Nutrition in Early Life

Edited by

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and
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PREFACE

The developing bodies of multicellular organisms are in a condition of 'plasticity', for changes in structure and function are continually taking place. There is a harmony in these processes as the multitude of changes associated with growth and development are interdependent and time-related. Moreover, the various processes are subject to moderation and control by genetic, nutritional, hormonal and other influences.

Each of us, the Editors, of the present book, has had an extensive interest over a long period of time in aspects of growth and development in both teaching and research. In these activities we drew considerable inspiration and help from a book, *Developmental Nutrition* by Lucille Hurley published in 1980. This book is now out of print and out of date. Moreover, increase in knowledge and the recognition of the importance of developmental aspects of nutrition in the training of health professionals pointed to the need for an up-to-date and extended text incorporating scientific aspects of the subject and their practical application. The recognition that disturbances in biochemical programming during development, resulting in aberrations of the normal harmony of growth, can influence the development of disease later in life provided a further incentive. The seeds of much that is in the book can be traced back to the work of R. A. McCance FRS and E. Widdowson FRS in the 1950s and 1960s. To them we would like to dedicate the book.

We have tried to trace the development of the human organism from the time when this can be investigated in the fetus through to maturity. We have approached the subject from structural, physiological and nutritional standpoints through to the application of these scientific principles in the feeding of babies and children. Also, we have recognized that the nutrition of the mother is central to the adequate provision of care and nutrition for infants at particular times in their lives. In developing these themes we have had to recognize that certain aspects of the subject are not amenable to direct observation or measurement in mothers and babies and alternative sources of information have had to be used.

We are grateful to our colleagues who have shared our enthusiasm for the theme of the book and have generously contributed to it in their particular field of interest. With two exceptions the authors are currently located in the UK, and this has led inevitably to the text having a UK focus. If the focus had been extended this would have resulted in a larger book with the danger of taking it beyond our prime aim, the provision of a student textbook.

We are deeply grateful to our publishers, John Wiley and Sons, for their unstinting support of this venture and we are particularly grateful to Nicky McGirr for her help in so many ways.

Jane B. Morgan and **John W.T. Dickerson**
Brook, Surrey
April 2002

FOREWORD

The effects of nutrition and nutritional stress depend on a triad of influences, the genes of an individual, the stage of development he or she has reached and the circumstances in which they live. This book describes the middle factor of the triad. If we take folic acid as an example then, depending on the stage of development, the effects of its presence or absence in the diet will vary from a neural tube defect during organogensis, to megaloblastic anaemia in pregnancy or malabsorption, cardiovascular disease due to homocystinaemia in middle age, and precipitation of spinal cord disease by masking the haematological clues to vitamin B_{12} deficiency in older people.

Conventional textbooks of nutrition describe in great detail the situation for healthy adults. They then dispose of the developmental aspects with a few added chapters on so called 'vulnerable groups' such as children, pregnant women and older people. This book therefore comes as a breath of fresh air with its developmental approach acknowledging that all individuals are either going through or have previously experienced various stages of development – hardly special vulnerable groups but rather the whole population.

The editors are well versed in the developmental approach – Morgan from her studies of dietary intake, in particular energy, and their effects on growth, initially in London and Southampton, and Dickerson from his studies of normal and retarded growth on body composition, initially in Cambridge and London. They came together at the University of Surrey and began a fruitful collaboration, including the concept and organization of this book. The authors are committed to the view that nutrition plays a vital role in growth and development throughout the entire life cycle. The contents of this book are an interpretation of this view. They, and their distinguished panel of contributors, describe the crucial role of biological age and developmental clocks in the nutritional health of people.

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1

GROWTH, DEVELOPMENT AND THE CHEMICAL COMPOSITION OF THE BODY

John W. T. Dickerson

LEARNING OUTCOMES

- Knowledge of the mechanisms of growth, and how it can be measured and recorded.
- How to assess developmental age and the factors that affect it.
- How the chemical composition of the body changes before and after birth.
- How the composition of organs and tissues changes during growth and development.
- What effects protein-energy malnutrition has on growth and development.

