VITAMIN-D-RESISTANT OSTEOMALACIA

BY

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[WITH SPECIAL PLATE]

Rickets in childhood and osteomalacia in adults are generalized disorders of bone in which the primary osseous defect is a lack of ability to calcify osteoid bone matrix. The essential biochemical abnormalities consist of a reduced serum inorganic phosphorus level, a low or normal serum calcium level, and a raised serum alkaline phosphatase. Radiologically there is usually generalized demineralization, with the well-known rachitic changes at the growing bone-ends in childhood, and with spinal compression and multiple lines of rarefaction, or pseudo-fractures (Looser's zones), in the adult.

Osteomalacia (using the term now to include rickets) may be produced by a lack of absorption of calcium and phosphorus from the gut. In this intestinal group there may be a simple lack of vitamin D, or an inability to absorb the vitamin and the minerals because of an intestinal disorder associated with steatorrhoea. In the renal tubular group there is a normal intestinal absorption of minerals, but an increased loss of either calcium or phosphorus, or both, in the urine. This is the case in Fanconi's syndrome, in renal tubular acidosis ("hyperchloraemic nephrocalcinosis"), in idiopathic hypercalciuria, and, presumably, in hypophosphataemic glycosuric rickets (Kyle, Meroney, and Freeman, 1954).

Having considered these (and omitting renal glomerular osteodystrophy and the new syndrome of "hypophosphatasia"), we are left with a form of rickets which is unaccompanied by any other outstanding biochemical lesion and which is highly refractory to the effect of vitamin D. This "vitamin-D-resistant rickets or osteomalacia" is frequently hereditary (Pedersen and McCarroll, 1951; Dent and Harris, 1956), and may first appear at any age from birth to adult life. It is uncertain whether the rarer adolescent type of "acquired" resistance (for instance, McCance's (1947) case) is fundamentally different from the childhood disease. The problem is one of basic aetiology. Albright and Reifenstein (1948) claimed that the condition was caused by a resistance to the normal effect of vitamin D on the intestinal absorption of calcium, whereas McCune *et al.* (1943) suggested, and later Dent (1952) strongly supported, the concept of a primary loss of phosphorus via the urine due to a diminished renal tubular reabsorption. Dent and Harris (1956), however, have recently agreed that some defect of intestinal absorption must also be present.

The present paper is written largely in an attempt to add something to the consideration of this problem. A second reason is to consider the mechanism of production of Looser's zones in osteomalacia, which have

recently been claimed to be caused by normal arterial pulsation against a weakened bone (LeMay and Blunt, 1949; Steinbach *et al.*, 1954).

Case Report

A coloured female aged 32 was referred from the orthopaedic department with inability to walk, painful back, and decalcified bones. Apparently she had always been small, but had walked normally until eight years previously, when, at the age of 24, she developed severe back pain, generalized muscular weakness, and reduced movement of lower limbs. She has not walked since. Her diet and upbringing had not been abnormal and there was no history of intestinal disorder. The menarche occurred at age 16, and menstruation had remained normal and regular. The family history was unreliable.

Inspection revealed a tiny, thin, feeble, short-necked, pigeon-chested, knock-kneed kyphoscoliotic dwarf (Fig. A) of moderate intelligence. She had limitation of movement of spine, hips, and knees and was unable to stand. Her bones were not tender. Secondary sexual characters were well developed. No cystine crystals were seen in the eyes. Weight 52 lb. (23.6 kg.); height 50 in. (1.27 m.), span 52 in. (1.32 m.), upper segment 22 in. (56 cm.), lower segment 28 in. (71 cm.). Haematological and urine examination showed no abnormalities. X rays revealed gross generalized decalcification with mollities. The vertebrae were uniformly compressed into biconcave disks. There were multiple near-symmetrical bands and zones of decalcification (Looser's zones) in shoulder girdles, ribs, and pelvis, and one mandible. None of the stigmata of old rickets were present. There were no changes suggestive of hyperparathyroidism, in particular no cortical erosions of the phalanges.

