STUDIES IN RICKETS IN THE CAPE PENINSULA

II. AETIOLOGY

C. P. DANCASTER, B.Sc., M.B. (RAND), M.R.C.P. (EDIN.),* and W. P. U. JACKSON, M.A., M.D. (CANTAB.), F.R.C.P., D.C.H. (LOND.)

Department of Medicine, Groote Schuur Hospital, Cape Town

Before 1920 the aetiology of rickets was something of an enigma. A few years later, however, an understanding of the beneficial effects of vitamin D,[1,2] and the protective value of ultraviolet rays and sunlight,[3-6] acting through a cutaneous vitamin-D mechanism, did away with much of the confusion. Rickets, however, was later found to be common in tropical and sub-tropical countries where ultraviolet exposure should be adequate.[7-12] Factors which predispose towards rickets might include prematurity, lack of breast feeding, low calcium intake, general undernutrition, hereditary predisposition, and lack of exposure to sunlight.

*Present address, Edendale Hospital, Pietermaritzburg.

PRESENT STUDY

1. *Aims.* We planned to investigate the reasons for the high incidence of rickets in the South African 'Cape Coloured' community, in view of the availability of abundant sunlight. Especially, we wished to examine the relative importance of prematurity (birth weight), breast feeding, intake of calcium, exposure to sunlight, undernutrition and malnutrition, and inheritance (familial incidence, excluding environmental factors as far as possible).

2. *Material.* We have examined 100 children with radiologically proved rickets, referred to us over a period of 2 years, and a control group of hospital outpatients of a

similar age. In some cases the mothers were not capable of providing an adequate history, and these children have been excluded.

3. *Methods.* Most of the data were obtained by direct questioning of the mothers of our patients. Admittedly the data here presented cannot all be accurate, in as much as some mothers were not certain of such factors as the amount of sunlight exposure and the birth weight. However, the discrepancies presumably apply equally to the rickety and control patients.

In assessing calcium intake we have considered only those infants who were not being breast fed and have included only that calcium taken as milk.

Only patients with definite radiological changes were included and, in them, the rickets was confirmed biochemically. Children were aged 3 months - 2 years 10 months, and all suffered from ordinary vitamin-D-lack rickets, to the best of our belief. Renal causes of rickets were excluded as far as possible. Urine was tested as a routine for protein and sugar, although it was not always possible to obtain specimens in outpatients. We were particularly careful to screen all children who (*a*) were over the age of 2 years, (*b*) had a family history of rickets, or (*c*) did not respond to 1 ml. 'ostelin forte'* (= 600,000 units of vitamin D).

During this investigation we did 'discover' 2 siblings in one family with cystinosis, which we shall describe in more detail later, and a family with vitamin-D-resistant rickets.

*Supplied by Messrs. Glaxo-Allenburys (S.A.) (Pty.) Ltd.

The mothers usually remembered fairly accurately how many teaspoons of dried milk they used for preparing feeds, and this was the commonest source of calcium. Two of the dried-milk preparations were analysed and found to contain 276 mg. of calcium per ounce, and, as a rough guide, this was considered to be present in 12 teaspoonsful. An analysis of whole milk has shown it to contain 600 mg. of calcium per pint.

