BODY COMPOSITION

The general information derived from methods of measuring body composition in vivo is fundamental to the understanding and treatment of disturbances of fluid and electrolyte metabolism, although the methods themselves have only limited use in the day-to-day management of patients. Such information is also important in assessing drug dosage since drugs of different partition coefficient will distribute differently between body fluids and fat. The ratio of these compartments varies greatly between individuals, and adjustment in dose may have to be made.

Dilution analysis.

The size of tissue compartments in living man is best determined by dilution analysis. Thus if a given concentration of a marker $C_i$ is introduced into the body in a volume $V_i$, then the distribution space $V_d$, relative to the marker’s concentration in a body fluid at equilibrium $C_d$, is given by

$$V_d = C_i V_i / C_d$$

Corrections may have to be made to the numerator for urinary or other loss of the marker.

Total body water (TBW), extracellular space (ECS), plasma volume, and red cell volume may be determined directly with suitable markers, but intracellular fluid volume must be estimated as the difference between TBW and ECS (fig. 1).

Total body water.

This is best measured as the volume of distribution of deuterium oxide (Schloerb et al., 1950) or tritiated water (Prentice et al., 1952) though other markers such as urea and antipyrine have been used. The values, as % body weight, have a large variation even for groups of similar age and sex. Mean values decrease during neonatal life till after 1 year, they are higher in men than in women, and further diminish after the age of 40 (table I).

Direct analysis of fat-free pieces of tissue gives a rather constant water content. Thus fat-free skeletal muscle contains 74–78% water (Manery, 1954). The big variation in TBW between individuals can be attributed largely to variable amounts of adipose tissue with a water content of 25 to 30% (Keys and Brozek, 1953). Thus females tend to have a greater ratio of adipose tissue to lean body mass than males. The similar variability in measurements of extracellular volume, and in total exchangeable sodium and potassium, is no doubt due to the same cause. Since there is no simple way of estimating precisely what these parameters should be in a given

TABLE I. Variation of total body water (l./kg body weight) in normal man with age and sex; average values from several workers, using different methods (from Edelman and Leibman, 1959).

<table>
<thead>
<tr>
<th>Age</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 month</td>
<td>75.7</td>
</tr>
<tr>
<td>1-12 months</td>
<td>64.5</td>
</tr>
<tr>
<td>1-10 years</td>
<td>61.7</td>
</tr>
<tr>
<td>10-16 years</td>
<td>58.9</td>
</tr>
<tr>
<td>17-39</td>
<td>60.6</td>
</tr>
<tr>
<td>40-59</td>
<td>54.7</td>
</tr>
<tr>
<td>60+</td>
<td>51.5</td>
</tr>
</tbody>
</table>

healthy individual, dilution methods of measuring body compartments have not been so useful in estimating the magnitude of fluid or electrolyte deficits or excesses as had been hoped originally.

**Extracellular fluid.**

The volume of this compartment cannot be estimated with the same certainty as the TBW. The standard indicators can be divided into two groups: non-electrolytes of moderate molecular weight (e.g. inulin and sucrose), and monovalent anions (e.g. thiosulphate, \( ^{87}\text{Br} \) and \( ^{35}\text{Cl} \)). The former underestimate the total ECF, because there are regions into which they penetrate with extreme slowness; also, practical problems arise since such compounds are rapidly excreted by the kidney with a clearance close to the glomerular filtration rate. Monovalent anions overestimate the space because they enter some of the cells, but they are simpler to handle. \( ^{87}\text{Br} \) is distributed in the same manner as chloride and is suitable for use in man. Better markers are probably divalent or polyvalent anions (e.g. sulphate) which, for electrical reasons, are less likely to enter cells in appreciable amounts. Sulphate, labelled with \( ^{35}\text{S} \), has been used in man. In young healthy men it distributes in about 18% of the body weight (Ryan et al., 1956). This space is midway between the volumes determined with non-electrolytes on the one hand and monovalent anions on the other.