Introduction

Growth and development are the processes by which the fertilized ovum is transformed into a mature individual. Growth occurs by cell multiplication (hyperplasia), by cell enlargement (hypertrophy) and by the synthesis of extracellular tissue. This latter process includes an expansion of the volume of extracellular fluid and an increase in the amounts of specific, but diverse proteins such as those in the plasma and the organic matrix of the skeleton. In most organs, cell multiplication ceases at a tissue-specific age and further growth is by enlargement of existing cells (Winick and Noble, 1965). We can measure the number of cells in an organ which has only mononuclear diploid cells by measuring the amount of DNA in the organ and dividing this by the amount of DNA in a diploid nucleus, which is about 6.2 pg. Changes in the size of cells can be estimated from the ratio of the amount of protein associated with a diploid nucleus or, to put it simply, by the protein/DNA ratio. Cell multiplication continues throughout life in the hair follicles, the epidermis and the mucosa of the alimentary tract. Increase in body fat does not constitute growth, although it may greatly increase body weight. The synthesis of new tissue uses energy and the energy cost of weight gain has been calculated to be 4.6 kJ/g after deducting the energy stored (Passmore and Eastwood, 1986).

Development constitutes those changes in structure, function and composition which are an essential part of the maturation process. Growth and development are complex, integrated processes that are closely related to time and are dependant on appropriate nutrition (McCance, 1962). If the food supply is reduced at an early age, including early postnatal life, growth and development are separated from time and are retarded in ways that are organ- and tissue-specific. Following such a period of growth retardation due to malnutrition or severe illness, nutritional rehabilitation is accompanied by a period of 'catch-up' growth during which the growth velocity is greater than normal for the age of the child. The magnitude of the increase in growth velocity depends on the age of the child and the severity and duration of the growth retardation. It may be as much as twice the normal velocity in young children with prolonged retardation. The ability of a malnourished animal or child then to return to its normal growth trajectory depends on the magnitude of the catch-up growth. The biological basis for failure of 'catch-up' growth to return the individual to the normal trajectory for the individual is at present not clear. An early hypothesis that it is due to a reduction in the period of hyperplastic growth has not been confirmed in the rat (Sands *et al.*, 1979).

The growth curve of the whole body and of its constituent parts has a sigmoid shape, but different organs and tissues grow at different rates and at different times. The four main types of growth curve are shown in Figure 1.1 (Tanner, 1962; from Scammon, 1930). The period of rapid increase in the 'General' curve

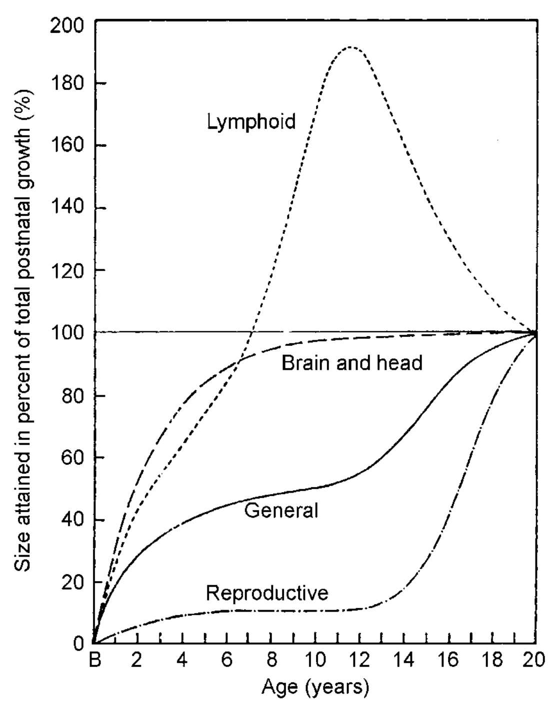

Figure 1.1 Growth curves of different parts and tissues of the body. All the curves are of size attained and plotted as percentages of total gain from birth to 20 years so that size at age 20 is 100 on the vertical scale. Data from Scammon [reproduced by permission of Blackwell Science from Tanner (1962) *Growth at Adolescence*, 2nd edn].

