Calcium, Phosphate and Magnesium Metabolism

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Clinical Physiology and Diagnostic Procedures

Edited by

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CHURCHILL LIVINGSTONE
Edinburgh London and New York 1976

CHURCHILL LIVINGSTONE
Medical Division of Longman Group Limited

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

ISBN 0 443 01188 5

Library of Congress Cataloging in Publication Data

Main entry under title:

Calcium, phosphate and magnesium metabolism.

Includes index.
1. Calcium metabolism disorders. 2. Phosphates in the body. 3. Magnesium in the body. 4. Chemistry, Clinical. I. Nordin, B. E. C. [DNLM: 1. Calcium—Metabolism. 2. Phosphates—Metabolism. 3. Magnesium—Metabolism. QV276 C144]
RC621.C34 616.3'9 75-13875

Printed in Great Britain

Preface

This book seeks to fulfil several functions. It is primarily an account of the physiology of calcium, and of phosphate insofar as it relates to calcium, but also embraces magnesium physiology because this is linked to that of calcium and phosphate at so many points. In addition, it brings up-to-date and replaces the work *Diagnostic Procedures and Disorders of Calcium Metabolism* published by Nordin and Smith in 1965, which proved impossible to revise satisfactorily without a review of the relevant physiology. Finally, it is designed as a companion volume to *Metabolic Bone and Stone Disease,* which was published in 1973 and deals primarily with clinical disorders without reviewing in depth the underlying physiology. Although physiology and medicine are interlocked disciplines in every field, this is perhaps nowhere more apparent than in the field of mineral metabolism. It is impossible to approach or understand any disorder in this area except through a knowledge of the normal state. The work is, therefore, addressed as much to clinicians as to basic scientists and is intended to provide reference material not only for general physicians and endocrinologists, but also for orthopaedic surgeons, urologists and others whose clinical interests take them into fields of disordered mineral homeostasis.

Multiple author texts have both strengths and weaknesses, their main weakness being perhaps a lack of integration between different chapters, which even the strongest editor may have difficulty imposing. This book is perhaps unusual in being the work of the members of a single department, an arrangement which should produce closer co-ordination between the different contributions than is possible when the authors are scattered in different centres and even different countries. Whether this object has been achieved will be for our readers to judge.

Every care has been taken to eliminate errors, but no doubt careful readers will still find mistakes in the text. The editor will be very pleased to hear of any such errors or omissions in case a second edition of this work is called for.

In addition to the named authors many other people have helped in the production of this book. I should like to mention in particular Mr P. Bower for helping with the radioisotope tests; and Mrs D. Oates, Mrs S. Rutter and Mrs B. Wild for untiring secretarial assistance. I must also thank the publishers for their patient co-operation throughout the editorial and production stages.

1976 B. E. C. Nordin

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INTRODUCTION

Calcium and phosphorus are elements which are widely, but generally independently, distributed in nature; such association as occurs between them arises from the existence of a series of naturally occurring, relatively insoluble calcium phosphate salts. Phosphorus is present in all biological systems, but the presence of calcium is much more variable, and the two elements are only closely associated in higher organisms possessing an endoskeleton which derives its rigidity from a solid phase of calcium phosphate.

Animal life arose in the sea, where calcium is the fifth most abundant element (after chlorine, sodium, magnesium, and sulphur) in a concentration of about 40 mg per 100 ml. The plasma water calcium of some primitive fish is also high (about 20 mg per 100 ml) though not as high as in the sea. In fresh water, on the other hand, the calcium concentration is low, and the plasma water calcium concentration of fresh water fish (about 6 mg per 100 ml) is higher than that of their environment (Urist, 1963). The evolution of life from salt water on to land and into fresh water has therefore required an adaptation from a high calcium to a low calcium environment, just as it has required adaptation to corresponding changes in environmental sodium. Unlike sea fish, mammalian vertebrates have actively to maintain an adequate concentration of calcium in the plasma water to permit calcification of the skeleton and to protect the neuromuscular system. To do this, they draw on their calcium stores if necessary. The result is that in calcium deficiency the plasma calcium is maintained but the skeleton becomes depleted.