Preliminary Investigations.—

Serum: calcium 9–11 mg. per 100 ml. (several estimations); inorganic phosphorus 1.2–2.5 mg. per 100 ml. (several estimations); alkaline phosphatase 16–28 units (Shinowara); cholesterol 151 mg. per 100 ml.; sodium 140, potassium 3.4, and chloride 99–106 mEq per litre; carbon dioxide 55 vols.%. Blood urea 17 mg. per 100 ml.; urea clearance 32% (standard) and 33% (maximum) of normal (uncorrected for body size; corrected = 64%). Phenolsulphonphthalein test: 2.5 mg. within 15 minutes (after 6-mg. intravenous dose). Urine calcium less than 20 mg. per day; phosphorus 150–350 mg. per day. Amino-aciduria: no excess of any amino-acid (paper chromatography). Stool rather hard, brown, and microscopically normal. Seven-day fat balance: 99% absorption of 70 g. daily intake. In response to acid feeding (120 gr. ammonium chloride in divided doses within 24 hours) urine pH fell from 6.85 to 4.75, urine ammonia rose from 1 to 3.3 mEq per hour, titratable acid rose from 0.1 to 1.0 mEq per hour, and chloride rose from 0.55 to 6.6 mEq per hour.

Diagnosis.—It was apparent from clinical, radiographic, and biochemical evidence that the patient suffered from osteomalacia, which, despite her story, had presumably been active before puberty to account for the shortness of the limbs. (It should be noted that, despite the limbs being relatively longer than the trunk, they are nevertheless abnor-

FIG. A.—The patient on her first admission.

FIG. B.—Metabolic balance studies. Total intake is plotted downwards from baseline, and faecal and urinary components are charted from bottom of intake. Thus a white portion below baseline indicates a positive balance while if column rises above baseline there is a negative balance. The calcium balances 1, 2, and 3 are repeated below the other calcium balances on a scale five times as large. Note excessive stool calcium on low calcium intake, effect of vitamin D in lowering stool calcium and phosphorus, and eventual raising of serum phosphorus while on 4.8 million units of calciferol per day. For further discussion see text.

mally short, being equivalent to a height of only 52–56 in. (1.37–1.42 m.), which would certainly be unusually small for a coloured woman. This makes it seem likely that the disease process had produced stunting of limbs as well as of spine.) As possible causes, steatorrhoea, Fanconi's syndrome, and renal tubular acidosis appeared to have been ruled out by the above-mentioned findings. It seemed most unlikely that the condition could be due to simple vitamin-D lack, but in order to exclude this possibility a trial of five weeks on 10,000 units of calciferol daily was made, but this was without effect on the patient's symptoms or biochemical abnormalities. A diagnosis of acquired vitamin-D-resistant osteomalacia without acidosis or evident renal tubular disease was therefore made.

Second Admission (one year later).—The patient received 1.2 million units of calciferol intramuscularly daily for about six months after her discharge from hospital. She had remained stronger and brighter, was pain-free, and was actively disporting herself with one crutch, despite the six months' discontinuance of vitamin D. In the ward her weight rose from 52 to 55 lb. (23.6 to 25.0 kg.).

Notwithstanding her clinical improvement, the radiological and biochemical findings were virtually the same as on the first admission; in particular, the Looser's zones were unhealed and biochemical osteomalacia was still present. On admission the serum phosphorus was 1.5 mg. per 100 ml. and the alkaline phosphatase 18 Shinowara units.

Special Metabolic Investigations

A. Metabolic Balance Studies (Fig. B)

During the patient's first admission, only three seven-day balance periods were possible. These studies were carried out after the method of Reifstein *et al.* (1945) and are so charted. Calcium and phosphorus were determined in aliquots of the diet, and the results were checked by calculation from food tables. After a change of diet two weeks were allowed for equilibration before a fresh balance was started.

First Period.—During the first balance the patient's diet was of her own choice. We were surprised to find how low in calcium this was (little more than 200 mg. per day); however, this sort of calcium intake is commonly found in the underprivileged classes in South Africa, whereas osteomalacia is not. On this intake she was almost in balance for calcium. The retention of phosphate may well have been related to the physiotherapy and muscle training she received the whole time she was in hospital, during which she gained some 4½ lb. (2.04

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FIG. 1.—Radiograph of pelvis. Note wide symmetrical Looser's zones in pubic and ischiopubic rami, and narrow zones running from angle of brim of pelvis.

FIG. 2.—Aortogram to show relation of arteries to Looser's zones. In tracing, continuous line indicates pelvic outline. Note that superior gluteal artery (1) appears to be in fairly close superimposition over one zone, whereas no arteries are to be found near wide pubic zones (2).

