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Familial hypophosphatemia and Vitamin D-resistant rickets

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FAMILIAL HYPOPHOSPHATEMIA AND VITAMIN D RESISTANT RICKETS

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FAMILIAL HYPOPHOSPHATEMIA AND VITAMIN D RESISTANT RICKETS

I. Definition

Vitamin D resistant rickets associated with hypophosphatemia may be characterized as a definite entity if four conditions are fulfilled. (1)

1) Hypophosphatemia associated with decreased renal tubular reabsorption of inorganic phosphate;

2) Familial occurence, the mode of inheritance being, most probably, sex-linked dominant;

3) The presence of some but not all affected persons with rickets or osteomalacia which does not respond to the usual doses of Vitamin D;

4) The absence of other related abnormalities.

There are other conditions such as non-familial Vitamin D-resistant rickets with hypophosphatemia and familial Vitamin D-resistant rickets, which in contrast to familial Vitamin D-resistant rickets associated with hypophosphatemia have a high serum concentration of inorganic phosphates. Patients with the Fanconi Syndrome who have multiple renal defects are also excluded by this definition.

II. Historical Development

Probably Christensen (2) was the first to recognize the familial occurence of Vitamin D-resistant rickets with hypophosphatemia in 1941. He described a mother, son and daughter with the typical findings of the disease. Earlier observations as to a probable familial trait in this disease were based on the skeletal findings. Winters and his co-workers (3,4,5) showed that there was a familial tendency in families with hypophosphatemia and that the pattern followed a sex-linked dominant mode of inheritance with almost complete penetrance. They assumed that rickets and osteomalacia were secondary manifestations to a basic disorder of the kidney which resulted in the excessive excretions of inorganic phosphates with a resulting hypophosphatemia.

Earlier than 1941, it was shown that there were cases of rickets resistant to Vitamin D therapy. Albright, Butler, and Bloomberg (6) in 1937 first showed that in cases of rickets which were resistant to the normal doses of Vitamin D, there was a response to large doses of Vitamin D. Robertson, Harris, and McCune (7) in 1942 were the first to recognize that the hypophosphatemia was due to decreased renal reabsorption of phosphates.

Since the recognition of this disease entity, there have been described in the literature similar disease entities

which might logically be classified as variants of the same syndromes. (8) In this view, at one end of the spectrum is familial hypophosphatemic rickets with abnormal phosphorus metabolism as the only finding; at the other end as in the Fanconi Syndrome, phosphorus, monosaccharides, amino acids, cations, bicarbonate, uric acid, water, proteins, and other compounds are involved.

III. Clinical and Radiologic Findings

The abnormalities range from mild to severe. In its mildest form the only related finding is hypophosphatemia with no marked clinical manifestations except for a slight decrease in height.

In children the condition is first recognized when the child first begins to walk, but X-ray shows abnormalities as early as the first year of life, such as skull deformities and late dentition. With growth, various deformities are noted. Bowing of the legs, shortening of the stature, frontal bossing, pseudo fractures, and elevated serum alkaline phosphatase, "rachitic rosary", are some of the more common findings.

These abnormal findings respond only to massive doses of Vitamin D ($\geq$ 100,000 I.U./day) whereas the normal condition of rickets respond to dietary supplement of Vitamin D.

Table I taken from a text summarizes the major clinical findings of the disorder.[1]

IV. Hypophosphatemia And The Abnormality In Renal Excretion Of Phosphate

A. Hypophosphatemia

Hypophosphatemia is a significant finding in Vitamin D resistant rickets since almost all reported cases have been shown to have a low serum concentration of inorganic phosphate. Secondly, hypophosphatemia is used in tracing the genetics of this disease.

In affected families studied so far, the female member shows a slightly higher serum phosphorus than the males in the same family. This was true regardless of the age. The enzyme alkaline phosphatase is often elevated in persons with active rickets or osteomalacia. However, after treatment with Vitamin D the serum alkaline phosphatase decreased toward normal values. Other biochemical studies - total serum proteins, albumin and globulin fractions, urea or non-protein-nitrogen, amino acids, sodium, potassium, chloride, carbon dioxide content, and PH were usually normal.

[1]Donald S. Fredrickson, M.D., John B. Stanbury, M.D., and James B. Wyngaarden, M.D., The Metabolic Basis Of Inherited Disease (New York, McGraw-Hall Book Company, Inc., 1960), p. 1182.

TABLE 1. SUMMARY OF FINDINGS IN FAMILIAL HYPOPHOSPHATEMIA AND VITAMIN D-RESISTANT RICKETS

Type of hypophosphatemia	Age at onset, yr	Clinical and Radiologic Abnormalities	Concentration in Serum			Other Observations
			Calcium	Inorganic Phosphate	Alkaline Phosphatase	
1. Asymptomatic hypophosphatemia	Under 1	Slightly shortened stature	Normal	Low	Normal	No other abnormalities
2. Hypophosphatemia in adults with inactive postrachitic deformities	Under 1	Lateral (and usually antero posterior) bowing of legs; shortened stature; occasionally coarsened trabeculation, rarefied areas	Normal	Low	Normal or slightly high	More frequent among hypophosphatemic males
3. Hypophosphatemia in adults with deformities and active osteomalacia	Under 1	Same as for (2) plus pseudo fractures	Normal	Low	Slightly high	
4. Hypophosphatemia with resistant rickets in childhood	Under 1	Active rickets; occasionally coarsened trabeculation; shortened stature	Normal or slightly low	Low	High	More severe in affected males; craniostenosis and convulsions in a few instances

In every case studied so far, hypophosphatemia has been associated with an increase in renal excretion and a decreased renal tubular reabsorption of phosphate. The mechanism of this renal dysfunction has not been fully elucidated.

