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SYMPOSIUM ON 'NUTRITION AND GROWTH'

Critical periods of growth

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There are many critical periods between conception, maturity and death and clearly in half an hour no one could deal with them all. I have, therefore, had to be highly selective and have confined myself to those periods of nutritional interest.

You must all be familiar with the percentile lines of human growth. Both weights and heights have been documented. These lines have now been extended backward into foetal growth by weighing material obtained from well dated abortions and from living foetuses by ultrasound techniques. These lines are really nothing more than cross-sectional growth curves and there are several reasons why any single child should not grow smoothly along the line on which he can be placed when first seen.

One reason is genetics, and this is a very interesting and important aspect of the subject, but it need not detain us just now. A second is sickness, for if each of the percentile lines is taken to represent the growth of a healthy child, and that child falls ill with any one of a number of unwelcome diseases, its growth is very likely to falter. The child's weight will then fall below the particular percentile line that it has been following. A third is nutrition, for if a child does not get enough food for any reason, it will certainly fail to grow along its percentile line. If the trouble is corrected—whether it has been a genuine shortage or merely bad management—and the child can be given an abundance of a good diet, it will begin to eat approximately what one would expect for its size (not its age), gain weight faster than its fellows of that age and rejoin its original line of growth. This is what has been termed 'catch up' growth (McCance & Widdowson, 1974). If the child's desire to eat does not fall off after it has rejoined its weight curve it may go above it, at least for a time, but overeating is most unlikely to make it exceed its height curve, unless it has been destined to do so genetically.

'Catch up' growth, or compensatory growth, is a common enough event in animal husbandry, for food supplies tend to vary from one time of year to another. The husbandman is always torn between the dictates of physiology and of economics, and the gains in weight of growing animals are often much less in

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seasons of hunger than in those of plenty when the animals are likely to show their compensatory growth.

If rats are undernourished after weaning, they invariably show 'catch up' growth if they are fed to capacity later, but whether it is complete or not depends upon its timing and duration. Pigs and guinea-pigs behave similarly if experiments of the same nature are made upon them after birth and the phenomenon of 'catch up' growth is so familiar to everyone interested in nutrition or growth that it requires no further discussion at the moment (McCance & Widdowson, 1974). We shall return to the completeness or otherwise of 'catch up' growth later.

If, however, two litters of rats born on the same day are mixed up together and suckled by one of the dams in a small group or three, and in a large group of eighteen or so by the other one, the ratlets suckled in the small group will be two to three times the size of the others at weaning. If now all the rats are offered an unlimited and fully. satisfactory diet, the small ones do not catch up or show any signs of doing so.

Why not? This is what I hope to explain in the rest of this talk, but first a short digression on developmental timing.

There are certain milestones of development that are well known. Baby cuts its first tooth; kittens open their eyes and one can watch it happening—but baby's were open at birth. These events are quite strictly clocked from the date of conception, and can be used to indicate the stage of development an animal has reached. Not so the date of birth, which, though equally well 'clocked', bears little or no relationship to the stage of anatomical and physiological development the young have reached when birth takes place.

So far as the development of the nervous system is concerned, birth may be regarded almost as an incident, and Flexner (1955) writing about the critical time for the initiation of cortical function in mammals, calculated that stages of development which took place in the pig and guinea-pig at about the beginning of the last third of gestation only took place at about 10 d after birth in the rat. The integration and commencement of hypothalamic function would be expected to precede these times, and one would expect from the above, moreover, that alterations in behaviour brought about by the treatment of rats after birth would only be brought about in pigs and guinea-pigs by the appropriate treatment before birth, and this has now been shown to be the case.

The rate of growth of the foetus depends upon its genetic endowment and its supply of nutrients. These can only reach it through its blood supply. In some species, of which the guinea-pig is one, the supply depends upon the nutrition of the mother, and large or small offspring can be produced by varying the amount of food provided for the pregnant dams. In other species nature sometimes makes a similar experiment for us, for if the blastocyst, derived from one of a large number of the ova discharged, imbeds in a part of the uterus where the supply of blood is poor, the foetus will get fewer nutrients through the placenta, and not grow as fast as one whose blastocyst has imbedded in a more favourable position. This happens sometimes in mice (McLaren & Michie, 1960) and is a well known phenomenon in pigs. We have used guinea-pigs and pigs for our experiments and in both species we have obtained the expected results; i.e. no 'catch up' growth (McCance & Widdowson, 1974; Widdowson, 1971) if one of the newborn in a litter is very much smaller than the others. We are forced to conclude that there is a critical period of growth in all animals when the centres in the hypothalamus that control the drive to eat are being organized neuronically to conform with the size (or perhaps the metabolic rate) of the growing organism at that time. Thereafter, the responsibility of appetite, whether conscious or unconscious, is to ensure that the intake of nutrients is sufficient for the animals' size, growth rate and activity. This is likely to be about the fifth day after birth in rats. Pigs and guinea-pigs, therefore, born smaller than their litter-mates, and rats, made small by limiting their intake of nutrients during suckling, eat according to their size and activity and have no abnormal feelings of hunger. The small ones therefore, grow up, but they do not catch up (Widdowson & McCance, 1975).

