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13

Stable strontium in human bone: geographical and age differences in the United Kingdom and their correlation with levels of strontium-90

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The levels of stable strontium (principally [88]Sr) in human tissues are now of some importance for two reasons. In investigation of bone disorders and of rates of calcification in man stable Sr has been used as a tracer for calcium in order to avoid the inevitable, if small, radiation dose to tissue which follows the use of radioactive Ca (Fraser, Harrison & Ibbertson, 1960). Secondly, when considering the uptake into the skeleton and turnover within the body of the ^{90}Sr derived from fallout, it has been realized that these must depend more closely on the behaviour of stable Sr than of Ca since there is some physiological discrimination between the two elements during intestinal absorption, renal excretion and milk secretion and across the placenta (Bryant & Loutit, 1961, 1964).

Numerous analyses have been made of the stable Sr in human bone ash in various countries, and results with British specimens have been issued in a series of reports (Bryant, Chamberlain, Morgan & Spicer, 1957; Bryant, Henderson, Spicer & Webb 1958; Bryant, Henderson, Spicer, Webb & Webber, 1959; Bryant, Cotterill, Henderson, Spicer & Webber, 1959; Arden, Bryant, Henderson, Lloyd & Morgan, 1960; Bryant, Henderson, Lee, Lloyd & Webb, 1960; Graham, Lenihan, Macdonald & Warren, 1960; Bryant, Henderson, Jones, Lee, Lloyd & Wordingham, 1961; Bryant, Henderson, Lee, Sweeney & Webb, 1961; Bryant, Henderson, Lee, Parker, Sweeney & Webb, 1962; Bryant, Henderson, Jenkins, Jury, Parker & Wordingham, 1962; Bartlett, Bryant & Loutit, 1963; Bryant, Henderson, Jury, Parker, Sweeney & Webber, 1963; Bryant, Henderson, Jury, Morton, Parker & Webber, 1963, 1964). A difference between neonatal specimens from London and from Lancashire and Wales has already been noted (Bryant & Loutit, 1964). A more detailed review of the data has now shown wider geographical differences within the United Kingdom and also a geographical difference in the change in concentration with age. In newborn infants there may also be variations with season of the year and with mode of death. During infancy and childhood there seems to be an inverse correlation between the levels of ^{90}Sr and stable Sr in bone when comparisons are made over wide geographical areas. A worldwide survey of stable Sr in bone has already been made (Thurber, Kulp, Hodges, Gast & Wampler, 1958) but this paper is confined to British data.

EXPERIMENTAL

The analytical methods have been described by those who made the estimations (Jury, Webb & Webb, 1960; Webb & Wordingham, 1963). All the values for stable Sr are given as concentrations of stable Sr relative to Ca(μg/g) in bone ash. The anatomical origin of the bone is given for each assay in the reports already cited. The femur in whole or in part was by far the commonest. Sometimes the bones of two or more individuals were combined into one specimen for analysis: these results have been ignored except in one instance (second footnote, †, Table 1).

When calculating means and standard errors of grouped data an individual result has sometimes been omitted, which is always stated in footnotes in the tables. An omission was made, not because there was any reason to doubt the result in question, but because the omitted result was so different from the others in its group that its inclusion might possibly mislead by exaggerating the difference between the group in question and the general mean. The information given in the tables allows the calculation of the mean and standard error of a group when a result is not omitted.

The geographical origin of each specimen is given in the reports already cited, but usually only in general terms according to county. The more detailed information required for the present purpose was obtained by reference to the original documents which accompanied the bone specimens. In this paper analytical results were used only for subjects whose home address was known.

RESULTS

Since deaths in children after the perinatal period are normally so rare, bones from individuals with uncommon disorders, such as hydrocephalus, made up a high proportion of all analyses in children. Leukaemia at all ages and Paget's disease at advanced ages occurred far more often than their general incidence in the living or indeed amongst deaths. No systematic variation of stable Sr levels with any particular diagnostic category was found except in one case which will be discussed later.

It should be emphasized that whenever the term 'level' or 'concentration' is used it is to be understood merely as a shorthand expression for ratio in bone: the usage is justified because Ca forms a hardly varying proportion of bone ash.

No analyses of adult bones were available from Scotland or Wales and the data from England will therefore be considered first.

Geographical variation in adult bones (21 years and more) in England

Inspection and mapping showed that there were distinct differences between different parts of England, sometimes over quite short distances. Stable Sr levels were around 250μg/g over wide areas of the country, but were much higher in the north-west and the south-east (Table 1). In the south-east the Sr level was around 350 μg/g both in London and its surrounding counties and in an area called for convenience Thames Valley. Cumberland as a whole showed even higher values (Table 1) and there was a clear distinction between Carlisle and its immediate environs

Table 1. *Stable Sr in bone (μg/g Ca) at different ages and in different parts of England*

Area	From 2+ to 9 years	From 10 to 14 years	From 15 to 20 years	Adult	From 2+ to 20 years combined	Perinatal*	Ratio Perinatal: adult	Perinatal: from 2+ to 20 years
Cumberland								
A Carlisle	310±10 (3)	286±18 (5)	360 (2)	475±49 (15)	308±21 (10)	250±23† (5)	0·53	0·81
B Wigton, Aspatria	—	—	—	427±88 (3)	—	—	—	—
C Southern fringe‡	—	—	—	320±24 (5)	—	228±40† (4)	0·71	—
Westmorland	265 (2)	230 (1)	255 (4)	245 (2)	254±8 (7)	—	—	—
Lancashire								
A Lancaster	214±26 (5)	230 (1)	348±28 (5)	293±17 (4)	276±26 (11)	—	—	—
B Blackpool and the Fylde	281±24 (6)	190 (1)	230 (1)	248±18 (5)	267±22 (8)	193±6 (84)	0·78	0·72
C South-east	218 (4)	278 (4)	360 (2)	—	270±26 (10)	—	—	—
Shropshire	226±25 (5)	—	210 (1)	242±20 (5)	—	—	—	—
Midlands								
A Birmingham and Warwickshire	274±15 (28)	248±21§ (6)	260 (1)	250 (2)	269±13§ (35)	201±15 (8)	0·80	0·75
B Worcestershire	—	—	320 (1)	253±18 (4)	—	—	—	—
C Nottinghamshire and Leicestershire	264±21 (14)	260±14 (9)	286±19 (23)	268±58 (4)	271±12 (46)	—	—	—
Thames Valley (Oxfordshire, Berkshire, North Wilts)	—	53 (1)	390±38 (5)	361±16 (19)	—	—	—	—
London and the south-east (Herts, Suffolk, Essex, Kent, Surrey, Sussex and Middlesex)	366±19 (39)	370±45 (14)	404±34 (19)	349±14 (57)	377±16 (72)	227±7 (86)	0·65	0·60
Devonshire	240±35 (3)	—	—	278±23 (4)	—	—	—	—

Each entry gives the mean, with the standard error of the mean if the data justify it, and below that, in parentheses, the number of analyses in the group.
* Combined from values for stillbirths and deaths within the 1st week of life.
† Four of the nine analyses were based on specimens not from single individuals but from two individuals combined.
‡ Analyses from Whitehaven, Maryport, Cockermouth & Penrith.
§ Omitting a single value of 1100.

