Metabolic

SOUTHWESTERN MEDICAL SCHOOL

MEDICAL GRAND ROUNDS

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ADULT-ONSET OSTEOMALACIA

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Quotations From Patients Affected

With Adult-Onset Osteomalacia

"In 1974 it was discovered that I had osteomalacia. After a four year fight of trying to find out why I was not able to walk and having the most excruciating pain one can imagine, GCRC confirmed the problem was osteomalacia. In June of 1974 I entered the General Clinical Research Center in Dallas, Texas. By August I was able to re-enter my teaching position with very little pain. In less than four years the osteomalacia was arrested." --- E.W.

"When suddenly, without warning, I was stricken by a very painful, weakening bone disease, I was unable for five years to find a doctor who could even diagnose it. It was steadily progressive. Within a few months I was barely able to walk, and within two to three years I was almost totally incapacitated, unable to move around the house without assistance. I was very fortunate that after five years of going from one doctor to another, one of them referred me to the General Clinical Research Center, where I was accepted as a patient with osteomalacia-hyperparathyroidism. There I have been treated, hospitalized, tested and carefully and regularly monitored. I have been (miraculously to me, my family and friends) restored to a normal life, walking without assistance or pain." --- D.M.

"I know from personal experience how important human research is. I suffer from osteomalacia, a rare bone disease, and I have been a participant in a research program at the General Clinical Research Center at the University of Texas Health Science Center, Dallas, Texas, for eleven (11) years and the benefits have been very rewarding. Without funding, the research would not have been possible and I most surely would not be alive today." --- V.H.

GENERAL OVERVIEW OF OSTEOMALACIA[1,2]

Although osteomalacia is the least common of the traditional forms of metabolic bone disease, it is very gratifying to diagnose and to treat. In osteomalacia, there is a defect in the mineralization of the bone matrix which leads to an accumulation of nonmineralized or poorly mineralized osteoid over the surfaces of both cortical and trabecular bone. During growth, impaired mineralization of the cartilaginous growth plate leads to the clinical picture of rickets. After closure of the growth plate, the adult syndrome of osteomalacia occurs.

The syndrome of osteomalacia consists of distinct clinical, biochemical and radiologic features and a characteristic pattern of bone histomorphometry. Dull, aching muscular skeletal pain in the lower extremities, pelvis and shoulders is very characteristic. Patients with this disorder frequently have a peculiar duck-waddling gait, stepping carefully and putting their weight down gingerly to avoid jarring the skeleton and aggravating the pain. They often have pronounced proximal muscular weakness, with difficulty in getting up from a chair and inability to lift their hands over their heads. Loss of height due to vertebral collapse is not infrequent. Occasionally, patients complain of pain in the chest on coughing and movement that may have resulted from rib fractures which frequently show up best on diphosphonate bone scan.

The biochemical changes depend on the cause of the osteomalacia. In conditions leading to vitamin D deficiency, the serum Ca may be decreased, but this is often less striking when the serum Ca is corrected for hypoproteinemia. A persistently low serum P is often a more significant clue to the presence of underlying osteomalacia than is hypocalcemia and may be a reflection of either vitamin D deficiency or renal tubular dysfunction with a lowered renal P threshold. The plasma Ca may be normal even though urinary Ca is extremely

low. Secondary hyperparathyroidism may or may not be present. Alkaline phosphatase is usually increased, sometimes to a very high level, as is the urinary hydroxyproline excretion.

Skeletal roentgenograms show a nonspecific decrease in radiodensity and vertebral biconcavity may be present. Rarely, subperiosteal resorption may be seen if secondary hyperparathyroidism is present. The most distinctive radiographic feature of osteomalacia is the occurrence of symmetric radiolucent bands, adjacent and usually perpendicular to the periosteal surface in ribs, pubic rami, outer borders of the scapulae, and near the ends of long bones. They are variously known as Looser's zones or pseudo-fractures and represent stress fractures in which the normal process of healing is impaired by the mineralization defect. Looser's zones may progress to complete fractures with separation of the bone fragments, but complete fractures lacking the characteristic features of Looser's zones may also occur with minimal trauma, especially in the ribs.