Table 1.1 Relative lengths (percentage) of parts of the human body during growth; values calculated from Medawar (1944) (from Tanner, 1962)

Age (years)[a]	Head	Trunk	Upper limbs	Lower limbs
0.42	33	43	26	24
2.75	21	41	34	37
6.75	16	41	34	41
25.75	12	43	37	43

[a]Age from 5 months postconception.

from about 12 to 15 years is called the 'adolescent spurt' and involves every muscular and skeletal dimension in the body. Maturity is not achieved until this has been completed, and again this is related to time and is separated from time by nutritional deprivation. The early rapid growth of the head and brain shown in Figure 1.1 is an example of a 'growth gradient', and this particular one is called the 'cephalocaudal' gradient. The head of a young child may be almost the same size as that of its mother. The changes in the relative size of different parts of the body with growth and development are also shown in Table 1.1, in which the sizes of different parts of the body are expressed as a percentage of the total body length. The proportion accounted for by the head and neck decreases from approximately 30 per cent in the 5-month-old fetus to approximately 12 per cent in the adult. In contrast, the percentage of length accounted for by the lower limbs increases from approximately 24 per cent in the fetus to 43 per cent in the adult. The percentage of the body length contributed by the trunk (about 40 per cent) hardly changes during growth. In the leg, another gradient may be distinguished, as growth in foot length ceases before that of the calf, and that of the calf before that of the thigh. Material in Chapters 2 and 7 should be read in relation to this chapter.

Growth curves

Each individual has his or her own growth curve, or 'trajectory', as it is called, if measured longitudinally. The oldest such curve is that of a boy measured every 6 months for 18 years by Count de Montbeillard (Figure 1.2; from Tanner, 1962). The longitudinal construction

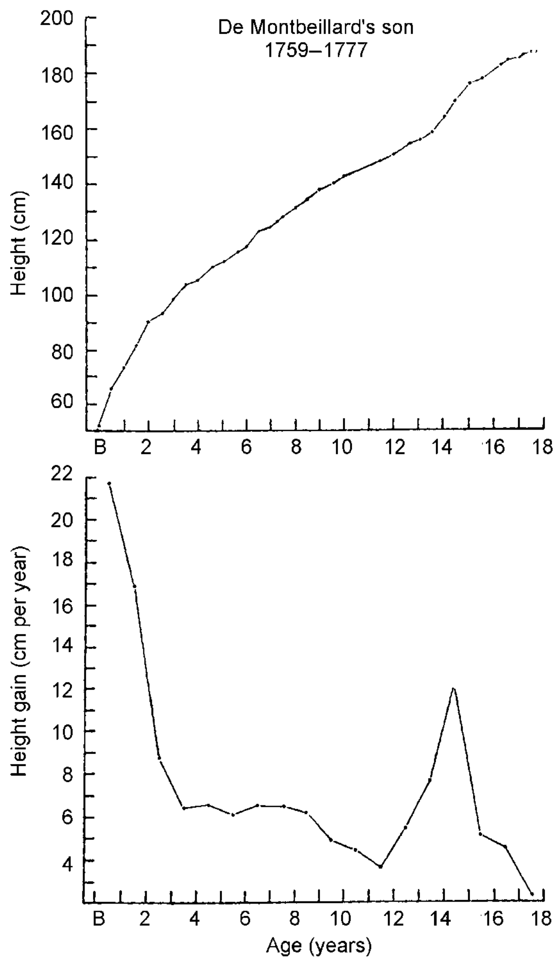

Figure 1.2 Growth in height of de Montbeillard's son from birth to 18 years, 1759–1777. Top, distance curve, height attained at each age; bottom, velocity curve, increments in height from year to year. Data from Scammon [reproduced by permission of Blackwell Science from Tanner (1962) *Growth at Adolescence*, 2nd edn]