**Sub-divisions of the extracellular fluid.**

Apart from fractions of the extracellular fluid into which solutes cannot exchange (e.g. inaccessible bone-water) these fluids are either closely related to blood plasma as dialysates, or are anatomically and functionally separate from it as transcellular fluids (fig. 1). Fluids of the first groups, e.g. interstitial fluid and lymph, are separated from plasma and each other by endothelia containing relatively large pores, the intercellular channels of 40 Å diameter (fig. 2). Since only the movement of proteins is restricted by these channels, the composition of interstitial fluid with respect to the smaller diffusible solutes is similar to that of blood plasma. The protein content is between 0.5 and 3 g/100 ml, which has a small Donnan effect on the distribution of sodium and chloride. Calcium and magnesium occur at about 60% and 70% of their respective concentrations in plasma, because of protein binding and the greater Donnan effect on divalent ions.

Transcellular fluids are separated from blood plasma by a tight cellular barrier without large pores (fig. 2), and therefore may have a different composition from plasma (Reese and Karnovsky, 1967). The protein concentration is very low unless this is secreted into the fluid for a specific purpose (e.g. the secretions of digestive glands). The electrolyte composition, though generally not dissimilar to that of plasma, may be totally different (e.g. endolymph...
in which potassium replaces sodium as the predomi-
nant cation). Further, this composition may be main-
tained quite independent of that in blood plasma.
Thus, the concentrations of \( \text{H}^+, \text{K}^+, \text{Ca}^{++} \) and
\( \text{Mg}^{++} \) in cerebrospinal fluid vary little in the face
of severe and prolonged disturbances in their con-
centrations in plasma (Davson, 1967). This stability
of ions in CSF undoubtedly reflects a similar homeo-
stasis of the ionic composition of the cerebral inter-
stitial fluid.

\textbf{Sodium space and exchangeable sodium.}

Since sodium is predominantly an extracellular
cation, its space, though larger than that of the extra-
cellular fluid, is likely to vary with it. The space
may be measured with \(^{22}\text{Na} \), values obtained at 24
hours after administration generally being used. The
exchangeable sodium at 24 hours may be derived
as follows:

\begin{align*}
\text{Exchangeable Na} = & ^{22}\text{Na space} \times \text{Na concn. in plasma } H_2O \\
\text{Mean values in young adults are about 43}
\text{m.equiv/kg in males and 40 m.equiv/kg in females}
(\text{Veall and Vetter, 1958}). \text{About 40}\% \text{of the total}
sodium in the body is in the bone and 70\% of this}
(i.e. 15–20 m.equiv/kg) is non-exchangeable. Bone
provides a small reservoir of sodium, and shifts to
and from bone may occur under certain conditions.

\textbf{Intracellular fluid.}

Determined by difference, this comprises almost
70\% of the TBW in adult males. That there is twice
as much water in the cells as outside them is of no
importance in assessing fluid deficits and their
replacement. The approximate composition of intra-
cellular fluid (it cannot be analysed directly) is given
in table II. Potassium is the predominant cation and
95\% of the potassium in the body is intracellular.
Thus, measurements of potassium in plasma are not
representative of potassium in the body as a whole.
Probably most of the intracellular potassium is
present as the free ion, not bound, and electrical
balance is maintained by the presence of non-perme-
ating polyanionic proteins and phosphate com-
ounds. In contrast to potassium, the concentration
of calcium ions in the intracellular fluid of skeletal
muscle is less than \( 10^{-7} \text{M} \) whereas the total calcium
is greater than \( 10^{-4} \text{M} \) (Winegrad, 1969). Most is
absorbed or accumulated in the endoplasmic reticu-
lim or the mitochondria. A similar situation probably
exists for the larger content of intracellular magnesi-
un.

