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Growth spurt in rat cranial bases transplanted into adult hosts

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INTRODUCTION

We have recently shown, by using transplantation to isohistogenic hosts as the principal experimental technique, that rat cranial bases are capable of growth independent of their normal environment and that there was no difference between the lengths of cranial bases and humeri transplanted to weanling and adult hosts and recovered one month later (Harkness, 1974; 1976). That the lengths of the transplants recovered from hosts of such widely separated ages were essentially similar suggested to us that factors additional to circulating hormones might be important in regulating the growth of the transplants.

Circulating hormones are generally held responsible for the spurt found in many skeletal dimensions in man around the time of adolescence (Blizzard *et al.* 1974; Tanner, 1975). A check in the decline of velocity or 'relative spurt' occurs in many measurements in rats about the time of puberty and is thought to correspond to the adolescent growth spurt in man (Hanada, 1967; Hughes & Tanner, 1970; Hughes, Tanner & Williams, 1978). But as Roche (1974) has shown, bones may differ in the timing of their maximum increments in length within individuals. It would appear, therefore, that intrinsic factors in the skeleton itself might be important in determining the changes in rate of growth at different ages.

In this study we have investigated the pattern of change in the growth rate of bones growing independently of factors operating *in situ* by following longitudinally the growth of young rat cranial bases transplanted to older hosts.

MATERIALS AND METHODS

All animals used in this study were of the AS2 strain of isohistogenic rats and they were housed under identical conditions. Twelve newborn rats, six male and six female, were used as donors and twelve older rats as hosts. On the day of transplantation the mean age of the male hosts was 54 days (S.D 15·26 days) and the female hosts 60·7 days (S.D. 9·58 days). On the day of birth the donors were weighed, anaesthetized singly with ether and decapitated. The mean weight of the male donors was 5·72 g (S.D. 0·21 g) and the female donors 5·43 g (S.D. 0·31 g). The cranial base, consisting of basioccipital, basisphenoid, a small fragment of presphenoid bones and the two synchondroses, was excised carefully (Fig. 1). Fragments of muscle, nasal epithelium and brain tissue were removed, care being taken not to damage the periosteum over the intracranial and ectocranial surfaces of the transplant. The transplants were then placed in subcutaneous pockets in the lateral abdominal walls of twelve sex-matched hosts.

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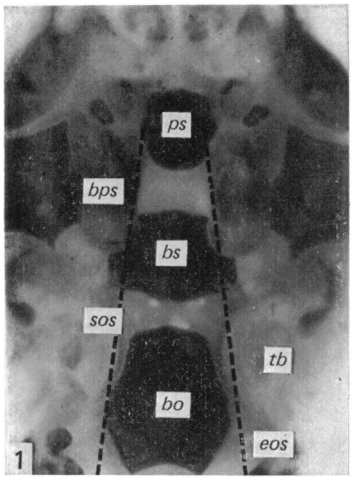

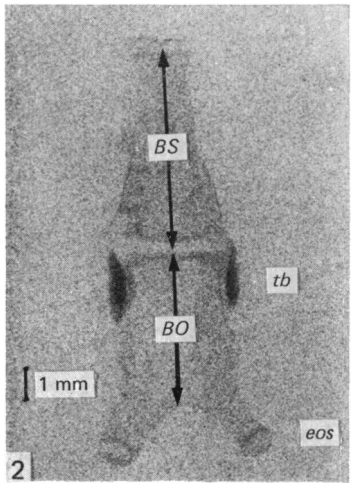

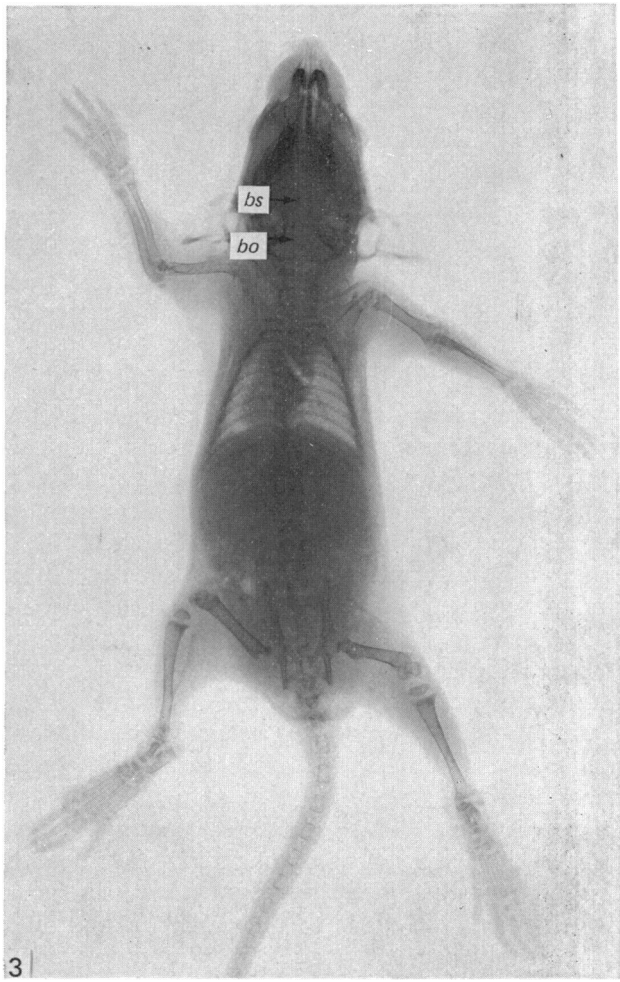

Fig. 1. Cranial base of a newborn rat exposed and viewed from above. The bones excised and transplanted are outlined (----). Abbreviations for all Figures: *ps*, presphenoid; *bps*, basipresphenoid synchondrosis; *bs*, basisphenoid; *sos*, spheno-occipital synchondrosis; *bo*, basiocciput; *eos*, exoccipita lsynchondrosis; *tb*, tympanic bulla. Basiocciput is approximately 3 mm long.

Fig. 2. Radiograph of a 33 days old cranial base transplant. *BO*, basioccipital length (basion – mid-point spheno-occipital synchondrosis); *BS*, basisphenoid length (mid-point spheno-occipital synchondrosis – mid-point basipresphenoid synchondrosis). All measurements were made along the long axis of the cranial base.

Fig. 3. Radiograph of a 19 days old female control rat. The lengths of basioccipital and basisphenoid bones were measured between the reference points given in Fig. 2.

