A STUDY OF CRANIOMALACIA IN INFANCY.

Thesis for the Degree of M.D.

Glasgow University

by

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I N D E X

SUTURE SOFTENING

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LOCALISED SKULL SOFTENING (CRANIOTABES)

AETIOLOGY:

PART III

PREFACE

The investigations on which this thesis is based were carried out in the Wards and Biochemical Laboratory of the Royal Hospital for Sick Children, Glasgow. Part of the work was completed during the tenure of a Muirhead Scholarship.

I wish to express my indebtedness to Dr. Stanley Graham for interesting me in this subject for research, and acknowledge with gratitude the advice and helpful encouragement which he has given me. I wish to thank Professor G. B. Fleming and Mr. Matthew White, for permission to investigate cases in their wards, Dr. H. E. C. Wilson, Dr. D. C. Suttie and the staffs of the Biochemical and Radiological Departments. To the House Physicians, Ward Sisters and Nurses, who attended to the children included in this survey I also wish to extend my thanks.

PART I

HISTORICAL SURVEY.

The year 1843 saw the first mention of softening of the cranial bones in infants, when Carl von Elsässer (1) published a detailed account of what he called "craniotabes infantum". In a translation of part of the work made by Ruhräh (1) it is apparent that Elsässer concluded that children so affected were rachitic, that is, they were late in standing and walking, were prone to infection and closure of the anterior fontanelle was delayed. He also remarked on their susceptibility to convulsions and laryngismus stridulus which he asserted was due to pressure upon the cranial contents. In such children the skull became softer during the fourth month of life; this softening was followed by a thinning of the bone on the posterior aspect of the skull. Attention was drawn to the fact that the thinning might be more marked on one side of the occipital region than on the other. It is probably this type of softening which today is associated with, and by many considered pathognomonic of rickets.

Subsequently in 1850, the presence of cranial softening at an earlier age was noticed by Bednar (2) and was confirmed ten years later by Broca (3) and by Freidleben (4). This cranial defect, which was present at birth and therefore congenital in origin, was found by Broca most commonly in the area/

area including the central point of the parietal bones and was thought by him to be due to incomplete ossification, while Freidleben found that the mineral content of the affected bones was diminished.

Kassowitz (5) working at the same time, concluded that all types of skull softening were of rachitic origin, his deductions being based on the following observations. Skull softening present at birth showed a seasonal incidence, occurred most frequently in urban districts and was followed by enlargement of the epiphyses. He therefore named the condition congenital or true craniotabes, and noted that it was positively affected by a poor maternal diet. This work appeared in the light of the medical knowledge of the period to be confirmed by Spietschka (6) who claimed to have cured skull softening present at birth by the administration of phosphorus. He also stated that the site of the softening depended on intrauterine pressure.

It was left to Rehn (7) and Bohn (8) while making general surveys of cranial softening, to advance the theory that several aetiological factors might influence the appearance of such softening and the following classification was made:-

a) Congenital softening, non-rachitic in origin, which disappeared between the ages of 2 and 3 months.

b)/

b) Rachitic softening similar to that described by Elsässer (1) which appeared at the end of the fourth month.

The histology of skull softening was first investigated about this time by Pommer (9) who found that soft skulls showed osteoporotic changes in the affected areas. His work with that of Rehn and Bohn appears to have been almost generally ignored at first and the theory of Kassowitz (5) remained practically unchallenged for the ensuing thirty years.

Barlow and Bury (10) while describing rachitic changes in the skull, included as signs the late ossification of the soft margins of the skull bones and, at a later date than is found in normal children, the presence of small bones between the parietal and occipital bones. They believed that craniotabes was rachitic in origin if the term referred to flexibility of the parietal and occipital bones. In discussing the causation of laryngismus stridulus they disagreed with von Elsässer (1) and thought that relationship existed between craniotabes and laryngismus stridulus only on account of their having the same aetiological origin. They also referred to foetal rickets which they believed with Kassowitz (5) was a clinical entity, and described a foetus they had seen which displayed multiple fractures which they thought/

thought were due to rickets. The possibility that these lesions may have been due to fragilitas ossium arises. They suggested, however, that some of the reports of severe foetal rickets previously published might have referred to achondroplasia.

In the same year Henoch (11) raised the question of the possibility of foetal rickets being due to deficient ossification while Mason (12) described an infant who showed almost complete absence of the parietal bones which might be regarded as a gross example of delayed ossification. While discussing craniotabes, Henoch described thinning of the skull bones near the lambdoidal suture which was present in early infancy. Pressure over these areas gave a crackling sensation. In some instances these areas disappeared as what he termed delayed ossification progressed, but following this statement he admitted that rachitic changes might exist elsewhere. Despite this he concluded that the softening was physiological in origin and quoted Freidleben's (4) findings. He also described skull softening which he considered to be rachitic in origin and which appeared first between the third and fourth month of life. He mentioned that in these infants the sutures were widely separated and the bone bordering them soft.

Lee (13) in 1894, described skull softening during the/

the first few months of life as being due to irregular development from the centres of ossification and also perhaps to bone absorption.

In Hoblyn's Dictionary (14) published in 1892, craniotabes was described by Price as being localised softening of the cranium, which yielded like cardboard and occurred in rickets.

That rachitic skull changes might appear in different areas of the head was suggested by Cohn (15) who inferred that such lesions comprised softening either in the occipital region in proximity to the parietal bones, or around the anterior fontanelle; when the latter area was affected the softening occurred after birth.

From the foregoing reports and extracts it is apparent that great diversity of opinion existed as to what relationship there was between cranial softening and rickets and as to what aetiological factors were associated with skull softening of all types. Some slight elucidation of the problem has resulted from reports of recent work which in some instances has combined clinical, biochemical and radiological examinations. Some of these results will now be referred to.

SURVEY OF RECENT WORK.

In an attempt to clarify the results of recent investigations, they are classified according to the conclusions resulting from them, namely, findings suggesting:-

1. That congenital and early skull softening is of non-rachitic origin, while late softening is rachitic.
2. That early softening is non-rachitic.
3. That early softening is rachitic or pre-rachitic.
4. That late softening is non-rachitic.
5. That late softening is rachitic.
6. That all softening is rachitic.

The term craniotabes is employed below only where the authors have used it without giving a description of the precise skull changes.

In assessing the value of radiological and biochemical findings, it is accepted that definite radiological changes are not apparent in the early stages of rickets. Likewise, as Wimberger (16), Hess (17), Stearns et alii (18) and Howland and Kramer (19) amongst others have shown, the biochemical findings are not always indicative of the activity of the rachitic process. Consequently proof of the presence or absence of rickets cannot be based on the results of one of these examinations alone.

1. That congenital and early skull softening is of non-rachitic origin while late softening is rachitic.

Wieland/

Wieland (20) (21) in 1910 reported his findings based on clinical and histological examinations and formed a dual conception of skull softening. In examining newborn infants he found that 11 per cent showed congenital cranial defects. These defects were most commonly situated in the parietal bones, in the region of the sagittal suture. As the infant developed, these areas either disappeared entirely, disappeared and later showed evidence of softening, or showed a gradual increase in the area of softening which became the site of rachitic craniotabes. This congenital softening which displayed no seasonal incidence was due, he thought, to rapid growth of the skull after birth associated with poor calcification. The areas affected showed no overgrowth of osteoid tissue such as occurs in rachitic bone changes. Although he concluded that softening present at birth was not a factor predisposing to the development later of what he considered to be rachitic skull changes, he stated that should such softening supervene in infants who had soft skulls at birth it was more severe in intensity. His findings were later confirmed by Comby (22) who also considered that softening, occurring later in infancy might be rachitic in origin.

This dual conception was also held by Huenekens (23), Davidson (24), Sanctis (25) and others. Huenekens classified/

classified skull softening as congenital, physiological softening occurring up to the age of 2 months and rachitic softening which appeared from that age up to 6 months.

The discovery of the blood changes present in rickets was followed by numerous estimations of the blood calcium and phosphorus in infants with skull softening. Hess (26), believing that softening could be either rachitic or non-rachitic in origin, was of the opinion that, if rachitic softening occurred before 5 months of age, it should not be used in the diagnosis of rickets as at that age it was easily confused with congenital softening. This congenital softening he thought was due to a physiological osteoporosis. He stated that serum phosphorus values were found to be within normal limits in infants under 6 months who had skull softening of the type which he considered to be rachitic in origin. This softening, which occurred as small discrete areas in the occipito-parietal region, was present in 30 per cent of infants aged 3 months, but occurred in only 10 per cent at 6 months. From these findings it appears that no definite distinction can be made between non-rachitic and rachitic softening.

Barenberg and Bloomberg (27) limited their investigations to infants showing softening of the parietal or upper occipital regions and did not include softening along the/

the sagittal suture. In these infants such softening was found from the age of 2 weeks up to 12 months; 68 infants under 4 months showed softening and of these one only, aged 14 weeks, had radiological evidence of rickets, while one, aged 8 weeks, had what they considered to be a low inorganic blood phosphorus (3.7 mgm. per cent). Of 28 children over 4 months with craniotabes, 21 had rickets as judged by the same criteria. They concluded therefore that such softening may be rachitic or non-rachitic in origin, and stated that it is intimately connected with rickets in infants over 4 months of age.

2. That early skull softening is non-rachitic.

It has been shown by many workers, Huenekens (23), Langstein (28), Capper (29) and Rosenstern (30) amongst others, that rickets is more prone to develop in premature infants. This fact was therefore used by Rosenstern (30) in order to show whether skull softening present at birth was rachitic in origin. He found localised circumscribed areas of softening less common at birth in premature infants and concluded therefore that such softening was non-rachitic in origin. Toverud (31), however, found that although twins and premature infants had hard skull bones at birth, these bones rapidly softened. This supported the belief that early softening was due to osteoporosis resulting from rapid expansion/

expansion of the skull bones. Still (32) expressed the opinion that softening of the edges of the parietal and occipital bones in infancy was due to delayed ossification.

Levinson (33) wrote that cod liver oil administration resulted in the disappearance of craniotabes in 4 children who were all over 4 months of age, and there is no mention of a cure being effected at an earlier age. The author, however, does not state whether he thought that softening was rachitic in origin.

Wilson and Kramer (34) found that the blood chemistry of infants under 4 months with skull softening showed no evidence of active rickets. Bang (35) (36) found no relationship between the blood phosphorus value at birth and the presence of congenital softening. He also found that histological examination of the long bones of infants with such softening showed bone atrophy and that the thin areas of skull bone were osteoporotic.

The belief that early skull softening was in no way associated with rickets was also held by Hughes (37) who considered that such softening was due to antenatal and post-natal mechanical action associated with decalcification. He ventured the suggestion that maternal dietary deficiencies resulted in the decalcification present. No histological examination, however, has supported this theory of decalcification/

decalcification. He also remarked that rachitic changes frequently occurred in infants with soft skulls. Toverud and Toverud (38) proved from the results of metabolism experiments which they conducted on pregnant women, that congenital softening was due to a lack of calcium in the maternal diet during pregnancy. Reiss and Boder (39) investigating the relationship between the occurrence of "congenital osteoporosis" and the maternal diet during pregnancy, were unable to confirm these findings. Regarding the incidence of congenital softening, Reiss and Boder found that such softening exhibited a seasonal incidence the peak of which preceded by three months that of what is termed rachitic craniotabes. They therefore concluded that a definite relationship existed between the two types of softening, but did not suggest what it might be.

3. That early softening is rachitic or pre-rachitic.

The belief that early softening is due to rickets is associated with the problem of whether foetal rickets is accepted as a clinical entity. Both Schmorl (40) and Weiland (20) found no histological evidence of rickets at birth while Hess and Weinstock (41) discovered no radiological changes suggestive of rickets; this latter evidence, however, as has been mentioned previously cannot be recognised until several weeks after the rachitic changes have commenced/

commenced. Freer (42) has remarked that infants with osteogenesis imperfecta may have been diagnosed as foetal rickets.

Maxwell, Hu and Turnbull (43) on the other hand have described rachitic changes present at birth in infants born to osteomalacic women, and Rector (44) described an infant aged 2 days who showed evidence of rickets at post-mortem examination.

Although rickets has seldom been shown to occur at birth, it appears that prenatal factors have a possible influence on its development. While not going so far as to state that rickets might occur congenitally, Byfield and Daniels (45), experimenting in rats, found that a maternal diet, low in Vitamin D, resulted in the early occurrence of rickets in the young, while Toverud and Toverud (38) obtained similar results in dogs.

Macciotta (46) found that rickets was more liable to develop in the child where the mother had lived under poor hygienic conditions and had been taking an unbalanced diet, while Jundell and Magnusson (47) have stated that the blood phosphorus level at birth varies according to whether or not the mother has been receiving additional amounts of Vitamin D during her pregnancy.

Jungwirth (48) and Rector (49) have both reported cases illustrating the positive effect of repeated pregnancies on/

on the development of rickets in the child.

Rachitic changes, as previously stated, have also been shown to occur frequently in premature infants. These have been thought to be due partly to deficient calcium storage in the foetus, as this storage occurs mainly during the last two months of gestation. Hamilton (50) has shown from the results of metabolism experiments conducted on premature infants that, although the calcium retention may be adequate after birth in these infants, they are liable to develop rickets.

From these investigations it is apparent that, although the presence of foetal rickets has seldom been conclusively demonstrated, there appears to be a prenatal factor associated with the development of rachitic changes.

Though not classing congenital skull softening as being rachitic in origin, Abels and Karplus (51) believed that such softening might be pre-rachitic. In an extensive survey they found it present in 84 per cent of newborn infants, and described the skull as being soft with sutures and fontanelles open; that is, it showed evidence of deficient ossification.

Korenchevsky (52) found that 50 per cent of children with soft bones at birth showed signs of rickets later. Of the infants who had craniotabes at birth, i.e.

5/

5 per cent of the infants examined, 95 per cent later developed rickets.

4. That late softening is non-rachitic.

In considering skull softening which occurred later in infancy, Wilson and Seldowitz (53) differentiated between suture softening, which they dismissed as bearing no relationship to rickets, and investigated the type of skull softening which gave the skull softening a membranous or crackling sensation and concluded that this type of softening was non-rachitic in origin and that its occurrence was coincidental with that of rickets. Jacobi (57) later confirmed these findings, while Hess and Lewis (58) and Gerstenberger (59) found that craniotabes may even increase in severity while the infant is receiving cod liver oil.

Rapoport et alii (60) found craniotabes present in infants who at no time displayed radiological evidence of active rickets, whereas Aldin (61) stated that he examined 100 rachitic infants and none had craniotabes. Kasahara et alii (62) found that such softening was non-rachitic in origin and recently it has been suggested by various authorities - Rustung (63), Roddy et alii (64) - that the clinical findings which are commonly considered to be evidence of mild rickets, e.g. craniotabes, cranial bossing/

bossing, slight broadening of the epiphyses and enlargement of the costo-chondral junctions, may be physiological in origin. Jundell (65) also considered it to be physiological hypoplasia.

5. That late softening is rachitic.

Skull softening present in the later months of infancy is regarded by most workers as being pathognomonic of rickets, but it is remarkable that comparatively little work has been done to substantiate this view. Langstein (66) writing in Abt's Paediatrics, was of the opinion that rachitic craniotabes was frequently found between the ages of 3 and 4 months, while Dalyell and MacKay (67) in their Vienna report, concluded that softening occurring in the occipito-parietal region in children over 3 months was rachitic in origin. Davidson and Merritt (68) write that the general consensus of opinion is that central softening occurring after the third month is pathognomonic of rickets.

Although his deductions were incorrect when he said that rickets was cured by semi-starvation, Jundell (69) appears to have been the first to investigate the fact which was suggested indirectly by Glisson (70) that the appearance of rickets bore a relationship to the rate of bone growth. In his publication he quotes the case of two infants aged 4 and 7 months with rickets and softening along the/

the lambdoidal sutures who were treated by semi-starvation. The skull softening disappeared simultaneously with the recognised signs of rickets.

That craniotabes is definitely a sign of rickets in older infants was believed by Rhoads et alii (71) and by Eliot (72) amongst others. Eliot investigated the curative properties of cod liver oil and of sunshine in the treatment of rickets. Skull softening was the only physical sign which, appearing alone, was taken as sufficient evidence on which to make a diagnosis clinically of rickets. Some dubiety as to her exact conception of rachitic skull changes arises from the statement that "unless the softening extended into the bodies of the cranial bones it has not been considered sufficient evidence for a diagnosis". It must also be noted that all the infants referred to showed evidence of rickets radiologically, and consequently the diagnosis was not made on the presence of craniotabes alone.

Brun (73), Williams (74) and Hess and Lundagen (75) found a seasonal variation in the inorganic blood phosphorus in infants, the lowest value occurring in February and March, the months when skull softening in older children showed its maximum prevalence. This seasonal variation is similar to that of rickets and supports the belief that there is possibly a relationship between the two conditions.

Eliot/

Eliot and Jackson (76) comparing two groups of children living under different climatic conditions, found that craniotabes occurred more frequently in the group displaying the higher incidence of rickets. Guild et alii (77) reported a case of rickets which occurred in a child of 17 months and mentioned that she had craniotabes.

6. That all skull softening is rachitic.

Marfan (78) after making histological examinations of affected skull areas, stated that all skull softening was rachitic, and in keeping with his theory concerning the aetiology of rickets included it as a manifestation of syphilis. This conception was upheld by de Stefano (79).

Schwartz (80) compared the prevalence of skull softening in coloured and in white children and concluded that such changes whether congenital or acquired were rachitic in origin as they were more common in coloured children - 79 per cent and 39 per cent respectively. In infants under 1 month, 6 per cent had craniotabes.

Moore and Dennis (81) were of the opinion that congenital softening which appeared first round the mastoid foramina and occipital regions was rachitic in origin. This softening was localised and did not involve either the vertex or the suture edges. Such softening which we must presume was present at birth or appeared shortly after birth, was present/

present in 120 of 193 infants examined in the first year of life. Its presence was used to diagnose rickets when few other clinical signs were apparent; that is, in infants under 5 months of age. The rachitic origin of such softening was based on the fact that it displayed a seasonal incidence, was more prevalent in the absence of adequate sunshine, was cured by the administration of Vitamin D and occurred in the bone which showed the maximum rate of growth for that age period. The authors also commented on the fact that softening was followed by definite rachitic changes elsewhere.

On considering the conclusions of the various authors, it is apparent that there is frank disagreement amongst them concerning the various aspects of craniotabes. The following investigations were thus undertaken in order to discover in which areas of the skull bones softening may be found and to investigate the aetiology of such softening and its possible relationship to rickets.

PART II

PRESENT INVESTIGATION.

Nine hundred and seventy-two children, below the age of one year, were examined and are included in this survey. These infants were either in-patients or attended the out-patient department of the Royal Hospital for Sick Children, Glasgow, within the year commencing 1st October 1941, and in the majority of the cases the home was either in Glasgow or in the surrounding district. The primary attendance at hospital was, in the case of 40 of the infants, due to minor surgical conditions, e.g. phimosis, hernia or minor injuries which did not affect their general health and nutrition. In the remaining 932 instances, the infants were seen in the Medical Department with various complaints, the majority of the infants suffering either from upper respiratory infections or gastro-enteritis. As is generally believed and indeed was mentioned in the first recognised description given by Whistler (82) of rickets, these infections are more liable to occur in rachitic infants. It may be concluded therefore that a higher proportion of rachitic infants will have been examined than would have been found in a survey of a cross-section of the infant population of Glasgow and its environs.

CLASSIFICATION OF TYPES OF SKULL SOFTENING.

Method of Examination:-

The infant was laid on his back and the examiner's thumbs placed in the region of the supra-orbital crests, while the palms of the hands embraced the sides of the head which was thus held firmly in position. With the fingers spread over the occiput, moderate pressure was applied to all areas of the vault of the skull in turn and any point at which the bone yielded to pressure was noted. Pressure appeared to cause slight pain, which was probably due to the susceptibility of the pericranium to pressure.

As has been seen from the work done in connection with skull softening, the character and extent of such softening show great variations and it is therefore difficult to form criteria on which to base a diagnosis. As a result of the examination made in this survey the following classification was evolved.

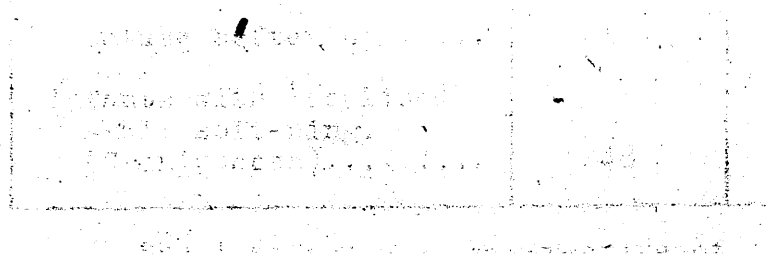
a. Softening which may be described as yielding of the whole or a large part of the bone on the application of pressure. These areas when they affect only part of the bone have ill-defined edges and gradually merge with the surrounding firm bone. This softening is found especially in the parietal bones and less frequently in the occipital and frontal bones and probably includes what has been termed vertex/

vertex softening.

b. Secondly, softening occurring along the sutures but not extending into the bodies of the bones. The most common point at which this softening may be found is at the asterion, that is, at the junction of the occipital, parietal and temporal bones; it may also occur along the coronal and sagittal sutures.

c. The third type may be described as localised circumscribed areas in the skull bones which yield to pressure and are surrounded by hardened bone. These areas exist in the occipital or parietal bones. To this variety of softening the term craniotabes is subsequently applied.

All three types of softening may be unilateral.



PREVALENCE OF SKULL SOFTENING.

The prevalence of skull softening in 972 infants examined and the relative frequency of the various types are shown in Table I.

Table I

Showing the prevalence of skull softening in 972 infants aged under I year.

	Number	Per Cent
Infants examined.....	972	
Infants with skull softening of any type.....	414	43
Infants with generalised skull softening	19	2
Infants with suture softening.....	135	14
Infants with generalised skull softening and suture softening.....	12	1
Infants with localised skull softening. (Craniotabes).....	248	26

Skull softening, irrespective of its type was present in 414 of the 972 infants examined, i.e. 43 per cent, and in considering the various types, it is seen that craniotabes was most commonly met with. It occurred in 248, i.e.

