The problem of making a firm diagnosis remains once the suspicion has been raised. The absence of typical clinical and radiographic features has already been discussed. In the early stages and even later the tuberculin test may be misleading.

Brunner and Haemmerli (1964) showed that liver biopsy was a valuable diagnostic investigation in miliary tuberculosis, with positive biopsies in 75% of 163 cases collected from the literature. In the present series liver biopsy was attempted in three patients with cryptic miliary tuberculosis and gave the diagnosis in one only.

Histological examination of bone marrow and culture for tubercle bacilli has been shown to increase the number of diagnoses in miliary tuberculosis in children (Emery and Gibbs, 1954); in only one out of four overt and three cryptic cases in our series was a positive culture obtained.

When all investigations fail to determine the cause of pyrexia the only method by which a diagnosis of cryptic miliary tuberculosis can be proved or refuted during life is to observe the response to a therapeutic trial with PAS and isoniazid. Streptomycin is not given because it would influence other bacterial infections. The clinical features in these cases are so striking in their seriousness that when improvement on chemotherapy takes place there is no doubt about its occurrence.

The criteria by which progress during antituberculosis therapy is assessed are of paramount importance. In 6 out of 10 patients diagnosed by means of a therapeutic trial the temperature fell to normal within a week of starting treatment. Improved well-being was usually obvious within two to six weeks, when gain in weight also became apparent. An important rise in haemoglobin was usually demonstrable within four to six weeks. Petersdorf and Beeson (1961) also found the response to antituberculosis drugs a useful diagnostic test in cases of pyrexia of unknown origin. They concluded that "when the condition of the patient will not allow liver biopsy to be done, or if this and other diagnostic manoeuvres fail, a therapeutic trial with antituberculous drugs is indicated." Such a trial was also advocated by Cleve, Young, and Vicente-Mastellari (1957). We wholeheartedly support this view.

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Role of Acidosis in Renal Osteomalacia

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Summary: Of nine patients with uraemic osteomalacia, the underlying renal lesion was pyelonephritis in seven. All of the patients were characterized by impairment of acidifying power and severe metabolic acidosis. It is suggested that metabolic acidosis may be a definite factor in the pathogenesis of uraemic osteomalacia, possibly by reducing the proportion of trivalent phosphate in the plasma and/or by reducing plasma calcium.

Introduction

Osteomalacia and rickets are seen in two main types of acidotic renal disease, which were effectively separated by Albright and Reifenstein (1948). In the first type (renal tubular acidosis) the metabolic acidosis is due to the tubular acidifying defect and is not associated with general (glomerular) renal failure. This type of renal osteomalacia is characterized by severe hypophosphataemia.

The second type of renal osteomalacia is that which occurs in some cases of general renal failure. This bone disease forms part of the spectrum that Stanbury (1967, 1968) calls azotaemic

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renal osteodystrophy, which is characterized by varying degrees of osteomalacia and osteitis fibrosa. Stanbury and Lumb (1966) have shown that there is a tendency for this osteomalacia to develop in the early stages of renal disease and to be superseded by osteitis fibrosa as renal failure progresses and the serum phosphate level rises. The serum calcium $\times$ phosphate product is generally normal and the cause of the calcification defect is unknown, but it has been attributed to the presence of a calcification inhibitor in the serum (Yendt and Howard, 1955).

The metabolic acidosis, which is always present in these patients, is usually discounted as a causal factor, partly because the associated malabsorption of calcium is said not to be corrected by alkali therapy (Stanbury and Lumb, 1962). In our experience, however, the cases of general renal disease that develop osteomalacia are precisely those in which the degree of metabolic acidosis is particularly severe owing to an impairment of acidifying power of the acquired type, which we have previously described in cases of renal stone disease with pyelonephritis (Cochran *et al.*, 1968). The present paper describes nine such cases, representing our total experience of proved osteomalacia with renal failure in Leeds from 1964 to 1968.