RESULTS

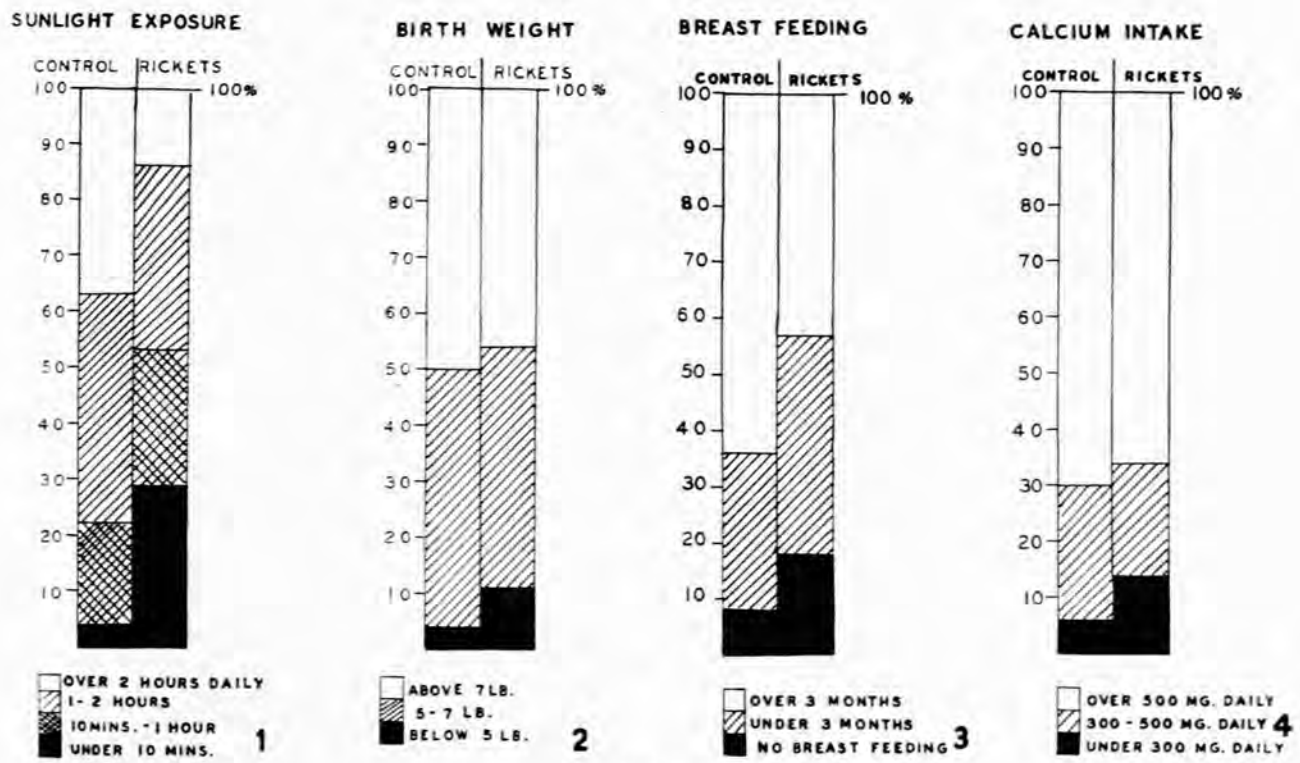
Exposure to Sunlight (Fig. 1)

On the whole, children with rickets saw far less sunlight than controls, more than half being exposed to less than 1 hour daily, and the difference is highly significant ($P = .001$). However, 14% were in the sun for more than 2 hours a day. (There were also 4 control children who were in the sun for less than 10 minutes a day, but had no radiological evidence of rickets.)

Seasonal Variation

Of our total series, 33 were seen in September/October 1959, during an investigation into the significance of craniotabes. These have been excluded from this section, to give an unbiased overall seasonal incidence. Furthermore, only children below 1 year of age are considered here.

Of the remaining 67 children, 51 were found to have rickets during the 5 months, September - January inclusive. These months correspond to spring and early summer in this region.



Figs. 1 - 4. See text.

Most of the children were born in late summer and autumn — 41 out of 53 being born during the 5 months, January - May inclusive.

Birth Weight (Fig. 2)

The children were divided into 3 groups according to their birth weight — below 5 lb., 5 - 7 lb., and over 7 lb. Few children weighed less than 5 lb., but there were 11 in the rachitic group against 4 in the control group. This difference was not significant (P = ·05). There was apparently no increased liability to rickets in the 5 - 7 lb. group.

Twins

Six of the children in the rachitic group were twins (6%). In 3 of the twin-pairs both children had rickets; in 2 of the twin-pairs only the rickety child had survived, and in the remaining pair the other twin, although brought up in the same way, was normal.

Breast Feeding (Fig. 3)

Many of the rickety children had received no breast feeding at all (17%), and the majority were breast fed for less than 3 months. This is in a community where breast feeding is notoriously prolonged — reflected in the control figures (64% were breast fed longer than 3 months). Comparing the 2 groups, the rickety children were on the breast for a shorter period. The difference between the number of normal children who received breast milk for under 3 months compared to the rickety group is possibly significant (·01 < P < ·02). Nevertheless there were many children with gross rickets who were still being breast fed.