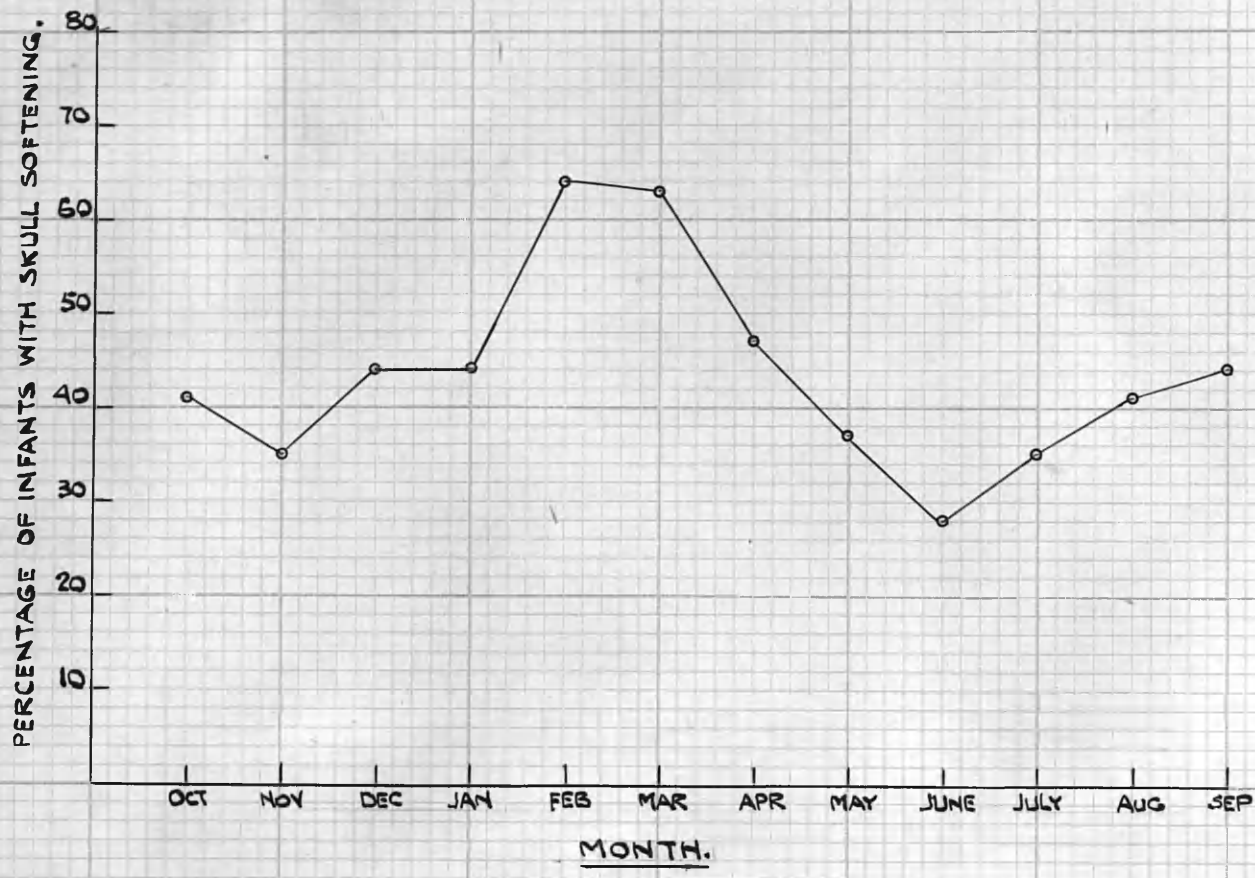
26/

26 per cent, while suture and general skull softening occurred separately or together in 15 and 3 per cent of the infants.

As there are no arbitrary facts governing the diagnosis of skull softening, it is difficult to compare these results with those of other workers. Moore and Dennis (81) working in Portland Oregon, where the climatic conditions are said to be comparable with that of the Western coast of Scandinavia, that is, comparable with the West coast of Britain, examined 193 unselected infants during the first year of life and found that 120 of them developed skull softening. This skull softening probably comprises all three types classified above. As the infants were examined several times during the first year of life, it is not possible to compare the results accurately with the present series. It appears, however, that of the 193 infants, 70 at least developed softening after their first visit, and the results therefore are roughly comparable with the present figures.

Wilson and Seldowitz (53) working in Orleans, described skull softening which appeared to include the generalised and localised types described above; 499 infants under 1 year of age were examined by them at intervals, and 35 per cent were found to have skull softening. In the present/

FIG 1- SHOWING THE SEASONAL INCIDENCE OF SKULL SOFTENING.



present study in which the infants were seen on one occasion only, 29 per cent were found to have softening similar to that described by these authors. Hess (17) found the same types of softening in 42 per cent of infants in New York City and quoted Jacobi (83) whose results were similar (40 per cent). It is not stated, however, whether or not these figures were based on the result of several examinations of each infant. Cohn (15) found that 35 per cent of infants examined on one occasion only had such softening.

It is apparent that, although the conception of skull softening may show great variations, infants under 1 year of age frequently exhibit skull softening of some type.

While examining the infants it was discovered that skull softening displayed a marked seasonal incidence which is indicated in Fig. 1.

The seasonal incidence is seen to increase greatly in the early spring months (February and March), this rise being followed by a fall in the early summer until in the month of June softening occurred in only 28 per cent of the infants examined.

It is also seen that skull softening exhibits a seasonal incidence similar to that of rickets, suggesting that there may be a possible relationship between the two conditions

conditions, especially as Rasmussen (84) found no seasonal variation in the North where there is no appreciable difference between the seasons.

Craniotabes and generalised softening when either occurred unilaterally commonly appeared on the side usually in contact with the pillow, and was often associated with asymmetry of the head.

As it is possible that the aetiological factors in the three types of softening described may vary, these types are now considered separately and several factors which were thought might influence the aetiology are investigated.

GENERALISED SKULL SOFTENING.

As generalised skull softening was found in only 31 of the 972 infants examined, it is not possible to base any definite conclusions on the findings in such a small number of infants. These findings are, however, stated below.

Aetiology of Generalised Skull Softening.

1. Seasonal Incidence.

The number of infants found to exhibit generalised softening in each month of the year is shown in Table II.

Table II

Showing the number of infants with generalised skull softening in each month of the year commencing 1st October 1941.

Month.	Number of infants examined.	Number of infants with generalised skull softening.
October	82	1
November	78	3
December	81	4
January	86	4
February	78	3
March	82	3
April	82	2
May	78	3
June	83	2
July	79	2
August	88	3
September	75	1

As the number of infants examined in each month of the year was relatively similar, comparisons may be easily made between the findings in each month. It is apparent that there was a slight tendency for this type of softening to occur more frequently in the winter months. Presuming that the seasonal incidence will not vary from year to year, the results may be divided into two groups, namely, November to April inclusive and May to October inclusive. Of the 487 infants examined in the winter months, 19 had generalised softening; in the summer months only 12 infants of the 485 examined had similar softening which suggests that infants born in the winter months are more liable to develop generalised skull softening.

II. Age Incidence.

The ages at which generalised softening was found are shown in Table III.(See over).

Table III.

Showing the number of infants with generalised skull softening from birth up to 16 weeks of age.

Age in Weeks	Number of infants examined	Number of infants with generalised skull softening
1	20	3
2	29	5
3	20	-
4	30	4
5	24	5
6	28	4
7	20	-
8	28	3
9	22	2
10	24	3
11	20	-
12	19	1
13	30	-
14	22	1
15	18	-

It is apparent from these results that this type of softening displayed a definite age incidence. Twenty-nine of the infants were under 11 weeks, while not one of them was over 16 weeks; the youngest child included in the group was 1 day old. From these results and also from the similarity between this type of softening and that described both by Reiss and Boder (34) and by Toverud (31) as congenital skull softening, it may be concluded that the softening must have been present at birth or have developed shortly afterwards.

III. Sex.

Of the 31 infants with generalised skull softening, 17 were males and 14 females. This showed no sex preponderance, as a greater number of boys were included in the survey.

IV. Height, Head Circumference and Weight.

Comparison of these measurements in infants with and without the type of softening under consideration is made in Table IV.(See Page 30).

Regarding the weight of the infants, it was found that both those with skull softening and those with hard skulls showed a great variation in each age group. The range and not the average weight is therefore given in Table IV. It is seen that there was no significance in the height and weight of the infant, but those with softening at birth had a larger average head circumference. In the older age groups the head circumference measurements did not show this variation.

Table IV.

Comparing the height, head circumference and weight of infants with generalised skull softening with that of infants with no skull softening.

	Age in Weeks			
	0 - 4	4 - 8	8 - 12	12 - 16
	Cms	Cms	Cms	Cms
Av. height of infants with generalised skull softening.....	51	53	53	58
Av. height of infants with no skull softening..	51	53	55	58
Av. head circumference of infants with generalised skull softening.....	37	37	38	38
Av. head circumference of infants with no skull softening	34.5	35.5	38	38.5
	K	K	K	K
Range of weights of infants with generalised skull softening	2.9-3.5	?	2.6-3.8	3-3.48
Range of weights of infants with no skull softening	2.8-3.75	2.8-3.8	2.9-3.4	3.1-5.4

V. Duration of Gestation and Multiple Pregnancies.

The number of premature infants under 16 weeks of age examined was small, namely 26, and only one of these infants was found to have generalised softening. The ages of the infants varied from 2 to 13 weeks. Twin pregnancies were similarly uncommon, and only 4 twins under 16 weeks were seen. One of these children showed evidence of skull softening, and the mother volunteered the information that the other twin had a soft head also. Toverud (31) has stated that premature infants and twins have hard skulls at birth which rapidly become soft as skull growth proceeds. It would, therefore, be necessary to examine the infants at frequent intervals to discover if this did happen to the infants in the present series. Unfortunately no opportunity to do this arose, but there were no findings to suggest that softening occurred more frequently in premature infants in any of the age groups.

VI. Parity of Mother and Interval Between Pregnancies.

Frequent pregnancies both in animals and humans in rapid succession have been shown to contribute to the appearance of rickets in the offspring by Mull and Bill (85) and others (86); the possibility of a relationship existing between frequent pregnancies and generalised softening was therefore considered and the results are shown in Table V.

Table V.

Showing the relationship between the parity of the mother and the incidence of generalised skull softening in 290 infants.

Parity of Mother	Number of infants examined under 16 weeks.	Number of infants with generalised skull softening.
1	99	5
2	63	6
3	43	5
4	21	5
5	24	3
6	19	3
7	5	-
8	3	-
9	3	1
10	2	-
11	3	2
12	1	-
13	2	-
14	2	1

If the relative frequency of generalised softening is compared in each group, it is seen to increase from 1 in 20 in first children, to 1 in 6 in the sixth children while the frequency in 7th to 14th children was 1 in 5. This showed a definite increase in generalised softening with a rise in the number of previous children in the family.

The intervals between the mothers' pregnancies was noted in 160 of the infants, 12 of whom had generalised softening, and was found to be similar in infants with and without skull softening. This interval varied in the majority/

majority of instances between 13 and 23 months.

VII. Previous Diet.

There is no evidence that the type of feeding, namely, breast or artificial feeding, can be significant at the age when generalised softening occurs, and furthermore, if it is significant, it is not possible to decide at what age it becomes so. For the purpose of dietary investigation, it was decided to neglect all infants up to 7 days, as during that time an infant does not normally gain weight and therefore cannot be having an adequate intake. The number of infants with generalised softening remaining was 28, 24 of whom were artificially fed and 4 breast fed. This ratio of 6 to 1 was similar to that of the infants examined in this age group with no skull softening.

VIII. Addition of Vitamin D to the Diet.

This was likewise considered only in infants over 7 days. Three of the 28 infants were given Vitamin D and in each instance the daily dose was decidedly subminimal viz. 80, 250 and 250 i.u. Of the infants without skull softening only 10 had a daily intake of over 500 i.u. and 17 had a daily intake of less than 500 i.u. No conclusions can be based on these results as so few of the children received additional Vitamin D.

IX./

IX. Locality of Home.

Twenty-five of the infants lived in urban districts, 4 in rural districts and the homes of 2 were not recorded. In comparison with infants with hard skulls, generalised softening showed a tendency to occur more frequently in urban dwellers.

X. Radiological Findings.

In assessing any departure from normal the following points were noted in an X-ray of the wrists:-

a. Density of the bones.

b. Irregularity of the epiphyseal ends.

c. Broadening of the epiphyses.

d. Presence of carpal centres which normally appear between the third and sixth months.

Examination was made especially for any possible radiological rachitic changes. According to Schmorl (4o) the first epiphyses to undergo rachitic changes are the sternal ends of the ribs. Unfortunately these epiphyses cannot be used for radiological diagnosis as the minute details are obscured by the thoracic contents and by the ribs on the posterior aspect of the thorax. The lower end of the ulna was therefore examined, as it is one of the first of the remaining epiphyses to undergo rachitic changes. The initial radiological evidence of the presence of rickets has/

has been variously described. Weech and Smith (87) stated that rarifaction is an early sign and Davidson and Merritt (60) described the first sign as being the appearance of a translucent area on the medial aspect of the ulna. According to Hess (17) the earliest visible changes are as follows:- Loss of exact delineation of the preparatory zone of calcification which lies between the metaphyses and epiphyses. This is followed by thinning of the cortex of the shaft and later by cupping of the ulna. Goldberger and Mellion (88) are of the opinion that delay in the appearance of carpal centres is evidence of active rickets.

Controversy concerning the radiological evidence of mild and early rickets exists, however, and it appears to be difficult to make such a diagnosis on radiological findings alone. As Cooley and Reynolds (89) have said when discussing the variations which occur in the interpretation of an X-ray plate which may show signs of mild rickets, "The use of the X-ray for diagnosis has by no means attained the status of an exact science". Slight broadening of the ulna has been mentioned by Hess (17) as being evidence suggestive of rickets, while Jeans (90) and others (91) consider that slight variations from normal may be physiological. In his study of rickets, Hood (92) queries the rachitic origin of radiological changes classed by/

FIG. 11

by Eliot as "incipient rickets".

In the following reports of radiological findings, slight departures from normal, such as are mentioned above, are termed "suggestive of rickets" and labelled "? rickets" in the accompanying tables.

Radiographs were taken of 10 of the infants with generalised softening and in 2 of them there was a deviation from normal. In one, aged 7 weeks, there was a translucent area on the medial aspect of the ulna (Fig. II) and in the other, aged 4 weeks, there was slight splaying of the ulna. As has been previously stated, both these changes may be suggestive of the presence of rickets, but in none of the infants was there definite evidence of radiological rickets.

XI. Biochemical Findings.

As the recognised clinical signs of rickets do not appear at an age when generalised skull softening occurs, estimations of the blood calcium, phosphorus and phosphatase were done in infants with generalised skull softening in order to discover if there was biochemical evidence of rickets present. The methods of estimation are given in Appendix I. Before discussing the results, it is first necessary to consider the accepted limits of normality of the three values.

The/

The normal serum calcium in children has been found to lie above 10 mgm. per cent (19), (93), (94) and does not alter in the presence of active rickets (19), (95). Regarding the inorganic phosphorus concentration in the blood, Harrison (96) has stated that reports of normal values vary between 3.2 and 6.5 mgm. per cent, but it is usual to consider values of much less than 4.0 mgm. per cent to be abnormal. The level has been shown to fall in rickets, and Howland and Kramer (19) obtained values of less than 3.2 mgm. per cent in 23 rachitic children. Hess and Lundagen (97), Anderson (98) and others (99) have shown, however, that clinical evidence of active rickets may exist in the presence of levels approaching normal, while Bodansky and Jaffe (100) recorded that similar values were obtained in rachitic infants receiving amounts of Vitamin D insufficient to have effected a cure. Freudenberg (101) has also shown that a fall in the blood phosphorus level may occur in other conditions besides rickets, e. g. pneumonia. It is therefore not possible to make a diagnosis of biochemical rickets on the inorganic phosphorus value alone. As a result of the alterations in the blood due to rickets, the calcium and phosphorus product is decreased and Howland (19) has stated that a product under 30 is evidence of active rickets and between 30 and 40 suggestive of/

of rickets.

Using the method of Jenner and Kay (102) which is employed in the estimations under consideration, the upper limit of normality of plasma phosphatase in children is considered by Morris et alii (103) to be 11 units. This level is increased in the presence of active and healing rickets, an increase being considered by Barnes and Monks (104) to be one of the first signs of the presence of rachitic changes. The level, however, can be raised in other conditions (Roberts (105)) and Morris et alii (103) have shown that normal values may be associated with definite radiographic evidence of rickets.

It is therefore apparent that a diagnosis of rickets cannot be made on a low inorganic phosphorus value or an increase in phosphatase activity alone; if, however, the phosphorus level lies below 4 mgm. per cent and the phosphatase value is increased above 11 units, I have taken this as conclusive evidence of active or healing rickets.

Biochemical examinations were carried out on 10 infants with generalised skull softening and the results together with the radiological findings in 9 of the infants are given in Table VI.

Table VI.

Showing the biochemical and radiological findings in 10 infants with generalised skull softening.

Case	Age in Weeks	Serum Calcium mgm. %	Plasma Phos. mgm. %	Plasma P'tse units	Calcium x Phos.	X-ray Wrist
W.W.	4	11.0	4.1	4.0	45	Slight Splaying
A.G.	4	12.3	4.6	10.0	56	Normal
M.M'G.	5	10.2	3.8	8.2	39	-
E.L.	8	10.8	3.9	7.0	41	Normal
J.A.	8	8.2	4.5	8.2	37	Normal
W.D.	8	10.0	4.1	11.1	41	Normal
A.M'L.	9	10.2	4.2	6.5	42	Normal
A.B.	10	8.9	5.6	11.0	48	Normal
V.M'G.	12	11.1	3.4	9.4	37	Normal
P.C.	14	10.4	3.9	10.5	40	Normal

It is seen that 2 of the infants had both normal biochemical and radiological findings, while in a third infant the only abnormality was a slight increase in the phosphatase value, namely, 11.1 units. Since the other findings in the latter infant were normal, and the rise in phosphatase activity so slight it has been included amongst those who showed no evidence of active rickets.

Regarding the 7 remaining infants, 4 of them were found/

found to have a diminution in the plasma inorganic phosphorus value; this fall in 3 of the infants was slight (3.8, 3.9 and 3.9 mgm. per cent) and as the remaining findings showed no abnormalities, the infants were considered to be non-rachitic. The other child had a marked fall in the phosphorus level to 3.4 per cent, which is suggestive of the presence of rachitic changes.

Two of the infants were found to have a low serum calcium value. This was associated in one of the infants with active tetany and the child was found to have developed rickets when examined one month later. It is possible that the rachitic process had commenced at the time of the first examination, the biochemical changes associated with tetany having masked those of rickets. The other child with a low calcium value (8.9 mgm. per cent) showed no evidence of active tetany nor of rickets when examined on several occasions during the ensuing six months.

The remaining child had normal biochemical findings but radiologically the ulna showed slight splaying and on subsequent examination he was found to have definite radiological rachitic changes.

Of the 10 infants under consideration, 6 were therefore considered to have shown no evidence of rickets at/

at the time of examination, while in the remaining 4 the results were suggestive of the presence of rickets. It is of interest to note that these 4 infants were all born during the late summer or within the first half of the winter period (August - December).

From these results it becomes apparent that definite conclusions cannot be based on the findings of one examination alone. Since 6 infants had marked softening without either biochemical or radiological evidence of rickets, it may however be concluded that the presence of generalised softening is not always associated with recognisable rachitic changes.

Whether such softening may be due in some instances to rickets or whether the affected children are more prone to develop rickets can only be shown by completing repeated investigations of the children.

THE SUBSEQUENT DEVELOPMENT OF 13 INFANTS WITH GENERALISED SKULL SOFTENING.

Although it was seen that active rickets did not always exist in the presence of generalised skull softening, the question arose as to whether rachitic changes were more liable to occur in infants with this type of softening. It was therefore decided to examine the infants at intervals during the first year of life.

Of the 31 infants with generalised skull softening, 10 died while in hospital and 8 were not traced or had died following dismissal.

One child of the remaining 13 infants had severe softening at the age of 2 weeks and was found to have fragilitas ossium. She was given Adexolin minims XX to XXX daily from the age of 2 months to 15 months, when skull softening was still found to be present. Blood and radiological examinations at no time showed evidence of rachitic changes.

Five infants who were not examined biochemically or radiologically when the softening was diagnosed were subsequently visited in their homes, and were examined for any evidence of rickets. Again, as with the radiological and biochemical findings in rickets, it is difficult to make a diagnosis of early rickets on clinical examination alone. The following findings were considered to be of significance in reaching/

reaching a diagnosis.

(a) Delay in eruption of the teeth.

(b) Delay in sitting up.

(c) Delay in closure of the anterior fontanelle, and

(d) Marked enlargement of the wrist epiphyses or beading of the ribs.

The development of these infants is shown in Table VII.(See over).

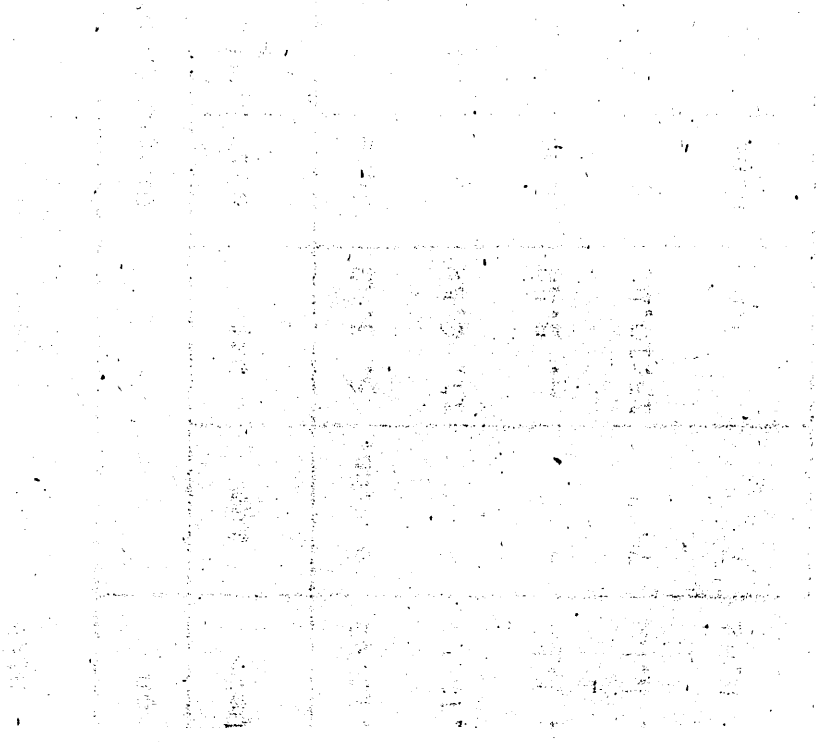


Table VII.

Showing the subsequent development of 5 infants with generalised skull softening.

Case	First Examination		Second Examination					
	Age	Date	Age	Date	Teeth	Sitting Up	Skull	Enlarged Epiphyses
J.F.	4 wks.	6.10.41	6 mths.	5. 3.42	None	No	Cranio-tabes +	Costochondral + Wrist ±
P.C.	2 wks.	19.10.41	8 "	11. 6.42	2	No	A.F. closing	Costochondral + Wrist +
P.O'C.	2 dys.	4. 1.42	4 "	4. 5.42	None	No	Sutures soft	Costochondral - Wrist -
A.B.	4 wks.	2. 4.42	7½ "	15.10.42	1	Yes?	-	Costochondral - Wrist -
J.C.	10 wks.	4.42	7	9.42	None	Yes	-	Costochondral - Wrist -

It is apparent that although rickets as commonly diagnosed may occur in infants who have had generalised softening, it does not appear in all cases. Two of the 5 infants developed clinical signs of rickets but again it is seen that they were both born at the commencement of the winter months and consequently were more liable to exhibit such changes. At the second examination, craniotabes was present in one of the infants who was then six months old.

The other 7 infants were examined clinically, radiologically and biochemically on several occasions after the initial visit. It was not possible to examine a greater number of the infants in this manner as the mothers would not agree to bring the children back to hospital. Four of these children received regular doses of Vitamin D and are considered later. The progress of the 3 infants who did not receive Vitamin D is now recorded in detail.

1. V.McG. Female. 4th Child. Feeding: Cows milk
Full Term Pregnancy. + solids at 6 months.

Diagnosis on admission: Upper Respiratory Infection.

Age	Date	Phos. mgm.%	Blood P'tse units	Ca. mgm.%	Ca. x P.	X-ray Wrist	Generalised Skull Softening
8 wks.	3.12.42	5.6	11.0	8.9	50	Normal	+
12 "	10.3.42	4.0	10.2	-	-	Normal	-
16 "	10.4.42	-	-	-	-	Normal	-
25 "	12.6.42	4.4	10.0	10.8	48	Normal	-
40 "	8.9.42	-	-	-	-	Normal	-

2. A.G. Male. 16th Child. Feeding: Cows milk

Full Term Pregnancy. + solids at 6 months

Diagnosis on admission: Incorrect Feeding.

Age	Date	Phos. mgm.%	Blood P'tse units	Ca. mgm.%	Ca. x P.	X-ray Wrist	Generalised Skull Softening
-4 wks.	3. 2.42	4.6	10.0	12.3	57	Normal	+ +
6 "	13. 2.42	4.1	7.5	12.6	52	? Early Rickets	+ -
9 "	10. 3.42	4.4	8.3	9.1	40	Normal	-
14 "	17. 4.42	4.3	14.6	10.1	44	Normal	-
30. "	8.42	4.0	11.0	10	40	Normal	-

3. P.C. Male. 11th Child. Feeding: Ostermilk 1 and 2

Full Term Pregnancy. + solids at 4 months.

