THE BONE CHANGES OCCURRING IN RENAL AND COELIAC INFANTILISM, AND THEIR RELATIONSHIP TO RICKETS

PART I. RENAL RICKETS.

BY

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The occurrence of bone deformities associated with the presence of albumin in the urine was first observed by R. C. Lucas ⁽¹⁾ who in the year 1883 published a paper entitled "A Form of Late Rickets associated with Albuminuria." A perusal of this paper, however, shows that the cases described were not examples of renal infantilism. The interest of British paediatricians in renal infantilism was first aroused by Morley Fletcher ⁽²⁾ who in the year 1911 showed before the Children's Section of the Royal Society of Medicine, a typical example of this condition occurring in a child who had developed genu valgum when five years of age. In a paper written by Miller and myself ⁽³⁾ in 1912 the occurrence of genu valgum in several of the cases was commented on. Naish ⁽⁴⁾ writing upon this subject in the same year said: "The presence of rickets usually of late origin in as many as five out of the eight cases is a striking phenomenon," but the credit for emphasising the importance and striking character of the bone changes is clearly due to Barber ⁽⁵⁾ who has published a series of papers on renal dwarfism, and to whose description of the bone changes there is, from a purely clinical standpoint, little to add. Barber regards the bone changes as typical of late rickets, but has not attempted any explanation of the reason why this should occur. Paterson ⁽⁶⁾ writing in 1920 discusses whether the bone changes should be regarded as those of rickets or not, and infers that in his view the condition is not rickets, but "would suggest that these bony changes are nutritional in origin." Shipley, Park, McCollum and Simmonds ⁽⁷⁾ recording their observations on one case, suggest that the condition may be a true renal rickets, whereas Lathrop ⁽⁸⁾ from the same medical school, in a paper recently published, states that although the clinical appearances are difficult to differentiate from rickets, the radiogram shows nothing suggestive of that disease, and the blood calcium and phosphorus are distinctly outside the rachitic zone.

I have recently had the opportunity of investigating somewhat fully the clinical characteristics, and the chemical and radiographic findings of five hitherto unpublished cases of renal infantilism with bone changes. These cases form the basis of the present communication in which an attempt is made to classify the bone changes and to explain their pathogenesis.

CLINICAL DESCRIPTION.

The clinical characteristics of renal infantilism, or dwarfism, are now so well known that, in a paper which concerns itself chiefly with the bone deformities, a lengthy description of the disease is not called for. It may, however, be advantageous to recall the salient points in its symptomatology. The children are always stunted in growth and there is a delay in the appearance of secondary sex characteristics. Apart from the retardation of development the most characteristic symptoms are polydipsia and polyuria, often of extreme degree and associated with nocturnal incontinence. The facies is frequently a typical one, being sallow in colour and characteristically wrinkled. The urine has a low specific gravity and usually contains a faint haze of albumin. Cardiovascular changes may be, but usually are not, present. The age at the onset of the symptoms varies. In quite a considerable proportion the symptoms appear to have been present from birth, whereas in others the child was apparently normal for the first few years of life. The disease is a fatal one, death occurring from uræmia, usually in the second decade of life.

The autopsy findings have in the great majority of cases shown very small kidneys the result of severe chronic interstitial nephritis, but cases are on record associated with pyelitis and apparently an ascending infection of the urinary tract, congenital cystic kidneys and bilateral renal calculi. The end result is, however, identical in all cases, *i.e.*, an almost complete destruction of the renal parenchyma.

Those cases in which bone deformities occur are now usually designated "renal rickets." Genu valgum, which may develop very rapidly, is the commonest manifestation of renal as of coeliac rickets. Enlargement of the epiphyses of the wrists and ankles may occur with or without genu valgum. In some instances bowing of the legs occurs, instead of genu valgum, and in others again the picture is that of severe rickets with well marked rosary, Harrison's sulcus, pigeon chest, enlargement of epiphyses, genu valgum, etc.

The most striking deformities that I have seen are those present in H.T., of whom a photograph is shown (Fig. 1). This boy is seventeen years of age, has a very marked rosary, a deformed chest, enlargement of the epiphyses, and extraordinary bending of the femora, tibiæ and fibulæ. In some cases there does not appear to be any bending of the shafts of the long bones, but the epiphyses are enlarged, and there is obvious bending or displacement of the enlarged epiphyseal end of the bone, the explanation of which will appear later on in this paper.

The ages of the children at the onset of the bone changes varies considerably. Barber states that the usual time for genu valgum to develop is between eleven and fourteen years of age. The earliest age at which I have seen bone changes is sixteen months. Paterson has described a case at twenty-one months, and also one in which, according to the parents' history, the deformities were present at birth⁽⁹⁾. On the other hand there are cases on record in which the bone deformities have not been recognised until the age of seventeen years. In my cases the onset has been earlier, all having occurred before the age of ten years, the usual time of onset being from five to seven years.

Fig. 1.—Photograph of H.T., aged 16 years, showing the severe nature of the deformities which may occur in renal rickets.

Fig 2.—Radiogram (H.L.) showing atrophic type of renal rickets. Note the thin cortex, well marked rickets at the epiphyseal line, fracture of the shaft of the ulna, and general fragile atrophic and osteoporotic character of the bones

Fig. 3.—Radiogram from the same case as Fig. 2, taken five and a half years later. The bone is still somewhat fragile and atrophic but the rickets has completely healed. Transverse striations are well seen at the lower end of the radius.