Standardised contact radiographs were taken of the transplants in the hosts and standardised whole body radiographs taken of six male and six female rats (the 'controls'), from the same strain at weekly intervals from 5 to 61 days of age and fortnightly intervals from 61 to 89 days of age. When radiographs of the transplants were taken each host was anaesthetized with ether, the skin overlying the transplants shaved and a fold of skin containing the transplant was drawn out laterally and held in contact over an ultra fine-grain dental film. Standardised whole body radiographs were taken of the anaesthetized controls using the method des-

cribed by Hughes & Tanner (1970) with the modification that the animal was positioned so that the central ray passed through the base of the neck. An ultra fine-grain non-screen industrial film, with similar grain characteristics to the dental film, was used for these radiographs (Fig. 3).

All radiographs were taken with a Siemens Heliophos 4S X-ray generator with a target size of 0·6 mm square. Exposures were made using the 'falling load' facility possible with this machine, the KVp and mAs being varied to suit the age of the transplant or animal. The anode-film distance was fixed at 97 cm for all exposures.

The lengths of basioccipital and basisphenoid bones were measured on the radiographs of the transplants and of the intact animals using the method described by Björk & Solow (1962) (Fig. 2). Two transparent mylar sheets scribed with fine lines were positioned over the landmarks with the aid of a ×2·5 loupe. The distance was measured with a × 8 eyepiece graticule and rounded down to the nearest 0·1 mm. The measurements were repeated three times after lifting and replacing the sheets and the mean of the three measurements used to calculate the statistics and construct individual distance and velocity graphs for the transplants and controls. These graphs were used to identify the adolescent growth spurt. The statistics for velocity of growth were calculated from actual increments for each animal between successive ages and the statistics for the lengths from the data available at each age. The means were compared by Student's *t* test and associations between host age and length and velocity of growth investigated by Pearson product-moment correlation coefficients.

To estimate the errors in the method of measurement 50 randomly selected radiographs of the transplanted bones and 50 randomly selected radiographs of the controls were re-measured several weeks later. No significant differences were found between the measurements taken on the two occasions. The mean differences varied between 0·005 mm (S.D. difference 0·061 mm) for basisphenoid lengths in the controls and 0·003 mm (S.D. difference 0·037 mm) for basioccipital lengths in the transplants. The errors in positioning the controls and the transplants were also investigated by repeating a number of radiographs on the same day. No differences were found in the lengths of either basioccipital or basisphenoid bones on the radiographs of the transplants. The standard deviation of the measurements taken from sixteen radiographs of a control was 0·03 mm for the lengths of both bones.

The standard deviation of the difference between duplicate measurements was 1·28 % of the mean value for basioccipital lengths in the controls, 1·03 % of the mean for basisphenoid length in the controls, 0·89 % of the mean for basioccipital length in the transplants and 0·76 % for basisphenoid length in the transplants. The reliability of these measurements is slightly less than those reported by Hughes & Tanner (1970) for longer arm, leg and pelvis lengths but greater than those reported by Hughes, Tanner & Williams (1978) for skull measurements. Greater difficulty was experienced in measuring the controls because of superimposition and slight blurring of some of the radiographs due to respiration. In general, landmarks on the radiographs of the transplants were easily identified and measured.

RESULTS

The results are given in Tables 1–3 and Figures 4–13.

The length and velocity curves for basiocciput and basisphenoid in the transplants are plotted against the mean postnatal age of the host and the period of implantation of the transplants. The latter is equivalent to the postnatal ages of the donors

Table 1. *Mean lengths, standard deviations and standard errors of the means of basi-occipital and basisphenoid bones in controls and transplants. Studied longitudinally by means of weekly or fortnightly radiographs*

				Controls					Transplants		
	Age (days)	*N*	Bone	Mean length (mm)	S.D.	S.E.	Mean host age (days)	*N*	Mean length (mm)	S.D.	S.E.
Males	5	6	BO	3·50	0·14	0·06	59	5	3·29	0·10	0·04*
			BS	3·25	0·08	0·03			2·77	0·09	0·04‡
	12	6	BO	4·08	0·07	0·03	66	5	3·88	0·07	0·03†
			BS	4·30	0·08	0·03			3·60	0·15	0·07‡
	19	6	BO	4·34	0·08	0·03	73	5	4·13	0·18	0·08*
			BS	4·92	0·12	0·05			4·36	0·28	0·13†
	26	6	BO	4·68	0·13	0·05	80	5	4·28	0·16	0·07†
			BS	5·42	0·09	0·04			4·85	0·31	0·14†
	33	6	BO	4·99	0·13	0·05	87	5	4·29	0·25	0·11‡
			BS	5·80	0·09	0·04			5·17	0·31	0·14‡
	40	6	BO	5·26	0·16	0·06	94	5	4·34	0·23	0·10‡
			BS	6·13	0·09	0·04			5·30	0·46	0·20†
	47	6	BO	5·50	0·17	0·07	101	5	4·40	0·33	0·15‡
			BS	6·38	0·09	0·04			5·41	0·46	0·20‡
	54	6	BO	5·77	0·22	0·09	108	5	4·33	0·37	0·17‡
			BS	6·62	0·17	0·07			5·57	0·50	0·22‡
	61	6	BO	6·04	0·26	0·11	115	4	4·19	0·28	0·14‡
			BS	6·85	0·18	0·07			5·73	0·57	0·28†
	75	6	BO	6·23	0·29	0·12	129	4	4·08	0·36	0·18‡
		5	BS	7·09	0·15	0·07			5·84	0·68	0·34†
	89	5	BO	6·38	0·42	0·19	143	4	4·06	0·29	0·15‡
			BS	7·22	0·15	0·07			5·85	0·69	0·35†
Females	5	6	BO	3·44	0·09	0·03	66	6	3·34	0·13	0·05
			BS	3·23	0·05	0·02			2·83	0·17	0·07‡
	12	6	BO	4·02	0·11	0·04	73	6	3·77	0·25	0·10*
			BS	4·27	0·08	0·03			3·40	0·16	0·06‡
	19	6	BO	4·35	0·13	0·05	80	6	4·08	0·26	0·11*
			BS	4·97	0·08	0·03			3·95	0·19	0·08‡
	26	6	BO	4·71	0·17	0·07	87	6	4·31	0·34	0·14*
			BS	5·36	0·09	0·04			4·38	0·19	0·08‡
	33	6	BO	4·91	0·19	0·08	94	6	4·41	0·40	0·16*
			BS	5·76	0·13	0·05			4·68	0·26	0·11‡
	40	6	BO	5·18	0·24	0·10	101	6	4·41	0·28	0·11‡
			BS	6·04	0·09	0·04			4·92	0·23	0·10‡
	47	6	BO	5·41	0·29	0·12	108	6	4·48	0·34	0·14‡
			BS	6·42	0·11	0·04			5·01	0·27	0·11‡
	54	6	BO	5·68	0·18	0·07	115	6	4·57	0·36	0·15‡
			BS	6·64	0·14	0·06			5·12	0·35	0·14‡
	61	6	BO	5·80	0·15	0·06	122	6	4·54	0·39	0·16‡
			BS	6·78	0·17	0·07			5·23	0·40	0·16‡
	75	6	BO	5·95	0·27	0·11	136	5	4·67	0·38	0·17‡
			BS	6·92	0·16	0·06			5·49	0·30	0·13‡
	89	6	BO	6·18	0·27	0·11	150	5	4·65	0·39	0·18‡
			BS	7·08	0·15	0·06			5·51	0·31	0·14‡

Control mean significantly different from transplant mean at: * 5% level, † 1% level ‡ 0·1% level.

had they lived. The curves for basiocciput and basisphenoid in the controls are plotted against postnatal age.