The position with regard to phosphorus is rather different. The phosphorus content of sea water is extremely low, generally less than 100 μg per 100 ml. The development of life from sea water has therefore involved the progressive accumulation of phosphorus from a phosphorus-poor medium and the final development of a system in which the protection of the body's stores of phosphorus appears to take precedence over the preservation of the inorganic phosphate concentration in the plasma. Phosphorus deficiency lowers the plasma and urine phosphate but has relatively little effect on the total body phosphorus until or unless the deficiency is very severe.

The magnesium concentration in sea water is high (130 mg per 100 ml) and it is widely distributed in nature, yet the plasma magnesium of animals is relatively low and the total body stores smaller than those of all the other major elements. Magnesium deficiency is therefore rare, but when it occurs the organism responds by lowering the plasma magnesium concentration rather than by depleting its body stores. In this respect, magnesium resembles phosphorus more than calcium.

Body composition

Calcium and phosphorus represent a large proportion of the elementary composition of the human body. Disregarding the oxygen and hydrogen in the body water, calcium and phosphorus rank third and fourth, respectively, after carbon and nitrogen (Table 1.1) and represent about 2 per cent and 1

Table 1.1 Elementary composition of the human body (Oser, 1965, and other sources)

	Per cent	Approximate amount in a 70 kg man (grams)
Oxygen	65·0	45 500
Carbon	18·0	12 600
Hydrogen	10·0	7000
Nitrogen	3·0	2100
Calcium	1·9	1300
Phosphorus	1·0	700
Potassium	0·35	245
Sulphur	0·25	175
Sodium	0·15	105
Chlorine	0·15	105
Magnesium	0·04	27

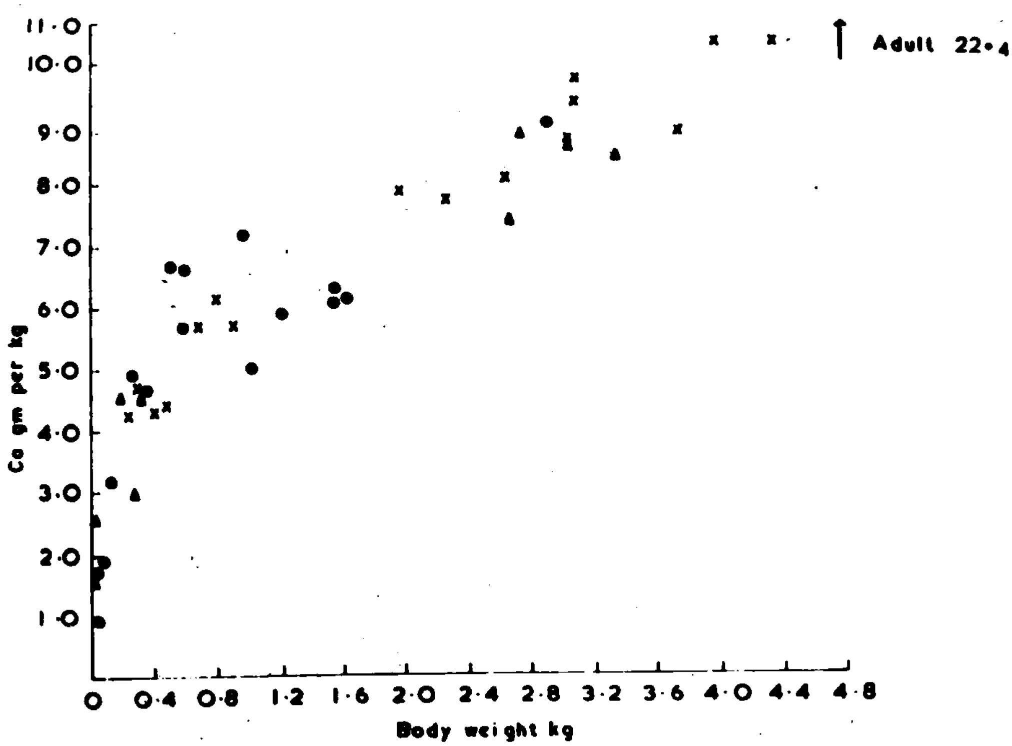

Fig. 1.1 Total body calcium as a function of body weight in the new born (Widdowson and Dickerson, 1964).