Calcium Intake (Fig. 4)

Children were again divided into 3 groups — those receiving under 300 mg. per day, 300 - 500 mg. per day, and over 500 mg. per day. There appears to be a greater susceptibility to rickets in those children receiving less than 300 mg. per day, although the numbers in this group are small and the difference between the controls and rickets is barely significant (P = ·05). Most children with rickets had high intakes of calcium — over 500 mg. daily in two thirds and over 800 mg. daily in one quarter. There was no correlation between the severity of rickets and the calcium intake — some of the children with gross rickets and osteomalacia had intakes of calcium exceeding 1 G. daily.

Combined Factors

There were 37 rickety children in whom more than 1 of these 4 possible aetiological factors were involved, i.e. sunlight exposure of less than 1 hour; breast feeding for less than 3 months; calcium intake under 300 mg. daily, and a birth weight of under 5 lb. In 30 of these, both sunlight exposure and breast feeding were deficient, and in 6 either sunlight exposure or birth weight was a possible factor.

In 25 cases only 1 factor could be incriminated — deficient sunlight in 9, short breast feeding in 13, low calcium intake in 2 and low birth weight in 1.

There were therefore only 4 patients in whom neither defective sunlight exposure nor short breast feeding was a possible aetiological factor, and in whom prematurity or low calcium intake was the sole defect discovered. There were, in addition, 9 children with rickets in whom none of these 4 factors appeared defective.

Familial Rickets

Twenty-three families were investigated for evidence of rickets in more than one sibling. In 13 of these only 1 child was affected, but in 10 families more than 1 sibling had radiological evidence of rickets — in some cases this had healed and only postrachitic deformities remained.

An underlying renal aetiology was discovered in 2 of the families (cystinosis and vitamin-D-resistant rickets). In the remaining 8 families there were no urinary abnormalities, and the rickets healed on small doses of vitamin D. In addition to these 8 instances of what is presumably 'familial ordinary vitamin-D-lack rickets', there were 3 other families in which the mothers stated that at least one other child had deformed legs — in one case she knew her child had been treated in hospital for rickets. These children were not seen by us.

Biochemistry in Mothers (Table I)

The serum-phosphorus and alkaline-phosphatase levels were determined in 17 of the mothers of these children.

TABLE I. BIOCHEMISTRY IN 17 MOTHERS OF RICKETY CHILDREN

Alkaline phosphatase (Shinowara-Bodansky units)	*Phosphorus (mg. per 100 ml.)*	*Alkaline phosphatase (Shinowara-Bodansky units)*	*Phosphorus (mg. per 100 ml.)*
8·4	4·3	2·2	4·9
6·1	4·2	6·0	3·5
16·2	4·5	2·7	5·5
5·1	5·2	5·9	4·3
5·2	4·2	18·3	2·9
2·2	4·1		5·2
3·1	4·2		5·4
13·5	3·9		3·4
6·3	4·4		

All were within the normal range.

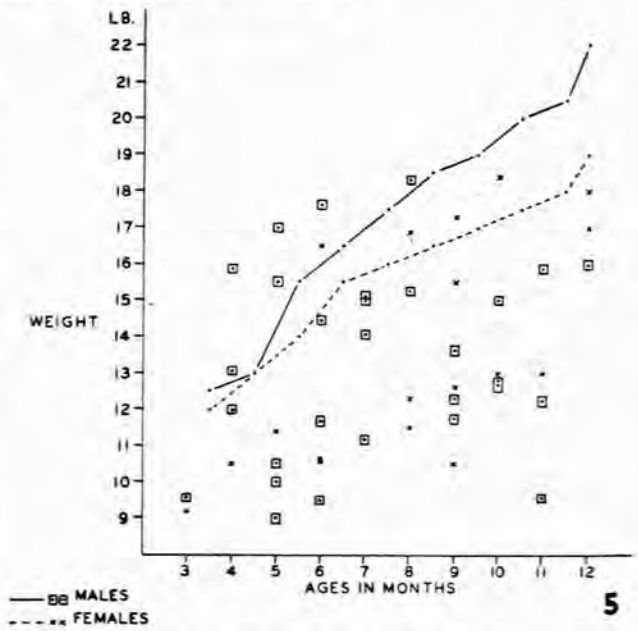


Fig. 5. Weights of children with active rickets compared with mean weights of normal Coloured children. Dotted and solid lines represent, respectively, the mean weights of normal female and male Coloured children under 1 year of age.