(Cumberland A 475 μg/g) and a belt of country 20–30 miles away running in a crescent east and west at the foot of the hill country (Cumberland C 320 μg/g). Another 20 miles further south in the hilly Lake District the values were around 250 μg/g, the same as in the flat country of the Fylde, Lancashire. Lancaster, however, between the Lake District and the Fylde, seemed to have appreciably higher levels than the Fylde itself ($P < $ o·o1 by t test for differences between means of combined data for from 15 to 20 years and for adult groups).

Isolated analyses in northern England gave the following results: Thornaby-on-Tees, North Riding, adult, 450 μg/g; Halton-le-gate, Northumberland, 13 years old, 440 μg/g; Tweedmouth, Northumberland, 2 years 6 months, 430 μg/g; Brampton, Northumberland, stillbirth, 410 μg/g; and just over the border in southern Scotland, Newcastleton in Roxburghshire, adult, 440 μg/g; and Thankerton in southern Lanarkshire, 7 years old, 400 μg/g. This evidence suggests that some common factor responsible for a high level of stable Sr in bone is to be found right across northern England from west to east and perhaps also in south-eastern Scotland.

Mapping of the analyses for children and adults from the Midlands suggests that there is a small tract of country between Derby, Leicester and Nottingham which gives analytical results in the London range (seven results, age 7–33 years, range 270–600, mean 443 ± 44 μg/g). These possible geographical variations should be borne in mind when considering whether there are real changes in Sr over the age range from 2 to 20 years.

Table 2. *Stable Sr levels in bone (μg/g Ca) from adults of different ages*

Area (see Table 1)	From 10 to 14 years	From 15 to 20 years	From 21 to 39 years	From 40 to 49 years	From 50 to 59 years	From 60 to 69 years	From 70+ years
London and south-east	370 ±45 (14)	404 ±34 (19)	362 ±25 (13)	369 ±49 (13)	346 ±19 (10)	327 ±19 (12)	336 ±31 (9)
Thames Valley		390 ±38 (5)	346 ±11 (7)	405 ±25 (2)	330 ±10 (2)	—	371 ±37 (8)
Cumberland A	286 ±18 (5)	360 ±110 (2)	400 (1)	414* ±31 (5)		407† ±47 (7)	

Each entry gives the mean, below that the standard error of the mean, and below that again, in parentheses, the number of analyses in the group.
* Omitting one value of 920.
† Omitting one value of 890.

Variations with age in childhood, adolescence and adult life in England

Fortunately the three largest groups of adult bones, from London and the south-east, Thames Valley and Cumberland A, allowed it to be established that there was no significant change in Sr level with age in adult life (Table 2). It was concluded that the means for the other smaller groups could be taken as valid estimates of adult levels.

When the data over the age range 2+ years to 20 years were combined it can be seen from six of seven comparisons (Table 1) that the means were not different from

the adult means. The exception was Cumberland A. When the data were divided up into the ranges from 2 + to 9, from 10 to 14 and from 15 to 20 years it is clear that there were few analyses on bones from adolescents and from those whose skeletons had just stopped growing except from the Midlands and the south-east areas. Here it is noticeable that values for the 15–20 year groups were slightly higher than for younger or older ages (though not significantly so). Half of the Midland specimens in the group from 2 + to 20 years came from cases of sudden accidental death and conclusions may therefore be taken to refer to normal bone.

In each area except Cumberland A the mean for the age range from 2 to 9 years was closely similar to that for adults. The two areas of Lancashire might be thought to show differences but these are in opposite directions. The broad conclusion is that there is little if any change in the ratio of stable Sr to Ca in bone after early childhood. Cumberland A is a clear exception, and it is noteworthy that the rise in Sr there appears to occur after the skeleton has ceased growing (Table 2).

Scotland

There were differences between different areas of central (lowland) Scotland (Table 3). (Only one of the Lanarkshire results came from the southern uplands in that county, see p. 16.) The highest values were found in eastern Stirlingshire, but there was insufficient evidence to show whether or not Edinburgh values were similar. The perinatal means in Glasgow and Lanarkshire were lower than any English mean.

Results for children in Inverness and northern Scotland were as high as for those in Stirlingshire and Midlothian (Table 2) and almost as high as for children of the same ages in south-east England.

Wales

North Wales (Flintshire and Denbighshire) had the lowest values for perinatal bones (Table 3). The values at older ages were correspondingly low and almost identical with those from the adjoining English county of Shropshire.

The perinatal values in south Wales were definitely higher than in north Wales (Table 3) and, when they were plotted on a map (Fig. 1), it seemed as if the values in some of the hilly (mining) areas were appreciably higher than elsewhere in these hills or than in coastal areas. Since it was the results that suggested a geographical factor, but no objective means was known to me for choosing one or other method of grouping the data, the values for all these mining areas together are given in Table 3 and Fig. 2.

There were scattered data for perinatal bones from west and central Wales, both rural areas. The values from central Wales gave a mean value higher than anywhere else in Great Britain, higher even than in Carlisle, contrasting with the mean for west Wales which was in the lowest quartile (Table 3). All the other group means in south Wales lay between these two extremes (Fig. 1 and Table 3). These maximum values from central Wales were obtained only about 80 miles away from the region of north Wales where minimum perinatal values were found. In each area there was an anomalous value characteristic of the other area (Table 3, second and fifth footnotes).