per cent of body weight, respectively. The carcase analyses reported by Widdowson and Dickerson (1964) showed that calcium constitutes 0·1–0·2 per cent of early foetal fat-free weight, rising to 2·2 per cent of adult fat-free weight (Fig. 1.1). In absolute terms, this represents a rise from about 20–30 g at birth to 1300 g at maturity in a 70 kg man with a fat-free weight of 60 kg. This requires a daily increment of 180 mg of calcium during the 20 years of growth. Nearly all of this calcium is in the skeleton, which represents 10–15 per cent of body weight (Mechanik, 1926; Shohl, 1939; Wilmer, 1940; Forbes *et al.*, 1956). Calcium constitutes 21–22 per cent of the wet weight of adult bone, and phosphorus 10–11 per cent (Woodard, 1964).

The calcium content of adult soft tissues ranges from about 50 to 200 mg per kg wet weight (Widdowson and Dickerson, 1964), and the total soft tissue calcium amounts to about 0·01 per cent of body weight or 7 g. (In the carcase analysis of Mitchell *et al.* (1945) the soft tissue calcium constituted 0·009 per cent of total body weight.) The total extracellular calcium is equivalent to the plasma calcium concentration multiplied by 15 per cent of body weight (Nordin and Smith, 1965). Since the former is normally 100 mg/l, the extracellular calcium represents only about 0·0015 per cent of body weight or 1 g. Thus the 70 kg man contains about 8 g of calcium in the soft tissues and tissue fluids; there is a further 7 g in the teeth (Weatherell; personal communication) and the rest is in the skeleton (Table 1.2).

Table 1.2 Distribution of calcium, phosphorus, and magnesium in 70 kg adult human

Organ		Ca content	% of total
Skeleton		1300 g	99
Teeth		7 g	0·6
Soft tissues		7 g	0·6
Plasma		350 mg	0·03
Extravascular fluid		700 mg	0·06
Total	about	1300 g	
Organ		**P content**	**% of total**
Skeleton		600 g	85
Teeth		3 g	0·4
Soft tissues		100 g	14
Blood		2 g	0·3
Extravascular fluid		0·2 g	0·3
Total	about	700 g	
Organ		**Mg content**	**% of total**
Skeleton		14 g	57
Soft tissues		12 g	40
Extravascular fluid		170 mg	0·5
Plasma		60 mg	0·2
Red cells		130 mg	0·4
Total	about	27 g	

The total body phosphorus rises from about 0·6 per cent of fat-free body weight at birth to 1·2 per cent in adult life (Fig. 1.2). Since the total body calcium is 2·2 per cent of fat-free body weight, 99 per cent of which is in the skeleton, and since the Ca:P ratio in bone ash is extremely close to 2·2:1 (Eastoe, 1961), the phosphorus in bone mineral is very close to 1 per cent of fat-free body weight, and the remaining 0·2 per cent of phosphorus in the body must be in the soft tissues. The soft tissue phosphorus varies from about 1 g/kg in muscle (Dickerson and Widdowson, 1960) to 4·4 g/kg in the brain (Ansell, 1961). A representative value is about 2 g/kg. Since soft tissues represent about 45 per cent of body weight, the soft tissue phosphorus accounts for 0·10–0·20 per cent of body weight or about 100 g. To this must be added: (1) the phosphorus in teeth—about 3 g; (2) the nonmineral phosphorus in bone—about 20 g; (3) the phosphorus in blood—2 g; and (4) the

