THE TREATMENT OF RENAL RICKETS

BY

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The condition now called renal rickets was first mentioned by Lucas (1883), and in the next twenty-eight years occasional cases were described. The close association between the kidney and the bony lesions was first clearly pointed out by Morley Fletcher (1911) in a communication to the Children's Section of the Royal Society of Medicine.

Miller (1911), Parsons (1911), Parkes Weber (1912), Naish (1912), and Barber (1913) reported cases in the next year, and since then a large number of cases have been described in England, Canada, the United States and recently in France, Germany and Norway. The important papers by Barber (1920, 1926, 1933) and Parsons (1927), and the reviews by Mitchell (1930), Hamperl and Wallis (1933) give an excellent account of existing knowledge. Although so many papers have been written describing cases, many of which have ended fatally, little has been said about treatment either of the rickets or the kidney lesion. There is a general opinion that neither vitamin D nor ultra-violet light is of any value, and Park (1933) says that 'large amounts of vitamin D may produce calcification in the rachitic intermediate zone, but is useless because the D merely depletes the skeleton at one point in order to affect bone salt deposition at another, and is dangerous because it may lead to injury elsewhere' (metastatic calcification). György (1928), Duken (1928), Schick (1929) and Karelitz and Kolomayzeff (1932), on the other hand, have each reported a case in which the condition of the bones improved after the administration of vitamin D. Salvesen (1934) found that the clinical condition as regards pain and comfort in walking improved when calcium lactate was given, although it deteriorated when ultra-violet light alone was given. Parsons (1927) and Barber (1926) have each reported one case in which the rickets healed although no vitamin D or ultra-violet light was given.

The kidney lesion is usually a chronic focal nephritis, and is often associated with a congenital lesion. The condition is regarded as unalterable and the treatment is not discussed. The changes which occur in the blood during the course of the disease are important. The observation by Green (1922) that an acidaemia may be present has been confirmed by many observers, and Schoenthal and Burpee (1930) and Salvesen (1934) have tried to correct it. We have treated two patients with sufficient alkalis to correct the acidaemia

and with large doses of vitamins A and D ; the results of this treatment have been striking.

Case records

Case 1, W. L., aged fifteen, was born at term of healthy parents, birth weight 9 lb. after a normal delivery. He was a healthy baby and, with the exception of rubella at the age of seven, never had any infectious fevers, sore throats or other serious illness. There is no family history of renal disease on either side of the family, and the only other child, a girl of twenty-six, is alive and well. The patient appeared normal until the age of four, when he ceased growing at the usual rate. For the next eleven years, although well, attending school and playing games, he grew slowly. In 1932, when fifteen, he first began to complain of pain in both knees and later also in ankles, heels and wrists, the joints being described as 'swollen and very painful.' This condition persisted for several months, during which the pain in the legs made walking difficult, and in April, 1933, the boy was brought to the Orthopaedic Department of St. Bartholomew's Hospital. He never complained of any thirst.

ON EXAMINATION he was of average mentality, but sallow and undersized, his height being only 51 inches and weight 65 lb., which is 11 inches and 38 lb. below the average for his age. The forehead was high and prominent and the teeth were well formed and in good condition ; the mucous membranes were not pale and his tongue was clean and moist. The chest was barrel-shaped with a wide sub-costal angle and prominent costo-chondral junctions, and the lungs were emphysematous. The cardio-vascular system appeared to be normal ; the retinal vessels were healthy ; the heart was not enlarged and the blood pressure was 108 mm. Hg. systolic and 84 diastolic. The abdomen was slightly protuberant but otherwise natural, neither kidney being palpable. The distal ulnar, radial and the proximal tibial epiphyses were enlarged, but there was no effusion into the joints. All movements of knees and ankles caused some pain. Slight bowing of the femora and tibiae resulted in one inch of genu varum deformity. The secondary sex characteristics were well developed.

The following investigations were made during his first admission to hospital in 1933 :

URINE : Pale ; specific gravity 1001 to 1006. Trace of albumin (less than 0.01 gm. per 100 c.c. by Aufrecht's method). No red blood cells or casts.

WASSERMANN AND SIGMA REACTIONS : negative.

BLOOD : Urea 80 mgm. per 100 c.c. ; serum calcium 8.8 mgm. per 100 c.c. ; plasma phosphorus 6.75 mgm. per 100 c.c. ; phosphatase 0.97 units. (Kay's method.)

A calcium balance which was carried out at this time gave an unsatisfactory result owing to severe constipation. An intravenous pyelogram showed such poor excretion of the dye that it was impossible to draw any conclusions regarding the condition of the renal pelvis or ureters. An x-ray examination of the bones showed evidence of active disease and the changes observed are described in detail below.