Diagnosis on admission: Pylorospasm.

Age	Date	Phos. mgm.%	Blood P'tse units	Ca. mgm.%	Ca. x P.	X-ray Wrist	Generalised Skull Softening
12 wks.	5.10.41	3.4	9.4	11.1	38	Normal	+
15 "	24.10.41	3.1	9.0	10.5	33	Normal	+
18 "	16.11.41	3.1	12.0	10.4	32	? Early Rickets	+ -
24 "	4. 1.42	3.0	14.2	10.2	31	Rickets	-

Although the first child (V.McG.) had blood examinations done on only three occasions, the results, together with repeated radiographs, showed at no time evidence/

evidence of rachitic changes. The skull softening had disappeared by the time the child was 12 weeks old, and on subsequent attendances the skull did not develop any further softening.

When the progress of A.G. is studied it is apparent that the recognised seasonal incidence of rickets must be considered in relation to the findings in this child. At 6 weeks (13.2.42) the wrist showed a slight change which was suggestive of early rickets, namely, slight irregularity of the epiphyses. This abnormality had disappeared three weeks later (10.3.42). If it is assumed that the change was rachitic, it is unlikely that healing would have occurred in the month of February when the exposure of the child to the sun's rays is minimal, unless the child had been receiving Vitamin D in addition to what was in the milk. It is therefore doubtful whether the X-ray change was due to rickets. An increase in phosphatase which is suggested by Morris et alii (103) to be an early sign of developing rickets occurred in April. In view of the extension of the hours of daylight and the increase in the amount of sunshine which occurs in late spring, any rachitic tendency would tend normally to disappear during this season. Although it is therefore not possible to decide whether the infant was developing rickets at this time, it is apparent that/

that such changes if they did occur were slight and had disappeared by September. As with V.McG. the skull softening disappeared rapidly and was not followed by the development of either of the other two types of softening found in infants.

The third child, P.C., alone showed definite evidence of rickets later in infancy, by which time the skull softening had practically disappeared.

Again, it was only the child who was born at the commencement of the winter months who developed definite signs of rickets.

As a result of these findings, it was decided to test the therapeutic effect of Vitamin D on generalised softening of the skull.

The four remaining infants were given Vitamin D. Before this was done it was necessary to investigate the dosage of Vitamin D required to prevent the development of rickets and to cure existing rachitic changes in infants living in Glasgow.

The Amount of Vitamin D Required -
(a) to prevent the development of rickets and
(b) to cure existing rickets in infants in Glasgow.

It is evident that the amount of Vitamin D required must necessarily depend in part on climatic conditions.

Park (106) found that the following dosage was adequate to prevent the development of rickets in New York children, namely; 200 i.u. daily at 4 weeks, 400 at 8 weeks and 800 at 12 weeks, while Robinson (107) found that breast fed infants receiving 1,000 i.u. daily did not develop rickets.

Working in New York, Vollmer (108) found that a single dose of 600,000 i.u. prevented the appearance of rachitic changes.

More recently, Park (109) while working with Eliot, stated that a dose of 800 - 1,000 i.u. daily was sufficient for full-term infants.

Dann and Davison (110) quote the Committee on Food and Nutrition of the National Research Council (May 1941) and the Committee on Vitamins of the American Academy of Paediatrics as allowing 400 to 800 i.u. per day.

In Britain, Sheldon et alii (111) in a report to the British Paediatric Association stated that the amount allowed daily by the British Government was 200 i.u. daily under 6 months and 400 over 6 months. The Association now state/

state that 700 i.u. are required daily for full-term infants and 1400 for premature infants.

It is known that premature infants are liable to develop rickets and Davidson and Merritt (85) report that premature infants in New York may develop rickets while receiving 350 i.u.

Barnes et alii (112) and Kemp and Marshall (113) amongst others have reported that various Vitamin D preparations are required in different international unit doses to prevent the appearance of rickets; Drake (114) however was unable to confirm this.

As the prevalence of rickets in Glasgow is still relatively high, it is probable that the required dosage will be large, and in order to determine the necessary amount, infants who had been receiving various quantities of Vitamin D were examined. As the amount must necessarily vary inversely with the amount of available sunshine, investigations were carried out in the winter months, (November to February), when the maximum amount would be required. All the infants were born in Glasgow and had remained there since birth. Vitamin D was given regularly throughout the late summer and winter months, that is, from August or September onwards and the children were examined for signs of rickets in December, January, February or March/

March. A diagnosis of rickets was made on clinical and radiological or biochemical findings in most of the infants.

Each child had been artifically fed from early infancy. Since the infants were treated as out-patients it was sometimes difficult to ascertain whether the child had received the Vitamin D regularly. The mother was given the oil and asked to report at hospital when the bottle was empty; according to whether she returned at the expected date, so it was decided whether the infant had received the correct dosage. This appeared to be the most satisfactory method to employ, but there must necessarily be several cases in which the infant did not receive the full dose. The mother was carefully instructed either to drop the oil straight into the child's mouth from a dropper or to give it on a spoon and was told not to put it in the feeding bottle.

Adexolin and Cod Liver Oil were supplied by the Hospital while some of the mothers preferred to give the infants proprietary preparations which had previously been recommended to them.

As some infants who have never received Vitamin D in addition to what is present in their food fail to develop rickets, it was decided to find out the maximum dose which had been given and which had been followed by the appearance of/

of rickets. One hundred and nine infants were investigated, 49 of whom received less than 500 i.u. daily, 33 between 500 and 1,000 i.u. daily and 27 between 1,000 and 2,000 i.units daily.

Details of the 49 infants who developed rickets are given in Table VIII.

Table VIII.

Showing the evidence of rickets found in 49 infants receiving varying amounts of Vitamin D in the city of Glasgow during the winter months.

Infants Receiving Less Than 500 i.u. Daily					
Case	Age in mths.	Vitamin D prep.	Clinical Rickets	Biochemical Rickets	Radiological Rickets
1	3	CLO	±	+	+
2	3	H.LO	±	Not done	+
3	3½	CLO	+	+	±
4	4	Adexolin	+	+ +	+ +
5	4	CLO	+	+	Not done
6	4	CLO	+	Not done	+
7	4	Adexolin	+	Not done	+
8	6	Adexolin	+	+	Not done
9	6	HLO	+	Not done	+
10	6	CLO	+	+	+
11	7	CLO	+	+	Not done
12	7	CLO	+	+	+
13	7	CLO	+	+	+
14	7	CLO	+	Not done	+
15	8	CLO	+	+	+
16	9	CLO	+	+	Not done
17	10	CLO	+	Not done	+
18	10	CLO	+	Not done	+
19	11	CLO	+	+	+
20	11	Adexolin	+	+	+?
21	12	CLOE	+	Not done	+
22	15	CLOE	+	+	+

Infants Receiving Between 500 and 1,000 i.u. Daily					
Case	Age in mths.	Vitamin D prep.	Clinical Rickets	Biochemical Rickets	Radiological Rickets
1	3	CLO	-	+	+
2	4	Adexolin	±	+	+
3	4	Adexolin	+	+	Not done
4	5	Adexolin	+	+	+
5	5	CLO	-	+	Not done
6	5	CLOE	+	+	+
7	6	Adexolin	+	±	+
8	6	HLO	+	+	Not done
9	7	CLO	+	Not done	+
10	7	Adexolin	-	+	+
11	7	CLOE	-	Not done	+
12	8	Adexolin	-	+	Not done
13	8	CLO	+	+	+
14	8	Clo	+	Not done	+
15	8	Adexolin	+	+	+
16	8	Adexolin	+	+	+
17	8	CLO	+	+	+
18	8	Adexolin	+	Not done	+
19	9	CLO	+	+	+
20	9	CLO	±	+	+
21	10	Adexolin	+	+	Not done
22	11	CLO	+	±	Not done

Infants Receiving Over 1,000 i.u. Daily					
Case	Age in mths.	Vitamin D prep.	Clinical Rickets	Biochemical Rickets	Radiological Rickets
1	6	Adexolin	+	+	Not done
2	6	Adexolin	-	+	±
3	7	CLO	-	Not done	+
4	7	Adexolin	+	+	+
5	8	Adexolin	±	+	+

Abbreviations: CLO : Cod Liver Oil
CLOE : Cod Liver Oil Emulsion
HLO : Halibut Liver Oil

When the results are examined, it is apparent that a daily dosage of over 1,000 i.u. was not sufficient to prevent the development of rickets in all infants in Glasgow during the winter, and that rickets was relatively common in those infants who received much less than 1,000 i.u. daily. Twenty-two of the 49 infants receiving less than 500 i.u. daily, developed rickets, as did 22 out of 33 infants receiving between 500 and 1,000 i.u. daily, while only 5 out of 27 infants receiving over 1000 i.u. daily developed rickets. No child receiving more than 1250 i.u. daily developed evidence of rickets.

The curative effect of Vitamin D was also investigated in 10 children who had radiological evidence of rickets. Radiological examinations were employed as it was considered the most reliable method of showing evidence of healing. The infants were treated during the winter months and were all in-patients of the hospital. They were given either varying doses of Adexolin, Cod Liver Oil or a single massive dose of Calciferol. As the children were in hospital it may be assumed that they received the prescribed amount.

The progress of the 10 infants is shown in Table IX.

Table IX

Showing the effect of varying amounts of Vitamin D on active rickets in 10 infants living in the city of Glasgow.

Age in yrs.	Daily Dose of Vitamin D i.u.	Period between commencing treatment and 2nd X-ray	2nd X-ray of Wrist
1 9/12	Adexolin 3750	1 week	Healing Rickets
8/12	" 2500	1 week	Healing Rickets
4/12	" 1200	3 weeks	Healing Rickets
1 2/12	" 360	3 weeks	No Healing of Rickets
11/12	CLO 960	3 weeks	Healing Rickets
10/12	Adexolin 975	2 weeks	Healing Rickets
1 4/12	Calciferol 600,000 (1 Dose)	3 weeks	Healing Rickets
1	Adexolin 1200 " 2500	3 weeks 2 weeks	No Healing Healing Rickets
10/12	Adexolin 360 " 960	2 weeks 2 weeks	No Healing Healing Rickets
8/12	Adexolin 960	3 weeks	Healing Rickets

From the results it is apparent that not only, as was previously shown, do infants require varying amounts of Vitamin D to prevent the occurrence of rickets, but they also require varying doses in the presence of active rickets before healing occurs. In one child healing did not/

not appear radiologically until the dose of Vitamin D had been increased from 1200 to 2500 i.u. per day.

Healing also occurred after a single dose of 600,000 i.u. in another of the children.

Combining these two series of results, it appears that a daily amount of over 1,000 i.u. will prevent the occurrence of rickets in the majority of infants living in Glasgow during the winter months. A similar dose was found to cure most of the infants with active rickets.

In assessing the therapeutic effect of Vitamin D in these experiments a daily dose of 1250 was considered ample.

THE EFFECT OF VITAMIN D ON GENERALISED SKULL SOFTENING.

Four infants with generalised skull softening were given Vitamin D in addition to what was present in their food and were subsequently examined at varying intervals. The progress of these infants was as follows:

1. A.McL. Male. 11th Child. Feeding: Cows milk
Full Term Pregnancy. + solids at 5 months (?)

Diagnosis on admission: Broncho-pneumonia.

Age Wks.	Date	Phos. mgm.%	Blood P'tse units	Ca. mgm.%	Ca. x P.	X-ray Wrist	Generalised Skull Softening	Vitamin D Dosage i.u.daily
7	14.10.41	4.0	12.1	10.0	40	Normal	+	Adex.1200
10	6.11.41	4.4	7.3	10.2	45	Normal	±	" 1800
14	10.12.41	-	-	-	-	Normal	±	" 1800 omitted at 20 wks.
26	12. 3.42	3.7	10.1	10.4	38	Normal	-	

2. E.L. Male. 3rd Child. Feeding: Various Artificial
Full Term Pregnancy. Feeds.

Diagnosis on admission: Inanition.

Age Wks	Date	Phos. mgm.%	Blood P'tse units	Ca. mgm.%	Ca. x P.	X-ray Wrist	Generalised Skull Softening	Vitamin D Dosage i.u.daily
4	17. 3.42	3.7	9	10.8	40	Normal	+	Adex.1200
8	4.42	-	-	-	-		±	Adex.1200
18	28. 6.42	3.8	7	11.2	44	Normal	-	Adex.1200

3. J.A. Male. 2nd Child. Feeding: ?

Full Term Pregnancy.

Diagnosis on admission: Tetany.

Age Wks.	Date	Phos. mgm.%	Blood P'tse units	Ca. mgm.%	Ca. X P.	X-ray Wrist	Generalised Skull Softening	Vitamin D Dosage i.u.daily
4	4. 2.42	4.5	10	8.2	37	Normal	+ +	Adex.1800
8	6. 3.42	-	-	-	-	Rickets	+	" 1800
12	3. 4.42	-	-	-	-	Rickets Healing	±	" 1800

4. W.W. Male. 3rd Child. Feeding: Ostermilk 1 and 2 + solids at 4 months.

Full Term Pregnancy

Diagnosis on admission: Pylorospasm

Age Wks	Date	Phos. mgm.%	Blood P'tse units	Ca. mgm.%	Ca. x P.	X-ray Wrist	Generalised Skull Softening	Vitamin D Dosage i.units
4	28.10.41	4.1	4.4	11.1	46	Slight Splaying	+ +	Radiostol 600,000
6	13.11.41	4.2	7.1	12.3	62		+	
10	29.12.41	3.8	7.5	12.0	45	Healed Rickets	- (Craniotabes +)	
16	19. 2.42	4.0	11.4	12.0	48	Normal	- (Craniotabes +)	
20	5. 3.42	4.0	9.0	11.6	46	Normal	-	
24	5. 4.42	-	-	-	-	Normal	-	
37	12. 7.42	4.0	7.0	11.0	44	Normal	-	

The first child, A. McL., who at no time showed radiological or biochemical abnormal findings, apart from an elevation in the phosphatase level to 12.1 units at 7 weeks, was given Adexolin from this age onwards. The generalised softening persisted until the child was over 14 weeks old in spite of his receiving regular doses of Vitamin D. As this type of softening has been previously shown to disappear at the age of 16 weeks there appears to have been no increase in the rate at which the skull became hard when Adexolin was given. It may be noted that the dose of Adexolin given to the child was sufficient to prevent the development of rickets.

The second child, E.L., similarly did not develop rickets while having Adexolin. The skull softening did not appear to be affected by the Vitamin D and persisted until the child was over 3 months but had disappeared when the child was 4 months old.

The two remaining children, J.A. and W.W. both had active rickets which responded to treatment with Vitamin D. In the case of J.A., the skull softening persisted until the child was 4 months old, by which time there was radiological evidence of healing rickets.

When examined first in October, W.W. had severe generalised softening and, although his blood chemistry

was/

was within normal limits, the phosphatase level having just reached the upper limit of normality, radiological examination suggested early rickets. The child was given a massive dose of Vitamin D (600,000 i.u.) and 6 weeks later X-ray examination showed slight rickets which had healed, while the plasma phosphorus had fallen below normal. This was the only occasion when the phosphorus fell below 4 mgm. per cent, and no explanation can be given for this finding, especially as the concentration has been shown to increase after such a massive dose of Vitamin D. It is also interesting to note that when the generalised softening had disappeared at the age of 10 weeks, it was replaced by localised skull softening, that is, craniotabes, which persisted until the child was over 4 months. In this child only, was it possible to say that the Vitamin D therapy might have had a beneficial effect on the skull softening which had disappeared by the time the child was 10 weeks old.

From these results it is apparent that in three of the children generalised skull softening was not influenced by giving Vitamin D and in fact persisted until the children were almost 4 months old. One of the children who had rickets was given doses of Adexolin sufficient to bring about healing of the rachitic process.

No/

No conclusions can be based on the findings in the fourth child (W.W.).

It may be therefore concluded that, as Vitamin D had no therapeutic effect on generalised skull softening, the softening is not rachitic in origin.

THE CALCIUM AND PHOSPHORUS METABOLISM IN TWO INFANTS WITH GENERALISED SKULL SOFTENING.

Normal ossification must necessarily require an adequate retention of calcium and phosphorus. Toverud (31) has shown from metabolism experiments that congenital skull softening was associated with a deficiency of calcium in the maternal diet. It is, therefore, possible that the retention in the infant may also be insufficient. It was decided to conduct metabolism experiments in two infants with generalised skull softening who had no clinical, biochemical or radiological evidence of rickets.

Method:-

A description of the method used to collect the stools and urine, together with details of the biochemical methods employed in estimating the calcium and phosphorus intake and output is given in Appendices II and III.

Each metabolism experiment lasted seven days and both infants were fed on boiled cow's milk and sugar, the amounts depending on their caloric requirement. Both experiments were conducted in the month of March when it was considered that the daily amount of sunshine would not affect the metabolism of calcium and phosphorus.

One infant was below his expected weight but at the time when the experiments were made both appeared well and had no fever.

Report of Case I.

W.D., male, 2nd child.

The parents were both healthy and there was nothing relevant in the family history. The mother was well during pregnancy and the child was born at term. The confinement was normal and the birth weight unknown. At birth the infant did not suck well but he improved rapidly and had been fed on increasing amounts of boiled milk. He was receiving a daily intake of 400 calories when he was admitted to hospital at the age of 2 months with a history of gastro-enteritis of 2 days' duration.

On admission on 22.3.42 he was found to be dehydrated and only 64 per cent of his expected weight. He had no evidence of rickets, his skin tests (Von Pirquet and Mantoux 1/5000) were negative and he had severe generalised skull softening.

His condition improved rapidly and the metabolism experiment was commenced after he had been receiving an adequate caloric intake for one week.

X-ray of his wrist was normal both at the beginning and end of the experiment.

The blood chemistry was normal at the onset and completion and the values were as follows:-

	Before	After
Plasma Inorganic Phosphorus	4.2 mgm.%	4.4mgm%
Plasma Phosphatase	6.5 units	8.3 units
Serum Calcium	10.2 mgm.%	10.0 mgm.%
Ca. x P.	43	44
Weight at beginning of period		2.89 K.
" " end " "		3.12 K.
Average gain in weight per day		30 g.
Feed: Cow's milk 105 cc.)		
Water 15 cc.)	6 times per day	
Sugar IV g.)		
Daily caloric intake:	459 calories.	
Daily caloric requirement:	440 calories.	(100 cal. per kilo of expected weight)

The child was well throughout the course of the metabolism experiment.

Details of the calcium and phosphorus metabolism are shown in Table X.(See Page 67).

Report of Case II.

A.B., male, 2nd child.

The parents were both healthy and there was nothing relevant in the family history. The mother had been well during the pregnancy and the child was born at term. The birth weight was 6½ lbs. The child was well at birth and was/

was breast fed for 8 days. The mother stated that she had had insufficient milk and that the child had then been given Ostermilk No. 1. The quantity of the feeds had been larger than was required by the child. He was given small amounts of cod liver oil at irregular intervals but never received orange juice. The child throve until he was 2 months old when he developed a cough and refused his feeds. He subsequently developed respiratory embarrassment and was admitted to hospital on 28.2.42. On admission he was found to be well-nourished and was 112 per cent of his expected weight. Physical examination revealed nothing abnormal apart from rhonchi throughout the chest and severe generalised skull softening. His condition improved and the metabolism experiment was started 2 weeks after admission when he was 2½ months old. His skin tests (Von Pirquet and Mantoux 1/5000) were negative and he had no clinical evidence of rickets. X-ray of his wrist was normal both before and after the experiment.

The blood chemistry was also considered to be normal at the onset and completion of the metabolism experiment, but the plasma inorganic phosphorus was at the lower limit of normality (3.9 mgm. per cent). The biochemical findings were as follows:-

	Before	After
Plasma Inorganic Phosphorus	3.9 mgm. %	4.0 mgm. %
Plasma Phosphatase	6.5 units	7.2 units
Serum Calcium	10.4 mgm. %	11.0 mgm. %
Ca. x P.	41	44

Weight at beginning of period 5.15 K.

" " end " " 5.16 K.

Average gain in weight per day 1.4 g.

Feed: Cow's milk 150 cc.)
Sugar IV g.) 5 times per day

Daily caloric intake: 510 calories.

Daily caloric requirement: 515 calories. (100 cal. per kilo of expected weight)

During the whole period of the experiment the child was well and had no fever. He had occasional loose stools which were yellow in colour and not foul-smelling. He showed no gain in weight during the period which was probably due to the fact that he was overweight on admission. The total gain in weight during his 4 weeks in hospital was 0.22 K. Details of the calcium and phosphorus metabolism are shown in Table X. (See over).

Table X.

Showing the calcium and phosphorus intake and excretion in two infants with generalised skull softening.

W.D.

Calcium Retention.

Total Intake	Total Output		Total Retention	Retention
	Urine	Faeces		
CaO g.	CaO g.	CaO g.	CaO g.	g. per kilo per day
6.9905	0.1289	6.1291	+ 0.7325	+ 0.035

Phosphorus Retention.

Total Intake	Total Output		Total Retention	Retention
	Urine	Faeces		
P_2O_5 g.	P_2O_5 g.	P_2O_5 g.	P_2O_5 g.	g. per kilo per day
9.0201	3.5900	4.3761	+ 1.0540	+ 0.051

A.B.

Calcium Retention.

Total Intake	Total Output		Total Retention	Retention
	Urine	Faeces		
CaO g.	CaO g.	CaO g.	CaO g.	g. per kilo per day
8.3210	0.2253	6.5760	+ 1.5197	+ 0.042

Phosphorus Retention.

Total Intake	Total Output		Total Retention	Retention
	Urine	Faeces		
P_2O_5 g.	P_2O_5 g.	P_2O_5 g.	P_2O_5 g.	g. per kilo per day
10.6040	3.1817	5.3270	+ 2.0953	+ 0.056

Before interpreting the results of these metabolism experiments, some of the results for average retentions found in normal infants will be summarised. Hamilton (50) has collected and tabulated the findings of some workers. A few of these results, which refer to breast fed infants, are given below:-

Table XI

Calcium and Phosphorus Metabolism in Breast-Fed Infants (compiled by Hamilton).

Author	Age in months of infant	Calcium (CaO)		Phosphorus (P_2O_5)	
		Total Retention	Retention g/K/day	Total Retention	Retention g/K/day
Tobler	2.5	.053	.013	.119	.029
Lindberg, I & II.	2.5	.060	.014	.166	.038
Muhl, B. I,II,	2.5	.091	.017	.120	.022
III.	2.5	.093	.017	.113	.020
Michael Perret	3.0	.149	.032	.121	.025

Findlay et alii (115) conducted calcium metabolism experiments on both breast-fed and artificially fed infants, from birth up to 6 months in the breast-fed infants, and from birth up to 12 months in the artificially fed infants. They showed that, although the calcium intake in artificially fed infants was much higher than in breast/

breast-fed infants, the retention per kilo bodyweight was only slightly greater. The CaO retention was below 0.05 g. per kilo bodyweight per day in both breast and artificially fed infants.

In metabolism experiments on artificially fed infants, Telfer (116) found that the output of calcium and phosphorus was proportional to the intake and in 4 normal non-rachitic infants receiving an adequate caloric intake - the exact daily intake of milk is not stated - the retention of calcium and phosphorus was as follows:-

Age of Child	Calcium (CaO) g/K/day	Phosphorus (P_2O_5) g/K/day
12 months	0.124	0.123
9 months	0.064	0.065
7 months	0.055	0.055
8 months	0.098	0.060

It is seen that the retention of both calcium and phosphorus in apparently healthy children can show a wide variation.

Regarding the faecal and urinary content of the minerals, it has been demonstrated by Shohl (117) that the calcium output in the urine is minimal, a high percentage being excreted in the faeces. The phosphorus output is more evenly distributed between the urine and the faeces (Myers and Fine - 118).

The/

SUMMARY.

