J. Anat. (1973), **114**, 2, pp. 185–199
With 7 figures
Printed in Great Britain

Changes in body weight of the growing and adult mouse in response to hypoxic stress

CAROLIN HUNTER AND E. J. CLEGG

Department of Human Biology and Anatomy, University of Sheffield, Sheffield S10 2TN

(*Accepted* 13 *November* 1972)

INTRODUCTION

The two basic factors responsible for the pattern of growth and the adult size of an animal are its inherited characteristics and the environment to which it is subjected during its growing period (Brauer, 1965; Harrison & Clegg, 1969). All environments, however, undergo a certain degree of variation, so that often the ability to survive in the habitual environment involves toleration of periods of mild stress. Homeostatic mechanisms are usually successful in stabilizing the internal environment under mild stress, but during severe stress these are not always sufficient. Many authors (Saxton & Silberg, 1947; Acheson, 1960; Tanner, 1962; Prader, Tanner & von Harnack, 1963; Harrison & Clegg, 1969; Mosier, 1969) have demonstrated that slowing and cessation of growth occur under many environmental stresses, but it is known that if the stress is continued, adaptation may allow normal growth of the animal to be restored. It is also apparent that when the stress is lifted, the animal may be capable of catch-up, when it grows with a velocity much higher than normal for that particular age and in this way compensates for the reduced velocity whilst under stress. Tanner (1963) has suggested that the body has a feedback mechanism which 'monitors' growth so that any discrepancies between actual body size and normal size produced by stress are corrected by catch-up growth after the stress is lifted.

The present investigations were designed to study the effects of changes in the duration, timing and severity of stress on the growth of body weight. Special attention was paid to the amount and duration of catch-up growth and the relevance of the results to Tanner's (1963) hypothesis.

Adaptation to a particular stress involves changes, either quantitative or qualitative, in the metabolism of those organs and systems whose functions mitigate the adverse effects of the stress on the body as a whole ('adapting' organs or systems) while changes in the remaining organs and systems reflect the overall success of adapting mechanisms and therefore the state of fitness of the animal (Harrison & Clegg, 1969). Body weight may therefore be considered a 'fitness indicator' under hypoxic stress, although it has the disadvantage that any alteration only becomes apparent some time after the animal has changed in fitness (Clegg & Harrison, 1966).

MATERIALS AND METHODS

In each of the first three experiments, 96 male (Tucks no. 1) albino mice (16 litters, each of six animals, weaned at 21 days) were distributed as follows: Three animals from each litter were randomly distributed into eight experimental cages, so that each cage contained six animals originating from different litters. The remaining three animals from each litter were then distributed in an identical way, so that for each experimental cage there was a control cage of six litter mates. All animals were allowed the usual laboratory food pellets and water *ad libitum*.

Hypoxia was produced by exposing animals to air at pressures below normal atmospheric in a decompression chamber of approximate dimensions $1{\cdot}2 \times 1{\cdot}2 \times 0{\cdot}5$ m. Control animals were kept in the same room as the chamber. Expired carbon dioxide was absorbed by trays of soda lime and excess water vapour by trays of calcium chloride. An air bleed into the chamber of one litre/minute was maintained. The pressure in the chamber was returned to normal atmospheric each day for body weight to be measured and for feeding, cleaning and replacement of chemicals (a period of approximately one hour). The experimental animals from each of the eight groups were subjected to hypoxia at the same time (and therefore the same age) but each cage was removed after a different period of time. Litter mates of animals which died during the experiment were removed from the corresponding cages.

Four separate experiments were performed.

Experiment 1. Experimental animals were subjected to a pressure of 390 mmHg at 22 days of age and cages were removed after 2, 4, 7, 10, 13, 15, 21 or 28 days exposure. Unfortunately, in this experiment intercurrent infection in animals exposed for 17 days made it impossible to follow body weight changes on return to normal pressures. For similar reasons observations were discontinued in animals exposed for 10 days, a week after return to normal pressures.

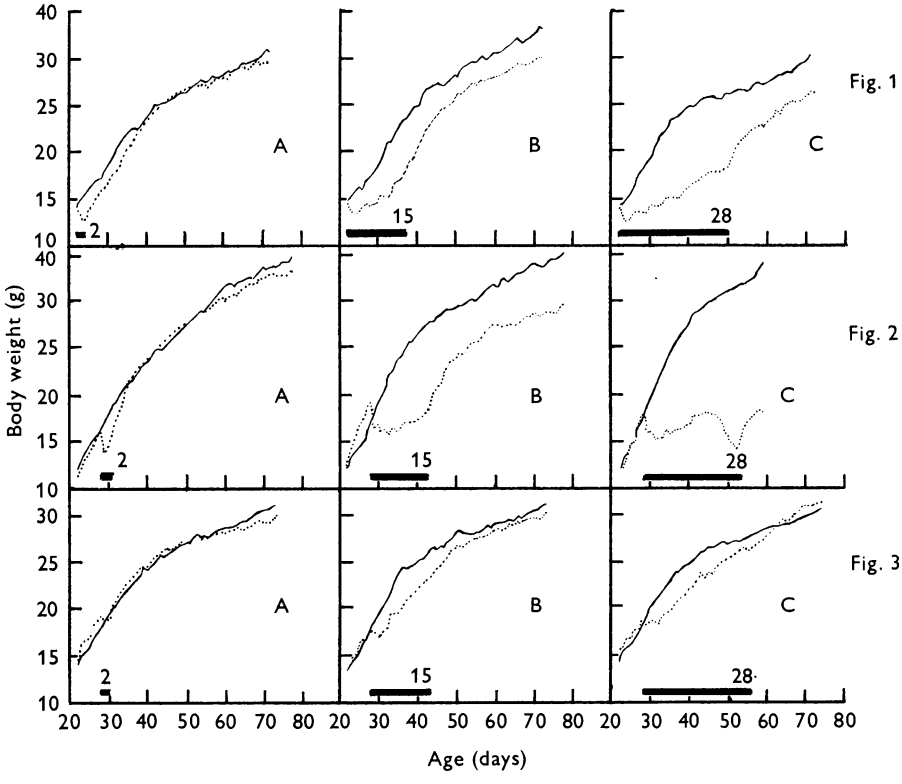
Experiment 2. This was identical to Experiment 1 except that the age at first exposure was 28 days.

