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SYMPOSIUM ON
'ANIMAL MODELS FOR THE STUDY OF HUMAN NUTRITION'

Animal models for growth

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The translation of nutrients into increased body mass is achieved in different ways by different organs and organisms. The dimensions to which the bodies of vertebrates grow can be classified as determinate or indeterminate. Determinate types include higher vertebrates in which a species specific stature is attained more or less at the time of sexual maturity. Many of the lower vertebrates have indeterminate body sizes. They may continue to grow throughout life, some of them reaching the impressive proportions of certain big game fishes, giant tortoises, or dinosaurs. Even those forms that stop growing seem to retain at least the capacity for further enlargement, something that is not possible in birds and mammals.

One may ask why these different modes of growth exist. There are two answers, the proximate and the ultimate. The proximate explanation relates to the developmental and physiological factors responsible for the programmed cessation of growth when body size is predetermined. The ultimate answer seeks to understand why one or the other type of growth evolved in the first place. Proximate answers can sometimes be found in experimental results. Ultimate ones arise from intelligent speculation.

Proximate explanations

Higher vertebrates are characterized by the limited sizes to which they can grow. This is correlated with the fact that some, but not all, of their organs lose their capacities for potentially unlimited growth sometime in the course of maturation. Early attempts to classify the organs and tissues of the body according to their potentials for growth used mitotic activity as a criterion (Bizzozero, 1894). Mitotically static tissues are those which lose the capacity for cellular proliferation early in development presumably because their pool of stem cells is depleted by

differentiation. Nerves and striated muscle fall into this category. Expanding organs, represented by many of the body's endocrine and exocrine glands, grow by cell division until they have expanded to meet the needs of the adult body, after which they remain mitotically quiescent unless compensatory hyperplasia is elicited by partial resection or increased functional demands. Renewing tissues undergo cell division throughout life, their germinative compartment replenishing cells as fast as they are lost from the differentiated compartment. However useful this classification may have been over the years, its usefulness in understanding the strategies of growth is limited by the fact that increasing the numbers of cells does not necessarily enhance the physiological efficiency of an organ to optimal levels. For example, the kidney is capable of hyperplastic responses in compensation for contralateral nephrectomy, but this does not augment the number of nephrons, and is not so efficient a mode of growth as might otherwise have been the case if mammals retained the capacity to generate new renal nephrons throughout life.

Accordingly, it is appropriate to reclassify the tissues and organs of the body in terms of their functional units (Goss, 1966, 1978). A functional unit may be defined as the smallest irreducible structure still capable of performing those specialized functions for which an organ may be adapted. In many instances, the cell itself is the functional unit (e.g. blood cells). In other cases, certain subcellular organelles, such as the sarcomere, is the functional unit of the tissue. There are still other organs in which the functional unit is a histological entity, made up of a number of cells that can perform their specialized physiological functions only as a team. These include follicles, acini, nephrons, alveoli, etc. If one classifies parts of the body according to these criteria, it is possible to determine which organs retain the capacity not only to grow in adult animals, but to do so in such a way that functional efficiency is increased as much as is the mass of the tissue. From this point of view, a determinate organ may be defined as one which loses the ability to augment its population of functional units prior to maturity, however capable it may be of cell division or cell hypertrophy. Its physiological potentials are thus limited by reduced capacities for growth. Indeterminate organs, on the other hand, are those which retain the lifelong potential for multiplying their functional units, and are therefore capable of unlimited regenerative capacities, both morphological and physiological.

Animals with determinate body sizes possess a combination of determinate and indeterminate organs. It is not known whether their limited growth is attributable to the inability of certain parts to grow indefinitely, or if their component organs cease to grow because the body as a whole does. Statural growth of birds and mammals ceases when the cartilaginous plates of their long bones disappear. Lower vertebrates lack such structures, as a result of which their skeletal elements are potentially capable of unlimited elongation.

As mentioned above, the mammalian kidney cannot increase its complement of nephrons beyond the number produced early in development. Compensatory renal growth is achieved by cell division and enlargement, resulting in an increase in the dimensions of each nephron, but not their numbers (Nowinski & Goss, 1969).