Weight of Children with Active Rickets (Fig. 5)

When compared with the mean weights of African and Coloured children (after Salber [33]), nearly all the children with rickets were underweight when first seen, some grossly so.

Serum Proteins (Table II)

The total serum proteins were above 6·0 G. per 100 ml. in 15 out of 21 estimations. Some of these patients had severe rickets with bone rarefaction and fractures. In only 2 children was the total protein below 5 G. per 100 ml., and in only 1 child was the serum albumin below 3·0 G.

TABLE II. SERUM PROTEINS IN G. PER 100 ML. IN 21 ESTIMATIONS

Albumin	*Globulin*	*Total*	*Albumin*	*Globulin*	*Total*
4·5	2·7	7·2	3·1	2·5	5·6
4·2	2·2	6·4	3·8	3·5	7·3*
4·4	1·8	6·2	3·8	2·4	6·2
4·7	3·0	7·7	2·2	1·6	3·8
4·4	1·8	6·2	3·8	2·3	6·1
4·5	2·8	7·3	4·5	2·2	6·7*
3·4	2·0	5·4	4·2	1·4	5·6
4·0	2·2	6·2	3·7	2·5	6·2
3·6	1·3	4·9	4·6	3·0	7·6*
3·2	2·5	5·7	4·5	3·3	7·8*
			4·0	2·0	6·0*

* Electrophoresis carried out. Normal in all 5 patients.

Electrophoretic patterns were done in 5 children who had a history of repeated respiratory or gastro-intestinal infections. The globulin and other fractions were normal in all cases.

DISCUSSION

Sunlight

The seasonal variation in the incidence of local rickets led to lack of sunlight being suspected as an important cause. The healing effect of sunlight has been demonstrated both experimentally in rats,[14] and in humans. Exposure for as little as half-an-hour daily was sufficient to cure rickets in a small group of children investigated by Hess in New York in winter.[4] It is only the short ultraviolet waves which are beneficial,[15] and there are many factors affecting the number of these reaching the earth's surface. Atmospheric absorption is increased by smoke, dust and cloud, and by the distance the rays travel through the atmosphere. The antirachitic quality of sunlight is therefore greatest at midday near the equator, at higher altitudes, and on clear summer days. Irving and Schwartz demonstrated that summer sunshine in Cape Town has marked antirachitic activity; as little as 5 minutes' exposure at 1 p.m. was sufficient to promote healing in rachitic rats.[16] Winter sun, however, had a very low antirachitic activity — exposure of 1 - 2 hours daily failing to heal rickets.

The value of sunlight exposure must also be surveyed in relation to other factors, skin pigment being particularly relevant in this community. Dark skin absorbs less ultraviolet light, and the practical importance of this has been shown in rats. Darkly pigmented rats need longer exposures to sunlight to protect them from rickets when compared with white rats.[17a] It is possible that an urbanized coloured population needs more than a half hour's daily sunlight, especially in winter. Lack of adequate exposure to sunlight appears to be the most definite aetiological factor in these children. Many are carried heavily wrapped on their mothers' backs, where they see little sun. Others are left indoors all day while their mothers work.

Most cases were found in spring and early summer. Any sunlight these children had been exposed to in the previous 6 months was during winter and therefore of poor quality. Likewise, children born in the late summer and autumn are exposed to these poor-quality rays for their first 6 months. Most of the children with rickets in this series were born during that time.

However, half the affected children had been exposed to sunlight for more than 1 hour daily. Even if the minimum requirement to prevent rickets were 2 hours, there are still 14% of children in whom an alternative aetiological factor must be sought.