Table 3. *Stable Sr in bone (μg/g Ca) at different ages in Scotland and Wales*

Area	From 2+ to 9 years	From 10 to 14 years	From 15 to 20 years	From 2+ to 20 years combined	Perinatal*	Ratio, perinatal:from 2+ to 20 years
Northern Scotland	327±36 (7)	590 (1)	—	—	—	—
Central Scotland						
A Glasgow and Renfrewshire	215±21 (12)	290 (3)	—	230±20 (15)	158±4† (5)	0·69
B Lanarkshire	293±23 (9)	263±39 (4)	—	284±18 (13)	165±12 (10)	0·58
C Stirlingshire and Clackmannanshire	295±27‡ (11)	280 (2)	280 (1)	291±21‡ (14)	—	—
D Midlothian	330 (3)	—	—	—	208±14 (10)	—
North Wales: Flintshire and Denbighshire	237 (3)	240 (2)	250 (1)	240±11 (6)	155±8§ (15)	0·65
South Wales						
A Cardiff and environs	278±31 (6)	259±14 (8)	320 (2)	274±15 (16)	184±5 (90)	0·67
B Swansea and environs, Port Talbot and Neath	298±16 (8)	220 (1)	210 (3)	269±19 (12)	201±6 (39)	0·75
C Mining valleys of Glamorgan and Monmouthshire	253±29 (8)	293±13 (4)	335±45 (4)	283±20 (16)	215±6 (83)	0·76
D West Wales (Pembrokeshire, western and central Carmarthenshire and Cardiganshire)	213±6 (4)	—	—	—	173±9 (11)	—
E Central Wales (Montgomery, Breconshire and eastern Cardiganshire)	—	—	—	—	288±19‖ (4)	—

Each entry gives the mean, with the standard error of the mean if the data justify it, and below that, in parentheses, the number of analyses in the group.

* Combined from values for stillbirths and deaths within the 1st week.

† Omitting a single value of 340.

‡ Omitting a single value of 760.

§ Omitting a single value of 400.

‖ With the addition of a single value of 150 from Radnorshire, mean of five analyses ± SE = 260±31.
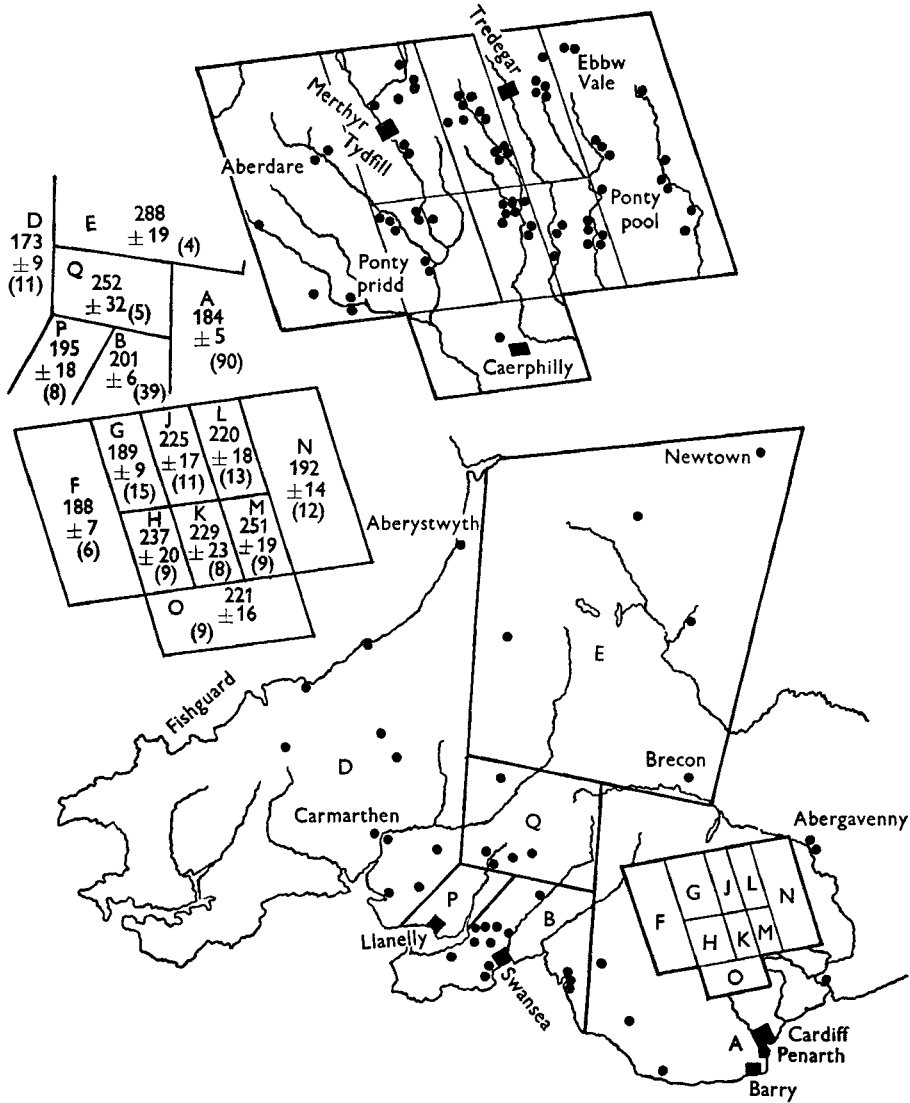
Stable strontium in bone

Fig. 1. Map of south Wales showing origin of perinatal bone specimens and divided into different areas to reveal differences in mean levels of stable Sr in bone (μg/g Ca). Each point represents one analysis. The black rectangles show localities providing eight or more analyses each. Area C of Table 3 is subdivided into areas F–O and is shown on a larger scale in the inset at the top. Areas A, B, D and E are as in Table 3. The values for stable Sr are given on the top left hand of the figure and each value for stable Sr is a mean for the area with its standard error below, and below that again, in parentheses, the number of analyses in the group.

Variation in the first 2 years of life

Perinatal values averaged about two-thirds of values for adults or individuals aged from 2 + to 20 years. An attempt has been made to discover when the perinatal values reach these higher adult levels, but the geographical variation already noted made it necessary to consider each area separately. For this reason no values were available

for some particular age groups and the numbers in any one group were usually small. However, if the same pattern of change is seen in many different areas then it is likely that the pattern really exists even if in each separate geographical area there may have been no statistically significant difference between the relevant age groups.

