Archives of Disease in Childhood 1990; 65: 1038–1042

Spontaneous resolution of bone mineral depletion in preterm infants

P J Congdon, A Horsman, S W Ryan, J G Truscott, H Durward

Abstract

Fifteen preterm infants and 17 born at full term whose gestational ages ranged from 25 to 34 weeks and 38 to 42 weeks, respectively, were examined initially at postconceptional ages ranging from 38 to 44 weeks and subsequently at 46 to 71 weeks. Each examination included measurement of bone mineral content of the mid-forearm by single photon absorptiometry. For the preterm group, the mean (SD) value of bone mineral content at the first examination was 109·0 (27·6) mg/cm and was significantly lower than the corresponding value of 194·4 (19·6) mg/cm for the whole full term group. The mean subsequent rate of mineral accretion in the preterm group was 8·70 (4·60) mg/cm/week, the mean individual duration of observation being 9·7 weeks. Rate of mineral accretion for the full term group was independent of the duration of observation and averaged 1·60 (2·20) mg/cm/week. The difference between mean values of rate of mineral accretion in the preterm and full term groups was highly significant.

Our results show that there is a phase of rapid mineral accretion starting at 40 weeks' postconception in preterm infants that substantially reduces the perinatal mineralisation deficit.

We and others have previously shown that at 40 weeks' postconception the bones of preterm infants are substantially undermineralised compared with those of full term infants at birth.[1 2] The bone mineral deficit, assessed by single photon absorptiometry of the mid-forearm,[3] is roughly 20% in very low birthweight (<1500 g) infants,[1] and the deficit is even larger (about 35% after adjustment for crown-heel length or weight differences) in extremely low birthweight infants (<1000 g) born earlier.[2]

In a subsequent investigation in which we studied preterm and full term infants in the postconceptional age range 65 to 100 weeks and examined the results in the context of earlier observations we found that, by about 60 weeks, the bone mineral deficit that had been noted in preterm infants at 40 weeks had largely disappeared.[4] That conclusion, which we had not anticipated, was based solely on cross sectional observations. The data none the less strongly suggested that individual preterm infants must mineralise their bones rapidly in the period from 40 to 60 weeks' postconception, at a time when mineral accretion in full term infants is relatively slow.

In this paper we report our first longitudinal observations of mineral accretion in preterm and full term infants, which were made to test the hypothesis that, in many infants, osteopenia of prematurity is a transient condition that heals with time without direct clinical intervention.

Patients and methods

This study was approved by the local ethics committee. Thirty two infants born between 1984 and 1989 were examined. They were all white singletons whose parents gave informed consent for the investigations to be carried out, and who were prepared to bring their babies back to the neonatal unit for measurement when necessary. Of the 32, 15 infants (eight boys) had been born prematurely and comprised the 'preterm group—group P. The remaining 17 (nine boys), who were born after roughly 40 weeks' gestation, comprised the 'full-term group'—group F—and served as controls. Group F included a subgroup—group F1—that comprised seven infants (five boys). Those in group F1 were infants born at full term who were measured at postconceptional ages closely similar to those in group P (see below).

Infants in group P were born in or referred to our neonatal intensive care unit during a 36 month period that began in 1985. Twelve of the 15 were of appropriate weight for gestational age at birth, but three were small for dates. While in the unit, 12 were included in studies of the efficacy of various feeding regimens in promoting bone mineral accretion during the neonatal period (SW Ryan, J James, PJ Congdon, A Horsman, JG Truscott. Effect of vitamin D supplementation on bone mineralisation in preterm infants. Unpublished observations).[5] All infants had been fed with standard neonatal formulas from the onset of milk feeding until weaning, including four control infants from the mineral supplementation study who received 400 IU/day vitamin D supplementation throughout.[5] Eight infants had taken part in a vitamin D supplementation study (0·15 μg 1 α hydroxyvitamin D/day (n=3), 400 IU vitamin D/day (n=3), or 1000 IU vitamin D/day (n=2)), until the time of the measurement, which was about 40 weeks' postconception. After this those infants subsequently received 400 IU/day vitamin D. The remaining three infants were fed standard neonatal formulas plus 400 IU/day vitamin D. Infants received a maximum of 180 to 200 ml/kg/day of formula feed while in hospital, and although such intakes were recommended for infants at home they often received more. Absorptiometry was first performed

The General Infirmary, Leeds LS2 9NS
Regional Neonatal Surgical and Intensive Care Unit
P J Congdon

Medical Research Council Bone Mineralisation Group, Department of Medical Physics
A Horsman
J G Truscott

Department of Paediatrics
S W Ryan
H Durward

Correspondence to:
Dr Ryan.

