The physiological determinants of fetal growth

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There are good reasons why the main features of fetal growth are of concern to farmers and to physicians. The appearance of runts in a litter reduces productivity, and small-for-dates infants cause problems in obstetric management in about 4% of human pregnancies.

It is not easy to make quantitative measurements of intrauterine growth retardation. At present we are still limited in our ability to make accurate longitudinal studies, i.e. sequential measurements on the same fetus *in utero*. Direct measurements have been made in animals by application of radio-opaque markers or by temporary removal of the fetus for measurement. More recently ultrasound measurements of the diameter of the fetal head, or of the total fetal mass estimated from transverse B-scan sections at right angles to the longitudinal axis have offered an acceptable means of estimating fetal growth (Campbell, 1974). Yet it still is difficult to estimate the growth of different organs, other than by sampling a population of animals sequentially.

The functional development of different structures of the body proceeds at very different rates, both in different species and within a species. For instance, Avery (1974) pointed out the wide variation between species in the time of appearance of lung surfactant in the fetus, expressed as a proportion of normal term. As an example of the variation within a species she quoted the results of an examination of litters of rabbits on Day 28 of gestation. The body weights of rabbits in the same litter can vary by nearly 100%. The number of ossification centres was closely related to weight but lung stability on gaseous expansion was independent of body weight at this age.

Another problem that confronts the investigator is to determine whether, in any organ or tissue, decreased mass is related to a decrease in cell size or to fewer cells being present. This has been investigated extensively during the past few years (Mendes & Waterlow, 1958; Enesco & Leblond, 1962; Cheek, 1963; Winick & Noble, 1965). Widdowson (1971) quotes measurements on the kidneys of newborn pigs in which the runts had a body weight of 625 ± 114 (S.D.) g, compared with that of 1606 ± 142 g for their larger litter mates. The weight of the two kidneys in the runts was less than that in their litter mates (4.0 ± 0.5 g compared with 10.1 ± 2.1 g). These small kidneys had relatively less DNA and therefore fewer cells, and the lower protein:DNA ratio showed that the cells were also smaller in size. The long-term effects of diminished cell number on functional capacity in the adult require more detailed study. And in some organs, such as the brain, the presence of more than one type of cell gives rise to difficult problems in interpreting the measurement of cell numbers.

The data on human fetal growth, as in the excellent studies from Birmingham (McKeown & Record, 1953), suggest that weight gain falls during the last 4–6 weeks of gestation, though it increases after birth to the rate which obtained during the middle trimester. This has been taken to suggest that there might be a limitation to continued fetal growth *in utero*. That this is not an absolute limitation is shown by the continued growth *in utero* of fetal lambs suffering from a cyclopean defect, involving the hypothalamus, in which parturition did not occur at the normal time (Binns, James & Shupe, 1964). Such lambs, delivered alive by Caesarean section after 230 days gestation, may be more than double the weight of lambs delivered normally at term (~149 days). While it can be argued that the continued growth of these unusual lambs *in utero* was less than might have been anticipated from the rate of growth during the last third of normal gestation, there should be no doubt that these lambs were much larger than normal.

Hormones

In 1947 Jost came to the conclusion, as a result of experiments on rabbits decapitated *in utero* in mid-gestation, that fetal growth was relatively independent of the integrity of the head and hence

of the pituitary and thyroid glands. Similar experiments have been done on the rat, mouse and hamster, and there are a few accounts of human decapitation *in utero* with apparent continuation of bodily growth. The generalization that the fetal hypothalamus and pituitary are not necessary for normal growth has been challenged by the observations of Liggins (1974) and Thorburn (1974). Experimental ablation of the pituitary in lambs and calves results in a considerable reduction in limb size and retarded bone growth. Retardation of fetal growth has also been recorded in congenital lesions of the anterior pituitary in cattle (Kennedy, Kendrick & Stormont, 1957). In the rat, observations by Swaab & Honnebier (1973) showed that aspiration of the brain caused a consistent reduction in fetal weight at term, even though the pituitary was left intact. These and other observations have suggested to Liggins that the normal growth of the fetal rat is indeed dependent on the integrity of both the hypothalamus and the pituitary. It looks as if the question is open and more work is required on these small laboratory animals.

