Archs oral Biol. Vol. 17, pp. 799–810, 1972. Pergamon Press. Printed in Great Britain.

DIFFERENCES IN GROWTH PATTERN OF BONE AND INCISOR OF RATS EXPOSED TO O_2 ATMOSPHERIC AND HIGH PRESSURE

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Summary—Three groups of young rats (age 22 days) were exposed intermittently (49 times), over a period of 44 days, group 1 to O_2 at atmospheric pressure (OAP), group 2 to O_2 at high pressure (OHP) (60 psig) and the third to air at atmospheric pressure (AAP) as controls. The average food consumption for the AAP group was 18·85 g, for the OAP 17·55 g and for the OHP 17·07 g per rat per day. The change in the body weights of each of these groups was followed throughout the experiment which continued 13 days after the last exposures. Bone growth of the maxilla, mandible and femur diaphysis and incisor growth were not altered by the OAP exposures, but were decreased by the OHP exposures; incisor growth, however, was increased. Hardness of the bone (by Tukon Hardness Tester) was increased in the OAP and OHP exposures as compared with that of the AAP, but the hardness of the incisors was not altered.

INTRODUCTION

NELSEN (1958) showed that the growth of chick and frog embryos was accelerated during some stages of development under increased oxygen pressure. GOLDHABER (1958) and VAES and NICHOLS (1962) reported that the pathway of bone metabolism was profoundly affected by a relatively small increase in oxygen tension. Repeated exposure of animals to oxygen at high pressure (OHP) results in residual motor disability associated with severe toxic action on the central nervous system (BEAN and SIEGFRIED, 1945; JAMIESON, 1964). Likewise OHP induces pulmonary damage (VAN DEN BRENK and JAMIESON, 1962), convulsive seizure (THOMSON, 1935) and alterations in the endocrine system (BEAN and JOHNSON, 1954). The literature contains no information concerning the possible modification of growth and development of either skeletal bone or incisors exposed to increased O_2 tension. Since incisors continue to grow throughout the life of the rat, they afford an excellent opportunity for a study of change in growth (SCHOUR and STEADMAN, 1935). Thus, the present experiments were carried out to determine what effect, if any, repeated short exposures to O_2 at atmospheric pressure (OAP) or to OHP might have on the growth and development of (1) skeletal bone and (2) the incisors in young rats.

MATERIALS AND METHODS

In these studies, 3 experimental environments were used: air at atmospheric pressure (AAP), oxygen at atmospheric pressure (OAP) and oxygen at high pressure (OHP). For the OAP exposures, a special glass-walled chamber (12 × 24 × 12 in.) was used. A copper coil for circulation of fluid to regulate temperature was suspended from the cover. Oxygen was supplied from commercial

cylinders connected to inflow and outflow tubes at opposite ends of the chamber through which a small continuous flow of O_2 was maintained. The exposures to OHP were made in two cylindrical pressure chambers 9 and 11 in. dia. and 20 in. long, equipped with light, thermometer, glass viewing port and screen floor under which soda lime was placed for the absorption of CO_2. The temperature was held at 26–27°C. Carbon dioxide of the chamber gas as analysed by Beckman Medical Gas Analyser Model LB-1 was found to be less than 0·1 per cent. A Beckman Oxygen Analyser Model E-2 was used to ensure continuous high concentration of O_2.

Thirty-eight Sprague–Dawley male rats were used. At age 22 days, these rats were divided into 3 groups, 12 for exposure to AAP, 12 for OAP and 14 for OHP. At the beginning of the experiment, each rat was anaesthetized with ether and weighed. Upper and lower incisors were marked at the gingival line as described previously (SCHOUR and VAN DYKE, 1932a; NAKAMOTO and WILSON, 1969), and measurements of growth were made at regular intervals over a period of 57 days. The first determinations of body weight and tooth growth were made on the seventh day (age 29 days) but because of the rapidity of tooth growth, all subsequent measurements were made at 5 day intervals.

The OAP and OHP groups were placed into and taken out of the respective environments at the same time, the AAP group was maintained in the home cages.