B. Normal Mechanism For Renal Excretion Of Phosphate

The following points on the normal excretion of phosphate by the kidneys have been well documented.

1) The inorganic phosphate of the plasma is ultrafiltrable at least up to concentrations of 17 mgm./100 ml. (9, 10,11) The phosphate is filtered through the glomerular apparatus at approximately the same concentration as is measured in the plasma. (12 ,13)

2) The overall affect of tubular function on filtered phosphate in man and dogs is reabsorption of phosphate. The excreted phosphate is only a minute fraction of the total filtered through the glomeruli. Pitts et al (14) has shown by using the stop flow technique, that reabsorption of phosphate probably takes place at the level of the proximal tubule. In man it is rare (15, 16, 17, 18) that net tubular secretion of phosphates occur, although tubular secretion of inorganic phosphates occur in chickens (19), in cats after infusion of inorganic phosphates, and possibly in acidotic dogs.

V. Gastrointestinal Absorption of Calcium and Phosphate

A. Normal Features And The Role Of Vitamin D

It has been well documented that a decrease in Vitamin D intake leads to decreased absorption of calcium. If Vitamin D intake is decreased sufficiently, fecal excretion of calcium equals calcium intake. The minimal requirements of calcium per day is 0.45 to 1.0 gm. for normal adults. (20, 21, 22) When doses higher than this are included in the diet with physiologic quantities of Vitamin D, enough calcium is absorbed to maintain calcium balance. If calcium absorption from the gastrointestinal tract is diminished sufficiently, urinary calcium excretion may equal zero.

The administration of Vitamin D to Vitamin D deficient subjects leads to an increase in calcium absorption. The role of Vitamin D in the normal metabolism of calcium and phosphate has been well established, however, the mechanism of action has not been satisfactorily elucidated.

The intestinal absorption of phosphates is not directly dependent on the availability of Vitamin D (23). It is true that in subjects with a deficiency of Vitamin D, the phosphate absorption is low, but this is thought to be secondary to the impaired calcium absorption with the consequent sequestration of calcium phosphate within the intestine. (23, 24)

B. Abnormalities In Absorption Of Calcium And Phosphorus In Familial Hypophosphatemia or Vitamin D-Resistant Rickets

Children with Vitamin D-resistant rickets excrete in their feces almost all their ingested calcium, and the calcium excretion in the urine is low. This is observed prior to any treatment with massive doses of Vitamin D. Normal children show a definite positive balance for calcium and phosphorus whereas affected children show a slightly positive or slightly negative balance for calcium. Total phosphate balance is comparable to the calcium balance; however, a larger proportion of the ingested phosphate is absorbed and excreted in the urine. The findings are similar in the few studies of patients with Vitamin D-resistant rickets with (2, 3, 25, 26) and without family histories. (6, 27, 28, 29)

Large doses of Vitamin D (2.5 to 37.5 mg./d.) administered to patients with Vitamin D-resistant rickets uniformly increases the absorption of calcium while urinary excretion remains low. There is also an increase in phosphate absorption with a resultant positive phosphate balance. This response to very large doses of Vitamin D is similar to the response of patients with Vitamin D-deficiency rickets to smaller doses.

Other subjects respond in a similar way to patients with Vitamin D-resistant rickets treated with massive doses of Vitamin D. For example, Albright and co-workers have demonstrated comparable increases in calcium absorption in patients with primary hypoparathyroidism and those with idiopathic hypercalcinuria who were given large doses of Vitamin D. (24, 30, 31) Normal man and rats have increased calcium absorption when given large doses of Vitamin D. (32, 33)

Saville et al (34), Fraser et al (35) have accumulated further evidence that poor absorption of calcium is not the only defect in Vitamin D-resistant rickets. These workers have shown that large amounts of phosphates administered either orally or intravenously, without large doses of Vitamin D, will produce positive calcium and phosphorus balance and initiate healing of the rickets.

> In summary, the gastrointestinal absorption of calcium and secondly, of phosphate, is probably abnormally low. This is particularly evident in children with active rickets who do not have a sufficiently positive balance for normal growth. In affected family members with asymptomatic hypophosphatemia, impairment in calcium and phosphate absorption may not be apparent. Bony development is normal both clinically and radiologically. Vitamin D in massive doses will induce increased absorption of calcium and phosphorus. This is probably no different from what occurs in normal persons, despite

> the lack of response to physiologic amounts of Vitamin D. Large increases in intake of phosphate also produce increased absorption of phosphate and probably of calcium.[2]

VI. Abnormalities In Metabolism Of Bone

In the mildest cases of Vitamin D-resistant rickets characterized only by hypophosphatemia and diminished tubular reabsorption of phosphates, there is no apparent bone disease. Although no bone tissue has been examined histologically from such subjects, there are no demonstrable radiologic abnormalities. In these mild cases the only distinguishable abnormality is a slightly shorter build than that of normophosphatemic siblings. (4) The absence of bone disease in the face of hypophosphatemia suggests two possibilities:

1) That the genetically transmitted abnormality is not concerned directly with bone metabolism.

