

Catch-up growth in the rat skull after retardation during the suckling period

By J. P. G. WILLIAMS¹ AND P. C. R. HUGHES¹

*From the Department of Growth and Development,
Institute of Child Health, University of London*

SUMMARY

In rats whose growth was restricted by rearing in large litters the skull was less affected than the spine and the brain case less than the face. No sex difference was apparent during undernutrition but on subsequent rehabilitation females had caught up to controls in four out of five skull measurements within 4 weeks and by the end of the experiment the skulls of the neonatally undernourished females were the same size and shape as the controls. In the case of males, however, the skull of the undernourished rats never attained the same width as the controls.

INTRODUCTION

Catch-up growth is growth with a greater than normal for age velocity (Prader, Tanner & Von Harnack, 1963). Such growth may enable an organism to attain its normal adult size in which case the catch-up is said to be complete; if the organism does not attain normal adult dimensions then catch-up is incomplete. The term compensatory growth has also been used to describe this phenomenon (Williams, Tanner & Hughes, 1974*a*).

The completeness of catch-up is said to depend largely on the time of onset of retardation, early onset making complete catch-up less likely (Widdowson & McCance, 1960). We have recently suggested (Williams & Hughes, 1975) that catch-up from growth retardation during the suckling period is due to an interaction of the normal time related growth pattern and some other factor.

Most studies of neonatal undernutrition follow the classic work of Widdowson & McCance (1960) and compare large and small litters of male rats. Widdowson & McCance were however examining 'accelerated growth'. In our studies of catch-up (Williams *et al.* 1974*a, b*; Williams & Hughes, 1975, 1977) we have used large litters of 16 pups and normals of 8 pups. Under these conditions complete catch-up has been shown in body length (nose–rump) and body weight in female rats and in body length but not in body weight in male rats. We present here an account of catch-up in skull length, skull width and spine length in animals whose weight, nose–rump and tail length have been previously reported (Williams, *et al.* 1974*a, b*).

Authors' address: Department of Biological Science, City of London Polytechnic, Old Castle Street, London E1 7NT, U.K.

MATERIALS AND METHODS

The animals used were random-bred black-hooded rats originally supplied by the Medical Research Council and maintained in our animal house for the last 10 years. They were kept at 20–22 °C, 45–48 % relative humidity and under a 12 h of light regimen. On the day of birth the pups from several dams were pooled and reallocated so that some of the dams had 8 pups ('normal or 8-pup litters') while others had 16 ('undernourished or 16-pup litters') (Kennedy, 1957). When possible the litters contained equal numbers of males and females. The six dams used were provided with unlimited food (Oxoid Breeding Diet) and water. The pups were weaned at 21 days and placed two to a cage (Hughes & Nowak, 1973) with unlimited food and water. The pups were weighed, and nose–rump and tail lengths measured on a measuring board with the animals relaxed under ether anaesthetic (Hughes & Tanner, 1970*a*). On days 3, 7, 14, 21, 28, 35, 49, 63, 77, 91, 105, 119 and 228 whole body radiographs were also taken, enabling bone lengths to be measured and an assessment of skeletal maturity to be made (Hughes & Tanner, 1970*b*). The experiment was continued until skeletal maturity reached 98 % of the adult value in both groups.

The means and standard deviations of each measurement at each age (distance curves) were calculated from the data available at the age in question in a cross-sectional way. The means and standard deviations of the rate of growth (velocity curves) were calculated from the actual increments of individual animals from one examination to the next.

In the 8-pup group 17 animals were present at each observation time till 77 days when 14 animals were present; this number remained unchanged until the last observation at 228 days when only 13 animals were present. In the 16-pup group 17 animals were present until 35 days after which 15 were present till day 119; at the 119 and 228 observations 14 animals were present; that is a total of 208 control observations and 206 experimental.

The measurements shown in Fig. 1 were recorded from whole body radiographs obtained using methods previously described (Hughes & Tanner, 1970*a*). The measurements taken were:

- TSL Total skull length: the anterior border of the foramen magnum to the tip of the nasal bone.
- NCL Neurocranial length: the anterior border of the foramen magnum to the anterior border of the frontal bone.
- VCL Viscerocranial length (nose length): Total skull length minus neurocranial length.
- BZW Bizygomatic width: the maximum width between the zygomatic arches.
- NCW Neurocranial width: the width between the most medial points of the external auditory meati.
- Spine length Nose–rump length minus total skull length.