All exposures were made in a lighted room between 8:00 a.m. and 7:00 p.m. Before each exposure, the OAP and OHP chambers were washed free of air by a rapid flow of O_2; thereafter, the OAP group was maintained in O_2 at atmospheric pressure. The O_2 pressure for the OHP group was then raised to about 60 psig for over a period of 3–5 min and maintained at this pressure over a period from 9 to 23 min, depending upon the severity of reaction due to wide individual difference in susceptibility to oxygen toxicity (BEAN, 1945).

Decompression was then carried out in 4–5 stages to OAP over a period of 15–25 min and animals removed to air at atmospheric pressure. At this time, the exposure of the OAP was also terminated. A total of 49 exposures of identical duration was given to both the OAP and OHP groups. In order to ensure equal feeding time for all groups, the food boxes of the AAP group were removed during the period of exposure of the OAP and OHP groups.

The daily food consumption in each group was carefully determined. After 79 days from birth, all animals were sacrificed by an overdose of sodium pentobarbital, the adrenals and testes were removed and weighed immediately. The left femur, left upper and lower incisors were removed and placed into air-tight plastic bags in order to prevent drying and subsequently tested for hardness. Cross sections of the femur, upper and lower incisors were embedded in Ward's Bioplastic (Natural Science Establishment Inc.). At least 5 different points of cortical areas of each femur and 3 or 4 different points of dentine of both incisors were tested by Tukon Hardness Tester (Wilson Mechanical Inst.) and the Knoop hardness number was calculated (K.500 g). The length between fovea and medial condyle of the right femur and the length of the diaphysis of the same femur between fovea and medial condyle were measured. The animals were then decapitated and the head boiled for 30 min to remove the muscle. The following 3 measurements were made on the maxillae: (a) from the central buccal cusp of the left first molar to the same position of its antimere, (b) from the outer surface of left zygomatic arch to the same position of its antimere, and (c) from the tip of the nasal bone to the external occipital crest. The following measurements of the mandibles were also made: (a) from the anterior aspect of the mandibular foramen to the most distal point on the head of the condyloid process, (b) from the most cephalad surface of the condyle to the most inferior border of the angular process, (c) from the posterior aspect of the mental foramen to the most caudal point on the head of the condyloid process and (d) from the junction of the mesial surface of the first molar with the alveolar bone to the junction of the lingual surface of the incisor with the alveolar bone. The data were analysed statistically using analysis of variance (F test), Scheffe's test and repeated measurement analysis. Differences at the 5 per cent level were considered statistically significant.

RESULTS

Effects of OAP

During the first 7 days of exposure to OAP (age 29 days), the weights of the AAP and OAP rats were the same ($P > 0·05$) (Fig. 1 and Table 1). At age 34 days, the OAP animals weighed more than the AAP. This difference was maintained up to age 59 days ($P < 0·001$). At age 64 days, the difference had about disappeared ($P > 0·05$) and at age 79 days the weights of the OAP group had dropped to below that of