2) Factors other than hypophosphatemia are participating in those patients who develop bone disease.

In patients with Vitamin D-resistant rickets, two abnormalities of bone that have been described, affect 1) - the epiphyseal region and 2) - the metaphyseal region. In the first instance, the most characteristic finding is the rachitic appearance of the epiphyseal region.

[2]Ibid., p. 1197.

There is a markedly expanded zone of proliferating cartilage, with increased osteoid tissue and invasion by wide, tortuous blood vessels. (6, 27, 36, 37) These changes are present whether there is a family history or not. In any event, the radiographic changes are quite characteristic of Vitamin D-deficiency rickets.

The second abnormality is not always present in the compact bone of the metaphysis of long bones. In biopsies from shafts, in two cases, Engfeldt et al (36) observed an abnormal, irregular, mosaic formation of the Haversian system and trabeculae, very little osteoid, and probably an increase in osteoblastic borders and "resorption cavities". Other workers in this field have described similar changes. (2) These changes, however, are not confined to patients with Vitamin D-resistant rickets because similar changes have been reported in patients with Pagets disease and in experimental hyperparathyroidism. (38)

Massive doses of Vitamin D promotes healing of the epiphyseal lesion typical of rickets. Healing, however, is not due to the action of Vitamin D on the bone itself, but rather on its action of promoting calcium and phosphorus absorption. Large amounts of phosphates given intravenously

will also promote healing Vitamin D-resistant and Vitamin D-deficiency rickets. In this respect, they are alike; however, they differ in that the administration of citric acid-sodium citrate promotes healing of Vitamin D-deficiency rickets but not of Vitamin D-resistant rickets. This difference to response to citrate needs further investigation.

As Nicolaysen and Ecg-Larsen have demonstrated (32), it is important and difficult while trying to establish the actions of Vitamin D, to distinguish between the effects of Vitamin D on calcium absorption and direct effects on bone. A similar problem exists in the study of the pathologic physiology of Vitamin D-resistant rickets. One is unable to establish from available evidence whether the response of the bone to normal levels of Vitamin D would be normal if the serum concentrations of calcium and phosphate were maintained at normal levels for prolonged periods by means other than very large doses of Vitamin D.

In osteochondrodystrophy, the metaphyseal and diaphyseal changes are quite similar to that of resistant rickets. This raises the question that this bony abnormality may be another congenital, presumably inherited, defect in these patients and not directly related to hypophosphatemia or to

Vitamin D. Although the changes are not entirely typical, they could be due also to the direct effect of parathyroid overactivity.

VII. Possible Mechanisms Of Pathogenesis And Questions Still Unanswered

The most characteristic features of the disorder are:

1) Hypophosphatemia and decreased renal tubular reabsorption of phosphate;

2) Low gastrointestinal absorption of calcium and the bony abnormalities.

A. A Genetically Determined, Intrinsic Renal Tubular Defect In Reabsorption Of Phosphate

In Vitamin D-resistant rickets and hypophosphatemia, there is a decreased reabsorption of phosphate and the above hypothesis provides a simple explanation. Consistent with this hypothesis are the facts that hypophosphatemia has a simple genetic pattern, and there is a decreased tubular reabsorption of phosphate in all instances in which it has been looked for. Robertson, Harris, and McCune (7) have suggested that there is an isolated defect in the tubular mechanism responsible for the transport of phosphate. A similar explanation has also been offered by Dent, Fanconi and others. (39, 40, 41, 42, 43)

It should be remembered, however, that reabsorption of phosphate is only decreased, not absent. The data

of Tables 2 and 3 show that these patients do have a significant rate of absorption of phosphate which is about one-half normal. It is possible therefore that there may be two "sites" or mechanisms by which phosphate is reabsorbed, only one of which is absent or blocked in familial hypophosphatemia.

There are some aspects of this disease that are not readily explained by a simple renal tubular defect; for example, the decreased gastrointestinal absorption of calcium and phosphate, and secondly, the bony abnormalities involving the metaphysis and diaphysis. It is quite possible that there is both a defect in intestinal absorption of phosphate and a renal mechanism producing a decrease in phosphate reabsorption.

Fanconi (42) has proposed a sequence of events as follows: the decreased tubular reabsorption of phosphate is the primary determinant of the low serum phosphorus concentration. Accordingly, deposition of bone salts in osteoid tissue is subnormal. Calcium absorption is in some way related to the rate of deposition of calcium in bone and is thus also low.