Experiment 3. This was identical to Experiment 2 except that the animals were exposed to the milder stress of 540 mmHg pressure.

Experiment 4. In this experiment a group of 18 male mice aged 202 days were exposed to a pressure of 390 mmHg for a period of 28 days. Litter mate control animals were maintained at normal atmospheric pressure.

RESULTS

Representative results from Experiments 1–3 are shown in Figs. 1–3. Fig. 1 gives the results for animals exposed to 390 mmHg at 22 days of age for 2 (A), 15 (B) and 28 (C) days. Fig. 2 gives the results for animals exposed to 390 mmHg at 28 days of age for 2 (A), 15 (B) and 25 (C) days and Fig. 3 gives the results for animals exposed to the milder stress of 540 mmHg at 28 days of age for 2 (A), 15 (B) and 28 (C) days. Although eight periods of hypoxia were used for each experiment, three illustrations only are given from each because the appearances of those not presented lay between those shown. However, later results and conclusions are based on all eight periods of hypoxia.



Figs. 1–3. Body weight plotted against age for hypoxic animals (dotted line) and controls (solid line). The duration of hypoxia is indicated above the abcissa by the black bar. Fig. 1. Exposure to 390 mmHg beginning at age 22 days. Fig. 2. Exposure to 390 mmHg beginning at age 28 days. Fig. 3. Exposure to 540 mmHg beginning at age 28 days.

Growth during hypoxic stress

The immediate effect of hypoxia was a drop in body weight which usually lasted no more than 3 days. Table 1 indicates the total amount of weight lost, the period over which this occurred and the amount of weight lost in the first 24 hours of exposure.

The greatest proportion of weight was lost in the first 24 hours, and the length of time for which weight loss occurred appeared to be independent of the severity of hypoxic stress and of age. However, this was not the case for the adult mice of Experiment 4. Fig. 4 indicates the means $\pm$ S.E. of body weight for these animals (202 days of age), experimental animals being exposed to 390 mmHg for 28 days. It can be seen that these animals continued to lose weight for 4–5 days, producing, when the weight loss finally ceased, a much greater deficit of experimental body weights than in younger animals. Consequently, when young and adult animals were compared, the duration of weight loss during stress *was* related to age. It is also clear from Table 1 that the total amount of weight lost by young animals was dependent on the severity of the stress. The mean weight loss by all animals exposed to 540 mmHg in the first 24 hours was $0{\cdot}22 \pm 0{\cdot}09$ g. This was highly significantly different from the loss at 390 mmHg

Table 1. *Weight loss in hypoxic mice*

Duration of hypoxia (days)	390 mmHg. 22 days of age			390 mmHg. 28 days of age			540 mmHg. 28 days of age			390 mmHg. 202 days of age		
	D	T	I	D	T	I	D	T	I	D	T	I
2	2	1·70 ±0·221	1·52 ±0·273	1	2·42 ±0·280	2·42 ±0·280	2	0·65 ±0·320	0·40 ±0·208	—	—	—
4	2	1·55 ±0·198	1·23 ±0·136	3	2·97 ±0·429	2·70 ±0·340	2	0·63 ±0·447	0·03 ±0·445	—	—	—
7	2	1·93 ±0·358	1·38 ±0·294	1	1·65 ±0·242	1·65 ±0·242	2	0·23 ±0·286	0·13 ±0·184	—	—	—
10	2	1·65 ±0·219	1·12 ±0·158	1	2·47 ±0·455	2·47 ±0·455	2	0·18 ±0·318	0·06 ±0·279	—	—	—
13	2	1·55 ±0·195	1·18 ±0·162	1	1·70 ±0·392	1·70 ±0·392	2	0·73 ±0·522	0·53 ±0·169	—	—	—
15	1	1·16 ±0·303	1·16 ±0·303	3	3·37 ±0·199	2·92 ±0·215	2	0·62 ±0·218	0·27 ±0·255	—	—	—
21	2	1·27 ±0·286	0·70 ±0·365	3	2·46 ±0·609	1·98 ±0·505	1	0·05 ±0·201	0·05 ±0·201	—	—	—
28	2	1·22 ±0·311	1·13 ±0·253	3	2·94 ±0·387	2·13 ±0·325	1	0·37 ±0·133	0·37 ±0·133	6	8·47 ±0·441	3·21 ±0·313

D = duration of the period of weight loss (days). T = mean total weight loss (grams). I = mean weight loss in the first 24 hours (grams).

for animals exposed at 22 days of age (mean = $1{\cdot}16 \pm 0{\cdot}10$ g; $P < 0{\cdot}001$) and 28 days of age (mean = $2{\cdot}40 \pm 0{\cdot}13$ g; $P < 0{\cdot}01$). Consequently, the severity of the stress determined the rate of weight loss, especially in the first 24 hours.