Accepted 4 April 1990

Table 1 Descriptive statistics for gestational age, postconceptional age, weight, crown-heel length, and bone mineral content at the first and second observation times.

	Gestational age (weeks)	At 39–44 weeks				At 46–71 weeks			
		Postconceptional age (weeks)	Weight (g)	Crown-heel length (cm)	Bone mineral content (mg/cm)	Postconceptional age (weeks)	Weight (g)	Crown-heel length (cm)	Bone mineral content (mg/cm)
Group P:									
No of infants	15	15	15	12	15	15	13	11	15
Mean (SD)	29·07 (2·87)	40·89 (1·28)	2377 (599)	44·99 (3·76)	109·00 (27·60)	50·61 (3·05)	4028 (737)	54·11 (3·32)	191·67 (53·02)
Range	25·00–34·00	39·14–43·86	1550–3600	39·50–50·60	60·14–153·17	46·14–56·86	2670–5250	48·80–59·00	100·08–286·32
Group F:									
No of infants	17	17	17	17	17	17	17	17	17
Mean (SD)	40·24 (1·20)	40·73 (1·28)	3402 (405)	50·57 (1·71)	194·37 (19·62)	60·24 (7·41)	6895 (1253)	64·85 (4·56)	230·26 (56·16)
Range	38·00–42·00	38·43–42·71	2795–4270	47·30–54·50	165·25–221·21	47·14–70·29	4100–9400	53·10–71·00	168·75–370·79
Group F1:									
No of infants	7	7	7	7	7	7	7	7	7
Mean (SD)	40·57 (0·79)	41·02 (0·91)	3576 (382)	50·91 (2·33)	195·01 (21·81)	54·16 (3·35)	5938 (870)	61·29 (3·83)	206·81 (35·60)
Range	40·00–42·00	40·14–42·57	3050–4270	47·30–54·50	166·06–221·21	47·14–57·14	4100–6505	53·10–64·10	168·75–268·34

within days of discharge or during a return visit shortly afterwards. All returned for a subsequent measurement.

The 17 full term infants in group F were recruited from the local postnatal ward and were measured before discharge. All returned for a subsequent measurement. Those who were below the 10th centile for birth weight on standard charts were not entered in the study.[6] With five exceptions, all the infants born at full term received formula feeds from birth; the remainder were breast fed, with weaning starting at about 3 months.

Gestational age (completed weeks), calculated from maternal menstrual history and confirmed, for the preterm group, by either external examination,[7] or ophthalmoscopic examination of the lens,[8] had been documented in each case. For group P, gestational age ranged from 25 to 34 weeks (mean (SD) 29·1 (2·9) weeks), and for group F it ranged from 38 to 42 weeks (mean (SD) 40·2 (1·2) weeks). The mean gestational age of group F1 was 40·6 (0·8) weeks (table 1).

On two occasions bone mineral content (mg/cm) was measured at the middle of the forearm of each infant by photon absorptiometry as previously described.[1 3] The radiation exposure is small, and only a narrow area of the forearm is irradiated during a scan; skin entrance dose is 0·03 mGy/investigation. Weight (g) and crown-heel length (cm) were usually measured whenever a scan was performed.

In the postconceptional age range of 39 to 44 weeks, complete data (weight, crown-heel length, and bone mineral content were obtained in 12 of the 15 preterm infants in group P; in three infants crown-heel length was not measured. Results obtained at that time are referred to as 'term data'. All 15 infants in group P were later scanned in the period 46 to 57 weeks' postconception, when they attended for outpatient review. In two infants, neither weight nor crown-heel length was measured on the day of the second scan; in another two, crown-heel length was not measured. Results obtained at that later time are referred to as 'endpoint data'.

Soon after birth, in the postconceptional age range 38 to 43 weeks, complete term data weight, crown-heel length and bone mineral content were obtained for all full term infants in group F. All 17 infants were later scanned in the period 47 to 71 weeks' postconception, and the data obtained in that interval were also complete.

