METABOLIC CARE

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Churchill Livingstone

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CHURCHILL LIVINGSTONE
EDINBURGH LONDON MELBOURNE AND NEW YORK 1982

CHURCHILL LIVINGSTONE
Medical Divison of Longman Group Limited

Distributed in the United States of America by Churchill Livingstone Inc., 19 West 44th Street, New York, N.Y. 10036, and by associated companies, branches and representatives throughout the world.

First published 1982

ISBN 0 443 01867 7

British Library Cataloguing in Publication Data
Tweedle, D.E.F.
Metabolic care.
1. Metabolism, Disorders of
I. Title II. Cockburn, F. III. Stoddart, J.C.
616.3'9 RC627.54

Library of Congress Catalog Card Number 81–70268

Printed in Singapore by Huntsmen Offset Printing Pte Ltd

Metabolic Care

This book is dedicated to the memory of
my brother-in-law, David Gourlay Dalrymple,
whose early death deprived medicine of
a skilful and considerate clinician
with an inquisitive mind.

Preface

> 'The basic components of medical knowledge are water, electrolytes, oxygen, lipids, protein and carbohydrates'.
>
> *Irvine Page*

Many patients have serious metabolic abnormalities, whose correction is essential for a successful outcome. In some these are readily apparent: in others they are recognised only by careful clinical and biochemical assessment. Several large texts are available which present in detail the complex alterations of physiology and biochemistry involved. This book attempts to present these problems in straightforward terms for the clinical practitioner.

I have been particularly fortunate in persuading two colleagues of international distinction to provide chapters on topics of which they have an exceptional experience. Professor F. Cockburn is the Samson Gemmell Professor of Child Health in the University of Glasgow. His knowledge and expertise in the field of neonatal nutrition is unique. Dr J.C. Stoddart is a Consultant Anaesthetist and the Consultant–in–Charge of a busy intensive therapy unit in the Royal Victoria Infirmary in Newcastle upon Tyne. Few clinicians have gained his experience of the day-to-day management of seriously ill patients. I am very grateful to them both.

As a young surgeon my interest in problems of surgical metabolism was stimulated by my late chief Mr A.M. Loughran, who as Consultant Surgeon at the West Cumberland Hospital provided a surgical education in its very broadest sense. Later, I was fortunate to spend four years in the Department of Surgery in Newcastle upon Tyne with Professor I.D.A. Johnston and a year in the Department of Surgery of Harvard University under Professor F.D. Moore. My attitude to metabolic care has been particularly influenced by these men and their help and encouragement has been of enormous value.

The manuscript was painstakingly typed by my wife, Dr I. Tweedle, with generous assistance from my secretary, Miss L. Shaughnessy. The illustrations were drawn by Mrs M. Harrison and the photographs were taken by Mr E. Hartles. Figure 4.1 was reproduced with the kind permission of Radiometer A/V and Professor Siggaard-Andersen. I am grateful to Messrs Churchill Livingstone, who have given invaluable advice and help during the preparation of the manuscript.

Manchester, 1982 D.E.F.T.

Contents

1

Body composition and homeostasis

It can be frustrating and frequently unrewarding to become embroiled in an argument about the relative merits of different forms of nutritional therapy with an expert on body composition, particularly if the latter has little contact with clinical medicine. The discussion will often be interspersed with arguments about the precise extent of the compartments under consideration and doubts concerning the methods used to measure their contents, and experts tend to be obsessed with their own particular narrow field of interest. Nevertheless, even experts will agree about certain basic facts concerning body composition and an elementary knowledge of these is an essential requirement to any attempt to maintain or to restore body composition. Although body composition varies considerably according to race, sex, age, weight and height, estimations of certain components provide valuable indices upon which to base individual requirements.