Clinical Material and Methods

The nine cases comprise six women aged 16 to 65, one man aged 54, and two boys aged 4 and 8 (see Table). All except two had unequivocal evidence of chronic pyelonephritis (chronic pyuria with urinary infection and radiological changes). No evidence of pyelonephritis was found in Case 7, but his underlying lesion was a congenital urethral obstruction, corrected at the age of 2. Case 2 was suffering from congenital hypoplasia of the kidneys.

Most of the serum biochemical measurements were made by conventional AutoAnalyzer techniques. Serum and urine calcium were determined by the method of Knowles (1968). Urine and arterial blood pH were measured by the Astrup procedure. The simultaneous serum and urine samples were collected as described by Nordin and Smith (1965). Calcium excretion (Ca_E) was expressed in mg./100 ml. of glomerular filtrate (G.F.) as described by Peacock *et al.* (1968). The upper normal limit of calcium excretion at normal or low serum calcium levels is 0.14 mg./100 ml. of glomerular filtrate.

Phosphate excretion (P_E) is also expressed in mg./100 ml. of glomerular filtrate. Phosphate excretion is a function of serum phosphate concentration, and a correction for this is provided by the "index of phosphate excretion," which is the difference between the observed and predicted phosphate excretion at any given level of serum phosphate. The normal limits of the index are ± 0.50 (Nordin and Bulusu, 1968).

Results

Presentation and Bone Status

Cases 4 and 8 presented with fractures of the femoral neck and tibia respectively; Cases 2 and 7 presented with knock knees; Cases 5 and 6 presented with bone pains and muscle weakness; and Cases 1, 3, and 9 were diagnosed in the course of investigation of their renal failure.

Bone x-ray films showed fractures or pseudofractures and/or rachitic changes in every case except Case 9, in whom the diagnosis of osteomalacia was confirmed by the reduced ash content (47%) of an iliac crest biopsy specimen (Morgan *et al.*, 1968). Spinal "density" by visual inspection was obviously increased in six of the cases. In all cases the metacarpal and femoral cortices tended to be thin, as previously reported by Nordin and Smith (1965) in the osteomalacia of steatorrhoea. Subperiosteal resorption of bone was not seen.

Serum Biochemistry

The blood urea levels ranged from 72 to 327 mg./100 ml. All the patients had severe metabolic acidosis (bicarbonate below 20 mEq/l.) with hyperchloraemia in all but the two cases (Cases 2 and 9) with the most severe renal failure. Arterial blood pH values ranged from 7.24 to 7.32. All the patients but one (Case 7) had hypocalcaemia (serum calcium below 9.0 mg./100 ml.), but the serum phosphate levels were variable—2.8 to 6.9 mg./100 ml. All the serum alkaline phosphate values were high except in Case 8, even allowing for the ages of the children. The serum calcium $\times$ phosphate products ranged from 25 to 50.