In September, 1933, he was re-admitted on account of occasional headaches and vomiting. The general condition was little changed, except for an increase of 13 lb. in weight and some dryness of the tongue. On admission his appetite was good and he did not feel ill, but two weeks later began to suffer from anorexia, nausea and attacks of vomiting. The blood urea, in spite of a diet containing only 30 gm. of protein, had increased to 224 mgm. per 100 c.c. He gradually became worse, with increasing drowsiness and vomiting, until, three weeks after admission, the blood urea was 400 mgm. per 100 c.c. and the clinical

picture, with its deep abdominal breathing, was typical of uraemia and acid-aemia. At this stage of the illness a large dose of alkali was given by mouth, 1.3 gm. (20 grains) each of magnesium oxide and sodium bicarbonate three

FIG. 1 shows the changes in the blood urea •—• alkali reserve ×—× van Slyke's urea clearance ••••• and the dose of alkali // in case 1.

times a day, or the equivalent of 20 gm. of sodium bicarbonate. The blood urea increased slowly for a further six days and reached the maximum figure of 430 mgm., but during the subsequent two weeks it fell to 190 mgm. and

by the end of a further four weeks of alkaline treatment had decreased to 60 mgm. per 100 c.c. The daily output of urine rose from 950 c.c. to over 2,000 c.c. during the first ten days, after the administration of alkalis. The general condition of the patient improved rapidly during this time, although he had lost 13 lb. in weight and his haemoglobin had fallen from 95 to 58 per cent. in the two months.

In view of this remarkable improvement in the function of the kidneys with the alkaline treatment, an attempt was made to determine the reaction at which maximum renal efficiency was obtained. Parallel estimations of blood urea, alkali reserve, and van Slyke's urea clearance test were made while the dosage of alkali was increased or decreased. The lowest blood urea figures were obtained when the alkali reserve was between 59 and 61 vol. CO_2 per 100 c.c. ; when the alkali reserve fell to 49 vol. CO_2 per 100 c.c. the blood urea rose to 102 mgm. per 100 c.c. The amount of alkali needed to keep the alkali reserve about the optimum level was equivalent to approximately 20 gm. of sodium bicarbonate, and was given in the form of 1.3 gm. (20 grain) each of sodium bicarbonate and magnesium oxide three times a day. Simultaneously with the attempt to determine the optimum dose of alkali a specific treatment for the rickets was started. A large dose of vitamin D, 3,000 units, together with 15,000 units of vitamin A and 3 gm. of calcium lactate, was given by mouth, and this dosage was maintained for the next sixteen months. During this period the patient grew 6 inches and striking changes occurred in the bones (see later).

Although the amount of calcium deposited in the bones had increased by May, 1935, it did not seem adequate, especially as the patient was growing so rapidly. The dose of vitamin D was therefore increased to 6,000 units and that of vitamin A to 30,000 units, the dose of calcium lactate being kept constant. During the next nine months the patient grew a further $1\frac{1}{4}$ inches. From March, 1934, to September, 1936, treatment was carried out as an out-patient except for one admission in 1935 for the purpose of repeating the chemical and radiological investigations. The blood urea was estimated at intervals and was usually between 70 and 96 mgm. It was once as low as 58 mgm. and once as high as 132 mgm. per 100 c.c. The van Slyke urea clearance test was estimated several times and varied between C.M. 13 per cent. and C.M. 19.9 per cent., and was no worse after three years. The alkali reserve varied between 56 per cent. and 67 per cent., but there was no direct relation between the height of the blood urea and the alkali reserve. The haemoglobin was 95 per cent. before he developed uraemia, and it decreased to 58 per cent. following this illness. He was given large doses of iron at intervals, and the haemoglobin increased to 74 per cent., with a colour index of 1.0. A year later it was 61 per cent.

In September, 1936, he was re-admitted to hospital with the following history. Six days before admission he had felt unwell and had lost his appetite. Three days before admission puffiness of the eyelids was noticed, together with general oedema. Shortness of breath and cough started about this time. Both the oedema and the dyspnoea increased considerably. On admission he was pale and presented the picture of severe nephrosis with general oedema, ascites and rales at the bases of the lungs.

URINE : Specific gravity, 1005 ; fair amount of albumin (considerably more than on previous admissions) ; no red blood cells or casts.

BLOOD : Urea 210 mgm. per 100 c.c. ; alkali reserve 43 vol. (the usual amount of alkali had been taken) ; haemoglobin 32 per cent. ; plasma proteins 5.5 gm. per 100 c.c.

Atropine sulphate 1/100 grain was given subcutaneously on account of the oedema of the lungs and 300 c.c. of 6 per cent. sodium bicarbonate solution

was injected intravenously, thus raising the alkali reserve to 57.4 vol. per 100 c.c. Later in the day an intravenous injection of 50 c.c. of 25 per cent. glucose saline solution was given in order to increase the urinary output. The usual dose of alkali was given by mouth. Next day, in view of the severe degree of anaemia, the patient was given 600 c.c. of his father's blood without any unfavourable reaction, and the haemoglobin rose from 32 to 41 per cent. A short period of general improvement followed the transfusion, the oedema decreased and the blood urea fell to 128 mgm., but at the end of ten days he was not so well; the blood urea had risen to 170 mgm. the alkali reserve being 69.1 vol. The alkali by mouth was therefore reduced by 1 gm. and the alkali reserve fell to 54.5 vol. and the blood urea to 132 mgm. On the twentieth day after admission the haemoglobin was 35 per cent. and a transfusion of 700 c.c. of group IV blood was given, the patient belonging to group II. Direct grouping showed no agglutination and nearly an hour was taken over the transfusion. Immediately after this he complained of shortness of breath and became restless. Many moist rales were heard all over the lungs. Atropine 1/100 grain, was injected, but he became rapidly worse with increasing dyspnoea and much frothy sputum. Oxygen, a further injection of atropine 1/50 grain and a venesection of 600 c.c. of blood produced a temporary improvement, but in less than two hours the patient died of acute pulmonary oedema.