Infants in group F1 were selected from all full term infants (group F) and comprised those with both term and endpoint data acquired in the postconceptional age range 40 to 58 weeks; this range is closely similar to the range for group P (39 to 57 weeks). Descriptive statistics for the term and endpoint data are given in table 1 for groups P, F1, and F.

STATISTICAL ANALYSIS

Rate of mineral accretion was derived for each infant as the change in bone mineral content

Table 2 Rates of change of the measurements in the interval between the first and second observations

	Interval between first and second observations (weeks)	Rate of weight gain (g/week)	Increase in crown-heel length (cm/week)	Rate of mineral accretion (derived from observed changes in bone mineral content (mg/cm/week))
Group P:				
No of infants	15	13	11	15
Mean (SD)	9·72 (2·87)	178·7 (32·1)	0·970 (0·153)	8·7 (4·60)
Range	5·14–16·72	139·2–247·1	0·725–1·226	−1·04–17·64
Group F:				
No of infants	17	17	17	17
Mean (SD)	19·51 (7·08)	180·0 (38·2)	0·754 (0·097)	1·60 (2·20)
Range	7·00–28·00	102·9–232·1	0·562–0·900	−0·98–6·91
Group F1:				
No of infants	7	7	7	7
Mean (SD)	13·14 (3·19)	176·0 (46·7)	0·793 (0·065)	0·87 (1·97)
Range	7·00–17·00	102·9–232·1	0·686–0·868	−0·98–4·29

divided by the time interval between absorptiometric observations. Rates of weight gain and linear growth were similarly calculated. Group mean values of these and other variables were compared among groups using Student's *t* test.

Results

When mean values in group P were compared with those of groups F1 and F (table 1) at the start of the study (near 40 weeks' postconception) the preterm infants were significantly lighter than the full term infants, the difference between the means exceeding 1000 g (group P compared with group F1—difference 1200 g, p<0·001; group P compared with group F—difference 1025 g, p<0·001). The preterm infants were also significantly shorter, the difference between the means exceedng 5 cm (group P compared with group F1—difference 5·92 cm, p<0·002; group P compared with group F—difference 5·58 cm, p<0·001). The mean values of bone mineral content differed widely at the start of the study between the preterm and full term groups, the difference between the mean values of term data exceeding 80 mg/cm, or approximately 40% of the value in full term infants (group P compared with group F1—difference 86·0 mg/cm, p<0·001; group P compared with group F—difference 85·4 mg/cm, p<0·001).

Whereas mean values of postconceptional age at the start of the study were closely similar in all groups, they were dissimilar at the end (table 1). It was noted that despite the fact that those in group P were on average three weeks younger, 1900 g lighter, and 7 cm shorter, than those in group F1, the mean values of bone mineral content at the end were similar in the two groups (192 mg/cm and 207 mg/cm, respectively) and were not significantly different from one another.

The mean rates of weight gain (table 2) were closely similar in preterm and full term infants, averaging roughly 175 g/week; differences in the mean rates between groups P and F1, or P and F, were not significant. Longitudinal growth was more rapid in the preterm infants than the full term infants, however; the mean value of the rate of increase of crown-heel length was 0·97 cm/week in group P, which was significantly greater than the corresponding values of 0·79 cm/week for group F1 (p<0·02), and 0·75 cm/week for group F (p<0·001). In the preterm group the mean rate of mineral accretion was 10 times higher than in group F1, and five times higher than in group F; mean values of rate of

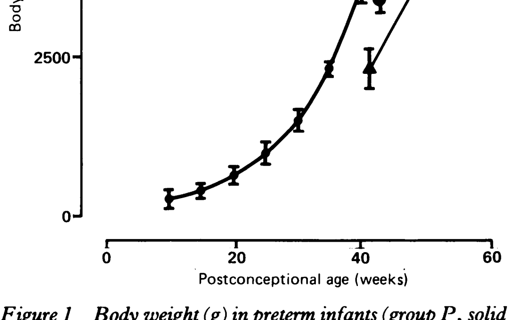

Figure 1 Body weight (g) in preterm infants (group P, solid triangles) and infants born at full term (group F1 and F, open and solid circles, respectively) in relation to postconceptional age. Points joined by straight lines represent the group mean (2 SEM) values measured at 39–44 weeks and 46–57 weeks, and are plotted at the group mean postconceptional ages. The curve approximates weight gain in utero.[10] Error bars on the curve indicate the expected mean (2 SEM) in relation to postconceptional age.