RADIOGRAPHIC MANIFESTATIONS.

A study of radiograms of renal rickets shows that the bone changes fall into three well defined groups, which I propose to call :—

1. The atrophic type.
2. The florid type.
3. The woolly, stippled, or honeycomb type.

1. *The Atrophic Type.*

In this group the radiogram (Fig. 2) presents a picture strikingly similar to that seen in coeliac rickets of a moderate degree. The whole bone presents a fragile, atrophic, osteoporotic appearance. Near the epiphyseal end of the diaphysis there may be seen one or two straight lines of cancellous tissue, running parallel to the epiphyseal line. The cortex is also thin and atrophic. A fracture, or fractures of the shaft may be present, but these are not so commonly seen as in coeliac disease, and finally there is well marked rickets at the epiphyseal line.

2. *The Florid Type.*

The appearances in this group are those characteristic of florid rickets. The shaft may perhaps be a little more fragile than that of a normal child of the same development, but not sufficiently so to call for comment, whilst the changes so characteristic of the atrophic type are absent. (Figs. 4, 5, 6, 9, 10.)

Fig. 4.—Radiogram of N.H., taken Jan. 30th, 1926, showing florid type of renal rickets.

3. *The Woolly, Stippled, or Honeycomb Type.*

This is the most extraordinary manifestation of renal rickets. It is quite unlike the picture usually associated with rickets, and yet is so characteristic that a radiographer who has had experience of these cases can make the diagnosis of renal rickets from the radiogram. (Figs. 11, 12, 14, 15.) In this type the

Figs. 5, 6, 7—Radiograms of N.H., taken on the following dates:—23/3/26, 11/5/26, 23/6/26, showing stages in the complete cure of rickets.

Fig. 8. Radiogram of N.H., taken on 30/8/26, showing stage in the complete cure of rickets.

epiphyseal end of the shaft of the bone is swollen, forming a large metaphysis. This portion of the bone presents a curious appearance which sometimes suggests a honeycomb, at other times shows marked stippling, whilst at others it has a woolly appearance, the bone looking moth-eaten as if the shaft were being eaten away subperiostally and giving at first sight the suggestion of osteomyelitis or syphilitic disease. The metaphysis extends over a much greater area than in ordinary rickets. Associated with these appearances is a degree of osteoporosis throughout the shaft of the bone, but the cortex does not appear thin as in the atrophic type. The condition of the shaft in the atrophic type is one which suggests that the bone has never been anything else but atrophic, whereas in the woolly type it is conceivable that osteoporosis has occurred in a bone which at some previous time might have approached the normal.

The bones of the vault of the skull sometimes show changes and in the case of H.T., these are most marked. (Fig. 16). These bones are greatly thickened and show extreme stippling presenting an appearance in the radiogram quite unlike anything with which I am acquainted with the exception of Paget's disease. Indeed my colleague, Dr. Teall reported on this case as follows :— " the bone change in the skull is, from the radiographic point of view, identical with that of Paget's disease."

The changes do not occur to the same degree in all the long bones, e.g., the radius and ulna of one arm may show changes much more marked than those of the other side. Thus the metaphysis on one side may be larger and show more stippling, whereas on the other, it may show a more eroded appearance and not so much enlargement. (Fig. 14).

I have recently had the opportunity of examining the bone changes in a case (B.T.) the antemortem radiograms (Fig. 11) of which showed the woolly type of bone deformity. Such an examination together with radiograms of the bones taken after death (Fig. 12) showed that the woolliness or stippling was due to irregular calcification and the presence of islets of cartilage deep down in the metaphysis. The proliferative cartilage was much more irregular and broken up than in ordinary rickets. The metaphysis was deeper, and although it showed broadening or splaying out, the degree of broadening was not so great as in uncomplicated rickets. As a result of the presence of these islets of cartilage deep in the metaphysis (Fig. 13), the whole metaphysis was bent on the diaphysis and this, together with bending of the shaft as a result of osteoporosis in the neighbourhood of the wrists and ankles, resulted in a deformity at these points which gave the epiphysis an appearance of being larger than it was in reality.

In the course of a paper based on three cases which conform to my woolly type, Paterson (6) describes the occurrence of fractures on the diaphyseal side of the epiphyseal line, and suggests that the "stippled" appearance is due to the throwing out of callus in an attempt to repair such fractures. Whilst the occurrence of fractures in this situation is obviously possible owing to the softness of the tissue, yet up to the present time I have not observed them in any of my cases and the stippling is due, as already explained, to the irregularity of calcification in the metaphysis. In a description of a case of renal infantilism with bone changes of the woolly type, Shipley (7) pointed out that the changes in the bones revealed by X-ray and histology were most extensive and differed from the changes ordinarily found in rickets. "The proliferative cartilage was most irregular and the calcification defective. In the deep metaphysis were large islands of cartilage bordered on one or more sides by dense calcium deposits. These islands of cartilage gave to the metaphysis as seen in the Röntgenogram a honeycomb appearance. The trabeculae were thin, and the osteoid borders comparatively speaking narrow. Surrounding the trabeculae and islands of cartilage, and lying between them, was a loose fibrous tissue. Obviously for a long time the pathological condition in the bone had been in a state of flux between healing and relapse." They have suggested the possibility that this condition may have "its origin in the extreme functional disability of the kidney properly to excrete phosphate," and that if this suggestion "should prove to be correct a true renal rickets exists, and rickets under certain conditions, may have an endogenous origin." I believe this suggestion to be correct. As evidence against the rachitic origin of the bone deformity Paterson mentions the absence of bowing of the bones in one of his cases, a child aged twenty months, but as I have already pointed out, extreme bending of the bones does occur in the woolly type. He also thinks that the histological changes in the bone are not those of rickets, but his description of these changes is almost identical with that I have quoted from the paper by Shipley and his co-workers. These investigators, whose experience of experimental rickets is unrivalled, accept the view that the changes are rachitic in nature and that they "may belong to the low calcium form of the disease."