When osteomalacia is suspected on clinical, biochemical and radiographic grounds, the diagnosis may be confirmed by examining an undecalcified bone biopsy specimen. Both the extent and width of osteoid seams covering trabecular and cortical (Haversian) bone surfaces are increased when compared with normal subjects of the same age and sex. Previous labeling of bone with tetracycline, which is deposited at the mineralization front, makes possible the measurement of the extent of the mineralizing surface and of the mineral apposition rate, both of which are reduced in osteomalacia. Osteoblasts appear flattened and inactive.

CAUSES OF OSTEOMALACIA[3]

Osteomalacia is not a primary disease but a secondary manifestation of any one of a number of disorders. The various causes reflect defects in the biochemical processes involved in bone mineral accretion. In simplified terms, adequate amounts of at least four substances are required for normal skeletal mineralization--namely, Ca, P, vitamin D and alkaline phosphatase. Ca and P are, of course, the major constituents of hydroxyapatite, or bone mineral. Alkaline phosphatase appears to be necessary for normal calcification of the skeletal matrix since osteopenia is seen in children with congenital hypophosphatasia. Vitamin D is also required for adequate absorption of Ca and P from the intestine and for direct actions on bone mineralization. In theory, a deficiency of any one of these factors could lead to defective mineralization, or osteomalacia, but in actuality only three of the constituents are involved. Dietary Ca deficiency doesn't cause osteomalacia in the face of adequate phosphorus and vitamin D intake; it produces osteoporosis instead. Osteomalacia, therefore, may result from a deficiency of alkaline phosphatase, vitamin D or phosphorus.

CLASSIFICATION OF OSTEOMALACIA

A simplified approach to the classification of the various forms of osteomalacia is depicted on the following table:

Causes of Osteomalacia

1. Vitamin D-dependent
   a. Reduced availability of vitamin D
   b. Reduced availability of 25-OH-D
   c. Reduced availability of 1,25-$(OH)_2D$
   d. Tissue resistance

2. Vitamin D-independent

   a. Hypophosphatemia

   b. Diphosphonate treatment

   c. Aluminum toxicity

(a) Reduced availability of vitamin D_3: low μV exposure or uptake, dietary deficiency, malabsorption

(b) Reduced availability of 25-OHD: cirrhosis (biliary), anticonvulsants, nephrotic syndrome

(c) Reduced availability of $24,25\text{-}(OH)_2D$: anticonvulsants, chronic renal failure

(d) Defective synthesis of $1,25\text{-}(OH)_2D$: hypoparathyroidism, chronic renal failure, vitamin D dependency rickets Type I, postmenopausal osteoporosis, oncogenic osteomalacia

(e) Resistance to $1,25\text{-}(OH)_2D$ action: familial hypophosphatemic rickets, vitamin D dependency rickets Type II

(f) Hypophosphatemia: excessive P-binding antacids or high renal excretion

(g) Diphosphonate: direct inhibition of mineralization

(h) Aluminum: inhibition of osteoblastic activity and mineralization

HYPOPHOSPHATEMIC OSTEOMALACIA

An important cause of osteomalacia is that which is related to phosphate (P) deficiency. A deficiency of phosphate can result from dietary lack, malabsorption or excessive loss in the urine. It is very difficult to produce phosphate depletion by dietary means alone since phosphate is abundant in almost all foods and is readily absorbed from the intestine. Phosphate deficiency has been produced experimentally in normal subjects by feeding the