Since most enzymes are intracellular and most
metabolic reactions take place within the intracellular
fluid, the maintenance of this environment has an
importance for the organism equal to or greater
than that of the maintenance of the extracellular
fluid. In this context, metabolic reactions may be
highly sensitive to pH changes, and such changes
induced by disease may have a marked effect on
normal function. The numerical value and indeed
the concept of intracellular pH have recently been
topics for controversy. The view is now becoming
established that for the cells of most tissues, the pH
lies between 6.8 and 7.2 (Waddell and Bates, 1969).

Intracellular potassium in man may be assessed
from measurement of the 24-hr exchangeable potas-
sium, using \(^{40}\text{K} \). At this time, probably about 90\%
of total body potassium is exchanged with the iso-
tope. Normal values are 45 m.equiv/kg in young
men and 35 m.equiv/kg in young women (Corsa
et al., 1950). Of this only about 1 m.equiv/kg is
extracellular. There is a marked decrease in later
life, reflecting a loss of lean body mass.

Alternatively, intracellular potassium may be
assessed from estimation of potassium in tissue
samples. The potassium content of erythrocytes does
not correlate well with other indices of total body
potassium (Keitel, 1957). Biopsy of skeletal muscle
yields variable amounts of blood and extracellular
fluid which are difficult to correct for, and obviously
cannot be used for serial measurements in man
(Flear and Florence, 1963). The potassium in leuco-
cytes is readily accessible to serial measurement and
correlates better with total exchangeable potassium
(Patrick and Bradford, 1972).

The potassium content of either the whole body
or of a tissue sample has to be related to some
standard. Exchangeable potassium in normal sub-
jects correlates better with total body water than
with body weight, since it is contained in the lean
cell mass. In chronic electrolyte disorders, not only
may the lean cell mass itself change due to wasting,
but the volume of extracellular fluid itself is likely
to be abnormal. Proper interpretation of the potas-

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|}
\hline
 & Plasma & Intracellular fluid \\
\hline
\textbf{Sodium} & 140 & 10 \\
\textbf{Potassium} & 4 & 150 \\
\textbf{Calcium} & 2.5 & \( 1 \times 10^{-4} \text{ (free ion) approx. 1} \text{ (total)} \) \\
\textbf{Chloride} & 100 & 3 \\
\textbf{pH} & 7.4 & 7.0 \\
\hline
\end{tabular}
\caption{Comparison of electrolyte composition in mM of blood plasma and intracellular fluid of skeletal muscle; approximate values based on information from literature.}
\end{table}
sium status involves relating the primary potassium measurement to several other measurements such as body or cell water, body or cell solids, and a baseline or normal value (Patrick and Bradford, 1972).

**MAINTENANCE OF INTRACELLULAR VOLUME AND COMPOSITION**

**Osmotic and electrical forces.**

The plasma membrane of an animal cell is considered to exert no mechanical constraint on the cell contents. Hence, if the cell is to remain at a constant volume, intracellular and extracellular fluids must be isotonic. Experiments have generally confirmed this. Also, cationic electric charges must equal anionic charges both outside and inside the cell. The anions within the cell are largely polyvalent and too large to penetrate the plasma membrane. The sole cation to which the plasma membrane is permeable, and which is present in sufficient free concentration to neutralize the fixed anions, is potassium. Sodium is present outside the cell, but is excluded by the low relative permeability of the membrane to this ion and by the sodium pump. Chloride is present also and can move freely across the membrane. Osmotic and electrical equality can only be satisfied by a high relative concentration of mobile potassium inside the cell, together with a low relative concentration of chloride. The discrepancy in the concentrations of these mobile ions between the inside and the outside results in the transmembrane potential, the interior of muscle and nerve cells being 60–80 mV negative to the exterior. In the steady-state the situation can be expressed mathematically as

\[ \frac{[K_i]}{[K_o]} = \frac{[Cl_i]}{[Cl_o]} \]

and

\[ V = 61 \log \frac{[K_i]}{[K_o]} = 61 \log \frac{[Cl_i]}{[Cl_o]} \]