1. Generalised skull softening was present in 31 of the 972 infants examined and showed a slight tendency to occur more frequently in infants born in the winter months.

2. This type of softening was present at birth or appeared soon afterwards and was not demonstrable in any infant over 16 weeks of age.

3. Infants examined during the first 8 weeks of life and found to have generalised skull softening, had a larger average head circumference than infants with hard skulls.

4. Softening occurred more frequently where the mother had several previous pregnancies, and in infants born and living in the city.

5. No relationship could be demonstrated between the occurrence of generalised skull softening and the sex, height, weight and diet of the infant, nor did it occur more frequently in the few twins and premature infants included in the survey.

6. Eleven infants with this type of softening were examined radiologically and biochemically for evidence of rickets. Eight of the infants showed no such evidence, while in the other 3 there were changes suggestive of rickets/

rickets.

7. Of 10 infants with softening who were examined on more than one occasion, 5 developed rickets.

8. Vitamin D was found to have no curative effect on the softening.

9. Metabolism experiments conducted on 2 infants with generalised skull softening showed adequate calcium and phosphorus retentions.

10. It was found that a daily dose of over 1,000 i.u. Vitamin D was required to prevent the appearance of rachitic changes and to cure active rickets in infants living in Glasgow.

SUTURE SOFTENING.

The second type of softening to be considered occurred along the sutures, especially at the junction of the temporal, parietal and occipital bones. This type of softening was present in 14 per cent of the infants examined, i.e. 135 infants.

Aetiology of Suture Softening.

I. Seasonal Incidence.

The number of infants found to exhibit suture softening in each month of the year under consideration is indicated in Table XII.

Table XII.

Showing the number of infants with suture softening in each month of the year commencing 1st October 1941.

Month	Number of infants examined	Number of infants with suture softening
October	82	16
November	78	13
December	81	18
January	86	10
February	78	14
March	82	12
April	82	10
May	78	7
June	83	8
July	79	15
August	88	8
September	75	14

From these results it is apparent that there was no marked seasonal incidence, but there was a slight tendency for softening to occur more frequently in the winter months.

II. Age Incidence.

The ages at which suture softening was found are shown in Table XIII.

Table XIII.

Showing the age incidence of 135 infants with suture softening.

Age in months	Number of infants examined	Number of infants with suture softening
1	99	17
2	106	51
3	86	34
4	89	23
5	78	5
6	92	2
7	96	-
8	84	-
9	99	-
10	92	1
11	22	-
12	18	-

From these results it is seen that suture softening exhibited a definite age incidence. The maximum incidence occurred in the infants examined during the second month of life while only 1 case was found/

found in the infants over 6 months. It is apparent, therefore, that this type of softening was present at birth or developed shortly afterwards. The youngest infant manifesting it was 1 day old.

That all suture softening is not present at birth is illustrated by the fact that the incidence rose in the second month of life, and 2 infants were examined who had no suture softening at 1 month and who developed it a few weeks later.

III. Sex.

Of the 135 infants, 72 were males and 60 females and in 3 infants the sex was not recorded. These figures show no variation from that of infants with no skull softening.

IV. Height, Head Circumference and Weight.

The average height and head circumference of the infants with suture softening was compared with the corresponding measurements in infants found to have no skull softening and the measurements obtained are shown in Table XIV.(See over).

Table XIV.

Comparing the height and head circumference of infants with suture softening with those measurements in infants with no skull softening.

	Age in Months					
	0 - 1	1 - 2	2 - 3	3 - 4	4 - 5	5 - 6
	Cms	Cms	Cms	Cms	Cms	Cms
Av. height of infants with no skull softening	52	53	55	58	60	62
Av. height of infants with suture softening	51	52.5	55	56.5	56 (5 cases)	52 (2 cases)
Av. head circumference of infants with no skull softening	35	35.5	38	39.5	40.5	41.5
Av. head circumference of infants with suture softening	34	36.0	36.5	38.0	37.5 (5 cases)	39 (2 cases)

It has been stated that it was not possible to compare the weights of the infants examined. From the accompanying table it is seen that there was a tendency for small infants to have suture softening.

V. Duration of Gestation and Multiple Pregnancies.

The number of premature infants examined under 6 months was 52, and of these 20 had suture softening (45 per cent) and of the 11 twins examined in the same age groups 5 had such softening (48 per cent). It is therefore apparent that this softening is frequently found in premature infants and in twins.

VI. Parity of Mother and Interval between Pregnancies.

The parity of the mothers whose infants had suture softening was compared with the parity of all mothers of the infants in the age groups affected by suture softening in Table XV.

Table XV.

Showing the relationship between the parity of the mother and the incidence of suture softening in 439 infants.

Parity of Mother	Number of infants examined under 6 months.	Number of infants with suture softening
1	146	39
2	94	14
3	57	10
4	48	12
5	35	8
6	25	7
7	12	4
8	8	2
9	2	1
10	2	-
11	5	1
12	1	-
13	3	-
14	1	-

From these results there appeared to be no relationship between the parity of the mother and the development of suture softening in the infants.

VII. Previous Diet.

In assessing the effect of diet on suture softening, as was done in the case of generalised softening, the diet was not considered in infants under 1 week. Of the remaining 128 children, 20 were breast-fed and 104 fed on cow's milk or dried milk. The ratio 1 to 5 is similar to that of the infants with no skull softening in the same age group.

VIII. Addition of Vitamin D.

Only 10 of the infants with suture softening had been given Vitamin D. Five of these received exceedingly small doses ranging from 20? to 85 i.u. daily and may therefore be ignored. The remaining infants received doses ranging from 240 to 620 i.u. which again is probably inadequate. Of the infants without softening in the same age groups, 17 received Vitamin D in amounts varying from 100 to 620 i.u. The incidence of suture softening was therefore unaffected by the administration of Vitamin D in the small number of infants considered.

IX. Locality of Home.

One hundred and eleven of the infants lived in urban districts, 21 in rural districts and in 5 the locality of/

of the home was not recorded. This showed much the same ratio as that found in infants without softening of any type.

X. Radiological Findings.

Sixty-four of the infants were examined radiologically and the findings are indicated in Table XVI.

Table XVI.

Showing the radiological findings in 64 infants with suture softening.

Age in Months	Number of Infants X-rayed	Number of Infants with radiological rickets
0 - 1	18	-
1 - 2	19	1?
2 - 3	12	-
3 - 4	8	3
4 - 5	3	1
5 - 6	2	2

It is seen that 6 of the 13 infants over 3 months had radiological evidence of rickets.

XI. Biochemical Findings.

Biochemical examinations were carried out in 36 infants with suture softening and the results together with the radiological findings in 18 of them are given in Tables XVII - XXII.

Table XVII

Showing the biochemical and radiological findings in 9 infants with suture softening in the 1st month of life.

Case	Plasma Phos. mgm. %	Plasma P'tse Units	Serum Calcium mgm. %	Ca.x P.	X-ray of Wrist
1	4.1	11.0	11.7	47	
2	3.6	9.0	11.2	40	Normal
3	3.7	7.6	8.7	31	
4	3.9	10.2	10.4	41	Normal
5	4.0	8.7	9.9	40	Normal
6	4.0	5.6	12.0	48	
7	3.8	5.6	11.6	45	Normal
8	3.9	10.4	7.9	31	(Tetany)
9	4.0	9.8	-	-	

Table XVIII

Showing the biochemical and radiological findings in 10 infants with suture softening in the 2nd month of life.

Case	Plasma Phos. mgm. %	Plasma P'tse Units	Serum Calcium mgm. %	Ca.x P.	X-ray of Wrist
1	4.1	6.2	10.0	41	Normal
2	3.4	7.5	10.0	34	? Normal
3	3.7	6.0	8.9	33	
4	3.4	11.2	12.2	40	Normal
5	3.8	10.4	11.4	42	
6	3.2	6.4	10.2	32	Normal
7	3.6	13.2	9.4	34	
8	3.9	8.6	10.3	40	Normal
9	3.8	7.4	-	-	
10	3.3	8.6	-	-	(Died shortly after admission.)

Table XIX.

Showing the biochemical and radiological findings in 7 infants with suture softening in the 3rd month of life.

Case	Plasma Phos. mgm. %	Plasma P'tse Units	Serum Calcium mgm. %	Ca.x P.	X-ray of Wrist.
1	3.5	4.8	-	-	
2	3.7	5.2	-	-	Normal
3	3.9	6.8	10.2	40	
4	3.8	11.1	-	-	Normal
5	4.0	7.7	11.6	46	
6	3.9	6.4	-	-	
7	3.8	9.4	10.2	40	Normal

Table XX.

Showing the biochemical and radiological findings in 5 infants with suture softening in the 4th month of life.

Case	Plasma Phos. mgm. %	Plasma P'tse Units	Serum Calcium mgm. %	Ca.x P.	X-ray of Wrist
1	3.2	14.9	12.0	38	{ Healing / Rickets
2	2.7	15.7	11.6	30	Rickets
3	3.9	8.4	10.6	41	
4	2.9	14.6	10.2	31	Rickets
5	3.8	7.6	10.8	41	

Table XXI.

Showing the biochemical and radiological findings in 3 infants with suture softening in the 5th month of life.

Case	Plasma Phos. mgm. %	Plasma P'tse Units	Serum Calcium mgm. %	Ca.x P.	X-ray of Wrist
1	3.2	17.4	11.8	38	Rickets
2	3.8	10.2	11.2	43	
3	3.9	8.4	9.8	39	

Table XXII

Showing the biochemical and radiological findings in 2 infants with suture softening in the 6th month of life.

Case	Plasma Phos. mgm. %	Plasma P'tse Units	Serum Calcium mgm. %	Ca.x P.	X-ray of Wrist
1	2.7	16.7	9.6	26	Rickets
2	3.2	14.2	-	-	Rickets

The biochemical findings in these infants are discussed under the age groups to which the children belong.

Infants in the 1st month of life:

From these results it is seen that in the 9 infants where the blood was examined biochemically in the first month of life in only 1 was there an abnormal finding, viz. a plasma phosphorus of 3.6 mgm. per cent. No explanation can/

can be given for this.

Infants in the 2nd month of life:

Ten infants in the second month of life were examined. Four of the infants had abnormally low plasma phosphorus values, while the other values were normal. One child had biochemical evidence of rickets. Of the 4 with a low plasma phosphorus, 1 had radiological changes suggestive of rickets, while a second was acutely ill when the blood was taken.

Infants in the 3rd month of life:

Seven infants in the third month were examined. In only 1 was there any abnormality. This infant had a plasma phosphorus of 3.5 mgm. per cent, and a normal phosphatase value.

Infants in the 4th month of life:

Of the 5 infants examined in the fourth month, 3 had biochemical rickets which was confirmed by radiological examination.

Infants in the 5th month of life:

Three infants were examined in the fifth month and 1 showed evidence of rickets confirmed radiologically.

Infants in the 6th month of life:

In the sixth month only 2 infants were examined and they had biochemical and radiological evidence of rickets.

It is, therefore, seen that of the 9 infants with suture softening examined from the 4th to 6th month (inclusive), 6 had rickets.

This suggests that suture softening may bear a relationship to the occurrence of rickets.

THE SUBSEQUENT DEVELOPMENT OF 24 INFANTS WITH SUTURE SOFTENING.

Eighteen infants with suture softening, who were not examined radiologically or clinically at their first visit, were examined at a later date in order to study the subsequent development of infants with such softening. The findings in these infants are given in Table XXIII.

Table XXIII.

Showing the subsequent development of 18 infants who had suture softening at their first examination.

Case	First Examination		Second Examination				
	Date	Age	Date	Age	Rickets (Clinical)	Craniotabes	Suture Softening
1	2. 1.42	2 mths.	4. 5.42	6 mths.	+	-	-
2	6.12.41	3 "	12. 2.42	5 "	-	+	-
3	7.11.41	2 wks.	4. 5.42	6 "	+	-	-
4	12.12.41	1 mth.	8. 5.42	6 "	-	+	-
5	10.11.41	1 "	26. 7.42	7 "	+	+	-
6	4. 3.42	2 "	12. 8.42	7 "	-	-	-
7	1.10.41	3 wks.	24. 2.42	5 "	-	-	-
8	4. 3.42	1 "	24. 8.42	6 "	-	-	-
9	20.12.41	2½ "	26. 2.42	4 "	-	-	-
10	6. 3.42	1 "	15. 7.42	5 "	+	+	-
11	17.11.41	1 "	26. 2.42	3½ "	-	+	-
12	17. 4.42	3 mths.	8. 7.42	6 "	-	-	-
13	14. 3.42	2 "	12. 6.42	6 "	-	-	-
14	2.10.41	2 dys.	14. 2.42	4 "	-	-	+
15	6. 4.42	4 "	28. 9.42	3 "	-	-	+
16	15. 7.42	2 wks.	24. 9.42	2½ "	-	-	-
17	4. 2.42	5 "	21. 4.42	3 "	-	-	+
18	12.12.42	1 "	24. 2.42	2½ "	-	-	+

Considering the results of these examinations, it is seen that 3 of the 5 infants whose second examination took place before they were 4 months old still had suture softening. Of the remaining 13 infants, 4 only were found to have clinical evidence of rickets. As 3 of these 4 were born during the winter, the appearance of the rachitic changes may bear no relationship to the presence of suture softening. Five infants had developed craniotabes, 3 of them belonging to the group which had clinical rickets.

Six infants with suture softening were examined both clinically, biochemically and radiologically on several occasions and are now discussed in detail.

1. M.O'N. Female. 1st child. Feeding: Not recorded.
1 month premature.

Diagnosis on admission: Gastro-enteritis.

Date	Age	Blood Phos. mgm.%	Blood P'tse units	Blood Ca. mgm.%	Ca. x P.	X-ray Wrist	Suture Softening
10.10.41	3 mths.	3.9	8.4	10.6	41	Normal	+
29.11.41	4½ "	3.8	7.4	10.2	39	[illegible]	+
4.1.42	6 "	3.8	9.6	11.0	41	Normal	-

2. M.M'K. Male. 5th child. Feeding: Breast Fed 6 weeks
Ostermilk 1 and 2.

Full Term Pregnancy.

Diagnosis on admission: Inanition.

Date	Age	Phos. mgm%	Blood P'tse units	Ca. mgm.%	Ca. x P.	X-ray Wrist	Suture Softening
18.10.41	3½ mths.	3.2	17.7	11.8	38	Rickets	+
10. 1.42	6 "	-	-	-	-	Rickets	- (Craniotabes +)
22. 2.42	7½ "	2.9	18.2	11.2	33	Rickets	- (Craniotabes +)

3. J.C. Male. 1st child. Feeding: Cow's milk

Full Term Pregnancy.

Diagnosis on admission: N.A.D.

Date	Age	Phos. mgm.%	Blood P'tse units	Ca. mgm.%	Ca. x P.	X-ray Wrist	Suture Softening
18.10.41	1 mth.	-	-	-	-	Normal	+
22.12.41	3 "	3.8	6.9	10.2	40	Normal	±
4.2. 42	5½ "	3.5	14.0	10.2	36 ?	Normal	-
4.42	8 "	-	-	-	-	Rickets	-

4. J.L. Male. 1st child. Feeding: Cow's milk + solids at 6 months.

Full Term Pregnancy.

Diagnosis on admission: Upper Respiratory Infection.

Date	Age	Phos. mgm.%	Blood P'tse units	Ca. mgm.%	Ca. x P.	X-ray Wrist	Suture Softening
12. 1.42	3 mths.	3.8	7.6	10.8	41	Normal	+
10. 3.42	5 "	3.4	12.6	10.2	35	Early Rickets	- (Craniotabes +)
7. 4.42	6 "	2.5	17.1	10.3	26	Rickets	-
10. 8.42	10 "	3.8	16.4	10.7	40	Healing Rickets	-

5. A.P. Male. 4th child. Feeding: Breast Fed.

Full Term Pregnancy.

Diagnosis on admission: N.A.D.

Date	Age	Phos. mgm.%	Blood P'tse units	Ca. mgm.%	Ca. x P.	X-ray Wrist	Suture Softening
6. 5.42	1 mth.	4.1	11.0	11.7	47		+
7. 6.42	2 "	3.8	10.2	10.4	40	Normal	+
22. 8.42	4½ "	-	-	-	-	Normal	±
4. 9.42	5 "	3.7	9.4	10.2	39		-

6. W.E. Male. 2nd child. Feeding: Cow's milk.

Full Term Pregnancy.

Diagnosis on admission: N.A.D.

Date	Age	Phos. mgm.%	Blood P'tse units	Ca. mgm.%	Ca. x P.	X-ray Wrist	Suture Softening
6. 5.42	4 mths.	-	-	-	-	Normal	+
8. 6.42	5 "	3.4	17.2	10.2	35		-
9. 8.42	7 "	-	-	-	-	Rickets	-

7. W.L. Male. 2nd child. Feeding: Breast Fed + solid food at 4 months.

Full Term Pregnancy.

Diagnosis on admission: Anaemia.

Date	Age	Phos. mgm.%	Blood P'tse units	Ca. mgm.%	Ca. x P.	X-ray of Wrist	Suture Softening
17. 1.42	10 mths.	4.1	8.4	10.9	42	Hyper-vitaminosis Advanced Ossification	+
4. 2.42	10½ "	3.9	9.2	10.5	41		±
14. 4.42	12 "	-	-	-	-	Normal	-

M.O'N. who was born in July was examined at intervals until the following January when, at the age of 6 months, she showed no evidence of rickets. The suture softening previously found had disappeared between the ages of 4½ and 6 months.

M.McK. was seen first at the age of 4½ months and was found to have both suture softening and rickets. Active rickets persisted until he was at least 7½ months old but the suture softening had disappeared by the time he was 6 months. At this age he was found to have developed craniotabes.

J.C. Suture softening was disappearing in this child at the age of 3 months when his blood biochemistry was found to be normal. Two and a half months later he showed evidence of rickets.

J.L. also developed active rickets after the suture softening had disappeared.

A.P. who was examined on several occasions during the summer did not develop rachitic changes. It is also seen that the suture softening did not disappear rapidly during the summer as would have been expected if the softening had been rachitic in origin.

W.E. The sixth child to be considered showed rachitic changes during the summer months following the disappearance of the suture softening. As this child developed rickets in the summer months, it is suggested that skull softening may bear a relationship to active rickets.

W.L. The last child was especially interesting as the softening was present at 7 months when the X-ray was suggestive/

suggestive of hypervitaminosis.

Of these 7 infants 4 developed evidence of rickets; 3 out of these 4, however, were born in the winter when rickets is prevalent. The other child was born in the spring and developed rickets during the summer months.

Summing up, it is seen that 21 infants in all were examined after they were 4 months old and 9 of them showed evidence of rickets.

THE EFFECT OF VITAMIN D ON SUTURE SOFTENING.

The findings in the 5th and 7th infants overleaf suggested that Vitamin D would have no curative effect on suture softening, while the findings in the 6th child would suggest the reverse.

Two infants were therefore given adequate doses of Vitamin D and the effect on the suture softening was as follows:

1. T.C. Female. 2nd child. Feeding: Sister Laura's.
Full Term Pregnancy.

Diagnosis on admission: Upper Respiratory Infection.

Date	Age	Blood Phos. mgm.%	Blood P'tse units	Blood Ca. mgm.%	Ca. x P.	X-ray Wrist	Suture Softening	Vitamin D Dosage
15. 1.42	2 mths.	3.6	13.2	10.4	39		+	Adex. 1250 i.u. daily
2. 2.42	2½ "	3.2	10.1	9.9	32	Normal	+	
8. 3.42	3½ "	3.4	12.8	10.2	36	? Rickets	+	
12. 5.42	5½ "	3.8	9.4	10.4	40	Normal	±	

2. A.F. Male. 3rd child. Feeding: Not recorded.
Full Term Pregnancy.

Diagnosis on admission: Pyuria.

Date	Age	Blood Phos. mgm.%	Blood P'tse units	Blood Ca. mgm.%	Ca. x P.	X-ray Wrist	Suture Softening	Vitamin D dosage
14. 1.42	3 mths.	3.9	8.4	10.6	41		+	Adex. 1250 i.u. daily
16. 2.42	4 "	3.7	7.4	11.2	41	Normal	+	
26. 3.42	5½ "	-	-	-	-		±	

In the infants, T.C. and A.F., Vitamin D in doses sufficient to prevent and cure rickets in most infants in Glasgow had no effect on the suture softening.

SUMMARY.

1. Suture softening was present in 135 of the 972 infants examined, and showed no marked seasonal incidence, although it tended to occur more frequently in infants born in the winter months.

2. This softening occurred most frequently in infants under 5 months, the maximum incidence occurring in the second month of life. Only 1 infant with suture softening was over 6 months of age.

3. No relationship was found between the occurrence of suture softening and the sex and diet of the child, locality of the home or parity of the mother.

4. Small infants were liable to develop suture softening, and the incidence of softening was found to be high amongst premature infants and twins.

5. Nine infants over 3 months of age, who had suture softening, were examined for evidence of biochemical and radiological rickets. This was found in six of the infants.

6. Of 20 infants who had suture softening at some time, and who were examined when over 4 months of age, 9 had evidence of rickets.

7. Vitamin D was found to have no curative effect on suture softening.

LOCALISED SKULL SOFTENING OR CRANIOTABES.

It is this type of skull softening now being dealt with which occurred most commonly in the infants examined. This variety is the one considered by many to be rachitic in origin and it is therefore of most interest in this investigation. As 248 infants out of 972 were found to have craniotabes, the number is large enough to permit of definite conclusions being drawn.

Aetiology of Craniotabes.

I. Seasonal Incidence.

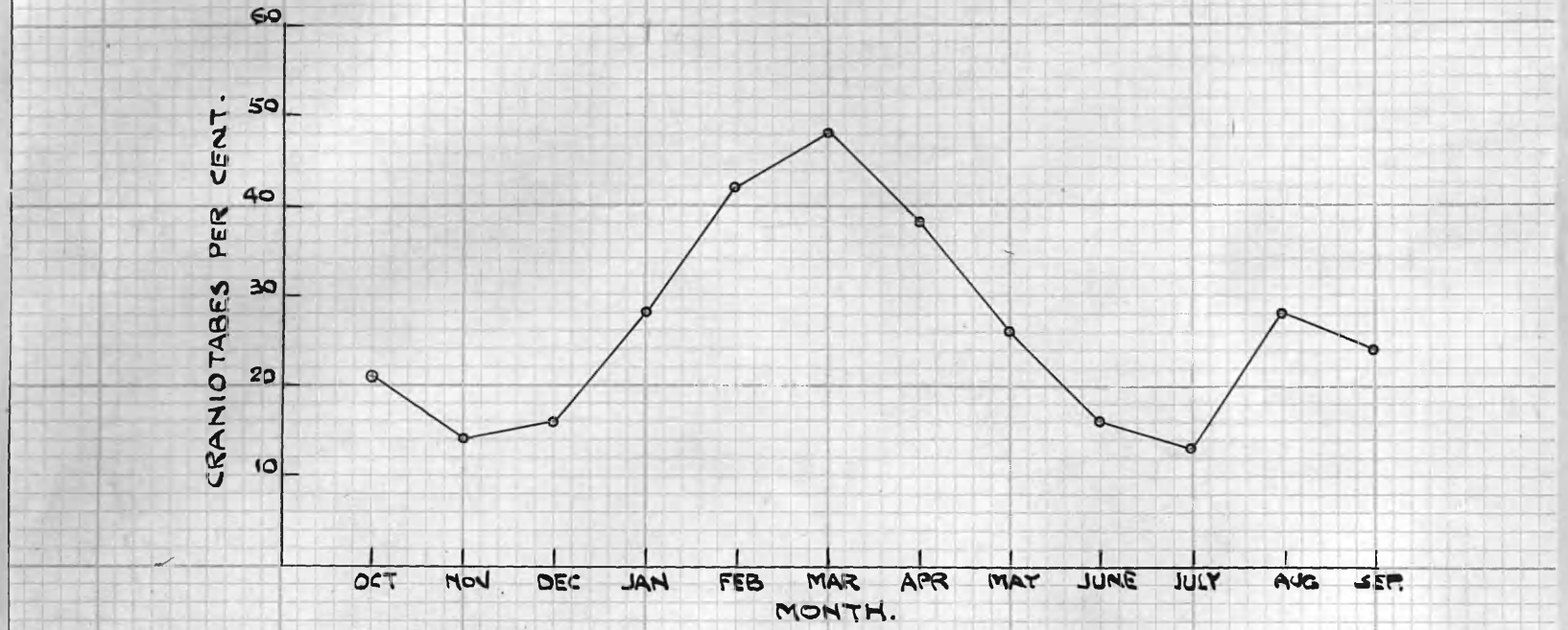
The number of infants found to have craniotabes in each month of the year under consideration is shown in Table XXIV.