types of antacid that bind phosphate, making it unavailable for intestinal absorption, resulting in an osteomalacic-like syndrome. Indeed, there have been several well-documented cases of hypophosphatemic osteomalacia developing in individuals who were ingesting massive amounts of antacids.[5,6] These patients had almost negligible urinary P excretion, and increased serum 1,25-$(OH)_2D$ levels. The most common cause of phosphate deficiency, however, is wasting by the kidney due to a defect in the tubular reabsorption of phosphate. This cause of osteomalacia, thought to be the most prevalent today,[7] is known variously as vitamin-D-resistant rickets, phosphate diabetes, or primary hypophosphatemic osteomalacia. The most common form of this disorder is inherited as an X-linked dominant trait and manifests itself as childhood rickets. Undermineralization occurs during the period of skeletal growth, leading to short stature and deformities of the skeleton. In addition to the familial disorder, there are sporadic cases in which it has an adult onset. Patients with this form are of normal height and do not have skeletal deformities. In common with patients with X-linked familial hypophosphatemic rickets, patients with sporadic adult-onset hypophosphatemic osteomalacia spill excessive quantities of P into the urine and despite hypophosphatemia, have inappropriately low serum 1,25-$(OH)_2D$ levels. Our goal for this presentation is to review in detail the case studies of three patients with adult-onset osteomalacia who presented to this institution over the past decade. A comparison of these affected individuals, hopefully, will provide a better understanding of how this disorder presents, the underlying pathophysiology, and the response to therapy. We will compare our cases to those reported in the world literature.

CASE STUDY 1: E.W.

62 WF noted low back pain, rib cage pain, leg pain beginning in 1970. There was progressive muscular weakness and inability to ambulate. Patient was confined to wheel chair.

Presented to Mineral Metabolism Section in 1974. Physical exam confirmed bone tenderness and muscular weakness. X-rays revealed generalized demineralization, bilateral hip fractures, pseudofractures and rib fractures. Biochemical survey was compatible with osteomalacia, subsequently confirmed by iliac crest bone biopsy.

Additional Data: Normal stature. No family history of rickets. Son and daughter had normal blood chemistry. Patient had normal electrolytes (venous bicarbonate 29), fasting urine pH-5. 24-hour stool fat 1.7 Gm/day. Serum carotene and protime were normal.

E.W.: INITIAL BIOCHEMICAL PRESENTATION

		Patient	Normal Range
	Calcium, mg%	9.0	8.5-10.5
	Phosphate, mg%	1.8	2.5-4.5
SERUM	Alk. Phos., IU/L	225	< 100
	PTH, µl-eq/ml	12	< 30
	25 OHD, ng/ml	18.5	7-42
	$1,25\text{-}(OH)_2D$, pg/ml	12.0	20-55

E.W.: INITIAL BIOCHEMICAL PRESENTATION

		Patient	Normal Range
URINE	Calcium, mg/day	74	100-250
	Phosphate, mg/day	350	500-1500
	Cyclic AMP, nmol/100 ml GF	4.4	< 5.4
	Hydroxyproline, mg/day	23	< 30
	Creatinine clearance ml/min	82	80-120
	TmP/GFR mg/100 ml	1.6	2.5-4.2

		Patient	Normal Range
OTHER STUDIES	True Ca Absorption, fraction	.07	.40-.60
	Ca Balance, mg/day	-136	±50
	Bone Density, gm/cm^2	.560	.65-.85

QUANTITATIVE MICRORADIOGRAPHY OF BONE BIOPSIES BEFORE AND AFTER TREATMENT WITH $25(OH)D_3$ (BY JOWSEY).

PATIENT

		$25(OH)D_3$	
	BASELINE	50 mcg/d x 1 yr.	NORMAL
Formation, %	0.03	0.9	2.0 ± 0.6*
Resorption, %	3.6	12.4	3.6 ± 1.0
Unmineralized osteoid, %	72.7	51.2	0
Osteoid width, μm	34	31	12.3 - 18.3

* mean ± SD

SERIAL DETERMINATIONS OF FASTING SERUM 25OHD

AND 1,25-$(OH)_2D$ CONCENTRATIONS

	25OHD (ng/ml)	1,25-$(OH)_2D$ (pg/ml)
NORMAL	7-42	20-55
BEFORE THERAPY	18.5	12
3 mo.- 25OHD, 20μg/d	15.6	15
6 mo.- 25OHD, 50μg/d	35.6	14
12 mo.- 25OHD, 50μg/d	50.7	21
24 mo.- 1αOHD, 1.5μg/d	16.2	40
48 mo.- 25OHD, 100μg/d	---	23