The number of animals and transplants studied was small and losses occurred in the controls because films of one rat were blurred slightly with the result that the

Table 2. *Mean velocities, standard deviations and standard errors of the mean velocities of basioccipital and basisphenoid bones in controls and transplants*

				Controls			Transplants			
	Age (days)	*N*	Bone	Mean velocity (mm/day)	S.D.	S.E.	*N*	Mean velocity (mm/day)	S.D.	S.E.
Males	5–12	6	BO	0·082	0·026	0·011	5	0·085	0·021	0·009
			BS	0·150	0·013	0·005		0·119	0·019	0·008†
	12–19	6	BO	0·036	0·015	0·006	5	0·035	0·021	0·010
			BS	0·089	0·023	0·009		0·109	0·022	0·010
	19–26	6	BO	0·048	0·025	0·010	5	0·022	0·017	0·008
			BS	0·071	0·012	0·005		0·069	0·010	0·004
	26–33	6	BO	0·045	0·010	0·004	5	0·002	0·021	0·010†
			BS	0·054	0·009	0·004		0·046	0·020	0·009
	33–40	6	BO	0·038	0·014	0·006	5	0·007	0·005	0·002†
			BS	0·048	0·009	0·004		0·019	0·026	0·011*
	40–47	6	BO	0·035	0·023	0·009	5	0·009	0·018	0·008
			BS	0·035	0·009	0·004		0·015	0·012	0·005*
	47–54	6	BO	0·038	0·024	0·010	5	−0·009	0·007	0·003†
			BS	0·034	0·021	0·009		0·023	0·008	0·003
	54–61	6	BO	0·037	0·017	0·007	4	−0·002	0·015	0·007†
			BS	0·033	0·024	0·010		0·014	0·007	0·003
	61–75	6	BO	0·014	0·006	0·003	4	−0·008	0·009	0·005†
		5	BS	0·020	0·009	0·004		0·008	0·009	0·004
	75–89	5	BO	0·013	0·015	0·007	4	−0·002	0·005	0·003
			BS	0·009	0·016	0·007		0·001	0·001	0·001
Females	5–12	6	BO	0·082	0·017	0·007	6	0·061	0·024	0·010
			BS	0·148	0·010	0·004		0·082	0·027	0·011‡
	12–19	6	BO	0·048	0·016	0·006	6	0·045	0·032	0·013
			BS	0·101	0·004	0·001		0·079	0·013	0·005†
	19–26	6	BO	0·052	0·023	0·009	6	0·032	0·014	0·006
			BS	0·056	0·011	0·005		0·061	0·005	0·002
	26–33	6	BO	0·029	0·029	0·012	6	0·015	0·022	0·009
			BS	0·056	0·008	0·003		0·042	0·016	0·006
	33–40	6	BO	0·038	0·025	0·010	6	0	0·024	0·010*
			BS	0·040	0·013	0·005		0·034	0·006	0·003
	40–47	6	BO	0·033	0·017	0·007	6	0·009	0·016	0·006*
			BS	0·054	0·011	0·005		0·013	0·013	0·005‡
	47–54	6	BO	0·039	0·020	0·008	6	0·013	0·005	0·002*
			BS	0·032	0·012	0·005		0·016	0·019	0·008
	54–61	6	BO	0·017	0·018	0·007	6	−0·004	0·007	0·003*
			BS	0·019	0·016	0·006		0·016	0·013	0·005
	61–75	6	BO	0·011	0·012	0·005	5	0·002	0·006	0·002
			BS	0·010	0·006	0·002		0·008	0·008	0·004
	75–89	6	BO	0·016	0·007	0·003	5	−0·001	0·003	0·001‡
			BS	0·011	0·008	0·003		0·002	0·003	0·001*

Control mean significantly different from transplant mean at: * 5% level, † 1% level, ‡ 0·1% level.

basipresphenoid synchondrosis could not be seen clearly. In the male transplants one bone was excluded from the start because it was distorted and shorter on recovery than at implantation. It was the only transplant that failed to increase in length and the only one to become distorted. However, even this transplant showed a marked spurt in the velocity of growth of basisphenoid at 45 days of age (Fig 12). The basipresphenoid synchondroses on two transplants, one male and one female, disappeared towards the end of the study. Typically this end of the transplants became extremely slender and it was thought that they may have been broken off

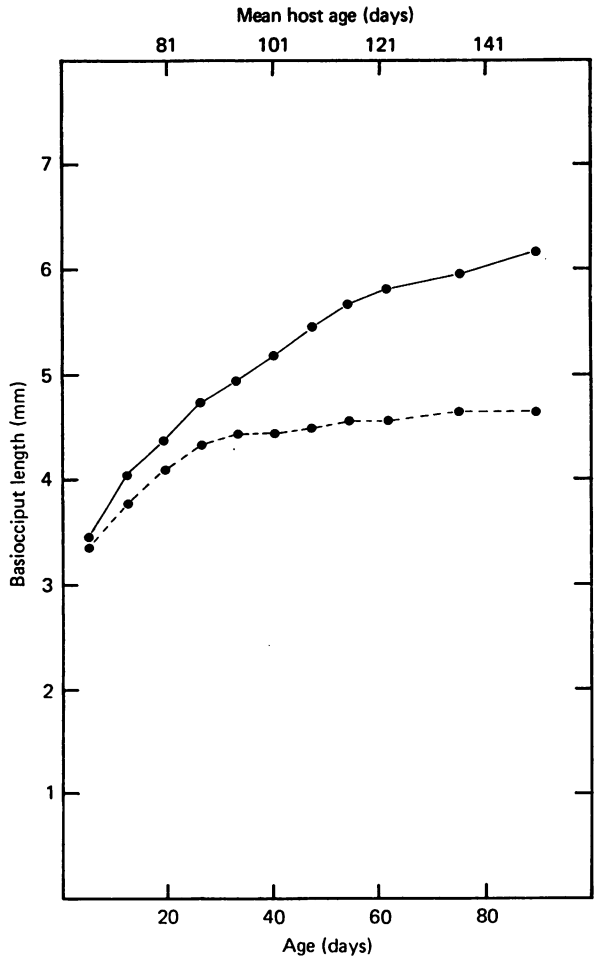

Fig. 4. Basioccipital length of female controls and transplants. Controls, ——; transplants, – – –.

during a radiography session. In these transplants we have excluded the measurement of basioccipital length as well because it is possible that growth at the sphenooccipital synchondrosis may have been altered by the absence of basipresphenoid synchondrosis (DuBrul & Laskin, 1961). Since both bones are enclosed by the same length of periosteum the activity of the synchondroses will place it under tension. Each synchondrosis will tend, therefore, to inhibit the other via the periosteum so that if one is absent growth at the remaining synchondrosis may be altered (Crilly, 1972; Pritchard, 1972; Dawson & Kember, 1974; Harkness & Trotter, 1978). No control or host rats were lost during the course of the study and all transplants were recovered although the anterior ends of two of them were missing as mentioned above.