Fig. 9.—Radiogram (L.M.) showing florid type of renal rickets.

Sections of the bone in the case (B.T.) to which I have just referred shows a condition similar to that described by Paterson and by Shipley. I have referred these sections to Professor Haswell Wilson, Professor of Pathology in the University of Birmingham, who considers that although the changes present differ from those ordinarily seen in rickets, yet they are definitely rachitic in nature.

Discussion. There appears no explanation why one case should show florid rickets, another atrophic, and yet another the woolly type, though the last is, I think, the most serious form of the disease. Again, although there seems no reason why the florid should not change into the atrophic type, yet in my experience all three types always breed true, and there is never any changing from one type to another, nor does one long bone show one type of change, and another bone in the same child a change of the other types. The cases reported by Barber appear to have been instances of florid rickets, and he does not seem to be familiar with the atrophic or woolly types.

From a study of my cases two striking, if apparently contradictory results, have emerged. First, that unlike the results obtained in coeliac

rickets, ultra-violet irradiation does not produce a cure of renal rickets; indeed I have obtained considerable evidence showing that it makes the condition worse.

Secondly, that the atrophic and florid types of renal rickets may show complete recovery. Recovery in the atrophic type results in the production of a bone, whose radiogram resembles that seen in mild coeliac disease before the production of rickets, *i.e.*, a somewhat fragile and osteoporotic bone with a thin cortex, showing one or more transverse lines, in the neighbourhood of, and running parallel to the epiphyseal line, the latter being perfectly sharp and straight. The reproduced radiograms of H.L. (Figs. 2 and 3) show the atrophic type of renal rickets, before and after cure, the first radiogram being taken four years ago when he was twelve years of age the second recently. He is now sixteen years of age and his condition is astonishingly good. Recovery in the florid type is well shown in the series of radiograms of N.H., a girl aged ten years. (Figs. 4, 5, 6, 7, 8.) I have not seen any case in which ossification is complete, since none of my cases have lived beyond seventeen years, but in Barber's last paper there are radiograms of a girl aged twenty who had been the subject of florid rickets, but in whom the epiphyses have joined up so that ossification is complete, and as far as can be judged from the reproduction of the radiograms the bone is normal. From the quotation given above from Shipley's paper, it is obvious that even in the woolly type, attempts at healing take place from time to time.

BLOOD CHEMISTRY IN RENAL RICKETS.

In many instances the serum shows an extreme degree of lipæmia, in one case an estimation showed that the serum contained almost nineteen per cent. of fat. In all cases there is a very high degree of nitrogen retention (azotæmia). The actual figures obtained are set out in tabular form (Table 1), but here it may be stated that in a series of twenty-three estimations on five cases the blood-urea values have varied from 113 mg. to 720 mg. per cent, the latter of course occurring shortly before death. Non-protein nitrogen and creatinin have also been very high. In chronic interstitial or azotæmic nephritis in adults the blood phosphorus is greatly increased, and roughly follows the curve of the blood urea, and this is found to be the case in renal rickets. The values

Fig. 10.—Radiogram taken *post-mortem* of costochondral junction of rib of L.M., showing the typical appearance of florid rickets.

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TABLE I.

Case.	Date.	Urea.	Non-Protein Nitrogen.	Creatinin.	Chlorides.	Calcium.	Inorganic Phosphorus.	Comments.
N.H. ♀ aged 10 years.	26/2/26	117						Florid rickets.
	8/4/26	180				10.0	13.9	
	16/4/26	138.3				11.7	6.0	
	19/5/26	150				9.0	6.1	Rickets healing.
	29/6/26	137	78.0	1.5	485	11.1	5.5	„ „
	15/9/26	226.5	115.4	1.3	548	10.3	6.5	Rickets healed, recently recovered from an attack of vomiting (? uræmia).
	1/11/26	178.6				10.09	5.58	
	17/11/26	111.5	79.0	1.63	574	9.12	5.23	
A.N. ♂ aged 16 months.	13/4/26					8.6	7.3	Woolly type rickets. Serum contained 18.97 % of fat.
	17/4/26						9.0	
	23/6/26	109.2	54.1	1.27	554			
	1/7/26	117.4	55	1.5	594	7.7	7.1	
	25/9/26	191.6	96.8	1.7	601	9.5	9.5	
	28/10/26	173.3	85.7	1.5		9.0	6.1	
	23/11/26	208.3	115.2	1.4	643	9.3	7.58	
B.T. ♂ aged 10 years.	14/5/26	339				8.2	14.3	Woolly type rickets. Uræmia.
	19/5/26	407.5			706.9	7.3	10.6	Blood taken a few hours before death.
	27/5/26	720.0	370	7.73	545	7.3	13.7	
H.T. ♂ aged 16 years.	21/9/26	136.5	110	2.0	561	12.7	8.5	Woolly type of rickets. Previously treated by ultra violet light, fall in phosphorus on cessation of this treatment.
	11/9/26	135	105	1.9	561	10.0	4.7	
	26/9/26	113.6	59.4	1.4		10.4	4.1	
	19/10/26	112.9	93.8	1.4		14.6	6.35	pH 7.16, p product of
	10/1/27	134.7				13.0	10.07	$[Ca^{++}]^3 \times [PO_4^{--}]^2$ is 23.40.
	14/1/27	134.7		1.85	597	12.7		
L.M. ♂ aged 16 years.	30/11/26	673.8		5.9	425.7	3.95	16.3	Florid rickets uræmia—death 2/12/26.