All the data for infants and children from nine different areas of the United Kingdom are plotted in Fig. 2, divided into age groups as shown. Individual results are plotted as separate points unless there were at least four values in an age group, when means ± SE were calculated and shown by bars. Only for Lanarkshire, the Midlands, the
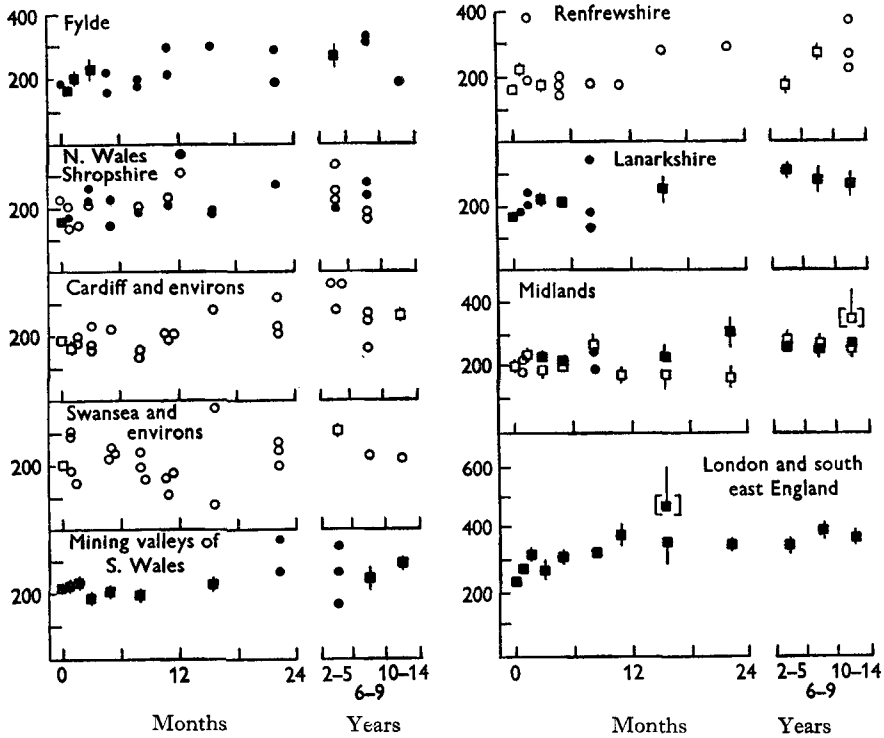

Fig. 2. Change with age in stable Sr ($\mu g/g$ Ca) in bone in nine different areas of the United Kingdom. Where sufficient data exist mean values with their standard errors are shown by square symbols. Otherwise each point indicates an individual analysis. Because there are no perinatal data from Nottinghamshire and Leicestershire the data from the Midlands are not pooled but different symbols are used for Nottinghamshire and Leicestershire (closed) and for Birmingham and Warwickshire (open). Two points are plotted for the 13–18 months group in the diagram for London and the south-east. The square brackets show the group mean when a single extreme value of 900 is included (see p. 22). Similarly square brackets around other means show that an extreme value has been included (cf. Table 1, last footnote).

mining valleys of south Wales and for London and south-east England were the analyses numerous enough for group means to be commonly available. The data from the Midlands and the south-east may be intrinsically more heterogeneous than from the other seven areas, partly because the areas are very much larger. However hetero-geneity was doubtless also important in south Wales (cf. Fig. 1).

The two diagrams of Scottish data suggest that the Sr level does not rise until

after the 1st year of life: the apparent rise in Lanarkshire early in the 1st year is offset by an apparent fall in Renfrew. Similarly, there is no evidence in the three diagrams from south Wales of a rise during the first 12 months of life; indeed there is a suggestion of a fall to a minimum in the second half of the 1st year. Where analyses are available, in the Cardiff and mining valley areas, there appears to be a progressive rise from the nadir at from 7 to 9 months to adult or nearly adult levels in the second half of the 2nd year of life. In north Wales and in the Fylde there may be an initial rise
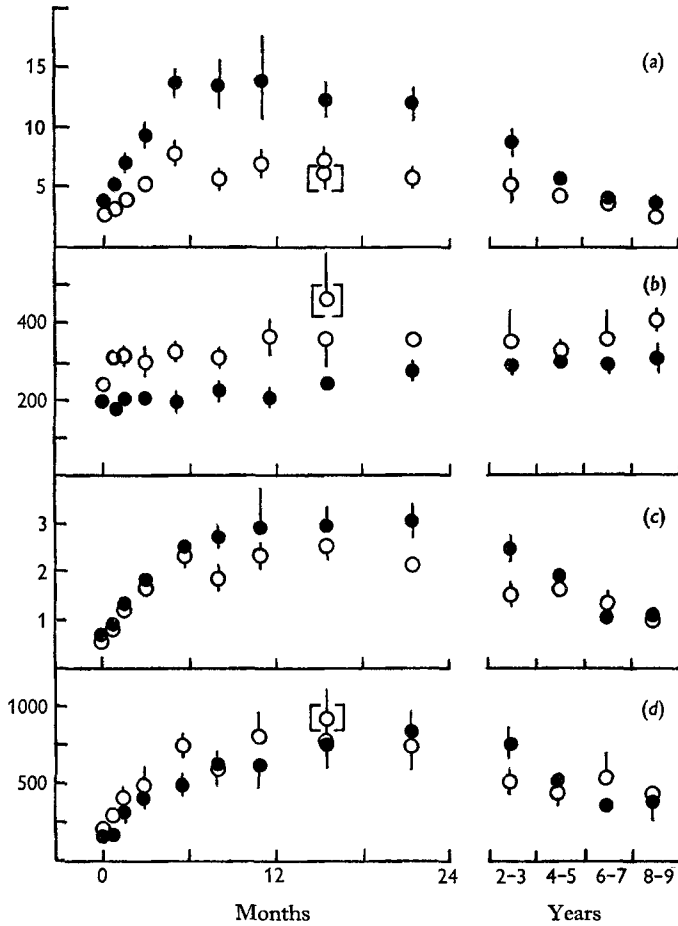

Fig. 3. Comparison for the 2-year period, 1960 second quarter to 1962 first quarter inclusive, of data from London and the south-east and from the rest of England, Scotland and Wales combined (see p. 22). (a) Specific activity of ⁹⁰Sr in bone (pc/mg stable Sr); (b) stable Sr (μg/g Ca) in bone; (c) ⁹⁰Sr (pc/g Ca) in bone; (d) product of (b) and (c). ○, London and south-east; ●, rest of United Kingdom. Square brackets have the same significance as in Fig. 2.

during the first 3 months of life (see penultimate footnote, Table 3) but not subsequently. The data are scanty, and adult levels may be reached by the second half of the 2nd and the second half of the 1st year respectively. Perinatal data are available from only part of the Midlands, and in the diagram Birmingham and Warwickshire

are distinguished from Nottinghamshire and Leicestershire. There is no sustained rise in either zone until the second half of the 2nd year or later.

The picture from London and the south-east is quite different from that of the other eight areas. There is a progressive increase in Sr levels from the 1st week of life, so that adult values are reached by 10–12 months of age. Thereafter mean levels fluctuate little. The apparent peak in the 13–18 month group is due entirely to a single value of 900 μg/g. If this value is excluded, the 13–18 month mean lies between the means for the 10–12 and 19–24 month groups (Fig. 2).

London and the south-east is an area with a population of many millions and, if there were systematic differences in the origin of bone samples in the different age groups, it might just be possible that the rise in stable Sr during the first 12 months of life (Fig. 2) is an artifact and the result of geographical non-homogeneity within the area. No evidence was found in support of this suggestion.