FIG. 3

FIG. 4.—Looser's zone close to last molar tooth. Incidentally lamina dura around teeth has largely disappeared.

FIG. 3.—Left shoulder girdle. Note Looser's zones at surgical neck of humerus, in scapula close to glenoid cavity, and traversing greater wing from lateral border.

M. RIDDLE *ET AL.*: NEPHROTIC SYNDROME COMPLICATING MERCURIAL DIURETIC THERAPY

FIG. 1

FIG. 2

FIG. 3

FIG. 4

FIG. 5

FIG. 1.—Epithelial degeneration and necrosis in proximal convoluted tubules (top left and bottom right), with regeneration of tubular epithelium (centre). (H. and E. ×75.)
 FIG. 2.—Proximal convoluted tubules showing epithelial necrosis with vacuolation of cytoplasm and nuclear pyknosis. Brush borders are preserved. Cellular debris in tubular lumina. (H. and E. ×200.)
 FIG. 3.—Proximal convoluted tubules showing hyaline droplet degeneration. (H. and E. ×200.)
 FIG. 4.—Tubules showing epithelial regeneration. A binucleate cell is present (lower centre). (H. and E. ×200.)
 FIG. 5.—Tubules showing regeneration. A mitotic figure can be seen near top left-hand corner. (H. and E. ×200.)

kg.) in weight. The urine phosphorus, however, is noticeably low in comparison with the high faecal level.

Second Period.—On a low calcium intake of only 100 mg. per day the negative balance of 100 mg. was almost entirely caused by the faecal loss being higher than the intake. This apparent paradox is possible if a proportion of the calcium excreted into the gut via the bile and other intestinal secretions is not reabsorbed.

Third Period.—This balance study was performed after the patient had already been on 1.2 million units of calciferol daily by injection for seven days. Her calcium intake was not increased over her original chosen amount, but there is now a positive retention of this mineral, due to reduction in faecal loss. There is also diminished faecal phosphate loss, but her diet during this balance period contained considerably less total phosphorus, so that the significance of this is difficult to assess. The second and third balance periods were each started three days after a phosphate infusion experiment.

Fourth Period.—The later balance studies on her return visit showed a remarkable retention of all elements examined. With regard to the calcium and the equivalent phosphate moiety, we wondered whether the calciferol received some months previously was still active in Period 4, having waited, so to speak, for a higher intake of minerals upon which it could work. The home intake of these was undoubtedly low.* It is to be noted that the faecal calcium and phosphorus are both considerably lower in Period 4 than in Period 1, despite a far higher intake.

Fifth, Sixth, and Seventh Periods.—The calciferol in Period 5 made no apparent change to the absorption. In Periods 6 and 7 the enormously high dose of nearly 5 million units daily produced a further fall in faecal calcium and phosphorus, indicating increased absorption. Some increase in urinary phosphorus has occurred, coincidental with a rise in serum phosphate. The retention of phosphorus, nitrogen, and potassium was accompanied by a weight gain of 2 lb. (0.907 kg.) over the period of balance study (15 days).

Comment on Balance Studies.—The absorption of calcium and phosphorus before treatment is poor. Vitamin D (as calciferol) in very large doses increases the absorption of these minerals. The effect of the first intensive course of vitamin D is still apparent after six months.

B. Effect of Parathyroid Extract (Ellsworth-Howard Test)

Parathyroid extract ("parathormone") of proved urine-phosphate-raising potency, was injected intravenously in the high dosage of 1,000 U.S.P. units after three control periods of one hour each. The urine was collected by catheter. There was no significant change in the urinary phosphate over the next three hours, nor in the serum level of calcium. The urine calcium, however, showed a distinct rise (Table I), and the serum phosphorus also became higher.

TABLE I.—Effect of Parathyroid Extract (1,000 Units Intravenously)

Time	Urine		Serum	
	Phosphorus (mg./hour)	Calcium (mg./hour)	Phosphorus (mg./100 ml.)	Calcium (mg./100 ml.)
8-9 a.m. . .	8.0	0.3		
9-10 " . .	10.4	1.0	1.24	9.7
10-11 " . .	Some of this specimen was lost			
	1,000 U.S.P. units "parathormone"			
11 a.m.-12 noon . .	9.5	2.5		
12-1 p.m. . .	9.4	1.7	1.83	9.5
1-2 " . .	8.3	±0.4		

*Gross errors in analyses are unlikely. The dietary intake was checked by estimation from tables. The low excretion in the case of calcium is conditioned by a low faecal figure, while in the case of nitrogen and potassium the urine is the important channel of excretion. Calculations were double-checked and each balance treated entirely separately.