of such growth curves for individual children is of considerable value in clinical paediatrics. There are many causes of growth failure, or 'failure to thrive', one of which is malnutrition; the construction of an individual child's growth curve permits the degree of growth failure to be assessed and the progress of rehabilitation to be followed. To help in this process, standard growth curves, and particularly percentile charts, have been constructed from measurements of large numbers of children of different ages, that is from cross-sectional measurements. In percentile charts (Figs 10.2a–d, the height or weight, or whatever other measurement is being considered, follows the 50th percentile for 50 per cent of the children measured at a particular age. Similar percentiles are drawn in such a way that a greater or a smaller number of children have values below the line. Ideally, growth charts should be available nationally in different countries. Perhaps the best known are those for the USA (Hamill *et al.*, 1977), and in the UK the curves produced by Tanner *et al.* (1966) have been replaced by those published by Freeman *et al.* (1995). It is often some time after the measurements were made before the charts become available. Thus, the US charts are based on data collected between 1929 and 1975 and Tanner *et al.*'s UK charts were based on data collected between 1952 and 1954. This poses a problem if infant feeding practices change as this might result in changes in infant and children's growth rates. Differences in infant feeding practices, for instance, in developing countries, suggest that growth charts should be kept under review (Whitehead and Paul, 2000). Prentice (1998) has suggested using body mass index (BMI; defined as weight/height^2, kg/m^2) charts available from the Child Growth Foundation (London W4 1PW, UK) for the assessment of nutritional status in children. Cole (2001) has discussed the use and abuse of centile curves for the BMI. The application of BMI charts to children was first suggested by Cole (1979).

Developmental age and physiological maturity

The age of a child can be expressed in two ways. It is usually quoted simply as the number of years, months or weeks since it was born. This is its 'chronological' age. Then we can also determine its 'developmental' age, which is a measure of how far the child has progressed towards maturity. This can be assessed in a number of different ways (Table 1.2). Each method has its own limitations and it is necessary to consider each method in some detail.

Skeletal age is the most commonly used indicator of physiological maturity (Tanner, 1962). It is a measure of the degree of development of the skeleton as measured by the appearance and size of the epiphyses of certain bones. Each bone begins with a primary centre of ossification. It then enlarges, changes shape and secondary centres of ossification develop in the cartilaginous epiphyses. Eventually, the epiphyses fuse and the epiphysial plate disappears. This sequence of changes is the same for all indivduals, whatever the rate of development. Skeletal maturity is judged both on the number of centres present and on the stage of development of each. The appearance of the epiphyses at birth may differ from one child to another with different numbers of primary centres developed and larger areas ossified. Areas of ossification are not of themselves considered good indicators of bone development as they differ according to the size of the individual.

Assessment of skeletal maturity is accomplished by comparing an X-ray with a set of

Table 1.2 Assessment of developmental age – systems in use (Tanner, 1962)

Skeletal age
Dental age
Morphological or shape age
Secondary sex characteristics age

standards. There are two ways of doing this. An older, atlas method involved matching an X-ray with standards representing the 'norm' for different ages, with a skeletal age being assigned to a test X-ray according to the age of the nearest match in the atlas. Tanner *et al.* (1961) refined this method by assigning a score to different changes in bone maturity. In this method, a test X-ray scored a number of development points. The bones for which there are standard atlases are the wrist and the knee, with separate standards for the two sexes. This is because girls are more mature at birth, before it and throughout the whole period of growth up to adolescence. It is to be noted that skeletal age can be assessed throughout the period of growth of the bones.

Dental age can be obtained using the same principle as skeletal age, with eruption and noneruption of teeth as the index corresponding to the appearance and non-appearance of an ossification centre. A refinement of this method involves more detailed observation and scoring of degrees of tooth eruption and root development. The use of dental age is clearly limited to the period when the deciduous and permanent teeth are erupting. For deciduous dentition this is from about 6 months to 2 years. The corresponding period for permanent dentition is from 6 to 13 years. There is a marked sex difference in the eruption of teeth, with all teeth appearing earlier in girls than in boys by an amount varying from 2 months for the first molars to 11 months for the canines (Tanner, 1962). It may be considered that the times of the eruption of teeth are just as crude a method of assessing developmental age as the timing of the presence of ossification centres. It has been suggested that in the absence of a birth certificate the state of teeth eruption can be used to estimate chronological age. To this end, published data from 42 studies of children's dentition transformed into chronological age have been examined (Towsend and Hammel, 1990). Lack of significant differences between the estimates of age seemed to justify the use of a single set of data. However, results of a longitudinal study of 129 Finnish children based on deciduous teeth (Nystrom *et al.*, 2000) led to the conclusion that estimates of age should not be based on teeth eruption alone because of marked variation in their homogeneous group of children.

Morphological or shape age has been considered as a means of assessing development. The idea that changes in shape of the body might be quantified and used in this way was probably first suggested by Godin in France in 1903 (quoted by Tanner, 1962) and was later developed by Medawar (1944) with reference to the shape change in vertical proportions (see Table 1.1). Tanner (1962) quotes Richards and Kavanagh (1945) as having outlined the mathematical procedures by which this might be achieved. The concept seems not to have been pursued further.