Table 2 indicates the percentage weight loss over the first 24 hours. At 390 mmHg adult animals lost proportionately the same amount of weight during this period as the 22 day old animals exposed to the same pressure. However, the percentage weight loss by the 28 day old group was double this value. Animals exposed to 540 mmHg lost proportionately less weight. Consequently the total amount of weight lost during hypoxic stress depended on both the age at which the animals were exposed and the severity of the stress.

If animals were removed from hypoxic conditions immediately after weight loss had ceased (Figs. 1A, 2A, 3A) they grew with a velocity much higher than normal (catch-up growth) until they regained control values. This was independent of the severity of the stress to which they were exposed. However, if the animals were allowed to remain under the stress for longer periods they began to grow again with a reduced velocity compared with control animals. The mean velocities (± S.E.) of body weight gain during the different durations of hypoxia are indicated in Fig. 5. Fig. 5A shows results for Experiment 1, Fig. 5B for Experiment 2 and Fig. 5C for Experiment 3. In all experiments the velocity of the growth of the controls decreased with age, as values were taken from increasingly flatter parts of the growth curve. However, after periods of more than 4 days hypoxia, for animals exposed to 390 mmHg (Figs. 5A, B) the mean velocity of the experimentals was more or less

Table 2. *Percentage reduction in body weight in the first 24 hours after exposure in mice exposed to pressures of 390 mmHg*

Severity and age of exposure to hypoxia	Mean percentage weight loss ± S.E.	'*d*' value comparison between adult (202 day old) and young (28 and 22 day old) mice
390 mmHg, 22 days	7·748 ± 0·640	22/202 days 0·036
390 mmHg, 28 days	13·636 ± 0·512	28/202 days 6·601****
390 mmHg, 202 days	7·783 ± 0·724	
540 mmHg, 28 days	0·950 ± 0·482	28/202 days 7·855****

**** $P < 0·001$.

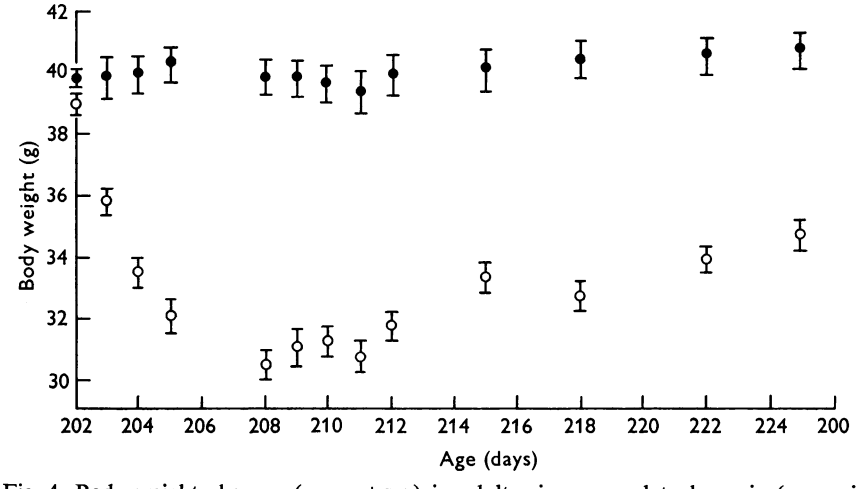


Fig. 4. Body weight changes (means ± S.E.) in adult mice exposed to hypoxia (open circles) and controls (solid circles) over a period of 28 days, commencing at age 202 days.

constant for all durations of hypoxia. The mean velocity of growth was lower for animals exposed at 28 days of age (Fig. 5B) than for those exposed at 22 days of age (Fig. 5A) (0·06–0·18 g/day compared with 0·22–0·30 g/day respectively). In fact, the straightening and depression of the growth curve occurred to such an extent in the former group that there was very little gain in weight during any period of exposure and longer periods resulted in continued loss of weight and death in some animals (Fig. 2C). At 540 mmHg (Fig. 5C) the velocity of growth was relatively constant compared with that of control animals, but coupled with this was the eventual tendency for the experimentals, during longer periods of stress, to gain similar amounts of weight to the control animals. In general, there was more variation in the velocities of growth of the hypoxic animals at the higher pressure than at the lower pressure.