**The sodium pump.**

The permeability of the cell membrane to sodium is generally one or two orders of magnitude less than its permeability to potassium. The large concentration gradient and the negativity of the interior force a continuous leak of sodium into the cell. This leak is balanced by the sodium pump, a mechanism present in the plasma membrane, which is capable of utilizing energy derived from the hydrolysis of adenosine triphosphate (ATP) for the ejection of Na+ ions from the cell (Whittam and Wheeler, 1970). The pump also actively moves K+ ions inwards, the proportion of K+ to Na+ ions moved being variable but usually about 2:3. The inward K+ transport is probably not of great physiological significance, being akin to the act of pedalling a bicycle whilst going downhill, since the membrane is permeable to K+ in any case. A specific "transport" ATP-ase which is activated by Na+ and K+ and inhibited by cardiac glycosides, can be extracted from cell membranes and presumably is directly implicated in the pump mechanism.

Final steady values for the composition and volume of the intracellular fluid are thus determined by these passive and active forces acting in the presence of a given extracellular environment. Metabolism within the cell also plays a role. Thus, net synthesis or degradation of cell proteins will lead to changes in the intracellular fixed anions and thus an increase or a decrease in cell volume. Hypoxia causes a shift in glucose metabolism towards anaerobic glycolysis rather than oxidation. The lactic acid released will reduce intracellular pH and may have many indirect effects.

If the function of the sodium pump is inadequate from lack of oxygen or substrates, or from the presence of metabolic poisons, leakage of sodium into the cell will occur unchecked. Net uptake of this cation will reduce the interior negativity and chloride will enter too. The increasing concentration of solute within the cell will lead to osmotic entry of water, cell swelling and disruption. Not only is this the probable cause of cell death in the central nervous system during anoxia, but the swelling of astrocytic glial processes may indirectly cause localized necrosis by obstructing capillary blood flow during less severe or prolonged hypoxia (Chiang et al., 1968).

**MAINTENANCE OF EXTRACELLULAR VOLUME AND COMPOSITION**

**Basic mechanism of control.**

The details of the function of the organs and tissues involved in salt and water exchange will not be discussed. Comprehensive recent reviews occur in the text edited by Maxwell and Kleeman (1972). Primary control appears to be over water exchanges, which are adjusted to maintain a constant total concentration of solute or osmolarity in the blood plasma and hence ECF. If osmolarity is set, then the volume of the ECF may be determined secondarily by a control over the exchanges of the principal solute, namely sodium chloride. There is some overlap, in that perturbations of ECF volume also have marked effects on water exchanges.
Osmolarity of ECF and water exchanges.

Gain of water to the body is in the form of liquids, the water contained in food and that derived from metabolism. Loss occurs as urine, as evaporation from the skin and respiratory passages, and in the stools. Control occurs at the kidney and in the oral intake of water.

Increasing osmolarity of the blood within the carotid artery increases the discharge of osmoreceptors in the anterior hypothalamus (Verney, 1947; Hayward and Vincent, 1970). This discharge is associated with (a) thirst and (b) synthesis and release of vasopressin (ADH) from the neurones of the supraoptic nuclei, part of the neurohypophyseal system. ADH has a profound effect on the reabsorption of water from the fluid in the distal tubules and collecting ducts of the kidney. In its absence the urine flow is copious and its osmolarity is very low, perhaps 15–30 m.osmol/l. corresponding to a specific gravity of 1.001. During maximum secretion in response to a hyperosmolar stress, urine flow is sparse (500 ml/day) and the urine is very concentrated, up to 1400 m.osmol/l. or a specific gravity of 1.035. The result is a control of the osmolarity of the blood plasma at 275–295 m.osmol/l. in normal individuals in a normal environment. If the hypothalamic—ADH—kidney control loop is defective (as in diabetes insipidus or the syndrome of inappropriate secretion of ADH) imperfect control of plasma osmolarity at an abnormal level is still possible by the thirst mechanism.