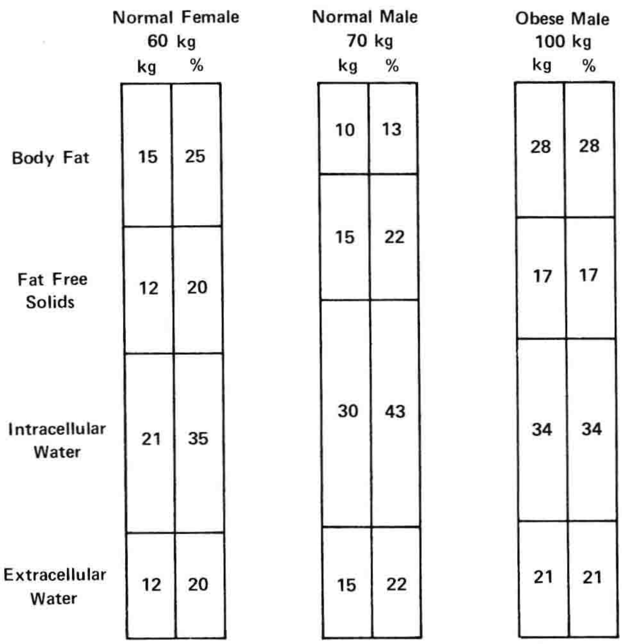


Fig. 1.1 Body composition

The body can be divided into two broad subdivisions, the body fat which may vary greatly and the lean body mass which is relatively constant in subjects of the same sex and height (Behnke 1942). As well as being convenient for descriptive purposes, this concept is important from a functional aspect. The body fat is to a great extent unnecessary for immediate survival, but the lean body mass is in effect the living body, responsible for synthesis of essential body components, energy exchange, excretion of waste products and defence. Any deficiency in the quality or quantity of the lean body mass has far–reaching consequences for survival and well–being.

The typical distribution of body fat, the fat–free solids and body water of a healthy 60 kg female and 70 kg male and a moderately obese 100 kg male is shown in Figure 1.1.

BODY FAT

This is predominantly neutral triglyceride (esters of glycerol and fatty acids) stored in the fat depots and amounting to about 10 kg in the 70 kg male. When energy intake exceeds requirements, the excess is stored as fat. When energy intake is insufficient to meet requirements, the fat stores are mobilised and oxidised. Being anhydrous with a calorific value of 39 kJ/g (9.3 kcal/g), fat is an ideal storage material (Fig. 1.2), and as these stores contain very little intracellular and extracellular water they have a calorific value of 33.6 kJ/g (8 kcal/g).

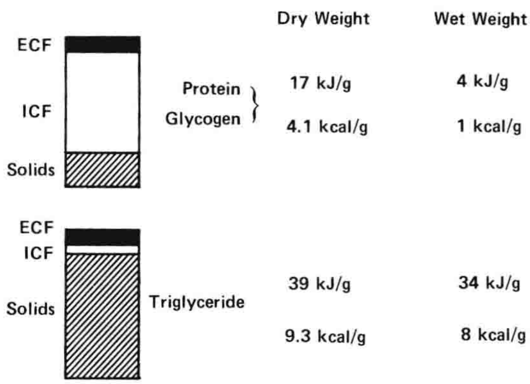


Fig. 1.2 Energy content of body substrates

Although these stores are unnecessary for immediate survival, they form a vital component of the defence against prolonged starvation, providing the major portion of endogenous energy supply and thereby reducing the draft on the protein of the lean body mass. Synthesis of vital components is not a function of this tissue but it is wrong to consider it inactive, for there is a continual synthesis and breakdown of triglyceride within it.

Fat also exists in the body as free fatty acids (that is, free from combination with other compounds) and as compound lipids (fatty acids combined with various substances such as choline, glycerol and phosphate). Although the amount is very small when compared with the triglycerides of the fat stores, this portion of the body fat is vital as it forms the major component of the membranes of cells and their intracellular organelles (see Ch. 8).

The intake of fat varies considerably from country to country and from individual to individual, influenced to a certain extent by economic status but mainly by taste or religious belief. Studies of an Indian aboriginal tribe have suggested that the minimum daily requirement may be extremely small, probably of the order of 4 g (Mitra 1942) which might be sufficient to provide 1 g of essential fatty acids (see Ch. 8 for further details). The recommended daily energy intake of healthy adult males is about 11 MJ (2600 kcal) for those in sedentary occupations and about 15 MJ (3600 kcal) for those in extremely active occupations (DHSS 1969). Although, as emphasised on many occasions in this book, protein should not be considered as a source of energy, these recommended intakes include the calorific value of protein which contributes at least 10% and in many diets as much as 20% of the total. Thus 80–90% of the total energy requirement must be provided in the form of fat and carbohydrate and in most Western diets the contribution of the two substrates is about equal.