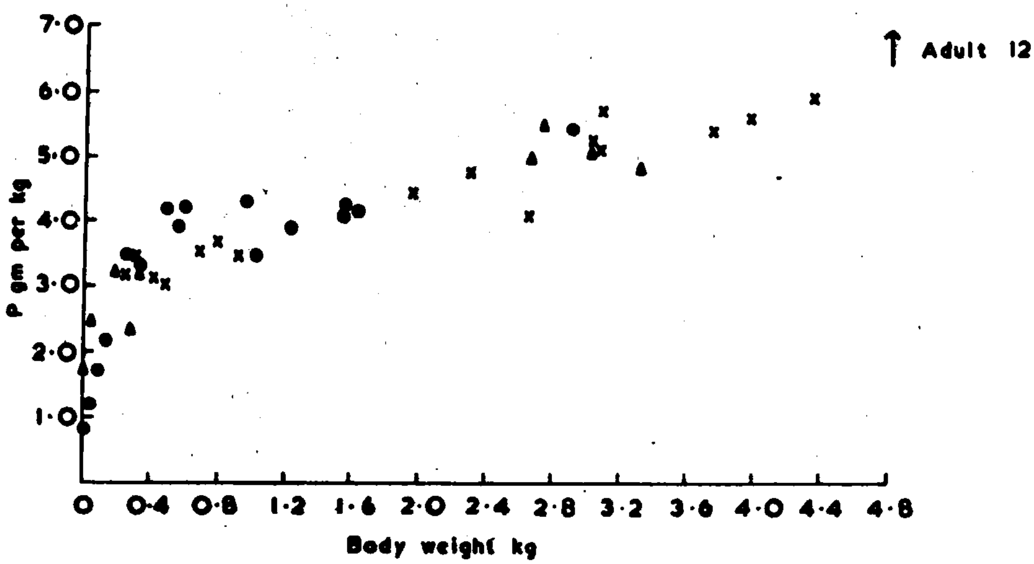

Fig. 1.2 Total body phosphorus as a function of body weight in the new born (Widdowson and Dickerson, 1964).

extracellular, extravascular phosphorus, which is about 200 mg. Converting these figures back on to a total body weight basis, we may say that a 70 kg man contains about 700 g of phosphorus of which about 600 g (85 per cent) is in the skeleton and teeth and the rest in the soft tissues and body fluids.

Total body magnesium rises from 200–300 mg per kg at birth to nearly 400 mg/kg in adults (Fig. 1.3). Of the 27 g in the adult, about 170 mg is present in the extravascular, extracellular fluid, where the concentration is about 1·7 mg per 100 ml. There is a further 60 mg in plasma (2 mg per 100 ml) and 130 mg in the red cells (6·5 mg per 100 ml). Soft tissues contain magnesium in concentrations from 300 to 450 mg per kg wet weight (Wacker and Vallee, 1964). Assuming soft tissues to be 45 per cent of body weight, soft tissue magnesium amounts to about 12 g in a 70 kg adult. The residue of the total body magnesium of 27 g is in the skeleton where it comprises 0·2 per cent of the wet weight (Woodard, 1964). Thus a 70 kg man has about 14 g of