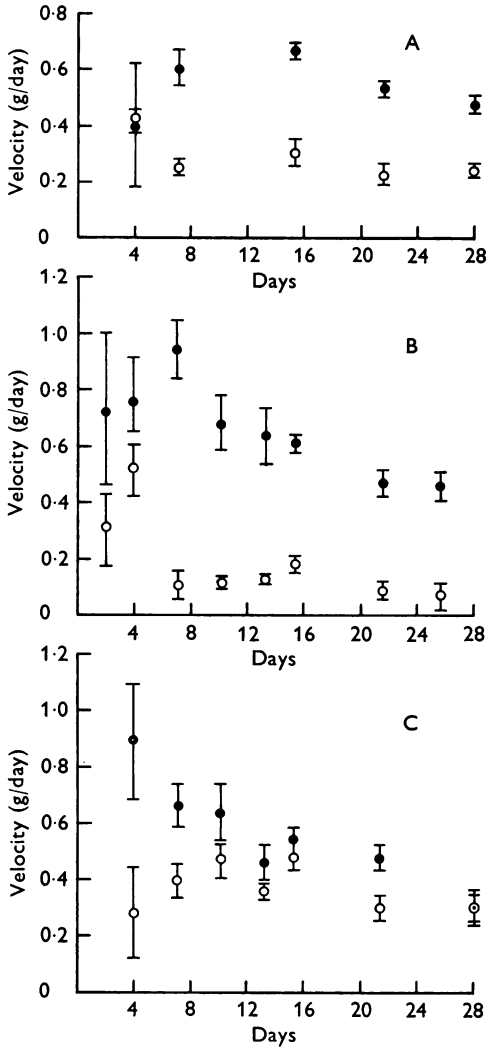


Fig. 5. Mean velocities (±S.E.) of body weight gain during different durations of hypoxia. Open circles are means for experimental animals; closed circles for controls. (A) Exposure to 390 mmHg beginning at age 22 days. (B) Exposure to 390 mmHg beginning at age 28 days. (C) Exposure to 540 mmHg beginning at age 28 days.

Catch-up growth

Table 3 indicates that during exposure to severe stress (Experiments 1 and 2) the discrepancy between body weights of the control and experimental animals on the day of return to normal atmospheric pressure increased with duration of exposure, and was greater on average for animals exposed at 28 days of age. It is also shown that for animals exposed to milder stress (Experiment 3) these values increased to a maximum after 13 days of exposure and subsequently decreased. The capacity for catch-up growth appeared to depend both on the severity and the duration of

Table 3. *Discrepancies in body weights between experimental and control animals (i) on return of experimentals to normal pressure; (ii) 100 days after initial exposure, together with period taken to catch up and duration of increased growth velocity*

Experiment no., pressure (mmHg), age of commencement	Duration of hypoxia (days)	Mean control experimental discrepancy in body weights (g) on return to normal pressure	Period taken by experimentals to catch up to control weights (days)	Period of increased velocity of growth of experimentals (days)	Mean control − experimental discrepancy of body weights 100 days from initial exposure (g)
1, 390 mmHg, 22 days	2	2·85 ± 0·69*	4		2·98 ± 0·81*
	4	2·73 ± 0·86*	1		−2·35 ± 1·43
	7	3·86 ± 1·17*	18		0·48 ± 0·79
	10	7·28 ± 1·35***	—	—	—
	13	4·83 ± 1·83	—	—	—
	15	8·58 ± 1·21***	Never	18	1·93 ± 0·54*
	21	7·82 ± 1·73**	Never	22	2·78 ± 1·96
	28	7·77 ± 0·09****	Never	26	1·83 ± 1·94
2, 390 mmHg, 28 days	2	3·65 ± 1·42*	7	7	1·87 ± 0·62*
	4	4·17 ± 1·67**	Never	4	0·67 ± 1·74
	7	9·30 ± 1·05****	Never	16	3·00 ± 1·15*
	10	9·56 ± 1·30***	Never	15	7·52 ± 1·73**
	13	10·73 ± 0·87****	Never	10	6·85 ± 1·43**
	15	9·62 ± 0·96****	Never	7	4·28 ± 2·56
	21	11·08 ± 1·13****	Never	6	—
	28	16·25 ± 0·85	Never	4	—
3, 540 mmHg, 28 days	2	0·65 ± 0·98	1	2	0·62 ± 1·36
	4	2·70 ± 1·05*	8	8	0·95 ± 1·42
	7	3·03 ± 0·51***	11	12	−2·17 ± 0·91
	10	3·13 ± 0·42***	11	9	−3·34 ± 0·82***
	13	4·68 ± 2·07	No significant difference on day of removal	11	0·98 ± 1·37
	15	3·00 ± 0·38****	10	6	−1·18 ± 1·27
	21	2·65 ± 1·27	No significant difference on day of removal	7	−1·92 ± 2·71
	28	1·50 ± 2·62		8	−0·93 ± 0·62

* $0{\cdot}02 < P < 0{\cdot}05$. ** $0{\cdot}01 < P < 0{\cdot}02$. *** $0{\cdot}001 < P < 0{\cdot}01$. **** $P < 0{\cdot}001$.

hypoxia. Table 3 also indicates the period of time taken for animals to complete catch-up. Clearly it was not always successful in restoring control weights. After periods of severe stress of up to 15 days when exposed at 28 days of age, curves tended to be parallel to those of the control animals, after a short period of true catch-up growth (see Figs. 1B, 1C, 2B). The period of increased growth velocity for the animals made hypoxic at 22 days (Experiment 1) appeared to be independent of duration of hypoxia except for short periods, while in the animals exposed at 28 days (Experiment 2) this period increased with duration of exposure up to 7 days and thereafter decreased. In animals exposed at 22 days of age to 390 mmHg for 4 days, the period of increased velocity was greater than that needed for catch-up to be completed, and 'over-shooting' occurred. This is also seen in Table 3 (the negative