Volume of ECF and salt exchanges.

Sodium intake, except in the therapeutic situation, is oral. Loss is in the urine, sweat and faeces. The latter two routes may become very significant at high environmental temperatures or in the presence of diarrhoea respectively. Although control of intake of NaCl may occur by the occurrence of “salt hunger” when the ECF is depleted, the main control is over urinary loss. In man, about 14,000 m.equiv/min of sodium is filtered through the glomeruli into the renal tubules. On an average intake of 200 m.equiv/day, all but 1% of the filtered sodium is reabsorbed by the tubules. Thus, it might be anticipated that urinary loss of sodium would be very sensitive to either a small change in glomerular filtration rate or in the amount reabsorbed. In fact, reabsorption of sodium bears a constant relation to glomerular filtration rate when the latter varies. The mechanism of this “glomerulo-tubular balance” is not understood. Homeostasis of ECF volume appears to depend mainly not on changes of glomerulo-filtration rate but on changes imposed on the reabsorption of sodium in the tubules (Earley, 1972).

The volume of the ECF compartment is sensed indirectly mainly by receptors which are sensitive to stretch of the walls of the left and probably also the right atria, the so-called “volume receptors” (Ledsome and Linden, 1968; Goetz et al., 1970; Kappagoda, Linden and Snow, 1972). For reasons connected with capillary filtration, the blood volume varies directly with the ECF volume. Blood volume, of course, influences the central and pulmonary venous pressures. Other receptors concerned in controlling salt and water excretion may be the juxtaglomerular apparatus, the baroreceptors of the carotid sinus, and the cells of the adrenal cortex itself which are directly sensitive to the potassium and sodium concentrations in blood plasma.

Aldosterone has a profound stimulant effect on sodium reabsorption from the distal renal tubule, and possibly also from the loop of Henle and the proximal tubule. Secretion in man is increased by sodium deprivation, haemorrhage, and changing environmental temperatures or in the presence of diarrhoea respectively. Although control of intake of NaCl may occur by the occurrence of “salt hunger” when the ECF is depleted, the main control is over urinary loss. In man, about 14,000 m.equiv/min of sodium is filtered through the glomeruli into the renal tubules. On an average intake of 200 m.equiv/day, all but 1% of the filtered sodium is reabsorbed by the tubules. Thus, it might be anticipated that urinary loss of sodium would be very sensitive to either a small change in glomerular filtration rate or in the amount reabsorbed. In fact, reabsorption of sodium bears a constant relation to glomerular filtration rate when the latter varies. The mechanism of this “glomerulo-tubular balance” is not understood. Homeostasis of ECF volume appears to depend mainly not on changes of glomerulo-filtration rate but on changes imposed on the reabsorption of sodium in the tubules (Earley, 1972).
the ECF of the donor animal is expanded with isotonic saline and blood is passed to the non-expanded recipient, have resulted in increased sodium excretion by the recipient (de Wardener et al., 1961). This increased excretion is most marked if the donor blood is led directly to the recipient's kidney (Blythe et al., 1971). A "natriuretic hormone" inhibiting sodium reabsorption has been suggested, but neither the compound itself nor its site of origin have been identified unequivocally (fig. 3).

Sodium reabsorption may be influenced also by haemodynamic or other physical factors acting directly on the kidney. Thus, sodium excretion is increased by factors which favour capillary filtration and expansion of the interstitial space within the kidney—e.g. an increase in renal venous pressure (Lewy and Windhager, 1968); and it is decreased by factors which reduce the interstitial space—an increase in the oncotic pressure of the perfusing blood (Goodyer, Peterson and Relman, 1949). The mechanism of these effects is unknown, but the rate at which transported sodium chloride is cleared from the interstitium is presumed to influence the transport process across the tubular cells. However, the effects are so directed as to favour homeostasis of the ECF volume (fig. 3).