Basioccipital length (*Figs.* 4–7, *Tables* 1, 2)

The basiocciput was longer in the controls than in the transplants; these differences are significant from 5 days in the males and 12 days in the females. The distance curves of both groups of transplants resemble the curves of their controls until

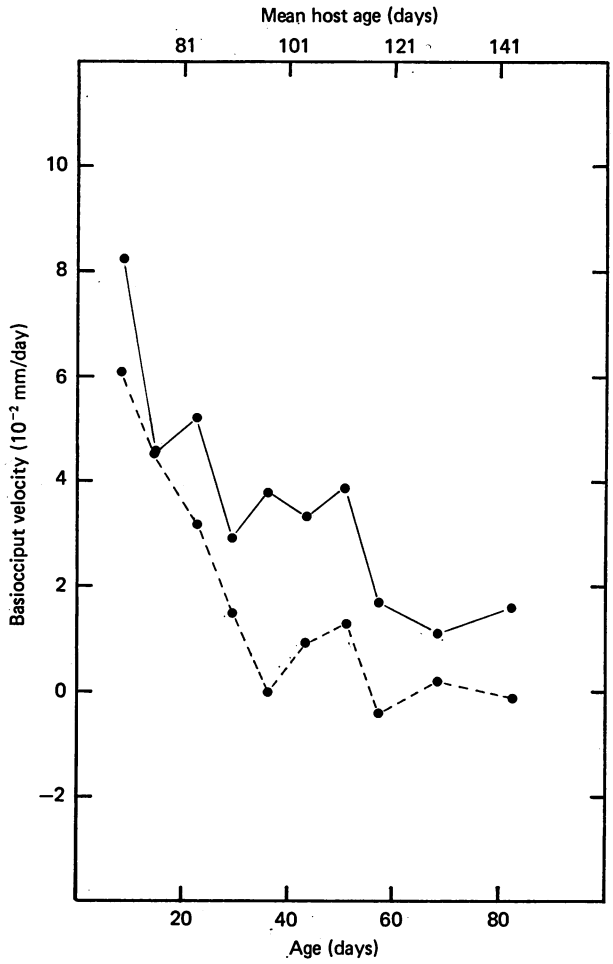

Fig. 5. Basioccipital velocity of female controls and transplants. Controls, ——; transplants, – – –.

about 20 days. The curve for the female transplants then levels off whereas the curve for the female controls increases steadily to about 60 days, levels off to about 75 days and increases to 89 days. The curve for the male transplants follows an undulating course to 50 days and then falls to 89 days. This shortening of basiocciput was greater in the transplants in the males and was due to resorption at basion. That such resorption occurred was confirmed histologically and radiographically with the aid of metallic implants (unpublished work).

The velocity curve for the male controls shows a marked fall to 15 days followed by an increase to 20 days which then falls gradually to 45 days, rises again to 50–55 days and then falls fairly sharply to 70 days and more gradually to 80 days. On the other hand the curve for the transplants falls sharply to 15 days, less sharply to 30 days and then rises to 45 days, falls to 50 days, rises slightly to 55 days, falls again to 70 days and rises slightly to 80 days. The velocity curve of the female controls falls sharply to 15 days, rises slightly to 20 days, falls fairly sharply to 30 days and then rises to give two peaks, at 35 and at 50 days. The velocity curve of

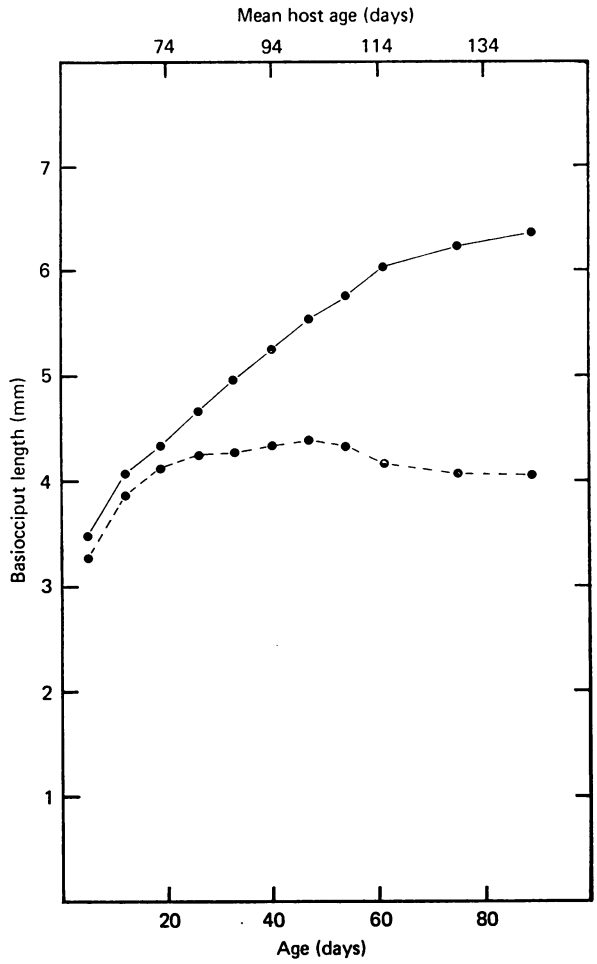

Fig. 6. Basioccipital length of male controls and transplants. Controls, ——; transplants, ---.

the female transplants closely resembles that of the male transplants with the exception that the peak occurs at 50 days, about 7 days later than in the males.

Basisphenoid length (*Figs.* 8–13, *Tables* 1, 2)

Basisphenoid length in the male controls increases rapidly to 50 days, increases more sharply to 60 days and then levels off to 90 days. Basisphenoid length in the transplants follows the general curve of the controls until 30 days when it levels off to 40 days, increases between 45 and 60 days and then levels off to 90 days. The curve of basisphenoid lengths in the female controls resembles that of the male controls with the exception that there is a noticeable increase in length between 40 and 45 days. The curve for the basisphenoid in the female transplants diverges from that of the controls but is of the same general shape. There is an increase in length between 60 and 75 days.