Clinical Data of Patients

Case	Age and Sex	Presentation	Renal Lesion	Bone Lesion	Serum or Blood								Urine					
					Urea (mg./100 ml.) (Normal Range 18-45)	Bicarbonate (mEq/l.) (Normal Range 20-30)	Chloride (mEq/l.) (Normal Range 99-112)	Arterial pH (Normal Range 7.35-7.40)	Calcium (mg./100 ml.) (Normal Range 9.0-10.6)	Phosphorus (mg./100 ml.) (Normal Range 2.5-4.0)	Ca $\times$ P (Normal Range 23-45)	Alkaline Phosphatase (K.A. units) (Normal Range 4-13 (in Adults))	Creatinine Clearance (ml./min.)	Lowest Urine pH (Normal < 5.4)	Calcium (mg./24 Hours) (Normal Range 100-300)	Ca_E (mg./100 ml. G.F.) (Normal < 0.14)	P_E (mg./100 ml. G.F.)	Index of Phosphate Excretion (Normal Range -0.50 to +0.50)
1	16 F	Renal failure	Pyelonephritis. Ileal bladder	L.Z.* (pelvis). Dense spine	184	16	112	7.29	7.7	4.9	38	53	8	6.8	27	0.25	3.7	+2.50
2	16 F	Myopathy rickets	Renal hypoplasia	L.Z. (pelvis). rickets	327	16	105	7.30	6.7	6.9	46	27	4	6.8	45	1.21	4.80	+2.60
3	53 F	Renal failure	Pyelonephritis. Colocystoplasty	L.Z. (pelvis). Dense spine	120	14	120	7.32	8.9	4.0	36	40	9	6.7	28	0.25	2.60	+1.85
4	60 F	Fracture	Pyelonephritis	Triradiate pelvis. Femoral neck fracture. Dense spine	140	17	110	7.30	8.2	3.4	28	15	10	6.9	20	0.21	3.10	+2.65
5	61 F	Myopathy	Pyelonephritis	L.Z. (pelvis). Dense spine	90	16	113	7.27	7.0	3.6	27	85	11	5.9	14	0.18	1.70	+1.15
6	65 F	Myopathy	Pyelonephritis. Colonic bladder	L.Z. (femur). Dense spine	72	17	126	7.29	7.5	4.1	31	49	19	6.9	23	9.96†	1.95†	+1.15
7	4 M	Rickets	Megaureter	Rickets	150	19	115	7.24	9.8	5.1	50	40	9	5.4	122†	0.15	2.18	+0.88
8	8 M	Fracture myopathy	Pyelonephritis. Ureterostomy	Rickets. Tibial fracture. Dense spine	98	17	109	7.29	8.8	2.8	25	20	13	6.5	50	0.20	1.90	+1.75
9	54 M	Renal failure	Pyelonephritis. Colonic bladder	Normal	200	13	105	7.29	7.3	5.8	43	24	5	7.7	52	0.45	4.23	+2.58

* Looser zones. † On vitamin D.

Urine Biochemistry

Creatinine clearances were all below 20 ml./min. The 24-hour urinary calcium was low in all cases (14 to 52 mg.), but when fasting calcium excretion was expressed in mg./100 ml. of glomerular filtrate it was raised—that is, over 0.14—in all cases. Phosphate excretion expressed in mg./100 ml. of glomerular filtrate was very high relative to the serum phosphate level in all cases, indicating reduced tubular reabsorption of phosphorus. This is most easily seen when the values are expressed as “indices of phosphate excretion,” all of which are well above the upper normal limit of +0.5. Despite the severe metabolic acidosis (which made acid loading unnecessary) the lowest urine pH was 5.4 (Case 7) and over 5.8 in the remainder. It is possible that the tubular lesion in this case was in fact a bicarbonate-losing state rather than a conventional acidifying defect (Cochran and Nordin, in preparation).

Discussion

The patients we have described were suffering from unequivocal osteomalacia or rickets as shown by bone x-ray films, serum alkaline phosphatase levels, fractures or pseudofractures, bone pain, and, in four cases, definite muscular weakness affecting the hip girdle in particular, which has been described by Stanbury and Lumb (1962) and others. In the only doubtful case (Case 9) the diagnosis was confirmed by bone biopsy.

The striking feature of this series was the severe metabolic acidosis, which characterized all the cases. The fact that this acidosis was associated with impairment of urinary acidification and hyperchloraemia implies that it was not simply due to general renal failure but had a tubular component similar to that in the acquired type of acidification defect, which we have previously described (Cochran *et al.*, 1968). It is noteworthy that in all but Cases 2 and 7 the underlying renal lesion was chronic pyelonephritis. Five of the patients had undergone some kind of reconstructive surgery to the bladder—Case 1 for spina bifida, Case 3 for tuberculosis of the bladder, Cases 6 and 9 for carcinoma of the bladder and Cases 7 and 8 for urethral obstruction.