C

On the second admission 400 units of parathormone were given intramuscularly daily for four days. There was a delayed (fourth-day) rise in urinary calcium and phosphorus. The calcium actually increased from 1.4 mg. to 64 mg. per 24 hours.

C. Renal Handling of Phosphate and the Effect of Infused Calcium

(1) Accurate investigation of the Tm (maximum tubular reabsorption) for phosphate (TmP) was carried out in the experiment in which calcium gluconate was infused. (*Inter alia* we desired to see whether intravenous injection of calcium affected the TmP.) The method was as follows. The patient was maintained on a diet of constant calcium and phosphorus content for several days before the experiment, which was done in the fasting state with the patient supine. A priming dose of inulin and buffered sodium phosphate at pH 7.4 was administered intravenously to raise serum levels of the inulin and inorganic phosphorus to approximately 40 mg. and 10 mg. per 100 ml. respectively, and these substances were infused at a constant rate thereafter to maintain these serum levels for the first 3½ hours of the experiment. Urine samples were obtained at accurately timed 20-minute intervals during the first 3½ hours by bladder washout with distilled water and air, and subsequently at two-hourly intervals through an indwelling catheter for 24 hours. Blood samples were taken without anticoagulant 2½ minutes before the midpoint of each 20-minute period. After two 20-minute periods 280 mg. of calcium (as 30 ml. of 10% calcium gluconate) was infused into a leg vein over a period of 20 minutes. We attempted to maintain the patient in a state of constant hydration, enough fluid being given by mouth to maintain a constant total intake.

Results are given in Table II. There was a mean inulin clearance of 76.5 mg. per minute which was not obviously affected by intravenous calcium. The serum phosphate was

TABLE II.—Results of Intravenous Calcium and Phosphate Infusion

Period	G.F.R. (Inulin Clearance)	Serum Ca (mg./100 ml.)	Serum P (mg./100 ml.)	Urine Ca (mg./spec.)	P Load (mg./min.)	Urine P (mg./min.)	Tubular reabs. (TmP) (mg./min.)	TmP × 100	G.F.R.
Blank									
1	70	9.1	1.7						
2	78	8.0	8.5	0.6	6.0	3.5	2.5	3.6*	
		7.4	8.0	0.5	6.3	4.2	2.1	2.7	
Calcium infusion starts									
3	88	7.4	7.5	0.4	6.8	4.7	2.0	2.3	
4	87	8.6	7.2	1.0	6.3	4.2	2.1	2.5	
Calcium infusion ends									
5	77	9.6	7.2	1.2	5.6	3.6	2.0	2.6	
6	65	8.8	7.0	0.6	4.6	2.9	1.7	2.6	
7	80	7.9	6.8	0.5	5.5	3.2	2.2	2.8	
8	72	7.7	6.7	0.4	4.8	3.2	1.6	2.3	
9	73	7.1	6.7	0.4	4.9	3.2	1.6	2.2	
10	74	7.4	6.6	0.3	4.8	2.9	2.0	2.7	

* TmP for the first period is always high and should be disregarded.

raised from 1.7 to 8 mg. per 100 ml. by the priming dose, but it fell gradually during the infusion. At serum phosphorus levels considerably higher than the mean threshold the TmP remained at some 2 mg. per minute, which means that some 2.5 mg. of phosphorus was reabsorbed per minute per 100 ml. of glomerular filtrate. This value was not affected by calcium infusion.

The final finding of this experiment refers to the rapid withdrawal from the circulation and the retention of the infused calcium. It may be seen from Table II that the serum calcium was depressed by the phosphate infusion, and rose only slightly and transiently after the calcium infusion, although the calculated elevation was to 14 mg. Furthermore, almost 100% of the injected 280 mg. was retained,

there being a total extra-urinary excretion of some 2-3 mg. only during the test period. (A similar depression of serum calcium by phosphate infusion was seen on another occasion when the TmP was measured.)

