Catch-up growth

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SUMMARY

Catch-up growth, defined as growth velocity above the statistical limits of normality for age or maturity during a defined period of time, is distinguished from compensatory growth since it makes up for a potential loss rather than an actual loss and is seen in the whole body as opposed to specific organs. The cellular explanation for catch-up based on the work of Winick is described and a recent challenge to this explanation is briefly discussed. The mechanism of mismatch between actual size and 'planned' size suggested by Tanner is described and tested. In a series of experiments conducted in rats of different ages the degree of mismatch and the role of catch-up are compared for two different parameters, body weight and nose-rump length. It was found that the two parameters behaved differently and it is suggested that while the concept of mismatch is still acceptable the idea of a single central mechanism is not supported. It is suggested that the mismatch mechanism is a cellular phenomenon.

INTRODUCTION

Catch-up growth is a term introduced by Prader, Tanner & von Harnack (1963) to describe the increased growth velocity which occurs in children after a period of growth retardation when the cause of the growth retardation is removed. Catch-up growth may be defined as a growth velocity above the statistical limits of normality for age or maturity during a defined period of time (Williams, Tanner & Hughes, 1974a). The effect of catch-up growth is to take an organism towards, or in favourable circumstances right onto, its original pre-retardation growth curve. In the former case catch-up is said to be incomplete; in the latter, complete.

The phenomenon has been recognized since at least 1914 when Osborne & Mendel reported that during refeeding after undernutrition, rats increased their body weight at a rate equal to or greater than that expected for their size. Bohman (1955), describing the same phenomenon in cattle after different feeding regimes, employed the term 'compensating growth' since the extra growth compensated for the lack of earlier growth. The term 'compensatory growth' is still used by some workers describing catch-up growth. The term 'compensating growth' is however commonly used to describe the type of growth that occurs after the loss of an actual mass of tissue and may be viewed...
Fig. 1. Possible outcome of removing a growth decreasing, $d$ or increasing, $i$ stimulus. The normal growth target is $b_2$. If the alteration of the growth rate is maintained then in the case of an increase the organism will reach the size target $b$ at the 'wrong' time 1 or at the 'correct' time the organism will be 'too large' $c_2$. If the growth rate is decreased then the organism will be 'too small' at the 'right time' $a_2$ or the organism may attain the 'correct' size at a later time $b_3$. The broken lines show catch-up and catch-down. In these cases the growth rate 'compensates' bringing the organism onto the original growth curve.

as being controlled by a simple feedback mechanism working on physical mass or physiological load. Catch-up growth on the other hand is rapid growth which 'compensates' for the loss of potential tissue and cannot be accounted for by a simple feedback mechanism. In a more abstract manner compensatory growth depends on an alteration in spatial parameters and catch-up is a response to an alteration in a temporal parameter.

In animals that attain a final adult size and cease growing before death a size target can be defined in terms of size attained at a specific time. The organism thus has a growth programme, it must reach a certain state at a certain time.

If growth is inhibited then the growth pattern or programme is altered and Fig. 1 indicates the various ways in which a time course might be changed. The target may be reached at a different time (growth delay), growth may cease at the target time thus giving rise to a small adult or the pattern may change so that the organism reaches the normal target on time, this last is catch-up. If the organism has a growth programme which responds to growth inhibition it should also respond to growth stimulation, i.e. catch-down. This is observed in the new born human where children who are born large for gestational age 'lag down' to the normal within the first year of life (Smith et al. 1976).

It is generally stated that the earlier the onset of inhibition the more long
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lasting and severe will be the consequences (Widdowson & McCance, 1960). It is also clear that the greater the deprivation the greater the period required for recovery and that the longer the growth inhibition goes on the greater will be the gap between the experimental and the control groups. Catch-up may be complete or incomplete and this seems to depend on the amount of time available for recovery and the degree of growth retardation that occurs. Failure to show complete catch-up may also be related to the mechanism for inducing the growth inhibition. Catch-up does not follow growth arrest produced by cortisone (Mosier, 1971). In catch-up after undernutrition the animals utilize food more efficiently (Miller & Wise, 1976) but after growth retardation due to cortisone rats show a ‘persistent decrease in gross energy efficiency’ (Mosier, 1972). Other workers however find complete catch-up in cortisone-treated rats (Mitchell, Barr & Pocock, 1978).