LEAN BODY MASS

The fat–free mass consists of skeletal and cardiac muscle, the protein of the gastro–intestinal tract (including its smooth muscle), the skeleton and the body fluids with their mineral content. The term lean body mass is usually used to denote a component that is smaller than the fat–free mass and excludes the skeleton. It can be considered to be soft, cellular and predominantly protein in nature and it is the metabolically active portion of the body that determines energy requirements, oxygen consumption, carbon dioxide production, creatinine excretion and many other commonly measured indices of body metabolism. A healthy 70 kg male will contain 6–7 kg of protein and a healthy 60 kg female 4.5–5 kg. The mineral content of the lean body mass is very small (a few grams) but, as discussed later in this chapter, has a crucial role in the distribution of water within the body.

Man and other animals can synthesise some amino acids by condensation of the carboxyl group of α keto acids and an amine radicle (NH_2):

$$\underset{\alpha\text{ keto acid}}{2\,RCOOH} + \underset{\text{urea}}{CO\,(NH_2)_2} \longrightarrow \underset{\text{amino acid}}{2\,RCONH} + \underset{\text{water}}{H_2O} + \underset{\text{carbon dioxide}}{CO_2}$$

However, neither animals nor the vast majority of plants are able to use the large amount of nitrogen in the air (about 80% by volume) to form amine radicals. The fixation of large quantities of nitrogen from the air is essential to the continuing existence of all plant and animal life on earth. Only a few plants are capable of such fixation and they require the help of various bacteria particularly those of the genus Clostridium, Pseudomonas and Aerobacter. It is fascinating to reflect that man could not exist without the help of these organisms, which in other circumstances are the harbingers of death.

The rate at which breakdown and resynthesis of protein occurs in the components of the lean body mass varies considerably. The epithelia of the gastro–intestinal mucosa is replaced every two or three days but the half–life of collagen may be measured in months. Like fat, the intake of protein varies considerably from country to country and from individual to individual, usually corresponding to economic status. A daily intake of 50 g is sufficient for a healthy 70 kg male providing that the protein is of good quality (see Ch. 8 for further details). The average diet of many Western countries contains twice this quantity. Although the nitrogen content of individual amino acids varies, mixed protein contains 16% nitrogen and this measurement is commonly used to determine protein content by multiplying the nitrogen values by 6.25. Body protein consists of 75% water and thus 1 g of nitrogen is equivalent to 30 g of hydrated protein. In the body, protein can only be partially catabolised and has a calorific value of 17.2 kJ/g (4.1 kcal/g). Consequently skeletal muscle and gastro-intestinal protein are poor sources of energy, releasing only 4 k J/g (1 kcal/g) of hydrated tissue (Fig. 1.2).

The lean body mass contains the body's meagre stores of carbohydrate, mainly in the form of glycogen in the liver and the muscle. The normal 70 kg male contains no more than 400 g. Oxidation of carbohydrate in the body will also yield 17.2 kJ/g (4.1 kcal/g), but, like protein, glycogen consists of 75% water and is also a poor source of energy, yielding the same 4 kJ/g of tissue. If carbohydrate intake exceeds immediate needs, the glycogen stores are rapidly repleted and the excess is converted into triglyceride.

This important difference in the function of the two basic subdivisions of the body, the fat stores and the lean body mass, is particularly evident during starvation and after injury as discussed in detail in Chapter 3. The concept of nitrogen balance is well known and accepted. Less commonly appreciated is the concept that the body's energy balance can be equated in a similar manner in terms of carbon balance (Kinney & Moore 1956). Thus nitrogen and carbon balance may be used to indicate changes in lean body mass and body fat respectively. Measurement of the former is relatively simple and may be done at the bedside. Measurement of the latter with any meaningful degree of accuracy requires sophisticated, expensive equipment. It is usually performed in special units and even then only for purposes of clinical research. Fortunately, body fat can be estimated relatively simply by calculation from skinfold thickness obtained with calipers (Durnin & Womersley 1974).

A more detailed consideration of the content, function and regulation of the individual components of these subdivisions is given below.