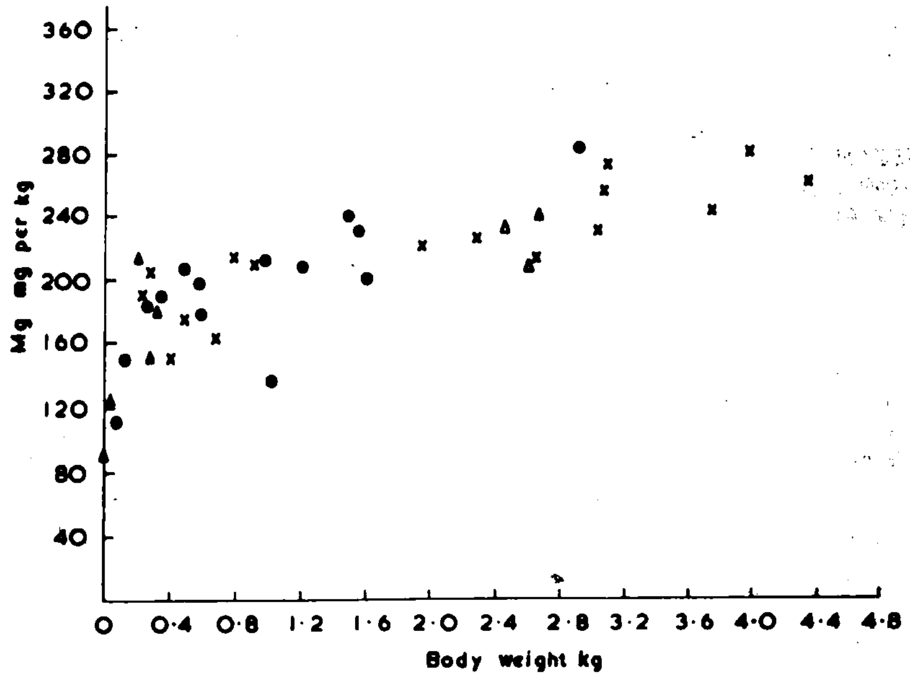

Fig. 1.3 Total body magnesium as a function of body weight in the new born (Widdowson and Dickerson, 1964).

Table 1.3 The principal components of the skeleton of a 70 kg adult (based on Long, 1961, and other sources)

	Absolute weight	% of total
Wet skeleton	7 kg	100
Dry skeleton	5·6 kg	81
Inorganic component	4·1 kg	59
(Ca)	(1·5 kg)	(22)
(O)	(1·5 kg)	(22)
(P)	(0·7 kg)	(10)
(CO_2)	(0·2 kg)	(3·0)
(Mg)	(0·02 kg)	(0·3)
Organic component	1·5 kg	22
(N)	(0·25 kg)	(3·5)

magnesium in the skeleton, most of which is in the mineral phase, and about 13 g in the rest of the tissues (Tables 1.2 and 1.3).

The distribution of these minerals in foodstuffs and the estimated daily rcquirements will now be considered.

CALCIUM

Dietary calcium

The United Kingdom

The mean calcium intake in the United Kingdom is about 1000 mg per head per day (National Food Survey, 1973) and has changed little in the last

10 years. This compares with a figure of about 600 mg of calcium per head per day moving into consumption at the turn of the century, which had risen to about 700 mg by 1940, mainly on account of increased production and consumption of milk (Greaves and Hollingsworth, 1966). During the Second World War, when flour was fortified with calcium carbonate, the mean calcium supply rose by about 300 mg per head but has risen very little since then. The statistical distribution of the estimated intakes has not been published but the coefficient of variation is believed to be about 25 per cent. In other words, 95 per cent of the population of the United Kingdom are consuming between 500 and 1500 mg of calcium per day.

Other countries

The calcium content of the food supplies of other parts of the world was summarized by the Food and Agricultural Organization/World Health Organization (FAO/WHO) expert group on calcium requirement in 1962 and their data are shown in Table 1.4. The lowest was 347 mg (India) and the

Table 1.4 Calcium in the food supplies of selected countries based on FAO food balance sheets (mg per head per day)

Country	Milk and milk products	Total
Denmark (1957–58)	749	1000
Finland (1958–59)	1170	1329
France (1958–59)	618	930
Italy (1958–59)	381	710
Norway (1958–59)	833	1026
Canada (1957–58)	856	1047
U.S.A. (1958)	856	1116
Argentina (1957)	460	651
Chile (1957)	280	520
Israel (1957–58)	496	884
South Africa (1958)	280	442
Turkey (1957–58)	234	547
United Arabic Republic (1957–58)	142	449
India (1957–58)	147	347
Japan (1958)	58	368
Australia (1958–59)	620	833
New Zealand (1958)	926	1165

highest 1329 mg (Finland). Further data are given in Table 1.15. Before the Second World War, calcium intake in Japan was probably the lowest in the world (about 200 mg), but since then the Japanese have developed dairy farming on an increasing scale and their mean calcium intake has risen to about 600 mg per day (see p. 20).