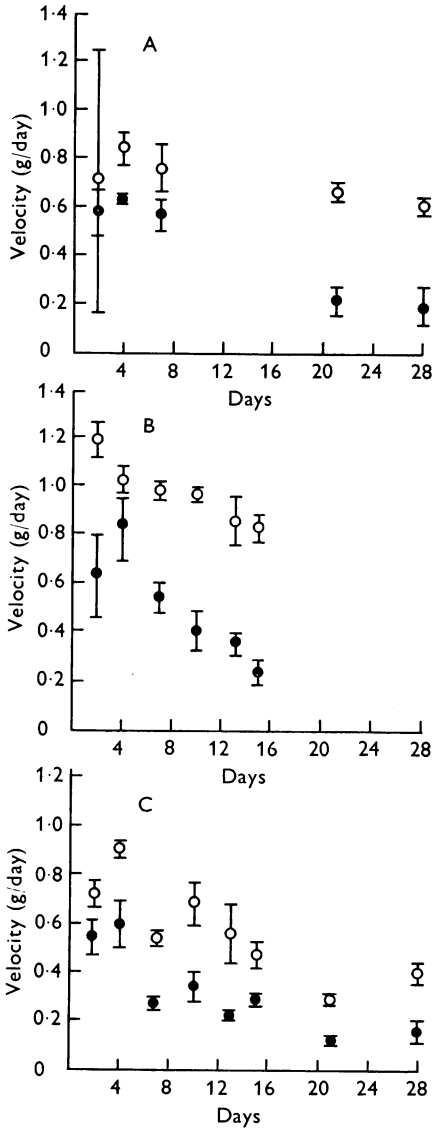


Fig. 6. Mean velocities (±S.E.) of body weight gain of experimental animals (open circles) during the first 7 days after return to normal pressure, compared with controls (closed circles) and plotted against duration of hypoxia. (A) Exposure to 390 mmHg beginning at age 22 days. (B) Exposure to 390 mmHg beginning at age 28 days. (C) Exposure to 540 mmHg beginning at age 28 days.

differerence between control and experimental weights 100 days from initial exposure). 'Over-shooting' also occurred in animals exposed to the milder stress of 540 mmHg (Experiment 3) but at this pressure the great variation in the velocities of growth in body weight, together with the relatively small differences observed between experimentals and controls made it difficult to determine these periods of

increased velocity, so the data presented provide no more than approximations. However, the fact that they reach a maximum after a period of approximately ten days suggests that they may have borne some relationship to the distance of the experimental curve from the equivalent point on the normal growth curve, since this was the period at which the experimental-control discrepancy was greatest (see Fig. 3B, C).

Fig. 6 indicates the mean velocity of body weight gain of the experimental animals during the first 7 days of catch-up growth and compares it with the velocity of the control animals over the same period. It is apparent that for more greatly stressed experimental animals (Fig. 6A, B) the velocity of growth was much higher, and decreased less rapidly with duration of hypoxia, than velocities in control animals of the same age. For animals exposed to 540 mmHg (Fig. 6C) experimental catch-up velocities decreased fairly rapidly with duration of exposure, as did those of the controls, but the velocities of the exposed animals remained higher. After the return of these mildly stressed animals to normal atmospheric pressure, differences between experimental and control values for the velocity of growth over the first 7 days increased with duration of exposure up to 4 days but decreased again after 15 days. Thus, in mildly stressed animals, catch-up, in the sense of an increase in velocity relative to that during exposure to stress, did not occur in animals exposed for over 15 days (see also Fig. 2A). However, if the term 'catch-up' is used in the sense of an increase above normal velocity at that age, then animals can be said to be catching-up *during exposure* to mild stress lasting longer than 15 days.

DISCUSSION

Growth under hypoxic stress

The immediate effect of exposure to hypoxic stress was a loss, or decrease in the rate of gain, of body weight, which was dependent on the age of exposure and the severity of the stress. The fact that animals exposed at 28 days of age to 390 mmHg lost double the proportion of weight lost by 22 and 202 day old animals suggests that this may be a particularly sensitive age for the mouse or that the particular batch of animals was less resistant to the degree of hypoxia used. It seems highly unlikely, however, that resistance would vary to such a great extent in animals originating from the same stock.

Weihe (1963) suggested that the duration of the period of weight loss was indicative of the period taken to adapt to stress. Concomitantly it must be accepted that once the animals begin to regain weight – whether it is at a velocity below that of the controls or not – it indicates that successful adaptive changes are taking place. Harrison & Clegg (1969) suggested that fitness is lowest when the animals are first exposed to stress (although there may be a 'carry-over' of fitness from the habitual environment). Incorporating the ideas of Weihe (1963) into this statement, it could be said that the rate and extent of body weight loss are greatest (indicating that fitness is lowest) during the initial exposure period. Following this, as adaptation proceeds, fitness (and therefore body weight gain) increase. These changes can be equated with those of the present experiment. The animals lost most weight in the first 24 hours of exposure, and the rate of weight loss continually decreased with

duration of exposure. This was particularly noticeable in the 202 day old animals, where weight loss continued for 4 or 5 days. At the end of the period of weight loss growth began again at a slower rate than in the controls (except in the 202 day old group where the experimental animals grew faster than in the controls) – the rate being dependent on the severity of the stress.

If the suggestions of Weihe (1963) are correct, then the older animals in the present experiment took longer to adapt than the younger ones. This is consistent with the findings of Weihe (1963) in rats exposed to high altitudes.