WATER

The major constituent of the body and the prime nutritional requirement is water, which comprises 50–80% of the body weight. The contribution of total body water is lower in females than in males of the same weight and in the obese. Its contribution to body weight decreases with age and the values shown in Figure 1.1 are useful working approximations. Thus a middle–aged man of average build weighing 70 kg has a total body water of 45 l and a middle-aged female of average build weighing 60 kg has a total body water of 33 l. Total body water is divided into two major compartments, the intracellular and extracellular water (ICW and ECW) by the semi-permeable cell wall (Figs 1.1 and 1.3) which is freely permeable to water but less so to electrolytes. The intracellular compartment is

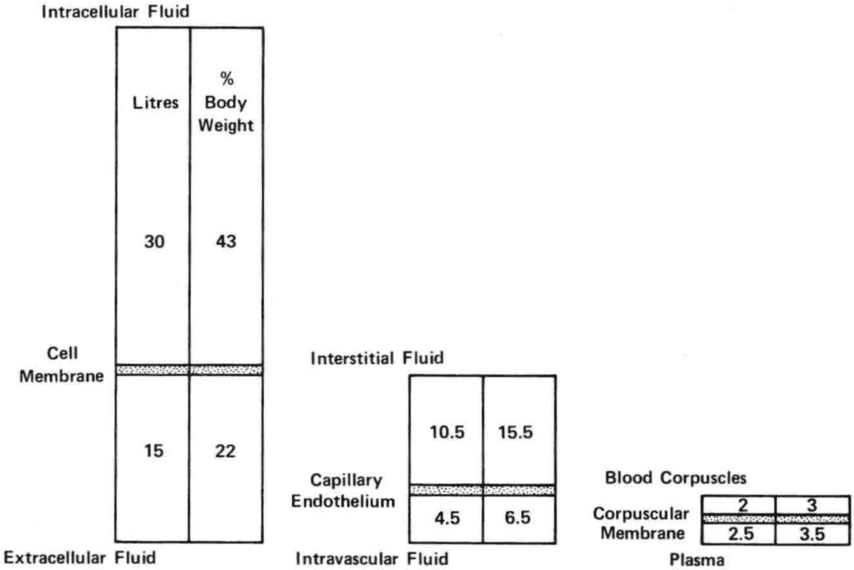


Fig. 1.3 The components of total body water (healthy 70 kg male)

greater and the intracellular fluid (ICF) of the 70 kg man is about 15 l. The extracellular fluid is further subdivided into interstitial fluid (IF) between the cells and intravascular fluid (IVF) separated by capillary endothelium which in health is permeable to water and electrolytes but not to protein (Fig. 1.3). The interstitial fluid compartment is the larger, comprising about 10.5 l. However, unlike other fluid compartments in the body, there is a portion (about 10%) of the interstitial fluid in some connective tissue that is relatively unavailable for equilibration. Finally the intravascular fluid volume of 4.5 l is subdivided into a red cell volume of 2 l and a plasma volume of 2.5 l.

This division of the total body water into compartments separated by membranes of varying permeability to solutes such as protein and electrolytes is a vital factor in homeostasis and changes in membrane permeability induced by disease processes have profoundly deleterious effects as will be discussed later. The function of these membranes and the mechanisms involved in the control of the flow of water and solutes between these compartments will now be considered in more detail.

Diffusion

The particles of a substance in solution are usually continually moving and if they are particularly concentrated in one area, they collide frequently. Consequently, they tend to disperse to areas of low concentration until uniformity of concentration is reached. If a solution of sodium chloride (NaCl) is separated from water by a membrane that is permeable to sodium (Na^+) and chloride (Cl^-), hydrogen (H^+) and hydroxyl (OH^-) ions, then these ions will pass through the membrane until the concentration of each ion is the same in both compartments (Fig. 1.4). The rate of diffusion will depend upon the difference in the concentration of the ions on either side of the membrane and its permeability.

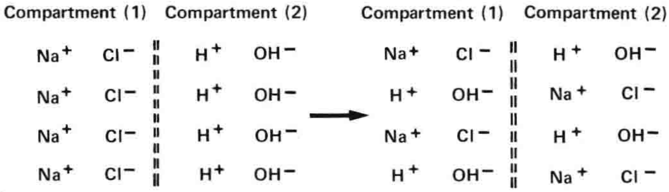


Fig. 1.4 Ionic diffusion across a permeable membrane determined by the concentration gradient

The Donnan equilibrium and electrical neutrality

If a solution of sodium chloride is separated from a solution of the sodium salt of a protein (NaR) by a semi-permeable membrane that will allow the passage of sodium and chloride ions but not the protein ions (R^-) then an equilibrium is reached when the product of the concentrations of the sodium and chloride ions is the same on either side of the membrane (Fig. 1.5):

$$\begin{array}{ccc} \text{Compartment (1)} & & \text{Compartment (2)} \\ 2Na^+ \times 2Cl^- & = & 4Na^+ \times 1Cl^- \end{array}$$