Milk

Breast milk has always been considered to be superior to cow's milk in preventing rickets. Hess, in 1922, showed that approximately all bottle-fed infants in New York developed rickets in the month of March unless they received specific therapy, whereas 'only' a half of the breast-fed infants showed definite signs at the seasonal peak.[17b] It is not clear why breast milk is superior to cow's milk. The calcium and phosphorus content of breast milk is less than in cow's milk, and it contains very little antirachitic factor.[18] (In premature infants there is evidence that cow's milk has superior antirachitic qualities.[19,20]) In the children we investigated many were breast fed when rickets developed, so that it is certainly not completely protective, although there did appear to be an increased likelihood of rickets, possibly significant, developing in those children who received less than 3 months' breast feeding.

Calcium

The calcium intake was adequate in nearly all the patients. There is no good evidence that lack of calcium ever plays any part in the development of rickets.[21,22]

Prematurity

An increased incidence of rickets among premature infants has frequently been observed.[17] Defective skeletal mineralization has been suggested as a factor (most of the calcium and phosphorus is laid down in the last 2 months of foetal life). Hess showed that the livers of premature infants contain as much antirachitic substance as those of full-term infants. In this series we were unable to demonstrate a significantly increased susceptibility to rickets in premature infants.

Main Aetiological Factors

In comparing these rickety children with controls the most significant aetiological factors appear to be deficient sunlight exposure and breast feeding. Prematurity and deficient calcium intake were not significantly different in the 2 groups.

This conclusion is confirmed by analysing these 4 factors as they affect individual children with rickets. In 62 cases where adequate histories were obtained on all 4 factors, a defect in sunlight exposure and/or breast feeding was present in 58, and in only 4 children was prematurity or deficient calcium intake the sole aetiological agent discovered.

There were, however, 9 additional children in whom all the factors so far considered appeared favourable, so that in these cases we were either misled by an incorrect history, or else there are other important aetiological factors which we have not considered.

Other Factors

The frequency with which more than one member of a family had rickets suggests a possible hereditary factor. The explanation of this may, of course, be merely environmental, in that the children were brought up in the same way with little or no sunlight exposure. We found no evidence of disturbed biochemistry in the mothers' blood (Table I).

During the 2-year period over which this investigation was conducted, only 3 European children were seen with ordinary vitamin-D-lack rickets, possibly indicating a racial susceptibility among both Bantu and Coloured. Difference in upbringing might also explain this.

According to Hess, rickets is rare in the marasmic child.[17c] However, in a recent comprehensive survey of rickets in Japan, the high incidence of rickets in marasmic children was stressed,[23] and most of our children were underweight — some severely. Wayburne and Dean have reported similarly.[24] We believe that the popular conception, that lack of growth protects from rickets, is incorrect.

During various severe illnesses serum levels of calcium and phosphorus may be depressed, returning to normal on recovery. Rickets has also been observed histologically during severe illness.[25] Such rickets may, however, have antedated the illness rather than have been caused by it.

In view of the severity of osteomalacia in some cases, we wondered whether the bone matrix was also involved, especially since the children's protein intake was extremely low in most instances. However, the serum proteins were normal in nearly all the patients examined, including some with the most severe bony rarefaction. The increase in bone density following vitamin-D therapy was often dramatic. We have therefore no evidence to support the suggestion of matrix deficiency.

The electrophoretic pattern of the serum proteins was normal in the cases in which it was evaluated. A deficient γ-globulin fraction did not appear to account for the frequency of superadded infection in rickety children.

SUMMARY

One hundred Coloured and Bantu children with active rickets have been seen over the course of 2 years. When compared to a control group, the most significant difference in possible aetiological factors was the exposure to sunlight, which was far less in the rickety group ($P = .001$). Most of the rickety children were born in the late summer and autumn months. There were more rickety children receiving less than 3 months' breast feeding than controls, the difference being probably significant ($.01 < P < .02$). There was no statistically significant difrerence in birth weight or calcium intake between the 2 groups.

Individual case analysis of rickety children confirmed that deficient sunlight exposure or breast feeding were probably the 2 most important aetiological factors. In only 4 of 62 children in whom adequate histories were obtained were neither of these factors incriminated. There were, however, an additional 9 children in whom all these factors were favourable. Serum proteins were normal in all the children, even in those with gross osseous rarefaction. The mothers of rickety children had normal serum biochemistry. In eight families more than 1 sibling suffered from ordinary vitamin-D-lack rickets.

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