Reduction of food and water intake are associated with the initial responses to hypoxic stress (Clegg & Harrison, 1967). These changes are probably the main cause of the loss of body weight during initial exposure (Jackson, 1936; Clegg & Hunter, unpublished data). The cause of these changes is unknown but it is possible that one of the adaptive responses on exposure to hypoxic stress is a reduction in the metabolic rate in an attempt to decrease oxygen utilization, with a consequent reduction in the need for food and water. Certainly a decrease in oxygen utilization has been reported in mice exposed to low atmospheric pressures by Chevillard (1966). Reduction in the metabolic rate may be related to the decrease in thyroid function reported by Gordon, Tornetta, D'Angelo & Charipper (1943) and Surks (1966), while Surks (1966) indicated that reduction in food and water intake may itself affect the secretion of the thyroid hormone.

Following the period of weight loss, prolonged hypoxic stress resulted in growth of the experimental animals with a fairly constant but reduced velocity compared with the constantly decreasing velocity of the controls. The period of reduced velocity in the *growing* animals of the present experiments may be equated with the equilibrium weight of *adult* animals in the experiments of Clegg & Harrison (1966). Clearly the depression of the growth curve in the present experiments was dependent on the severity of the stress, and possibly on the resistance of the animals, while the equilibrium weight of Clegg & Harrison (1966) also depended on the severity of the hypoxic stress. However, the adult animals of the present experiments began to gain weight during exposure to stress of 390 mmHg after the period of loss of weight, while those of Clegg & Harrison (1966), exposed to a pressure of 380 mmHg, continued to lose weight. Perhaps these differences may be explained by the use of different strains of animals, the individual resistance of the animals, and the fact that at these very low pressures a reduction of 10 mmHg may be critical for survival.

Catch-up growth after severe stress

(390 mmHg; 22 and 28 days of age)

It is apparent from the present experiments that exposure to a severe hypoxic stress of 390 mmHg pressure resulted in catch-up growth, which, at least during the first 7 days after return to normal pressure, was of a fairly constant velocity irrespective of the velocity of growth of the controls at that time. However, the values for the experimental animals did show a slow decrease with time – possibly the result of some relationship to the shape of the normal growth curve and/or damage to the homeostatic mechanisms. Catch-up in the more severely retarded animals (28 days of age, exposed to 390 mmHg) was greater than for the less retarded (22 days of age,

exposed to 390 mmHg) but its velocity and duration decreased more rapidly with duration of exposure, suggesting that the homeostatic mechanisms were indeed damaged.

Catch-up was not always successful in restoring control weights. All animals removed after 2 days hypoxia were capable of catch-up growth at whatever age and to whichever pressure they were exposed. After this time, however, the ability to catch up depended on the age and pressure: animals exposed at 28 days of age to 390 mmHg were more severely affected than those exposed at 22 days of age. In the 22 day old group there appeared to be a limit to the period of catch-up growth (about 20 days). Clearly, as the deficit of experimental body weights increased, catch-up would become increasingly less successful in restoring experimental weights to parity with control weights. It is interesting that at this pressure, although catch-up to control weights after 4 days of hypoxia required only 11 days, the period of increased velocity continued for 19 days, resulting in 'over-shooting'. This suggests that 4 days' hypoxia was sufficient to stimulate the maximum catch-up response. In 28 day old animals, the period of catch-up increased to approximately 10 days with duration of exposure and then decreased again. The fact that there may be a limit to the period of catch-up in less stressed animals suggests that in the severely stressed ones there was interference with the homeostatic mechanisms, so that, as the duration of hypoxia increased, the period of catch-up became increasingly shortened.

The results do, so far, agree with the mechanism proposed by Tanner (1963) for monitoring body growth. He suggested that there is a 'time-tally' mechanism located in the brain, consisting of a substance accumulating at a constantly decreasing rate. Growing cells and tissues release inhibitors which occupy receptor sites in the 'time-tally' so that the 'mismatch' would be the number of unoccupied sites, and this would be the stimulus to growth. Consequently, the inhibitor concentration would be low in the young animal and the velocity of growth would be high, but as the animal aged the number of 'mismatches' would decrease. If growth stopped under stress the inhibitor concentration would fall for a time. This would cause an abnormal increase in the number of unoccupied sites and therefore in the number of 'mismatches', so that as soon as growth could begin again it would do so with an increased velocity for that particular age. On the basis of this hypothesis he suggested that the velocity of catch-up growth would be greater than that present when application of the stress caused growth to cease. This suggestion is substantiated by the results of the present experiments, as shown in Table 4. Here the growth velocities of experimental animals during the week following removal of the stress are compared with those of controls during the first week of exposure of experimental animals to hypoxia. These latter values should be similar to the velocities the experimental animals would have had, had they not been made hypoxic, and it will be seen that in all cases the experimental animals had the higher velocity. In the majority of instances this difference was significant statistically.

One may speculate from the hypothesis that if growth began again slowly whilst the animal was still under stress, there would be fewer 'mismatches' than if growth ceased completely, and consequently there would be less catch-up. This is what did happen in 22 and 28 day old animals exposed to 390 mmHg; 22 day old animals

Table 4. *Mean differences in daily velocities of growth between experimental animals during the first week after return to normal pressure and controls during the week following the first exposure of experimental animals to hypoxia*

Experiment no., pressure (mmHg), age at commencement	Period of exposure							
	2	4	7	10	13	15	21	28
1, 390 mmHg, 22 days	0·132 ±0·215	0·214**** ±0·035	0·200* ±0·064	0·504*** ±0·100	—	0·781** ±0·193	0·451**** ±0·066	0·410*** ±0·085
2, 390 mmHg, 28 days	0·557** ±0·174	0·190 ±0·143	0·443**** ±0·050	0·563*** ±0·097	0·500**** ±0·118	0·594**** ±0·093	—	—
3, 540 mmHg, 28 days	0·176**** ±0·021	0·307* ±0·102	0·264**** ±0·025	0·343* ±0·113	0·334* ±0·120	0·195*** ±0·048	0·163*** ±0·027	0·232* ±0·071

* $0{\cdot}02 < P < 0{\cdot}05$. ** $0{\cdot}01 < P < 0{\cdot}02$. *** $0{\cdot}001 < P < 0{\cdot}01$. **** $P < 0{\cdot}001$.

grew more quickly than 28 day old ones whilst under stress, and exhibited a lower velocity of growth during catch-up.