Finally, it should be noted that information derived from the "volume receptors" (as in the atria) influences not only the reabsorption of sodium, but also the reabsorption of water in the kidney by the secretion of ADH. Reduction in blood volume by haemorrhage is a potent stimulus to ADH release. Over the physiological ranges, the release of ADH appears to be about equally sensitive to changes in either osmolarity or venous pressure (Johnson, Zehr and Moore, 1970).

**Examples of Adaptation of Body Fluids to Stress**

*Isotonic volume change.*

Addition of isotonic NaCl or extracellular-type fluid to the ECF compartment may be performed experimentally and occurs effectively with the salt retention of heart failure, cirrhosis of the liver and certain renal diseases. Similarly, loss of isotonic fluid is the effective deficit when NaCl is depleted from the body by excessive sweating without replacement, by diarrhoea, salt-losing nephritis, Addison's disease or following gastrointestinal surgery. An increase or a decrease in the volume of the ECF will not, without a corresponding change in its osmolality, lead to a change in intracellular volume or composition. The brunt of acute changes in ECF volume falls on the circulation, a decrease causing a loss of plasma volume with raised haematocrit and finally circulatory collapse. Similarly, expansion of the ECF volume will lead acutely to raised venous pressure, and chronically to oedema.

Chronic salt depletion is likely to be associated with a low concentration of sodium in the plasma, as well as with volume depletion. The body adapts to the reduced volume by controlling water excretion to give a lower than normal osmolarity of the body fluids, the mechanism being the feed-back from the atrial receptors on the secretion of ADH discussed above.

*Osmotic stress.*

Water taken into the body distributes itself rapidly throughout the extracellular and intracellular compartments. Under normal conditions excess water is rapidly excreted. Dehydration (pure water depletion) is associated with hyperosmolarity of both ECF and cells. Rapid changes in the osmolarity of the ECF lead to swelling and shrinkage of the brain with corresponding pressure changes in the
cerebrospinal fluid (Weed and McKibben, 1919). Hence it is not surprising that many of the symptoms of hypo- and hyperosmolarity are referable to the CNS. There is evidence that acute hypernatraemia in infancy may cause physical damage to the brain, the pathological mechanism being rupture of blood vessels due to the mechanical stress of shrinkage (Macaulay and Watson, 1967).

**Disturbances of potassium distribution.**

A reduction in exchangeable potassium will follow any condition causing wasting of lean tissue. This is to be distinguished from primary potassium depletion, resulting from loss of potassium from the body. Because of the large reservoir of intracellular potassium, potassium depletion is likely to follow only chronic gastrointestinal or renal loss of this ion (Black, 1972). Hypokalaemia, a low concentration of potassium in the extracellular fluid, may or may not accompany potassium depletion, and may occur independently of it in response to factors favouring the influx of potassium into cells, e.g. alkalosis and the administration of insulin.

Excess of total body potassium is not a recognized disorder as is hyperkalaemia (an increased concentration of potassium in the extracellular fluid). The potassium concentration in the ECF is normally well maintained because orally administered potassium is taken up readily by the cells or excreted by the kidneys. Hyperkalaemia can be due to intravenous infusion of solutions of too high a potassium content, to inadequate excretion of the ion due to renal failure or aldosterone lack, or to a shift of potassium from cells into the ECF. In the latter connection, an important relation exists between potassium and hydrogen ion distribution across the cell membrane.

Extracellular acidosis, particularly of metabolic origin, is associated with hyperkalaemia, and conversely extracellular alkalosis leads to hypokalaemia. The mechanisms are partly renal, but shifts of potassium between cells and ECF are important. The converse also holds in that infusion of KCl into animals leads to a metabolic alkalosis. These processes are in part controlled by the concentrations of the substances determining the rates of transport and metabolism, and in part by the overriding influence from nervous and hormonal control. Disturbances initially affecting only one substance will secondarily cause changes in composition and volume throughout the whole system.

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