Table XXIV.

Showing the number of infants with craniotabes in each month of the year commencing 1st October 1941.

Month	Number of infants examined	Number of infants with craniotabes
October	82	17
November	78	11
December	81	13
January	86	24
February	78	33
March	82	38
April	82	26
May	78	19
June	83	13
July	79	10
August	88	25
September	75	18

FIG III. SHOWING THE SEASONAL INCIDENCE OF CRANIOTABES IN 372 INFANTS EXAMINED IN 12 MONTHS FROM 1ST OCT 1941.



As the number of infants examined each month did not show a great variation, it is possible to compare the findings in each month.

In Fig. III the percentage of infants found to have craniotabes in each age group is shown in the form of a curve.

From these results it is apparent that craniotabes exhibited a definite seasonal incidence, the maximum intensity occurring in early spring (February and March); the incidence fell during the summer months until in July only 13 per cent of the infants had such softening. A further rise in incidence then occurred in August and September.

It has been suggested that craniotabes occurring at different ages may depend on varying aetiological factors, and it was therefore decided to investigate the seasonal incidence of such softening occurring in each month of the first year of life. As is shown in a later part of these investigations, craniotabes was found to occur rarely in infants over 9 months of age and details of the seasonal incidence of softening occurring in monthly age groups up to this age are indicated in a series of charts in Fig. IV. It is seen that this incidence did not vary in the several age groups.

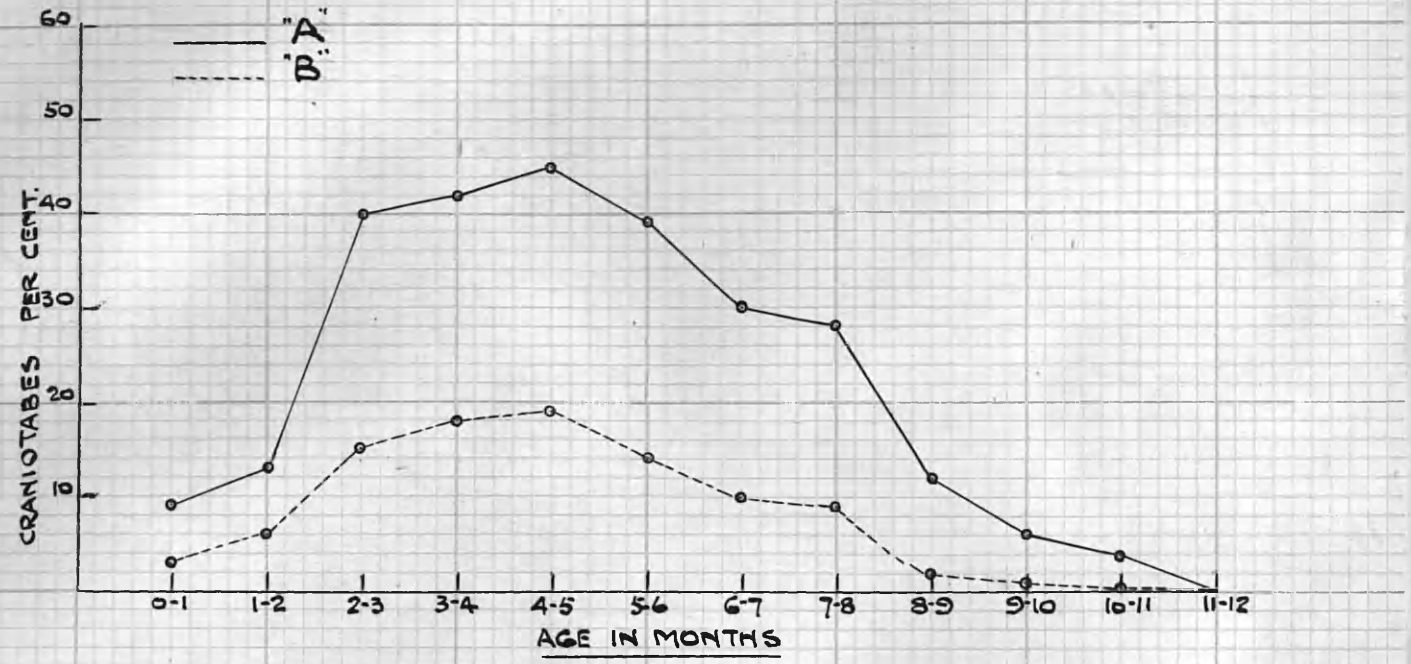
II. Age Incidence.

The/

FIG IV. INDICATING THE SEASONAL INCIDENCE OF CRANIOTABES IN EACH AGE GROUP FROM BIRTH TO 9 MONTHS

NUMBER WITH CRANIOTABES SHOWN THUS

FIG V. SHOWING "A" THE PERCENTAGE OF INFANTS IN EACH GROUP FOUND TO HAVE CRANIOTABES
"B" THE AGE DISTRIBUTION OF THE INFANTS WITH CRANIOTABES.



The age incidence of craniotabes is indicated graphically in Fig. V.

As the number of infants examined in each group showed a slight variation, the age incidence was recorded in two ways as follows:-

(A) The percentage of infants in each age group found to have craniotabes.

(B) The age distribution of the infants with craniotabes.

Craniotabes, as is seen from the accompanying figure (A), was seldom present in the first few weeks of life. The incidence increased gradually from 1 month onwards until it was found that, of the infants examined in the fifth month of life, 45 per cent had this type of softening. The incidence then fell slowly and it was found that no infant of 11 months had craniotabes. The youngest child exhibiting craniotabes was 12 days and the oldest 10½ months.

In curve (B) it may also be seen that most of the infants found to have craniotabes were aged between 4 and 5 months when examined.

III. Sex.

One hundred and twenty-six of the 248 infants found to have craniotabes were males, 77 were females and the sex of the remaining 45 was not recorded. This showed no/

no sex preponderance as the number of infants examined included a larger proportion of males.

IV. Height, Weight and Head-Circumference.

The average height, head circumference and weight of the infants with craniotabes was compared with the corresponding measurements in infants found to have no skull softening. The variations in these values are shown in Table XXV. (See over).

Table XXV.

Comparing the height, head circumference and weight of infants with craniotabes with that of infants with no skull softening.

	Age in Months										
	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10-11
	Cms	Cms	Cms	Cms	Cms	Cms	Cms	Cms	Cms	Cms	Cms
Av. height of infants with craniotabes	54	54	55	57	58	59	64	64.5	66	67	72
Av. height of infants without craniotabes	52	53	55	58	60	62	64	65	67.5	67	71
Av. head circumference of infants with craniotabes	35.5	35.5	37.5	37.5	38.5	39	41	41	41	43	41
Av. head circumference of infants without craniotabes	35	35.5	38	38.5	39.5	40.5	41.5	42.5	42	43	43
	K	K	K	K	K	K	K	K	K	K	K
Av. weight of infants with craniotabes	2.9	?	?	3.9	4.9	5.2	6.0	6.6	6.5	?	?
Av. weight of infants without craniotabes	2.9	3.4	3.2	4.6	5.5	5.6	6.4	6.5	7.2	?	?

In considering the weight of the infant at the time of examination, it was found that owing to the extreme degrees of malnutrition and dehydration found in many of the infants, the range in weight in each age group was very wide. The weight, as far as could be ascertained, appeared to bear no relationship to the occurrence of craniotabes.

The height and head circumference measurements showed only a slight range in each age group and consequently comparison is possible between the infants with and without craniotabes. These measurements showed that in the early months of life the presence of craniotabes was associated with height and head circumferences which were above the average, while in infants over 3 months these measurements were below the average.

Craniotabes, however, was found to occur in a microcephalic infant aged 6 months and was absent in a child aged 5 months with hydrocephalus, indicating that the head circumference was not the sole determining factor in the production of craniotabes.

V. Duration of Gestation and Multiple Pregnancies.

Of the 972 infants examined 71 infants were proved to be premature, that is they weighed less than 2.50 kilos at birth. The incidence of craniotabes in these infants is shown in Table XXVI. The children were arranged in two groups, according to whether they were below or above 2.0 kilos/

kilos at birth. If the birth weight had not been recorded but the history of prematurity which the mother gave appeared to be reliable, the infant was included amongst those who weighed between 2.0 and 2.5 kilos.

Table XXVI.

Showing the incidence of craniotabes in 71 premature infants.

	Age at time of examination in months										
	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10-11
No. of infants born in eighth month of pregnancy	1	-	1	3	5	1	2	2	-	1	-
No. of infants born in eighth month of pregnancy with craniotabes	-	-	-	2	4	1	2	2	-	-	-
No. of infants born in ninth month of pregnancy	7	3	9	5	11	6	5	4	-	1	-
No. of infants born in ninth month of pregnancy with craniotabes	-	1	2	1	9	4	2	1	-	-	-

It is seen from these findings that 31 of the 71 premature infants had craniotabes at the time of examination. An increase in the incidence occurred with a rise in the age of the infant at the time of examination. Of the 21 premature infants examined below 3 months of age, only 3 had craniotabes, while of the 50 infants over 3 months, 28 had such softening. The prevalence of craniotabes increased as the period of gestation became less, as 10 of the 16 infants who had weighed less than 2.0 kilos at birth had craniotabes while in only 21 of the remaining 51 was there softening.

Comparing these results with the incidence of craniotabes found in the 972 infants in the whole series, it is seen that the percentage of premature infants with craniotabes was 41, while the percentage amongst all the infants examined was 26. These results show a marked increase in incidence amongst those born prematurely.

Twin Pregnancies.

Sixteen twins were included in the 972 infants and of these 8 had craniotabes.

Details of the ages of these 8 infants and the occurrence of craniotabes amongst them are given in the accompanying table.

Table XXVII.

Showing the incidence of craniotabes in 16 twins.

	Age at time of examination in months.						
	0-1	1-2	2-3	3-4	4-5	5-6	6-7
No. of twins examined	-	-	3	3	5	3	2
No. of twins with craniotabes	-	-	-	1	4	2	1

As in the case of premature infants, craniotabes occurred commonly in twins over 3 months and was present in 64 per cent of those examined between 4 and 8 months of age. No twin under 3 months exhibited this type of softening.

In both premature and twin pregnancies, the number of children with craniotabes was greatest amongst those examined in the 5th month of life.

VI. Parity of Mother.

Details of the parity of the mother are shown in the accompanying Table XXVIII.

Table XXVIII.

Showing the relationship between the parity of the mother and the incidence of craniotabes in 734 infants.

Parity of Mother	Number of infants examined	Number of infants with craniotabes
1	259	75
2	143	44
3	104	22
4	68	9
5	59	17
6	43	10
7	26	4
8	8	1
9	6	1
10	6	1
11	6	3
12	2	-
13	3	1
14	1	-

The parity of the mother was recorded in 734 instances and from the results obtained it is seen that there was a tendency for craniotabes to occur more frequently in first children.

As it is possible that the aetiological factors associated with the production of craniotabes at different ages may vary, the parity of the mother was investigated in each age group in which craniotabes occurred and is presented in Table XXIX.

Table XXIX.

Showing the relationship between the parity of the mother and the incidence of craniotabes in each monthly age group.

	Parity of Mother				
	1	2-4	5-7	8-10	11-14
1st month					
No. of infants examined	33	40	10	-	1
No. of infants with craniotabes	-	4	1	-	-
2nd month					
No. of infants examined	30	40	13	1	4
No. of infants with craniotabes	1	4	2	1	1
3rd month					
No. of infants examined	38	30	7	2	1
No. of infants with craniotabes	4	7	1	1	1
4th month					
No. of infants examined	28	34	20	5	2
No. of infants with craniotabes	8	10	6	2	1
5th month					
No. of infants examined	26	41	20	2	-
No. of infants with craniotabes	13	17	-	1	-
6th month					
No. of infants examined	32	36	11	1	-
No. of infants with craniotabes	17	5	2	-	-
7th month					
No. of infants examined	23	30	17	2	1
No. of infants with craniotabes	13	5	5	1	-
8th month					
No. of infants examined	22	33	14	-	1
No. of infants with craniotabes	14	12	2	-	-
9th month					
No. of infants examined	15	40	16	2	1
No. of infants with craniotabes	5	6	8	-	1

From the results obtained it is apparent that the number of previous pregnancies which the mother had did not appear to be related to the occurrence of craniotabes at any age.

With regard to the intervals between each pregnancy, it has been stated before, in connection with the investigation of generalised softening, that the average interval between pregnancies varied, in the majority of families under consideration, between 13 and 23 months. A similar frequency was found in the families to which infants with craniotabes belonged.

VII. Previous Diet.

As craniotabes was found to be present at all ages during the first 11 months of life, it is possible that the type of diet which the child was receiving may have influenced the production of the softening.

Feeding during the first year belonged to one of the following groups, namely:-

(a) Breast milk.

(b) Breast milk with solids (soup, puddings and vegetables).

(c) Cow's milk or modified dried cow's milk.

(d) Cow's milk or modified dried cow's milk with solids (soup, puddings and vegetables).

When/

When the type of feeding had been altered during the first two weeks of life, the initial feeding was ignored and it was found that in most cases where the infant was not breast fed, the alteration had occurred at the end of the puerperium.

Particulars of the type of feeding which was employed in 572 of the infants examined are given in Table XXX.(See over).

Table XXX.

Showing the relationship between the incidence of craniotabes and the diet of 672 infants between the age of 2 weeks and 11 months.

	Age in Months										
	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10-11
No. of infants fed on breast milk alone	16	27	15	13	3	3	5	7	3	2	-
% of infants fed on breast milk alone who had craniotabes	6	15	20	39	33	33	20	57	33	50	-
No. of infants fed on cow's milk alone	52	77	78	69	54	36	39	10	6	1	1
% of infants fed on cow's milk alone who had craniotabes	13	9	18	28	33	41	33	50	50	100	-
No. of infants who had received mixed diet + breast milk	-	-	-	-	2	-	4	2	-	1	-
% of infants who had received mixed diet + breast milk who had craniotabes	-	-	-	-	-	-	50	-	-	-	-
No. of infants who had received mixed diet + cow's milk	-	-	-	-	1	12	3	7	20	3	-
% of infants who had received mixed diet + cow's milk who had craniotabes	-	-	-	-	-	48	-	14	10	-	-

That craniotabes occurred equally in wholly breast fed infants and in infants fed on cow's milk only during the first 10 months is apparent from the accompanying figures. It is also seen that in the older infants craniotabes was present more frequently in those who had not had any solid food added to their diet. As the numbers of infants in each age group fed in the various ways showed such variation and as the total number of infants included in the different age groups also varied, it is not possible to make absolute comparisons between the results; these, however, do suggest that the mode of feeding during the first few months does not affect the incidence of craniotabes at that age, but that infants who do not receive solid food during the later months of the first year are more prone to exhibit craniotabes at that age.

VIII. Addition of Vitamin D to the Diet.

It has been previously stated that when Vitamin D had been given to the infants included in this survey, it was found that in the majority of cases the dose was considered to be insufficient. Fifty-seven infants of 904 examined had received Vitamin D in amounts which could be estimated with certainty. A further 31 infants received cod liver oil in doses varying from 1 to 18 drops daily which/

which was given in the feeding bottle with the feed.

It is not possible, therefore, to base definite conclusions on the findings in such a few children. Details of the incidence of craniotabes in the 57 infants receiving known amounts of Vitamin D are given in Table XXXI.

Table XXXI.

Showing the incidence of craniotabes in 57 infants receiving various amounts of Vitamin D.

Infants Receiving Less than 500 i.u. Daily			
Age in Months	No. of infants examined	No. of infants with craniotabes	Remarks
2	3	1	
3	8	3	
4	3	1	
5	10	2	
6	6	2	
7	6	4	Premature
8	2	-	
9	2	-	

Infants Receiving 500 - 1,000 i.u. Daily			
Age in Months	No. of infants examined	No. of infants with craniotabes	Remarks
1	1	-	
6	1	-	
7	1	-	
8	1	1	
9	3	1	
11	1	-	

Infants Receiving Over 1,000 i.u. Daily			
Age in Months	No. of infants examined	No. of infants with craniotabes	Remarks
1	1	-	
5	1	1	Premature
7	2	-	
8	2	-	
9	2	-	
11	1	-	

The prevalence of craniotabes is seen to vary with the amount of Vitamin D received. Of 40 infants receiving less than 500 i.u. daily, 13, i.e. 32 per cent, had craniotabes. Two out of 8 infants receiving between 500 and 1000 i.u. daily had craniotabes i.e. 25 per cent, while of 9 infants examined who were receiving over 1000 i.u., only 1 child exhibited this type of softening. It was noted that this last infant was premature.

The foregoing results suggest that Vitamin D in adequate doses may either prevent the development of craniotabes or hasten the disappearance of such softening. It must be noted that these results may give an erroneous impression, as 4 of the infants receiving what was considered to be an adequate amount of Vitamin D belonged to age groups in which craniotabes seldom occurred.

IX./

IX. Locality of Home.

One hundred and sixty-six infants with craniotabes lived in urban districts, 39 in rural districts and the homes of 43 were not recorded. Craniotabes, therefore, showed a tendency to occur more frequently in infants living in urban districts.

X. Radiological Findings.

A radiograph of the wrist was taken in 118 of the 248 infants with craniotabes. The radiological evidence considered to be diagnostic of rickets has been previously discussed.

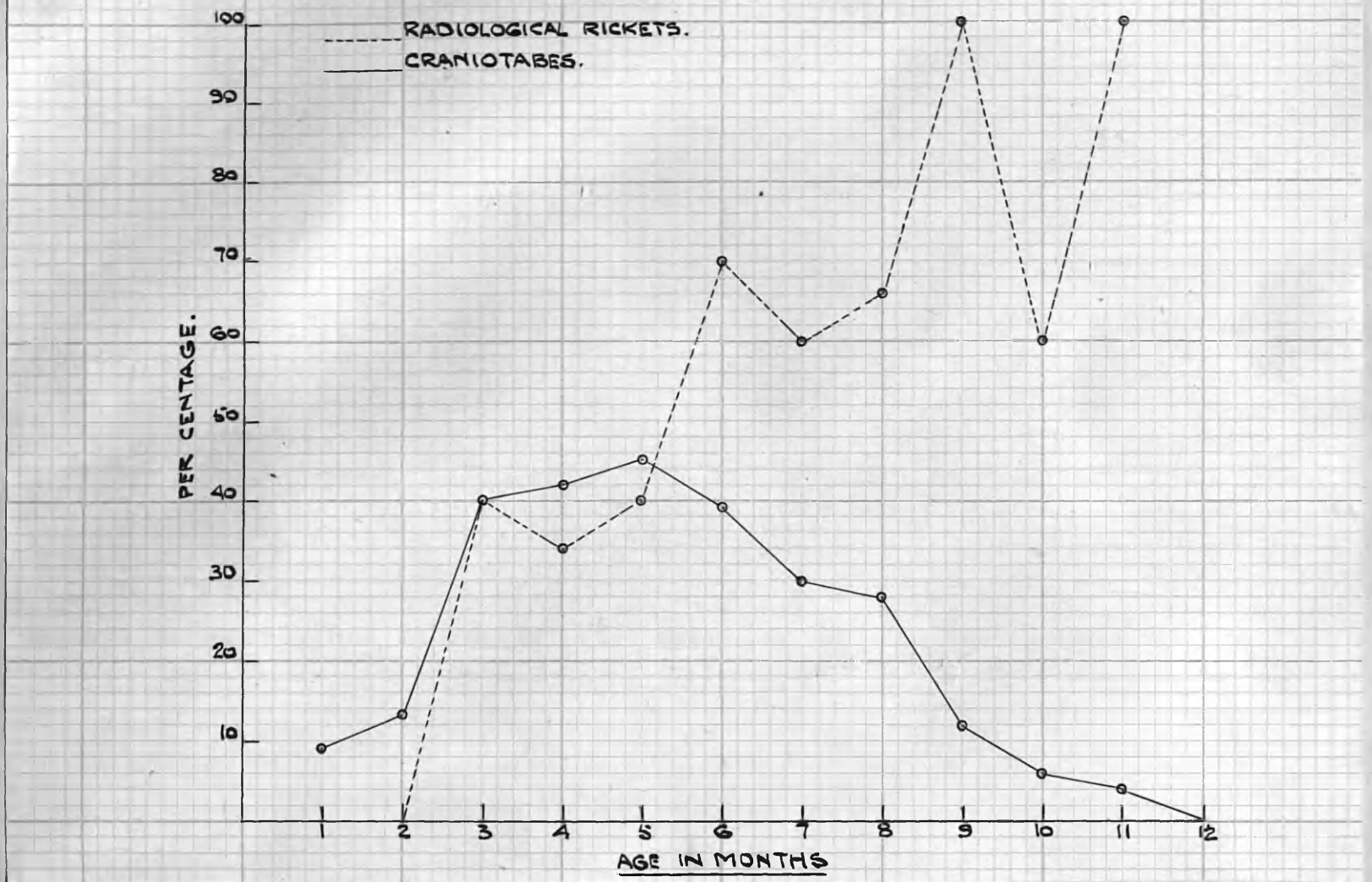
The number of infants with definite radiological signs of rickets is indicated in the accompanying Table XXXII; the percentage with such evidence in each age group is also tabulated.

Table XXXII.

Showing the frequency of radiological evidence of rickets in 118 infants with craniotabes.

Age in Months	No. of infants X-rayed	No. of infants with radiological evidence of rickets.	
0-1	4	0	0
1-2	9	0	0
2-3	12	5	42 per cent
3-4	14	4	29 per cent
4-5	26	12	48 per cent
5-6	15	11	73 per cent
6-7	17	9	53 per cent
7-8	10	6	60 per cent
8-9	3	3	100 per cent
9-10	6	3	50 per cent
10-11	2	2	100 per cent

FIG VI - COMPARING THE AGE INCIDENCE OF CRANIOTABES WITH THE INCIDENCE OF RADIOLOGICAL RICKETS IN INFANTS WITH CRANIOTABES.



It is clearly seen that radiological rachitic changes occurred relatively frequently in infants with craniotabes, and were present in 55 of the 118 infants examined. Thirteen infants, whose ages ranged from 2 to 8 weeks showed no radiological changes suggestive of rickets. As has been stated, such evidence does not appear in the earliest stages of rickets and the infants in the first 2 months of life may therefore be excluded when the incidence of radiological rachitic changes is considered. Amongst the remaining infants examined, 52 per cent had radiological rickets at the time of examination.

The number of infants between the 8th and 11th months who were examined is small in comparison with the younger age groups. It is, therefore, not possible to compare the findings in each of the age groups. Of the infants whose ages lay between the 3rd and 9th months, the maximum incidence of radiological rachitic changes occurred in the 6th month of life. It is not possible at this stage to demonstrate whether this variation in incidence may not be due solely to the age incidence of craniotabes. It is seen in the older age groups that the incidence of rickets diagnosed radiologically did not fall with the decrease in the incidence of craniotabes (Fig. VI). This may be due either to a rise in the incidence of rickets

in/

in all infants over 6 months, or to an increase in the incidence of rickets amongst older infants with craniotabes, and will be discussed later.

XI. Biochemical Findings.

Biochemical estimations were carried out on 119 infants with craniotabes. The criteria for diagnosing rickets was again (a) a fall in the plasma inorganic phosphorus below 4 mgm. per cent associated with (b) an elevation in the plasma phosphatase above 11 units.