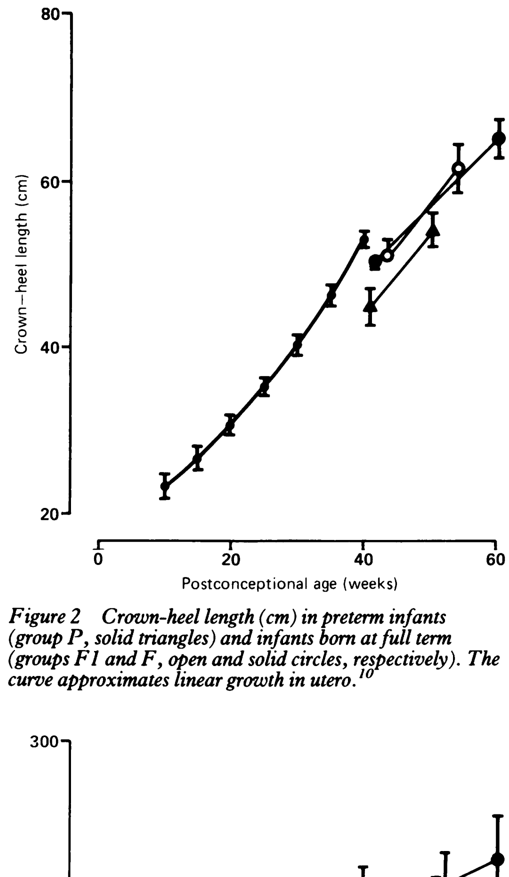

Figure 2 Crown-heel length (cm) in preterm infants (group P, solid triangles) and infants born at full term (groups F1 and F, open and solid circles, respectively). The curve approximates linear growth in utero.[10]

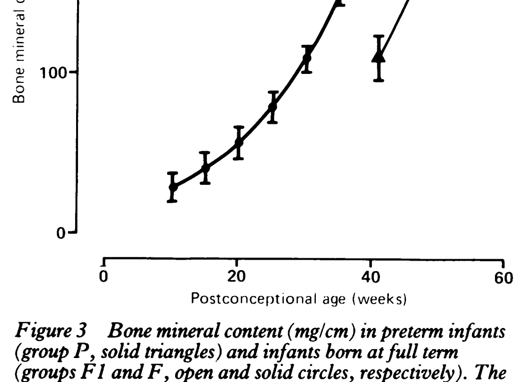

Figure 3 Bone mineral content (mg/cm) in preterm infants (group P, solid triangles) and infants born at full term (groups F1 and F, open and solid circles, respectively). The curve approximates bone mineralisation in utero.[10]

mineral accretion in groups P, F1, and F were 8·70 mg/cm/week, 0·87 mg/cm/week, and 1·60 mg/cm/week, respectively. Differences between mean rate of mineral accretion in groups P and F1, and groups P and F, were highly significant ($p<0.001$); the difference between mean rate of mineral accretion in groups F1 and F was not significant.

These results are displayed graphically in fig 1 (weight), 2 (crown-heel length), and 3 (bone mineral content). In each figure, the slope of the line joining the term and endpoint data for each group is closely similar but not identical to the mean of the individual rates of change given in table 2. Figures, 1, 2, and 3 also contain previously published curves based on observations of preterm infants near to the time of birth[9]; the curves approximate weight gain, linear growth, and bone mineralisation in utero.

Discussion

The results of our previous cross sectional study of preterm and full term infants in the postconceptional age range 65 to 100 weeks showed that if residual differences exist in bone mineral content between the groups, by 60 weeks those differences must be small in relation to the differences existing at 40 weeks.[4] On the basis of intermediate observations, we were able to narrow down a period within which rapid mineral deposition must occur in preterm infants, and we suggested that this period was between about 40 and 60 weeks.

The results of the present longitudinal study confirm that hypothesis. At a time between 40 and 60 weeks, when body weight and crown-heel length are increasing at about the same rate in preterm and full term infants, the rate of mineral accretion is of the order of five times greater in preterm than in full term infants. The changes we observed in preterm infants during that period are in stark contrast to the changes occurring before 40 weeks' postconception, and previously observed in other studies: from birth to 40 weeks, the net increase in bone mineral content is virtually nil in preterm infants.