Following the observation of Widdowson & McCance (1963) that recovery after growth retardation depended in part at least on the age of onset of the malnutrition, Winick & Noble (1965, 1966) and Winick, Fish & Rosso (1968) undertook a series of studies to examine the cellular basis of this response.

Winick’s experiments were based on the earlier study of Enesco & Leblond (1962) which examined cellular aspects of growth. These workers measured the amount of DNA present at different ages in various tissues of the rat. In addition they measured organ and tissue weights and were thus able to produce an index of cell size i.e. weight per unit DNA. With the knowledge that each cell contained 6.2 pg of DNA they were able to calculate the number of cells. Enesco & Leblond reported that during early development the number of cells (= amount DNA) increased rapidly and then more slowly. They also found that cell size showed nearly continuous increases in most tissues, such as muscle and epididymal fat. In most organs the increase in cell size was distinctly observed only between 17 and 48 days of age. They summarized their findings thus: ‘Until about 17 days of age growth of organs and tissue is due to rapid cell proliferation with little or no change in cell size. Between about 17 and 48 days of age cell proliferation continues in all locations but at a slower rate than in the early period. Meanwhile, cell size increases in most organs and even more so in tissues. Finally after 48 days, cell proliferation slows down or even stops, while cell enlargement proceeds in most tissues but is slight or absent in organs.’

From a series of similar studies Winnick & Noble (1965) concluded that normal growth is partitioned into three periods: cell division alone; cell division with concomitant cell enlargement; and cell enlargement alone with no further increase in the number of cells. The age span of these periods varies for individual organs, but before weaning all organs grow primarily by cell division. Between weaning and about 65 days of age, beginning in the brain and lung, the pattern shifts. After 65 days growth in all organs is due primarily to cell enlargement. From these observations Winnick & Noble
argued that 'the effect of any stimulus on growth inhibition may, therefore be time dependent'. They then examined the effect of undernutrition during suckling, from weaning to 42 days of age and from 65 to 86 days, with the severity of the malnutrition being kept relatively constant by maintaining the body weight without any weight gain. They reported that caloric restriction prevented the normal increase in weight, total protein and RNA in all groups of animals regardless of the time of onset of malnutrition. DNA however was only affected in the period before it had ceased to increase. There was no recovery after refeeding in those organs where cell division had been curtailed. They concluded that caloric restriction resulted in curtailment of normal growth no matter when the onset but that the effect could only be reversed if cell division had not been affected. Growth failure observed with malnutrition may thus be of two types dependent on the age of onset. Reduction in cell numbers results in permanent stunting whereas reduction in cell size results in recovery of normal size after refeeding.

The explanation for the greater severity of early undernutrition is that tissues have a finite cell number and that this is reached before the adult size. Thus growth is made up of two different phenomena, an increase in cell numbers and separately an increase in cell size. This principle has recently been challenged. Sands, Dobbing & Gratrix (1979) have reported that cell size measured as protein per unit DNA increases much earlier than had been described previously and quickly reaches a steady value. They further reported that cell multiplication continues unabated throughout tissue growth until growth itself comes to an end.

Although this challenge needs to be confirmed the consequences are of interest. The figures of Sands et al. (1979) only show total DNA but it seems likely that the plot of rates of accumulation or rate of synthesis would be like that shown in Fig. 2. If it is assumed that growth retardation inhibits DNA synthesis then the block is represented by the area a, b, c, d, in Fig. 2. To finish with the same number of cells as the control in the same period of time an increase in the rate of synthesis is needed and this would be most effective soon after growth restarts. These predictions of the rate of cell replication are identical to the theoretical curve of catch-up shown by Forbes (1974). Failure to catch-up completely may be due to too little time or too great an insult. Further, since cell replication and DNA synthesis can be inhibited at a number of points in the synthetic pathways failure to catch-up may be due to different sites of action of different inhibitors, (e.g. cortisone).