Pathological examination.—A necropsy was performed sixteen hours after death by Dr. H. A. Magnus. The body was well nourished and measured four feet nine inches in length. Rigor-mortis and hypostasis were present. There was no lumbar cushion and no oedema of the legs.

SKELETON : There was no bossing of the skull, which was of normal thickness and density, and the vertebral column showed no deformity. There was some thickening of the costo-chondral junctions, but the ribs broke with the greatest difficulty. The ends of the long bones were thickened in the regions of the epiphyses and the femora and humeri were bowed. The epiphyseal lines were irregular but the bone was hard.

CARDIO-VASCULAR SYSTEM : The pericardium was natural. The heart weighed 328 gm. The auricles and ventricles were not dilated and there was no hypertrophy of the left ventricle. The valves and coronary arteries were normal and no atheroma or calcification was present in the aorta or smaller arteries.

RESPIRATORY SYSTEM : The pharynx was normal and the tonsils were small and contained no pus. Small serous effusions were present in both pleural cavities and there were numerous sub-pleural petechial haemorrhages. The larynx, trachea and bronchi contained a large amount of frothy fluid and the lungs were filled with oedema fluid which poured out on section.

PERITONEUM AND ALIMENTARY TRACT : The peritoneal cavity contained one and a half pints of serous fluid. There was no evidence of peritonitis. The whole of the alimentary tract was normal and there was no evidence of uraemic colitis.

LIVER, SPLEEN, PANCREAS, GALL-BLADDER AND DUCTS : The liver weighed 1,805 gm. It was firm in consistency and normal in appearance. The spleen weighed 155 gm. and showed no naked-eye abnormality. Neither the spleen nor the liver contained any free iron. The pancreas and gall-bladder and ducts were normal.

DUCTLESS GLANDS : The pituitary, thyroid, suprarenals and testes were normal. Four parathyroid glands of normal size were found.

BRAIN AND SPINAL CORD were normal.

URINARY SYSTEM : The bladder was dilated and hypertrophied, and showed well-marked trabeculation. No stricture was present in the urethra and a sound was passed down the urethra into the bladder with ease, but unfortunately it

was not passed from the bladder to the penis. A careful dissection by Mr. W. E. Underwood subsequently showed that the prostatic urethra was dilated and that a small valve of mucous membrane was present distal to the verumontanum. The prostate gland was normal. Both ureters were dilated and their walls thickened, but the ureteric orifices were normal.

The kidneys were extremely small; the left weighed 35 gm. and the right 30 gm. The capsules stripped easily leaving coarsely granular surfaces. It was difficult to define any cortex at all on the cut surface of the kidney, but in a few places it could be made out blending with the underlying medulla without any clear line of demarcation. The blood vessels were not unduly prominent and there was no increase in the amount of intrapelvic fat. Both pelves were dilated but there was no suggestion of pyelitis.

Histological examination.—Microscopic examination of all the organs, apart from the kidneys, showed no abnormality.

KIDNEYS: The appearances were those of a chronic focal glomerulonephritis in which there was extensive destruction of glomeruli and an equally extensive hypertrophy of the surviving glomeruli and their tubules. Associated with this there was a moderate degree of subacute intra-capillary glomerulitis, suggesting that, in addition to the chronic process, there had been a subacute exacerbation. Glomeruli could be seen in every stage of destruction up to complete fibrosis, but the capillaries of the surviving glomeruli were considerably obstructed by collagenous thickening of the sub-endothelial connective tissue. There was a well-marked diffuse interstitial fibrosis in which large numbers of completely atrophied tubules could be seen. A moderate amount of neutral fat was present, mainly in the glomeruli, but lipoid was absent, and no collections of cystine crystals were seen. There was no change in the medial coat of the arterial walls such as accompanies hypertension, but many arteries especially those of the calibre of the inter-lobular arteries, showed well-marked endarteritis obliterans of the type found associated with any chronic inflammatory process.

X-ray appearances.—The radiological appearances in renal rickets were divided by Parsons (1927) into three main types: atrophic, florid and woolly, stippled or honeycomb. Teal (1928), who had worked with Parsons, came to the conclusion that he could not make any real distinction between atrophic and florid types. Brailsford (1935), has confirmed this view and suggested that the types should be called A and B. In type A, which includes the atrophic and florid types, the calcification of the bone itself is comparatively normal, while in type B, which includes the stippled or honeycomb type, the calcification is deficient. This classification will be used throughout.

On admission in April, 1933, the following x-ray appearances were present:

SKULL showed absence of trabeculation of the cancellous bone of the vault but normal sutures. The cranial sinuses were not pneumatized and the longitudinal diameter of the pituitary fossa was small for the age of the patient: longitudinal, 10 mm.; vertical, 9 mm.; interclinoid, 6 mm.

The dentition was fair and up to the age of the patient except for the fact that the root canals were patent in the molar region.

VERTEBRAE were as for a child of eight years.

The most typical changes were found in the wrists and knees. The **WRISTS** (fig. 4a) showed changes of the A type of renal rickets. The cortex of the radius and ulna and the outlines of the epiphyses, even on the metaphyseal side, were comparatively good, but the metaphyses of both bones showed the concave cupping and splaying as well as the irregularity which is characteristic of the disease. The calcium content of the trabeculae appeared to be fairly normal, and there was a moderately good distinction between the cortex and the cancellous bone.

FIG. 2.—Photograph of the kidney split.

FIG. 3.—Microphotograph of the kidney.