Since these nine cases represent our total experience of uraemic osteomalacia over a four-year period, and since all of them had particularly severe chronic metabolic acidosis, we suggest that acidosis may be a factor in the genesis of this bone lesion, despite the contrary view expressed by Stanbury (1968). We have seen five other patients with a comparable degree of chronic metabolic acidosis. In only one of these was osteomalacia excluded by thorough investigation. The other four presented some features of osteomalacia but were not included in this study owing to the incompleteness of the data.

There are at least two ways in which acidosis might affect bone mineralization. Firstly, the proportion of total serum phosphate present in the trivalent form (PO_4''') falls with pH. Although the proportion of phosphate present in this form at physiological pH is very small, it is this ion species that is directly involved in the precipitation of calcium phosphate in alkaline media (Nordin, 1959). Reduction of plasma pH from 7.4 to 7.2 reduces the proportion of phosphate present in the trivalent form by about half (Holt *et al.*, 1925), and it could therefore be argued that severe metabolic acidosis produces a form of metabolic “hypophosphataemia” even in the presence of an apparently normal total serum phosphate concentration. This is not to imply that the phosphate concentration at the bone surface is necessarily the same as that of serum, but simply that the former is probably a function of the latter.

Secondly, acidosis may also have contributed to our patients' hypocalcaemia by reducing calcium absorption (Litow *et al.*, 1967) and tubular reabsorption (Lemann *et al.*, 1967). The concentration of calcium in the serum must reflect an equilibrium between the rates at which calcium enters and leaves the blood

stream. This being the case, renal tubular reabsorption of calcium is an important determinant of serum calcium concentration. Although the total urinary calcium of our patients was low and might therefore seem unimportant in this respect, it is clear that their calcium excretion was high relative to filtered load and that the reabsorption of calcium per nephron was abnormally low. This may be significant in the presence of malabsorption of calcium. Expressed differently it could be said that the same rate of calcium throughput (25–50 mg. per day) would sustain a higher serum calcium if tubular reabsorption were normal.

Thus while our cases confirm the well-known observation that the serum calcium $\times$ phosphate product is generally normal in uraemic osteomalacia, the serum calcium concentration was generally low (as it was in many of the cases of Stanbury and Lumb, 1966) and so was the concentration of trivalent phosphate ions. Either or both of these abnormalities might affect bone mineralization even if this process is under cellular control, since the cells concerned have still to extract the necessary calcium and phosphorus from extracellular fluid. It may be that transport through the cell is reduced when either the calcium or the relevant phosphate ion concentration falls. This would explain the common association between a low serum calcium $\times$ phosphate product and defective mineralization, since either hypocalcaemia or hypophosphataemia or both must tend to reduce the product. On the other hand, we have examined the data of Garner and Ball (1968) on bone mineralization in malabsorption and renal failure and find that in both these groups the serum calcium $\times$ phosphate products reported by them correlate significantly with the degree of mineralization ($P < 0.01$ in malabsorption, and < 0.02 in renal failure), whereas when the calcium and phosphorus levels are considered separately the correlations are less significant in malabsorption and not significant in renal failure. In our cases we cannot say whether hypocalcaemia or a low trivalent phosphate ion concentration or the product was responsible for the osteomalacia, but we do suggest that their severe acidosis was relevant to their disease and could have operated in one or other of the ways we have described.