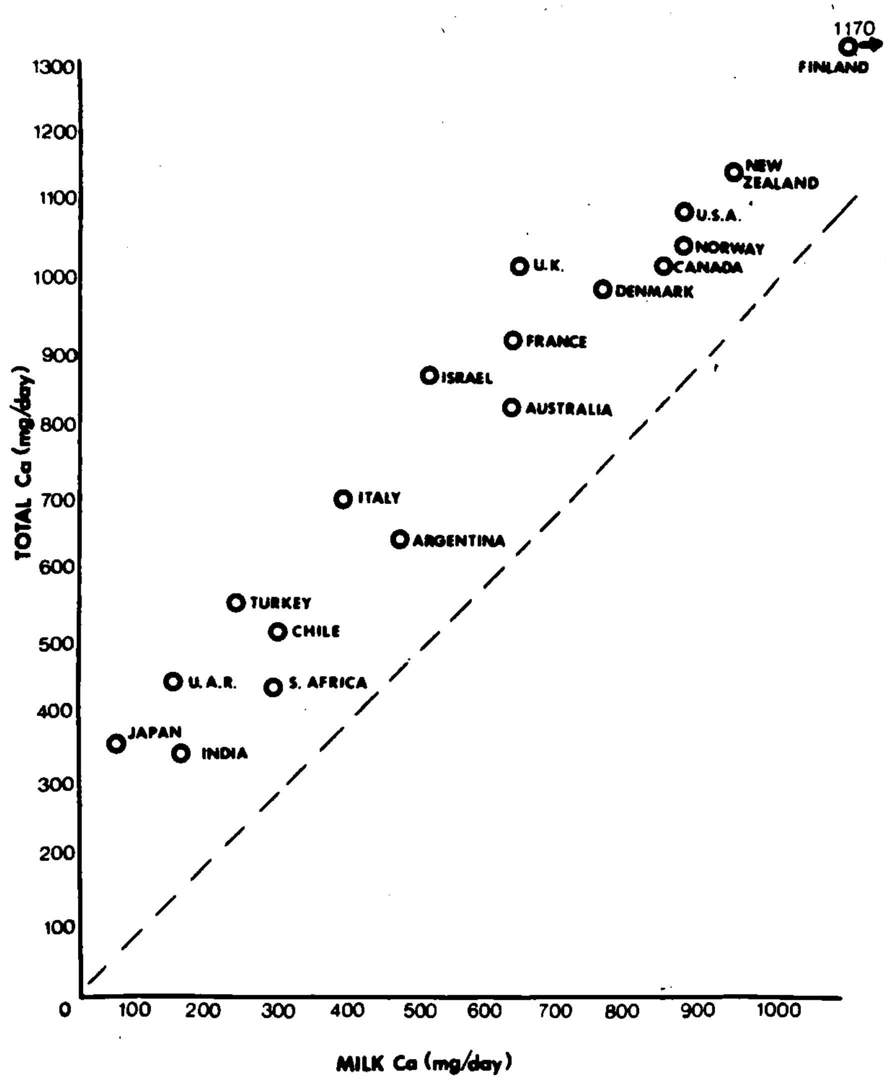

Fig. 1.4 The relation between milk calcium and total dietary calcium in different parts of the world, showing the line of equality.

Sources of dietary calcium

The principal source of dietary calcium in Europe and the U.S.A. is milk, which contributes about 50 per cent of the total. In other parts of the world, this is not necessarily so (Table 1.4). In fact, the contribution of nonmilk foods to calcium intake is relatively constant in different countries (about 200–300 mg), and the great variation in calcium intake is largely due to the difference in the intake of milk and milk products (Fig. 1.4). The calcium content of some representative foods is shown in Table 1.5. There are some nondairy foods with a strikingly high calcium content, such as parsley (325 mg/100 g), spinach (595), tea (426), curry powder (637) and mustard (333), but their contribution to the total dietary calcium is very small.