Although this mode of growth makes it possible for the hypertrophic kidney to restore the excretory needs of the organism, it is clearly not the optimal response to the demands for increased renal function. Lower vertebrates, however, seem not to outgrow their capacity for nephrogenesis. Not only is the population of nephrons proportional to the size of the body, but, in fishes at least, it is correlated with physiological demands. More nephrons develop in fishes living in fresh water than in the same species raised in a marine environment (Ford, 1958). The nephrogenic capacities of mammals may not be as limited as was once thought, in view of the production of supernumerary nephrons in unilaterally nephrectomized infant rats and mice (Bonvalet, 1978). On the other hand, less than the normal complement of nephrons is produced in rats born to malnourished mothers (Zeman, 1968).

The heart is another organ in which the capacity for regeneration is conspicuous by its absence in higher vertebrates (Alpert, 1971). Although the cardiac ventricles are capable of considerable hypertrophy in response to vascular resistance, this is achieved solely by the enlargement of existing muscle fibres, not their multiplication. Although the numbers of myofibrils and sarcomeres may increase in the hypertrophic heart, their augmentation is limited by the maximum dimensions to which a heart muscle fibre can grow without stretching its supply lines to the physiological breaking point. In the absence of stem cells (cardiac muscle lacks satellite cells), and of the capacity for differentiated cardiac muscle fibres to divide, the hearts of higher vertebrates are singularly limited in their compensatory capabilities and seem intentionally vulnerable to cardiac insufficiency. Such is not the case in fishes, whose hearts not only grow to keep pace with the enlargement of the body as a whole, but do so without resorting to cellular hypertrophy. The diameters of ventricular fibres in fishes are the same from small fry to the largest trophy specimens and in amphibians, the heart has been shown to be capable of regenerating new ventricular muscle following its partial resection (Oberpriller *et al.* 1979). There is evidence that in these forms myocardial fibres are capable of cell division despite their differentiated states, as well as the possibility that undifferentiated cells may persist as a source of new muscle fibres.

The skeletal muscle fibres of mammals are almost as incapable of proliferation as are their cardiac muscle fibres (Mauro, 1979). Their growth is achieved by hypertrophy, coupled with the augmentation of their nuclear populations by fusion with mononuclear cells believed to be derived from satellite cells. Although some regeneration may be possible under conditions of extreme injury, there is little evidence for the multiplication of skeletal muscle fibres in the adult, except perhaps as a result of occasional longitudinal splitting. In fishes, skeletal muscle fibres increase in number throughout life (Luquet & Durand, 1970). This creates an interesting problem that mammals and birds are not faced with, namely, the need for the nerve supply to keep pace with the population of muscle fibres. How this may be achieved remains to be determined, but one wonders if lower vertebrates might have retained the capacity for neurogenesis throughout life.

It is axiomatic that birds and mammals cannot replace missing nerve cells, and that the regeneration of fibres is limited to the peripheral nervous system. In

contrast, lower vertebrates are endowed with greater capacities for plasticity in their central nervous systems. Not only can they regenerate missing segments of their spinal cords, but some of the amphibians can also differentiate new spinal ganglia in the course of regenerating missing tails (Goss, 1969). The brain itself must keep pace with somatic enlargement in animals with indeterminate body size. Not surprisingly, therefore, DNA synthesis has been found to continue in the brains of adult fishes, albeit at a progressively diminishing rate (Richter & Kranz, 1971). Even the retinas of fishes expand by the addition of new photoreceptors at their margins (Blaxter & Jones, 1967). This is in marked contrast to the poor capacities for growth and regeneration that prevail in the mammalian brain, not to mention the latter's susceptibility to retardation under conditions of prenatal malnutrition (Zamenhof *et al.* 1971).

Ultimate explanations

Given the fact that mammals are so poorly endowed with growth and regenerative abilities compared with their vertebrate ancestors, it is challenging to contemplate how this discrepancy may have come about. In higher vertebrates, there are a number of organs in which the proliferation of functional units is turned off at some predetermined stage of development (Goss, 1966). This occurs first and earliest in the case of the central nervous system. Heart and skeletal muscle fibres cease to multiply shortly thereafter. The kidney may continue to add nephrons into the early postnatal stages in some species, and pulmonary aveoli differentiate for even longer periods. Similarly, the testes lose the capacity to differentiate new seminiferous tubules, and the small intestine stops producing villi. It is curious that a significant number of these determinate organs are so vitally essential to survival, in contrast to many of the glands which are of less importance to the organism but possess greater capacities for growth and regeneration. One can only conclude that this pattern of growth distribution has evolved for the benefit of the species, if only to insure our ageing and ultimate demise.