The same basic data reviewed here were also considered by Bryant & Loutit (1964). A comparison of their Fig. 3 (in which all the analyses in an age group were combined) with my Fig. 2 (in which geographical distinctions have been made) shows that geographical differences need to be taken into account when considering the physiological implications of changes in stable Sr levels in bone.

Correlation of radioactive and stable strontium concentrations in bone

The amount of ^{90}Sr taken up into bone salt must depend on the amount in the diet (food and drink), and there are known to be geographical differences within the United Kingdom in the ^{90}Sr content of milk for example (Agricultural Research Council Radiobiological Laboratory, 1959). Since there are striking geographical differences in stable Sr levels in bone, as shown in this paper, a correlation was sought between the concentration of the radioactive and the stable isotopes. One difficulty in attempting to establish such a correlation is that the amount of fallout has been varying from year to year, and another is that bone analyses over any short period of time from any one geographical area are inevitably few in number. However, during the period from the second quarter of 1960 to the first quarter of 1962 inclusive, ^{90}Sr levels in fresh cow's milk were fairly constant in each zone of milk production (Agricultural Research Council Radiobiological Laboratory, 1962), and there seem to have been enough bone specimens from individuals dying in the same 2-year period to justify an attempt to use the data.

Fig. 3 a gives the ratio of ^{90}Sr to stable Sr, the specific activity, in bone samples over the age range from stillbirths to 9 years. Since there was a difference between London and the south-east and all other areas in the rate of change of stable Sr during infancy (Fig. 2) results are shown separately for London and south-east England and for the rest of England, Scotland and Wales combined, omitting only results from the high Sr zone of northern England and the perinatal results from central Wales. One-third of the analyses in this combined group came from Lancashire and Cheshire, one-third from north and south Wales and one-quarter from the Midlands.

In each group there was a progressive increase in specific activity of $2\frac{1}{2}$- to 3-fold in the first 6 months of life, a plateau from 7 to 24 months and then a decline. However,

in the south-east area with high stable Sr levels the specific activity was always lower than in the rest of the United Kingdom, at the plateau age by a factor of about two. The values for children from 2 to 9 years of age show a quantitatively smaller geographical difference, but data on fallout in these older children are inevitably difficult to interpret. The rate of bone remodelling decreases as the skeleton grows in size, and the older the child the less closely does the composition of its bone salt reflect the composition of the current diet. Stable Sr in diet has presumably not varied greatly so that Sr levels in bone show little secular change. Fallout of ^{90}Sr, however, has varied greatly and began to be appreciable in the United Kingdom only since 1956 when the 8- to 9-year-olds of Fig. 3 were already from 3 to 5 years of age.

If stable Sr and ^{90}Sr are inversely correlated with each other in bone salt, the product of the two ratios, of stable Sr to Ca and of ^{90}Sr to Ca, would be relatively independent of the value of either. Fig. 3d shows that there is indeed less geographical difference in the value of this product than in the specific activity (Fig. 3a), or in the levels of stable Sr or ^{90}Sr (Figs. 3b and c), suggesting that the levels of these two isotopes in bone are indeed inversely proportional to each other.

This is a somewhat surprising finding since the amount of stable Sr in children's food would be expected to depend on the stable Sr available in the soil in those regions from which their food comes, whereas the amount of ^{90}Sr would be expected to depend primarily on the amount of fallout deposited in rain. There is no obvious environmental reason why these two should be correlated at all. Regional differences in the ratio of ^{90}Sr to Ca in milk are not greater than 40 % above or below the weighted national average (Agricultural Research Council Radiobiological Laboratory, 1959), and the differences in the ratios in milk between the two groups illustrated in Fig. 3c may well be much less than this. London and the south-east are supplied with milk produced in various parts of Great Britain, and this milk has a composition fairly close to the national average simply because it is a mixture. Milk produced in the Midlands has a ^{90}Sr:Ca ratio close to the national average. Although the ratio ^{90}Sr:Ca in milk produced in Wales is 40 % higher than the national average, the ratio in milk produced in the north-west (mainly Lancashire and Cheshire) is less than the national average, and the pooled data in Fig. 3 therefore come from a population whose milk (by and large) will have been fairly near to the national average. The effect of regional differences in fresh milk will be additionally reduced in proportion to the amount of dried milk used in infant feeding.

Differences in the ^{90}Sr levels in fresh milk cannot be the only factor concerned when infants begin to take a mixed diet, and something else must be looked for to account for the geographical differences over the age range from 7–9 months to 2–3 years of age (Fig. 3a and c). It seems necessary to assume either that there is some metabolic reason for an inverse correlation between the concentrations of stable Sr and radioactive Sr in bone (for which there is no physiological evidence at present); or, if the concentrations are not metabolically correlated, that infants and children outside south-east England consume articles of food other than fresh milk with a relatively high content of ^{90}Sr; or both factors could operate together.

Heterogeneity in perinatal samples according to season of year and cause of death

The numbers of perinatal specimens (stillbirths and deaths within the 1st week of life) from some districts were so large that it was possible to find significant heterogeneities. For instance, the stable Sr levels in south Wales seem to have shown a 10–15 % decrease over the 6 years during which observations have been accumulated (Table 4). The reason is not clear, though the hospitals from which samples have been obtained and the pathologists concerned in sample collection have not been the same throughout.

Table 4. *Secular changes in stable Sr levels in perinatal bone*
(stillbirths and deaths within the 1st week)

Area	Period	Mean with its SE	No. of specimens	P value of comparisons
Swansea and environs	1957 to 1960 first quarter	207 ± 7	24	
	1960 second quarter to 1962 first quarter	190 ± 9	15	0·10 < P < 0·20
Cardiff and environs	1957 to 1959	205 ± 10	22	
	1961 first quarter to 1962 first quarter	188 ± 8	26	P < 0·01
	1962 second quarter to 1963 first quarter	171 ± 8	42	
London and south-east England	1956 to 1960 first quarter	227 ± 7	46	Not significant
	1960 second quarter to 1962 first quarter	243 ± 10	39	

In one area, Blackpool and the Fylde, specimens were selected by one pathologist and came from one hospital. Nearly 100 samples from the second quarter of 1960 to the second quarter of 1962 inclusive were analysed, and there seems to have been not only a seasonal variation but also a difference according to the mode of death (Table 5). Babies dying in the two winter quarters had lower mean values than those dying in the two summer quarters for both stable Sr and ^{90}Sr and babies dying with serious congenital defects usually showed lower values of stable Sr than those without these lesions. Both these conclusions seem as true of babies dying after the immediate perinatal period as of babies dying within 48 h of birth, but it should be noted that there are not many analyses for babies more than 2 days old without serious congenital defects.

