THE ESTIMATION OF THE PHASE OF THE DISEASE IN RICKETS.

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In many diseases, particularly in those with a tendency to spontaneous cure, various therapeutic agents have been unjustifiably credited with possessing valuable curative properties. In perhaps no instance is this more striking than in the case of rickets, in which claims have been made for the efficacy of many different forms of treatment.

Much of the misunderstanding in the question in the case of rickets has arisen from the want of certainty in the examples tested whether the disease was in a progressive or a retrogressive stage. At the outset therefore of any investigation it is essential that we have standards by which this matter may be decided, and the present communication deals with this aspect of the problem, namely, the relative value of different methods of determining the phase of the disease.

It has frequently been the custom to decide whether an individual example of rickets were active or healing from an isolated radiological examination. We have not infrequently noted, however, that a case of rickets which has been judged from a single radiological examination to be active may, within 2 to 3 weeks, and that in spite of the conditions remaining the same, show unequivocal radiographic evidence of healing. Experience has taught us that it may also take this time after the inception of healing, or at least after the administration of efficient cod-liver oil, before definite signs of healing are visible radiologically. It has been our custom, therefore, in order to establish the activity of the disease, to require radiograms failing to reveal any evidence of healing taken at an interval of three weeks. But as this method involves the expenditure of a considerable amount of time, a pre-observation period of at least three weeks, it was hoped that a study of the behaviour of the inorganic phosphorus content of the blood serum, and the retentions and modes of excretion of calcium and phosphorus, might provide data on which to base a simple and time-saving, but still reliable, test of the stage of the disease.

The findings from this point of view are considered under two headings, namely, (1) that dealing with the inorganic phosphorus content of the serum, and (2) that dealing with the metabolism of calcium and phosphorus.

1. THE INORGANIC PHOSPHORUS CONTENT OF THE BLOOD SERUM.

Many observations have been made on the variations of the inorganic phosphorus content of the blood serum in rickets. Iverson and Lenstrup¹ in 1920 published the results of a study of the concentration of acid-soluble, acid-insoluble, and total phosphorus of the plasma and whole blood of normal

and rachitic infants. They found that in rickets the acid-soluble phosphorus was low. A year later Howland and Kramer² described a definite lowering of the inorganic phosphorus of the serum in active rickets. They based their diagnosis of the stage of the disease on clinical grounds supported by radiograms. In 16 non-rachitic children the inorganic phosphorus varied from 4 to 7.1 mgrm. per 100 c.cm. of serum. In 22 rachitic children it varied from 0.6 to 3.2 mgrm. per 100 c.cm. of serum. From a study of the calcium and inorganic phosphorus of the serum in children with uncomplicated rickets, and with rickets complicated by tetany, Howland and Kramer were led to believe that the determining factor in the calcification of the bones is the presence of calcium and phosphorus in such amounts that the product of their concentration in mgrm. per 100 c.cm. of serum equals a certain minimal figure, which ranges between 30 and 40. In rickets they found that the concentration of calcium in the majority of instances is essentially normal, whereas the phosphorus concentration is definitely low.

Hess and Unger³, however, state that a low inorganic phosphorus does not indicate whether the rachitic process is healing or advancing, since they have met with examples where radiological examination revealed healing although the inorganic phosphorus had increased but little from the previous low figure found during the active phase. These authors considered that the most valuable criterion of healing was the radiogram. A year later Hess, Calvin, Wang and Felcher⁴ concluded that consecutive blood examinations are of greater importance than radiographic evidence in the determination of the stage of rickets.

In the present investigation the behaviour of the inorganic phosphorus of the serum was studied in order to determine the relative value of (1) a single observation, and (2) a series of observations. The observations were controlled by X-ray findings. Tisdall's⁵ method was employed for the estimations of the inorganic phosphorus of the serum, and in most of the cases the calcium concentration of the serum was also determined, the method used being that of Kramer and Tisdall⁶.

Single observations were made in 27 cases which have been classified into 3 groups according to the radiological appearances:—

Group I includes 7 cases of rickets in which radiograms taken at weekly intervals over a period of 3 weeks showed no evidence of healing.