The velocity curve for basisphenoid in the male controls falls steeply to 30 days, levels off slightly to 35 days, falls to 45 days where there is a noticeable plateau or

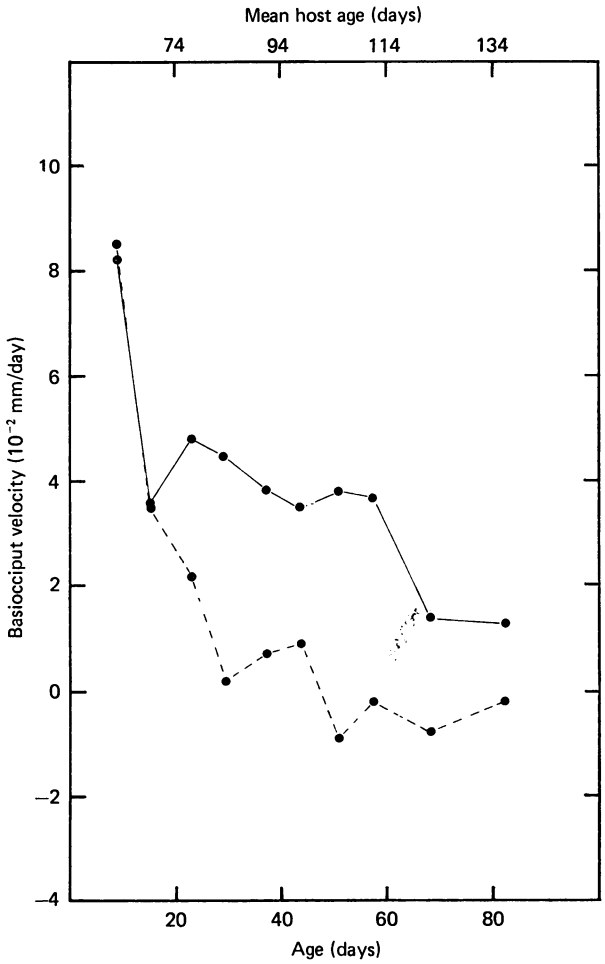

Fig. 7. Basioccipital velocity of male controls and transplants. Controls, ——; transplants, ---.

relative spurt to 55 days. It then falls from 55 to 80 days. The velocity curve in the transplants resembles closely that of the controls; there is a small spurt at 50 days coinciding with the relative spurt in the controls.

The velocity curve of basisphenoid in the female controls shows the same rapid decline in velocity as in the males to 20 days followed by a small plateau to 30 days and a prominent spurt at 45 days. Although both plateau and spurt occur about one week earlier than in the male controls, in both cases they are one week apart. In the female transplants the velocity curve falls less sharply to 30 days, has a small step to 35 days then falls to 45 days. This is followed by a small flat-topped spurt between 50 and 55 days. The curve of basisphenoid velocity in the female transplants resembles the curves in both male controls and transplants more closely than the female controls which had earlier and more prominent spurts.

Associations between host age, length and velocity of growth (*Table* 3)

In the male transplants a positive and statistically significant correlation coefficient was found between the age of the host and the length of basiocciput at 5 days.

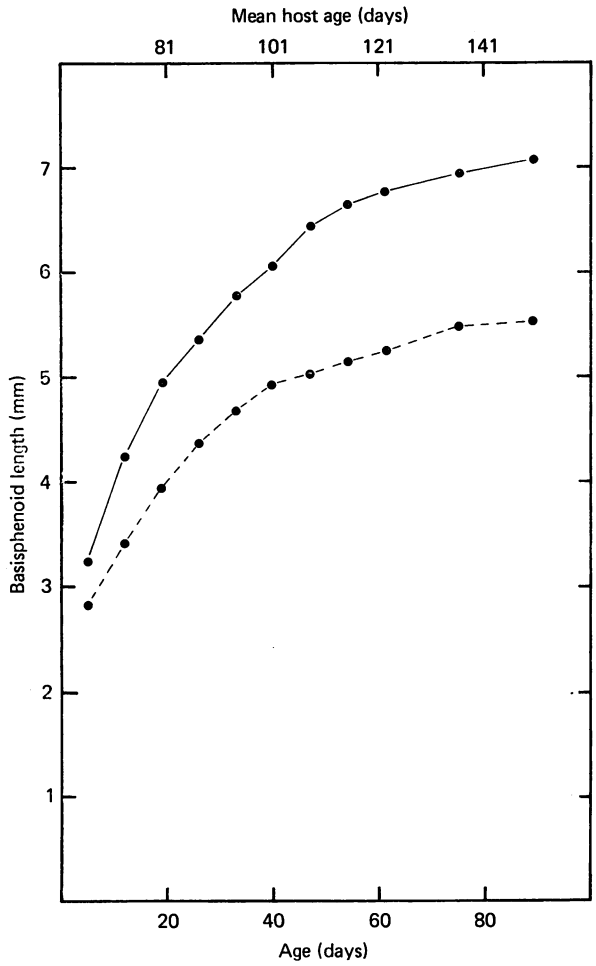

Fig. 8. Basisphenoid length of female controls and transplants. Controls, ——; transplants, ---.

Significant negative correlations were found for basisphenoid length at 33 days and basisphenoid velocity between 47 and 54 days. High negative correlation coefficients were found between host age and the length of basisphenoid from 12 to 89 days.

Negative and statistically significant correlation coefficients were found between host age and basioccipital length in the female transplants between 19 and 89 days and for basioccipital velocity between 19 and 26 days and 54 and 61 days. The coefficients for basisphenoid length in the female transplants were generally negative and lower than those for the male transplants. Between 19 and 26 days basisphenoid velocity in the females was positive and significantly correlated with host age.

No significant differences were found between the time the spurt occurred in basisphenoid in either the male transplants (mean age 50·5 days, S.D. 4·95 days) and the male controls (mean age 51·7 days, S.D. 10·06 days) or the female transplants (mean age 50·5 days, S.D. 8·85 days) and the female controls (mean age 42·9 days, S.D. 3·44 days). Likewise no significant associations were found between host age and the time when the adolescent growth spurt occurred in basisphenoid in the six male transplants ($r-0{\cdot}29$) or the six female transplants ($r-0{\cdot}33$).