If lower vertebrates are indeed capable of potentially unlimited growth, one wonders if they are as susceptible as birds and mammals to senescence (Goss, 1974). Although they may die from infections, predation, or starvation, it is not clear whether or not lower forms undergo the kind of programmed ageing that characterizes higher vertebrates. It is conceivable that ageing as we know it is a consequence of our lack of bodily growth beyond maturity. Unable to make up for the inexorable loss of functional units in vital organs, the bodies of birds and mammals undergo an accelerated depreciation that reduces the margin for safety that is built into all organs. Since lower vertebrates do not suffer from a net attrition of functional units, they are potentially capable of living as long as they grow, perhaps because they can grow as long as they live.

What are the selective factors that may have been responsible for these changes in growth capacity during the course of vertebrate evolution? First and foremost, the transition from indeterminate to determinate body size seems to have been correlated in general with the adoption of a terrestrial habitat. Land animals

increase in mass at their own risk. Without the bouyancy of an aquatic environment, their bodily bulk necessitates stronger skeletal parts and is correlated with increased nutritional requirements. Perhaps it is significant that the world's largest mammals are the ones that have become secondarily aquatic. Conversely, a lack of body growth control would have been incompatible with the evolution of vertebrates adapted to an aerial existence.

It is no coincidence that those vertebrates with determinate body sizes are also warm-blooded. Whatever may be the advantages of being homoeothermic, elevated metabolism necessitates a rate of food consumption unparalleled by our cold-blooded ancestors. Although large mammals have the advantage of being able to conserve body heat, they must also consume large quantities of food. Such a nutritional intake would lead to prodigious rates of growth if mechanisms for holding this in check had not evolved.

It was probably the warm-blooded condition that enabled evolving vertebrates to develop enlarged brains and the intelligence of which they are capable. This is believed to have been a factor that may have outweighed the retention of regenerative abilities, at ·least in the central nervous system (Elder, 1979). Intelligent animals can also avoid injuries and are less at the mercy of their environment. It could be argued that it is better not to be injured in the first place than to be able to repair vulnerable organs. Indeed, man's relative lack of regenerative potential cannot be so bad when one considers that we outlive practically all other vertebrates.

REFERENCES

Alpert, N. R. (1971). *Cardiac Hypertrophy*, New York: Academic Press.
Bizzozero, G. (1894). *Br. med. J.* i, 728.
Blaxter, J. H. S. & Jones, M. P. (1967). *J. mar. biol. Assoc.* **47**, 677.
Bonvalet, J. P. (1978). *Yale J. Biol. Med.* **51**, 315.
Elder, D. (1979). *J. theoret. Biol.* **81**, 563.
Ford, P. (1958). *Can. J. Zool.* **36**, 45.
Goss, R. J. (1966). *Science, N.Y.* **153**, 1615.
Goss, R. J. (1969). *Principles of Regeneration*, New York: Academic Press.
Goss, R. J. (1974). *Perspect. Biol. Med.* **17**, 485.
Goss, R. J. (1978). *The Physiology of Growth*, New York: Academic Press.
Luquet, P. & Durand, G. (1970). *Ann. Biol. Anim. Biochem. Biophys.* **10**, 481.
Mauro, A. (1979). *Muscle Regeneration*, New York: Raven Press.
Nowinski, W. W. & Goss, R. J. (1969). *Compensatory Renal Hypertrophy*, New York: Academic Press.
Oberpriller, J. O., Bader, D. M. & Oberpriller, J. C. (1979). In *Muscle Regeneration*, p. 323 [A. Mauro, editor]. New York: Raven Press.
Richter, W. & Kranz, D. (1971). *J. Hirnforsch.* **13**, 109.
Zamenhof, S., van Marthens, E. & Grauel, L. (1971). *J. Nutr.* **101**, 1265.
Zeman, F. J. (1968). *J. Nutr.* **94**, 111.