TABLE 2 . SUMMARY OF DATA OF PHOSPHATE EXCRETION IN PATIENTS WITH VITAMIN D-RESISTANT RICKETS RECALCULATED

Author and reference	Age when studied, yr	Sex	GFR or similar, ml/min	Serum P, mg/100ml	C_{PO4}, ml/min	Nonloaded reabsorption of P, uM/100 ml GFR	P-loaded reabsorption of P (Tmp), uM/100 ml GFR
A. Familial involvement							
Christensen..	15	M	.....	2.2	P excretion	8/10 that of normal subjects on same diet	
(3)	13	F	Blood urea 27 mg/100 ml	2.0	P excretion	7/10 that of normal subjects on same diet	
Tobler et al	12	F	NPN 26 mg/100ml	2.7	10.7+		
	14	F	NPN 29 mg/100ml	2.4	18.2+		
Fanconi and Girardet	2 7/12	M	CI_n*99	2.0-3.3	7.9-16.4		
(?-more than simple D-resistant rickets)	31	F	BUN 14 mg/100ml	1.1-1.6	10.0		
12 normal subjects	5.10	....	.....	3.7	1.7-3.5		
Rupp and Swoboda:							
Case 1....	6	M	C_{In70}	2.0	.....	56	62-100
Case 3....	9	M	C_{In93}	1.8	.....	43	68- 84
Case 5....	5	F	C_{In62}	2.2	.....	62	100-140
Normal....	?	...	$C_{In\ 111}$	4.3	.....	118	167-207
Lamy et al..	13	F	$C_{creatine}$ 106	1.9	11		
Kajdi (88)	6,8(brothers)	M	"Normal" (mannitol)	"High"			
B. No family history:							
Klein & Gow	5	M	$C_{In\ 55}$	3.3	.....	.....	84-99
Robertson et al	10	M	.....	2.6	8.8		
Tobler et al	4	F	NPN 27 mg/100ml	2.2	29.1+		
			NPN 35 mg/100ml	2.3	5.6		
Lambert et al 5 normal girls	.....	F	.....	2.3-3.0	2.5,2.9,3.2, 4.9,11.8		

*CIn - clearance of inulin + 1.73 m^2 surface area

TABLE 3. RENAL TUBULAR REABSORPTION OF PHOSPHATE IN MEMBERS OF "E" KINDRED

Subject, Generation and No.	Age, Yr	Sex	Height, In.	Mean Values Before Phosphate Loading*					Mean Values After Phosphate Loading*	
				P_{PO4}, mg/100 ml	mM/l	CIn ml/min	Excr.P, uM/min	Reabs.P, uM/100 ml GF	CIn, ml/min	Reabs. P, uM/100 ml GF
A. Hypophosphatemic patients with deformities:										
V-12	41	M	65	1.28	0.41	144	13.8	31.6	135	67
V-12+	.....	.....	.....	1.96	0.63	131	18.5	60.3	120	81
IV- 5	58	M	58	2.48	0.80	98	10.6	59.2	101	54
IV- 5‡	.....	.....	.....	2.11	0.68	.....	3.6	.....	111	56
IV- g	.....	.....	.....	2.40	0.77	105	20.0	58.0	93	81
V-153	32	M	67	1.78	0.58	.....	.....	.....	166	79
V-13	28	F	62	2.20	0.71	.....	.....	.....	93	66
B. Hypophosphatemic patients with no deformities:										
V-3	33	F	64	2.48	0.80	112	20.5	59.7	120	84
V-4	27	F	62	2.14	0.69	.....	.....	.....	109	75
V-102	23	F	64	2.50	0.81	.....	.....	.....	92	66
V-28	25	F	62	2.40	0.78	.....	.....	.....	134	75
C. Normophosphatemic siblings:										
V-8	.....	F	68	3.00	0.97	.....	.....	.....	158	121
V-25	31	M	71	3.54	1.14	.....	.....	.....	141	131

*Column headings: P_{PO4} - serum concentration of inorganic phosphorus; C_{In} - clearance of inulin; Excr. P. - rate of phosphate excretion; Reabs. P - rate of phosphate reabsorption; GF - glomerular filtrate.

+After vitamin D, 300,000 I.U./day, for 6 months.

‡After low-calcium diet plus Basaljel, 180 ml/day, for 7 days.

gNormal diet; intravenous loading with calcium gluconate (13 mg calcium per kg over 6 hr). Values before phosphate loading were obtained at 4 to 5 hr, and after phosphate loading at 5 to 6 hr, after start of calcium infusion.

SOURCE: R. W. Winters et al. (4), and previously unpublished observations of the authors.

Consistent with this proposal is the fact that healing of the bone disease, and increased calcium absorption, are initiated by large intravenous or oral loads of phosphate. (35) The last link in the above sequence, the dependence of calcium absorption upon rate of bone deposition, has not been established.

B. Hyperparathyroidism, Secondary To A Defect In Gastrointestinal Absorption Of Calcium

Albright et al (6, 24) from their first studies on patients with Vitamin D-resistant rickets suggested that the primary event was a decreased absorption of calcium because of resistance to Vitamin D. From this a sequence of events followed; first, a low serum calcium concentration, which in turn stimulates parathyroid secretion. Increased parathyroid hormone activity decreases renal tubular reabsorption of phosphate, and hypophosphatemia occurs. Secondary to the hypophosphatemia (as Albright proposed), or due to another, direct action of parathyroid hormone on bone (as subsequent work has shown), (44, 45, 46) resorption of calcium from bone occurs and raises the serum calcium concentration. If the hyperactivity of the parathyroid glands in this compensatory effort were just sufficient, the end result could be normal serum calcium (and normal ionized calcium), (47) low serum phosphorus concentration and

diminished renal tubular reabsorption of phosphate, all of which are the findings of patients with Vitamin D-resistant rickets.