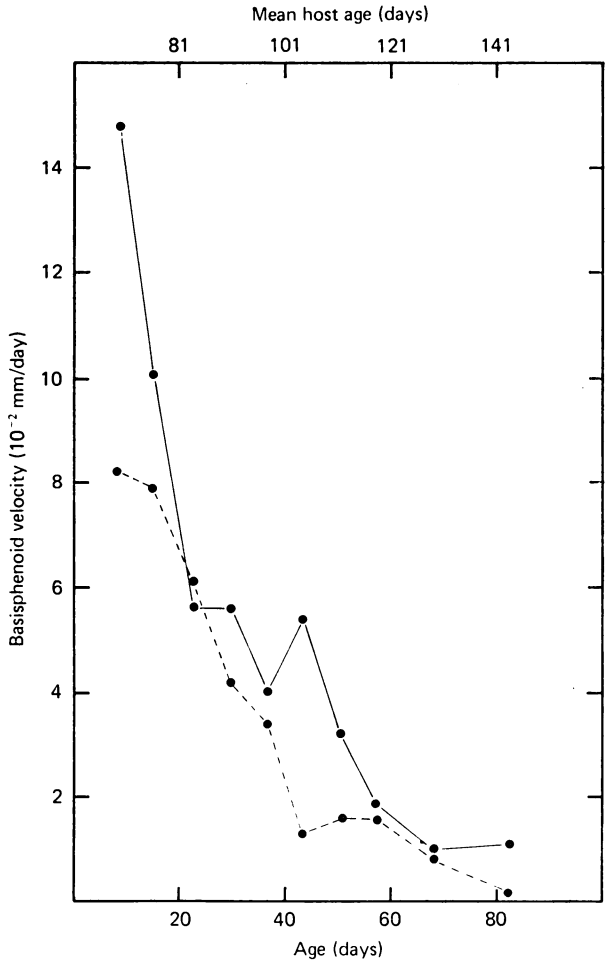

Fig. 9. Basiphenoid velocity of female controls and transplants. Controls, ——; transplants, ---.

A negative and statistically significant correlation coefficient was found between host age and the magnitude of the spurt in basisphenoid in the five male transplants ($r-0{\cdot}92$, $P < 0{\cdot}05$) but not the female transplants ($r-0{\cdot}40$).

DISCUSSION

The results of this study in which the growth of transplanted cranial bases was followed longitudinally and compared with the growth of cranial bases *in situ* support the hypothesis that the control of the timing of growth velocity changes is autonomous to the cranial base. Factors present in the host affected the lengths of both basiocciput and basisphenoid to different extents in male and female host but did not affect the timing of the adolescent growth spurt.

In the rat most measurements of the head, body and limbs show a spurt or check in the decline of velocity or relative spurt at about the time of puberty (Hanada, 1967; Miura *et al.* 1969; Hughes & Tanner, 1970; Vilmann, 1973; Hughes, Tanner & Williams, 1978) which is thought to correspond to the adolescent growth spurt

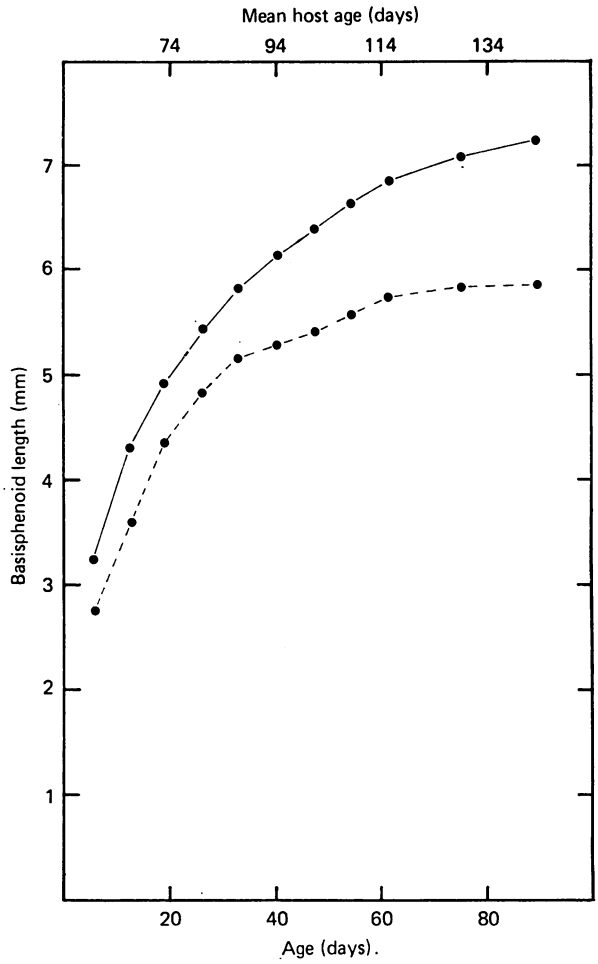

Fig. 10. Basisphenoid length of male controls and transplants. Controls, ——; transplants, – – –.

seen in man and other primates (Tanner, 1962). In this study the velocity curves of body weight of the controls were similar to curves given by Hanada (1967) and Hughes & Tanner (1970). Likewise Vilmann's (1973) longitudinal data of the growth of the basisphenoid *in situ* had relative spurts corresponding to the relative spurt in our male controls and the spurt in our female controls. After summing the lengths of basiocciput and basisphenoid we compared data from our controls with Hanada's (1967) results. The inflections in the velocity curves of his controls and ours corresponded closely. His females, however, showed a double-peaked spurt between 25 and 40 days. In both studies the spurt in the females occurred just before the relative spurt in the males. We have concluded from these comparisons that the velocity curves given for our controls are essentially similar to those for other strains of rats.

Growth spurts occurred in the basisphenoid at about the same time in both transplants and controls. There was, however, less similarity between the velocity curves of basiocciput in the transplants and controls. We attribute this to the fact

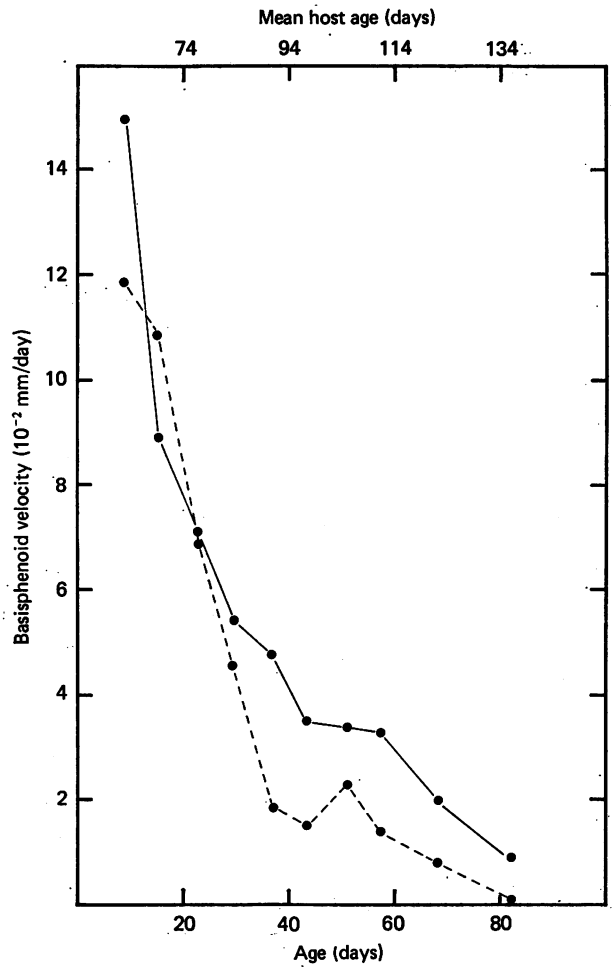

Fig. 11. Basisphenoid velocity of male controls and transplants. Controls, ——; transplants, ---.