The results of these estimations are classified according to the age of the infant and are presented in the accompanying tables (Table XXXIII - XLIII). Where the infant had also been examined radiologically, the latter findings are included in the table.

Table XXXIII

Showing the biochemical and radiological findings in 5 infants with craniotabes in the 1st month of life.

Case	Plasma Phos. mgm. %	Plasma P'tse units	Serum Calcium mgm. %	Ca.x P.	X-ray of Wrist
1	4.1	11.0	11.7	47.9	
2	3.8	4.0	11.0	42.0	Normal
3	5.0	7.7	9.1	46.0	
4	3.8	10.0	8.3	31.5	Normal
5	3.6	9.4	11.2	40.2	Normal

Table XXXIV.

Showing the biochemical and radiological findings in 12 infants with craniotabes in the 2nd month of life.

Case	Plasma Phos. mgm. %	Plasma P'tse units	Serum Calcium mgm. %	Ca.x P.	X-ray of Wrist
1	3.8	10.4	10.5	40	Normal
2	4.0	12.1	10.4	42	Normal
3	3.6	10.0	11.1	40	
4	3.9	7.1	10.0	39	Normal
5	4.0	7.2	10.4	42	
6	4.5	10.9	11.6	51	Normal
7	3.3	14.5	11.9	39	
8	3.8	9.1	9.8	37	
9	4.2	5.2	10.4	44	Normal
10	4.1	6.4	9.5	37	Normal
11	3.8	6.2	11.8	45	Normal
12	4.5	-	11.1	50	

Table XXXV.

Showing the biochemical and radiological findings in 14 infants with craniotabes in the 3rd month of life.

Case	Plasma Phos. mgm. %	Plasma P'tse units	Serum Calcium mgm. %	Ca.x P.	X-ray of Wrist
1	3.8	9.4	11.1	42	Normal
2	3.0	10.3	11.0	31	Early Rickets
3	3.8	5.3	11.3	43	Normal
4	3.1	19.5	10.7	33	Normal
5	3.2	16.8	11.9	38	? Rickets
6	4.7	9.1	11.0	52	Normal
7	4.6	10.1	10.9	50	Normal
8	4.2	6.9	11.1	47	Normal
9	3.6	10.1	10.8	39	Normal
10	3.5	9.1	10.9	38	
11	3.9	6.0	11.2	43	Normal
12	4.1	6.7	10.8	43	Normal
13	2.9	14.5	6.5	19	Early Rickets
14	3.7	15.9	8.6	30	Early Rickets

Table XXXVI.

Showing the biochemical and radiological findings in 17 infants with craniotabes in the 4th month of life.

Case	Plasma Phos. mgm. %	Plasma P'tse units	Serum Calcium mgm. %	Ca.x P.	X-ray of Wrist
1	4.1	8.3	11.4	47	Rickets
2	4.0	10.9	11.8	47	
3	2.4	15.3	11.5	28	Normal
4	2.5	16.1	11.1	29	
5	3.0	10.2	-	-	
6	3.6	12.7	-	-	
7	3.4	13.9	10.2	35	
8	2.9	17.1	-	-	
9	4.2	7.5	-	-	
10	3.2	18.3	8.2	26	Rickets
11	2.6	16.5	10.8	28	Rickets
12	3.5	8.1	11.7	40	Normal
13	3.6	8.2	9.7	35	
14	3.0	6.9	9.9	30	Normal
15	3.8	11.0	11.1	42	Normal
16	4.2	-	9.0	38	Normal
17	3.9	10.1	9.7	38	

Table XXXVII.

Showing the biochemical and radiological findings in 18 infants with craniotabes in the 5th month of life.

Case	Plasma Phos. mgm. %	Plasma P'tse units	Serum Calcium mgm. %	Ca.x P.	X-ray of Wrist
1	2.7	14.0	9.8	21	Rickets
2	2.9	8.8	11.0	32	Rickets
3	3.9	9.6	11.1	43	
4	3.8	6.5	-	-	
5	4.0	5.0	11.0	44	
6	3.0	17.4	10.4	31	Rickets
7	3.3	8.3	9.4	30	
8	2.8	13.5	8.2	24	Normal
9	3.1	13.0	9.9	30	Normal
10	4.2	9.0	10.4	44	Normal
11	2.7	14.1	10.2	27	Rickets
12	4.0	12.1	10.0	40	
13	2.8	8.0	9.7	27	Healing Rickets
14	2.5	14.6	11.0	28	Early Rickets
15	2.5	4.9	9.8	25	Early Rickets
16	4.2	7.9	11.1	47	Normal
17	3.1	10.6	11.2	35	Rickets
18	3.9	14.0	11.9	44	Normal

Table XXXVIII.

Showing the biochemical and radiological findings in 10 infants with craniotabes in the 6th month of life.

Case	Plasma Phos. mgm. %	Plasma P'tse units	Serum Calcium mgm. %	Ca.x P.	X-ray of Wrist
1	3.0	11.5	10.0	30	Normal
2	2.8	16.0	10.0	28	Rickets
3	3.9	10.2	-	-	
4	2.5	12.4	9.0	23	Rickets
5	3.3	19.8	9.2	30	Rickets
6	3.0	15.0	10.6	32	
7	3.4	12.2	9.5	32	Healing Rickets
8	3.2	17.2	10.1	32	
9	3.1	8.2	10.1	31	Rickets
10	3.8	10.3	11.0	42	

Table XXXIX.

Showing the biochemical and radiological findings in 18 infants with craniotabes in the 7th month of life.

Case	Plasma Phos. mgm. %	Plasma P'tse units	Serum Calcium mgm. %	Ca.x P.	X-ray of Wrist
1	3.3	18.0	10.0	33	
2	3.3	15.8	-	-	
3	1.8	18.1	11.8	21	
4	3.2	14.5	10.5	37	
5	4.1	5.2	9.9	40	
6	2.7	13.5	6.5	18	Rickets
7	2.6	14.3	10.3	27	
8	3.4	8.1	10.3	35	Normal
9	3.7	11.1	13.2	46	Normal
10	3.7	6.7	9.7	37	Normal
11	3.6	14.7	11.8	42	Normal
12	3.3	9.4	6.0	20	Rickets
13	2.3	13.6	10.1	23	Rickets
14	3.2	18.0	10.1	32	Normal
15	3.5	27.0	10.2	36	
16	2.8	11.3	11.5	32	Rickets
17	4.5	9.3	11.0	50	Normal
18	2.4	17.7	7.6	18	Rickets

Table XL.

Showing the biochemical and radiological findings in 10 infants with craniotabes in the 8th month of life.

Case	Plasma Phos. mgm. %	Plasma P'tse units	Serum Calcium mgm. %	Ca.x P.	X-ray of Wrist
1	3.1	8.2	-	-	(Died)
2	3.7	14.4	11.7	43	
3	3.5	17.7	10.1	35	
4	3.2	14.4	10.8	35	Rickets
5	2.9	18.1	11.3	33	
6	2.5	12.0	10.5	26	Rickets
7	3.1	15.2	9.3	29	
8	4.0	5.2	11.7	47	Normal
9	3.8	7.8	12.1	46	?
10	2.8	15.4	11.5	37	Rickets

Table XLI.

Showing the biochemical and radiological findings in 6 infants with craniotabes in the 9th month of life.

Case	Plasma Phos. mgm. %	Plasma P'tse units	Serum Calcium mgm. %	Ca.x P.	X-ray of Wrist
1	3.8	11.7	9.4	36	Healing Rickets
2	4.0	7.0	10.9	44	
3	3.2	12.1	9.2	29	Rickets
4	2.0	21.9	9.0	18	Rickets
5	3.4	14.2	10.8	37	
6	3.8	8.7	11.0	43	

Table XLII.

Showing the biochemical and radiological findings in 5 infants with craniotabes in the 10th month of life.

Case	Plasma Phos. mgm. %	Plasma P'tse units	Serum Calcium mgm. %	Ca.x P.	X-ray of Wrist
1	3.7	11.0	10.1	38	Normal
2	3.9	10.0	11.2	43	
3	2.1	16.1	9.5	20	
4	3.1	9.8	9.0	28	Rickets
5	2.7	16.3	6.9	19	

Table XLIII.

Showing the biochemical and radiological findings in 3 infants with craniotabes in the 11th month of life.

Case	Plasma Phos. mgm. %	Plasma P'tse units	Serum Calcium mgm. %	Ca.x P.	X-ray of Wrist
1	4.0	9.4	11.0	44	
2	3.9	12.0	10.1	40	
3	2.9	11.0	10.9	32	

The biochemical findings in these infants are discussed under the age group to which the child belonged.

Infants in the 1st month of life:

Five infants were examined in this age group. One child was critically ill at the time of admission and died soon after; there was a diminution in his plasma phosphorus/

phosphorus. Of the 4 remaining infants, one was admitted on account of convulsions and was found to have hypocalcaemia (serum calcium 8.3 mgm. per cent). The 3 remaining had all normal blood biochemical findings.

Infants in the 2nd month of life:

Normal biochemical findings occurred in 7 of the infants. In 3 of these the plasma phosphorus was slightly below 4 mgm. per cent, but as the other findings were found to be within normal limits it was concluded that the infants displayed no biochemical evidence of rickets. Another had a value of 3.6 mgm. per cent which was suggestive of rickets. One infant showed definite biochemical evidence of rickets.

Infants in the 3rd month of life:

Fourteen infants were examined in this group, and 5 of them had the biochemical changes associated with rickets; the diagnosis was confirmed radiologically in 4 of the infants. Two infants had markedly reduced plasma phosphorus values (3.5 and 3.6 mgm. per cent) and these findings were suggestive of rickets. The remaining 7 showed no abnormal biochemical values.

Infants in the 4th month of life:

Six of the 17 infants included in this group had normal biochemical values, while 8 had definite biochemical evidence of rickets. The remaining 3 infants had all phosphorus/

phosphorus values which fell well below the value taken as the lower limit of normality (3.5, 3.6 and 3.0 mgm. per cent). Eight of the infants in this group had been examined radiologically and of these 3 showed rachitic changes, although 1 of the 3 children had normal biochemical findings.

Infants in the 5th month of life:

Eighteen infants were examined at this age and 9 showed definite biochemical evidence of rickets. X-ray examination of one of these infants with biochemical changes showed normal bone growth; this may be explained by the fact that biochemical alterations very often precede radiological changes. In only 6 of the 18 infants were normal readings obtained, while there was a low phosphorus (3.3 mgm. per cent) in one and a high phosphatase (14.0 units) in the remainder; the findings in the last 2 were classed as suspicious of rickets.

Infants in the 6th month of life:

Rachitic changes were absent in only 2 of the 10 infants examined, and in the 8 with suspected rickets the diagnosis was confirmed radiologically in 5 of the infants.

Infants in the 7th month of life:

Twelve infants of the 18 included in this group showed biochemical evidence of rickets which was confirmed radiologically/

radiologically in 4 of the infants. In 4 there was no evidence of rickets while of the remaining 2 children one showed radiological rickets while her biochemical findings were normal, and the other had a definite low plasma phosphorus content (3.4 mgm. per cent).

Infants in the 8th month of life:

Ten infants were examined in this age group and 6 of them showed rachitic changes confirmed in 3 of the infants by radiological examination. Only 2 of the infants had normal biochemical findings. One abnormal value, either low plasma phosphorus (3.1 mgm. per cent) or high phosphatase (14.4 units) appeared in the 2 other children.

Infants in the 9th month of life:

Four of the 6 infants in this group had biochemical evidence of rickets which was confirmed radiologically in 3 of them. The other 2 had normal blood findings.

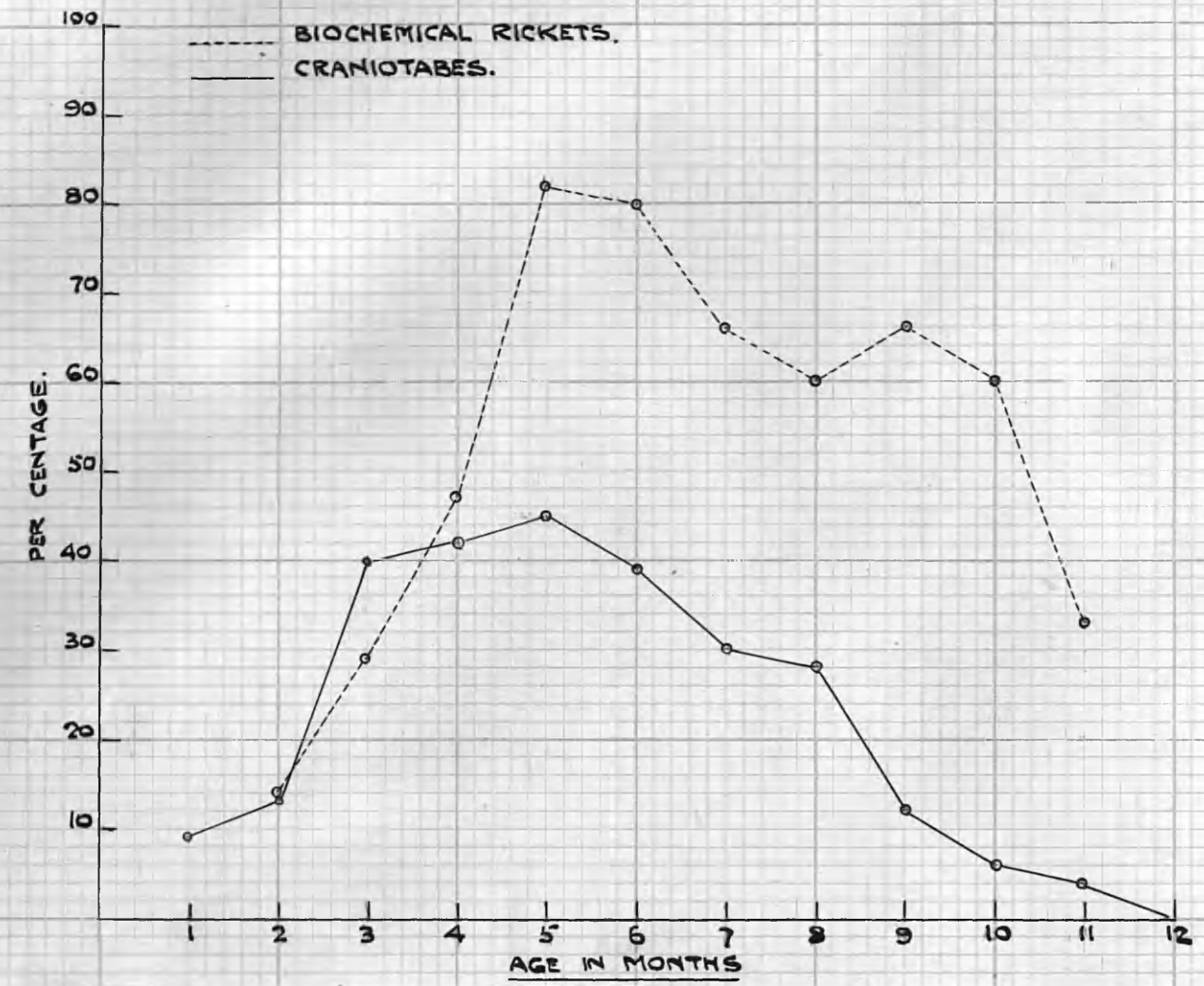
Infants in the 10th month of life:

Three of the 5 children examined had blood changes typical of rickets, while the other 2 children had normal findings.

Infants in the 11th month of life:

Only 3 infants were available for examination in this age group and 1 had evidence of rickets. The other infants/

FIG VII. - COMPARING THE AGE INCIDENCE OF CRANIOTABES WITH THE INCIDENCE OF BIOCHEMICAL RICKETS IN INFANTS WITH CRANIOTABES.



infants had normal blood values.

It is seen that 57 of the 117 infants (49 per cent) had biochemical evidence of rickets.

The incidence of radiological rickets in infants with craniotabes was previously noted to remain at a high level in the older age groups; similar results were obtained when biochemical evidence of rickets was considered (see Fig. VII).

Correlating the total radiological and biochemical examinations made, it is seen that 168 infants with craniotabes were examined both biochemically and radiologically or either biochemically or radiologically. These findings are now investigated and are classified as follows:-

(a) Infants who had both biochemical and radiological evidence of rickets.

(b) Infants who had either biochemical or radiological evidence of rickets.

When the child had been examined both biochemically and radiologically and one of the findings was suggestive of rickets while the other showed definite evidence of rachitic changes, the former finding is ignored.

Two further groups are included in which either radiological findings alone were suggestive of rickets or one biochemical value suggested rickets. From the

foregoing/

foregoing results where both biochemical and radiological examinations were carried out in several of the infants, it appears that a plasma phosphorus value of 4.0 mgm. per cent is rather high for the lower limit of normality. A phosphorus value of above 3.7 mgm. per cent occurring without other evidence of rickets has therefore been taken as normal in the accompanying table. A value below this, occurring alone, is suggestive of the presence of rachitic changes. (See Table XLIV).

Table XLIV.

Showing the number of infants with craniotabes who had evidence of rickets, radiologically or biochemically.

Age in months	No. of infants examined	No. of infants with radiological and biochemical evidence of rickets	No. of infants with radiological evidence of rickets alone	No. of infants with biochemical evidence of rickets alone	
1	7	-	-	-	-
2	15	-	-	1	1?
3	15	4	1	1	2?
4	23	2	2	7	3?
5	30	8	4	3	1?
6	19	5	6	3	-
7	24	5	4	8	1?
8	16	3	4	4	1?
9	6	3	-	1	-
10	5	1	-	2	-
11	7	-	2	1	1?
Total:	167	31	23	31	10?

It is seen that 85 of the 167 infants had definite evidence of rickets, while in 10 infants there was a change suggestive of rickets. Again it is apparent that craniotabes and rickets are frequently present in the same infant, but it is also seen that craniotabes can occur at any age up to 11 months in the absence of biochemical or radiological evidence of rickets. It cannot be stated at this stage whether craniotabes may be an early rachitic change, or whether rickets occurs more frequently in infants with craniotabes.

THE SUBSEQUENT DEVELOPMENT OF 19 INFANTS WITH CRANIOTABES AND 17 INFANTS WHO HAD NO EVIDENCE OF CRANIOTABES AT THEIR INITIAL EXAMINATION.

It has been shown above that rachitic changes and craniotabes frequently occurred simultaneously. In order to trace this relationship further, 36 infants have been examined on more than one occasion. Nineteen of these children had craniotabes at the time of their first examination.

Eleven infants who had craniotabes when first examined, but on whom no biochemical or radiological examinations were made, were re-examined clinically at a subsequent date. The findings in these infants are given in Table XLV.

Table XLV.

Showing the subsequent development of 11 infants with craniotabes at their first examination.

Case	First Examination		Second Examination			
	Age	Date	Age	Date	Craniotabes	Rickets (Clinical)
J.M.	2 mths	28. 9.41	4 mths	12.12.41	+	+
E.M.	3 "	9.10.41	7 "	6. 2.42	+	+
J.M.	2 "	17. 1.42	6 "	5.42	+	?
A.D.	6 "	17. 2.42	7 "	19. 3.42	+	+
M.L.	1 "	20. 2.42	5 "	16. 6.42	-	+
J.L.	1 "	20. 2.42	15 "	4. 4.43	-	+
J.B.	3 "	10. 3.42	5 "	16. 5.42	+	+
W.B.	2 wks.	30. 4.42	7 "	6.11.42	-	-
J.D.	7 mths	30. 4.42	16 "	6. 3.43	-	+
F.R.	6 "	4. 5.42	8 "	6.42	-	-
L.	3½ "	16. 5.42	6 "	4. 8.42	-	+

On the second examination of these children it was found that 8 of them, 4 of whom had no craniotabes at that time, had clinical evidence of rickets, that is, as stated before, markedly enlarged wrist epiphyses, beading of the ribs, etc. No evidence of either rickets or craniotabes was found in 2 of the infants and the third had craniotabes and ? beading of the ribs. It is important to emphasise the fact that, of the 3 infants with rickets but no craniotabes, 2 of the infants were over the age period when craniotabes usually occurs. In only one child was there craniotabes without evidence of rickets.

Summing up, therefore, it is seen that of 11 infants with craniotabes 8 developed rickets and that in only 3 of the 8 infants who were under 1 year old at the time of the second examination were craniotabes and rickets present separately. These results suggest that craniotabes may be rachitic in origin as the clinical evidence of rickets must necessarily vary at different ages.

In comparison with the foregoing groups, infants who displayed no evidence of craniotabes or of rickets at the initial attendance were examined on a later occasion. The results of these examinations are given in Table XLVI.

Table XLVI.

Showing the subsequent development of 17 infants with no evidence of craniotabes at their first examination.

Case	First Examination		Second Examination			
	Age	Date	Age	Date	Cranio-tabes	Rickets (Clinical)
J.L.	5 mths	7.11.42	7 mths	12. 1.42	+	+
A.C.	4 "	1.10.41	10 "	14. 4.42	-	-
J.B.	1 "	4.10.41	8 "	5. 5.42	+	-
M.M.	1 "	18.10.41	8 "	12. 5.42	-	+
P.L.	1 "	13.10.41	7 "	6. 4.42	+	-
J.M.	2 "	16.11.41	3 "	21.12.41	-	-
R.M.	3 "	30.11.41	8 "	9. 5.42	+	+
T.M.	2 "	10. 1.42	6 "	18. 5.42	-	-
E.M.	2½ "	26. 1.42	10 "	9.42	-	-
J.C.	1 "	30. 1.42	5½ "	15. 5.42	+	-
I.B.	2½ "	17. 2.42	5½ "	6. 6.42	±	-
A.B.	2½ "	17. 2.42	8 "	6. 8.42	+	-
J.B.	3 "	19. 2.42	6 "	23. 5.42	-	-
C.C.	3 "	10. 3.42	5 "	19. 5.42	+	+
J.H.	2½ "	16. 3.42	4 "	12. 4.42	-	-
A.	2 dys	26. 3.42	4 "	8. 7.42	-	+
A.N.	2 mths	6.42	5 "	6. 9.42	-	-

Seventeen children are included in the group; 7 of them showed no evidence of either rickets or craniotabes. Two had evidence of rickets but no craniotabes and 4 had craniotabes and no evidence of rickets, while in a fifth child there was a suggestion of craniotabes. The remaining 3 infants had both craniotabes and rickets.

It is therefore apparent that only 5 of the 17 infants/

infants developed rickets. In 2 children the rachitic changes were not associated with craniotabes. These results illustrate further that there appears to be a relationship between the two conditions as rachitic changes occurred more frequently in the infants with craniotabes.

To investigate further this correlation, 8 infants were examined at repeated intervals, in most instances clinically, biochemically and radiologically, and the findings are now considered separately.

1. J.L. Male. 3rd child. Feeding: Ostermilk 1 and 2. Full Term Pregnancy.

Diagnosis on admission: Gastro-enteritis.

Age	Date	Phos. mgm.%	Blood P'tse units	Ca. mgm.%	Ca. x P.	X-ray Wrist	Craniotabes
3 wks.	3.10.41	4.2	7.0	-	-	Normal	-
6 mths.	24. 4.42	3.2	16.2	10.4	33	Rickets	+

2. F.I. Male. 2nd child. Feeding: Sister Laura's Food Full Term Pregnancy

Diagnosis on admission: Incorrect feeding; marasmus.

Age	Date	Phos. mgm.%	Blood P'tse units	Ca. mgm.%	Ca. x P.	X-ray Wrist	Craniotabes
2 mths.	11. 4.42	3.8	6.4	-	-	Normal	+
3 "	16. 5.42	3.9	7.0	11.2	43	Normal	-

3. V.M'G. Female. 1st child. Feeding: Sister Laura's Food.

Full Term Pregnancy.

Diagnosis on admission: Upper Respiratory Infection.