In Group II are included 8 cases in which the observations were made at the time when the first appearance of healing radiographically declared itself.

In Group III are 12 cases in which radiographic evidence of healing had been in progress for at least 2 weeks. In all of these cases the serum calcium was normal.

In Group I (active rickets) the inorganic phosphorus of the serum varied between 2.1 and 3.8 mgrm. per cent. with an average of 2.9 mgrm. In Group II (early healing) the serum phosphorus varied between 2.5 and 5.8 mgrm. per cent., the average value being 3.9, and in Group III (more advanced healing) the serum phosphorus was still definitely higher, varying between 3.8 and 6.5 mgrm. per cent., with an average of 5 mgrm. (Table I).

TABLE I.
SINGLE OBSERVATIONS ON SERUM PHOSPHORUS IN RICKETS.

Stage of disease.	No. of cases.	INORGANIC PHOSPHORUS OF SERUM.		
		Maximum value. mgrm. %	Minimum value. mgrm. %	Average value. mgrm. %
Active (Group I.)	7	3.8	2.1	2.9
Early healing (Group II.)	8	5.8	2.5	3.9
More advanced healing (Group III.)	12	6.5	3.8	5.0

Table II shows the products of the calcium and inorganic phosphorus contents of the serum in the three groups of cases.

In Group I this product varied between 22 and 36, the average being 28 ; in Group II it varied between 24 and 60, with an average of 38 ; and in Group III between 38 and 68, with an average of 52.

TABLE II.
PRODUCTS OF THE CALCIUM AND INORGANIC PHOSPHORUS CONTENTS OF THE SERUM IN RICKETS.

Stage of disease.	No. of cases.	PRODUCT OF CALCIUM AND PHOSPHORUS OF SERUM.		
		Maximum.	Minimum.	Average.
Active (Group I.)	7	36	22	28
Early healing (Group II.) ...	6	60	24	38
More advanced healing (Group III.)	11	68	38	52

In each of six cases of rickets a series of observations on the serum phosphorus was obtained during the active and healing phases. In one patient in this group healing commenced spontaneously, but in each of the other five healing was induced by one or other of the recognized forms of treatment. In the treated cases (Charts I and II) the general level of the serum phosphorus rose before radiological examination revealed healing. Subsequent, however, to the appearance of healing in the radiographic picture, the serum phosphorus showed a further and more marked increase. In the case of spontaneously healing rickets (Chart III), the inorganic phosphorus of the serum fell from 3.4 to 2.5 mgrm. per cent. over a period of two weeks, during which time progressive healing was apparent in the successive X-ray pictures.

CHART I.

INORGANIC PHOSPHORUS CONTENT OF SERUM IN THREE CASES OF RICKETS BEFORE AND DURING TREATMENT.

|| Commencement of Treatment.

× First appearance of Healing in Radiograms.

CHART II.

INORGANIC PHOSPHORUS CONTENT OF SERUM IN TWO CASES OF RICKETS BEFORE AND DURING TREATMENT.

|| Commencement of Treatment.

× First appearance of Healing in Radiograms.

CHART III.

INORGANIC PHOSPHORUS CONTENT OF SERUM IN CASE 3 WITH SPONTANEOUS HEALING.

First appearance of Healing in Radiograms.

Discussion.

(1) *Isolated observations.*—A study of the results of the isolated determinations of the serum phosphorus shows quite clearly that the average values in active, slightly healing, and more advanced healing rickets are in ascending order. It is, however, equally noteworthy that there is a very marked overlapping of the figures of these groups, the value 3.8 mgrm. per cent. being common to all three. One must therefore conclude that an isolated observation of the serum phosphorus cannot be taken as an unequivocal index of the stage of the disease.

(2) *Product of the calcium and phosphorus contents of the serum.*—It will be noted that in all the cases of active rickets the product of the calcium and inorganic phosphorus contents of the blood serum is below the upper limit of 40 described by Howland and Kramer for active rickets. That this limit, however, is of no practical value for determining the activity of the disease is shown by the fact that three (50 per cent.) of the cases of early healing and one (9 per cent.) of these presenting more advanced healing also showed products below this limit.