FIG. 4a.—X-ray of wrist in April, 1933.

FIG. 4b.—X-ray of wrist in October, 1934.

FIG. 4c.—X-ray of wrist in June, 1935.

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FIG. 5b.—X-ray of knee in October, 1934.

FIG. 5a.—X-ray of knee in April, 1933.

FIG. 5c.—X-ray of knee in June, 1935.

FIG. 5d.—Tibia after death in October, 1936.

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FIG. 6.—X-ray of humerus in April, 1933.

KNEES (fig. 5a) : The changes in the knees, especially in the upper end of the tibiae, were also of the A type, but the calcification was more marked and there was some loss of distinction between the cortex and cancellous bone. Other interesting radiological appearances included a marked coxa vara deformity due to bending of the neck of the femur on both sides and incomplete fusion of ischium and pubis such as is seen in the normal child of eight. There was a varus deformity at the proximal end of the humerus (fig. 6) which also showed gross rickety deformity. In October, 1934, after eleven months' treatment, both wrists (fig. 4b) and knees (fig. 5b) showed an increase in the depth of the sub-metaphyseal irregular area, the degree of calcification remaining about the same. In June, 1935, there was narrowing of the epiphyseal line of the tibiae (fig. 5c) and a pseudocystic area due to trabecular absorption in the proximal end of the fibula. The calcium content of the bone had improved. The wrists (fig. 4c) showed similar changes.

At this time a small cystic area was noted in the distal end of the diaphysis of the fourth right metacarpal bone. In November, 1935, the wrists and knees showed no appreciable radiological change. In October, 1936, an x-ray of the tibia (fig. 5d) taken after death showed further narrowing of the epiphyseal line with commencing union. Trabeculation in the sub-metaphyseal region was nearly normal, the cortex was wider and the degree of calcification much greater than in the previous skiagrams.

FEMUR (decalcified) : A section through the lower end of a femur did not show any evidence of active rickets. The epiphyseal line was somewhat irregular but ossification was taking place normally.

Calcium and Phosphorus.—The results of individual estimations of serum calcium and plasma inorganic phosphorus of the two balance experiments are shown in table 1 and figs. 7–10. From these it will be seen that the calcium is low throughout, the lowest figure being 7.9 mgm. and the highest 9.3 mgm. ; the phosphorus was high before the treatment was started, the maximum being 6.75 mgm. and the lowest figure was 2.0 mgm. per 100 c.c.

TABLE 1

DATE	SERUM CALCIUM, MG. PER CENT.	PLASMA INORGANIC PHOSPHORUS, MG. PER CENT.
9/4/33	8.8	6.75
5/10/33	7.9	6.2
4/2/34	9.3	4.0
14/3/35	8.0	2.0
7/6/35	8.0	4.4

The calcium and phosphorus balance was estimated in May, 1934, before he had developed uraemia, but the figures are unreliable as the patient was constipated. The second calcium and phosphorus balance was carried out in March, 1934, about five months after the patient had recovered from uraemia. The blood urea was 55 mgm. per 100 c.c. blood ; the alkali reserve was 71 vol. of CO₂ per 100 c.c. blood ; the serum calcium was 9 mgm. and the plasma phosphorus 3.7 mgm. The calcium intake was 889 mgm. in the food (calculated) with an additional 376 mgm. in the form of calcium lactate = 1,265 mgm. The average output in the first four days was 1,230 mgm., giving a retention of 35 mgm. per day. In the second period of four days the amount excreted in the faeces was less and the average excretion was 1,046 mgm. and 119 mgm. of calcium was retained each day. The amount of calcium excreted in the urine was 10.5 per cent. and 8.5 per cent. of the total excretion in the two periods respectively.

FIG. 7 shows the calcium balance in March, 1934.

Calcium in food	..	..	889 mgm.
Calcium lactate	..	..	376 mgm.
Total			1,265 mgm.
Serum calcium	..	..	9 mgm.
Plasma inorganic phosphorus	..	..	3.7 mgm.
Blood urea	..	..	58 mgm.
Alkali reserve	..	..	71 vol.

FIG. 8 shows the inorganic phosphorus balance in March, 1934.

FIG. 9 shows the calcium balance in May, 1935.

Calcium in food	..	..	931 mgm.
Calcium lactate	..	..	376 mgm.
Total			1,307 mgm.
Blood urea	..	..	72 mgm.

FIG. 10 shows the inorganic balance in May, 1935.

The inorganic phosphorus balance showed that the average amount of phosphorus excreted in the first three days was 418 mgm., giving a retention of 216 mgm. ; in the next four days the average excretion was 400 mgm. and 234 mgm. were retained. The percentage amount of phosphorus excreted in the urine was 25.6 per cent. and 24 per cent. respectively.

The third calcium balance was carried out fourteen months later. The blood urea was 72 mgm. per 100 c.c. blood. The calcium and phosphorus were unfortunately not estimated at the time the balance was carried out, but two months earlier the serum calcium was 8 mgm. and the plasma phosphorus 2 mgm., and one month later the calcium was 8 mgm. and the phosphorus 4.4 mgm. per cent. The calcium intake in the food had been increased to 931 mgm. (calculated) while the calcium lactate was still 376 mgm., total 1,307 mgm. The balance had altered considerably, as the small positive balance of 35-114 mgm. a day had been converted into a large positive balance of 407-419 mgm. The output of calcium in the urine had decreased by about 40 mgm., while the output in the faeces had decreased by over 265 mgm. and was responsible for the positive balance.