Sexual age is derived from observations of the development of secondary sex characteristics. The adolescent growth spurt, and the development of these characteristics, occurs later in boys than in girls. The age ranges over which the changes begin and end are shown in Table 1.3. A scoring system of 2–5 is used to

Table 1.3 The sequence of events at adolescence in boys and girls used to assess developmental age (adapted from Tanner, 1962)

	Beginning (years)	End (years)
Boys		
Height spurt	10.5–13	16–17.5
Penis growth	11–13.5	14.5–17
Testis growth	10–14.5	13.5–18
Pubic hair (grades 2–5)	10–14	15–18
Girls		
Height spurt	9.5–14.5	
Menarche	10–16.5	
Breast (grades 2–5)	8–13	
Pubic hair (grades 2–5)	8–14	

assess breast development in girls and pubic hair in both sexes (Tanner, 1962). Sexual development, and particularly the age of menarche, is occurring earlier now than it was, say, 100 years ago due to what is called the 'secular trend' (Wyshak and Frisch, 1982). Obviously, the ages over which these assessments of development can be used are limited to those ages over which the changes occur. Key factors which influence their development are sex hormones and nutrition. In the disease anorexia nervosa, which occurs most commonly in adolescent girls, who are often severely emaciated although secondary sex characteristics are usually well developed, amenorrhoea is a common feature. This feature of the disease is closely linked with body weight (Frisch, 1994).

Factors which influence growth and development

The rate of development can be assessed, as we have seen, by the age at which certain milestones of development occur. This age can be affected by genetic constitution, nutritional status (often associated with poverty), severe illness, psychological disturbance and the secular trend.

Early observations about the influence of genetics pertained to the age of menarche in mothers and daughters (quoted by Tanner, 1962). Pairs of identical twins were closest in age of menarche, with an average difference of 2.8 months; non-identical twins, with a difference of 12 months, were not very different from sisters (12.8 months), with unrelated women showing a difference of 18.6 months. According to Tanner, evidence of genetic control has also been noted for the reaching of peak growth velocity, skeletal maturity and in the growth of specific muscles. Undernutrition and, often with it, poverty or famine can have a profound effect on growth, separating it from time. The effects may manifest themselves in the fetus, with the result that the baby is born 'small-for-dates', or after birth, when the child's growth is stunted. In rats, which are born at an earlier stage of development than humans, it is easy to show a permanent stunting when the animals are nutritionally deprived at an early age. In human babies, in which there is, by comparison, an extended period of growth and development, it is much more difficult to show permanent stunting. The greater a mother's size before pregnancy, the more likely she is to have a normal birth-weight baby (Naeye, 1981). For women who are underweight when they conceive, the amount of food they consume during pregnancy affects the birth-weight (Papoz *et al.*, 1981). In mothers with protein-energy malnutrition (PEM), or who have a preconception daily energy intake of 7.5 MJ (1800 kcal) or less, appropriate food supplementation during pregnancy, depending on the size of the deficiency, increases fetal growth and decreases the number of low-birth-weight babies (Lechtig and Klein, 1981). As to the effect of supplementation after birth, the following examples will suffice. During the post-war famine in Europe in 1947–1948, children in a German orphanage whose diets averaged about 80 per cent of their desirable nutrient intake were supplemented for a year with bread and other foods (see Widdowson, 1951). During the period of the supplement their heights and weights increased at a greater than normal rate (that is they showed 'catch-up' growth) and their skeletal maturity changed in parallel with their growth. In a second example, a group of 141 Korean girls were admitted to the USA and adopted into American families (Winick *et al.*, 1975). The girls were divided into three groups of whom 42 were severely malnourished and below the 3rd percentile for both height and weight by Korean standards. Another 52 were marginally malnourished, between the 3rd and 25th percentile for height and weight, and 47 were well-nourished and above the 50th percentile for height and weight. The families who adopted them before their second birthday had no idea of the children's previous nutritional history. By the time they were 7 years of age there were no differences in the average weight of the three groups of children although the average height of the previously malnourished Korean children remained statistically below those of the well-nourished children. All the Korean children remained shorter and lighter than the American standards.

