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How the foetus is fed

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Man, like all mammals, starts life as a single cell, but the rate at which this original cell multiplies itself, and therefore the rate of growth in size of the foetus, varies by a factor of about 100 000 from one species of mammal to another. Table 1 illustrates this. The mouse grows at a mean rate of 0·09 g a day, the blue whale at a mean rate of 9 kg. Man comes in between, but, even so, during prenatal life his weight increases 6 billion (10^{12}) times. On the whole the rate of growth is related to the size the foetus becomes because there is a far bigger variation between species in the weight at birth than there is in the length of gestation.

Table 1. *Rate of growth of nine species before birth*

Species	Length of gestation (days)	Weight at birth (g)	Mean growth rate (g/day)
Mouse	21	2	0·09
Rat	21	5	0·24
Cat	63	100	1·6
Dog	63	200	3·2
Pig	120	1 500	4·2
Man	280	3 500	12·5
Elephant	600	114 000	190
Hippopotamus	240	50 000	210
Blue whale	330	3 000 000	9000

The rate of growth before birth, like the rate of growth afterwards, depends primarily upon the food supply, and upon the ability of the foetus to take in and make use of the food. The nutrition supplied to the foetal whale is clearly many times greater than the nutrition supplied to the foetal mouse, and the whale is able to make use of its nourishment because it has cells which are ready to divide at a far higher rate than those of the foetal mouse. The rate of cell division is determined genetically, and there is close integration between the food supply to the foetus, the rate of cell division, and hence the rate of growth. The food supply usually depends more upon the quantity of blood reaching the foetus than upon the concentration of nutrients in the maternal plasma, and this is certainly true of comparisons between species. The foetal whale grows faster than the foetal mouse because of the greater blood flow to it, and not because of any differences in composition of the maternal plasma, which is in all probability very much the same in the two species. Similarly, undernutrition of the foetus generally arises, not because of the deficiency of any specific nutrient in the maternal plasma, but because for some reason there is a reduction in the total blood supply. This is not to say that the composition of the maternal plasma does not matter. Specific nutritional deficiencies in the foetus due to a deficiency in the mother can occur and an example is rickets in the foetus as a consequence of a deficiency of vitamin D in the mother (see Bicknell & Prescott, 1946).

The embryo or foetus is fed in three different ways between the time the ovum is fertilized and the baby is born. First there is the stage when the blastocyst is free and unattached in the uterus, which lasts for a varying number of days according to the different species. During this time it absorbs nutrients through its outer layer, the trophoblast, from the secretions of the uterine glands, the so-called uterine milk. This must vary in composition from one species to another. Table 2 sets out some values for the composition of this material in the mare (Amoroso, 1958). The 'milk' also contained some iron but the concentration was not determined.

Table 2. *Composition (g/100 g) of uterine milk of mare (from Amoroso, 1958)*

Water	79·6
Total N	3·2
Protein	18·0
Fat	0·006
Calcium	0·14
Phosphorus	0·2
Chloride	0·2

After the blastocyst has become implanted in the uterine epithelium, but before the placental circulation has been established, a sinusoidal space, the syncitium, is formed between the foetal and maternal tissues, and the blood and degenerating cells within it provide the nutriment for the developing organism until the placenta has developed and placental circulation is ready to take over, which, in the case of man, has occurred by the 3rd month. Once the placental circulation has been established, all the nutrients required by the foetus reach it through its umbilical blood vessels. At the end of the first 3 months of gestation the human foetus weighs only 30 g or so, as compared with over 3000 g at term. Almost all its growth in size, therefore, and hence the transfer of most of the material in its body at term, takes place during the last 6 months. Table 3 shows the total amounts of water, nitrogen, fat, carbohydrate and minerals in the body of a full-term baby (Widdowson & Spray, 1951; Widdowson, 1964), and the average amounts which the foetus incorporates into the body each day during the second and third trimesters. Growth does not proceed along a straight line, however, but becomes faster and faster, and the foetus needs more and more of most bodily constituents every day. This is illustrated