(2) On the patient's second admission the TmP was again measured by the same method. Calcium was not infused. The serum phosphorus was maintained at 6 mg. per 100 ml. and the percentage of reabsorption of the glomerular load was around 50% (indicating that the Tm had been exceeded). The mean TmP was found to be 2.3 mg. per minute—that is, 2.8 mg. per 100 ml. of glomerular filtrate. This was a little higher than the previous level, but still below our normal range. (Our figure for normal values for TmP, taking the mean of 48 investigations in different subjects, is 4.05 ± 0.7 mg. per 100 ml. filtrate formed.)

(3) A calcium infusion experiment was again performed, this time without concomitant intravenous phosphate. Because of the rapid withdrawal of extra calcium from the blood stream found in the first experiment, a total of 930 mg. of calcium was infused, some three times the calculated amount necessary for raising the serum calcium to 14 mg. per 100 ml. In this experiment the calcium was infused at an increasing rate from the beginning of the first period until the end (of Period 9). As may be seen from Table III: (a) the serum calcium rose from 10.1 to 14.1 mg. per

TABLE III.—Results of Second Intravenous Calcium Infusion

Period	Minute Vol. (ml.)	G.F.R.	Serum Ca (mg./100 ml.)	Serum P (mg./100 ml.)	Urine Ca mg./spec.	P. Load mg./min.	Urine P mg./min.	TmP	TmP $\times 100$	G.F.R.
Blank										
1	10-0	70	10-2	1-6	0-4	1-13	0-09	1-04	1-49	
2	9-8	62	10-5	1-7	0-5	1-03	0-08	0-95	1-53	
3	11-0	63	10-7	1-7	1-9	1-07	0-09	0-98	1-56	
4	12-2	65	10-7	2-1	3-8	1-35	0-08	1-27	1-95	
5	8-5	58	11-2	2-0	4-8	1-17	0-07	1-10	1-90	
6	9-0	69	11-8	2-4	9-5	1-64	0-09	1-55	2-25	
7	8-8	67	13-0	2-6	13-8	1-71	0-10	1-61	2-40	
8	8-5	56	13-5	2-4	15-0	1-45	0-80	1-37	2-45	
9	9-4	57	14-1	2-4	51-0*	1-35	0-07	1-28	2-25	

* Remainder of 24-hour period. Total (24 hours) = 112 mg.

100 ml.; (b) the serum phosphorus rose from 1.6 mg. to a maximum of 2.6 mg.; (c) there was no appreciable change in urine phosphorus; (d) there was no appreciable change in glomerular filtration rate; (e) despite some increase in phosphate load and minute tubular reabsorption, the latter never reached the previously calculated Tm, so that no change in this function could be measured; (f) no increase in minute volume was produced; (g) some 89% of the infused calcium was retained (apparently permanently).

Comment on Results of Infusion Experiments.—(1) The low capacity of the renal tubules to reabsorb phosphorus might be primary tubular defect or an effect of secondary parathyroid overactivity (see below). (2) Calcium gluconate (or laevulinate) infused into normal subjects always produces a diuresis in our experience (18 subjects). It failed to have this effect in the present case. (3) The remarkable retention of the infused calcium and its rapid removal from the circulation indicate that the bones were avid for this mineral. Kyle, Schaaf, and Erdman (1954) found similar retention in other varieties of osteomalacia, but in the vitamin-resistant case of Segar *et al.* (1956) the bones appeared incapable of extracting the infused calcium, so that 75% was recovered in the urine. (4) The rise in serum phosphorus in the third experiment was unaccompanied by any change in urine phosphorus, and must therefore be a result of internal redistribution of phosphate or, less likely, of sudden absorption from the gut. In both normal and hypoparathyroid subjects it is also necessary to invoke a shift of phosphorus from intracellular to extracellular fluid compartment to explain the phenomena following calcium infusion.

D. Effect of Calciferol on Phosphate Metabolism

(1) During the patient's first admission, after she had been treated with parenteral calciferol in doses of 600,000 units for 10 days followed by 1,200,000 units daily for four days, the TmP was again measured. The infused phosphate raised the serum level to around 6 mg. per 100 ml., and, since only 27% of the filtered load was reabsorbed, it may be presumed that the maximum reabsorptive capacity of the tubules had been exceeded. The TmP was unchanged by the calciferol at 1.7 mg. per minute, or, correcting for glomerular filtration rate (G.F.R.), 2.5 mg. reabsorbed per 100 ml. of filtrate formed. It is noteworthy that our estimations of the capacity of the tubules of the patient to reabsorb phosphorus are remarkably constant (2.5-2.8) when expressed as mg. reabsorbed per 100 ml. of glomerular filtrate formed.*

We conclude, therefore, that the low capacity of the patient's tubules to reabsorb phosphorus was unaffected by intravenous calcium or by calciferol in the dose given. Because of the length of time which may be required for the full effect of calciferol to become apparent, it is possible that a change in tubular reabsorption capacity would have been found had the test been repeated after longer treatment.