This equilibrium is named after its discoverer, the British physicist Donnan. The ionic concentration in each compartment is also influenced by the need for electrical neutrality in each compartment. Thus in Figure 1.5 the concentration of sodium ions in compartment (1) must be the same as the concentration of chloride ions, but in compartment (2) the concentration of sodium ions must be the same as the sum of the concentrations of the chloride and protein ions. As the products of the concentrations of sodium and chloride are the same on both sides of the membrane, it follows that the concentration of sodium ions is greater in compartment (2) than in compartment (1) and the converse holds for the concentration of chloride ions. It also follows that the concentration of osmotically active particles is greater in compartment (2).

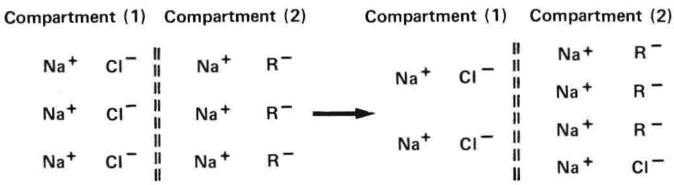


Fig. 1.5 Ionic diffusion across a semi–permeable membrane determined by the Donnan effect

This is the situation that exists in the body, the concentration of sodium in the plasma being slightly higher than in the interstitial fluid, the converse being the case for the chloride ion and, most important of all, the concentration of osmotically active particles is greater in the plasma. These features explain why the osmotic influence of the plasma proteins is greater than the 1–2 mosmol/l that they would be expected to exert.