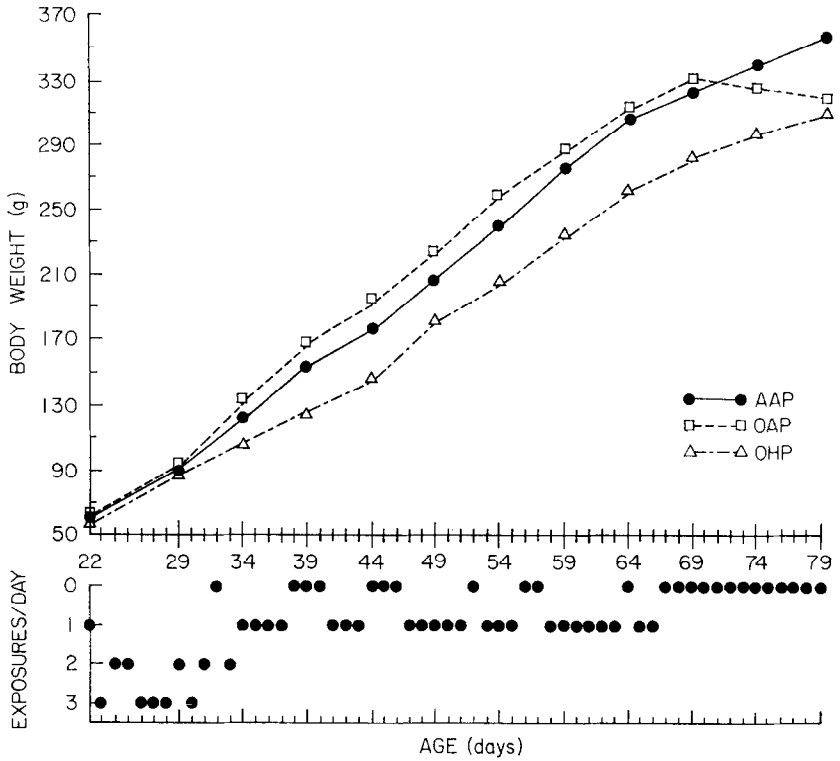

FIG. 1. The average increase of body weight with age. The number of exposures to OAP and OHP per day is indicated by solid circle below the graph.

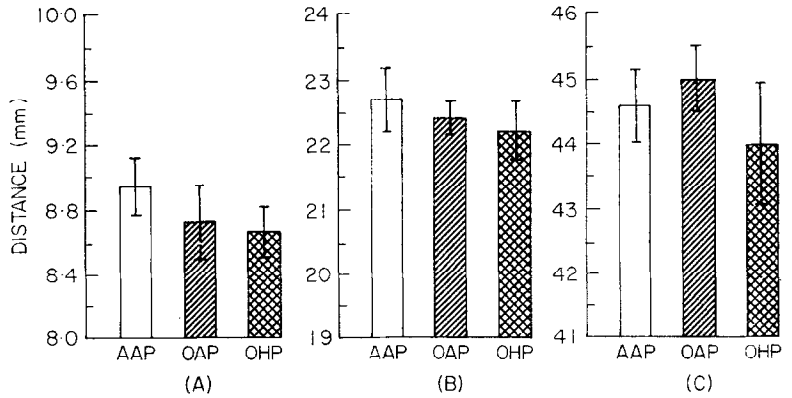

FIG. 2. The effect of intermittent exposures to OAP and OHP on the growth of maxilla in young rats as determined by three measurements between two specified points (A). Central buccal cusp of the left first molar to its antimere, (B) outer surface of zygomatic arch to its antimere, (C) nasal bone to the external occipital crest.

TABLE 1. BODY GROWTH AS INDICATED BY WEIGHT (g)*

	Age (days)											
	22	29	34	39	44	49	54	59	64	69	74	79
AAP	55·08	89·67	123·55	152·17	176·50	208·83	245·08	273·50	307·08	322·08	339·80	358·10
S.D.†	± 2·39	± 5·37	± 7·18	± 8·24	± 9·10	± 12·78	± 13·22	± 14·74	± 16·67	± 15·57	± 19·49	± 19·38
OAP	56·58	93·74	134·17	168·33	196·33	226·83	260·83	287·33	312·00	331·82	329·10	318·60
S.D.	± 4·60	± 5·03	± 8·29	± 8·77	± 12·35	± 12·46	± 12·98	± 15·29	± 17·63	± 15·82	± 18·74	± 18·78
OHP	56·07	89·71	104·69	126·17	147·08	181·83	205·91	238·30	263·40	282·00	297·00	311·14
S.D.	± 2·26	± 4·44	± 8·70	± 10·04	± 11·69	± 12·29	± 13·77	± 14·21	± 17·52	± 16·35	± 19·47	± 18·02

* Each figure represents the average for 9–12 animals.
† Standard deviation.

the AAP ($P < 0{\cdot}001$) (Fig. 1 and Table 1). At the end of the experiment, the width of the maxillary arch in the OAP rats ($P < 0{\cdot}05$) (Fig. 2A) was smaller than that of the controls (AAP) but there was no difference in other measurements of the maxilla between the OAP group and controls ($P > 0{\cdot}05$) (Fig. 2, B, C). The measurements of the mandible, the total length of the femur and of its diaphysis and the weight of testes were not significantly different from that of the controls ($P > 0{\cdot}05$) (Figs. 3