It has not been possible to make similar comparisons within data from other centres and it is not inconceivable that these observed differences in the Fylde were due to some other factor or factors than the two chosen for analysis, season of the year and mode of death. Whatever the reasons for this heterogeneity it is clear that too much weight should not be placed on deductions from mean values for groups quoted in this paper or indeed from similar group means in the literature.

In specimens coming from the Fylde the lowest stable Sr values were found in babies dying between 7 and 30 days after birth (Table 5). It is tempting to imagine that these babies, with serious congenital defects, failed to thrive, that their food intake was inadequate, and that they were at least partly deficient in phosphorus. Babies

Table 5. *Variation of (a) stable Sr and (b) ⁹⁰Sr in bone with season and with mode of death in the Fylde*

	Summer 1960 second and third quarters	Winter 1960 fourth quarter 1961 first quarter	Summer 1961 second and third quarters	Winter 1961 fourth quarter 1962 first quarter	All data combined (mean ± SE)
(a) Stable Sr (μg/g Ca)					
Stillbirths and deaths within 48 h					Deaths 0–1 days
With serious congenital defects	205 (2)	148 (8)	192 (9)	158 (6)	171 ± 8 (25)
Without serious congenital defects	260 (1)	196 (11)	221 (14)	151 (7)	199 ± 9 (33)
					Deaths 2–6 days / Deaths 7–30 days
Deaths between 2 and 30 days					
With serious congenital defects	180 (2)	168 (6)	223 (4)	167 (10)	198 ± 10 (11) / 159 ± 6 (11)
Without serious congenital defects	—	230 (1)	227 (3)*	233 (3)	238 ± 13 (6)* / 180 (1)
Combined data for stillbirths and deaths within the 1st week					
With serious congenital defects	193 (3)	160 (11)	208 (12)	167 (10)	—
Without serious congenital defects	260 (1)	199 (12)	222 (17)*	176 (9)	—
(b) ⁹⁰Sr (pc/g Ca)					
Stillbirths and deaths within 48 h					Deaths 0–1 days
With serious congenital defects	0·75 (2)	0·62 (8)	0·68 (9)	0·67 (6)	0·66 ± 0·02 (25)
Without serious congenital defects	0·50 (1)	0·66 (11)	0·76 (14)	0·54 (7)	0·67 ± 0·03 (33)
					Deaths 2–6 days / Deaths 7–30 days
Deaths between 2 and 30 days					
With serious congenital defects	0·9 (2)	0·66 (6)	0·80 (4)	0·60 (10)	0·70 ± 0·06 (11) / 0·65 ± 0·06 (11)
Without serious congenital defects	—	0·60 (1)	0·68 (3)†	0·57 (3)	0·66 ± 0·03 (6)† / 0·40 (1)
Combined data for stillbirths and deaths within the 1st week					
With serious congenital defects	0·72 (3)	0·64 (11)	0·72 (12)	0·65 (10)	—
Without serious congenital defects	0·5 (1)	0·65 (12)	0·74 (17)†	0·56 (9)	—

Numbers of results from which the means are calculated are given in parentheses.

* Omitting one value of 430.

† Omitting one value of 1·5 corresponding to the value for stable Sr of 430 μg/g (cf. first footnote).

from 6 to 8 days old on a lower P intake were in negative stable Sr balance whereas on a higher P intake stable Sr was retained (Widdowson, Slater, Harrison & Sutton, 1960; Widdowson, McCance, Harrison & Sutton, 1963). If this suggestion is true, stable Sr and ^{90}Sr are handled differently to some extent since there was no corresponding difference in ^{90}Sr levels in bone according to the mode of death (Table 5).

There was the same seasonal variation in ^{90}Sr as in stable Sr, presumably for the same reason, a greater consumption by mothers in summer than in winter of vegetables which have higher stable Sr and ^{90}Sr levels than an average diet (Agricultural Research Council Radiobiological Laboratory, 1959).

Perinatal Sr levels and placental discrimination

By far the most numerous specimens were those from stillbirths and from babies dying within the first 7 days of life. The majority were presumptively normal, but some were premature and some died with gross congenital defects. The sample from one individual often consisted of several different bones and in a certain number the calvarium and spine were utilized and no femoral bone was included in the ashed specimen. It is not believed that the anatomical origin of the bones is of any moment from the present point of view.

Values for stable Sr (μg/g Ca) in bones coming from English areas are given in Table 1 and from Welsh and Scottish areas in Table 3. In England the perinatal levels showed geographical differences in the same direction and of the same order as the levels in adults, but were always smaller. This was due to the well-known fact that the placenta does not transport Ca and Sr from the maternal to the foetal side with equal efficiency (Bryant & Loutit, 1961) but shows some discrimination between these two chemically very similar elements.

An estimate of the degree of placental discrimination can be obtained by comparing the Sr:Ca ratio of perinatal and of adult bones. The ratio between these ratios (Table 1) ranges from 0·53 to 0·80 in different geographical areas, averaging 0·69. The lowest value, 0·53, is probably the most suspect, since in this area, Cumberland A, the adult mean for 21–80+ years was so different from the observed values for younger age groups (Table 2): most children were born of mothers in the early twenties.

The adult means in most groups are based on rather small numbers and, since it has been noted that the mean for the age group from 2+ to 20 years is about the same as the adult value, a more reliable estimate of the degree of discrimination may be derived by comparing the perinatal level with the mean for from 2+ to 20 years. The four English values (Table 1) range from 0·60 to 0·81 averaging 0·72. Values for Wales and Scotland range from 0·58 to 0·76 (Table 2) averaging 0·71 and 0·63, respectively. Overall it would appear that a value of about 0·7 is the best estimate from the data now presented of the ratio of stable Sr in bone ash in perinatal and in adult bones. The value of 0·6 given elsewhere (Loutit, 1963; Bryant & Loutit, 1964) was derived without geographical differences in stable Sr levels being taken into account.

A value for this ratio can also be deduced from Australian data (Bryant, Moroney, Stevens & Titterton, 1963). Bone levels of stable Sr in five different cities for babies from 0 to 1 month old were higher than in the United Kingdom, ranging from 290 to

520 μg/g Ca, but so were adult levels, 420–650 μg/g. The ratio of values for babies from 0 to 1 month old to adult values in different areas and seasons ranged from 0·51 to 0·84 with a mean for ten values of 0·69 in agreement with the British data.