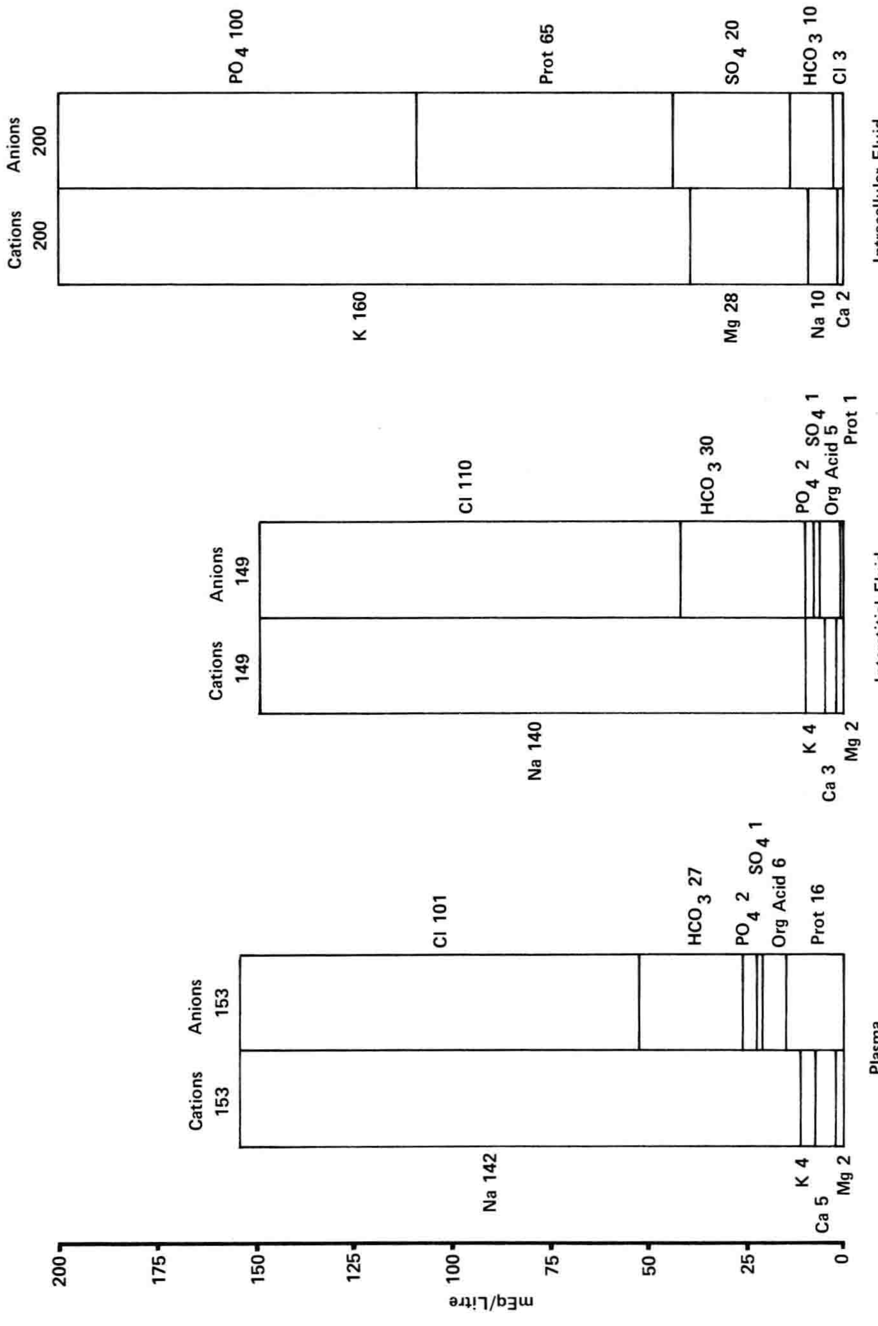
Osmosis

With the exception of water in connective tissue, water may move rapidly between the various compartments through the cell membranes and vascular endothelium. Although hydrostatic pressure (arterial and venous blood pressure) influences fluid movement between the intravascular and interstitial compartments, the major force which determines fluid movement in the body is osmosis, (particularly between the intracellular and extracellular compartments). Osmosis is the attraction of particles for water which flows through a semi-permeable membrane such as the cell wall into the compartment containing the greater concentration of particles. Osmotic pressure is the number of osmotically active particles per unit volume and is usually expressed in milliosmoles per litre (mosmol/l), one millimole (mmol) of a substance in solution exerting one milliosmole of osmotic pressure. The osmolarity of body fluids can be determined in the laboratory by measuring the depression of freezing point, 1000 mosmol/l lowering freezing point by 1.86°C. Plasma, extracellular fluid and intracellular fluid osmolarities are the same and the normal range is 280–300 mosmol/l. Solutions within this range are termed isotonic and those of greater or lesser osmolarity are termed hypertonic or hypotonic accordingly. Osmotically active particles may be ionised (such as sodium) or non-ionised (such as glucose).

The composition of extracellular and intracellular fluid is shown in Figure 1.6 (modified from Gamble 1954). The concentrations of the cations and anions are shown in both mEq/l as originally defined by Gamble and in mmol/l as defined in the Système internationale. As discussed above, there must be electrical neutrality within each compartment. Consequently, when the concentrations of the substances in the compartments are expressed in mEq/l then the sum of the cations equals the sum of the anions. However, when the concentrations of these substances are expressed in mmol/l, then this convenient and understandable relationship apparently disappears, particularly in the intracellular compartment where the major ions are multivalent. The direction of this apparent distortion is reversed and of greater magnitude if the substances are expressed in mg/l when the contribution of protein to the anionic pool appears to be massive due to its large molecular weight.

The composition of the intracellular fluid varies according to the type and function of the cell and obtaining and analysing samples of pure intracellular fluid is a difficult procedure. The concentrations shown in Figure 1.6 should be considered to be approximate values only. The predominant osmotically active particles of the intracellular fluid are the ions potassium and phosphate, and of the extracellular fluid the ions sodium and chloride. However, osmotically active substances that cannot pass through membranes easily (if at all) have the greatest effect upon the intercompartmental movement of fluid between the intravascular and interstitial compartments. This factor is termed the oncotic or colloid osmotic pressure.