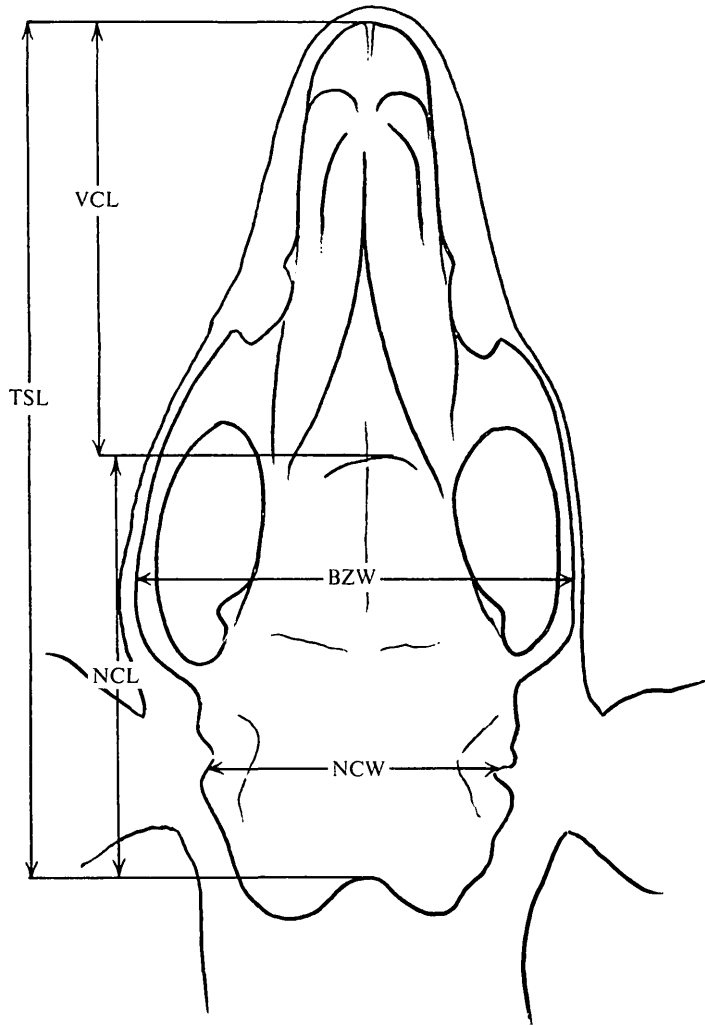


Fig. 1. Diagram of rat skull showing measurements recorded, details in text.

RESULTS (Fig. 2)

In males the length of the skull of the animals raised in large litters is 7.5 % ($P < 0.001$) shorter than the controls at weaning and remained significantly different until 119 days when the difference of 1.7 % was no longer statistically significant. The length of the cranium was 5.7 % ($P < 0.001$) shorter at weaning, at 77 days the difference between the two groups was no longer significant. The length of the nose in rats raised in litters of 16 was 11 % ($P < 0.001$) shorter than the nose length of animals reared in litters of 8, but this difference had disappeared by day 49. Bizygomatic width measures the width of the face and was 7 % ($P < 0.001$) less in rats from litters of 16 at 21 days of age; at 228 days, the termination of the experiment, the difference in this measurement

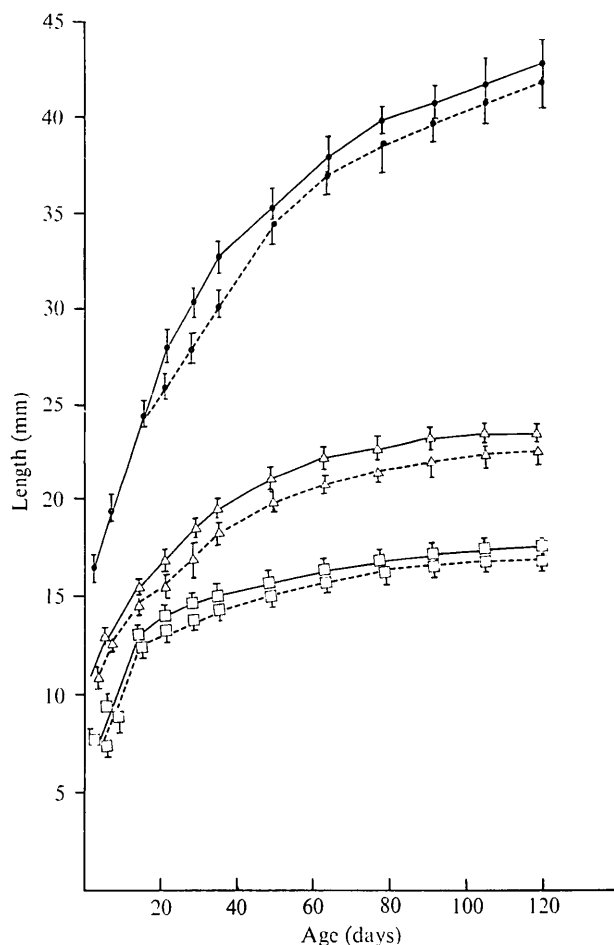


Fig. 2. Effects of neonatal growth retardation in, total skull length (●-●, controls; ●-●, restricted), bizygomatic width (△-△, controls; △-△, restricted), neurocranium width □-□, controls; □-□, restricted) of male rats. Means and standard deviations shown.

was still significant (4 % $P < 0.001$). Neurocranial width which measures the width of the posterior skull, was 3 % ($P < 0.05$) less in rats from large litters, and this difference was still present at 218 days (4 % $P < 0.01$). Thus in the males the skull caught up in length measurements but not in width. Spine length in the male rats from large litters was 81.3 % ($P < 0.001$) of that of rats from control litters of eight animals at weaning; the difference was not significant after 77 days.