The Ca and Sr in a stillborn infant must be wholly derived from the mother's plasma, which would be effectively true also for infants dying within the 1st week of life. If the mother's plasma is in analytical equilibrium with the maternal skeleton then a comparison of infant and maternal bones will indicate the magnitude of any discrimination by the placenta. Analytical equilibrium will exist if either of two conditions applies: (1) the Sr of the maternal skeleton is all rapidly exchangeable with that in the maternal plasma, or (2) the diet of the mother has been constant on average in its ratio of Sr to Ca during the growth of her skeleton and the duration of her pregnancy. Since it is usually believed that the bone salt, including the Sr, of the adult skeleton is subject to only slow turnover, it is the second condition which is relied on. If the mean dietary ratio of Sr to Ca has indeed been constant during the growth of a future mother's skeleton and thereafter, it is likely to have been constant for all individuals (in a given area) and therefore it is legitimate to use values obtained for males and non-pregnant females as estimates of the values in the maternal skeleton during pregnancy.

The ratio of perinatal bone to maternal bone will be a biased estimate of placental discrimination to the extent to which maternal plasma and maternal bone are not in equilibrium during pregnancy. The value for the ratio 0·7 obtained here is larger, implying a smaller discrimination, than the factor of about 0·5 derived from comparisons of levels of [90]Sr (from fallout) in the average national diet, in maternal plasma and in perinatal bone (Loutit, 1963). The difference in the two derivations is in the direction to be expected given the slow turnover of bone salt in the adult. Because of this the maternal skeleton cannot be in radioactive equilibrium with the maternal plasma.

A single example in fact exists in the British data where values from mother and child can be compared directly. Femoral bone from a 21-year-old woman who died from toxaemia of pregnancy contained stable Sr 240 μg/g Ca and [90]Sr 0·36 pc/g Ca and the pooled ash of several bones from her stillborn child contained stable Sr 210 μg/g Ca and [90]Sr 0·90 pc/g Ca. The stable Sr ratio is 0·9, in agreement with the pooled data considered above, whereas the ^{90}Sr ratio of 2·5 shows clearly the lack of radioactive equilibrium.

DISCUSSION

Any conclusions to be drawn from analytical results depend in the first place on analytical reliability. The spectrographic method originally used for the determination of stable Sr was carefully checked (Bryant & Loutit, 1961) and a later method gave indistinguishable results (Bryant *et al.* 1964).

The bone specimens came from a large number of hospitals but it is not believed that contamination was responsible for the observed geographical differences. When specimens of bone were obtained, they were placed in clean, new cellophane bags provided from the same central store to all collecting centres for storage and transport. Occasionally by chance bones in the same batch of specimens from one hospital came

from individuals with widely differing domiciles and gave widely different analytical results but in agreement with the geographical area of domicile.

Another important question, if general conclusions are to be drawn from the results, is how representative the original bone specimens were. They were not selected on a deliberately planned basis, with the single exception of about 100 specimens from the London area in 1961 (Bartlett *et al.* 1963), and, even if they had been, specimens from people who have died will not necessarily provide results representative of those who remain alive. Rather over half the adult specimens from the Thames Valley and London and the south-east were from cases of sudden death and these may probably be regarded as physiologically representative, if it can be assumed that arterial disease is not specifically correlated with the metabolism of bone salt. Rather more than half the specimens from individuals between 10 and 20 years of age in the Midlands and in the London area were from cases of accidental death and these can surely be regarded as definitely providing physiological information. It is with the younger children that there must be most doubt about the 'normality' of the specimens. For instance, one-quarter of specimens from children between 4 and 24 months of age from London and the south-east were from individuals with hydrocephalus or other gross cerebral abnormalities. Congenital defect of the heart was an equally common cause of death in young children of a variety of ages. There is no need to assume more than indirect correlations with bone metabolism: even if prolonged under- or mal-nutrition altered the growth of bone more quickly and easily than the composition of bone salt, the level of dietary P in relation to the body's needs might affect Sr levels, as discussed later. Whatever the magnitude of any differences there may possibly be between the analysed specimens and the bones of healthy 'normal' individuals of the same age, and however important these may be when deductions are to be made about the rate of turnover of bone salt, it is to be expected that this source of bias will have been similar in all the different geographical areas and thus not in itself responsible for the observed geographical differences.

No particular correlation was found between categories of death and Sr levels except in perinatal specimens in which mean levels differed by about one-sixth between babies dying with or without serious congenital defects. In the same babies there was a seasonal difference of similar magnitude in both stable Sr and ^{90}Sr. The bones of newborn children might well be more subject to short-term secular variation than the bones of older individuals, because the bones in the developing foetus would be expected to reflect corresponding variations in maternal diet. In Australia too, the values obtained for stable Sr in babies dying in July to December 1961 were usually less than for January to June 1961, but it is perhaps unexpected that there were similar seasonal differences in adult bone levels (Bryant, Moroney *et al.* 1963).

It may be objected that only small numbers of analyses are available in many of the groups in Tables 1 and 3. This is true although in some, like the adult groups from London and the south-east and from the Thames Valley, the numbers of specimens are enough to give standard errors of less than 5 % of means of about 350 μg/g. The combined data for the thirty adult specimens from the rest of England (excluding Cumberland) have a mean of 260 μg/g, again with a standard error of less than 5%.

Thus there can be no question that real geographical differences exist, although small numbers of specimens from widely scattered areas necessarily provide an inadequate basis for detailed study.

Granted that geographical differences in a relatively small country have been clearly established, it is tempting to look for environmental differences in stable Sr levels, in drinking water or in milk, for example, which might be correlated with differences in bone levels. However, if it is accepted that the bone salt of the adult skeleton undergoes little physiological turnover, then what needs to be correlated with analyses for individuals 40–80 years old may be the factors which were in existence a long time ago, perhaps even 40–80 years ago. Present-day analyses of drinking water or of milk may be misleading, not merely irrelevant: the distribution and pooling of milk supplies have been revolutionized since the Milk Marketing Board came into existence 31 years ago, and the distribution of other foodstuffs must have been markedly altered since the First Great War by the development of the lorry and of intensive market gardening. Considering the degree of social mobility of the population of Great Britain, it is perhaps additionally surprising that consistent geographical differences were found at all.

Correlations of analyses for individuals under 20 years of age should be much less open to secular error since their whole lives were postwar and differences in the diet of infants and children between different social classes and different geographical areas may not have been so great as formerly. However, except for one area, Carlisle, the same geographical differences were seen in the age range 2–20 years as in adults; Carlisle was the only area where levels in adults and teenagers were clearly not the same.

The most striking geographical difference and the one with the least obvious explanation is the way in which the ratio of stable Sr to Ca in bone increased progressively from birth in south-east England but remained nearly stationary in all other areas during the 1st year or so of life. It has commonly been assumed that tissue levels of stable Sr depend merely on overall levels in food and drink and on physiological factors which affect the discrimination between Sr and Ca. To explain the difference between south-east England and all other areas it would then be necessary to assume that dietary levels of stable Sr were quite different since there can hardly be marked physiological differences between children in different parts of the same small country with a high overall standard of physical well-being. The dietary levels of stable Sr would have to be such that in the rest of England, Wales and Scotland the change in level with change in composition of the diet during the 1st year of life just neutralized the changes in physiological discrimination in intestine and kidney which have been believed to occur at this time.