There is yet another factor which may contribute to the hypocalcaemia in cases of this kind—namely, the paradoxical increase in calcium deposition in bone which has been shown by isotope studies (Caniggia and Gennari, 1967; Joplin *et al.*, 1967; Miravet *et al.*, 1967; Nordin and Smith, 1967) and confirmed by the quantitative histological measurements of Frost (1967). This seems to be due to the fact that although the mineralization of individual osteons is slowed down in osteomalacia, the number of mineralizing sites is so greatly increased that the total rate of calcium deposition is frequently higher than normal. Not only would this high rate of calcium removal from plasma tend to lower the calcium concentration but it may be the cause of the spinal osteosclerosis which is a feature of osteomalacia of all kinds (Nordin and Smith, 1967) unless it is superimposed on a preceding osteoporosis. Another factor in the development of the sclerotic spine may be the progressive coating of the trabeculae with osteoid, which makes the bone resistant to resorption (Stanbury, 1967). These hypocalcaemic factors are of course opposed by other processes which tend to maintain the serum calcium. The most important of these is parathyroid-induced bone resorption, which appears to involve cortical bone in particular (Pellegrino and Biltz, 1965), possibly because it turns over more slowly than trabecular bone and is therefore less liable to be coated with osteoid. This parathyroid-induced bone resorption may explain the cortical bone loss seen in our cases and the long bone fractures and pseudofractures which are characteristic of osteomalacia.

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Effect of Propranolol on Exercise Tolerance of Patients with Atrial Fibrillation

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Summary: Six patients with atrial fibrillation who were taking digitalis were exercised before and after 30 mg. of propranolol twice daily. Though there was a lower pulse rate at rest and on exercise in all patients, three suffered deterioration of exercise tolerance. It is concluded that propranolol does not improve the exercise tolerance of patients with atrial fibrillation whose resting ventricular rate is controlled with digitalis.

Introduction

It has been shown experimentally in animals that, under exercise conditions, increasing pulse rate is associated with increasing cardiac output up to a critical value, after which diastolic filling of the ventricles is impaired and the cardiac output falls (Corday and Irving, 1961). It is not known at what level the change occurs in human hearts in sinus rhythm, but some physiologists have suggested that it is between 160 and 180/minutes (Rushmer, 1960; Wood, 1968). Ventricular rates during submaximal and maximal exercise are about 10% higher than this in patients with atrial fibrillation who are taking digitalis (Hornstein and Bruce, 1968). Propranolol, which is known to reduce the ventricular rate at rest and during exercise (Harrison *et al.*, 1965; Chamberlain, 1966; Schulman *et al.*, 1967), may improve the exercise tolerance of patients with atrial fibrillation via this mechanism. This improvement might outweigh the negative inotropic action of the drug and produce a net benefit.

A double-blind trial was therefore devised to determine whether the addition of propranolol resulted in clinical improvement in the exercise tolerance of patients with atrial fibrillation taking digitalis.

Patients and Methods

Outpatients with chronic atrial fibrillation taking digitalis and whose general medical condition had been stable for some weeks were selected. The clinical details are shown in the Table. Five of the six had rheumatic heart disease and one was euthyroid after radiation therapy for thyrotoxicosis.

The patients continued to take their usual therapy, including digitalis, and were subjected to exercise on three occasions, each a week apart. After the first test they were allocated, by double-blind method, either propranolol 30 mg. twice daily or a placebo for the first week, and were given the alternative after the second test.

Before each exercise test the patients were interviewed, their pulse rate and arterial pressure were taken, and they were examined for signs of cardiac failure. Each patient then undertook the same three levels of exercise on a treadmill at a 5° slope for three minutes. The maximum level achieved by each patient on the first test was attempted at both subsequent tests.

The heart rate and electrocardiograph were monitored throughout the test, and the heart rate over the last 30 seconds was recorded by means of a Royal Melbourne Hospital cardiac cycle counter (Mark II). The arterial pressure was taken immediately the exercise was completed.

Results

Fig. 1 illustrates the difference in heart rate at rest and on exercise with and without propranolol. In the one patient who did not actually exercise at 3 km./hour an estimated pulse rate was determined from the line of best fit on a pulse-rate/work-load graph. In all cases there was a reduction in pulse rate after propranolol, and the mean reduction of pulse rate was 28/minute at rest, 39/minute at 3 km./hour, and 36/minute at the maximum exercise level.

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