Table 3. *Correlation coefficients expressing the relation between the age of the host and the length and velocity of growth of the transplants*

Age (days)	N	Male transplants: Basiocciput	Male transplants: Basisphenoid	N	Female transplants: Basiocciput	Female transplants: Basisphenoid
5	6	0·83*	−0·45	6	−0·34	0·11
12 (5–12)	5	0·33 (−0·33)	−0·63 (−0·25)	6	−0·32 (−0·22)	−0·29 (−0·33)
19 (12–19)	5	0·23 (0·11)	−0·74 (−0·74)	6	−0·93‡ (−0·72)	−0·18 (0·11)
26 (19–26)	5	0·32 (0·09)	−0·81 (−0·65)	6	−0·95‡ (−0·85*)	−0·02 (0·92‡)
33 (26–33)	5	−0·13 (−0·56)	−0·88* (−0·16)	6	−0·93‡ (−0·35)	−0·16 (−0·32)
40 (33–40)	5	−0·19 (−0·33)	−0·76 (−0·40)	6	−0·88* (0·79)	−0·20 (−0·15)
47 (40–47)	5	−0·02 (0·32)	−0·69 (0·36)	6	−0·94‡ (−0·69)	−0·25 (−0·21)
54 (47–54)	5	−0·08 (−0·46)	−0·75 (−0·99‡)	6	−0·91† (−0·13)	−0·31 (−0·32)
61 (54–61)	4	−0·20 (−0·37)	−0·76 (0·14)	6	−0·94‡ (−0·87*)	−0·31 (−0·15)
75 (61–75)	4	0·11 (0·74)	−0·72 (−0·47)	5	−0·88* (−0·33)	0·29 (−0·38)
89 (75–89)	4	0·13 (−0·04)	−0·72 (−0·44)	5	−0·91* (−0·68)	0·35 (0·63)

Host age significantly correlated with transplant at: * 5% level, † 2% level, ‡ 1% level.

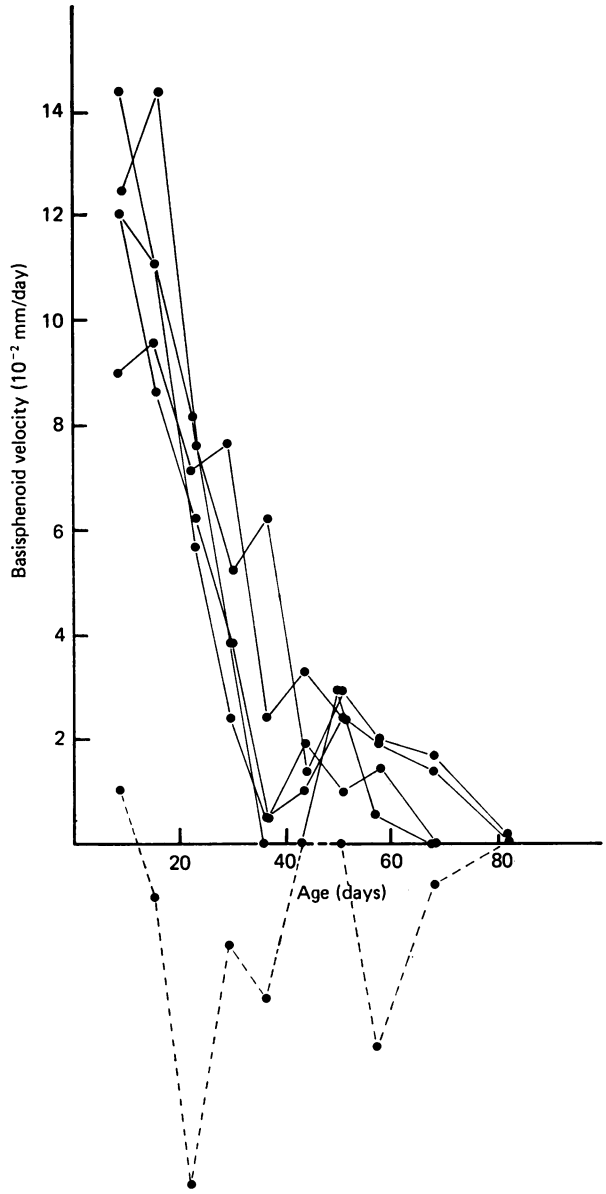

Fig. 12. Basisphenoid velocity of individual male transplants.
Distorted transplant, ---.

that *in situ* new bone is deposited at both ends of the basiocciput whereas in the transplants it is deposited at the rostral end only. The velocity curves of the basiocciput in the two groups of transplants were similar and we postulate that this may represent the basic pattern of growth from the caudal half of the spheno-occipital synchondrosis. The finding of a spurt in the basisphenoid, even in the distorted transplant, supports this suggestion (Fig. 12).

The similarity in the velocity curves of the basisphenoid in the male transplants and controls is striking. The curve for the male transplants shows a small spurt

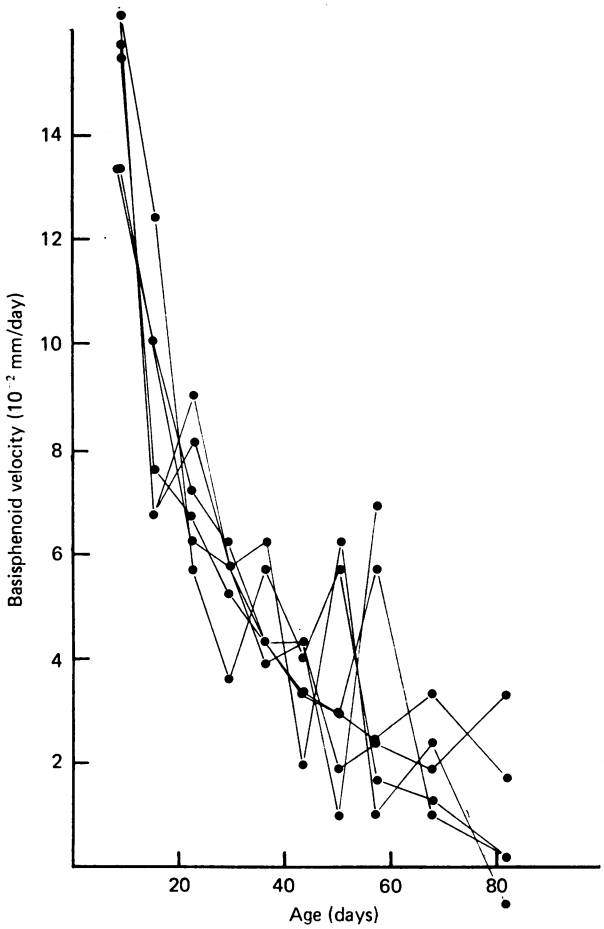

Fig. 13. Basisphenoid velocity of individual male controls.