For the third phosphorus balance the intake was 620 mgm., which was slightly less than before. The average output for the three day periods was 640 and 626 mgm., so that a small negative balance was present instead of the positive balance of 234 mgm. fourteen months earlier. This change is partly due to the increase of the phosphorus excretion in the stools from 300 mgm. to 440 mgm. and partly to the increase in the average urine excretion from 100 mgm. to 191 mgm. The percentage amount of phosphorus excreted in the urine rose from 25.6 per cent. and 24 per cent. to 33 per cent. and 27 per cent. respectively. These figures are very low, as the percentage in the urine in health is usually over 50 per cent. Boyd Courtney and MacLachlan (1926) estimated the output in seven children with severe nephritis, and found that the percentage amount excreted in the urine was just over 50 per cent. in three cases, 43 to 40 per cent. in two cases, 28.6 per cent. in one case and 11.6 per cent. in one case. The amount of phosphorus in the diets was much larger than in the present case, as it varied from 1,250 to 2,200 mgm.

Case 2, A. B., aged seven years, was admitted to St. Bartholomew's Hospital in May, 1936. Born at term of healthy parents, he weighed $4\frac{3}{4}$ lb. at birth. was breast fed for nine months and was always small. He cut his first tooth at seven months, but did not sit up until eleven months. At eighteen months he crawled well, but his legs were beginning to bend, and he was not able to stand until he was three years old. At the age of five he was admitted to the Royal National Orthopaedic Hospital, and the following estimations were made.

URINE : Pale ; specific gravity was low.

BLOOD : Urea 160 mgm. per 100 c.c. ; calcium 7.1 mgm. per 100 c.c. ; phosphorus 6.9 mgm. per 100 c.c.

He was in hospital for two months and was discharged with splints for his legs. In the last two years he has walked about and been fairly active in spite of the bending of the legs. In May, 1936, he was admitted to St. Bartholomew's Hospital for treatment on the same lines as the first case.

CONDITION ON ADMISSION : He was a small boy, aged seven, weighing 22 lb., or 28 lb. under the average weight for a boy of his age. It was impossible to measure his height accurately on account of the bending of his legs. When these had been straightened by December, 1936, his height was $37\frac{1}{4}$ inches, or $8\frac{3}{4}$ inches under the average height. His head was well shaped and measured $18\frac{1}{2}$ inches. The milk teeth were intact, except for the lower incisors, but they were all loose and a moderate amount of pyorrhoea was present. The chest

was pigeon-shaped and the bending of the ribs was well marked. The arms were well proportioned, but the epiphyses of the wrists were large. The thighs were normal, but the tibiae were bent outward, and the internal malleoli were nine inches apart. The heart was not enlarged and the blood pressure was 110 mm. Hg systolic and 70 diastolic. His intelligence was poor, as he did not know his alphabet or numbers. He was observant and easily learnt to do things with his fingers, but he was either unable or would not concentrate on any lessons. His appetite was small and fanciful. The usual protein intake by choice was about 18 gm.

SPECIAL TESTS.

URINE : Pale, like water ; specific gravity, 1,005 ; trace of albumin ; no casts or cells seen.

The van Slyke urea clearance test was 10 per cent. of normal. Alkali reserve 45.8 vol. per 100 c.c. Serum calcium 5.8 mgm. per 100 c.c. Plasma inorganic phosphorus 3.4 mgm. per 100 c.c.

The general condition had changed very little in the last two years, except that the plasma phosphorus was now below normal limits instead of being raised. The bones showed well-marked changes of renal rickets. No investigations of the urinary tract were made, as it was thought that an intravenous pyelogram would be of no value as the urine was so dilute, and that a retrograde pyelogram with its attendant risks of sepsis was too dangerous a proceeding in a patient whose blood urea was over 100 mgm. per 100 c.c.

Treatment. This was carried out on similar lines to that of case I. A large dose of vitamin D, 6,000 units, together with 30,000 units of vitamin A was given. The alkali reserve was raised to normal with an alkaline powder containing calcium carbonate. Considerable difficulty was experienced in making him take these powders regularly, but after two months a mixture of bismuth carbonate, 0.33 gm. ; magnesium oxide, 0.33 gm. ; sodium bicarbonate, 0.66 gm. ; and sodium citrate, 0.66 gm. was given four times a day. The mixture was equivalent to 12.4 gm. of sodium bicarbonate. Through an oversight no additional calcium was given until March, 1937, when 3 gm. of calcium lactate was added.

The alkali reserve was easily raised above 60 vol. and has occasionally been as high as 70 vol. The blood urea fluctuated in a very extraordinary manner, and varied between 70 mgm. and 190 mgm. per 100 c.c. These changes were sometimes associated with obvious causes like dental extractions, but as a rule no other ailment was present. He had a considerable amount of pain and discomfort during the process of stretching of the external lateral ligaments of the knee-joints and bending the tibiae straight. He often appeared unwell with loss of appetite when the discomfort was great, and it is possible that this discomfort was responsible for the fluctuation of the blood urea.

