, rupture of surgical anastomosis, or systemic infection. Glucose and insulin may be of use (Allison, personal communication), but the treatment of the underlying complication is the first essential. Graber, Beaconsfield and Daniel (1956) found cortisone to be helpful under these circumstances. Furthermore, it is possible that aldosterone and other steroids, which are reputed to protect in experimental endotoxic shock, act by correcting cellular disturbances. Circulatory collapse may occur because of abrupt shrinkage of the ECF as a result of cell swelling provoked by the action of E. coli endotoxins on cell membrane permeability (Flear, 1970, 1973; Singh, 1971) (fig. 6). We believe this to be true also in respiratory failure (Flear et al., 1973). In these situations in particular, we consider that a direct attempt to increase the plasma Na+ concentrations should be avoided. Yet, hypertonic saline has been reported to be of benefit in this and other types of circulatory collapse accompanied by hyponatraemia (Brooks et al., 1963; Bergentz and Brief, 1965; Baue, Tragus and Parkins, 1967; Monafo, Blanke and Deitz, 1969). We believe that its occasional success can be ascribed to expansion of the plasma volume and interstitial fluid. Shrinkage of the former affects the circulation; shrinkage of the latter influences diffusion through the interstitial fluid, aggravates cell disturbances and impairs tissue perfusion (Flear, 1973). Expansion of plasma volume with hypertonic saline is short-lived, and experience has attested to the hazards of its use, for example pulmonary oedema. Moreover, by increasing the plasma Na+, it may elevate intracellular Na+. Accumulation within heart fibres impairs contractility, predisposes to dysrhythmia and reduces the cardiac output. For these reasons, we believe that it is better to expand the circulation directly with blood when shock is the result of haemorrhage, or with plasma when this has been lost. Indeed, even when plasma has not been lost (as in respiratory failure), we have found it necessary to transfuse substantial volumes of plasma in order to stabilize the circulation. This poses a problem on account of its Na+ content, and salt-free human serum albumin is to be preferred.

At times, it may be necessary to expand the interstitial fluid, although this is a difficult decision.

![Fig. 14. Change in pK, with dilution of plasma Na+. Findings with plasma from four healthy persons; lines drawn by eye (unpublished data of Watson and Flear). Diluted and undiluted samples of plasma were equilibrated at 37°C with 3.9% CO2 fully saturated with water (Fco2 approx. 28 mm Hg) using the Astrup method. Total CO2, pH and Na+ levels were measured on undiluted plasma; pH and Na levels only on diluted samples. ΔpK, calculated from equation

\[
\Delta(pK) = (pH)_u - (pH)_d + \log [HCO_3^-]_u - \log [HCO_3^-]_d
\]

where superscripts u, d denote undiluted and diluted plasma respectively. [HCO3⁻] is the millimolar concentration of bicarbonate, and is taken as TCO2/2Pco2 where Pco2 expresses the millimolar concentration of dissolved CO2 plus carbonic acid. (TCO2)2p is calculated as ([Na]2)^p/([Na]2p). (TCO2)u.

![Diagram](https://academic.oup.com/bja/article-abstract/45/9/976/265926)
to take. Particularly in the presence of hyponatraemia, we would urge that this be attempted with an isosmotic saline having approximately the same Na⁺ concentration as that of the patient’s own plasma. Parity with the osmolality of the patient’s plasma should be achieved with the appropriate addition of glucose. Cardiac glycosides are helpful in situations of circulatory collapse, and it is of interest that we have found that in therapeutic doses ouabain reduces the permeability of heart fibre membranes, and increases Na⁺ pumping (Flear, Greener and Bhattacharya, to be published; Flear and Greener, 1970).

Many hyponatraemic patients are depleted of potassium. Supplementing dietary gains by K⁺ salts has been tried. It has been largely unsuccessful in tuberculous meningitis (Harrison, Finberg and Fleishman, 1952), in congestive heart failure (Flear, 1965), and in liver failure (Phillips, 1968). This is to be expected where depletion results from a decrease in the quantity of non-diffusible organic anions within cells, which cannot be replaced from outside. At times, however, supplements have been successful in restoring potassium and, as a result, reversing hyponatraemia. This can be said of congestive heart failure (Cort and Matthews, 1954; Laragh, 1954; Davidson, Flear and Donald, 1960; Flear and Cawley, 1962) and of cirrhosis of the liver and tuberculous meningitis (Laragh, 1954). In our opinion, the reasons for success or failure are not a simple matter of whether or not K⁺ is given as its chloride (Flear, 1972), as has been sometimes asserted. Success at times may have resulted from increased sodium pumping initiated by a rise in the plasma K⁺, which would reduce the resting membrane potential and thus the electrochemical gradient across cell membranes against which Na⁺ is pumped; this would allow K⁺ to replace Na⁺ cleared from the cells. Certainly, we have found that potassium supplements are retained during periods of clinical improvement when cells will be returning to normal the quantity of non-diffusible anions, and it seems possible that their use may ease recovery. The value of K⁺ supplements as an adjuvant to glucose and insulin is worth further investigation. It was suggested that KCl supplements at times may bring about a rise in plasma Na⁺ by provoking a hyposmotic solute diuresis (Orloff et al., 1959); but it was noted that correction of hyponatraemia in oedematous nephrotics by intravenous mannitol and oral urea was not attended by obvious clinical improvement.

Finally, we would like to comment on acid-base changes in hyponatraemia. Abrupt expansion of the ECF with 0.9% saline solution is known to reduce the pH. The concentration of bicarbonate throughout the ECF is reduced, whilst the Pco₂ remains constant. When hyponatraemia is brought about by a rapid gain of water, pH will likewise decrease. It will not decrease when a reduction in plasma Na⁺ results from the redistribution of solutes and water caused by an abrupt and widespread increase in cell membrane permeability. Nevertheless, the pH is likely to show variable changes when this happens, and there is cell swelling and shrinkage of ECF. Under these circumstances the ECF bicarbonate will increase, thus raising the pH if the Pco₂ remains constant. However, when solutes leaking from cells include lactate or other organic acids, the bicarbonate concentration will decrease.

Observations shown in figure 14 indicate that the value for pK in the Henderson-Hasselbach equation will increase. When hyponatraemia is provoked by dilution, the pH falls as the consequences of dilution of bicarbonate exceed those from an increase in pK. When hyponatraemia is sustained, some adjustment of Pco₂ may take place. The situation is complex and further clarification is needed before therapeutic advice can be offered. It should be noted that actual and standard bicarbonate (and base excess) obtained from Astrup graphs will be overestimated.

In 1956 Elkinton wrote “... it is difficult, however, to believe that cellular factors alone could result in this electrolytic pattern (hyponatraemia) without concomitant failure of regulatory and of renal function”. We think it is no longer difficult to believe this, but we agree that “hyponatraemia is a biochemical sign of a series of complex disturbances of body fluids. At best, these disturbances are still incompletely understood and present a challenge to the physician to exercise his physiologic knowledge, his clinical astuteness, and his therapeutic ingenuity.”

ACKNOWLEDGEMENTS

Research was supported by the Wellcome Trust, the Scientific and Research Committee of the Royal Victoria Infirmary, Newcastle-upon-Tyne, and by an equipment grant from the Royal Society. Thanks are due to Miss Barbara James (Department of Photography, University of Newcastle-upon-Tyne) for help with the figures.

Some of the work referred to here was undertaken whilst C.M.S. was in the Department of Surgery, Newcastle-upon-Tyne. He wishes to thank Professor I. D. A. Johnston for the kind hospitality of his department and for his encouragement.
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BRITISH JOURNAL OF ANAESTHESIA


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