Table 1.5 Ca content of some representative foods (Sinclair and Hollingsworth, 1969)

Food			Ca content (mg/100 g)
Cereals	Rice		4
	Oatmeal		55
	Bread (unfortified)		11
	(fortified)		57
Meat	Duck		7
	Sausages		30
	Tripe		127
Fish	White	Cod	11
		Skate	24
	Fat	Smelts	686
		Whitebait	859
	Shell	Crab	18
		Shrimps	144
Dairy Products	Cheese	Hard	810–1200
		Soft	362–540
	Milk	Whole	120
		Skimmed	124
		Condensed	290–384
		Dried	895–1225
	Butter		15
Fruits	Fresh	Apples	3
		Rhubarb	77
	Dried	Apples	30
		Currants	95
		Figs	284
Nuts	Coconut		9
	Barcelona		102
Vegetables	Broadbeans		8
	Carrots, cabbage		46
	Kale		108
	Watercress		189

Apart from milk and other dairy products, the most important nutrient source of calcium in the United Kingdom is fortified flour, to which calcium carbonate is added at the rate of 300 mg per 100 g. This has been done since the Second World War when it was thought that the increased phytic acid content of high extraction wheat flour (introduced to save shipping space)

Table 1.6 Milk chemical composition, per 100 ml whole milk (ranges are given in parentheses) (Spector, 1956; and other sources)

Constituent	Human	Cow
Water, g	88(83–90)	87(80–92)
Calories, utilizable[a]	65	65
Total solids, g	12·4(10–17)	12·7(8–20)
pH	6·6–6·8	6·6–6·8
Ash, g	0·21(0·1–0·5)	0·72(0·3–1·2)
Protein, g	1·2(1–6)	3·3(2–6)
Amino acids, total,[b] g	1·28(0·9–1·6)	3·3(2·7–4·1)
Casein, g	0·4(0·04–0·7)	2·8(1·4–6·3)
Lactalbumin, g	0·3(0·1–0·6)	0·4(0·2–0·6)
Lactoglobulin, g	0·2	0·2(0·1–0·4)
Whey protein, g	0·6(<0·3–1·1)	0·6(0·2–1·4)
Carbohydrate, g (mainly lactose)	7·0(4·2–9·2)	4·8(2·1–6·1)
Fat, g	3·8(0·5–9·0)	3·7(0·9–9·8)
'Essential' fatty acids,[c] mg	346	96
Vitamin A, estimated total,[d] mg	0·06(0·01–0·25)	0·04(0·015–0·95)
Asorbic acid, mg	4·3(0–11·2)	1·6(0·2–3·1)
Biotin, µg	0·4(Trace–1·8)	3·5(0·2–11·0)
Choline, mg	9(5–14)	13(4–28)
Citric acid, mg	80	150
Cobalamin,[e] µg	Trace	0·56(0·07–1·15)
Vitamin D, as calciferol,[f] µg	0·01(0–0·25)	0·06(0·01–0·1)
Vitamin E, mg	0·6(0·1–1)	0·1
Folic acid group,[g] µg	0·2(0·1–0·36)	0·2(0·1–5)
Inositol, mg	39(19–56)	13(3–39)
Vitamin K, as K_1,[h] µg	2(0–17)	8(0–33)
Niacin,[i] µg	172(66–690)	85(19–150)
Pantothenic acid, µg	196(80–584)	350(155–568)
Pyridoxine group,[j] µg	11(2–22)	48(3–95)
Riboflavin, µg	42·6(13–100)	157(20–342)
Thiamine, µg	16(1–43)	42(27–90)
Calcium, mg	33(15–61)	125(56–381)
Chlorine, mg	43(9–355)	103(70–290)
Cobalt, µg		0·06
Copper, mg	0·04(0·01–0·07)	0·03(0·003–0·40)
Fluorine, g		16(7–28)
Iodine, µg	7(4–9)	21(0·4–187)
Iron, mg	0·15(0·02–0·45)	0·10(0·01–1·0)
Magnesium, mg	4(2–6)	12(7–22)
Manganese, µg	0·7	2(<1–4)
Phosphorus, mg	15(7–35) (40% inorganic)	96(56–129) (70% inorganic)
Potassium, mg	55(27–81)	138(38–287)
Silicon		Trace
Sodium, mg	15(2–44)	58(31–214)
Sulphur, mg	14(5–30)	30(24–44)
Zinc, mg	0·53(0·02–>1·38)	0·38(0·17–0·66)