Illness only has a transient effect on children's growth unless it is severe; then its effects mimic those of malnutrition. That the psychological state of children affects the effects of food on body growth was a serendipitus observation during the supplementation study in the German orphanages mentioned above (Widdowson, 1951). During the supplementation it was found that it was the presence of a Sister (called 'B', in the write-up) in the orphanage, rather than the food available, that determined the children's growth, as the mealtimes were chosen by her as an opportunity to severely reprimand the majority of the children, other than those who were 'B's favourites; it was these favourites who gave the expected response to the rations. There was no doubt that the children who did not respond consumed the supplements.

The 'secular trend' is the term used to describe the striking tendency for the age of adolescence, for example menarche, and the growth spurt to take place earlier than they did 100 years ago. Similar trends have been reported in all Western countries. These trends are greater than the differences between social classes (Tanner, 1978). In countries with large populations such as India, trends in growth and development may be induced by racial, ethnic and genetic factors as well as those caused by socioeconomic status and nutrition. This may make it necessary to construct local/regional growth standards (Singh, 1995). The secular trend has had sociological and medical effects; the latter are shown by the occurrence of myopia in children at the earlier age of puberty (Tanner, 1962).

Body Composition

The composition of the mammalian body can be considered from three different viewpoints – anatomical, physiological and chemical – each of which has importance for the nutritionist and implications for public health and clinical medicine. Anatomically, our bodies consist of a number of organs and tissues which contribute varying proportions to the total body weight. Physiologically, our bodies contain 60–70 per cent water, which is distributed between the cellular and extracellular compartments, with the different composition of the intracellular fluid (ICF) and the extracellular fluid (ECF) being maintained by energy-dependent mechanisms in the cell membranes. Also, physiologically, our bodies can be divided into energy-expending tissues, collectively called the 'lean body mass' (LBM) and energy-storing adipose tissue, collectively called the 'fat mass' (FM). Chemically, the body consists of various organic and inorganic substances that are functionally integrated, with the mineral composition of the body necessarily depending on its organic structure. There are nevertheless three factors which predominantly affect the proportion of inorganic elements in the body and its tissues. The first is the amount of fat, as fatty tissue contains comparatively little inorganic material, so that it acts mainly as a diluent. The second is the amount of ECF in the body or tissue at the moment of analysis. Structurally and functionally this is important in the process of development, in which there is a decrease in the volume of ECF consequent upon the increase in the cell mass (CM), and in disease, in which malnutrition produces the opposite changes – an increase in the volume of ECF consequent upon a decrease in the CM. The magnitude of the changes in the proportion of ECF far outweigh the changes in its composition or in that of the cells. The third factor is the amount of bone and its degree of calcification, as the adult skeleton contains 99 per cent of the body's calcium. Changes in the concentration of calcium in the body fluids have important physiological consequences, but they have no appreciable effect on the composition of the body.

It is important to remember, as we discuss the chemical composition of the body, that we are considering a static picture of a dynamic scene, for the molecules of which our bodies are composed are in a state of individual and collective activity, and what we are considering is like a snapshot of a busy street full of pedestrians and automobiles (Widdowson and Dickerson, 1964).

Methods for determining whole body composition

Chemical analysis

Detailed discussion of the methods available for the analysis of the human body is outside the scope of this chapter. However, it should be noted that chemical analysis is essentially a destructive process and can be carried out only after death or on tissue obtained by biopsy. Quantitative analysis of whole bodies presents considerable difficulties. In the first place, it is necessary for the investigator to obtain permission from the relatives or guardians of the body to deal with it in this way. This is not easy. It is even more difficult to obtain the body of a healthy person. This problem, together with that of handling such a large amount of material in a quantitative fashion, has limited the number of adult human bodies that have been analysed. In fact, up to 1945, our knowledge about the chemical composition of the adult human body was derived from work carried out in Europe about 100 years ago; since that time the composition of five more human bodies (four men and one woman) has been determined (see Widdowson and Dickerson, 1964). It is likely that this will remain the total information that we have of the elemental composition of the adult human body. The bodies of human fetuses and stillborn babies are much easier to deal with and the results of the analysis of these will be considered here. Again, though, trends in public opinion and ethical considerations make it unlikely that there will be any further analyses of this nature. This adds value to the work of Fomon *et al.* (1982) in producing calculated data for the composition of 'reference' children up to 10 years of age, and these will be considered later.