This table gives the details of blood chemistry findings, the values are all expressed as milligrammes per cent.

for serum phosphorus (normal, 5 mg. per cent.) have varied between 4.1 mg. and 16.13 mg. per cent., whereas those for serum calcium (normal, 9-10 mg. per cent.) have varied from 3.95 mg. to 14.6 mg. per cent. The blood calcium of 3.95 mg. per cent. occurred shortly before death, and is by far the lowest figure obtained, the next lowest figure being 7.3 mg. per cent. I would, however, emphasise the fact that in only six out of twenty-one estimations was the calcium under 9.0 mg. per cent., but that in every patient the calcium was low, when compared with the amount of blood phosphorus.

Further evidence in favour of the view that in renal rickets the serum calcium functions as low calcium, although the actual figures may be normal or even higher than normal, is found in the fact that some of these cases are complicated by tetany. Tetany does not occur with such frequency as in coeliac rickets, but nevertheless it is a well recognised complication of renal rickets.

Now the combination of tetany with rickets is always associated with a low serum calcium, and the onset of tetany is dependent not only on the total amount of calcium but also on the amount of calcium ions. The work of Loeb, Matthews and others ⁽¹⁰⁾ shows that the excitability of the neuro-muscular mechanism varies directly with the ratio $\frac{\text{Na} + \text{K}}{\text{Ca} + \text{Mg}}$ and that increased irritability can theoretically occur, either from a decrease in calcium, or an increase in sodium ions. In infantile tetany the increased irritability is due to a decrease in calcium ions for the magnesium, sodium, and potassium in the serum are essentially normal (Kramer, Howland, and Tisdall ⁽¹¹⁾).

The problem of the occurrence of tetany in renal rickets is, however, even more complicated because the following additional data have to be considered. The injection of phosphates into animals and children has been found to raise the blood phosphorus, lower the blood calcium, and in some cases produce tetany. Binger ⁽¹²⁾ found that the injection of normal or alkaline phosphates into dogs produced all these results, but acid phosphates on the other hand, whilst lowering blood calcium and raising blood phosphorus, did not produce tetany. Klercker and Odin ⁽¹³⁾ administered acid and normal phosphates to children, with resulting lowering of calcium increase of phosphorus, and an increase of electrical excitability. In those cases in which latent tetany was present the administration of these salts produced acute tetany. In chronic azotæmic nephritis there is a retention of phosphorus with the production of a high blood phosphorus, but the blood calcium is low. Thus in a recent investigation, Boyd, Courtney, and MacLachlan ⁽¹⁴⁾ have found consistently low calcium values in such cases, and De Wesselow ⁽¹⁵⁾ has shown that the higher the retention of phosphorus in nephritis, the lower is the calcium in the serum. Although this inverse relationship does not hold in renal rickets, yet it seems very clear that the mere presence of a high blood phosphorus means a low calcium, and the consequent production of tetany unless some mechanism is brought into play to prevent its occurrence.

Fig. 11.—Radiogram (B.T.) illustrating woolly type of renal rickets. Note the large extent of the metaphysis, the stippling, and the appearance of subperiosteal erosion; the general osteoporosis but without the atrophic character of the bone in Fig. 2.

Fig. 12.—Radiogram of the same bones taken *post-mortem* showing some bending of the lower epiphyses of the radius and ulna on the shafts of these bones, and the irregular manner in which calcification is proceeding.

In dealing with the problems presented by renal rickets it is therefore necessary to find answers to the following questions :—

- (1) Why is the serum calcium so frequently normal in renal rickets, although the phosphorus is high; whereas in azotæmic nephritis without rickets, and in animals and children after the injection of phosphates, the serum calcium is low?
- (2) If the rickets is a low-calcium rickets, why does not tetany occur with greater frequency?

- (3) Why does tetany occur in this form of nephritis and not in other form of chronic nephritis ?
- (4) What is the evidence that the bone deformities are of rachitic origin and why does cure sometimes occur ?

We have seen that, contrary to what usually obtains in azotæmic nephritis and after the injections of phosphates, in renal rickets with high phosphorus the serum calcium may be normal or even higher than normal. It seems conceivable that the serum calcium is maintained at this level to prevent the occurrence of tetany, which is such a very serious complication, and to which the young and growing child is much more prone than the adult. Now the rise in serum calcium produced by the injection of parathyroid hormone in tetany parathyropriva and in normal animals is due to washing out of calcium from the bones (Greenwald and Gross ⁽¹⁶⁾). It is therefore not improbable that in renal rickets there is a washing out of calcium from the bones with resulting osteoporosis and rickets and the maintenance of the blood calcium at such a level that tetany shall not occur.