(2) In the second admission, calciferol in doses of 4.8 million units daily led to a rise in serum phosphorus to normal levels (Fig. B). Albright and Reifstein (1948, p. 127) made similar observations in a case of resistant osteomalacia, and concluded that the raised serum phosphate was caused by a reduction in parathyroid activity consequent upon a raising of serum calcium. However, neither their nor our balance charts indicate any fall in urine phosphorus, which would have to be the first happening on this line of reasoning.

E. Effect of Calciferol on the Patient's Disease

During the first admission calciferol in the large doses mentioned above had no discernible effect on serum or urinary calcium or phosphorus: there was no clinical change or alteration in weight after 17 days on 1.2 million units. On the other hand, the increased absorption and retention of calcium shown by balance study suggested that other good effects would later accrue. In fact, as was seen a year later, a clinical improvement had continued. Nevertheless nearly 5 million units of calciferol daily was necessary before elevation of serum phosphorus occurred, while even on this dose there was no rise in serum or urinary calcium.

Discussion

Pathogenesis

In order to state the problem of pathogenesis or resistant osteomalacia the rival theories are shown diagrammatically.

(1) "Albright Theory" (intestinal block).

*It may be noted that this method of expression of TmP automatically corrects both for body size and for incomplete bladder emptying.

On this theory the healing effect of massive doses of vitamin D is produced by overcoming the block. The parathyroid activity should then return to normal.

(2) "McCune-Dent Theory" (low phosphate threshold).

On this theory the healing effect of massive doses of vitamin D is more complicated and may be partly due to the "forcing-in" effect of calcium and phosphorus through the gut. Dent believes that vitamin D in large doses actually raises the TmP; this effect would plainly be curative.

Consistent with either theory are: (1) Low TmP (about 1.0 mg. per minute in the case of Segar *et al.* (1956); about 2.0 mg. per minute in our case). (2) Curative effect of massive dosage of vitamin D. (3) Failure of phosphate diuresis after parathyroid extract. On the first theory the tubules would already be responding, possibly maximally, to endogenous parathyroid hormone, while on the second theory the abnormally low TmP might well be resistant to further depression.

In favour of the first theory: (1) Secondary hyperparathyroidism with hyperplasia has been found on exploration of parathyroid glands (Linder and Vadas, 1931; Highman and Hamilton, 1936; Albright *et al.*, 1937). (2) Poor absorption of calcium and phosphorus has been found by Albright and Reifstein (1948) and by Saville *et al.* (1955) and is clearly shown in the balance data of our case. (3) Intravenous calcium would be expected to raise the serum calcium, to depress parathyroid activity, and so raise the depressed tubular reabsorption of phosphorus. In our case the phosphate load presented to the tubules during the second calcium infusion never exceeded the low maximal reabsorption, so we cannot draw any conclusions along these lines. In the case of Segar *et al.* (1956) the TmP was almost doubled by the calcium infusion. (4) In our case calciferol increased calcium absorption and produced symptomatic improvement without any change in tubular reabsorption of phosphate. (5) Some, but not all, cases (including ours) have shown a lowered urinary calcium with a normal serum level. By analogy with ordinary vitamin-D-lack rickets this is not unexpected.

Against the first theory: (1) Not all cases have low urine calcium (McCance, 1947; Albright and Reifstein, 1948; Segar *et al.*, 1956), although this is probably invariable in ordinary rickets. (2) No cases with a low serum calcium seem to have been reported; this again is unlike ordinary rickets. (3) The bones show no features of osteitis fibrosa, as would be expected with secondary hyperparathyroidism. This comment applies also to ordinary rickets. (4) The occurrence of glycosuria in some cases cannot be explained.

In favour of the second theory: (1) There is a consistently normal serum calcium. (2) There is an analogy with other functional renal tubular disorders (for example, Fanconi syndrome). (3) The glycosuria in some cases is easily explicable on the basis of associated tubular dysfunction.