(3) *Serial observations.*—As can be seen from Charts I, II, and III the serum phosphorus rises as healing progresses in all cases except Case 3 (see Chart III). In this last patient early healing, as indicated by radiograms, is accompanied by a slight fall in the serum phosphorus value, but it should be

noted that this is the only case in which a series of observations was obtained during spontaneous healing and from it, therefore, far-reaching conclusions cannot be drawn.

In the other patients, in all of whom healing followed some definite course of treatment, the value for the serum phosphorus showed a considerable increase before the appearance of X-ray evidence of healing. This increase exceeded in three cases the maximum value obtained in admittedly active rickets, and in the other two cases reached the upper limit of the values obtained in the active group. The question arises as to the significance of this rise, and it might be suggested that it should be taken as evidence of healing occurring previous to the appearance of a positive X-ray finding. In support of this view is the fact that on the whole the rise in serum phosphorus, once commenced, is fairly steady. There are, however, occasional falls but the main tendency as shown in the graphs is upward. It would naturally be expected that such a rise would occur before increased calcification of the bones could be detected radiographically, and it is probable that a steady rise in the value for serum phosphorus is evidence of healing despite the absence of positive X-ray findings.

2. THE METABOLISM OF CALCIUM AND PHOSPHORUS.

That there is a diminution in the retention of lime in active rickets is well recognized. Schabad⁷ in 1911 found a very low calcium retention in early rickets, in fact in some instances more lime was excreted than was ingested. In cases of longer duration he found that the retention returns to normal, or is increased above the normal, before any clinical signs of recovery are apparent. With the lowering of the retention of lime there occurs a corresponding decrease in the retention of phosphoric acid due to an increased elimination of P_2O_5 in the fæces. Some years later Findlay, Paton and Sharpe⁸ in studies of the calcium metabolism in rickets found an increased excretion of lime during the active stage, but in no instance did they obtain a negative balance, *i.e.*, more excreted than ingested. These authors pointed out for the first time that the metabolic picture differs according to the activity or non-activity of the disease and not according to its duration. Five years later Telfer⁹, confirming their findings, drew attention to the difference in the mode of excretion of P_2O_5 in the active and healing phases. He showed that during the active period the greater part of the phosphorus is excreted in the fæces, and during the healing stage the urine contains the larger amount. Thus in active rickets the ratio $\frac{P_2O_5 \text{ in urine}}{P_2O_5 \text{ in fæces}}$ is less than unity, and during healing it is much greater than unity.

The metabolism studies forming the basis of the present communication were made in cases of active rickets, in cases of spontaneously healing rickets and in examples of rickets where healing had been induced by treatment. The three groups comprise in all five cases. Two observations were obtained in patients during the active stage of the disease, three observations during a spontaneously healing phase, and two observations during a period of healing induced by treatment.

The diet given was undiluted cow's milk and each child was kept on this diet for three days before the metabolic study was commenced. The urine and faeces were collected for seven days. The analyses of P_2O_5 in the milk, urine and faeces, and the analyses of lime in the urine, were made by the usual gravimetric methods. The CaO in the milk and faeces was precipitated as oxalate, the precipitate washed and titrated with $\frac{N}{10}$ $KMnO_4$.

The results are given in Table III.

TABLE III.
METABOLISM OF CALCIUM AND PHOSPHORUS IN ACTIVE RICKETS,
TREATED RICKETS, AND SPONTANEOUSLY HEALING RICKETS.