Other methods

There has been, and is continuing to be, research into other methods for the determination of aspects of the composition of the living human body. Much of this development has stemmed from a concept of the body as consisting of two components, fat and lean tissue (Behnke *et al.*, 1942). This is now referred to as the 'two-compartment model' of body composition. A four-compartment model for the assessment of body composition of humans has been devised which involves the determination of body fat by underwater weighing, total body water (TBW) by deuterium, total body mineral by dual-energy X-ray absorptiometry (DXA) and fat-free body mass as body weight minus fat (Fuller *et al.*, 1992). Coward *et al.* (1988) reviewed the established techniques available at that time: measurement of body fat from measurements body density, TBW, total body potassium and determination of body fatness by anthropometry. They also reviewed the newer technique of electrical conductivity and impedence. In a study in which body fat was measured in lean and obese individuals (McNeill *et al.*, 1989) by six different methods [skinfold thickness, underwater weighing, whole body ^{40}K counting, deuterium dilution of body water, tetrapolar bioelectrical impedence and magnetic resonance imaging (MRI)], it was found that, despite high correlations between any two different methods over a wide range of fatness, there was substantial disagreement between the results by the different methods in the same individual. Measurements of gross body fat in rats by DXA, compared with absolute values determined by carcase analysis (Jebb *et al.*, 1994), showed that this method overestimated body fat in the rats by 30–39 per cent. Bioelectrical impedence analysis has been shown to be of greater value in assessing lower limb muscle area in groups of subjects rather than in individuals (Fuller *et al.*, 1999). The need for simple (and preferably inexpensive) methods for the determination of aspects of body composition at the bedside has led to research into methods that could be used to calibrate such instruments (Elia and Ward, 1999). The BOD POD body composition system developed in the US (Life Measurement Systems, Concord, CA, USA) can be used to measure body volume by air, rather than by water, displacement, as in the method described by Behnke *et al.* (1942) for the determination of body density. This method of determining body fat then becomes possible in children. Alternatively, deuterium dilution can be measured by infrared spectroscopy rather more cheaply than by mass spectroscopy. Bioelectrical impedance can be used to accurately measure skinfold thickness. Again, both these methods can be used in children.

The main conclusion that can be drawn from the literature on this subject is that a variety of expensive research tools are available which are essentially difficult to calibrate against absolute values. Reproducibility of results, availability, cost and expertise all need to be considered in the use of any of them. The reason for making the measurement also needs to be considered, whether it is for research or to follow the progress of treatment in a single individual. If it is simply a matter of assessing a change in nutritional status, repeated careful measurement of body weight under standard conditions together with triceps skinfold thickness may suffice.

The composition of the whole body

The effect of development

Table 1.4 shows the changes in the chemical composition, determined by chemical analysis, of human fetuses and stillborn babies varying in weight from 0.75 to 4373 g. The smallest of the foetuses contained 924 g of water per kg of body tissue, which is about the same amount that exists in serum after birth. The heaviest stillborn baby (4373 g) contained only 585 g of water per kg of tissue. Part of the difference in the amount of water was due to the difference in fat content, 5 g compared with 282 g per kg, and on a fat-free basis the proportion of water in the body fell from 930 to 820 g per kg of body tissue. It is important to note that the amount of fat in the body did not rise above 100 g per kg until a fetus weighed more than 2600 g and reference will be made to this again later. When information from other workers is included (Figure 1.3), we find that the water content of the body falls rapidly during early growth, reaching 880 g per kg fat-free tissue when the fetus weighs 50–100 g and then declining more gradually to 820 g per kg when the fetus reaches full term. This fall in water content is due to a reduction in the amount of ECF consequent on an increase in the CM and is reflected in a fall in the concentrations of the EC ions, sodium and chloride, and a rise in the concentration of the predominantly intracellular ion, potassium. However, not all the sodium in the body is located in the ECF and it has been calculated