The legs were placed in a rack splint, and the screws were turned every day. After three months the legs were sufficiently straight to enable a caliper splint to be used, the pressure being maintained with bandages. The straightening has been due both to the stretching of the lateral ligaments, which now allow a play of three inches, and also to the bending of the tibiae. This bending is partly permanent, as can be seen in the x-ray, and partly temporary, as it disappears when the splint is removed. He has been anaemic all the time, as the haemoglobin has never been higher than 58 per cent. in spite of large doses of iron, and in May it had decreased to 48 per cent. and was 47 per cent. in July.

Some three weeks after leaving hospital he joined a party of boys from his village and raided a plum orchard. Although his appetite while in hospital was always very capricious, he ate many unripe plums. On his return home he

complained of feeling unwell. One hour later he had a little diarrhoea and vomited. He was put to bed and two hours later a doctor was sent for as he seemed very ill. When Dr. Hay arrived an hour later the boy was dead, the whole illness having lasted four hours. At the post-mortem examination the stomach still contained many unripe plums. Portions of liver, spleen,

FIG. 11 shows the changes in the blood urea • — • alkali reserve × — — × and dose of alkali // // // in case 2.

pancreas, ulna bone and the urinary tract were sent to Dr. Magnus at St. Bartholomew's Hospital for histological examination.

Post-mortem examination.

The liver, spleen and pancreas showed no abnormality apart from fatty change in the liver and marked post-mortem change in all three organs.

The lower end of the ulna bone showed no macroscopic evidence of rickets and a longitudinal section through the epiphysis showed no evidence of active or healing rickets.

The kidneys, ureters and bladder had been removed in toto. The bladder was small but its wall was hypertrophied and trabeculated. Only one centimetre of the urethra was included in the specimen, but this showed no evidence of a stricture or of a urethro-vesical valve. The ureters were slightly dilated and their walls definitely hypertrophied. The kidneys presented a remarkable picture; they were both very greatly reduced in size, the left weighing 12 gm.

FIG. 12a.—Knees not quite touching.
Photographs taken in February, 1937, to show the amount of lateral movement permitted at the knee joints.

FIG. 12b.—Knees slightly overlapping.
Photographs taken in February, 1937, to show the amount of lateral movement permitted at the knee joints.

FIG. 12c.
Photographs taken in July, 1937, to show the amount of lateral movement permitted at the knee joint.

FIG. 12d.
Photographs taken in July, 1937, to show the amount of lateral movement permitted at the knee joint.

FIG. 12e.—Photograph showing his appearance on discharge in July, 1937.

FIG. 13.

FIG. 14.

FIG. 15a.—X-ray of wrist in May, 1936.

FIG. 15b.—X-ray of wrist in August, 1936.

FIG. 15c.—X-ray of wrist in March, 1937.

FIG. 15d.—X-ray of wrist in July, 1937.

FIG. 16a.—X-ray of both legs in May, 1936, showing bending of the knees.

FIG. 16b.—X-ray of both legs in March, 1937, showing the straightening of the legs.

FIG. 16c shows the state of the legs in July, 1937.

FIG. 17a.—X-ray of knee-joint in May, 1936.

FIG. 17b shows the state of the knee-joint in July, 1937.

and the right 15 gm. The capsules stripped easily, leaving smooth surfaces. The cut surfaces (fig. 13) showed slight dilatation of the pelves, which were surrounded by a very thin rind of kidney tissue in which no line of demarcation between cortex and medulla could be determined; there were no retention cysts. The blood-vessels were not unduly prominent and there was no increase in the amount of intrapelvic fat.

Sections of the kidney (fig. 14) showed a different appearance from that observed in the previous case. There was a gross reduction in the amount of secretory tissue present in the cortex. The general picture was one of diffuse atrophy with no corresponding hypertrophy of surviving tissue. Although the few remaining glomeruli showed no striking alteration of structure, apart from patchy ischaemic obliteration, no scars of those that had disappeared could be identified. There was interstitial fibrosis, moderate in degree, in the cortex but becoming marked as the medullary portion was reached. In the patchy areas where glomeruli were few or absent there were focal accumulations of lymphocytes. There was no noteworthy change in the arteries beyond some increase in thickness of the internal elastic laminae.

The appearances in the kidney were not those of any type of Bright's disease, but were much more suggestive of the end result of a healed pyelonephritis of long standing.

The x-ray appearances in case 2 approximated more closely to the B type. The skull resembled that described under case 1 the pituitary fossa again being undersized: long diameter, 10 mm.; vertical, 5 mm.; and interclinoid, 6 mm.

The dentition, however, was backward, many milk teeth being present. The wrists (fig. 15*a*) showed the typical changes of cupping, splaying-out and irregularity of the metaphyses of the radius and ulna, but in addition there was marked decalcification of both bones and their epiphyses. The degree of epiphyseal development was that of a normal child of five. The long bones of both lower limbs (fig. 17*a*) also showed decalcification of the cortex and trabecular absorption, a severe degree of genu valgum being present owing to the bending of the tibiae and fibulae (fig. 16*a*) at the junction of the upper and middle thirds of both bones. Although the changes in renal rickets are usually more marked in the metaphyses than in the epiphyses, the proximal epiphysis of both humerus and femur in this case were more severely affected than the corresponding metaphysis. In August, 1936, after three months of treatment, the metaphyseal irregularity in the wrists (fig. 15*b*) and knees was greatly diminished and the cortex was well differentiated from the cancellous bone; three new carpal bones had appeared and the calcium content of the bones as a whole was considerably improved. In January, 1937, the calcification had further increased, and the tibial epiphyses were better defined. In March, 1937, the bowing of the legs (fig. 16*b*) had decreased as a result of splinting, and three additional carpal bones (fig. 15*c*) had increased in size and the metaphyses had improved. In July, 1937, the metaphysis of the radius (fig. 15*d*) was better defined, the carpal bones and epiphyses showed normal increase in size for the period under consideration and the calcification had slightly increased. The tibiae (fig. 16*c*) showed a well-marked growth line below the epiphysis, but the degree of bending and calcification remained unchanged. In the region of the knee joint (fig. 17*b*) the epiphyses and general bony definition had also improved.