SERIAL DETERMINATIONS OF Ca BALANCE, SERUM P

AND THEORETICAL RENAL THRESHOLD FOR P

	Ca Balance mg/day	Serum P mg/100ml	TmP/GFR mg/100ml
NORMAL	±50	2.5-4.5	2.5-4.2
BEFORE THERAPY	-136	1.8	1.6
3 mo.- 25OHD, 20μg/d	-172	2.2	2.0
6 mo.- 25OHD, 50μg/d	-82	1.9	1.5
12 mo.- 25OHD, 50μg/d	-44	1.8	1.5
24 mo.- 1αOHD, 1.5μg/d	+75	1.7	1.1
48 mo.- 25OHD, 100μg/d	-213	1.9	1.6

In 1975, 5 years after onset of osteomalacia, the patient noticed a "lump" in right upper jaw. Biopsy was read as benign ossifying fibroma.

By 1977, the right maxillary lesion had increased in size and x-ray studies showed involvement of almost entire right maxillary cavity extending to

the orbit. Repeat biopsy was interpreted either as low grade osteogenic sarcoma or mesenchymal chondrosarcoma.

In January 1978, patient was to undergo partial maxillectomy, but when the antrum was entered, the surgeon encountered a rather meaty, soft tissue tumor which, upon biopsy, bled profusely. External carotid ligation was required to stop the bleeding, and the tumor could not be removed.

From January to March 1978, the patient received neutron beam therapy at M.D. Anderson Hospital in Houston, followed by progressive regression of the tumor to half its former size.

BIOCHEMICAL RESPONSE TO TUMOR SHRINKAGE

	CA	P	Aϕ	25-(OH)D	$1,25(OH)_2D$	^{47}Ca Abs
BEFORE RADIOTHERAPY (No Treatment)	9.0	1.8	225	19	12	.08
BEFORE RADIOTHERAPY (25-(OH)D Challenge 100 $\frac{mcg}{d}$)	9.5	1.8	180	203	15	.27
4 YRS POST-RADIOTHERAPY (No Treatment)	9.7	3.1	95	73	24	.35
4 YRS POST-RADIOTHERAPY (25-(OH)D Challenge 100 $\frac{mcg}{d}$)	9.7	2.6	92	192	49	.45

SUMMARY OF ADDITIONAL INFORMATION FROM E.W. CASE

1. Co-occurence of adult-onset hypophosphatemic osteomalacia and malignant osteogenic sarcoma.
2. Inability to increase serum 1,25-$(OH)_2D$ despite progressive challenge with increasing amounts of 25OHD, prior to tumor shrinkage.
3. Correlation of measurements of vitamin D metabolites with isotopic determination of intestinal Ca absorption and balance studies.
4. Additional evidence for occurrence of hypophosphatemia despite normal levels of serum PTH and urine cAMP; and for persistence of hypophosphatemia and low TmP despite adequate treatment with 1,25-$(OH)_2D$. (Suggests tubular abnormality independent of increased PTH or decreased 1,25-$(OH)_2D$).
5. Clinical and biochemical improvement following successful radiotherapy of tumor.

CASE STUDY 2: D.M.

This 68 year old WF was in excellent health until 1965, when her heels became painful and swollen. This was followed by increasing pain in the rib cage, back, hips and knees. Because of skeletal pain and muscular weakness, the patient gradually became unable to walk.

1969: Pseudofractures of pelvis

Trans-iliac bone biopsy: increased osteoid

Serum Ca 11.2 mg/dl, P 1.5 mg/dl

IMP: Adult-onset osteomalacia → 3^{o} hyperparathyroidism

1969: Search for cause of osteomalacia:

No dietary abnormalities or diarrhea

UGI Series - normal

D-xylose absorption - normal

Fecal Fat: 3.5 g/day

Jejunal Biopsy - normal mucosa

CONCLUSION: No evidence of steatorrhea or sprue

1969: 1st Parathyroidectomy:

2 hyperplastic glands and 1 adenoma removed

Discharged on vitamin D, Ca and P supplements

1976: Hypercalcemia recurs (and persists off treatment)

Serum Ca 11.8 mg/dl

Serum PTH 115 μl-eq/ml (normal < 30)