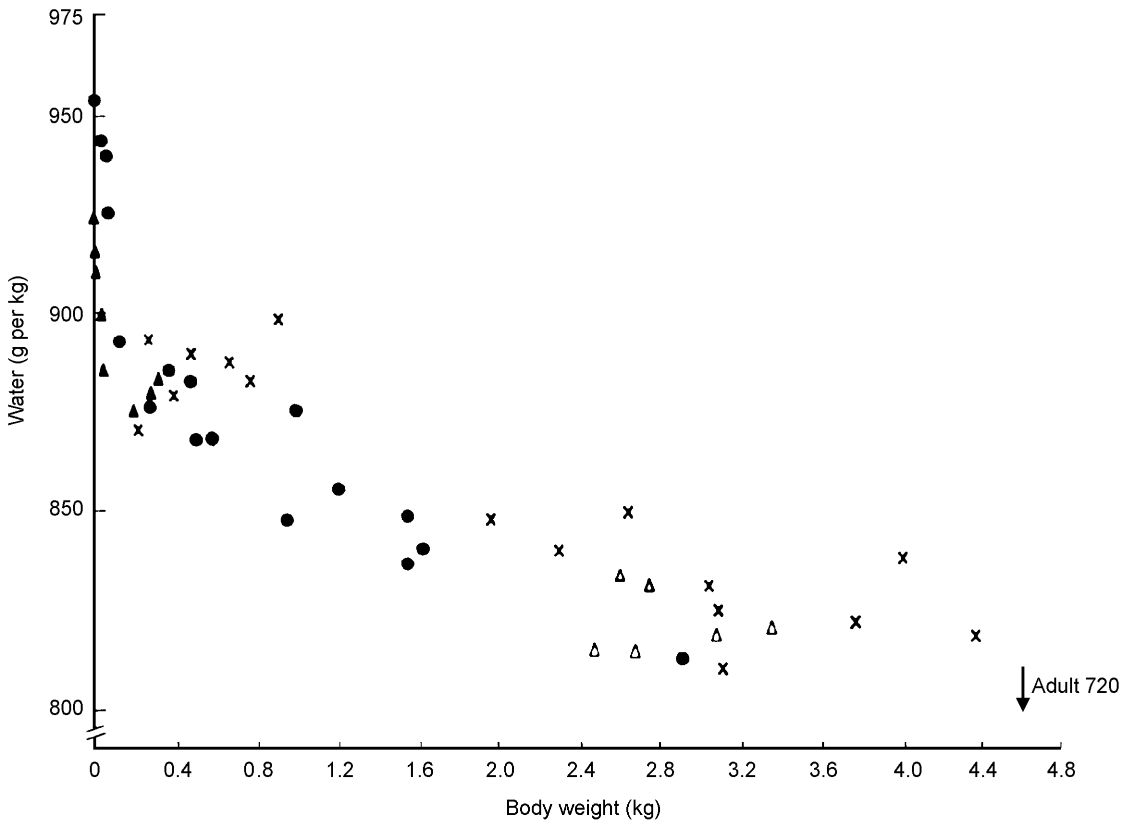

Figure 1.3 Water (g/kg) in the fat-free body tissue of the human foetus during growth [different symbols signify different sources of data; reproduced from Widdowson and Dickerson (1964). *Mineral Metabolism*, Vol. 2A, pp. 1–217, by permission of Academic Press]

that at term about 13 per cent of the body's sodium is found in the bones and that from about the seventh month of prenatal life the fall in the proportion of extracellular sodium is approximately counter-balanced by increases in sodium in the skeleton. The skin also contains much sodium and chloride at all ages and the concentration of chloride in adult skin is at least as high as that in the skin of a full-term baby. The changes in the amount of calcium in the body are a reflection of the ossification of the skeleton and this begins to occur when the fetus weighs between 700 and 900 g and rises to term. The increase in the mineralization of the skeleton also contributes to the rise in the amount of phosphorus in the body; the soft tissues also contain phosphorus and thus the increase in the CM also contributes to the increase in the body's content of this mineral. The concentrations of iron, copper and zinc in Table 1.4 show little evidence of regular trends with the progress of gestation.

Using information obtained by 'dilution' methods, it is possible to extend the developmental curve for some body constituents to find what Moulton (1923) described as the age of 'chemical maturity'. Using this information (Widdowson and Dickerson, 1964) it is possible to conclude that total water, 'exchangeable'