In females the difference in total skull length at weaning was 6.3 % ($P < 0.001$), but the difference was not significant after 49 days. The difference in the neurocranial length did not become significant until day 28 (4.5 %, $P < 0.01$) but by day 49 the difference was no longer significant. The nose was significantly

shorter at weaning (12.6 %, $P < 0.001$) in animals from large litters but within 3 weeks (at day 49) the difference became non-significant. Bizygomatic width was 8.3 % ($P < 0.001$) less at the onset of rehabilitation and remained less than the control until the last observation at day 220 when it was no longer significantly different. The differences in neurocranial width did not become significant until 20 days of age (3.7 %, $P < 0.05$), the difference became non-significant by day 49. Spine length in the female rats from the litters of 16 pups was 81.1 % ($P < 0.001$) of that of rats from control litters at weaning; the difference was not significant by 64 days of age.

DISCUSSION

In earlier reports (Williams *et al.* 1974*a, b*) the body weights and nose-rump lengths of these animals were presented. At weaning the male rats that were reared in litters of 16 were 60 % of the weight and 87 % of the nose-rump length of rats reared in control litters of 8 pups. At 288 days the body weight of the two groups was still different (12 % $P < 0.001$) while nose-rump length was the same in both groups. At weaning the female rats that were raised in litters of 16 were 63 % of the body weight and 84 % of the nose-rump length of the rats reared in control litters of 8 pups. By day 63 the nose-rump length and by day 77 the body weights of the females from the two groups were similar. The skeletal maturity of the neonatally undernourished and normals were similar in both sexes at the end of the experiment. It was concluded that 'the sex difference in catch-up ability relates to soft tissue only and not to the skeleton'.

The present report indicates that the shorter nose-rump length mentioned above is due to reduction in length of both the skull and the spine. The reduction is however greater in the spine (13 % in males and 15 % in females) than in the skull (7.5 % in males and 6.3 % in females). These results accord well with those of Dickerson & Hughes (1972) studying catch-up after intra-uterine and post-natal insult. The sex difference seen in the nose-rump length is also seen in the spine length. The difference is in part due to the larger size of the males; the undernourished males have further to go to catch up to the controls than do the similarly restricted females. This is not however the complete explanation as the rate of catch-up in the females is reduced just as is the normal growth rate. Up to 35 days both male and female undernourished animals are growing at the same rate but after that time the female rate declines. Thus the intrinsic growth pattern influences the catch-up growth; similar conclusions have been reached concerning the catch-up growth seen immediately after short periods of neonatal undernutrition (Williams & Hughes, 1975).

The skull of the pups raised in large litters was disproportionately smaller than that of the control animals, the nose length was 11 % smaller in males and

12.6 % shorter in females but the length of the cranium was only reduced by 5.7 % and 4.5 %. The bizygomatic width was more affected than the neurocranial width. Thus the skull was less affected than the spine and the brain case less than the face. This probably reflects the brain's high priority for growth and its relative resistance to undernutrition (Dickerson & McAnulty, 1972) compared with the remainder of the body.

No sex difference was apparent in the effect of undernutrition on the skull but a sex difference was apparent in rehabilitation. The female rats had caught up in four out of five of the skull measurements by day 49. The bizygomatic width did not catch up until after 119 days but at the final observation point the skulls of the neonatally undernourished females were the same size and shape as the control females. In the case of the males the first measurement to attain control size was the nose length at 49 days followed by the neurocranial length at 105 days. The width of the face and the neurocranium were both significantly different ($P < 0.01$) at 228 days. Thus our previous conclusion that sex differences relate only to soft tissue no longer seems valid. But the growth of the skull is greatly influenced by the growth of the brain. Indeed the skull seems to enlarge to contain the volume of its contents as is seen for instance in hydrocephalics, and thus the sex difference may again be a reflection of the growth of a soft tissue.

Bray, Shields, Wolcott & Madsen (1969) have reported that the head circumference in the human, which is analogous to the rat cranium measurement, is an accurate reflection of brain size and Winick & Rosso (1969) have reported that total brain DNA, or cellularity, is linearly related to head circumference. It seems reasonable to suppose that the changes seen in the brain case of our rats may reflect changes in brain size. Complete catch-up in cranium size was found in the female rats but not in the males. The final difference between treated and control males was however only 4 %. Benton, Moser, Dodge & Carr (1966) using a somewhat similar undernutrition protocol, reported that brain weight was essentially equal to their controls at 6 weeks but Dobbing (1974) has reported that 'comparatively mild restriction' during suckling leads to permanent distortion as well as deficits in the adult rat brain.

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