Against the second theory: (1) The low urine calcium usually found is inexplicable. (2) There is no apparent reason for parathyroid hyperplasia. (3) Since intestinal absorption is unimpaired, there appears to be no explanation for the high faecal calcium and phosphorus. (This fact has been admitted by Dent and Harris, 1956.) (4) Intravenous calcium would not be expected to alter an abnormally depressed tubular reabsorption of phosphate (which clearly happened in the case of Segar *et al.*).

It is plain that there are arguments in favour of both theories. Certainly it should not be assumed (as appears to be done by British authors recently: Rose, 1956) that the renal tubular theory is correct. There is perhaps more in favour of the Albright theory.

We should like to suggest another possibility—namely, that there is more than one variety of resistant osteomalacia, with more than one basic pathogenesis. In favour of this idea are: (1) The irreconcilability of the arguments in favour of either *single* theory. (2) The strange finding of very low urinary calcium in some cases (as in ordinary rickets) and of normal or even high urinary calcium in others. In this connexion, a raised urinary calcium secretion has been found in the *glycosuric hypophosphataemic* group (Anderson *et al.*, 1952), suggesting a syndrome with multiple defects of tubular function (Jackson and Linder, 1953), of which one may be a diminished reabsorption of filtered calcium, reminiscent of "idiopathic hypercalciuria." (3) The case reported by Segar and co-workers, in which neither theory seems to afford adequate explanation. This patient was unable to retain either absorbed or infused calcium, so that large doses of vitamin D, although increasing calcium absorption, were not curative. In this case there appears to have been an additional "internal" or skeletal defect. (4) Dent (Dent and Harris, 1956) claims certain distinctions between the childhood and later types of the disorder, in particular an excess of urinary glycine in the adolescent cases he has examined. (This was not present in our case.)

Diagnosis

The present patient seems to have a primary defect in intestinal absorption. Thus she has a defective absorption shown on balance studies, correctable by massive doses of calciferol. She also shows a lowered tubular reabsorptive capacity for phosphate, but whether this is a primary defect or secondary to parathyroid activity or other agency we cannot say. We therefore label her condition as acquired vitamin-D-resistant osteomalacia with intestinal block and reduced tubular reabsorption of phosphate.

Pathogenesis of Looser's Zones

Looser's zones are bilaterally near-symmetrical bands of uncalcified tissue (*Umbauzonen*) which occur particularly in the ribs, shoulder girdle, pelvis, upper end of femur, tibia, and fibula. They are probably pathognomonic of osteomalacia, and may appear even when there is no radiographic evidence of demineralization (Milkman's syndrome). LeMay and Blunt (1949) found by anatomical dissection that the zones coincided with sites in which bones came into close connexion with arteries, and suggested that they were caused by continuous pulsation beating against a softened cortex. Steinbach and co-workers (1954) claimed to confirm this by arteriography, showing some of the pseudo-fractures to be in proximity to an abnormal obturator artery in one case. (We are, however, not at all impressed with the relation of the lower pair of zones to the artery as shown in these authors' Fig. 6.)

After consultation with Dr. E. L. Allen, Professor of Orthopaedic Surgery, Dr. R. H. Goetz, Professor of Experimental Surgery, and Dr. E. N. Keen, of the Department of Anatomy, we should like to criticize this theory on the following grounds: (1) it is difficult to explain certain of the zones which seem to be remote from traversing arteries, as in the ischio-pubic ramus and the ribs; and (2) in other sites where arteries wrap themselves directly around bone Looser's areas are not usually found, as in relation to the radial artery, the external iliac artery, and the facial artery (in the mandible). Professor Goetz, with great difficulty, performed transaortic arteriography in the present case, as shown in Fig. 2 of the Special Plate. Comparison of this with the straight radiograph (Special Plate, Fig. 1) indicates that the superior gluteal artery appears closely superimposed upon a zone, at least on the left side. However, the gluteus minimus muscle lies between the artery and the bone. The wide zones in the pubic ramus have no arterial relation. Turning to the shoulder girdle, the circuitous zone on the scapula (Special Plate, Fig. 3, arrow) is very suggestive of an arterial course and might be imagined as being in relation to the circumflex scapular artery. Dr. Keen, however, assures us that the zone is considerably superior

to the usual position of this artery. The zones on the surgical necks of the humeri again appear to us to be far too high to coincide with the normal course of the circumflex humeral arteries. Other wider zones in the shoulder region do not appear to have any possible arterial relationship. The zone in the mandible (Special Plate, Fig. 4), opposite the second molar tooth, is nearly half an inch (12.5 mm.) distant from the facial artery, as judged by the site of its pulsation. We therefore suggest that the arterial origin of Looser's zones is, at the most, only partly true, and does not appear applicable even to the narrower and tortuous zones, while some other explanation is certainly needed for the wide transverse bands.