Malnutrition during the suckling period is not however a source of irreversible reduction in cell numbers. The adult body size of children born during the Amsterdam famine in 1945 now show a normal distribution and when rats raised in large litters until day 9 of age were suckled in small litters the number of cells returned to the normal by day 21, (Winnick, Fish & Rosso, 1968). Even more surprising perhaps is the 'catch-up' in cell numbers but not cell size.
observed in rat fetuses from undernourished dams. These rats are born with normal total body DNA but with 25% reduction in body weight and total body protein (Williams & McAnulty, 1976). It may be that there is a critical time by which the total cell number must be reached and that in the examples sited here that time had not been reached.

Using the clinical cases reported by Prader et al. (1963), Tanner (1963) proposed a generalized mechanism to describe the events occurring during catch-up growth. Tanner’s model was based on self-stabilizing systems. Essentially the model required two components, a ‘flight plan’ and a method for determining position. Tanner’s supposition was that in the normally developing central nervous system a substance accumulated, or some cells matured, in a manner that traced out the brain’s growth curve, and this was called the ‘time tally’. Tanner further suggested that body growth is represented by some hypothetical substance called ‘inhibitor’. The normal velocity of growth was thought to be proportional to the ‘mismatch’ between the two signals, in other words to the ‘gap’ in growth advancement between the CNS and periphery. Tanner also suggested that the effects of growth retardation were age dependent. In the case of early retardation the CNS is not mature and the ‘time tally’ is altered in such a way that the gap can never be fully bridged and catch-up is
Fig. 3. Growth retardation during the suckling period followed by ad lib feeding from weaning at three weeks. Top panels show distance curves and the lower panels show growth velocity curves. The figures on the left show nose-rump length and the figures on the right show body weight.
incomplete. In the situation where catch-up is complete Tanner suggests that the CNS has matured and the 'time tally is fixed'. Although radiation of the brain has been reported to reduce growth (Mosier & Jansons, 1970) and it has been suggested that the appetite centre may be of importance in catch-up (Widdowson & McCance, 1975) there is no convincing evidence for the time tally in the CNS. In the period since Tanner suggested this hypothesis many growth-stimulating factors have been reported but few inhibiting agents.

A series of growth studies carried out in Tanner's laboratory have been analysed to examine parts of Tanner’s hypothesis (Williams et al. 1974a, b; Williams & Hughes, 1975; Williams & McAnulty, 1976; Williams & Hughes, 1978).

**MATERIALS AND METHODS**

Three different age groups of animals were used to represent different normal growth rates and different degrees of maturation at the onset of undernutrition. The period of growth retardation was always three weeks.

The first group of animals were undernourished during suckling. This was brought about by using large (16 pup) and normal (8 pup) litters. The animals in the larger litters all survived well but were smaller.

Growth arrest was also introduced, in different groups of animals, at three weeks and at seven weeks of age. The rationale for the times was that many tissues would be producing cells predominantly during the suckling period, that during the three-week period following weaning a peak of body weight growth occurred and it was assumed that both cell number and cell size were increasing.

The group subject to zero growth after seven weeks should have made most of their cells and the subsequent catch-up would be due to cells 'filling up'. After the three weeks of reduced- or zero-growth animals in all groups were provided with food *ad lib.* Body weight, nose-rump length, and skeletal maturity were measured in the same animals throughout the experiments, i.e. they were longitudinal studies. The studies were terminated at 228 days at which time all of the animals showed 98% bone maturity.

**RESULTS AND DISCUSSION**

The figures 3, 4, 5, show the effects of undernutrition at the various ages, in male rats. Table 1 shows the percentage mismatch at the end of each period of growth retardation on both male and female rats.

The percentage mismatch is always greater for body weight than for body length. Table 2 shows the time taken for male and female rats that have been undernourished at different ages to catch-up to their respective controls.

In the case of the male animals from large litters complete catch-up was not seen. Table 3 shows the rate of recovery.