[a] Kilocalories, calculated on basis of 'physiological fuel values' of 8·80 calories per gram of fat; 3·85 calories per gram of carbohydrate (lactose); and 4·25 calories per gram of protein.

[b] Represents only the total of values that are available.

[c] Arachidonic, octadecadienoic acid.

[d] Milligrams of carotenoids × 0·75 ÷ (0·6 × 4·3), plus mg preformed vitamin A = estimated total vitamin A.

[e] Vitamin B_{12}, cyanocobalamin.

[f] 0·025 µg calciferol = one I.U.

[g] Pteroylglutamic acid (folacin), vitamin M, vitamin B_c, factor U, *L. casei* factor, Norite eluate factor.

[h] 0·083 µg vitamin K_1 = one Dam unit.

[i] Nicotinic acid (niacin) and nicotinic acid amide (nicotinamide).

[j] Includes pyridoxine, pyridosal, pyridoxamine.

might produce a danger of rickets which could be offset by the addition of calcium to the bread (McCance and Widdowson, 1942). The reasoning was probably incorrect, but the fortification of the flour has continued. The latest recommendation of the Food Standards Committee to retain the fortification was apparently based not so much upon the calcium requirement of the adult population as such but rather upon suggestive evidence that hard water (and therefore possibly calcium) may protect against cardiovascular disease (Crawford *et al.*, 1968).

Milk

The importance of milk as a source of dietary calcium has already been stressed. It also contains a wide range of other nutrients (Table 1.6) which enable it to sustain the life and growth of young animals and human infants. In fact, it provides all the essential nutrients in adequate amounts for normal life and health with the exception of iron and possibly copper, the infant being born with sufficient stores of these to last until weaning. Nonetheless, as Table 1.6 shows, there are considerable differences in the composition of milk from different species, and the difference between human and cow's milk creates problems when the latter is used for infant feeding. A major difference lies in the protein content, which is more than twice as high in cow's as in human milk; this is generally overcome by diluting the cow's milk with water and then adding sugar to restore the carbohydrate level. Needless to say, the resulting mixture is still very different from human milk, notably in respect of its lower fat and much lower essential fatty acid content. On the other hand, the phosphorus content remains, even after dilution, almost twice as high as in human milk, which raises the plasma phosphate of infants on artificial feeds and may predispose to hypocalcaemic tetany (Oppe and Redstone, 1968).

Table 1.7 Nutrient content of some milk products (McCance and Widdowson, 1960)

	Protein (g/100 g)	Fat (g/100 g)	Calories (per 100 g)	Ca	Mg	Fe	Ca	P	S
						(mg/100 g)			
Butter	0·4	85·1	793	15	2·4	0·16	0·03	24	9
Cheddar cheese	25·4	34·5	425	810	46·9	0·57	0·03	545	230
Cream	2·4	21·2	219	79	6·0	0·31	0·20	44	—
Dried milk	27·0	29·7	530	960	112·0	0·64	0·16	760	234

The nutrient content of the main milk products is shown in Table 1.7 and the contribution of milk and milk products to the intake of the main nutrients in Table 1.8. Note the large contribution milk makes to riboflavine as well as calcium intake.

Protein content Nearly all the milk proteins are synthesized in the mammary gland. The main ones are a group of phosphoproteins known as the caseins (or caseinogens in the strict English terminology) believed to be present as a micellar dispersion of aggregates of calcium caseinate (see p. 13). Precipitation of these proteins by milk acidification, as when milk turns sour from the