Fig. 13.—Drawing of the antero-posterior section of the lower end of the radius, seen in the two preceding radiograms (Figs. 11 & 12) showing the depth of the rachitic metaphysis, the presence of islets of cartilage deep in the metaphysis, and the bending of metaphysis and epiphysis on the shaft of the radius.

Recent work by Ross and Scriver ⁽¹⁷⁾ has demonstrated the possibility of such mobilisation of calcium from the bones. These workers have shown that in cases of infantile tetany, ammonium chloride, by virtue of its acid producing effect, causes a mobilisation of calcium from the tissues and presumably from the bones. According to Kramer ⁽¹⁸⁾ their results furnish an explanation of the fact that ammonium chloride, whilst capable of restoring calcium to its normal value in those cases of rickets in animals and children in which the calcium is low and phosphorus normal, is yet, contrary to expectation, not capable of producing healing of the rachitic process. The observations, indeed, show that such treatment would aggravate rather than ameliorate the condition.

De Wesselow and others have shown that in severe nephritis, there is usually a diminution in the bicarbonate content of the plasma and an acidosis and that these favour the ionisation of "the diminished amount of calcium present" ⁽¹⁵⁾, and so probably prevent the more frequent occurrence of tetany. The observations of Ross and Scriver show that the occurrence of an acidosis will also mobilise calcium ions from the calcium reservoirs, and estimations of the hydrogen-ion concentration show that a definite acidosis is present in renal rickets.

Considerable evidence has recently been forthcoming to show that the total content of calcium in the blood is not an index of the calcium ions in the circulatory fluids. There is no method by which the actual calcium-ion concentration of serum or plasma can be measured, but Pincus, Peterson and Kramer ⁽²⁰⁾ have attempted to obtain some index of the ion concentration by using the method of ultrafiltration through collodion sacs under moderate pressure. Assuming that the calcium which does not filter is bound to protein and practically un-ionised, and that all the calcium that does filter is ionised, then the concentration of calcium in the filtrate is a measure of ionised calcium. They refer to the former as "bound" and the latter as "free" calcium.

An objection has been urged against the method of ultrafiltration under moderate pressure, that removal of the calcium ions by such means leads to the ionisation of the previously un-ionised calcium phosphate held in solution in the plasma, but this obviously does not invalidate the assumption of these workers that the calcium which does not filter is bound to protein. They found that in tetany there is a marked decrease in the "free" calcium in the serum, and that in chronic nephritis uncomplicated by uræmic convulsions the total calcium was decreased but the free calcium was normal, but that in one case with convulsions "free" calcium was reduced.

If the view of Pincus be correct, it is obvious that the reason tetany occurs in the nephritis of renal rickets and not in chronic nephritis is due to diminution, either relative or absolute, in the "free" as well as in the "bound" calcium. In this connection, however, it should be borne in mind that a degree of azotæmia comparable with that occurring in renal rickets, while not infrequent in adults, is of extreme rarity in childhood apart from renal rickets, and that the child is more liable to show tetany than the adult. I have not had the opportunity of estimating the calcium in the case of renal rickets with tetany and have

therefore not been able to test the correctness of this deduction, but in a case unaccompanied by tetany Lathrop ⁽⁸⁾ found that the "free" calcium was normal, although the total calcium in the serum was very low.

Fig. 14.—Radiogram of H.T. taken 30/10/25, showing the woolly type of renal rickets. Note the variations in the picture in the different bones. The metaphysis of the right ulna shows marked "honeycombing" and "stippling" whereas that of the left ulna shows erosion and woolliness.

WHAT IS THE EVIDENCE THAT THE BONE DEFORMITIES ARE TRUE RICKETS ?

The evidence, so far presented, that the condition is a truly rachitic one in the atrophic and florid types is based mainly on the results of X-ray examinations of the bones which show appearances at the epiphyseal line indistinguishable from those of rickets. The metaphysis is on the whole somewhat deeper than

Fig. 15.—Radiogram taken from the same case after nine months treatment with ultra violet light. The bone disease shows definite advance and the right radius shows more bending than in Fig. 14,

in ordinary low-phosphorus rickets, but the rachitic nature of the change would be admitted by anyone conversant with the X-ray findings in rickets. Histological evidence proving that the florid type of deformity is rachitic in nature has also been obtained in one of my cases (L.M.) This boy who showed marked infantilism, genu valgum, enlargement of the epiphyses at the wrists, a definite rosary, and rickets of the florid type in the radiogram, developed a fatal attack of uræmia shortly after admission to hospital. (Figs. 9 and 10). The autopsy was performed by Professor Haswell Wilson who reported on the histological examination of the bones as follows :—"Sections were prepared from a costochondral junction, and from the lower epiphyses of the right radius. The changes seen in these two situations are essentially of the same nature. The line of ossification is broad and irregular and very little calcification is present in the matrix of the cartilage. The columns of cartilage cells are distorted and broken up by irregular masses of vascular osteoid tissue. Much fibrous tissue is seen between the trabeculæ of osteoid tissue and of the spongy bone beyond it, and in this a few detached islands of cartilage are lying. The histological picture is indistinguishable from that of ordinary rickets."