Urine cyclic AMP 14.3 nmol/100 ml GF (normal < 5.4)

1977: 2nd Parathyroid Exploration:

2 hyperplastic glands removed

Path Report: nodular hyperplasia

Fragments totalling 20 mg transplanted to left forearm

Post-op: Ca 9.4, P 1.9, Aϕ 128

Discharged on vitaminD, Ca and P supplements

SERIAL CHANGES IN SERUM iPTH (μl-eq/ml)

Date	Left	Right
1977	61	41
1978	49-105	8-31
1979	131	99
1980	204-212	84-120
Feb. 1981	290	180
Sept. 1981	637	413

NOTE: -Rise in PTH was accompanied by recurrent hypercalcemia.

-P supplement discontinued 1979; vitamin D discontinued 1980.

-Severe osteomalacic symptoms recurred May 1981.

-Renal function improved off vitamin D and P supplement from C_{Cr} 40 ml/min to 60 ml/min.

SEPTEMBER 1981 - GCRC EVALUATION

Serum Ca 9.8 mg/dl (10.5 - 11.2 outside)

Serum P 1.6 mg/dl

Alk Phos 419 (normal < 100)

Urine OHP 55 mg/day (normal about 20)

PTH: L-637, R-413 (normal < 30)

C_{Cr} 61 ml/min

25-(OH)-D 36 ng/ml (normal 7 -42)

1,25-$(OH)_2$D 19 pg/ml (normal 20 - 50)

Intes. ^{47}Ca abs .29 (normal .40 - .60)

OCTOBER 1981 - THIRD PARATHYROIDECTOMY

All parathyroid tissue removed from left forearm - 1500 mg

Path Report: The parathyroid tissue consists of ribbons of parathyroid cells in a richly vascular stroma separated into distinct nodules by hyalinized septae. Chief cells predominate, but there are numerous nodules of oxyphilic and occasional nodules of water-clear cells. This multinodular appearance is strongly suggestive of that seen in MEN.

Post-op: Ca 9.6, P 2.2, Aϕ 337, PTH: L-105, R-100

AUGUST 1982 - GCRC: Response to 1,25-$(OH)_2$D (0.5 mcg daily)

Serum Ca 10.2 mg/dl

Serum P 1.6 mg/dl

Alk Phos 225

Urine OHP 22 mg/day

PTH: L-44, R-39

C_{Cr} 47 ml/min

25-(OH)D 37 ng/ml

1,25-$(OH)_2$D 40 pg/ml

Intes ^{47}Ca Abs .55

NOVEMBER 1982 - GCRC: Responsiveness to PTE

	Control (off $1,25\text{-}(OH)_2D$ x 10d)	PTE
Serum Ca	10.1 ± .1	10.8 ± .2
Serum P	1.5 ± .2	1.5 ± 0
Alk Phos	200 ± 6	178 ± 13
Urine OHP	23 ± 4	29 ± 3
PTH	68 ± 4	64 ± 7
C_{Cr}	60	53
25-(OH)D	28 ± 2	27 ± 3
$1,25\text{-}(OH)_2D$	11 ± 1	15 ± 5
Intes ^{47}Ca Abs	.29	.24

MAY 1983 - GCRC: DOCUMENTATION OF SUPPRESSIBILITY OF PTH AND PERSISTENCE OF PHOSPHATURIA

A. Supressibility of PTH

Control Measurements on $1,25\text{-}(OH)_2D$ Treatment:

Ca-10.5, P 1.7, Aϕ 184, OHP 23, PTH 32

4-hr Ca Infusion Test (2 mg/kg/hr):

TIME:	0	1H	2H	3H	4H
S_{Ca}	10.3	11.3	11.5	12.5	12.7
PTH	29	28	26	24	24

B. Persistence of Inappropriate Phosphaturia

	Serum P	24-hr Urine P	TRP	TmP/GFR
CONTROL	1.6 mg/dl	645 mg/d	45%	0.8 mg/dl
POST-CA INF	1.7 mg/dl	592 mg/d	50%	0.9 mg/dl