For Albright's hypothesis to be correct, there would be histologic changes consistent with parathyroid hyperplasia and also changes in the bony architecture characteristic of hyperparathyroidism. The parathyroid gland in Albright's patient did show hyperplastic changes. (6) Frame and Smith (43) made a similar observation. The parathyroid glands from patients with familial disease have not been examined.

The tubular reabsorption of phosphates in patients with Vitamin D-resistant rickets is probably responsive to changes in parathyroid activity. 500 units a day of parathyroid hormone given intramuscularly for 3 days (6) caused an increase in phosphate excretion. In a normal person this dose increased phosphate excretion by decreasing tubular reabsorption without any change in glomerular filtration rate. (48) When parathyroid extracts were given intravenously to affected subjects, variable increases in phosphate excretion were observed. Hiatt and Thompson (48) have shown that parathyroid extract given intravenously increases glomerular

filtration rate to such a degree that a valid interpretation of a change in tubular reabsorption cannot be made.

Calcium infusions in normal subjects cause a suppression of parathyroid function, which in turn causes a decrease in phosphate excretion, presumably because of an elevated concentration of serum calcium. Winters et al (4), observed a 30 to 60% decrease in phosphate excretion when intravenous loading of calcium was given to these patients. This is similar to the response of normal subjects. (49, 50, 51)

From the available evidence, one is only able to infer that hyperparathyroidism is not a prominent feature of familial hypophosphatemia. In those patients in which hypophosphatemia is the only finding, it seems unlikely that a defect in calcium could be so intricately balanced by parathyroid overactivity that the concentration of serum calcium could be maintained at a normal level during life without signs of hyperparathyroidism other than increased phosphate excretion. The lack of clinical or radiologic findings of bone resorption in the asymptomatic patients is added evidence of the absence of chronic hyperparathyroidism. It is impossible to decide at present whether the hypophosphatemia and decreased renal tubular reabsorption of phosphate are due to an intrinsic renal tubular defect or to hyperparathyroidism secondary to an intestinal

defect in calcium absorption. It is conceivable that parathyroid hormone depresses the reabsorption of phosphate in all tubules more or less equally, whereas in familial hypophosphatemia an intrinsic tubular defect might involve some tubules to a greater extent than others, leading to a lower "threshold" for phosphate.

C. An Abormality In The Absorption Of Vitamin D

Absorption of Vitamin D is little affected in familial hypophosphatemia and Vitamin D-resistant rickets. Workany has measured the blood vessels of Vitamin D in these subjects. (29, 52, 53) He has found it to be normal prior to the administration of massive doses of Vitamin D and markedly elevated following oral intake of large doses of Vitamin D. Furthermore normal doses of Vitamin D given parenterally do not alter the course of the bone disease. (6, 55, 56, 64) Neither is ultraviolet light successful in treating Vitamin D-resistant rickets. (6, 28, 29 57)

D. An Abnormality In The Action Of Vitamin D

Although large doses of Vitamin D will cure the rickets, this should not be considered primafacie evidence that the disease is caused by a resistance to normal amounts of Vitamin D because it has been already shown that phosphate will initiate healing of the bony defects without additional

Vitamin D. However, these patients do show a resistance to Vitamin D in doses to which normal individuals respond. There are some patients who are only partially resistant and have been cured by intermediate doses of Vitamin D, (25, 58) while others have shown increasing resistance requiring larger doses of Vitamin D. Some patients responded to dihydrotachysterol and failed to respond to Vitamin D_2 or D_3. Hence, it is suggested that some of these patients have a resistance to specific sterols as have been described for some patients with hypoparathyroidism. Tobler et al have made reference to studies by Fluckiger of a sereologic reaction to Vitamin D, seen in patients with Vitamin D-resistant rickets but not in normal subjects' serum. Further work in this area needs to be done.

Citrate metabolism may give some clues to the role of Vitamin D in familial hypophosphatemia and Vitamin D-resistant rickets. Citrate will promote healing of Vitamin D-deficient rickets but not of resistant rickets. In Vitamin D deficiency states, a low content of citrate is found in bone, intestines, kidney, serum and urine. These levels readily return to normal on treatment with Vitamin D. Furthermore, when Vitamin D intoxication is produced while treating Vitamin D deficiency and Vitamin D-resistant rickets, the serum

citrate levels rise to greater than normal levels. (17, 59, 60) Citrate metabolism may not be significant in the pathogenesis of this disease since Cortisol, given to rats deprived of Vitamin D, prevents a rise of citrate in serum and bone in response to Vitamin D. Cortisol does not prevent the increase of serum calcium and phosphate when healing is brought about by the administration of calcium and phosphate alone but again the citrate content of bone and serum remains low. (61)