With regard to the woolly type, the histological evidence already detailed and the radiograms show that the similarity between this type and experimental low-calcium rickets cannot be doubted. The results of blood chemistry also show that in all types when bone deformities are present, the calcium can be regarded as functioning as a low blood calcium.

There are two chief theories on the mechanism of the deposition of calcium phosphate as bone ; that of Howland and that of Robison, the former being perhaps the more usually held. According to Howland, the rachitic bone tissue remains uncalcified just so long as calcium and phosphorus are supplied to it in such low concentrations that precipitation of tertiary (or normal) calcium phosphate cannot take place. The whole process can indeed be predicted with mathematical accuracy. Normally the serum and circulatory fluids are saturated solutions in which the calcium phosphate of bone is in equilibrium with the dissolved salt, and this in turn with calcium and phosphate ions, and this may be represented as follows :—

An increase of Ca^{++} or PO_4^{--} causes the reaction to proceed to the right and results in deposit of bone, whereas a decrease in concentration would result in some of the solid calcium phosphate in bone going into solution, the reaction proceeding to the left. Now according to mass action law, at equilibrium the product of the concentration on one side divided by the product of concentration on the other side is constant at constant temperatures and therefore we have :—

$$[\text{Ca}^{++}]^3 \times [\text{PO}_4^{--}]^2 = K [\text{Ca}_3(\text{PO}_4)_2].$$

Tertiary calcium phosphate is a sparingly soluble salt and in such $[\text{Ca}^{++}]^3 \times [\text{PO}_4^{--}]^2 = K$. This K is called the solubility-product constant and whenever the product of the concentration of calcium and phosphate

ions becomes greater than the solubility product solid calcium phosphate will be deposited.

The occurrence of carbonic dioxide in considerable concentrations in the serum has, however, an influence on tertiary calcium phosphate which may be expressed thus :—

If the CO_2 tension of this solution is reduced, the reaction proceeds to the left and calcium phosphate is deposited. Howland suggests that because cartilage and the trabeculae of bone are inactive tissues, it is to be expected that the CO_2 tension would be low in them, and it is in them that precipitation occurs if the solubility product be exceeded. The truth of the foregoing general principles can, he states, be proved by clinical observations, using as factors for a rough product the total concentrations of calcium and phosphorus in serum, each being expressed in milligrams per 100 c.c. This product in the normal child is between fifty and sixty. "When the product is below thirty rickets is invariably present. When it is above forty either demonstrable healing is taking place, or there has never been any rickets. With products between thirty and forty rickets is usually present ⁽²¹⁾."

Robison on the other hand, does not agree that the deposition of calcium phosphate is purely a physico-chemical process, such as is outlined above. His hypothesis may briefly be summarised as follows (Kay ⁽²²⁾): "the osteoblasts and the hypertrophic cartilage cells of the young animal secrete a very active phosphatase which, by hydrolysing the phosphoric esters of the blood, brings about a local increase of PO_4^{--} concentration. The solubility product of tertiary calcium phosphate is thereby exceeded and the deposition of this salt occurs in the ossifying zone."

It is of interest to note that Howland ⁽²³⁾ in his last paper on this subject, written in collaboration with Shipley and Kramer, published shortly before his death, appeared to regard the physico-chemical theory as not the complete explanation since he concludes: "the process is clearly not one of simple precipitation, it depends upon the activity of living tissue. It cannot occur unless the concentration of calcium and phosphorus in the serum and presumably in the fluid bathing the cells, exceeds a certain minimum value."

Now it is clear that in all my cases on most occasions the product $\text{Ca} \times \text{P}$ is greatly in excess of fifty, and for this reason Lathrop will not accept the view that the bone deformities of renal infantilism are true rickets. The co-existence of bone changes—which in my view are undoubtedly rickets—with a $\text{Ca} \times \text{P}$ product of over fifty may be difficult to explain, but the occurrence cannot be denied, and therefore some explanation must be sought.

A series of papers by Holt, La Mer and Chown ⁽²⁴⁾ furnishes some interesting points in this connection. They have found that the blood serum is normally supersaturated with tertiary calcium phosphate and have devised a method by which the calcium and phosphate ions can be calculated. They have also

calculated out the product of the ions $[Ca^{++}] \times [PO_4]^{-3}$ in rachitic and normal sera in order to ascertain the relationship between the ion product and the solubility product constant for $Ca_3(PO_4)_2$ in blood serum. The results obtained show that even in active rickets the ion product is considerably greater than that

Fig. 16.—Radiogram of skull from the same case as Fig. 14, and 15. The bones of the vault are greatly thickened and show "stippling" to an extreme degree.

required to precipitate tertiary calcium phosphate. Precipitation of tertiary calcium phosphate is comparatively a slow process, and proceeds with very great slowness when the ion product is only slightly in excess of the value of the solubility product constant, and therefore they think that in active rickets calcification is proceeding but so slowly that it is not ordinarily detected. In

support of the latter view there is given a personal communication from Shipley to the effect that rats fed on a diet rich in phosphorus but poor in calcium (McCollum's diet 3143), showed during the first six weeks a broad rachitic metaphysis free of calcium, but as the condition became chronic the metaphysis not infrequently became peppered throughout with fine deposits of lime salts. This description appears to correspond very closely with the "stippling" which occurs in some cases of the woolly type of renal rickets. These workers would define rickets "not as a state in which the concentrations of calcium and phosphate are so low that $\text{Ca}_3(\text{PO}_4)_2$ cannot be precipitated, but as a state in which, as the result of lowered ion concentration, $\text{Ca}_3(\text{PO}_4)_2$ is deposited so slowly that new bone production exceeds it in rapidity, and consequently uncalcified bone or osteoid tissue is produced." Such a conception explains the fact that in adult life after growth has finished, the concentrations of calcium and phosphorus are similar to those found in active rickets in infants.