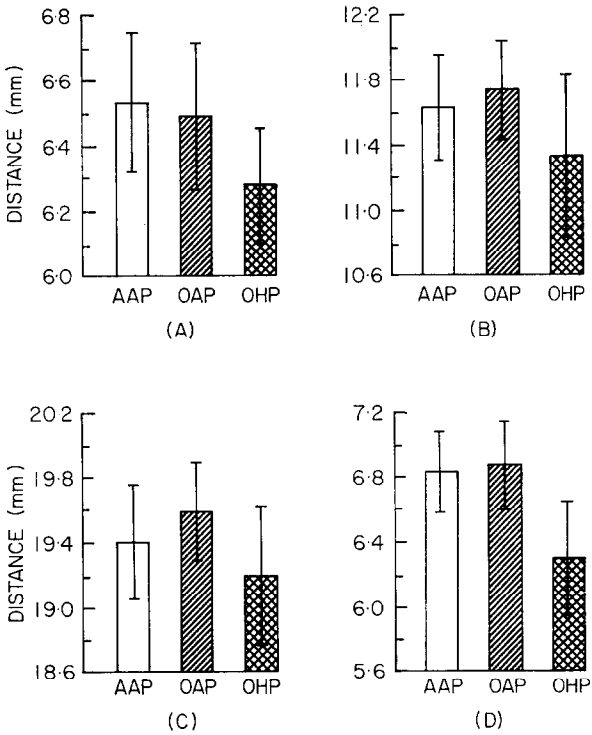

FIG. 3. The effect of intermittent exposures to OAP and OHP on the growth of mandible in young rats as determined by four measurements between two specified points (A) Mandibular foramen to head of condyle, (B) Cephalic surface of the condyle to inferior border of the angular process, (C) Mental foramen to head of condyle, (D) Mesial surface of first molar to lingual surface of the incisors.

and 4). The adrenals of the OAP weighed more than those of the AAP group ($P < 0{\cdot}001$) (Fig. 4).

The growth rates of the upper and lower incisors of the OAP group (Tables 2 and 3) were the same as those of the controls ($P > 0{\cdot}05$) (Fig. 5). The dentine hardness of both incisors was also the same as that of the controls (K.500 g) ($P > 0{\cdot}05$) (Fig. 6). The hardness of the femur in the OAP animals was increased over that of the controls ($P < 0{\cdot}01$) (Fig. 6). Average daily food consumption per rat per day of the OAP group was 17·55 g and that for the control AAP 18·85 g.

Effects of OHP

Five rats exposed to the OHP died, autopsies of these showed lung damage. After 7 days exposures to OHP (age 29 days), the average body weight of these animals, like that of the OAP group, were essentially the same as that of the controls (AAP), ($P > 0{\cdot}05$) (Fig. 1 and Table 1). However, at the 12th day of exposures (age 34 days), the weight of the OHP group was 18 g less than that of the AAP group ($P < 0{\cdot}001$).

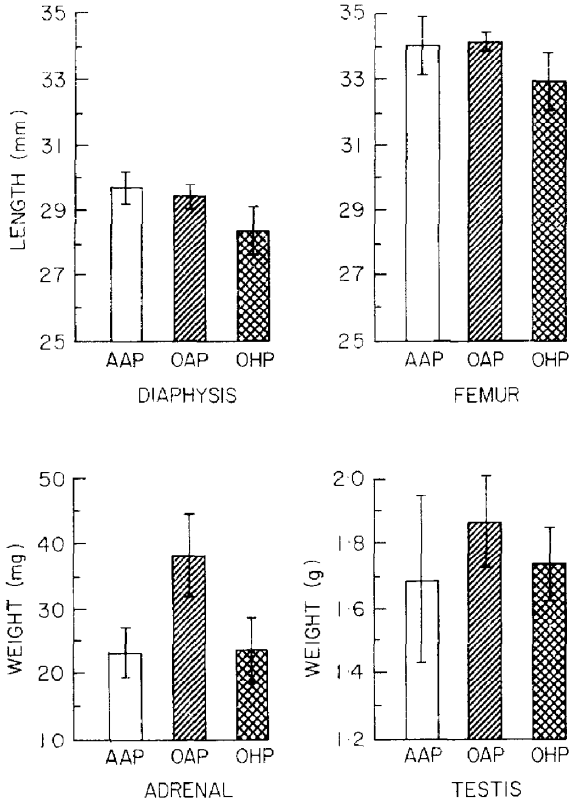

FIG. 4. The influence of intermittent OAP and OHP exposures on the length of the femur between fovea and medial condyle, the length of its diaphysis and weight of adrenal and testis.