corresponding to a relative spurt in the male controls. The mean host age at this time was approximately 100 days. Greater variation in the time of the spurt in the male controls compared to the transplants had an averaging effect on the mean which resulted in a step rather than a definite spurt. The spurt in the basisphenoid velocity in the female transplants occurred about one week later than the spurt in the female controls. We attribute this to the fact that three of the transplants were by chance 'late developers' with spurts occurring between 36 and 43 days of age. Although we are dealing with a carefully inbred strain of rats it should be emphasized that the basis of selection for homozygosity has been transplantation antigens and that there can still be individual differences in the other genes, for example, that for age at maturity.

The basisphenoid, capped by cartilaginous growth plates at both ends, was not shortened by resorption in either the transplants or the controls whereas the basi-occiput with a cartilaginous growth plate at the rostral end only, actually decreased in length in the transplants, but not *in situ*. This was due to resorption at basion, the caudal end of the bone. In the growing rat new bone is deposited at this margin and along the caudal end of the ectocranial surface (Cleall, Wilson & Garnett, 1968;

Vilmann, 1971). We postulate that this occurs because the periosteum in the area of basion is put under tension to a greater extent by the activity of the exoccipital synchondroses, the growing cervical spine and muscular action than by that of the spheno-occipital synchondrosis with the result that new bone is deposited at this margin (Pritchard, 1972; Donnelly, Swoope & Moffett, 1973). In the transplanted specimens tension arising from growth of the cervical spine and muscle action was absent, although fragments of the exoccipital synchondroses were present in the transplants for some of the time (Fig. 2). We think that the periosteum passing over the centre of the transplant and around basion is put under tension by the activity of the spheno-occipital synchondrosis with the result that it was compressed against the surface of the bone, thus producing bone resorption (Ackerman, Cohen & Cohen, 1966; Harkness & Trotter, 1978).

The basiocciput was longer in the female transplants compared with the male transplants and correlated significantly with host age (Tables 1, 3). These differences in basioccipital length appear to be due to differences in amount of resorption at basion rather than differences in endochondral growth at the spheno-occipital synchondrosis. Basisphenoid was longer in the female transplants at 5 days than in the males and shorter at 89 days which indicated that less endochondral growth had occurred in the females. If endochondral ossification was affected to the same extent on both sides of the spheno-occipital synchondrosis the greater length of basiocciput must have been due to a slower rate of resorption at basion in the females. This conclusion is supported by our finding that less resorption and less endochondral growth occurred in transplanted humeri in female hosts compared with transplanted humeri in male hosts. These humeral transplants were also followed longitudinally but with the added advantage that we used metallic implants to enable areas of resorption to be identified (unpublished observations).

The correlation coefficients between the host ages and the lengths and velocities of growth of the transplants were calculated from the same hosts and transplants at each age and are, therefore, mutually inter-dependent. Under most circumstances the coefficients at one age would serve for all ages. In this study the strength of the relationships varied from one age to the next and several significant coefficients occurred at different ages. This is possibly due to sampling variation and the significant correlations may be due to chance but they may also be the reflection of some biological process operating at that time. We postulate that the significant coefficient for velocity of growth of the basisphenoid in the males between 47 and 54 days occurred in response to some biological process, but we have no satisfactory explanation of the significant coefficient in the females. Age-related levels of oestrogen may be responsible for these findings because it is known to inhibit resorption *in vivo* (Budy, Urist & McLean, 1952; Lindquist, Budy, McLean & Howard, 1960). However, little is known about actual tissue levels of oestrogen in rats of ages similar to those of the female hosts (Döhler & Wuttke, 1975; Germain, Campbell & Anderson, 1978) or of the mode of action of oestrogen on bone and cartilage (Caputo, Meadows & Raisz, 1976; DeLuca, 1977). Furthermore it is possible that more than one factor may be involved as Raisz *et al.* (1978) suggest.

In the male transplants there was a significant negative correlation between host age and velocity of growth between 47 and 54 days and a trend for the basisphenoid to be longer in the younger hosts. These findings may be due to higher levels of growth-stimulating substances, such as somatomedin, in the younger hosts but again it seems likely that other factors such as testosterone and insulin may well be

involved (Blizzard *et al.* 1974; Raisz *et al.* 1978). The finding that the timing of the adolescent growth spurt in the basisphenoid was not affected by the age of the host indicates that the potential for determining the timing of the spurt resides within the donor bones and most probably in the synchondroses. Had host factors, such as a rise in the level of circulating hormones, been responsible for the spurt we should not have found a spurt in the transplants in the adult hosts; while in the transplants in the pre-adolescent hosts, the spurt should have occurred shortly after transplantation. The importance of donor factors is further illustrated by the finding that humeri removed from the same immature donor and transplanted to different hosts were frequently of similar size and shape whereas humeri from different donors in the same host were not (unpublished observations).

This study provides evidence that the control of the pattern of growth is autonomous to cells of the cranial base. It suggests that circulating hormones do not determine the timing of the adolescent growth spurt; their role appears to be to augment a pattern of growth determined genetically.

SUMMARY

The growth of young rat cranial bases, consisting of the basioccipital, basisphenoid and a fragment of presphenoid bones, transplanted to older sex-matched isohistogenic hosts has been studied longitudinally.

Detailed figures are given for absolute growth and velocity of growth both in transplants and *in situ*.

Similarities between the pattern of growth of basisphenoid and in particular the timing of the so-called adolescent growth spurt in the transplanted bones and *in situ* were found. There was less similarity in the pattern of velocity changes in basiocciput. This was attributed to resorption of basion in the transplants.

Significant negative correlations were found between host age and basioccipital length in the females and the velocity of growth of the basisphenoid in the males between 47 and 54 days. There was also a trend for host age to be negatively correlated with basisphenoid length in the males.

These findings support the view that intrinsic, presumably genetic, factors regulate the pattern of timing of growth velocity changes in the cranial base.

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