SUMMARY OF FINDINGS IN DM

- Adult-onset osteomalacia
- Decreased renal production of $1,25\text{-}(OH)_2D$ and enhanced renal loss of P
- No evidence of tumor
- No evidence of Fanconi syndrome (normal urinary acidification and no glycosuria or amino aciduria)
- Reduced intestinal Ca absorption
- Strong tendency for secondary hyperparathyroidism

CASE STUDY 3: VH

62 year old WM in good health until 1972 when he developed pain in rib cage, back and hips. Eventually could barely walk, even with cane. In 1973, fractures of the ribs and both hips were found. The patient required right hip prosthesis and left hip pinning.

1974 - EVALUATION BY MINERAL METABOLISM SECTION

Serum Ca 8.7

Serum P 2.1

Alk Phos 290

24-hr urine Ca 63 mg/day

24-hr urine cyclic AMP 4.8 - 10.8 $\frac{\text{nmol}}{100\text{ ml GF}}$

Intes Ca Abs 15%

Trans-iliac bone biopsy: increased osteoid

IMPRESSION: Adult-onset Osteomalacia

1974: SEARCH FOR CAUSES OF OSTEOMALACIA

No history of dietary abnormality or diarrhea

Fecal Fat 5.5 g/day

Normal: Serum carotene, D-xylose test, 25-(OH)D 13 ng/ml

Marked phosphaturia, but normal urinary acidification; no glycosuria or amino aciduria

1974: LACK OF RESPONSE TO 25-(OH)D_3 (20 mcg daily x 3 mos)

Serum Ca 9.0

Serum P 2.2

Alk Phos 290

24-hr urine Ca 95 mg/day

24-hr urine cyclic AMP 6.0 nmol/100 ml GF

25-(OH)D 25 ng/ml

1,25-$(OH)_2$D 15 pg/ml

Intes Ca Abs 12%

1975: RESPONSIVENESS TO 1α-(OH)D (2 mcg daily x 6 mos)

Serum Ca 9.4

Serum P 1.7

Alk Phos 127

24-hr urine Ca 106 mg/day

24-hr urine cyclic AMP 2.9 nmol/100 ml GF

25-(OH)D 14 ng/ml

1,25-$(OH)_2$D 42 pg/ml

Intes Ca Abs 59%

(Marked improvement in musculoskeletal pain occurred on this regimen).

1979: GCRC RE-EVALUATION (off 1,25-$(OH)_2D$ and P x 3 wks)

Serum Ca 8.9

Serum P 1.8

Alk Phos 97

24-hr urine Ca 83 mg/day

24-hr urine cyclic AMP 5.2 nmol/100 ml GF

25-(OH)D 37 ng/ml

1,25-$(OH)_2D$ 7 pg/ml

Intes Ca Abs 33%

1979: GCRC RE-EVALUATION (continued)

Renal P Handling:

Serum P 1.8 mg/dl

24-hr urine P 567 mg/day

C_{Cr} 81 ml/min

TRP 74% (Normal > 82%)

Tm_p/GFR 1.4 mg/dl (Normal 2.5 - 4.2)

Search for Tumor:

Careful physical examination, skeletal survey and bone scan did not disclose any tumor of soft tissue or bone.

V.H. Current Status

Enjoys frequent travels with only occasional mild discomfort in bone and hip joints.

Current Meds: 1,25-$(OH)_2D$ 0.5 mcg/day

Oscal 250 mg qid

Neutraphos 250 mg qid

Out-Patient Chemistry: Ca 9.4, P 2.2, Alk Phos 98,

PTH 32 - 64 µl-eq/ml

The key features of our three patients presenting with adult onset osteomalacia may be summarized as follows:

PRESENTATION OF ADULT-ONSET OSTEOMALACIA

Patient	E.W.	D.M.	V.H.
Musculoskeletal Sx's	++++	++++	++++
Pseudofractures and Fx's	Yes	Yes	Yes
Serum Ca	N	N or ↑	N
Serum P	↓	↓	↓
Tm_p/GFR	↓	↓	↓
Serum Alk Phos	↑	↑	↑
Serum iPTH	N	↑↑↑	N to ↑
Serum $1,25\text{-}(OH)_2D$	↓	↓	↓
Intes Ca Abs	↓	↓	↓
Tumor	Yes	No	No
Response to Rx	Partial	Partial	Partial