This difference increased progressively so that at the end of the experiment the average weight of the OHP animals was 47 g less than that of the controls ($P < 0{\cdot}001$) (Fig. 1 and Table 1). All measurements made as described above for the maxilla, mandible, femur and diaphysis were less in the OHP animals than in the controls (AAP), indicative of a retardation of skeletal development ($P < 0{\cdot}01$) (Figs. 2–4). The average weights of the adrenals and of the testes of the animals in this group were not significantly different from those of the controls (AAP) ($P > 0{\cdot}05$) (Fig. 4).

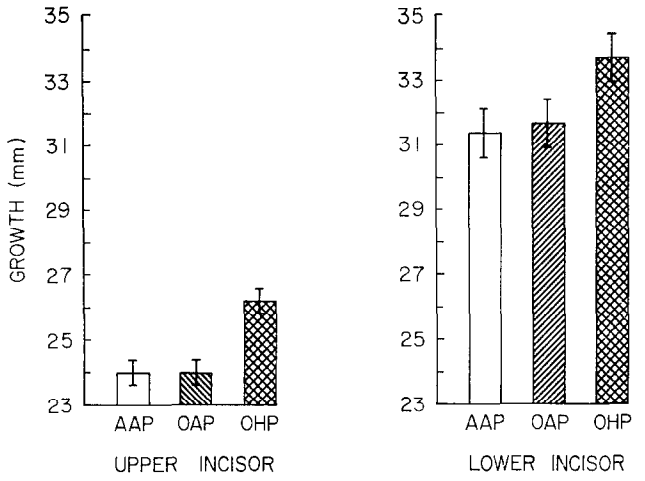

FIG. 5. Total growth of incisors in young rats as influenced by intermittent exposure to OAP and OHP over a period of 57 days.

The growth rates of upper and lower incisors (Tables 2 and 3) were significantly greater in the OHP than in the controls (AAP) ($P < 0{\cdot}001$) (Fig. 5). The hardness of the dentine of both incisors of the OHP group was not significantly different from that of the controls (K. 500 g) ($P > 0{\cdot}05$) (Fig. 6), but the hardness of the femur in the OHP group was much greater than that of the controls (AAP) ($P < 0{\cdot}001$) (Fig. 6). Average daily food consumption per rat per day of the OHP group was 17·07 g.

The body weights of the OAP and OHP group were the same during the first 7 days of exposure ($P > 0{\cdot}05$) (Fig. 1 and Table 1). Following this there was a progressive separation of the average body weight in these 2 groups which continued to

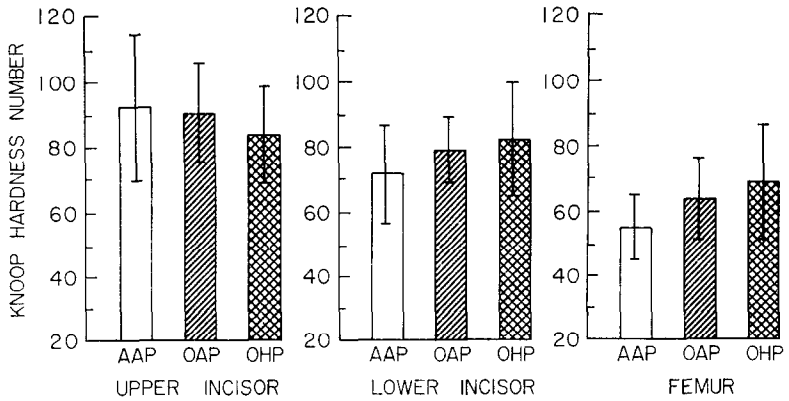

FIG. 6. The influence of intermittent OAP and OHP exposures on the hardness (*K* 500 g) of incisor and femur in young rats. Each bar represents the average of 40–50 measurements.