It can be seen from Figure 1.7 that at the arterial end of a capillary, the hydrostatic pressure acting in an outwards direction (32 mmHg) is greater than the oncotic pressure acting in an inwards direction (25 mmHg) and so water flows into the interstitial space. At the venous end of the capillary the hydrostatic pressure acting outwards (15 mmHg) is less than the oncotic pressure acting inwards (10 mmHg) and water flows into the capillary. This description ignores the usually trivial interstitial pressure (1 mmHg). Even the healthy capillary endothelium is not totally impermeable to protein and consequently small quantities of protein



Intracellular Fluid
Cations 200
Anions 200
K 160
Mg 28
Na 10
Ca 2
PO 4 100
Prot 65
SO 4 20
HCO 3 10
Cl 3
Interstitial Fluid
Cations 149
Anions 149
Na 140
K 4
Ca 3
Mg 2
Cl 110
HCO 3 30
PO 4 2
SO 4 1
Org Acid 5
Prot 1
Plasma
Cations 153
Anions 153
Na 142
K 4
Ca 5
Mg 2
Cl 101
HCO 3 27
PO 4 2
SO 4 1
Org Acid 6
Prot 16
mEq/Litre
200
175
150
125
100
75
50
25
0

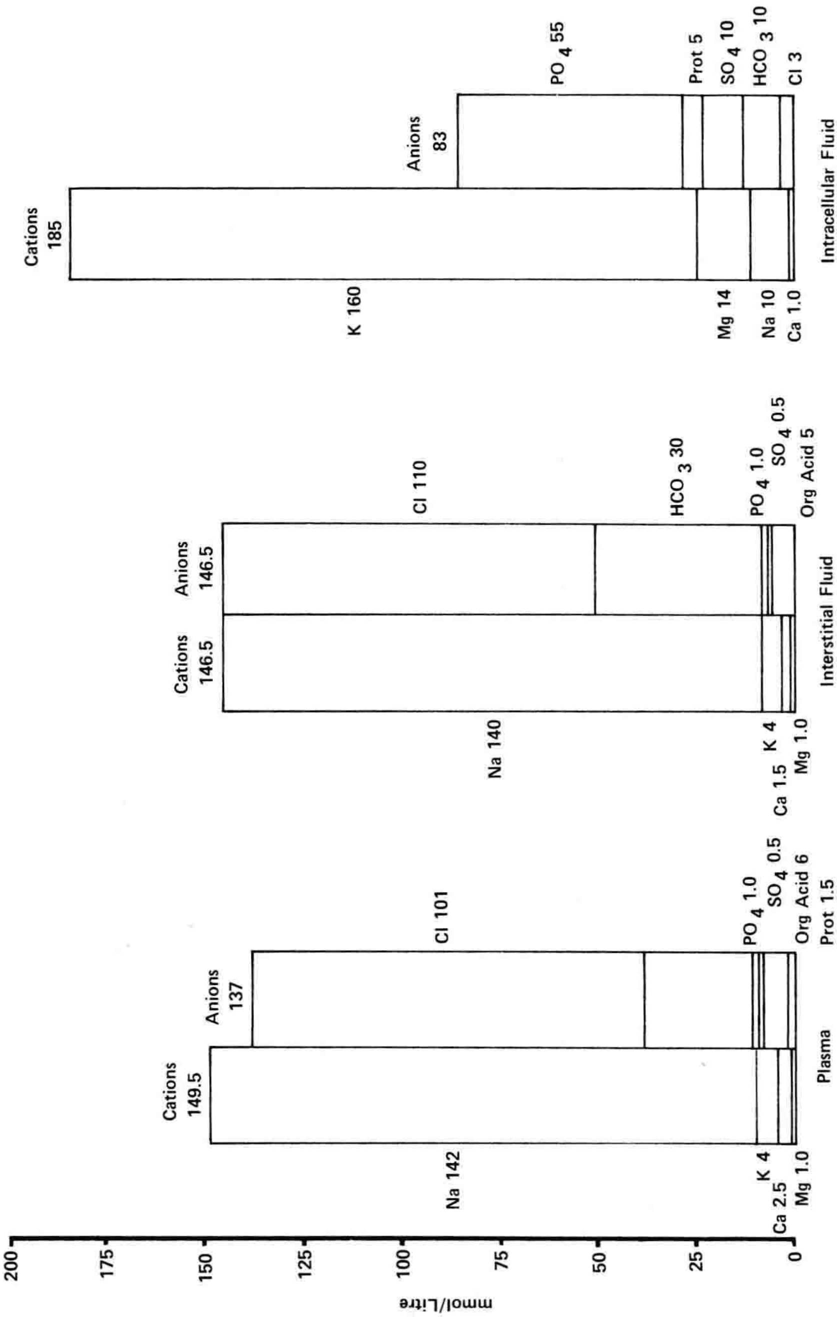


Fig. 1.6 The composition of intracellular and extracellular fluids (modified from Gamble 1954)