Table 3. *Total amounts of water, nitrogen, fat, carbohydrate and minerals in the body of a full-term baby weighing 3·5 kg*

	Amount in body	Mean increment per day over last 6 months
Water (g)	2400	13
Fat (g)	560	3·1
N (g)	66	0·36
Carbohydrate (g)	34	0·19
Ca (g)	28	0·15
P (g)	16	0·09
Mg (g)	0·76	0·004
Na (m-equiv.)	243	1·3
K (m-equiv.)	150	0·8
Cl (m-equiv.)	160	0·9
Fe (mg)	320	1·8
Cu (mg)	14	0·08
Zn (mg)	53	0·29

in Fig. 1, which shows the total amounts of calcium and phosphorus in the foetal body at different ages, and Fig. 2 shows the calcium and phosphorus requirements for the growing foetus per day. At the end of the 3rd month it deposits about 7 mg at the end of the 6th month 110 mg, and at the end of the 9th month 350 mg calcium/day. At one time the placenta was thought of as a semi-permeable membrane between maternal and foetal blood, and it was believed that what was transferred to the foetus was an ultrafiltrate of maternal plasma. It was then realized that this concept was far too naïve, for many of the nutrients being transmitted to the foetus are at a higher concentration in foetal than in maternal plasma. This is illustrated in Table 4, which compares foetal and maternal plasma in man. Potassium, phosphorus, calcium and magnesium are all higher in foetal serum and the same thing applies to amino acids, to vitamin C, and also to iron and zinc. It seems likely that gases and water diffuse freely across the placenta but we still do not know exactly how the other materials are transmitted. It is often said that active transport is involved; this must be so, but Hytten & Leitch (1964) have also emphasized the importance of the different parts of the placenta in this transport. The gradient is not directly from maternal blood to foetal blood but from maternal blood to the syncitiotrophoblast, the maternal part of the placenta, where concentration may go on and proteins, enzymes, nucleic acids and hormones may be synthesized. Further synthesis and conversions go on in the cytotrophoblast, the foetal part of the placenta, and we have no idea at all at present about the gradients within the different parts of the placenta, or between the foetal side of the placenta and the foetal blood.

Carbohydrate reaches the foetus as glucose and the foetus synthesizes its own glycogen. The serum of the foetal lamb, and of other ungulates, has high concentrations of fructose, and this has been shown to be formed from glucose in the maternal serum by the placenta (Huggett, 1961). Here, therefore, is a clear example of the placenta altering a nutrient during its passage through it. The fructose disappears from the serum of the animal within a few days after birth, and what its function is is still unknown.

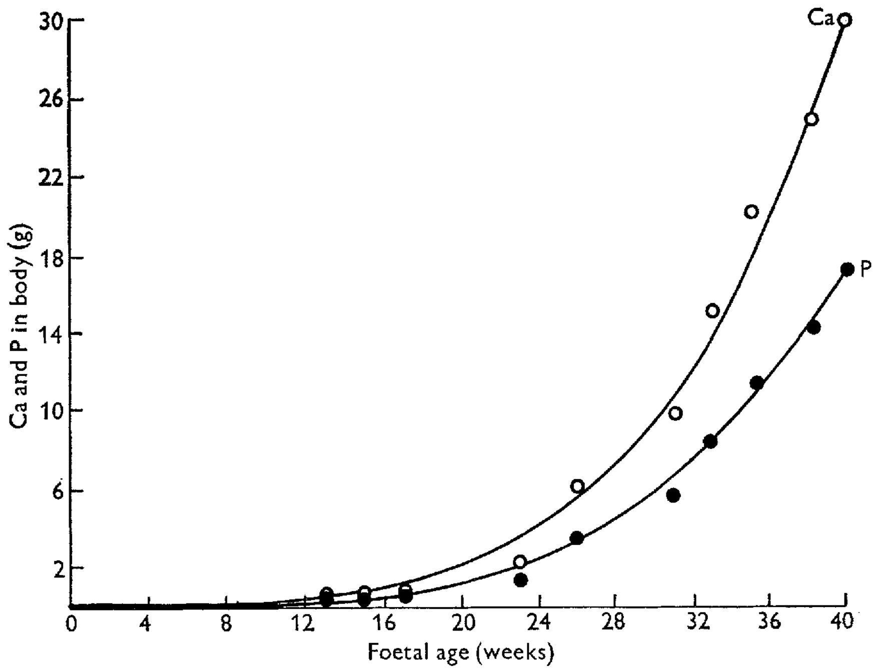

Fig. 1. Calcium and phosphorus in the body of the developing foetus.