In broad terms, our observations fit the following hypothesis. For an infant of any given weight and length there is an appropriate value of bone mineral content both in utero, and similarly after birth in a full term infant. When an infant is born prematurely, the in utero relationships are not maintained after birth, with the discrepancy between the infant's bone mineral content and that expected on the basis of weight and length increasing with time, at least up to 40 weeks' postconception. Thereafter, some mechanism comes into play that restores the relationship between bone mineral content, weight, and length in a preterm infant towards that present in full term infants of the same postconceptional age. Whatever the mechanism that tends to restore to normal the relationships between skeletal mineral content and body size, it is clearly inhibited until the time the preterm infants should have been born, and it would seem to have run its course by about 60 weeks' postconception.

With the measurements available it is impossible to disentangle two separate processes that might be occurring during the catch up phase. Those processes are the laying down of bone mineral on existing, previously undermineralised, bone matrix, and increasing overall cross sectional area of the bone at the measurement site, the bone tissue being rapidly and completely mineralised as the bone is laid down. If by 40 weeks' postconception, the bones of preterm infants are of normal cross sectional area (for length), then these and previously published data suggest that they must be undermineralised in the sense that the mineral density/unit volume of bone tissue is reduced. In the catch up phase, both processes could then be occurring in parallel. On the other hand, if by 40 weeks the bones of preterm infants are of reduced cross sectional area (for length), then it is possible that only the second process is operating in the catch up phase. In the first case, a disproportionately large amount of mineral must be deposited in relation to the new bone matrix being laid down. In the second case, bone matrix and mineral have to be rapidly deposited, but with the proportions expected in fully mineralised tissue. Given the familiar radiological appearance of 'rickets of prematurity', we believe it is likely, at least at the start (soon after 40 weeks), that the first process predominates, taking advantage of increased mineral supply to calcify undermineralised matrix. With normalisation of the mineralisation density of existing matrix, it is possible that—towards the later stages of the catch up phase—the second process might start to predominate.

Our findings are supported by the small amount of reported data about bone mineral content between 40 and 100 weeks' postconception in preterm and fullterm infants.[4] Helin *et al* conducted the only long term controlled follow up study in preterm infants, although the subjects were not recruited until 4 to 16 years old.[10] In that study children who had been born prematurely and with low birth weight, but at an unrecorded gestational age, were compared with historical controls. Among girls there was no difference in bone mineral content between preterm and full term children. Among boys bone mineral content was 7% lower ($p<0.01$) for age in the preterm group, but this difference disappeared when height or weight was taken into account. Dahlenburg *et al* found that preterm infants were not at increased risk of fracture in childhood,[11] although in infants of less than 33 weeks' gestation fractures occurred at a significantly earlier age. Gross found that the bone mineral content of the humerus of preterm babies weighing less than 1600 g at birth more than doubled between the postconceptional ages of 34 and 44 weeks. Between 34 and 37 weeks' postconception bone mineral content remained unchanged. The bone mineral content of preterm infants at 44 weeks' postconception exceeded that of infants born at full term and measured at 40 weeks postconception.[12]

The rapid mineral accretion seen between 40 and 50 weeks' postconception in preterm infants is accompanied by falling alkaline phosphatase activity and increasing phosphate concentration in plasma, which other authors have described in preterm infants over the same age range.[12–14] The mechanisms responsible for this rapid mineral accretion remain unknown. Studies in infants between 30 and 40 weeks' postconceptional age show a rising level of 1,25-dihydroxyvitamin D,[15] and increasing retention of dietary mineral with age.[16 17] Such mechanisms may be important, but further research during the appropriate postconceptional period is required. Hillman and Salmons postulated after investigating the relationship between 25-hydroxyvitamin D, calcium, and phosphorus levels in plasma, that classical vitamin D responsiveness only develops after 40 weeks' postconception in preterm infants.[18] Further research is required to validate this interesting hypothesis, which could certainly help to explain the rapid mineralisation.