TABLE 2. AVERAGE GROWTH RATE OF UPPER INCISOR TEETH (mm)*

	Age (days)											Total growth (mm)
	29	34	39	44	49	54	59	64	69	74	79	
AAP	3·22	2·09	2·34	2·21	2·06	2·30	2·14	1·99	2·04	1·95	1·66	24·00
S.D.†	± 0·34	± 0·24	±0·18	± 0·20	±0·24	± 0·20	± 0·23	± 0·14	± 0·23	± 0·16	± 0·20	± 0·39
OAP	3·41	2·10	2·13	2·00	1·98	2·29	2·31	1·97	1·86	2·06	1·90	24·01
S.D.	± 0·35	± 0·35	± 0·17	± 0·18	± 0·20	± 0·18	± 0·21	± 0·26	± 0·16	± 0·17	± 0·23	± 0·43
OHP	3·48	2·42	2·30	2·49	2·20	2·42	2·23	2·18	2·22	2·05	2·11	26·10‡
S.D.	± 0·32	± 0·24	± 0·12	± 0·25	± 0·15	± 0·22	± 0·24	± 0·21	± 0·19	± 0·14	± 0·27	± 0·39

* Each figure represents the average for 9–12 animals.
† Standard deviation.
‡ This figure is significantly higher ($P < 0·001$) than for the other groups.

TABLE 3. AVERAGE GROWTH RATE OF LOWER INCISOR TEETH (mm)*

	Age (days)											Total growth (mm)
	29	34	39	44	49	54	59	64	69	74	79	
AAP	5·02	2·79	3·02	2·66	2·85	2·69	2·59	2·44	2·54	2·43	2·37	31·40
S.D.†	± 0·27	± 0·23	± 0·20	± 0·22	± 0·18	± 0·23	± 0·25	± 0·13	± 0·21	± 0·15	± 0·21	± 0·74
OAP	5·05	3·07	2·72	2·89	2·57	2·74	2·68	2·44	2·52	2·42	2·55	31·65
S.D.	± 0·23	± 0·23	± 0·25	± 0·21	± 0·12	± 0·18	± 0·34	± 0·19	± 0·20	± 0·12	± 0·20	± 0·75
OHP	5·23	3·78	3·15	3·15	2·97	2·73	2·67	2·36	2·52	2·27	2·89	33·72‡
S.D.	± 0·34	± 0·37	± 0·45	± 0·34	± 0 ·20	± 0·40	± 0·60	± 0·44	± 0·43	± 0·18	± 0·18	± 0·83

* Each figure represents the average for 9–12 animals.
† Standard deviation.
‡ This figure is significantly higher ($P < 0·001$) than for the other groups.

age 69 days. The differences then rapidly diminished, largely due to the decreasing weight of the OAP group, so that at age 79 days the weights were about the same (Fig. 1 and Table 1). Measurement of the maxillary arch and the width of the maxilla in the OAP and OHP groups were the same ($P > 0{\cdot}05$) (Fig. 2, A, B) but the long axis of the maxilla was greater in the OAP than in the OHP animals ($P < 0{\cdot}01$) (Fig. 2C). The several measurements made of the mandible, femur and diaphysis showed that bone growth was greater in the OAP than the OHP group ($P < 0{\cdot}01$) (Fig. 4). The growth rates of the incisors (Tables 2 and 3) were greater in the OHP group than in the OAP group ($P < 0{\cdot}001$) (Fig. 5). The hardness of dentine of both incisors and of the femur was the same in OAP and OHP groups ($P > 0{\cdot}05$) (Fig. 6). The adrenals in the OAP group were heavier than those of the OHP ($P < 0{\cdot}001$) (Fig. 4). The weights of the testes were not significantly different from those of the controls (AAP) ($P > 0{\cdot}05$) (Fig. 4).