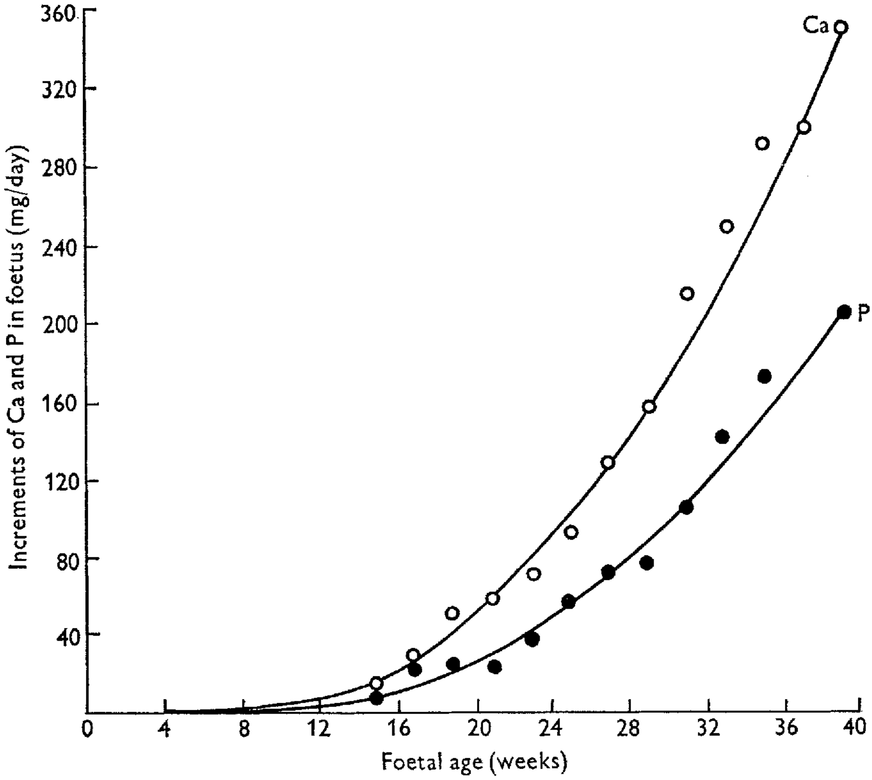

Fig. 2. Daily increments of calcium and phosphorus in the body of the foetus.

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Table 4. *Composition of serum of foetus compared with that of mother*

	Foetus		Mother
	Immature	Full-term	at term
Na (m-equiv./l.)	140	140	140
Cl (m-equiv./l.)	105	105	105
K (m-equiv./l.)	10·0	6·8	5·0
Ca (mg/100 ml)	9·0	11·0	10·0
P (mg/100 ml)	14·9	5·8	4·0
Mg (mg/100 ml)	2·8	2·5	2·0
Urea (m-moles/l.)	—	3·4	3·4

During the early stages of gestation the developing organism lays down no fat apart from the essential lipids and phospholipids in the nervous system and cell walls. Some species, for example the mouse, rat, cat, dog and pig, are born before the deposition of white fat begins, and in the human foetus there is only about 0·5% of fat in the body until the middle of gestation, but then white fat begins to be laid down, and the percentage in the body rises to about 3·5 by the time the foetus is 28 weeks, 7·5% at 34 weeks and 16% at term. The human foetus lays down 14 g or so of fat a day over the last month *in utero*. There is evidence that the foetus synthesizes its own fat from glucose, as it does its glycogen, and that no fatty acids, except perhaps the essential ones, cross the placenta. Acetyl co-enzyme A does cross the placenta, and this may act as a precursor of fatty acids and lipids (Hytten & Leitch, 1964).