We have often observed that infants who are discharged from our unit have increased their milk intake when they next attend the outpatient clinic. Intakes between 200 and 300 ml/kg/day are not uncommon compared with normal intakes of 150 to 180 ml/kg/day. The increase in intake is usually mediated by the hunger of the baby and obviously results in an increased dietary intake of mineral. In our study, although the rate of weight gain (g/day) was similar in full term and preterm infants, the weight gain relative to body weight (g/kg/day) is greater in the smaller preterm group. This could indicate a greater milk and hence mineral intake in these infants, which could also help to explain our observations, as increased mineral supply is known to increase bone mineral accretion.[5]

The mechanism that allows the rapid rate of mineral accretion, which we have seen, is of great interest. We intend to carry out further investigations to attempt to identify the underlying mechanism. It may then be possible to make use of the effect to benefit both preterm infants, with some of the more serious manifestations of osteopenia of prematurity, and other groups of patients with failure of mineralisation.

Dr Peter J Congdon died tragically at the early age of 44 while this work was being carried out. His sustained dedication to the group's work on osteopenia of prematurity will always be remembered with admiration by the other authors. All felt that, in view of the importance of the findings reported above, it would be an appropriate tribute to dedicate this paper to him, which we do with a deep sense of affection and respect.

A Horsman and JG Truscott were supported by the Medical Research Council. Heather Durward was supported by a grant from Clinitech. The authors are grateful to Margaret Simpson for her contribution to the collation and statistical analysis of the data.

1 James JR, Congdon PJ, Truscott J, Horsman A, Arthur R. Osteopenia of prematurity. *Arch Dis Child* 1986;**61**:871–6.
2 Horsman A, Ryan SW, Congdon PJ, Truscott JG, James JR. Osteopenia in extremely low birthweight infants. *Arch Dis Child* 1989;**64**:485–8.
3 James JR, Truscott J, Congdon PJ, Horsman A. Measurement of bone mineral content in the human fetus by photon absorptiometry. *Early Hum Dev* 1986;**13**:169–81.
4 Horsman A, Ryan SW, Congdon PJ, Truscott JG, Simpson M. Bone mineral content and body size 65 to 100 weeks' postconception in preterm and full term infants. *Arch Dis Child* 1989;**64**:1579–86.
5 Horsman A, Ryan SW, Congdon PJ, Truscott JG, Simpson M. Bone mineral accretion rate and calcium intake in preterm infants. *Arch Dis Child* 1989;**64**:910–8.
6 Gairdner D, Pearson J. A growth chart for premature and other infants. *Arch Dis Child* 1971;**46**:783–7. (Revised, Ware: Castlemead Publications, 1985.)
7 Parkin JM, Hey EN, Clowes JS. Rapid assessment of gestational age at birth. *Arch Dis Child* 1976;**51**:259–63.
8 Hittner HM, Hirsch NJ, Rudolph AJ. Assessment of gestational age by examination of the anterior vascular capsule of the lens. *J Pediatr* 1977;**91**:455–8.
9 Ryan S, Congdon PJ, James J, Truscott J, Horsman A. Mineral accretion in the human fetus. *Arch Dis Child* 1988; **63**:790–808.
10 Helin I, Landin LA, Nilsson BE. Bone mineral content in preterm infants at age 4 to 16. *Acta Paediatr Scand* 1985;**74**: 264–7.
11 Dahlenburg SL, Bishop NJ, Lucas A. Are preterm infants at risk for subsequent fractures? *Arch Dis Child* 1989;**64**: 1384–5.
12 Gross SJ. Bone mineralisation in preterm infants fed human milk with and without mineral supplementation. *J Pediatr* 1987;**111**:450–8.
13 Callenbach J, Sheehan M, Abramson S, Hall RT. Etiologic factors in rickets of very low birthweight infants. *J Pediatr* 1981;**98**:800–5.
14 Kulkarni PB, Hall RT, Rhodes PG, *et al*. Rickets in very low birthweight infants. *J Pediatr* 1980;**96**:249–52.
15 Markstead T, Asknes L, Finne P, Aarskog D. Plasma levels of vitamin D metabolites in premature infants. *Pediatr Res* 1984;**18**:269–72.
16 Barltop D, Oppe TE. Calcium and fat absorption by low birthweight infants from a calcium-supplemented milk formula. *Arch Dis Child* 1973;**48**:580–2.
17 Day GM, Chance GW, Radde IC, Reilly BJ, Park E, Sheepers J. Growth and mineral metabolism in very low birthweight infants. II. Effect of calcium supplementation on growth and divalent cations. *Pediatr Res* 1975;**9**:568–75.
18 Hillman LS, Salmons ST. Evidence for a postconceptually timed development of classical vitamin D responsiveness in human premature infants. *Calcif Tissue Int* 1983;**35**:695.