22 day old animals exposed for longer than 7 days and 22 day old animals exposed for longer than 4 days to 390 mmHg pressure showed signs of permanent stunting of growth. This agrees with Tanner's (1963) hypothesis. He suggested that if the stress were severe or long lasting, the 'time-tally' mechanism itself would be affected and the animal would be permanently stunted in size. Clearly, if the damage caused the rate of increase in receptor sites to be reduced, the number of 'mismatches' would also be decreased, and growth would be stimulated to a lesser degree when the stress was lifted.

Fig. 7. Diagrammatic representation of a modified 'time-tally' hypothesis of growth regulation. In the left-hand diagrams age-dependent changes in the number of receptor sites (R) and inhibitor concentrations (I) are indicated. The right-hand diagrams show the degree of 'mismatch' (R−I).

(A) Normal growth. As the 'mismatch' decreases, so the rate of growth declines.

(B) The effect of stress, as suggested by Tanner (1963). Throughout the period of stress (indicated by the horizontal bar), inhibitor concentration remains constant while the rate of increase in receptor sites is normal. When the stress ceases the high level of 'mismatch' allows of rapid catch-up growth.

(C), (D) and (E) show the modifications suggested by the present investigation.

(C) The effect of mild stress. There is a temporary decline in the rate of increase of receptor sites and inhibitor concentration remains constant for a short period. Growth begins again while under stress and little or no catch-up occurs when it is lifted.

(D) The effect of a more severe stress. Inhibitor concentration remains constant during the period of stress and the rise in the number of receptor sites is small. On removal the increased 'mismatch' (for that age) allows catch-up growth to occur. The size of the 'mismatch' at the end of the period of stress is greater than at the beginning, so that the rate of catch-up growth is greater than that of the control animals at the time of first application of the stress.

(E) The effect of a very severe stress. There is permanent damage to both receptors and inhibitors. As a result levels of both decline. The amount of mismatch is never greater than normal, so that when the stress is lifted growth rates are normal for that age and the final size of the animal is less than normal.

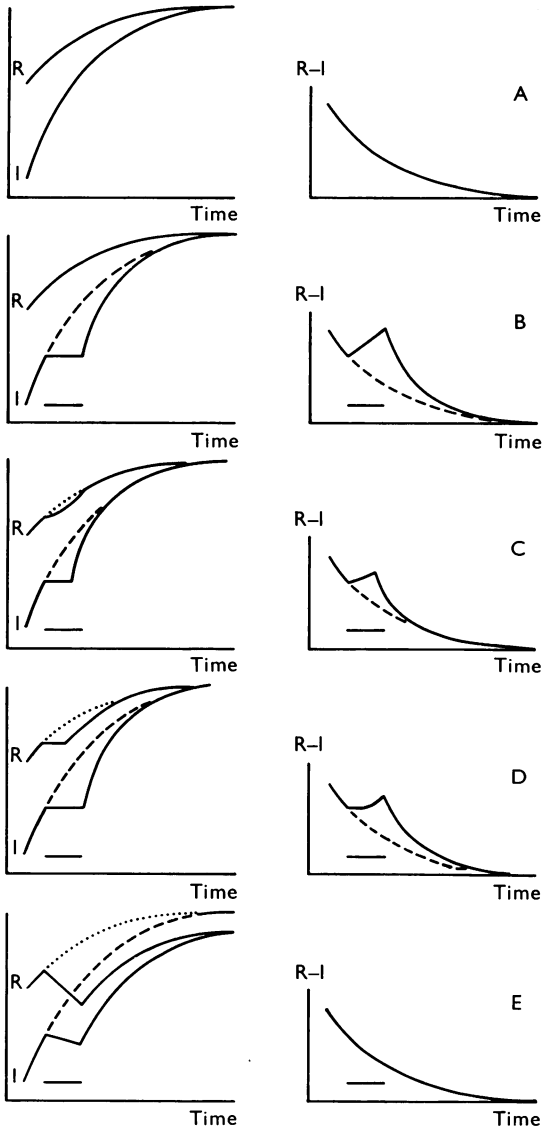


Fig. 7. For legend see opposite.