COMPARISON OF OUR CASES WITH THOSE REPORTED IN WORLD LITERATURE

Recently there have appeared two excellent reviews of adult-onset osteomalacia, particularly of the type associated with tumors.[8,9] A modified table describing the clinical and biochemical characteristics of a group of 44 patients with oncogenic osteomalacia, including the site and histology of the associated tumor, is appended at the conclusion of this Grand Rounds. This table was derived from reference 8.

Sporadic, non-familial, vitamin D-resistant rickets first appearing in adulthood was initially described by McCance in 1947.[10] Over the next 25 years, approximately 20 patients were characterized by Dent and Stamp.[11] In

1970, Salassa, Jowsey and Arnaud called attention to the syndrome of recovery from adult-onset hypophasphatamic osteomalacia after removal of benign soft-tissue tumors.[12] The authors reported two patients and reviewed four others from the literature. It is interesting that one of those four was McCance's original patient who completely recovered from phosphate wasting coincident with the removal of a tumor of the femur.[13] To date, approximately 45 patients with tumor-induced osteomalacia have been reported.[8-45] (See appended table). Over the same period of time, there have been about 55 cases reported of idiopathic hypophosphatemic osteomalacia (without associated tumor).[8] This distribution of patients is probably misleading. There is often a lag between the initial diagnosis of osteomalacia and discovery of the oncogenic nature of the disease. The tumors may be small and difficult to find. In many of the reports, the tumors were found because they were close to the surface, large, or because they invaded skeletal structures. One can speculate that small, clinically inapparent tumors hidden in extra skeletal connective tissue may go undetected in some patients currently thought to have sporadic hypophosphatemic osteomalacia. With or without tumor, the clinical and biochemical presentation of adult-onset osteomalacia is quite unform.

PRESENTATION The syndrome usually becomes manifest in early to mid-adult life. The symptoms are generally severe. In the recently reported series, [8,9] 93% of the patients had bone pain, 63% had severe muscle weakness, and 39% had symptoms to a degree that prevented walking. The course is typically protracted. In some cases, the initial clinical presentation is mistaken for rheumatoid arthritis, muscular dystrophy or a primary neurologic disorder. In some instances, a pathologic fracture is the first presenting problem. On average, there is a 6 year gap between onset of symptoms and definitive diagnosis. Men and women are affected equally.

Biochemically, adult-onset hypophosphatemic osteomalacia is generally characterized by marked hypophosphatemia, renal phosphate wasting, and low levels of $1,25\text{-}(OH)_2D$ in the presence of normocalcemia and normal levels of PTH. In the series of Ryan and Reiss,[8] the patients with oncogenic osteomalacia had a mean serum P level of 1.5 mg/dl which increased to 3.5 mg/dl after removal of the causative tumor ($P < .001$, Fig.1).