Summary

The place of so-called "vitamin-D-resistant rickets and osteomalacia" is considered, followed by the report of the case of a woman aged 32 with osteomalacia and Milkman's syndrome. Other causes for osteomalacia were ruled out, and various metabolic investigations were then performed. Balance studies showed a high faecal calcium and phosphorus, phosphorus infusion studies showed a low tubular maximal reabsorption of phosphorus (high phosphate clearance), and calcium infusion studies showed several points of difference from the normal. The bones gave evidence of great avidity for calcium. The response to parathyroid extract was slight, delayed, and affected calcium more than phosphorus metabolism.

The effect of calciferol given parenterally in large doses was examined. On 1.2 million units per day the calcium and phosphorus absorption increased, but it was not until a dose of 4.8 million units daily was used that the serum phosphorus showed any rise. No toxic effects were seen on this dose after 14 days. The smaller dose of 1.2 million units had no effect on the tubular reabsorption of phosphate.

Finally the mechanism of production of Looser's zones is considered. The relation of some of the zones to arteries was studied by means of contrast medium introduced into the aorta. It is concluded that the zones are not in close connexion with pulsating blood vessels.

APPENDIX

The main chemical methods used were as follows. Serum calcium: Greenblatt and Hartman (1951); serum and urinary inorganic phosphate: King (1951); urinary, faecal, and food calcium: Jackson and Irwin (1958); nitrogen: micro-Kjeldahl; inulin: Roe *et al.* (1949); potassium: flame photometer (Jackson and Irwin, 1958).

The results of balance studies have been given in charts rather than tables, in order to conserve space. The exact figures may be obtained from the authors on request.

We are pleased to express our thanks to Professor J. F. Brock and Professor F. Forman for their interest and advice; to those who helped with the section concerning Looser's zones (particularly Professor R. Goetz); to Mr. B. Todt for the photographs; to the interns, the nursing and technical staff concerned, and to the dietitians. We gratefully acknowledge grants from the Council for Scientific and Industrial Research of South Africa and from the University of Capetown Staff Research Fund, which covered the expenses entailed.

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THE NEPHROTIC SYNDROME COMPLICATING MERCURIAL DIURETIC THERAPY

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[WITH SPECIAL PLATE]

Mercurial diuretics are powerful weapons in the treatment of congestive heart failure. Their proper use can maintain reasonable health and activity for long periods in individuals who would otherwise be seriously disabled. It is well recognized, however, that these drugs are potentially dangerous on account of their action on the renal tubular epithelium. For this reason they are usually withheld from patients with established renal disease, though Gold *et al.* (1947) state that a mercurial diuretic may be given to patients with congestive failure "regardless of the state of the kidneys."

Isolated reports of the nephrotic syndrome occurring after prolonged administration of mercurial diuretics have appeared (Waife and Pratt, 1946; Derow and Wolff, 1947; Bruno, 1948; Siegel and Friedman, 1949; Preedy and Russell, 1953; Munck and Nissen, 1956), but we are not entirely satisfied that the renal tubular damage in all these cases should be attributed to mercury. In the patients reported by Bruno (1948) and by Siegel and Friedman (1949) the clinical and pathological findings suggest that the renal tubules had been damaged by mercury, but diabetic intercapillary glomerulosclerosis (Kimmelstiel-Wilson disease) was also present. Munck and Nissen (1956) describe the nephrotic syndrome occurring in four patients who had received mercurial diuretics, but very limited pathological data are given, and in the one case which came to necropsy the kidneys were normal. The case reported by Derow and Wolff (1947) is acceptable on clinical grounds, but post-mortem examination was not performed and there is therefore no histological evidence. In the cases reported by Waife and Pratt (1946) and by Preedy and Russell (1953), on the other hand, there is