The calcium and inorganic phosphorus. The serum calcium was 5.8 mgm. per cent. on admission, but had risen to 9.8 mgm. during the year (table 2). The plasma inorganic phosphorus was 3.4 mgm. and varied from 3.1 to 5.0 mgm. during the year (table 2). It was impossible to estimate the calcium and phosphorus balance when the boy was first admitted as he was sometimes incontinent of urine. The first calcium balance was carried out in March, 1937, and

FIG. 18a shows the calcium balance in March, 1937 : calcium intake (average calculated), 1,110 mgm.

FIG. 18b shows the calcium balance in June, 1937.

Calcium in food	..	..	924 mgm.
Calcium lactate	..	..	376 mgm.
Total			<u>1,300 mgm.</u>

FIG. 18c shows the calcium balance in July, 1937.

Calcium in food	..	..	1,288 mgm.
Calcium lactate	..	..	376 mgm.
Total			<u>1,644 mgm.</u>
Serum calcium	..	..	9.8 mgm.
Plasma inorganic phosphorus	..	..	3.4 mgm.
Blood urea	..	..	124 mgm.
Alkali reserve	..	..	64.3 vol.

FIG. 19a shows the inorganic phosphorus balance in June, 1937 ; inorganic phosphorus (average intake), 723 mgm.

FIG. 19b shows the inorganic phosphorus balance in July, 1937 ; inorganic phosphorus (average of two periods), 1,090 mgm

owing to an accident in the collection of the stools the estimation for the first few days was spoilt. The average intake of calcium in the food was 1,110 mgm. (calculated) and the average total output was 1,069 mgm., giving a small positive balance of 41 mgm. a day. The urinary calcium was 54.6 mgm. or 5 per cent. of the total excretion. The inorganic phosphorus was unfortunately not estimated at this time.

TABLE 2

DATE	SERUM CALCIUM, MGM. PER CENT.	PLASMA INORGANIC PHOSPHORUS MGM. PER CENT.
12/5/36	5.8	3.4
10/7/36	8.8	4.0
14/1/37	8.8	3.1
8/4/37	10.6	5.0
23/4/37	9.4	—
23/6/37	10.3	3.8
15/7/37	9.8	3.4

The second calcium balance was carried out in April, 1937, when 3 gm. of calcium lactate had been added to the diet for four weeks. The test was not satisfactory, as the amount of food which he ate each day was variable, and the intake of calcium varied in consequence from 550 mgm. to 1,245 mgm. (calculated). The average for the four days was 926 mgm., making 1,302 mgm. with the 376 mgm. from the calcium lactate. The average output for the four days was 1,247, giving a small positive balance of 55 mgm.

The intake of inorganic phosphorus was variable: in the four days before the estimation of the balance it was 888 mgm. (calculated) and in the actual four days of the experiment was 723 mgm. (calculated) and varied from 421 to 960 mgm. The inorganic phosphorus excreted in the urine averaged 256 mgm. and, in the faeces, 1,321 mgm., making a total of 1,577 mgm. This gives a negative balance of 832 mgm. It is unfortunate that the intake was small and varied so widely from day to day. But the total excretion of the phosphorus in the urine and faeces is very large and much greater than that found in case 1 when the intake was rather smaller.

A third balance experiment was carried out in July. The dose of vitamin D had been increased to 9,000 units and the vitamin A to 45,000 units to aid the recovery from an attack of acute tonsillitis and was maintained at this figure partly because the positive balance of calcium had been only 55 mgm. in the second balance and partly because he was growing fast. The blood urea was 124 mgm.; the alkali reserve was 64.3 vol.; the serum calcium was 9.8 mgm.; and the plasma phosphorus was 3.4 mgm. The boy was much less capricious over his food and the daily intake of calcium and phosphorus was much greater and varied little from day to day. The collection of the stools into two three-day periods was not satisfactory, as some mixing had obviously taken place, and figures for the six-day period are used. The average intake of calcium in the food was 1,288 mgm. (calculated) and 376 mgm. as calcium lactate, making 1,664 mgm. in all, which is an increase of 362 mgm. over the second balance experiment. The average total output per day was 1,074 mgm., giving a large positive balance of 590 mgm. The average urinary calcium was 42 mgm. or 3.9 per cent. of the total output.

The daily intake of inorganic phosphorus was 1,100 mgm., which is an increase of 380 mgm. per day. The average total output was 653 mgm., giving a positive balance of 254 mgm. in contrast to the negative balance

of 832 mgm. in the second balance. This change is partly due to the decrease in the urinary inorganic phosphorus from 256 mgm. to 182 mgm., but mainly to the decrease in the faecal inorganic phosphorus from 1,321 to 653 mgm. The percentage amount of inorganic phosphorus excreted in the urine was 22 per cent.