An analogy has been drawn between these experimental observations and spontaneous human anencephaly. Honnebier & Swaab (1973) have shown that the birth weight of human anencephalics is on average much below that of normal infants, when due allowance is made for gestational age and for the weight of the brain in the normal group. In the anencephalic the hypothalamus is usually absent; some pituitary tissue is normally present but systematic studies on fetal pituitary hormones are not available as an index of function. Anencephaly is often associated with other malformations and the data are therefore difficult to interpret.

Extensive investigations have been made on the role played by the thyroid in fetal growth. There is no doubt that the thyroid is necessary for full growth during pouch life in the marsupial in which there is little likelihood of any substantial amount of thyroid hormone reaching the infant via the mother's milk, as compared with placental mammals. Thus Hopkins (quoted by Thorburn, 1974) has shown gross differences in bodily development between control and athyroidal brush-tailed possums. Thyroidectomy in the fetal lamb results in gross developmental changes (Thorburn, 1974), but it is clear that the thyroid is less necessary in rats until the 2nd week after birth. Kerr, Tyson, Allen, Wallace & Scheffler (1972) studied the effect on the weight of fetal organs of ablating the thyroid in the rhesus monkey. They recorded not only a reduction in mean fetal body weight but also a fall in placental weight, and this demands further investigation.

Insulin, or perhaps pancreatic glucagon, also may be a principal determinant of fetal growth. Thus Hill (1974a) reported a case of pancreatic agenesis in which the twins were much under-weight at term. Similarly Heather Shelley (personal communication) has observed intrauterine growth retardation in fetal lambs treated with streptozotocin to cause β -cell ablation. In rhesus monkeys this drug also may cause growth retardation if the fetus survives (Cheek, 1975).

In summary, recent evidence suggests that pituitary and other hormones take an active part in controlling fetal growth but it is uncertain to what extent, if any, their function is disrupted in spontaneously occurring intrauterine growth retardation, or whether such conditions in animals and man are related to a defect in placental function.

More evidence is required to assess the part played by somatomedins (Van Wyk *et al.*, 1974), epidermal growth factor (Cohen & Taylor, 1974; Cohen & Savage, 1974) and nerve growth factor (Levi-Montalcini & Angeletti, 1968; Bradshaw, Hogue-Angeletti & Frazier, 1974; Levi-Montalcini, 1976) in both normal physiological development and in runts.

Animal models of intrauterine growth retardation associated with a reduction in placental blood flow

It is well known that some of the clinical conditions associated with small-for-dates babies involve a small or infarcted placenta or maternal hypertension. Aherne & Dunnill (1966) measured the exchange area of human placentae and found this to be proportionately very much reduced in pregnancies associated with small-for-dates infants. Growth retardation is also common in infants with a single umbilical artery. It is therefore natural to examine more closely situations in which maternal placental or fetal blood flow was restricted or to produce such restriction experimentally.

In 1967 the isotope-labelled microsphere method was introduced, and this made it possible to

measure simultaneously the blood flow to all the placentae in polytocous species such as the rabbit, as well as to the adjacent myometrium and other pelvic organs. Duncan (1969) observed in rabbits that runts, defined as being less than 2 standard deviations below the mean weight at a given gestational age, were commonly associated with a position close to the cervical end of the uterine horn. The more fetuses in the horn the more likely there was to be a runt and the lower was maternal blood flow to that placenta. There was no evidence of reduced flow to the myometrium adjacent to those placentae which had a relatively low maternal blood supply. So it seems unlikely that the phenomenon was due to a fall in pressure down the arterial arcade. The fact that implantation near to the cervix in the rabbit may be unfavourable can be compared with implantation in a bicornuate uterus in man, which also commonly leads to the development of a small-for-dates infant.

Table 1 gives a list of some of the experimental models which have been investigated in recent years. All have produced growth-retarded fetuses with evidence of defects similar to those naturally occurring in man. For instance, Hill (1974b) has compared the changes in organ weights of rhesus monkeys in which the secondary placenta had been tied off with those in human growth retardation from the data of Gruenwald (1963) and Naeye (1965). Over the spectrum of different organs growth retardation is similar. The brain is relatively spared while the weights of the liver and spleen are much reduced as compared with controls. It is worth noting that the fetal liver is an active metabolic organ lying right across the fetal supply line from the placenta (the umbilical vein).