Age	Date	Phos. mgm.%	Blood P'tse units	Ca. mgm.%	Ca. x P.	X-ray Wrist	Cranio-tabes
3 mths.	2.12.41	4.2	7.5	12.0	50	Normal	+
3½ "	18.12.41	2.8	15.9	11.8	33	? Rickets	+

4. W.P. Male. 5th child. Feeding: Cow's milk + solids at 6 months.

Full Term Pregnancy

Diagnosis on admission: Inanition.

Age	Date	Phos. mgm.%	Blood P'tse units	Ca. mgm.%	Ca. x P.	X-ray Wrist	Cranio-tabes
5½ mths	10.11.41	3.8	17.6	10.0	38	? Rickets	+++
10 "	27. 4.42	3.8	12.0	10.2	40	Normal	+

5. W.B. Male. 1st child. Feeding: Not recorded.

Full Term Pregnancy

Diagnosis on admission: Upper Respiratory Infection.

Age	Date	Phos. mgm.%	Blood P'tse units	Ca. mgm.%	Ca. x P.	X-ray Wrist	Cranio-tabes
3 mths.	2.10.41	-	-	-	-	Normal	+
3½ "	10.10.41	3.8	7.7	11.5	43	Normal	-
4 "	6.11.41	4.0	9.8	10.1	40		-
5 "	16.12.41	4.2	8.4	12.0	51	Normal	-
8 "	26. 3.42	-	-	-	-	Normal	-

6. E.M. Female. 2nd child. Feeding: not recorded.

Full Term Pregnancy.

Diagnosis on admission: ?

Age	Date	Phos. mgm.%	Blood P'tse units	Ca. mgm.%	Ca. x P.	X-ray Wrist	Cranio-tabes
2 mths.	19. 1.42	2.6	12.6	14.0	26	Normal	+
3 "	22. 2.42	3.1	5.4	-	-		+

7. W.K. Male. 2nd child. Feeding: Cow's milk.

Full Term Pregnancy.

Diagnosis on first visit: Upper respiratory infection.

Age	Date	Phos. mgm.%	Blood P'tse units	Ca. mgm.%	Ca x P.	X-ray Wrist	Cranio-tabes
4 mths.	26. 1.42	3.7	17.1	10.0	37	? Early Rickets	+
6 "	6. 4.42	3.8	12.2	-	-	Healed Rickets	-

8. J.C. Female. 1st child. Feeding: Breast Fed + solids at 4 months.

Full Term Pregnancy.

Age	Date	Phos. mgm.%	Blood P'tse units	Ca. mgm.%	Ca. x P.	X-ray Wrist	Cranio-tabes
4 mths.	21. 4.42	3.9	10.4	10.2	41	Normal	+
6½ "	1. 6.42	3.8	7.6	10.4	40	Normal	+
10 "	10. 9.42	-	-	-	-	Normal	±

J.L: This child was seen on two occasions only. At the age of 3 weeks his blood and X-ray of wrist showed no abnormality and there was no craniotabes. When examined in April at the age of 6 months he had biochemical, radiological and clinical evidence of rickets and craniotabes.

F.I: Whereas the above child (J.L.) had no evidence of craniotabes when examined for the first time in October, the second child had this type of skull softening when examined in April at the age of 7 weeks. Biochemical and radiological examinations revealed no abnormality. One month later the softening had disappeared and the blood and wrist examinations were again normal. Comparing this child with J.L., it is suggested that disappearance of craniotabes may depend in part on the amount of sunshine to which the infant is exposed.

V.McG: When first examined at 3 months this child had craniotabes but no abnormal blood or radiological findings. Two weeks later the blood phosphorus and phosphatase showed typical rachitic changes while the X-ray was suggestive of rickets.

W.P: This child had definite biochemical and radiological changes suggestive of rickets when 6 months old; at that time craniotabes was severe. Five months later/

later in April 1942 when examined at the age of 10 months, the craniotabes was disappearing, the radiological findings were normal but the biochemistry still showed evidence of rickets. It is, therefore, apparent that craniotabes may persist when definite radiological rachitic changes have disappeared although it must be noted that the craniotabes was disappearing at the time of the second examination.

W.B: Craniotabes was present in this child at the age of 3 months, and had disappeared 14 days later. Unfortunately the biochemistry of his blood was not done at the time of the first examination, but if rachitic changes had been present they would probably have been so slight as to show no radiological alteration 14 days later. As this child was first examined in October it might be expected that he would develop rickets at a later date, especially as there were signs of craniotabes. This, however, did not occur.

E.M: This child on admission was seriously ill and it is doubtful if the blood biochemical findings at that time may be considered. At the age of 3 months the craniotabes had almost disappeared. Although the plasma phosphorus was low, the phosphatase activity at that time was normal. No conclusions can be based on the findings in this child.

W.K./

W.K: When examined at the age of 4 months this child had radiological and biochemical findings suggestive of rachitic changes. Two months later, in April, the phosphatase activity had fallen and the wrist showed X-ray evidence of healed rickets; the craniotabes had also disappeared.

J.C: Craniotabes was present in this child up to the age of 10 months without signs of rickets.

In summing up, it is seen that five of the eight infants examined had, at some time, evidence of rickets. Regarding the three infants who did not develop rickets during the period in which they were under observation, one child was not seen after he was 3 months old, and it is not known whether he developed rickets at a later date. The child, W.B., was examined at intervals until he was 8 months old and at no time did he show signs of rickets; his skull softening had disappeared by the time he was $3\frac{1}{2}$ months. The remaining child had craniotabes which persisted until she was 10 months old, and at no time was there evidence of rachitic changes.

These results emphasise further the fact that

(1) Rachitic changes frequently appear in infants with craniotabes.

(2)/

(2) Rachitic changes, however, do not invariably occur in infants with craniotabes.

(3) Craniotabes may still be present when all evidence of rickets has disappeared.

Vitamin D was therefore given to infants with craniotabes in order to decide if it had a curative effect on the skull softening.

THE EFFECT OF VITAMIN D ON CRANIOTABES.

Since the craniotabes present in 2 of the above infants apparently disappeared when healing of the associated rickets occurred, and as it has previously been shown that the skull softening is less often found in the summer months, it was therefore decided to study the effect of adequate dosage of Vitamin D on craniotabes.

Seven infants were examined and the findings were as follows:-

1. J.McL. Male. 2nd child. Feeding: Breast fed 2 months, cow's milk 1 month, + solids at 3 months.
   6 weeks premature.

   Diagnosis on admission: Inanition.

Age	Date	Phos. mgm.%	Blood P'tse units	Ca. mgm.%	Ca. x P.	X-ray Wrist	Cranio-tabes	Vitamin D dosage
3 mths.	19. 9.41	3.8	10.0	11.0	42		+	Adex. 1250 i.u. daily
4 "	21.10.41	3.3	9.6	11.1	37	Normal	+	-do-
4½ "	4.11.41	-	9.0	10.0	-	Normal	+	1875 i.u.
5 "	17.11.41	3.4	5.0	10.5	36		+	-do-
5½ "	2.12.41	4.2	11.5	11.5	48		+	-do-
6 "	18.12.41	4.0	11.1	10.5	42		+	625 i.u.
7 "	12. 1.42	-	-	-	-	Normal	+	2500 i.u.
8 "	2. 2.42	3.7	10.9	11.0	41		±	-do-
9 "	11. 3.42	4.1	7.4	10.0	41	Normal	±	-do-

2. A.M. Female. 1st child. Feeding: Ostermilk 1 & 2 + solids at 7 months

Full Term Pregnancy

Diagnosis on admission: Upper respiratory infection.

Age	Date	Phos. mgm.%	Blood P'tse units	Ca. mgm.%	Ca. x P.	X-ray Wrist	Cranio-tabes	Vitamin D dosage
2½ mths	7.11.41	-	-	-	-		-	
8 "	29. 4.42	3.5	14.2	11.9	42	Healing Rickets	+	Adex. 1250 i.u. daily
8½ "	13. 5.42	3.8	11.7	11,6	45	Healed Rickets	±	

3. P.McK. Male. 2nd child. Feeding: Ostermilk 1 & 2 + solids at 6 months

Full Term Pregnancy.

Diagnosis on admission: Gastro-enteritis.

Age	Date	Phos. mgm.%	Blood P'tse units	Ca. mgm.%	Ca. x P.	X-ray Wrist	Cranio-tabes	Vitamin D dosage
5 mths	28.10.41	2.5	6.4	11.1	28	Normal	+	Radiostol 600,000 i.u.
5½ "	16.11.41	3.7	4.0	11.4	42	Normal	+ +	
6 "	26.11.41	4.5	4.2	11.5	52	SL.rickets healing	+ +	
7 "	19.12.41	4.3	4.0	11.4	49	Normal	+	
8½ "	2. 2.42	3.9	9.3	9.8	37	Normal	+	
9 "	18. 2.42	-	-	-	-		+	
10 "	13. 3.42	-	-	-	-		+	Adex. 2500 i.u. daily
10½ "	26. 3.42	3.8	6.7	10.6	40	Normal	+	-do-

4. G.L. Male. 6th child. Feeding: Breast fed + solids at 9 months.

Full Term Pregnancy

Diagnosis on admission: Anaemia.

Age	Date	Blood Phos. mgm.%	Blood P'tse units	Ca. mgm.%	Ca. x P.	X-ray Wrist	Cranio-tabes	Vitamin D dosage
8 mths	7.11.41	3.6	8.4	10.0	36		±	Radiostol 600,000i.u.
8½ "	26.11.41	3.7	7.2	11.7	42	Normal	±	
9 "	19.12.41	3.9	7.2	11.1	43	Normal	-	

5. G.McA. Male. 5th child. Feeding: Cow's milk + solids at 6 months.

Full Term Pregnancy.

Diagnosis on admission: Anaemia.

Age	Date	Blood Phos. mgm.%	Blood P'tse units	Ca. mgm.%	Ca. x P.	X-ray Wrist	Cranio-tabes	Vitamin D dosage
7 mths	19.12.41	3.3	15.8	10.1	36	Healing Rickets	+	Adex. 1875 i.u. daily
7½ "	2. 1.42	2.7	10.7	10.0	27	Normal	+	-do-
8 "	30. 1.42	4.0	5.2	10.7	42		+	-do-
8½ "	10. 2.42	-	-	-	-		-	-do-
10 "	13. 3.42	4.0	6.4	10.9	44		-	-do-

6. P.M. Female. 2nd child. Feeding: Cow's milk

Full Term Pregnancy.

Diagnosis on admission: N.A.D.

Age	Date	Phos. mgm.%	Blood P'tse units	Ca. mgm.%	Ca. x P.	X-ray Wrist	Cranio-tabes	Vitamin D dosage
4 mths	26. 1.42	2.8	14.5	10.5	29	Rickets	+	Adex.1875 i.u.daily
4½ "	9. 2.42	2.8	12.0	12.6	35	Normal	+	-do-
5½ "	9. 3.42	4.0	7.4	10.9	44	Normal	+	Radiostol 600,000i.u.
6 "	30. 3.42	3.5	7.0	11.5	40	Normal	+	
8 "	20. 5.42	-	-	-	-	Normal	+	

7. A.M. Male. 3rd child. Feeding: Not recorded.

Full Term Pregnancy.

Diagnosis on admission: Anaemia.

Age	Date	Phos. mgm.%	Blood P'tse units	Ca. mgm.%	Ca. x P.	X-ray Wrist	Cranio-tabes	Vitamin D dosage
6 mths	11. 1.42	-	8.1	11.8	-		+	
6½ "	1. 2.42	3.1	6.2	-	-		+	
7 "	15. 2.42	3.8	6.1	11.0	42		+	
7½ "	25. 2.42	2.0	10.2	11.3	23		+	
8 "	11. 3.42	3.6	8.1	10.1	37	Normal	+ +	Radiostol 600,000i.u.
8½ "	24. 3.42	3.8	9.0	9.1	35	Normal	+	
9½ "	24. 5.42	-	-	-	-	Normal	±	

J.McL: This child was 6 weeks premature and had severe craniotabes at the age of 3 months. Despite the fact that he had over 1000 i.u. of Vitamin D daily from that age until he was 6 months old, the craniotabes persisted. Apart from a diminution in the plasma phosphorus level to 3.3 and 3.4 mgm. per cent between the ages of 4 and 6 months, he showed no evidence of rickets. At the age of 7 months he was given 2500 i.u. of Vitamin D daily and the craniotabes began to disappear. Whether this was due to the increase in the vitamin dosage or to a natural cure resulting when the child reached the age of 10 months cannot be stated but, as the biochemical findings were normal from the age of 6 months onwards, the latter explanation is assumed to be the correct one.

A.M: This infant was found to have healing rickets and craniotabes at the age of 8 months and Adexolin was given to assist the healing process. Two weeks later the craniotabes had almost disappeared suggesting that it was rachitic in origin. The age factor, however, must again be recognised.

P.McK: Although the rachitic changes disappeared rapidly at the age of 6 months after the administration of a massive dose of Vitamin D, the craniotabes persisted until he/

he was over 10 months, although there had been no evidence of active rickets since the child was below 6 months of age. At 10 months he was given a daily dosage of 2500 i.u. but the craniotabes showed no change in the following fortnight. As the child had had more than an adequate amount of Vitamin D, it may be concluded that the craniotabes was not affected by Vitamin D administration.

G.L: The findings in this child support the previous statement. The child had mild craniotabes at 8 months when he was given a massive dose of Vitamin D. At no time was there evidence of rachitic changes. When examined a fortnight later the craniotabes was unchanged.

G.McA: Radiological examination of this child showed signs of healing rickets when the child was 6 months old. Adexolin was then started and the craniotabes disappeared 2 months later, i.e. when the child was 8 months old. It is not possible in the case of this child to decide whether the Vitamin D had a curative effect on the craniotabes as the rickets was healing when the therapy was started.

P.M: After receiving Adexolin regularly for 2 weeks, this child showed evidence of healing rickets; craniotabes, however, persisted for a further 3½ months until he was 8 months old. Vitamin D did not appear to have a curative/

curative effect on the softening.

A.M: Craniotabes was noted in this child at the age of 6 months, and biochemical values were normal apart from a fall in the phosphorus to 2.0 mgm. per cent when the child was 7½ months. Fourteen days later the biochemical findings were normal and it is possible that the previous reading may have been an experimental error, especially as there was no radiological evidence of rickets at subsequent examinations.

The craniotabes persisted until the infant was 9½ months old, although 600,000 i.u. Vitamin D had been given 6 weeks previously.

From the results in these 7 infants it may be concluded that Vitamin D has no beneficial effect on craniotabes, even when given in amounts which will cure active rickets.

THE CALCIUM AND PHOSPHORUS METABOLISM IN THREE INFANTS WITH CRANIOTABES

Metabolism experiments were conducted on two infants with craniotabes and on a third who had hypocalcaemic convulsions and craniotabes. In the latter child the experiment was divided into two parts. Following the investigation of his metabolism, he was given Vitamin D for one week and the experiment repeated in order to discover if there was any alteration in the mineral retention.

Report of Case I.

F.I., male, 2nd child.

The parents were both healthy and there was nothing relevant in the family history. Their other child was 1½ years old and according to the mother he was well and had walked at the age of 13 months. The mother had been in good health during the second pregnancy and the child was born at term, his weight being "over 7 lbs". The child was well at birth and was breast fed for 5 weeks at which time he was taken off the breast on account of vomiting, which the mother stated had commenced when the child was 4 days old. It is questionable if that is correct as the child was born in a maternity hospital and dismissed on the tenth day with the mother and there is no record of the child having vomited while in hospital. When breast feeding/

feeding was stopped the child was given cow's milk and later Ostermilk. From the details given by the mother the infant received an adequate caloric intake but always vomited a little after his feed.

He was admitted to this hospital at the age of 7 weeks and was dismissed one week later. During his stay in hospital he was well after the first day when he had several loose stools. Physical examination revealed no abnormality apart from craniotabes and the fact that the child was 63 per cent of his expected weight. Skin tests (Von Pirquet and Mantoux 1/5000) were negative.

He was readmitted 9 days after dismissal and was found to have gastro-enteritis which rapidly responded to treatment. He quickly regained weight and the metabolism experiment was started on 21.3.42, a fortnight after admission.

X-ray of his wrist was normal both before and after the experiment was carried out.

The blood chemistry was also normal at the onset and completion of the metabolism and the findings were as follows:-

	Before	After
Plasma Inorganic Phosphorus	3.9 mgm.%	4.2 mgm.%
Plasma Phosphatase	7.0 units	7.0 units

	Before	After
Serum Calcium	10.0 mgm.%	11.2 mgm.%
Ca. x P.	39	47
Weight at beginning of period		3.04 K.
" " end " "		3.07 K.
Average gain in weight per day		4.2 g.

Feed: cow's milk 105 cc.)
sugar IV g.) 6 times per day

Daily caloric intake: 459 calories

Daily caloric requirement: 475 calories. (100 cal. per kilo expected bodyweight)

The child was well throughout the course of the metabolism experiment.

The results are included in Table XLVII.(See over)

Table XLVII.

Showing the calcium and phosphorus intake and excretion in three infants with craniotabes.

F.I.

Calcium Retention.

Total Intake CaO g.	Total Output		Total Retention CaO g.	Retention g.per kilo per day
	Urine CaO g.	Faeces CaO g.		
5.8510	.1792	4.5629	+ 1.1089	+ .052

Phosphorus Retention.

Total Intake P_2O_5 g.	Total Output		Total Retention P_2O_5 g.	Retention g.per kilo per day
	Urine P_2O_5 g.	Faeces P_2O_5 g.		
7.4263	2.5550	3.4609	+ 1.4104	+ .066

W.B.

Calcium Retention.

Total Intake CaO g.	Total Output		Total Retention CaO g.	Retention g.per kilo per day
	Urine CaO g.	Faeces CaO g.		
7.4972	.2036	5.6879	+ 1.6057	+ .042

Phosphorus Retention.

Total Intake P_2O_5 g.	Total Output		Total Retention P_2O_5 g.	Retention g.per kilo per day
	Urine P_2O_5 g.	Faeces P_2O_5 g.		
9.1732	3.5461	4.4550	+ 1.1721	+ .031

T.G.

Calcium Retention.

I before Vitamin D administration.
II after Vitamin D administration.

Period	Total Intake	Total Output		Total Retention	Retention
		Urine	Faeces		
	CaO g.	CaO g.	CaO g.	CaO g.	g.per kilo per day
I	5.0124	.2338	4.7116	+ .0670	+ .002
II	4.9894	.1418	4.5386	+ .3090	+ .012

Phosphorus Retention.

I before Vitamin D administration.
II after Vitamin D administration.

Period	Total Intake	Total Output		Total Retention	Retention
		Urine	Faeces		
	P_2O_5 g.	P_2O_5 g.	P_2O_5 g.	P_2O_5 g.	g.per kilo per day
I	6.3921	3.2472	2.9365	+ .2084	+ .008
II	6.3804	3.1563	2.8583	+ .3658	+ .014

Report of Case II.

W.B., male, 3rd child:

There was nothing relevant in the family history and the parents and the other two children were well. The mother had been well during her pregnancy and the child was born at term. He throve and developed normally and was breast fed until 3 months old when "he was started on Ostermilk as he was irritable". Two weeks later he developed broncho-pneumonia and was admitted to hospital on 24.2.42. His condition improved rapidly and the metabolism experiment was started one week later. On admission he was well-nourished, had no evidence of rickets and was 104 per cent of his expected weight. Skin tests (Von Pirquet and Mantoux 1/5000) were negative.

X-ray of his wrist was normal both before and after the metabolism experiment was completed.

Biochemical findings were also normal at the onset and completion and the values were as follows:-

	Before	After
Plasma Inorganic Phosphorus	3.8 mgm.%	3.6 mgm.%
Plasma Phosphatase	11.0 units	10.6 units
Serum Calcium	11.1 mgm.%	11.2 mgm.%
Ca. x P.	42	40

Weight at beginning of period 5.40 K.

" " end " " 5.55 K.

Average gain in weight per day 21.0 g.

Feed: cow's milk 135 cc.)
) 6 times per day
sugar IV g.)

Daily caloric intake: 561 calories.

Daily caloric requirement: 540 calories (100 cal. per kilo expected bodyweight)

The child was well during the experiment. Details of the metabolism are given in Table XLVII.(See Page 150).

Report of Case III.

T.G., male, 2nd child.

The parents of the child were alive and well and the other child was thriving and developed normally. The mother was well during her pregnancy and the child, T.G., was born at term. He was fed on Sister Laura's Food and was well until 2 weeks old when he began to have convulsions. These persisted at intervals until he was admitted to hospital on the following day - 19.5.42.

On admission he appeared healthy and was 102 per cent of his expected weight. He had 10 convulsions during the 24 hours following admission. Chloral gr. 1, 2 hourly, was given, the convulsions controlled and the metabolism experiment was started when he was 3 weeks old. There was no evidence of muscle spasm and Chvostek's sign was negative.

The/

The biochemical findings before the metabolism experiment was started were as follows:-

Plasma Inorganic Phosphorus	6.1 mgm.%
Plasma Phosphatase	12.8 units
Serum Calcium	7.3 mgm.%

The blood examination was not repeated until the end of the experiment.

The child was then given 1250 i.u. of Vitamin D daily for one week and the metabolism repeated. The biochemical findings at the end of this period were as follows:-

Plasma Inorganic Phosphorus	5.7 mgm.%
Plasma Phosphatase	19.2 units
Serum Calcium	10.9 mgm.%
Weight at beginning of Period I	3.60 K.
" " end " " I	3.78 K.
Average gain in weight per day (Period I)	26.0 g.
Weight at beginning of Period 2	3.85 K.
" " end " " 2	3.95 K.
Average gain in weight per day (Period 2)	22.0 g.

Feed: cow's milk 45 cc.
water 7.5 cc.) 12 times per day
sugar 1.0 g.

Daily caloric intake: 357 calories

Daily caloric requirement: 360 calories (100 cal. per kilo expected bodyweight)

This child was well during the metabolism experiments but it was necessary to feed him two-hourly as he vomited the larger feeds which had been given four-hourly. Details of the experiments are given in Table XLVII.(Page 150).

Considering the results it is seen that both the calcium and phosphorus retentions in F.I. were adequate (CaO: .057; P_2O_5: .066 g/k/dy). Although his retention was normal while he was in hospital receiving his required caloric intake, it is possible that as he was only 63 per cent of his expected weight on admission, his intake and retention may have been inadequate at that time. The second child, W.B., who was overweight on admission, was found also to have an adequate mineral retention. It is seen that the phosphorus retention was lower than that of the calcium in this child, that is suggestive of rickets. The amount of mineral retained, however, fell within the accepted limits of normality. Assuming also that the ratio of P_2O_5 to CaO required for bone formation is 1.3 to 1, the retention of both minerals was still adequate for bone formation, as 0.031 g. P_2O_5 would be required by 0.024 g.CaO.

In the third child, T.G., it is demonstrated how

the/

the amount of calcium retained may be diminished in active tetany. In this child the retention of calcium was sub-minimal (0.002 g/k/dy). At the same time the phosphorus retention was also diminished, but the balance was positive. Normally in the presence of rickets the phosphorus retention is less than that of the calcium, a condition not manifest in this child. Following the administration of Adexolin, the retention of both minerals improved.

SUMMARY

1. Craniotabes was present in 248 of the 972 infants examined and showed a marked seasonal incidence, the peak occurring in the early spring months, February and March.

2. This softening was found in infants whose ages ranged from 12 days to 10½ months, the maximum incidence being in the 4th and 5th months of life.

3. No relationship was found between the occurrence of craniotabes and the sex and weight of the child, the locality of the home and the parity of the mother.

4. Infants with craniotabes examined in the first 2 months of life, had head circumference and height measurements above the average. In older infants with craniotabes, these measurements were below the average.

5. Craniotabes was frequently present in twins and premature infants who were examined when they were over 3 months of age.

6. When present in older infants, craniotabes was more commonly found in those who were not receiving solids in addition to milk.