The figures for the serum calcium and plasma inorganic phosphorus and those for the final balance experiment suggested that the development of the bone could proceed normally, provided that no substantial change took place in the state of the kidney.

Discussion

The change in the condition of these two patients during the period of their supervision is great, and it is important to consider whether it is due to the alkalis or to the vitamin D. All other workers with the exception of György (1928), Duken (1928), Schick (1929), Karelitz and Kolomoyzeff (1932) have said that neither vitamin D nor ultra-violet light is of any value. György treated a girl aged ten who had such severe pains in her legs that she had to stay in bed. She was given 4–6 mgm. of vigantol daily for seven months. Within three months she was able to walk about, but the rachitic lesion had not completely healed in seven months. Duken (1928) treated a boy aged six with vigantol, 4 pastilles a day for thirteen days only, and, judging from the x-ray photographs good healing of the bones took place in the next six weeks. Both these patients suffered from gross infection of the urinary tract and, although no mention is made of treatment, it is possible that the usual treatment with alkalis was given. Karelitz and Kolomoyzeff (1932) treated a child aged six with 0·3 c.c. of vigantol daily for six weeks, and in the next twelve weeks definite healing of the bones began. A further course of 0·25 c.c. of vigantol for six weeks was terminated by an attack of mumps, which made her very ill. The condition of the bones became much worse and she died shortly afterwards. Treatment with alkalis is described by Schoenthal and Burpee (1930), who concluded that 'replacement of depleted base calcium and phosphate is a logical method of treatment, but the effects are but temporary unless the treatment is continuous. This may be accomplished by the administration of an alkaline ash diet together with calcium acetate.' They did not give any vitamin D and did not report any improvement in the bones. Karelitz and Kolomoyzeff (1932) approve of this form of treatment, but think that ultra-violet light might also help. Salvesen (1934) noticed an improvement in his patient's capacity for walking when he gave ultra-violet light and at the same time raised the alkali reserve with calcium lactate. Ultra-violet light by itself made the patient's symptoms worse, while the calcium lactate by itself caused an improvement. Two months after the calcium lactate was given x-ray examination did not show any change in the bones, and the patient died of uraemia one month later.

The alkali reserve was not estimated in the early cases, but Green (1922) found that it was lowered and his findings have been confirmed by many other observers : Lathrop (1926), Hertz (1929), Mikulowski (1930), Faxen (1932), Meier (1934-5), Debré, Marie, Dayras and Bernard (1935), Elliott (1933), Bader (1934), Shelling and Remsen (1935), and Roberts (1936). The alkali reserve in these cases is usually below 55 vol. of carbon dioxide per 100 c.c. blood, and may be as low as 20 vol. in patients dying of uraemia. Patients with severe kidney damage may be considerably benefited when the alkali reserve is raised to within normal limits. The ability of the kidney to excrete urea will often improve considerably if any septic focus is present which can be removed. This is especially the case after operation on the urinary tract.

The lesion of the kidney in renal rickets is a peculiar one as it tends to progress very slowly, and in the second case here reported the blood urea at the age of six was exactly the same as at the age of four. This is perhaps explained by the condition of the kidney in case 1, for whereas a great many tubules and glomeruli were destroyed the remaining ones were hypertrophied and presumably healthy before the last attack of nephritis associated with oedema. If the hypertrophied glomeruli and tubules are healthy and no superadded infection is present the excretion of urea should remain unaltered, and would explain why in case 2 the blood urea remained unaffected for two years. Since the excretion of urea is aided when the alkali reserve is within normal limits it is possible that the excretion of other substances like phosphorus is also improved. In case 1 the positive phosphorus balance of 234 mgm. was replaced fourteen months later by a small negative balance of 20 mgm., and the change is partly due to the increase of 90 mgm. of phosphorus excreted in the urine and partly to the increase of 140 mgm. in that excreted in the faeces. The positive calcium balance in the same time was increased from 35 to 410 mgm. In case 2 a large negative phosphorus balance occurring at a time when the calcium balance was just positive and the rickets was healing was converted fifty weeks later into a positive phosphorus balance at the same time as the positive calcium balance increased considerably. The lower output of phosphorus into the gut, which was detected once in both cases, is difficult to reconcile with one of the hypotheses, for the altered amounts of calcium and phosphorus in the blood. Mitchell (1930) suggested that the relative failure of the kidney to excrete phosphorus in the urine caused an increase in the inorganic phosphorus in the blood and an increased secretion of phosphorus into the gut. He thought that this excess of phosphorus in the gut caused a precipitation of the calcium of the food as an insoluble phosphate which was absorbed with difficulty. It is possible that this factor is important when the disease is developing, and that the action of the high phosphorus excretion into the gut in the present cases was prevented by the large doses of vitamin D and the alkalis.

There is no evidence as to whether the alkali or the vitamin D is really responsible as they were given simultaneously. It is possible that alkalis alone might enable the amount of vitamin D in an ordinary diet to effect the absorption of sufficient calcium though the recovery of the bones would be slow. The problem was also complicated by the use of a trade preparation of vitamin D

which contained a large amount of vitamin A, as it was hoped to improve the general health of the patients, and this may have played some part in the improvement.

Summary

Two patients with renal rickets have been treated with sufficient alkali to restore the alkali reserve to within normal limits, and at the same time with large doses of vitamins D and A. The general condition improved ; they grew in height and gained weight ; the state of the kidney was slightly improved ; the anaemia was little altered, while the condition of the bones was greatly improved.

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