Apart from the γ-globulins, which are in a special position, nitrogen is transferred to the foetus primarily as amino acids. It was demonstrated as long ago as 1913 that the concentration of free amino acids is higher in foetal than in maternal blood (Van Slyke & Meyer, 1913) and this has been confirmed many times since (Christensen & Streicher, 1948; Clemetson & Churchman, 1954). It seems that the L-isomer passes to the foetus more freely than the D-isomer (Page, Glendening, Margolis & Harper, 1957), which suggests that an active process is responsible for their transport. Räihä (1958) showed that dehydroascorbic acid rapidly crosses the placenta whereas L-ascorbic acid does not, and he suggested that the vitamin C reaches the foetus as dehydroascorbic acid and that this is then reduced by the foetus to the laevo form. Thiamine passes easily through the placental barrier, and the same is true of folate and vitamin B_{12} (Baker, Ziffer, Pasher & Sobotka, 1958).

Vitamin A has been found in varying amounts in the liver of the human foetus (Wolff, 1932; Lewis, Bodansky & Shapiro, 1943). The concentration of vitamin A, and more strikingly, of carotenoids, is lower in the foetal than in the maternal blood (Lewis, Bodansky, Lillienfeld & Schneider, 1947). These authors also found that the administration of large doses of vitamin A or carotene to the mother during the last part of pregnancy produced no increase in their concentrations in the blood of the foetus. Just how vitamin A, and indeed also vitamin D, are transferred to the foetus and what controls the transfer does not seem to be completely clear.

We have more quantitative information about the rate of movement of inorganic substances across the placenta than we have about the organic, because the introduction of isotopes has enabled direct measurements to be made. For example, it was shown that at term 500–1000 times as much sodium reaches the human foetus as it requires for growth (Flexner, Cowie, Hellman, Wilde & Vosburgh, 1948; Cox & Chalmers, 1953), and almost the whole of it returns to the mother's circulation. Calcium and phosphorus do not seem to be supplied in such generous amounts, at any rate in small laboratory animals, for studies when ^{45}Ca and ^{32}P were injected into pregnant rabbits and rats showed that the quantities of calcium and phosphorus reaching the foetuses were only just about enough to meet their requirements, particularly if the litter was a large one (Wilde, Cowie & Flexner, 1946; Wasserman, Comar, Nold & Lengemann, 1957). Foetal guinea-pigs and rats near term incorporate into their bodies amounts of calcium and phosphorus equal to the whole of the calcium and inorganic phosphorus in their mother's serum every hour (Wilde *et al.* 1946). The human foetus grows more slowly than the rat and guinea-pig, and it is smaller in proportion to the size of its mother, but Table 5 shows that the foetus requires 5% of the total calcium in the plasma of the mother and 10% of the inorganic phosphorus every hour during the last 3 months of gestation (Widdowson, 1962).

Table 5. *Requirements of the human foetus for calcium and phosphorus in terms of the amounts in the mother's plasma*

	Ca	P
Total amount required by foetus during last 3 months gestation (g)	28	16
Amount required by foetus per h (mg)	13	7·4
Total amount in mother's plasma (assuming volume of 2·5 l.) (mg)	250	75
Foetal requirement per h as % of amount in mother's plasma	5	10

The problem as to how iron, copper and zinc cross the placenta is a particularly interesting one. They are all wholly or mainly attached to specific proteins in the plasma, and there are some extraordinary differences, if the findings are correct, between the concentration in maternal and foetal plasma. Table 6 shows that up to the 6th month of gestation the concentration of iron in the foetal plasma is low, but it rises, so that at term the foetal plasma has nearly three times as high a concentration as the maternal (Vahlquist, 1941). Copper seems to move in exactly the opposite direction for the concentration falls, not rises, during gestation, and foetal plasma has much less copper than maternal (Lesné, Zizine & Briskas, 1936). The serum of a sow which has just had a litter also contains three or four times as much copper as the serum of her newborn piglets (Moustgaard & Olsen, 1951). It seems that the difference between mother and foetus is due to the higher concentration of the copper–protein enzyme caeruloplasmin in the mother's plasma, and the concentration of copper not in this form is approximately the same on both sides of the placenta (Scheinberg, Cook & Murphy, 1954). Presumably it is only the non-caeruloplasmin part that passes over to the foetus.