7. Craniotabes was infrequently found in the few infants receiving adequate amounts of Vitamin D.

8./

8. Of 167 infants examined with craniotabes, 85 had either radiological or biochemical evidence of rickets.

9. Thirty-six infants were examined on more than one occasion, and it was found that those with craniotabes were more liable to develop rickets.

10. Seven infants with craniotabes were given Vitamin D in doses sufficient to cure active rickets and it was found to have no curative effect on the craniotabes.

11. Calcium and phosphorus retentions were found to be adequate in 2 infants with craniotabes and no evidence of rickets, while the retention of both minerals was diminished in an infant with craniotabes and tetany.

PART III

COMMENT.

From the foregoing investigations it is seen that softening of the cranial bones in infancy is a relatively frequent finding and, for the convenience of study, it has been divided into three types which have been considered separately. Table I showing the incidence of the several types of softening is reproduced in part below:

Infants under 1 year with generalised skull softening alone	2 per cent
Infants under 1 year with suture softening alone	14 per cent
Infants under 1 year with generalised skull softening and suture softening	1 per cent
Infants under 1 year with craniotabes	26 per cent
Total percentage of infants under 1 year with softening	43 per cent

The following observations on the results of the investigations can now be made.

Generalised skull softening occurred especially in the parietal bones, was diffuse in character and showed a definite age incidence being present in infants whose ages ranged from 2 days to 16 weeks. It is not possible to state whether the softening was congenital in origin as few infants were examined at birth; the prevalence, however, decreased rapidly in infants over 6 weeks of age and it/

it must be considered that the softening was present relatively soon after birth, if not at the time of birth in most of the affected infants. This softening showed no marked seasonal incidence, although there was a slight rise in frequency in the winter months.

In investigating the aetiology of the softening the possible relationship with rickets was considered especially as the two conditions tended to show the same seasonal incidence. Eleven infants with generalised softening were examined either biochemically and radiologically or by means of one of these methods alone. At the time of examination the infants were considered to be too young to show clinical evidence of rickets. Radiological examination showed changes suspicious of rickets in 2 of the 10 infants examined, while biochemical examination in 10 infants showed alterations suggestive of rickets in 1; in none of the infants was there definite evidence of active rickets. It was found that generalised softening was less common amongst the few infants who had been receiving Vitamin D regularly. Doses of Vitamin D which were proved adequate to cure rickets were therefore given to 4 children with softening and the subsequent development of the infants investigated. In 3 of the children the Vitamin D had definitely no curative effect

on the softening which persisted until the infants were 4 months old. Metabolism experiments conducted on 2 infants with generalised skull softening showed no abnormality in the calcium and phosphorus retention; while softening was not prevalent amongst the few premature infants examined as would have been expected had it been rachitic in origin.

This softening was found to be more common in infants where the mother had had several previous pregnancies. Ferguson (121) has shown that the incidence of rickets rises with the number of preceding pregnancies. She explained this as being due to a lowering of the social conditions of the family with an increase in the size of the family and no increase in the income. The explanation, however, is no doubt more complex and probably associated with the problem of the relationship existing between intra-uterine development and mineral storage as it has been suggested that rachitic changes may be partly the result of deficient pre-natal calcium storage. That Vitamin D administration did not result in the disappearance of the type of softening under consideration, together with the finding of normal mineral metabolism in infants with softening, makes it probable that the calcium retention was adequate after birth.

The/

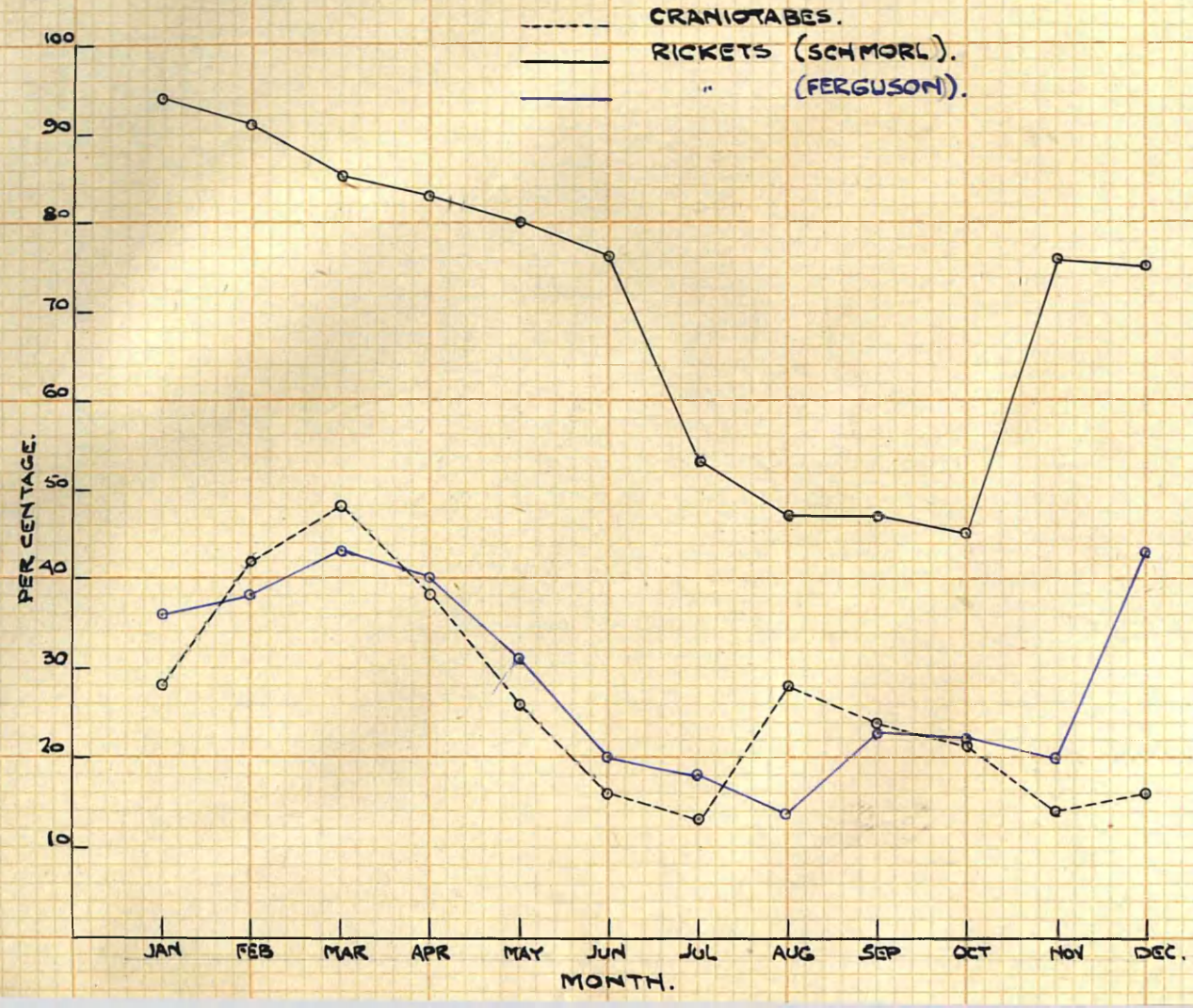
The question of whether rachitic changes occurred more frequently in infants who had generalised skull softening is difficult to answer owing to the prevalence of rickets in Glasgow children. Both Morris (122) and Graham (123) found that about 50 per cent of infants in the same age group in that city showed evidence of rachitic changes, and in the present series it was found that 5 out of 10 infants examined with generalised skull softening subsequently developed rickets. Conclusions cannot be based on the results of such a small number of investigations but the incidence is comparable with the figures quoted above.

It has not been possible to discover the causative factors of the softening, but it is suggested that, in keeping with Toverud's (31) findings, the presence of generalised softening is associated with pre-natal calcium storage and with the rate of growth of the infant. It was found that the skull circumference in infants with such softening was above the average. Healing of the softening will occur naturally when the retention of calcium becomes adequate after birth and, in correlation with the continuation of bone growth, takes up to 16 weeks to become complete.

Suture softening which was present in 15 per cent

of/

FIG. VIII. COMPARING THE SEASONAL INCIDENCE OF CRANIOTABES AND OF RICKETS DIAGNOSED PATHOLOGICALLY BY SCHMORL, AND BY FERGUSON FROM THE DATE ON WHICH THE CHILD WAS THOUGHT TO STOP THRIVING



considered by many workers to be rachitic in origin. It most frequently affected the parietal bones and occurred in infants whose ages ranged from 2 weeks to 10 months. As the incidence was slight during the first month of life (4 infants out of 88), it may be concluded that this type of softening is seldom present at birth. The incidence increased with a rise in age until 45 per cent of the infants examined in the fifth month of life had craniotabes; it then fell gradually in the remaining age groups until at 11 months no evidence of craniotabes was found in any of the infants. Of the 972 infants examined 268, i.e. 26 per cent had craniotabes at the time of examination. Wilson and Seldowitz (53) found that 35 per cent of the infants they examined under 1 year had softening similar in type, their results being roughly comparable with those obtained in the present survey. Schwartz (80) found that 39 per cent of white children in New York had either congenital or acquired softening, while 29 per cent of the infants examined in this series had either generalised skull softening or craniotabes.

A marked seasonal incidence was found to exist in the occurrence of craniotabes and, as is seen in Fig. VIII, this incidence resembled that of rickets reported by Schmorl (95) and Ferguson (121). These findings suggest

that craniotabes and rickets may have a similar aetiology.

The other aetiological factors studied in relation to the occurrence of craniotabes may now be considered. Owing to the great variations found in the weights of the infants in each of the age groups examined, no deductions could be made regarding the possible relationship which might exist between the appearance of craniotabes and the weight of the child. Softening was present during the first 3 months of life in infants who were on the average taller and had a larger head circumference than infants with no softening. This was reversed in older age groups which, however, contained several premature infants and twins who had craniotabes. That growth is not the only factor associated with the production of craniotabes is illustrated by the fact that a microcephalic infant had craniotabes, while an infant with hydrocephalus had no softening.

With regard to the type of feeding employed in the rearing of the children, the incidence of craniotabes in the first few months was found to be unaffected by the feeding; it was noticed, however, that infants who were over 6 or 7 months and who had never received any feed apart from milk were more liable to have craniotabes.

Unlike the findings in generalised skull softening, there/

there was no apparent relationship between the parity of the mother and the development of craniotabes. No relationship between the situation of the infant's home, i.e. urban or rural, and the incidence of craniotabes was noted.

Radiographs and biochemical blood examination of 168 of the 248 infants with craniotabes showed that 85 of the infants had evidence of rickets. Metabolism experiments were done on 2 infants with craniotabes and with no evidence of rickets, and the mineral retention in both was found to be within normal limits.

Seven infants with craniotabes were given adequate amounts of Vitamin D and in at least 4 of the infants it was demonstrated definitely that Vitamin D had no curative effect on the skull softening, although it had been found in the general survey that craniotabes was uncommon in the infants who had been receiving adequate amounts of Vitamin D. These infants, however, belonged to age groups in which craniotabes seldom occurred.

Craniotabes was frequently present in premature infants and twins and, as the mineral metabolism was found to be normal in infants with such softening, it is suggested that pre-natal factors may be associated with the appearance of the skull changes. That this is not the only

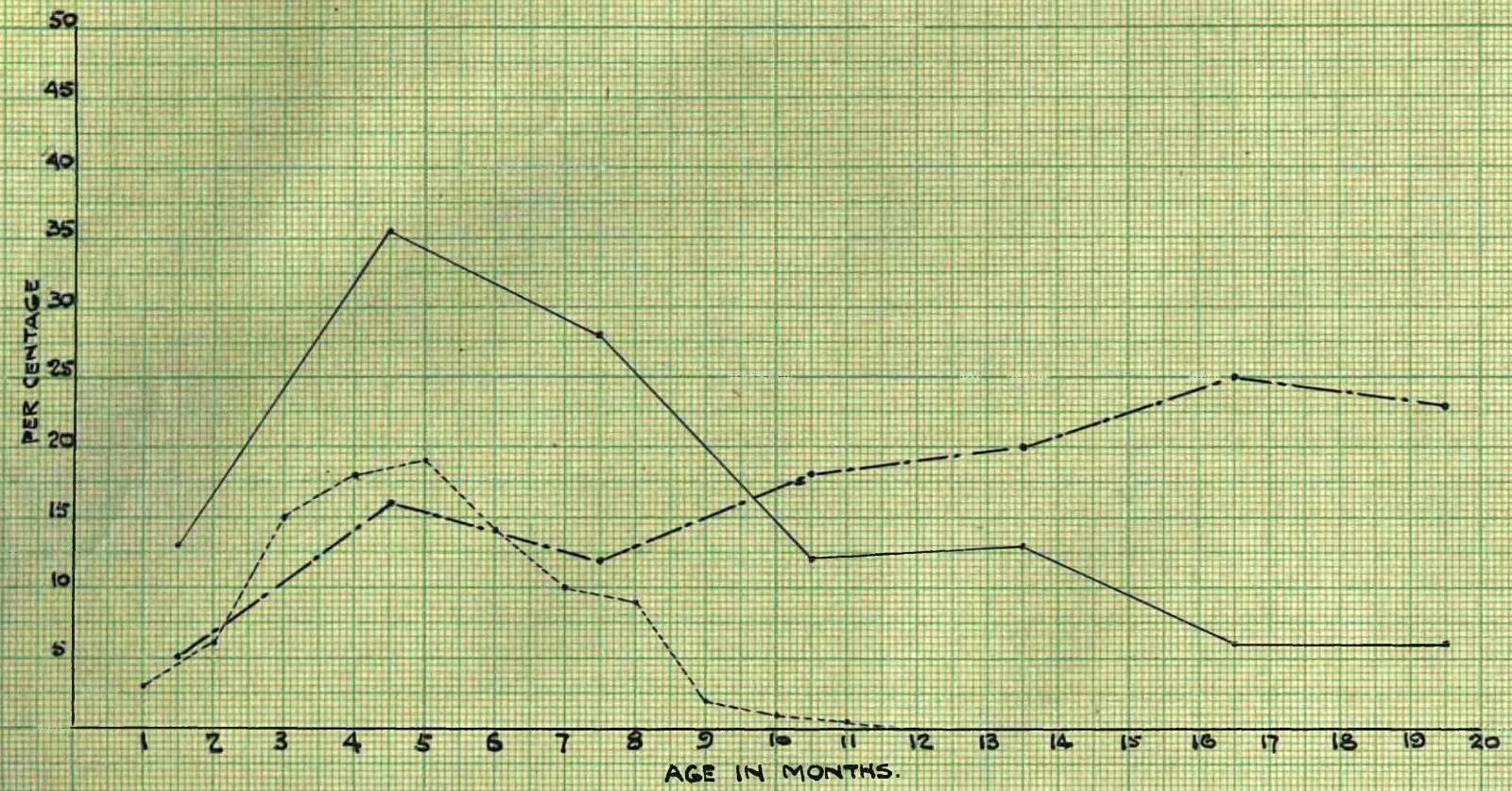
aetiological/

aetiological factor is discovered when the seasonal incidence is investigated. Toverud has shown that maternal mineral retention falls during the winter months, and as the greater part of the foetal calcium storage is laid down in the last two months of intra-uterine life, it would be expected that craniotabes would appear in infants born between November and March. The maximum incidence, however, occurred in those born between September and January. The other suggested explanation of the seasonal incidence was that craniotabes might tend to occur at an earlier age in infants born in the winter months. This, however, was not found to be the case.

None of the remaining aetiological factors investigated appear to be of significance in the development of craniotabes. Local pressure may determine the site of softening as unilateral craniotabes will develop where the child has been lying continually on the affected side.

The incidence of radiological and biochemical rickets in infants over 5 months of age with craniotabes was found to be over 60 per cent (Fig. V), this high incidence being due either to an increase in the susceptibility of infants in these age groups to develop rickets, or to the liability of infants with craniotabes to develop signs of Vitamin D deficiency. If the first suggestion is/

FIG IX. COMPARING THE AGE INCIDENCE OF CRANIOTABES WITH THAT OF MILD AND SEVERE RICKETS RECORDED BY PONK AND SOUTHER.



is considered, it is seen that the incidence is higher than that found by both Morris (122) and Graham (123) in Glasgow. The alternative explanation that infants with craniotabes are more liable to develop rickets appears therefore to be more probable and is supported by comparison of the subsequent development of infants with and without craniotabes. Rachitic changes occurred more frequently in infants who had craniotabes than in those with no skull softening.

It has not been possible to arrive at a conclusion concerning the precise aetiology of craniotabes, but its occurrence cannot be dismissed as being completely unrelated to rickets. The suggestion that it is due to some fault in calcium storage appears to be justified but whether this is of the same nature as the changes which precede the recognisable evidence of rickets is not known.

Eliot and Souther (124) have divided rickets into "mild" and "severe" rickets diagnosed clinically and radiologically. They found that these two types showed a different age incidence and in Fig. IX the age incidence of craniotabes is compared with these results. This incidence is seen to be similar to that of "mild rickets". Park and Souther (125) have suggested that as the curve

of/

of mild rickets rises at the age when maximum growth is occurring, these changes are due chiefly to this rapid growth and they have termed it "growth or physiological rickets". It is conceivable and indeed is suggested that true craniotabes falls into this category and should be regarded as a common manifestation of growth rickets.

CONCLUSIONS.

In a series of 972 infants under 1 year of age, skull softening was found in 43 per cent. Of the three types described true craniotabes occurred most frequently (26 per cent) and it is suggested that it should be regarded as a manifestation of growth or physiological rickets.

APPENDIX I.

Estimation of Serum Calcium:

Method: Clark, E.P., Collip, J.B. Modification of the Kramer-Tisdall Method; J. Biol. Chem., 1925, LXIII, 461.

Estimation of Plasma Phosphorus:

Method: Kuttner, T.T., and Cohen, H.R. J. Biol. Chem., 1927, LXXV, 517.

Estimation of Plasma Phosphatase:

Method: Jenner, H.D., and Kay, H.D. Brit. Jour. Exp. Path., 1932, XIII, 22.

APPENDIX II

Method of Conducting Metabolism Experiments.

Before commencing the experiment the child was examined in order to eliminate the possibility of his having any infection. The temperature was recorded four-hourly in order to make certain that there was no fever.

Four days before the metabolism period started the child was given the feed which would be received throughout the period. The amount given was based on the supposition that an infant over 66 per cent of his expected weight requires 100 calories per kilo of his expected weight per day.

The metabolism bed was constructed with two half mattresses lying transversely across the cot at a distance of 6 inches apart. The child was suspended in a hammock-like arrangement (Findlay et alii (115)), so that his buttocks lay exposed immediately over the space between the mattresses. The stools were collected in a rubber sheet in this space and urine was collected by means of a rubber tube attached to a Paul's tube which in turn was held by adhesive tape round his penis; the rubber tube led into a Winchester placed below the bed.

The metabolism experiments were carried out in seven day periods as it has been shown (Findlay et alii (115))/

(115)) that smaller periods give inaccurate results.

The child was weighed at the beginning and end of the experiment and his average daily gain in weight calculated from these figures.

Several experiments had to be abandoned for one of the following reasons:-

Loss of faeces.

Loss of urine.

Occurrence of diarrhoea.

Occurrence of fever.

Occurrence of vomiting.

Collection of Specimens:

1. Collection of milk specimens.

Each morning the calculated amount of milk required for the day plus an extra 30 cc. was placed in a flask and stirred well. 30 cc. were then removed and kept with a few drops of toluol. The 30 cc. daily amounts were collected together at the end of the experimental period and estimations were made on aliquot samples.

2. Collection and preparation of faeces.

As each stool was passed it was added to the previous stools which had been placed in a large evaporating basin on the hot plate. The total amount of faeces was dried to a constant weight. This weight (of the bowl plus/

plus faeces) was noted and the faeces transferred to a mortar. The bowl was washed, dried and weighed, the difference in these two weights being that of the total amount of faeces passed during the metabolism period.

The faeces were pulverised and ashed in a platinum capsule until the weight was constant. The ash was then washed into a beaker with sterile water and the capsule filled with dilute HCI and heated to remove the ash completely. This HCI was added to the beaker, together with 5 cc. conc. HCI and the total dissolved with heat. 5 cc. conc. HNO_3 were added, the solution boiled and allowed to cool. The fluid was then transferred to a measured flask, the volume made up to 500 cc. and the flask tightly stoppered.

100 cc. of this solution ≡ 1 g. dried faeces.

3. Collection and preparation of urine.

The total output for each day was collected in a Winchester containing a few ccs. of toluol. The Winchester was changed every 24 hours. The amount of urine passed in each completed 24 hour period was measured and the volume made up with sterile water to the nearest 500 cc. and stored in a bottle. Each daily output was made up to the same volume with water and an aliquot portion of each placed in a flask. Estimations were made on this specimen.

APPENDIX III.

Estimation of Calcium in Milk.

Method:

50 cc. milk were evaporated on the hot plate and when dry, ashed in a platinum crucible to constant weight. The ash was then washed into a beaker and the crucible cleansed with dilute HCl which was then added to the beaker. 10 cc. conc. HCl were added and the whole boiled.

The calcium was precipitated with Ammonium Oxalate - about 1 g. - and the beaker allowed to stand overnight. The precipitate was then collected by filtering through two layers of ash-free filter paper and ashed to a constant weight in a previously weighed platinum crucible. The amount of calcium in 50 ccs. of milk was thus determined.

Estimation of Phosphorus in Milk.

Method:

20 cc. milk plus 10 cc. conc. HNO_3 plus 20 cc. H_2SO_4 were heated in a Kjeldahl flask until fumes (N_2O) were given off. The flask was then allowed to cool until effervescence had finished. It was then reheated, metallic Cu. added when charring just commenced and heating continued for 6 to 8 hours.

The flask was allowed to cool and the contents washed into a beaker with water. The solution was made alkaline/

alkaline with NH_4OH and re-acidified with HCl. 30 cc. citrated magnesia solution were added and the solution cooled while being continuously stirred.

The precipitate was collected on 2 layers of ash-free filter paper and ashed to a constant weight in a previously weighed platinum crucible. The difference between the weight of the ash plus crucible and of the crucible gave the weight of the ash.

This weight x 0.0064 g. = amount of P_2O_5 in 20 cc. milk.

Estimation of Calcium in Faeces.

Method:

100 cc. of faecal solution were measured into a beaker. NH_4OH was added till a white precipitate appeared which was re-dissolved by the addition of Glacial Acetic Acid. The solution was then boiled and allowed to cool for 2 minutes when Ammonium Oxalate (2 g.) was added. The precipitate was collected next day by filtering through ash-free filter paper and ashed as in the milk calcium estimation.

Estimation of Phosphorus in Faeces.

Method:

100 cc. of faecal solution were measured into a beaker. Conc. NH_4OH was added till a white precipitate appeared which was re-dissolved by the addition of conc. HCl/

HCl. 30 cc. citrated magnesia solution were added and the phosphorus precipitated as in the milk phosphorus estimation.

Estimation of Calcium in Urine.

Method:

250 cc. of urine were boiled for five minutes with 1 g. Potassium persulphate and 10 cc. conc. HCl. After cooling, the solution was filtered and conc. NH_4OH added to the filtrate until a white precipitate appeared. Glacial Acetic Acid was then added and the estimation continued as with faecal calcium.

Estimation of Phosphorus in Urine.

Method:

50 cc. of urine were boiled for 45 minutes in a Kjeldahl flask with 10 cc. conc. HNO_3 and 10 cc. conc. H_2SO_4. The flask was then allowed to stand for 24 hours when the contents were washed into a beaker with water. Conc. NH_4OH was added to the solution until a dark yellow colour appeared, and the solution re-acidified with conc. HCl until the colour became light yellow. 30 cc. magnesia mixture was added and the estimation continued as with faecal phosphorus.

Citrated Magnesia Mixture.

400 g. citric acid was added to 500 cc. water

and/

and heated. 20 g. of MgO (light) were added to the hot solutions. After cooling, 400 cc. conc. NH_4OH were added and the solution then made up to 1500 cc.

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