Table 1. Some experimental methods used to cause intrauterine growth retardation

Reference	Species	Method
Wigglesworth (1964)	Rat	Tie uterine artery
Alexander (1964)	Sheep	Remove maternal uterine caruncles
Emmanouilides <i>et al.</i> (1968)	Sheep	Tie one umbilical artery
Creasy <i>et al.</i> (1973)	Sheep	Microembolism of maternal placenta
Hill (1974b)	Rhesus monkey	Tie interplacental vessels

These experiments suggest an approach to defining the mechanisms involved. It is uncertain whether diminished fetal growth, as a result of diminished blood flow to either side of the placenta, is attributable to a reduction in oxygen supply, in carbohydrate, amino acid or lipid supply from the mother, alone or in combination. We know that in man and experimental animals the fetus reacts to chronic hypoxaemia by a rise in packed cell volume. The metabolic consequences of fetal growth retardation have not been fully explored, even as to the control of intermediary metabolism.

Changes in the environment

Among the changes in the environment which can limit fetal growth are temperature, cigarette smoking and maternal starvation. One of the more interesting experimental models is that produced by heat stress during the last half of pregnancy in sheep, as encountered in South Australia (Alexander & Williams, 1971). The weight of the placental cotyledons was reduced by this treatment and birth weight was correspondingly less. Whether this was a causal association is not yet clear.

Maternal smoking has been associated with fetal tachycardia, and also with a substantial reduction in the proportion of time during which the fetus makes breathing movements (Manning, Wyn Pugh & Boddy, 1975). The reduction in fetal breathing is associated with the nicotine content of the cigarette rather than the rise in maternal carboxyhaemoglobin concentration. The phenomenon is probably due to a moderate degree of fetal hypoxaemia, consequent on maternal uterine vasoconstriction; this is consistent with animal experiments.

The effects of maternal starvation have been explored in experimental animals, and also as a result of conditions in Holland and in Leningrad during the Second World War. There is little doubt that a sufficient reduction in maternal food intake can reduce fetal size but the reduction has to be substantial. This is more an experimental tool for examining the ability of mother and fetus in com-

bination to cope with extreme conditions rather than a subject of practical clinical interest in Western Europe.

Chromosomal and immunological factors

Many congenital abnormalities are associated with a reduction in birth weight as well as anencephaly. A good example is Down's syndrome (mongolism); such infants tend to be born 1–1.5 weeks earlier than normal controls, but the birth weights are below expectation when compared with those of normal infants of similar gestational age.

There have been conflicting reports about the effect on pregnancy of antigenic differences between mother and fetus. Billington (1964) and James (1967) suggested that such differences might have an influence on placental and fetal growth, as a result of experiments using two strains of mice. Clarke (1971) was unable to confirm that previous immunization of the mother with paternal strain antigens led to an increase of placental size. On the contrary she found a reduction of fetal weight and litter size. These results have been repeated and extended in mice, hamsters and rats by Beer, Scott & Billingham (1975). The effects of in- and out-breeding between pure strains, and of prior maternal immunization were examined. The results appeared to vary with the strains and species used but one certain conclusion can be drawn from these and the other published data. This is that such experiments show a variation in fetal and placental weights which is relatively small compared with that encountered in naturally occurring animal or human runts. It was a very attractive idea that antigenic dissimilarity between mother and embryo might determine the magnitude of the decidual reaction and hence the subsequent development of placenta and fetus. The present evidence suggests that if this does occur at all (and as to that there is doubt) the effect is small.

Conclusion

As was to be expected, placental and fetal growth depend upon a large number of factors. Accurate sequential measurement of fetal and placental growth *in utero* is difficult. We have no test of any single placental function. Multiple pregnancy is associated with a reduction in placental and fetal size. Endocrine and metabolic factors interact in a complex fashion which is not fully understood. In some instances there is clear evidence that fetal growth can be limited by umbilical or maternal placental blood flow. Chromosomal or antigenic dissimilarities seem to play a minor role. Intra-uterine growth retardation continues to be important for the farmer and the obstetric physician and remains an intriguing intellectual problem.

And we may well wonder, with Widdowson & McCance (1975), whether there is a critical period of development when the size of an animal already attained determines its subsequent rate of growth, just as in some organ systems the chance to pass one critical phase of functional development may be lost for ever.

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