With regard to the $\text{Ca} \times \text{P}$ product, they say that whilst a high product is usually associated with a high ion product and *vice versa*, yet it is only a rough guide to the true ion concentration and not as good as the ion product for several reasons, the chief of which is that it does not give enough weight to calcium concentrations. The suggestion is made that the ion product should be used instead of the $\text{Ca} \times \text{P}$ product, and that it should be expressed as the negative logarithm of molecular concentration (*p* product) as is so usually done with hydrogen ions (*pH*). If this be done, the *p* product for active rickets is usually greater than 24·10, whereas when the disease is healing or absent, it is usually less than 24·10. The *p* product for the solubility-constant of tertiary calcium phosphate in blood serum is 26·0.

For the purpose of comparison with these results the *p* product has been calculated in all my cases, and in every instance the result is less than 24·10, *i.e.*, rickets should either be healed or absent. The calculations have been made on the assumption that the *pH* of the blood serum in each case was 7·35, but we know that in chronic nephritis an acidosis occurs, and Holt has shown that small variations in *pH* produce considerable changes in that fraction of the total phosphorus ionised as $\text{PO}_4^{\equiv}$. The *pH* of the blood has been estimated in only one of my cases. The method used was that described by Drucker and Cullen⁽¹⁸⁾ and gave a *pH* of 7·16. When the correction was made for this factor a higher *p* product was obtained but it did not exceed 24·10, being in fact 23·40. The influence of acidosis is, however, well demonstrated if the *p* product of the case described by Lathrop⁽⁸⁾ to which reference has already been made, be calculated. The $\text{Ca} \times \text{P}$ product in this case was 43·7, a result which made him regard the bone changes as non-rachitic. The *pH* of the blood was 6·98 and the *p* product at that *pH* is 24·30, a figure which is quite compatible with active rickets.

The importance of acidosis has also been emphasised by Freudenberg and György⁽²⁵⁾ who have expressed the relationship between the calcium bicarbonate and phosphate ions, and the hydrogen ion concentration of the blood by the following formula :—

$$\frac{[\text{Ca}^{++}] [\text{HCO}_3^-] [\text{H PO}_4^{\equiv}]}{[\text{H}^+]} = K$$

or, in words, the concentration of calcium ions decreases as the bicarbonate and phosphate ions increase, and increases as the hydrogen ion concentration increases; *i.e.*, as there is a shift of the reaction to the acid side, and *vice versa*. Now, as we have seen, in renal infantilism there is an increase in phosphate ion, sometimes a diminution in carbon dioxide, usually an acidosis and not infrequently a normal calcium. This must mean, if the formula be correct, that the increase in phosphate ion is balanced by the degree of acidosis.

Finally, I would again draw attention to the similarity between the effects produced by the injection of parathyroid hormone and the findings in renal rickets. In the former the calcium and phosphorus in the blood are both raised above normal, *i.e.*, the blood previously supersaturated becomes even more supersaturated, so that it is clearly possible under such conditions to obtain a $\text{Ca} \times \text{P}$ product that exceeds fifty and to obtain this increased calcium from the body reservoirs (of Greenwald and Gross⁽¹⁶⁾).

Admitting, therefore, that it is possible under certain conditions, *e.g.*, acidosis, after administration of parathyroid hormone, for the factor $\text{Ca} \times \text{P}$ to exceed fifty, the occurrence of rickets in renal infantilism becomes easy of explanation, because the calcium relative to the phosphorus is low and we thus have one of the conditions laid down by Howland under which rickets will occur. Further evidence in favour of this view is found in a case of florid rickets (N.H.) in which cure occurred. (Figs. 4, 5, 6, 7, 8.) When admitted into hospital in January, 1926, this child was severely ill with symptoms of uræmia. Her condition improved and in August the rickets had completely healed. As the bone healed the blood phosphorus fell, whereas the calcium remained at about the same figure until when the cure was complete the phosphorus was only slightly above the normal figure. I do not think that any explanation other than alteration in the relative proportions of concentration of the calcium and phosphorus can explain such a cure.

I would, therefore, submit that the clinical, radiographic, histological, and chemical evidence presented, show that the bone deformities are rachitic in nature.

Earlier in this paper I have made the statement that I have not been able to produce a cure in renal rickets by ultra-violet irradiation, whereas in coeliac rickets such treatment results in cure. The explanation of these results is probably to be found in the fact that ultra-violet light raises the blood phosphorus by increasing phosphorus absorption, and therefore treatment by this method makes the disparity between the calcium and phosphorus even more marked. Indeed, I think the tendency is very definitely to make the disease worse. If the radiograms of the case H.T. be examined it is obvious that the disease is more marked after nine months irradiation (Fig. 15) than before this treatment was started (Fig. 14). During that period the bending of the lower limbs also increased greatly. It may be objected that this is only evidence that the disease has progressed in spite of, and not because of, the treatment.