Case No.	X-ray findings before metabolism study.	X-ray findings after metabolism study.	Treatment.	CaO in urine. Percentage total output.	Ratio of P_2O_5 in urine to P_2O_5 in faeces	Daily retention per kgrm. body weight.	
						CaO grm.	P_2O_5 grm.
1. D.D.	active	active	nil.	0.3%	$\frac{1}{2.7}$	0.04	0.04
2. D.B.	active	active	nil.	0.4%	$\frac{1}{1.6}$	0.04	0.04
1. D.D.	active	healing	Irradiation	3.7%	$\frac{4.7}{1}$	0.25	0.22
2. D.B.	active	healing	Radiostol	2.6%	$\frac{4.4}{1}$	0.10	0.08
3. J.P.	active	slight healing	nil.	0.4%	$\frac{2}{1}$	0.07	0.07
4. H.W.	? healing	definite healing	nil.	0.8%	$\frac{1}{3.1}$	0.05	0.08
5. D.B.	healing	further healing	nil.	1.9%	$\frac{2.4}{1}$	0.13	0.13

The following is a brief description of the cases.

CASE 1. D. D., *æt.* $2\frac{1}{2}$ years, was kept under observation for three weeks during which period radiographic examination showed no evidence of healing. A metabolism study was then made. The daily retentions of CaO and P_2O_5 were each .04 grm. per kgrm. body weight, the urinary excretion of lime was 0.3 per cent. of the total output, and the ratio $\frac{P_2O_5 \text{ in urine}}{P_2O_5 \text{ in faeces}}$ was $\frac{1}{2.7}$. At the end of that period the patient was given daily exposures to radiations from a mercury vapour quartz lamp and during the second week of this treatment the daily retentions

of CaO and P_2O_5 were found to have increased respectively to 0.25 gm. and 0.22 gm. per kgrm. body weight. The output of lime in the urine increased to 3.7 per cent. of the total output and the ratio $\frac{\text{P}_2\text{O}_5 \text{ in urine}}{\text{P}_2\text{O}_5 \text{ in faeces}}$ became $\frac{4.7}{1}$. Healing was first noted radiographically at the end of this period, that is, the end of the second week on treatment.

CASE 2. D. B., æt. 6 months. For four weeks there was no evidence of healing in the radiograms. The daily retentions of CaO and P_2O_5 were each .04 gm. per kgrm. body weight. Radiostol, 3 minims three times daily, was then given. During the second week of treatment the daily retentions of CaO and P_2O_5 were increased respectively to 0.10 and 0.08 gm. per kgrm. body weight. The urinary output of lime increased from .4 per cent. to 2.6 per cent. of the total output and the ratio $\frac{\text{P}_2\text{O}_5 \text{ in urine}}{\text{P}_2\text{O}_5 \text{ in faeces}}$ which was $\frac{1}{1.6}$ during the first period, became $\frac{4.4}{1}$.

CASE 3. J. P., æt. $1\frac{1}{2}$ years. Weekly radiograms were taken for a period of three weeks before patient was admitted to hospital. There being no evidence of healing, the child was admitted to hospital and a metabolic study carried out which showed that the daily retentions of CaO and of P_2O_5 were each .07 gm. per kgrm. body weight. The urinary output of CaO was 0.4 per cent. of the total output and the ratio $\frac{\text{P}_2\text{O}_5 \text{ in urine}}{\text{P}_2\text{O}_5 \text{ in faeces}}$ was $\frac{2}{1}$. A radiogram at the end of this period showed definite healing.

CASE 4. H. W., æt. $1\frac{1}{2}$ years. Radiograms taken for four weeks before admission to hospital showed no evidence of healing. The patient was then admitted to hospital and at the end of two weeks' residence in the ward a suspicion of healing was noted in the radiographic picture. A metabolism study made at this time showed that the daily retentions of CaO and P_2O_5 were respectively .05 gm. and .08 gm. per kgrm. body weight. The urinary output of lime was 0.8 per cent. of the total output and the ratio $\frac{\text{P}_2\text{O}_5 \text{ in urine}}{\text{P}_2\text{O}_5 \text{ in faeces}}$ was $\frac{1}{3.1}$. A radiogram taken at the end of this period showed definite healing.

CASE 5. D. B., æt. $3\frac{1}{2}$ years. For three weeks before admission there was no radiographic evidence of healing. After one week in the ward slight healing was noted. During the second week in hospital a metabolic study was made. The daily retentions of CaO and P_2O_5 were each 0.13 gm. per kgrm. body weight. The output of CaO in the urine was 1.9 per cent. of the total output, the ratio $\frac{\text{P}_2\text{O}_5 \text{ in urine}}{\text{P}_2\text{O}_5 \text{ in faeces}}$ was $\frac{2.4}{1}$. Further healing was noted in the radiogram taken at the end of the study.