Not many analyses have been reported of the ratio of stable Sr to Ca in milk produced in the United Kingdom. After allowing for seasonal variations, the data (Agricultural Research Council Radiobiological Laboratory, 1960, 1961 a, b) show that the lowest annual averages of $310–320 \mu g/g$ were found in the north-west milk-producing zone (which includes Lancashire) and the west Midlands zone (which includes Shropshire and Worcestershire) whereas the highest level of $440 \mu g/g$ was in

the northern milk-producing zone (including Cumberland, Northumberland and the North Riding of Yorkshire). The south and south-east zone (which includes much of the Thames Valley and London areas of Table 1) was intermediate with $400 \mu g/g$. Apart from the discrepancy in Devonshire (with low bone levels but included in the far-west milk zone with high milk Sr), the geographical differences in milk levels of stable Sr are well correlated with the geographical differences in bone levels in child-hood, adolescence and adult life (Table 1 and p. 14). This correlation presumably reflects a correlation between levels in diet and in bone but only in an indirect fashion, since after the 1st year of life only one-seventh to one-eighth of the stable Sr intake comes from fresh milk and milk products (Agricultural Research Council Radio-biological Laboratory, 1959, 1961b). Further, the marketing arrangements for fresh milk allow some flexibility in the source of supply to some areas.

Nearly 40 % of the daily intake of stable Sr in the national diet is believed to come from the chalk which is added to flour from which bread is baked (Agricultural Research Council Radiobiological Laboratory, 1959). No information is available about possible regional variations.

Water for drinking and cooking accounts for one-seventh of the intake, so that very large variations in Sr level in water would be needed to account for the observed differences in bone level of more than 50 % (Tables 1 and 3, Fig. 2). However, these geographical differences are maximal during the 1st year of life, and so little is known about the Sr level of the diet of infants under 12 months of age (Bryant & Loutit, 1961) that discussion about the reasons for the observed differences can only be discursive and hypothetical. The 'national diet' is in any event an abstract idea, and it may be noted that analysis of the excreta of a number of human subjects, from 3 to 50 years of age, all in Social Class I and living in the Thames Valley area of Table 1, showed that their daily intake of stable Sr must have been appreciably higher than suggested by the national statistics (Harrison, Raymond & Tretheway, 1955; Bedford, Harrison, Raymond & Sutton, 1960). Urinary and faecal excretion together amounted to 1–3 mg stable Sr per day in four children from 9 to 14 years old and 2–3 mg per day in three adults, whereas the average 'national diet' provides 1 mg more or less (Bryant & Loutit, 1961). Since the Thames Valley area of Table 1 is an area with levels of stable Sr in bone well above the national average, these metabolic studies may be thought to confirm a correlation between levels in bone and in diet.

One corollary of the findings reported here is that it may be hazardous to use changes in stable Sr levels with age as evidence for changes in such physiological phenomenons as discrimination in intestinal absorption between Ca and Sr or in rates of turnover of bone salt in the skeleton. Similarly, the geographical differences in levels of ^{90}Sr and in its specific activity will need to be taken into account if changes in ^{90}Sr levels with age are to be used to deduce something about the metabolism of bone salt and the turnover of the skeleton, as in the tentative suggestions of Bryant & Loutit (1961, 1964) and Loutit (1963).

It may be useful to mention the possibility that changes in bone levels of Sr, stable or radioactive, could occur without changes in dietary levels of Sr or changes in intrinsic physiological discrimination. The level of P in the diet has been shown to

control the Sr balance in the 6–8 days old human infant (Widdowson *et al.* 1960, 1963) and the retention of Sr in the bones of experimental animals (literature cited by Kostial, Lutkic, Gruden, Vojvodic & Harrison, 1963). Animal experiments have also shown that a reduction in dietary P beginning several weeks after the incorporation of Sr into bone can lead forthwith to a loss of Sr from the bone continuing until after the dietary P has been restored to its former level (van Putten, 1962). If it be generally true that when the available P in the diet is relatively deficient, the body burgles its bones for their phosphate (cf. Loutit, 1960), then the fact that there is renal discrimination inevitably entails a difference in Sr levels in bone when there are sufficiently large differences in the levels of P in the diet. The reason is that the more rapid the turnover of bone salt the greater will be the renal leak of Sr as compared with Ca. Is it possible that the diet of infants less than 1 year old in the relatively prosperous south-eastern area of England is generally richer in P than elsewhere? The lower perinatal mortality in the south-east than in the north or west in 1958 was correlated in a number of ways with differences in prosperity and in physiological attributes (Illsley & Kincaid, 1963). Human milk contains less P than the milk used for bottle-feeding and a low incidence of breast feeding in the south-east might help to account for the rise in bone Sr during the first few weeks and months of life in babies living in this region (Fig. 2). Bone levels must also be affected by the amount of Sr in the diet, and analysis of excreta for P, Ca and Sr in different areas of the country and of children of different social classes might provide a direct test of the relative importance of these various factors.

SUMMARY

1. A re-assessment has been made of published data of other workers on Sr and ^{90}Sr in human bone. In different parts of Great Britain the mean ratio of stable Sr to Ca in adult human bones ranged from 240 to 475 μg/g. Extreme values were found even as close as 40 miles apart (Carlisle *v.* Westmorland).

2. Perinatal levels of stable Sr were correlated with adult levels. An estimate of placental discrimination may be derived from the ratio, perinatal level: adult level of about 0·7.

3. The concentration of stable Sr in bones of children from 2 to 5 years old or more was not demonstrably different from that of adults except in one area, Carlisle. With the striking exception of London and south-east England the change from perinatal to adult levels occurred in the 2nd year of life: there was no particular change during the first 9 months or so. In London and south-east England the pattern of change with age was quite different: there was a progressive rise in Sr level from shortly after birth to the end of the 1st year by which time adult levels were reached. It is concluded that geographical differences need to be taken into account when making physiological deductions about turnover of bone salt from changes with age in the level of stable Sr.

4. When children in the south-east of England and the rest of the United Kingdom were compared, there seemed to be a broad inverse correlation between levels of stable Sr and of [90]Sr.

5. Detailed analysis of perinatal results from one area suggested that the level of

stable Sr in bone was somewhat higher in summer than in winter and somewhat higher in anatomically normal babies than in babies dying with gross congenital defects. ^{90}Sr showed the seasonal change only.

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