Catch-up growth after mild stress (540 mmHg: 28 days of age)

All animals were capable of complete catch-up at this pressure, and often 'overshooting' occurred. For analysis of the data, the animals may be split into two groups – 2–15 days, and 15–28 days duration of hypoxia. The growth rate of the first group of animals during stress was initially lower than that of the controls. However, in the second group the growth rate of the experimental animals became increasingly greater than that of the controls as the growth curves of the latter began to flatten out, after about 43 days of age. The subsequent increase in velocity on return to normal pressure was determined by this difference in velocities at the time of removal from hypoxia. Animals exposed for less than 15 days exhibited a further increase in velocity above that during exposure, while those exposed for longer than 15 days exhibited no such increase. The animals exposed for longer than 15 days could be said to be catching up while still under stress. It seems likely that catch-up growth occurring under stress is a manifestation of a successful adaptation of the whole animal. How it is to be interpreted on Tanner's (1963) model is a matter for speculation. A suggestion which appears to fit the observed facts, and which is to some extent indicated in Tanner's work, would be that stress has the general effect on the 'time-tally' of reducing the rate of increase of receptor sites. This response would vary according to the severity and duration of the stress, and is indicated diagrammatically in Fig. 7. Where it is mild (Fig. 7C) the receptor sites continue to increase in number, albeit at a slower rate, and after the initial successful adaptation of the organism the 'mismatch' is sufficiently large to allow growth to be renewed at a rate greater than that in unstressed animals of the same age (catch-up). Following removal from the stress there is little or no increase in the growth rate. If the stress is more severe (Fig. 7D) the number of receptor sites does not increase and the adaptation is less successful, so that for two reasons (smaller 'mismatch' and poorer adaptation) the amount of growth which occurs under stress is less than in normal animals. However, on removal from the stress the number of receptor sites rapidly increases to normal and this, together with the animal's greater fitness in its habitual environment, enables successful catch-up growth to occur. Finally, as Tanner has suggested, in the most severe stress, permanent damage to the 'time-tally' may result in a permanent reduction in the number of receptor sites (Fig. 7E), and a consequent failure of what little catch-up growth does occur to restore normal size.

Animals exposed to 540 mmHg for 7, 10, 15 and 21 days exhibited 'overshooting' above control weights, as the period of increased velocity was continued for a longer time than that necessary to complete catch-up. 'Overshooting' also occurred in 22 day old animals exposed to 390 mmHg for 4 days. Apparently mild stress, or severe stress for a short period, may stimulate growth to the extent that bigger adults are produced. Why this should occur is uncertain, and no provision is made for it in Tanner's (1963) model. It may possibly be a manifestation of a 'hunting' phenomenon in a self-regulating, target-seeking process.

SUMMARY

Growing mice were subjected to hypoxic stress produced by decompression. Changes in body weight were observed which depended on the timing, severity and duration of stress. These factors were also responsible for the success or otherwise of catch-up growth during recovery. Successful adaptation to stress was associated with resumption of growth in body weight. The data support, to a limited degree, the idea that there is a feedback mechanism regulating changes of body weight.

We are indebted to the Medical Research Council for financial support and to Mrs D. Barraclough for her skilled technical assistance.

REFERENCES

ACHESON, R. M. (1960). Effects of nutrition and disease on human growth. In *Human Growth* (Ed. J. M. Tanner), pp. 73–92. Oxford: Pergamon.

BRAUER, R. W. (1965). Irreversible changes. In *The Physiology of Human Survival* (Ed. O. G. Edholm and A. R. Bacharach), pp. 492–493. London: Academic Press.

CHEVILLARD, L. (1966). Effect of oxygen tension and environmental temperature on the oxygen consumption and body temperature in albino mice. *Federated Proceedings* **25**, 1306–1309.

CLEGG, E. J. & HARRISON, G. A. (1966). Changes in body weight as a parameter of fitness in mice exposed to diminished atmospheric pressure. *Proceedings of the 3rd International Congress of Biometeorology*, pp. 184–190.

CLEGG, E. J. & HARRISON, G. A. (1967). Some phenotypic modifications in rats exposed to reduced atmospheric pressures. *Environmental Research* **1**, 231–239.

GORDON, A. S., TORNETTA, F. J., D'ANGELO, S. A. & CHARIPPER, H. A. (1943). Effects of low atmospheric pressures on the activity of the thyroid, reproductive system and anterior lobe of the pituitary in the rat. *Endocrinology* **33**, 366–383.

HARRISON, G. A. & CLEGG, E. J. (1969). Environmental factors influencing mammalian growth. In *Physiology and Pathology of Adaptation Mechanisms* (Ed. E. Bajusz), pp. 74–85. Oxford: Pergamon.

JACKSON, C. M. (1936). Recovery of rats after a prolonged suppression of growth by dietary deficiency of protein. *American Journal of Anatomy* **58**, 179–193.

MOSIER, H. D. Jr. (1969). Allometry of body weight and tail length in studies of catch-up growth in rats. *Growth* **33**, 319–330.

PRADER, A., TANNER, J. M. & VON HARNACK, G. A. (1963). Catch-up growth following illness or starvation. *Journal of Pediatrics* **62**, 646–659.

SAXTON, J. A. & SILBERG, M. R. (1947). Skeletal growth and ageing in rats receiving complete or restricted diets. *American Journal of Anatomy* **81**, 445–476.

SURKS, M. T. (1966). Effects of hypoxia and high altitude on thyroidal iodine metabolism in the rat. *Endocrinology* **78**, 307–315.

TANNER, J. M. (1962). *Growth at Adolescence* (2nd ed.), pp. 121–134. Oxford: Blackwell.

TANNER, J. M. (1963). The regulation of human growth. *Child Development* **34**, 817–847.

WEIHE, W. H. (1963). Some examples of endocrine and metabolic functions in rats during acclimatization to high altitude. In *The Physiological Effects of High Altitude* (Ed. W. H. Weihe), pp. 33–44. Oxford: Pergamon.