Discussion.

The normal daily retention of lime in young children varies from about 0.06 to 0.12 gm. per kgrm. body weight. By far the greater part of the lime excreted is eliminated in the faeces, only a very small percentage (1 to 2 per cent.) being found in the urine. The retention of P_2O_5 is approximately the same as that of lime. The mode of excretion, however, is different. About 40 per cent. of the total output of P_2O_5 is excreted by the kidneys and about 60 per cent. is found in the faeces (Telfer).

Of the cases recorded above it will be seen that in the two patients where the metabolism studies were made during the active stage of the disease the retentions of CaO and P_2O_5 were below normal, the urinary output of lime was also low and the greater proportion of the phosphorus was eliminated in the faeces. After seven days' treatment by irradiation or the administration of radiostol, there resulted a marked increase in the retentions of both CaO and P_2O_5 , the urinary output of lime was also increased and the larger proportion of phosphorus left *via* the kidneys.

Of the three examples of spontaneously healing rickets, Case 3, where the first radiographic evidence of healing was noted at the end of the metabolic study, had a low but normal retention of CaO and P_2O_5 , while Case 5, where the first radiographic evidence of healing was noted before the metabolic study commenced, had a retention of CaO and P_2O_5 exceeding the upper limit of normality. Only the latter case, which showed the most advanced healing, presented a normal percentage output of lime in the urine. In the other two cases the urinary output of lime resembled that met with during the active stage of the disease. It will thus be seen that the retention of lime increases from a low normal retention in the case of earliest healing to a retention slightly above normal in the case of more advanced healing. It would appear probable from these results that in spontaneous healing a slight increase occurs in the retentions of CaO and P_2O_5 before radiological evidence of healing and that with the advance of healing noted in the radiographic picture a further gradual increase occurs.

It is interesting to contrast the results obtained in spontaneously healing rickets with those obtained in the treated cases. In the treated cases, there occurred a marked increase in the retentions of CaO and P_2O_5 during the week preceding the first radiographic appearance of healing. The increase in the urinary output of lime was more marked in the treated cases as was also the change in the mode of excretion of P_2O_5 . This early marked change in the mineral metabolism in treated cases is comparable to the increase noted in the serum phosphorus in treated rickets before X-ray evidence of healing, and is probably to be attributed to the greater rapidity with which healing takes place when efficient treatment is given.

CONCLUSIONS.

The following conclusions seem to be justified in view of the results of the above described experiments carried out in cases of rickets to determine the relative value of various methods in arriving at a decision as to the stage of the disease.

1. Isolated observations on the inorganic phosphorus content of the blood serum are of no practical value because figures obtained from such observations in early healing often fall within the limits of those of the active stage. The same objection applies to the use of the figure representing the product of the phosphorus and calcium contents (mgrm. per 100 c.cm.).
2. Serial observations on the serum phosphorus over a period of two to three weeks are of assistance only when the disease is healing rapidly, as, for example, when active treatment is being employed.
3. A determination of the calcium balance is the most reliable means of arriving at a decision. The objection to this method is the time and labour involved, as after the metabolic study which extends over seven days is finished, a further week or ten days is required before the necessary analyses can be completed.

4. Radiograms taken over a period of three weeks are on the whole a fairly reliable means of determining the phase of the disorder, and they involve much less trouble, though they may fail to show such an early stage of healing as can be demonstrated by the calcium balance estimations.

5. Whichever method is used, a period of about three weeks is necessary to arrive at a satisfactory decision. Also it is to be remembered that if the three weeks' observations are made while the case is an out-patient, the results of these observations may indicate an active stage, and yet because of change in environment healing may be evident very shortly after the patient is admitted to hospital for investigation of the value of treatment. This happened in three of the cases recorded above. It is therefore essential that the observations be made while the patient is in the ward where all conditions can be controlled.

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