E. Summary Of Possible Mechanisms Of Pathogenesis

The development of the abnormalities in familial hypophosphatemia and Vitamin D-resistant rickets is not yet understood. The presence of a simple genetically determined renal tubular defect in reabsorption of phosphate would account very well for the findings in those patients with asymptomatic hypophosphatemia, but any attempt to explain the frequent additional findings - the bony abnormalities and defective absorption of calcium - on the basis of a renal tubular defect immediately becomes speculative. The possibility that the primary defect is in the absorption of calcium, with an associated secondary hyperparathyroidism, has been neither proved or disproved but seems an unlikely explanation for the existence of asymptomatic hypophosphatemic individuals in the involved families. There is no direct supporting evidence for the proposal that there is an

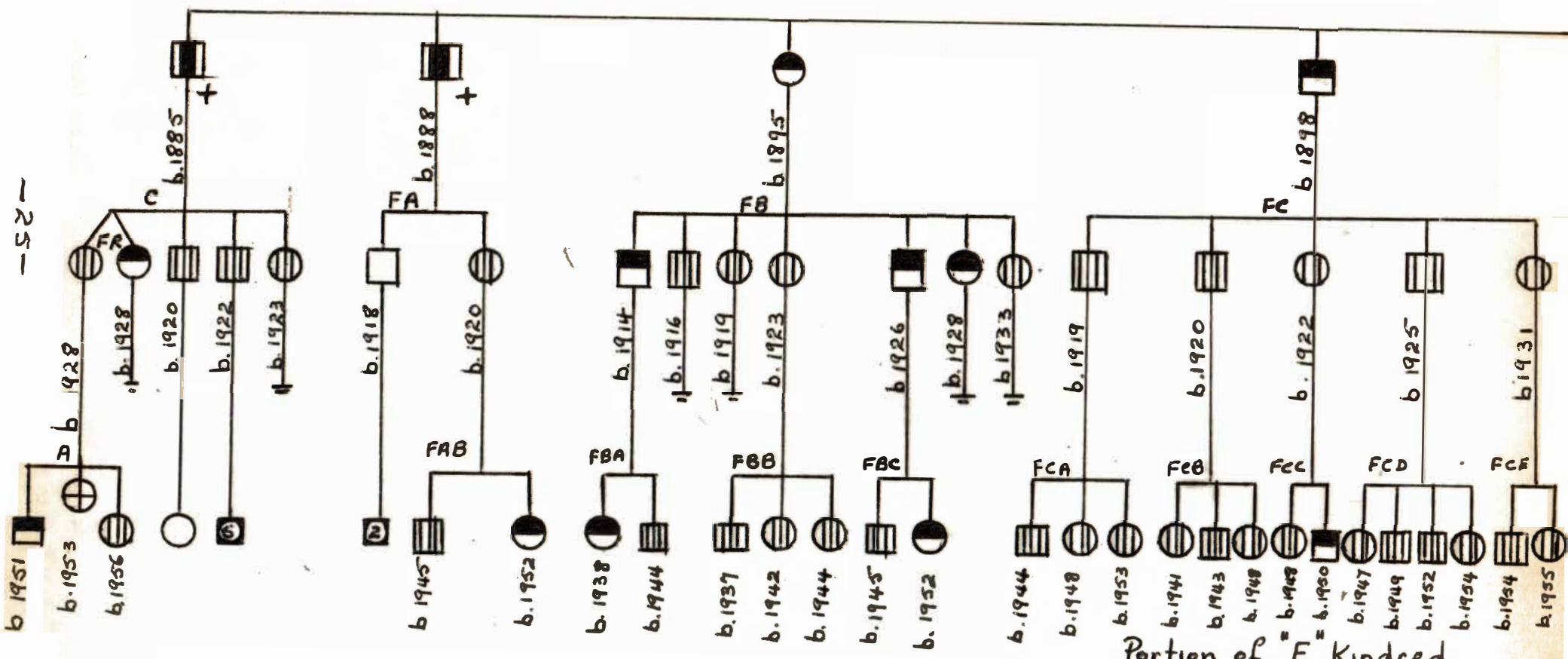
abnormality in the metabolism of Vitamin D or a resistance to its action at normal levels. The action of large doses in curing the rachitic lesions can be explained in terms of the action of such doses in normal persons. The evidence for a disturbance in steroid metabolism may be a promising lead.

VIII. Genetic Aspects

That there is a marked tendency for Vitamin D-resistant rickets to occur in families has been adequately demonstrated. There are 65 cases reported in the literature since 1958 and more than one-half of the cases reported had a positive family history. (4) Several workers (25, 62) studying the disease on the basis of bony manifestations put forward the hypothesis that the defect was transmitted by an autosomal dominant trait; but the disease in its overt form had been seen more frequently in females than in males. Critical analysis of the distribution of normal and affected females and males in earlier studies showed a deviation from the 1:1 ratio expected in an autosomal dominant, the primary cause of the deviation being an increase of affected females. (4) These observations would lead one to believe that there is a strong sexual influence in the expression of an autosomal trait or that there is some other mode of transmission.