The plasma of the immature foetus has a high concentration of zinc (Berfenstam, 1949, 1952). Babies born prematurely have a higher concentration than those born at full term, and the plasma of the baby has a higher concentration than that of its mother whether birth is premature or not (Vikbladh, 1951). All the zinc in plasma

Table 6. *Iron, copper and zinc in serum* (*μg*/100 *ml*)

	Foetus		Mother
	Immature	Full-term	at term
Fe	40	160	60
Cu	200	50	250
Zn	300	125	70

it attached to proteins, and how it is transmitted to the foetus is still an unsolved puzzle.

This short description of how the foetus is fed would not be complete without a few words about excretion by the foetal gut and kidneys. The foetal intestine becomes filled with a sticky material, meconium, which is passed by the baby during the first days after birth and sometimes into the amniotic cavity before birth. Meconium has an extraordinary mineral make-up, illustrated in Table 7 (Widdowson, McCance, Harrison & Sutton, 1962; Cavell & Widdowson, 1964). It has as much magnesium as calcium per 100 g, and twice as much magnesium as the body as a whole. It has more copper and much more zinc. It has a higher calcium:phosphorus ratio than bone.

Table 7. *Composition* (*per* 100 *g*) *of meconium compared with composition of whole body of baby at term*

	Meconium	Body
Na (m-equiv.)	13·6	8·2
K (m-equiv.)	3·1	5·3
Ca (mg)	46·4	960
Mg (mg)	47·7	26
P (mg)	16·4	560
Fe (mg)	1·7	9·4
Cu (mg)	1·7	0·5
Zn (mg)	6·5	1·9

The foetus is enclosed by the amniotic membrane, and is surrounded by amniotic fluid. This is similar in composition to a plasma ultrafiltrate, but it becomes more dilute towards the end of gestation, and it is thought that this is because the foetus passes quite large volumes of urine into it (McCance, 1964). This urine is hypotonic, and contains much lower concentrations of sodium, chloride and urea than the mother's urine being formed at the same time (Table 8; McCance & Widdowson,

Table 8. *Composition of urine of foetus compared with that of mother*

	Foetus, full-term	Mother
Urea (m-moles/l.)	17	194
Na (m-equiv./l.)	44	146
Cl (m-equiv./l.)	41	154

1953). It is also more dilute than the plasma, or the amniotic fluid into which it is passed. The human foetus is known to drink amniotic fluid—this has been shown by injecting methylene blue into the amniotic cavity and finding large amounts in the maternal plasma and foetal urine (De Snoo, 1937). De Snoo estimated that the foetus probably drinks something of the order of a litre a day. Almost the whole of

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the ingested salts and water must be absorbed by the foetal gut into the circulation. Where and how this takes place in the human foetus is quite unknown, but sodium and water have been shown to be absorbed from the stomach of the rabbit foetus. This is interesting, because the absorption of water and salt is not generally considered an important function of the stomach in adult life.

The foetus can swallow solid objects as well as fluid according to a recent happening in Brooklyn, New York, and reported in the *Times*. Under the headline 'Unborn baby swallows bullet' came the story: 'Mrs Lucy Ortiz, 20, who was eight months pregnant, was standing at the open window of her apartment at about 1 a.m. on Tuesday morning. An unknown attacker fired a ·22 gun at her and the bullet entered the right side of her abdomen. Doctors were unable to find the bullet but when they X-rayed the child were astonished to find the bullet lodged in its stomach. They are still trying to decide whether the bullet would work its way out through the child's intestines or whether an operation will be necessary. Police are hunting the attacker. The mother is in fair condition.' (*Times*, 14 June 1968).

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