If the treatment were not to blame it is difficult to explain the rapid drop in blood phosphorus from 8.5 mg. to 4.7 mg. per cent. which occurred in twenty days after this treatment was stopped, and which was unaccompanied by any fall in blood urea or non-protein nitrogen. During the same period the blood calcium also fell, but not to a degree at all comparable with the fall in phosphorus, and this also may quite probably have been due to the cessation of ultra-violet ray treatment.

Complete cure does, however, occur, as we have seen, both in the florid and atrophic types, and even in the woolly type there is evidence of attempts at cure. The mechanism differs somewhat according to the age of the child. Those rare cases of renal rickets which survive to sixteen years and over, have reached for them almost the limit of the growth period, and therefore the call to mobilise calcium to prevent tetany becomes less insistent and there is also less required to ossify cartilage. This is particularly the case when the epiphyses have united with the shafts of the bones, and the growth period has ended. In children suffering from renal rickets the blood urea is always high, but it varies considerably, and at times for some unexplained reason the blood urea rises even higher. At the same time the child shows signs of uræmia, *e.g.*, vomiting, headache, drowsiness, etc., or the blood urea remains at a higher level for some time without such marked signs of uræmia, but with some considerable increase of the general symptoms. After a time a degree of recovery usually occurs, the blood urea falls and the child returns to its normal condition. In precisely the same way and correlated with the rise in blood urea, the blood phosphorus rises. As the child recovers the phosphorus is better excreted and the blood phosphorus, as in the case already quoted, may reach a normal figure and the calcium phosphorus ratio thus become normal. Also owing to the fact that the phosphorus is nearer the normal level, the blood calcium would tend to become normal, and therefore there would not be any need to mobilise calcium from the bones to prevent tetany. In either case healing of rickets will occur. Such an explanation accounts for cure, for relapse, and also for the state of "flux between healing and repair" referred to by Shipley.

The factors necessary for the prevention of rickets are usually stated to be an adequate supply of calcium, phosphorus, and Vitamin D in the dietary. Renal rickets develops and persists in spite of an adequate supply of all these factors, and hence the suggestion of Shipley that under certain conditions rickets may have an endogenous origin appears to be incontrovertible. In view of a statement made by Ashcroft that "sufficient evidence has been found to warrant the suggestion that the disease may be due to a fibrosis of the suprarenal gland" ⁽²⁶⁾ I would add that in the case of L.M. the suprarenals were large and showed a normal appearance under the microscope. The suggestion of Ashcroft appears to be based on very slender evidence, especially as Swingle ⁽²⁷⁾ has recently shown that whilst total removal of the adrenals of cats results in a rapid rise of blood phosphorus, blood urea and non-protein nitrogen, these changes do not occur as long as any adrenal cortex remains.

The answers put forward to the questions asked may therefore be summarised thus :—

The bone deformities associated with renal infantilism are those of true low-calcium rickets, and have their origin in the inability of the kidney properly to excrete phosphate. As a result of this inability on the part of the kidney to excrete phosphorus the blood calcium becomes relatively low and rickets occurs. During those periods in which the kidney is functioning better and excreting more phosphorus the calcium-phosphorus ratio becomes relatively more normal and healing may take place.

The blood calcium is maintained at a higher figure than is usual in severe nephritis with phosphate retention, by the mobilisation of calcium from the bones, and this is another factor in producing rickets. When the phosphate is better excreted the serum calcium automatically tends to rise to a higher level (see Freudenberg's and György's formula) and therefore the necessity for obtaining calcium from the bones is lessened and healing may occur.

The mobilisation of calcium from the bones may be considered as a protective mechanism for the prevention of tetany and therefore be, in part, the explanation of its infrequent occurrence.

Another factor in the prevention of tetany is the occurrence of acidosis, for this also mobilises calcium from the bones and favours its ionisation.

Tetany sometimes occurs in renal rickets because the "free" calcium is reduced relatively and may indeed be reduced absolutely; whereas in chronic nephritis the free calcium is normal, the reduction in calcium being due to diminution in the amount of "bound" calcium.

CONCLUSIONS.

1. The bone deformities of renal infantilism are those of true low-calcium rickets. The radiograms show that a case of renal infantilism may develop bone changes of one of three types :—

- (a) atrophic rickets.
- (b) florid rickets.
- (c) woolly rickets.

2. The primary cause of renal rickets is the inability of the kidney properly to excrete phosphate, *i.e.*, a true endogenous rickets exists.

3. The blood shows marked lipæmia, nitrogenous and phosphate retention, and an acidosis.

4. Blood calcium, whilst low compared with blood phosphorus, frequently shows normal values, in contra-distinction to what usually obtains in azotæmic nephritis and after the injection of phosphate. The suggestion is made that this is due to mobilisation of calcium from the bones as a preventative mechanism against tetany.

5. Healing of rickets may occur in those periods in which phosphorus excretion improves materially, or when the growth period is over.

6. Treatment of renal rickets by ultra-violet irradiation is contraindicated, and evidence is produced to show that such treatment aggravates the bone changes.

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