DISCUSSION

The results (Fig. 1 and Table 1) show that the average body weight of the OAP group exceeded that of the controls (AAP) whereas that of the OHP group was less. This difference became particularly evident only after 20–27 exposures. The question arises whether this difference could be related to the food intake. During the first week, (age 29 days) the average increase in body weight of the OAP group exceeded that of the controls by about 4 g (4·6 per cent), at age 44 days, after 33 exposures, by 20 g (11·2 per cent), at age 59 days, after 43 exposures, by 14 g (5·1 per cent). In contrast with this, the average food intake of the OAP group over each of these 3 periods was about the same, i.e. only slightly greater than that of the controls (0·5g per rat per day). Thus, it would appear that this disproportionately greater increase of the body weight of the OAP group over that of the controls cannot be explained simply on the basis of a difference in food intake. This might suggest that the intermittent OAP exposures had some salutary effect on the growth. Shortly after age 66 days (i.e. after the 49th and last exposure), the OAP group began to lose weight, so that at age 79 days the average body weight had fallen to 40 g below that of the controls. During this final period, the average food intake in the OAP group was 3 g less than that of the controls. The cause of this unexpectedly abrupt decrease in food intake with the cessation of the OAP exposures was not immediately evident, particularly because of the general healthy appearance of the animal. The abrupt decrease in body weight may represent some late adverse effect of the O_2 due to a post-oxygen exposure anorexia. However, because of the intermittency and the relatively short O_2 exposure, one would have hardly expected such pronounced effects.

During the first week (age 29 days), after 19 exposures, the average body weights of the OHP and AAP control groups were identical, although the food intake of the OHP was 0·7 g per rat per day less than that of the controls. At age 44 days, after 33 exposures, the average body weight of the OHP rats was 30 g less than that of the controls, but the food intake of this group was only 2 g less. This difference in body weight became more apparent as the experiment continued (Fig. 1 and Table 1) in spite of the fact that the food intake of the OHP group was still only 2 g per rat per

day less than that of the controls. At age 79 days, after 49 OHP exposures, the average body weight was 47 g less. It would appear that this progressively increasing difference in body weight between OHP group and the controls (AAP) cannot be attributed simply to the difference in food intake. This decreased body weight is in accord with previous findings (BEAN and JOHNSON, 1954). If the decreased growth rate of the OHP group cannot be reasonably attributed to decreased food intake, it may be related to the toxic action of OHP due to some neuro-endocrinological influence on metabolism (BEAN and JOHNSON, 1954; EPSTEIN, ERIKSON and REYNOLD, 1960).

Excessive prolongation of repeated exposure to OHP may cause not only an initial hypertrophy (BEAN and JOHNSON, 1954; EPSTEIN *et al.*, 1960), but also a secondary late decrease in the adrenal weight (unpublished observation). This may explain why the adrenal weight in the OHP group at the end of the experiment was no greater than that of the controls (Fig. 4). In the OAP group, the increased weight of the adrenal gland at the end of the experiment, usually indicative of a condition of stress (Fig. 4), was associated with the terminal decrease of body weight as compared with that of the controls (Fig. 1 and Table 1).

At the end of the experiment, the body weights of the OAP and OHP groups were less than that of the controls (Fig. 1 and Table 1), but the weights of the testis were the same (Fig. 4). This lack of positive correlation is in contrast to previous finding (NAKAMOTO and WILSON, 1969).

The measurements of the mandible, maxilla, femur, diaphysis, and growth rate of incisor were about the same in both the AAP and OAP groups ($P > 0{\cdot}05$) (Figs. 2–5). Other investigators have found that, under increased O_2 tension over a short period, the periosteal proliferation and growth rate were initially increased and later decreased (MANSPLIZER and TONNA, 1967; PERSSON, 1967; PERSSON, 1968). Present data, however, show that over a period of 57 days (age 22–79 days) skeletal development and incisor growth were not affected by intermittent exposure to increased O_2 tension at atmospheric pressure. On the other hand, in the OHP group, the bone growth on all parameters studied was less than that of the controls (Figs. 2–4). This was particularly evident in those animals which were exposed to the point where the toxic action of OHP on the CNS precipitated O_2 convulsions.