The genetic aspects of the disease in a North Carolina kindred ("E" kindred) was investigated by Winters et al (4) and the subjects were tabulated both on the skeletal findings and the serum inorganic phosphate concentrations. These studies revealed that hypophosphatemia is a better criteria than clinical disease for measuring the trait. Consult figures 1 and 2 where a part of the "E" kindred is reproduced. In figure 1, the subjects were classified according to clinical, radiologic, and historical evidence of active rickets (children) or post rachitic deformities (adults). These criteria showed no clear cut pattern of inheritance and there were many instances of "skipping" of a generation. In figure 2, the results were compiled of the findings of hypophosphatemia. In this case, there was a clear cut generation transmission of the trait without skipping.

Similar results were obtained in subsequent studies of unrelated kindred. From a total of 78 cases of hypophosphatemia, the following conclusions were drawn:



Portion of "E" Kindred

UNIVERSITY of North Carolina

Skeletal disease (examined professionally)

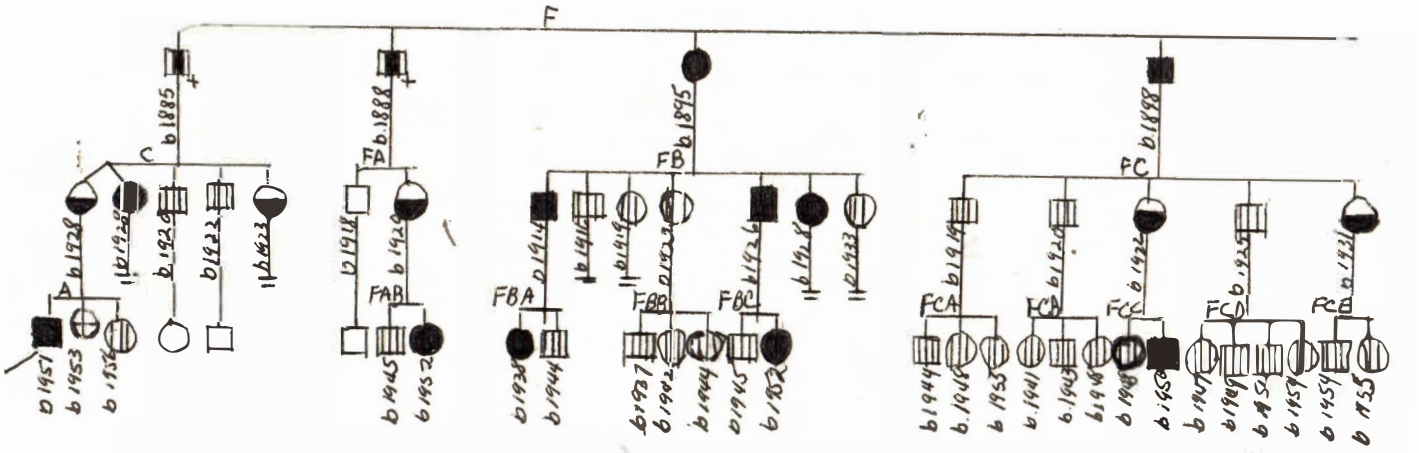
Skeletal disease (reliably reported)

No skeletal disease (examined professionally)

No skeletal disease (reported)

+ Deceased

Fig. 1.



■ Hypophosphatemia with skeletal disease (examined professionally)
■ Hypophosphatemia without skeletal disease (examined professionally)
■ Skeletal Disease (reliably reported; probably hypophosphatemic)
■ Normophosphatemia And No skeletal disease (examined professionally)
□ Not Tested
\+ Deceased

Portion of "E" Kindred
University of North Carolina

Figure 2.

1) Hypophosphatemia was present in the 40 cases who had manifested skeletal disease or deformities.

2) There were 38 other cases who showed only hypophosphatemia without positive evidence of past or present skeletal disease.

3) There were 11 instances of proved or probable "skipping" out of the 38 when the criteria used for evaluation were the clinical or radiologic findings of skeletal disease.

4) Hypophosphatemia was inherited in a clear and simple fashion: each hypophosphatemic individual had one parent who was hypophosphatemic in all of the 50 instances where the requisite data was available.

5) No hypophosphatemic person had more than one hypophosphatemic parent in a number of matings where both parents were examined.

6) Brothers and sisters of hypophosphatemic persons included both normal and affected persons in approximately equal numbers.

These results show that hypophosphatemia is inherited as a dominant trait with a high degree of penetrance. One can safely say that hypophosphatemia is an important, but not only determining factor, of the bony defects seen in this condition.

These studies also show that this disease is sex-linked and not autosomal in transmission. (Table 4) The chance that this distribution will occur, on the basis of an autosomal dominant mechanism, is virtually nill. (1)

TABLE 4. CLASSIFICATION OF HYPOPHOSPHATEMIC PERSONS BY SEXES ACCORDING TO SEVERITY OF BONE DISEASE

	Absent	Mild	Moderate or Severe	Total
Males.....	2	1	27	30
Females.....	36	2	10	48
Total.....	38	3	37	78

Source: From studies by four kindreds by R. W. Winters et al. (4) and J. B. Graham et al (5). Classification made according to the general criteria used in (4).

Some workers have reported cases of resistant rickets in which both parents showed no clinical evidence of the disease (of Winters et al. (4) for review). But in no instance were these parents examined biochemically for the possibility of hypophosphatemia.