Interesting confirmation of the timing of these critical periods in rats and human beings has come about since Flexner was writing (1955). Dörner, an East German anatomist has worked out the time during growth when the hypothalamic nuclei and tracts are being developed and taking over their functions. He finds it to be from the fourth to seventh month of foetal life in man and roughly the first 10 d after birth in the rat (Dörner & Staudt, 1972). He has produced statistical evidence, moreover, that men conceived and born during times of 'affluence' are heavier for their height than those born during a period of privation (Dörner, 1973, 1974). The fifth day after birth is certainly a very critical one in the development of the hormonal responsibilities of the hypothalamus in rats, for the injection of one minute dose of testosterone at that date into a female will alter its sexual behaviour for the rest of its life (Barraclough, 1961; Harris, 1964; Harris & Levine, 1962).

One interesting point remains (McCance, 1976). Were these small rats, pigs and guinea-pigs undernourished? They may have been, but they showed none of the physiological criteria of it. They were not over-hungry; they showed no sign of 'catch up' growth; they behaved as though they were genetically small, slow growing, but perfectly proportioned animals (McCance, 1976). The matter requires thought, but the whole thing seems to be something new to physiology.

There are critical periods of growth in later life also. Puberty is one of these and one interest here lies in the fact that sexual maturity does not depend upon chronological age but upon the body attaining a certain mass and composition. The secular trends in height and weight, whatever may be causing them, taken with the fall in the average age of menarche to less than thirteen years both point to this and so does considerable statistical evidence (Frisch & Revelle, 1971 *a,b*; Frisch, Revelle & Cook, 1973).

Malcolm (1970 *a,b*) has published a very instructive study of an upland tribe in New Guinea, and compared their mean growth curves with those of British children. His curves show the following features: (1) the British boys and girls grew much faster than the Bundi children; (2) they reached sexual maturity about 5 years earlier. The Bundi girls in fact did not begin to menstruate till their mean

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age was between 18 and 19 years; (3) the British children reached their maximum height and weight some time before the Bundi children; (4) the mean heights and weights of Bundi of the same age were then considerably below those of the British, but the former went on growing for some years, the men till they were about 24 years of age. They were, however, still below the British in height and weight when growth ceased; (5) the Bundi females fared relatively better than the males. This is the usual result in undernourished animals, and rehabilitation does not equalize matters.

If rats are undernourished after weaning from say 9th to 12th weeks after birth they invariably show 'catch up' growth and the 'catch up' growth will be complete. This is not so, however, if the undernutrition has lasted from 3rd to 12th or later week, certainly not in the males. Indeed, the longer one keeps animals undernourished the less complete the 'catch up' growth becomes. The same is found with pigs (McCance & Widdowson, 1974). Growth always starts off vigorously enough but, as time goes on, the sooner the upsurge in weight begins to level off. The Bundi children were never well enough nourished to show any sign of catching up the British children before the latter were 18 years of age, but why did they not go on growing after the British children had stopped, and ultimately attain the same height and weight? Someone may reply by suggesting that the Bundi may have been genetically smaller, or that, maybe, they could not go on growing after their epiphyses had fused. There is more to it than that.

Ross (1959; 1961) carried out some experiments with rats which gave us the answer, or may do. He worked with a highly inbred colony of pathogen-free rats. One group he kept on the control diet from weaning, which had been designed to give the fastest growth attainable. At the same time another group was given a poorer diet, so far as protein and energy were concerned, but was otherwise completely satisfactory. On this diet the rats grew more slowly. They went on growing, however, after the others had stopped, but they never attained the same size although their average life span was prolonged. The controls died earlier, and this was probably because the diet that gave the fastest growth was not the right diet after maturity (Miller & Payne, 1968). The failure of the slow growers to attain their full genetic stature was unlikely to be due to the epiphyses undergoing fusion, for the epiphyses in rats never really fuse. These rats, however, were very old animals before they stopped growing, and we suggest that the cessation of growth was but one of the aspects of age. There must come a time in the life of every warm-blooded mammal when it can grow no more, and one must always remember two things about growth. Firstly, the rate of cell division falls off steadily from conception and ceases at a certain chronological age which is peculiar to each species, and perhaps organ also. Secondly, it is always the later stages of growth which are the first to fail.

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