It has been shown that vitamin A deficiency (SCHOUR and MASSLER, 1949) and hypophysectomy (SCHOUR and VAN DYKE, 1932b) retarded the growth of incisors. Exposures of the animals to fluorescent tube lighting increased growth of both bone and incisors (NAKAMOTO and WILSON, 1969), but exposure to low O_2 in simulated high altitude did not alter the incisor growth (GERSH and RESTARSKI, 1944). It is of particular interest in our experiments that, while the exposure to OHP retarded the body and bone growth, it strikingly increased the growth of the incisors (Fig. 5 and Tables 2 and 3). Past experiments have shown that incisor growth is closely related to pituitary function (SCHOUR and VAN DYKE, 1932b; NAKAMOTO and WILSON, 1969). It has also been shown that OHP has a profound effect on the pituitary and corticoadrenal function (Bean, 1952). Possibly the increased growth of the incisors was due to the effect of OHP mediated through the pituitary to the odontogenic epithelium from which incisors develop (SCHOUR and MASSLER, 1949). Thus, finding

that tooth growth was increased in those animals which experienced convulsive seizure might indicate that the convulsions influenced tooth growth through neuro-endocrinological changes. This apparent difference in effect of OHP might suggest 2 diverse actions on the pituitary, one which increases the tooth growth and the other which decreases the growth of bone and body weight.

The data show that there was no difference statistically in the hardness of the dentine in any of the groups ($P > 0{\cdot}05$) (Fig. 6) but that of the bone was increased in both OAP and OHP groups (Fig. 6). This effect of increased oxygen on the bone hardness may be mediated through the parathyroid gland which influences bone hardness (WEINMAN and SICHER, 1955).

Acknowledgements—We wish to express thanks to Dr. JAMES K. AVERY and Dr. ROBERT G. CRAIG for their suggestions, and to Mr. EDWARD DOOTZ for his assistance in measuring hardness. This investigation was supported in part by Grant H.E.O. 1646 and USPHS DE 00013 from the National Institutes of Health.

Résumé—Trois groupes de jeunes rats (âge 22 jours) ont été exposés par intermittence (49 fois) sur une période de 44 jours, le groupe 1 à l'O_2 à une pression atmosphérique (OPA), le groupe 2 à l'O_2 à haute pression (OHP) (60 psig) et le troisième groupe à l'air, pression atmosphérique normale (APA) comme contrôle. La consommation moyenne de nourriture pour le groupe APA a été de 18,85 g, pour le OPA 17,55 g et pour le OHP 17,07 g par rat par jour. Le changement pour cent du poids corporel de chaque groupe a été suivi dans tout le cours de l'expérience qui continua pendant 13 jours après la dernière exposition. La croissance de l'os de la machoîre, de la mandibule, du fémur, de la diaphyse et la croissance de l'incisive étaient cependant accrue. Le dureté de l'os (déterminée avec le Tukon Hardness Tester) était accrue dans les expositions OPA et OHP, comparées avec celle de l'APA, mais la dureté des incisives n'était pas altérée.

Zusammenfassung—Drei Gruppen junger Ratten, (22 Tage alt), wurden für eine Dauer von 44 Tagen abwechselnd wie folgt ausgesetzt: Gruppe 1 einem atmosphärischen Druck von O_2, (OAP), Gruppe 2 einem Hochdruck (OHP) (60 psig) von O_2, und die dritte Gruppe als Kontrolle einem atmosphärischen Druck (AAP) von Luft. Die durchschnittliche Nahrungsaufnahme der AAP Gruppe war 18,85 g, für die OAP Gruppe 17,55 g und für die OHP Gruppe 17,07 g pro Ratte und Tag. Die prozentuale Änderung des Körpergewichts jeder dieser Gruppen wurde für die Dauer des Experiments verfolgt, was für 13 Tage nach den letzten Begasungen fortgesetzt wurde. Knochenwachstum der Maxilla, der Mandibula, des Schenkelbeins, der Diaphyse und Wachstum der Schneidezähne wurden durch die OAP Begasungen nicht geändert, nahmen aber bei der OHP Begasung ab, Wachstum der Schneidezähne nahm allerdings zu. Knochenhärte, (nach Tukon Härtetest), nahm für die OAP und OHP Begasungen im Vergleich zu der AAP zu, die Härte der Schneidezähne änderte sich aber nicht.

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