Differences between the tissues and the sexes are quite clear. Body weight shows the greatest mismatch during the period 21–42 days, the period in which
Fig. 4. Growth retardation for three weeks from three weeks of age followed by ad lib feeding. Top panels show distance curves and the lower panels show velocity curves. The figures on the left show nose-rump length and the figures on the right show body weight.
Fig. 5. Growth retardation for three weeks from seven weeks of age followed by ad lib feeding. Top panels show distance curves and the lower panels show velocity curves. The figures on the left show nose–rump length and the figures on the right show body weight.
the normal body weight shows the greatest rate of increase (Figs 3–5). The sex difference in the degree of mismatch is only evident in the oldest group of animals in which the sexual difference in growth is clearly established. Sex differences in the time taken to achieve complete catch-up are most marked in the younger animals. The rate of recovery is faster in the male for nose–rump length but the female shows the fastest rate of recovery for body weight.

In Fig. 6 the velocity of catch-up is plotted against the degree of mismatch, according to the hypothesis these two measurements should be directly proportional and would therefore fall on the same line. The data for the nose–rump length appear to fall on a straight line whilst those for body weight do not. The mismatch hypothesis seems to hold for the nose–rump length but not for the body weight.

Since the two parameters, nose–rump length and body weight within the same animal behave differently it seems unlikely that a single central signal or substance or mechanism controls the phenomena of catch-up growth.

Although only body weight and nose–rump length are shown there are several cases of tissues catching up at different rates, e.g. tail and body length (Williams et al. 1974a), and different muscles (Dickerson & McAnulty, 1975). While
catch-up appears to be a whole body response the parts of the body seem to respond in an individual manner. Further, different tissues and organs have their normal peak growth spurts at different times. Where it has been examined in some detail (Williams & Hughes, 1975) the spurt of growth following a period of undernutrition was found to be greatly influenced by the normal pattern of growth velocity. If catch-up growth started at a time when the natural growth pattern was declining the subsequent growth rate was less than when catch-up began on an upsurge in the normal pattern of growth.

It seems then that while Tanner's idea of comparing the actual size with the programmed size may still be acceptable some other features of his thesis such as the time tally being in the CNS and the rate of catch-up being directly related to the period and intensity of the insult are now less likely.

There have been several attempts to relate the rate of normal growth and of catch-up to substances, especially hormones or growth factors (Mosier, Dearden, Jansons & Hill, 1978) in the blood but none of these correlate significantly with the rates of growth that together make up the growth of the body.
Lieber (1977) has proposed a model in which information regarding the body mass is supplied to the CNS by a 'humoral radar system' employing an insulin-like molecule as a signal. The intensity of the signal would vary as a function of the organism's total adipose cell surface area. While such a system is attractive in relation to body fat and perhaps via appetite control to total growth it does not deal with the problem posed here or by any growth study where the parts of the whole grow at different rates.

The analysis described here appears to show that there is no single mechanism regulating catch-up.

The alternative to this is a number of mechanisms. The most feasible system would be at the tissue level, with the regulation in some or all cells. This view is in accord with the increasing number of tissue-specific growth factors (Nero & Laron, 1979) and is supported by Winick's studies. The various tissues may be co-ordinated by permissive hormones such as somatotropin (growth hormone).

Completeness of catch-up depends on the normal or control. In rat experiments different workers have used different normal litter sizes and different end points. The male rats described above caught up in length but not weight. Rat experiments are also complicated by alterations in the rate of maturity (the time tally) (Williams et al. 1974a). The animal data is further complicated by age effects which must influence these often long experiments.

In the human cases complete catch-up is said to be achieved when the child reaches its predicted size or a normal size for the population. The situation is complicated by the likelihood that different growth-retarding agents behave differently e.g. cortisone. In general, in incomplete catch-up growth, cessation occurs before complete catch-up can be achieved, and this growth arrest is often associated with the onset of sexual maturity.

From the analysis of catch-up growth a generalized theory is presented. Growth regulation is a cellular phenomena in which the cell has a programme and a mechanism to recognize where it is in that programme; if it is diverted from the programme then a stabilizing mechanism will tend to return it to the right course. The cells of a given tissue type have the same programme, and are co-ordinated by tissue-specific diffusable agents. The tissues and organs are co-ordinated at the programme level and also by permissive hormones.

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REFERENCES