There have been a few cases of Vitamin D-resistant rickets in which the parents and many relatives showed no clinical or chemical evidence. (63) This would suggest that there are a few cases that are not of the dominant variety.

Possibly these represent a new mutation, a recessive trait, or a phenocopy.

IX. Treatment

One has to take into consideration many factors when contemplating treating Vitamin D-resistant rickets. The individual's age, growth potential, the severity of the bony manifestation, and chances of hypervitaminosis D should be taken into account and the patient treated accordingly.

A. Vitamin D Therapy

The urgent need for treatment arises for children presenting overt bone disease. The usual mode of therapy is to start with Vitamin D[1] in the range of 25,000 to 50,000 I.U. daily, which is increased by 25,000 I.U. daily at one to one-half month intervals. Increments in dosage of Vitamin D will depend on the clinical course of the patient. Remission of the disease is manifested by radiographic evidence of healing or a falling serum alkaline phosphatase level.

[1]Vitamin D_2 (calciferol) is most widely used. Vitamin D_3 is also effective, as is dihydrotachysterol (A.T.10), but the latter two agents are not preferred because of expense and relative unavailability. The fact that dihydrotachysterol, in doses which increase the intestinal absorption of calcium (75,103), will heal Vitamin D-resistant rickets, whereas its effectiveness in healing ordinary rickets is poor compared with Vitamin D, is further evidence for the view that the corrective action of these sterols in Vitamin D-resistant rickets is a nonspecific effect on calcium absorption. Consistent with this view is the healing action of dihydrotachysterol in Vitamin D deficiency rickets due to a low-calcium diet in rats. (64)

Generally, a dose of 150,000 to 250,000 I.U. will bring about clear cut healing. Once healing has begun, there must be constant attention for reoccurance of the disease or signs and symptoms of hypervitaminosis D.

Hypervitaminosis D is a constant threat and in some cases the effective therapeutic dose lies in the frankly toxic range. Although the Sulkowitch test for urinary calcium is not very helpful in the early detection of Vitamin D poisoning, the parents may be instructed to perform the test regularly in order to impress upon them the need for frequent medical evaluations.

If frank deformities remain, surgical correction (osteotomy, etc.) may be necessary but not until the active process is fully controlled. In some patients the rachitic lesions may be fully controlled but linear growth does not take place and the patients remain dwarfed.

B. Other Therapeutic Measures

Other therapeutic measures may be instituted. Even in the absence of Vitamin D, administration of phosphate will initiate healing (35), but Fraser has suggested that long term phosphate therapy may be harmful and as such should not be used.

C. Treatment Of Affected Adults

Adults with hypophosphatemia and a history of Vitamin D-resistant rickets rarely present overt osteomalacia. Winters et al (4) studied 23 adults with hypophosphatemia and only 2 had evidence of osteomalacia. They presented single pseudofractures. Vitamin D therapy is not necessary for those adults with residual deformities who are without osteomalacia.

D. Treatment Of Asymptomatic Hypophosphatemia

Children with asymptomatic hypophosphatemia need not be treated on this basis alone. If treatment will improve growth, then it should be considered.

E. Preventative Measures

Preventative measures should include genetic counseling, and children born of parents where this condition is suspected should be followed closely with multiple determinations of serum phosphate levels. If the child is suspected of developing deformities, therapy may prevent serious degrees of deformity.

X. Summary

1) Familial hypophosphatemia and Vitamin D-resistant rickets is a disorder in which the most distinctive features are hypophosphatemia and diminished tubular reabsorption of inorganic phosphate.

2) The inheritance pattern is that of sex-linked dominance with complete penetrance.

3) The manifestations of rickets or osteomalacia do not respond to the usual therapeutic doses of Vitamin D and massive doses must be utilized before remission is obtained.

4) Those children with bony involvement probably have low intestinal absorption of calcium. Large doses of Vitamin D increases absorption of calcium. Normal individuals respond similarly to large amounts of Vitamin D.

5) Administration of large amounts of phosphate without the simultaneous administration of Vitamin D will initiate healing of the rickets. This would seem to suggest that the bony manifestation is secondary to a defect in phosphate metabolism rather than to a lack of a direct action of Vitamin D on bone.

6) There are two leading explanations proposed for the disease:

a) There is an intrinsic defect in the function of the renal tubular cells. If this is true, this is a highly specific defect, for it is not associated with any other known tubular defect. Not even the aminoaciduria of Vitamin D-deficiency rickets is found in individuals with familial hypophosphatemia.

b) There is overactivity of the parathyroids, secondary to diminished intestinal absorption of calcium, which depresses renal tubular reabsorption of phosphate. If so, the compensatory adjustment is remarkably exact, for serum concentration is almost always normal and hyperparathyroidism is not detectable clinically.

7) Further investigation into the tubular reabsorption of phosphate in relation to parathyroid function, the action of Vitamin D, to the reabsorption of other substances which may affect phosphate reabsorption should be undertaken to unveil the basic abnormality in familial hypophosphatemia.

8) It is feasible to predict the individuals, from a genetic standpoint, who are most likely to develop this condition and utilize the necessary diagnostic aids and institute prophylactic therapy.

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