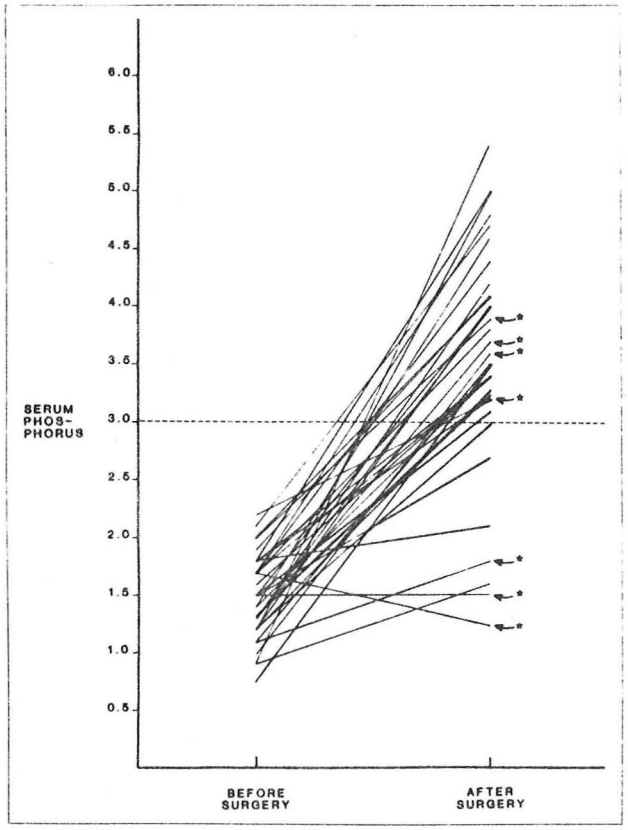

Figure 1 *Response of serum phosphorus to surgical excision of tumor in 35 patients for whom data are available. The* ***arrows*** *identify patients with incomplete resection of tumor. Of the three patients with apparently complete resection of tumor who remained hypophosphatemic postoperatively, one had a clinical remission, and the other two showed slight improvement.*

Fig. 1

Despite the severe hypophosphatemia, the TRP was reduced in these patients usually to 40 - 60% (normal TRP >82%). In 9 of 11 patients in whom $1,25\text{-}(OH)_2D$ was measured, it was low (mean value 15 pg/ml, normal range 20 -60 pg/ml). Following tumor resection, serum $1,25\text{-}(OH)_2D$ concentration increased in four of

six patients in whom it was measured from 21.5 to 46.5 pg/ml. Serum Ca was normal in all 44 patients. In 24 patients in whom PTH was measured, it was normal in 20, but increased in 4. Aminoaciduria was found in 8/25 patients (usually glycine) and glucosuria in the absence of hyperglycemia was noted in 12/44 patients.

DIFFERENTIAL DIAGNOSIS OF CHRONIC HYPOPHOSPHATEMIA

Hypophosphatemia can reflect a negative phosphate balance and body deficits of phosphate. It can also be produced acutely if the cellular uptake of phosphate is increased at the expense of extra cellular fluid concentration. The latter occurs with acute disturbances such as respiratory alkalosis, insulin administration or with hyperalimentation.[9] Because phosphate is absorbed from the gastrointestinal tract and undergoes renal excretion, negative phosphate balance reflects a disturbance in one or both of these organ systems. Under normal conditions, approximately 60 - 70% of dietary phosphorus is absorbed from the gastrointestinal tract, principally in the small bowel. At the same time, approximately 200 mg of phosphate per day is secreted into the stool. Gastrointestinal phosphate absorption can be increased by the administration of vitamin D metabolites, but there seems to be little modulation or control of gastrointestinal secretion. Thus, although the kidney adapts quickly to dietary P deprivation, continued loss of P into the stool over a prolonged period can produce negative P balance and hypophosphatemia.[46] A more severe negative P balance due to increased P loss in the stool occurs with antacid administration because antacids bind phosphate in the intestinal lumen. Thus, clinical situations exist in which significant chronic hypophosphatemia and osteomalacia can be a manifestation of gastrointestinal phosphate loss.[5,6] This entity can be suspected from the patient's medical history and can be documented by an evaluation of urinary P excretion. The renal adaptation to decreased P intake is characterized by virtual elimination of P from the urine.

The presence of significant amounts of P in the urine, that is, more than 50 mg per 24 hours, in the presence of severe hypophosphatemia (less than 2 mg/dl) indicates that the kidney is not responding appropriately and further indicates that renal P wasting is contributing, in part or in total, to the hypophosphatemia.

In addition to dietary P intake, PTH is the other important regulator of urinary P excretion. Inappropriate urinary P excretion, therefore, implies either increased secretion of PTH or a defect in the normal tubular transport of P. Increased PTH levels may be seen in primary hyperparathyroidism or secondary hyperparathyroidism due to a disturbance in Ca homeostasis that lowers the serum Ca, such as intestinal malabsorption or disturbances in vitamin D metabolism. Urinary P wasting in the absence of increased levels of PTH can be an isolated defect, can exist in association with idiopathic hypercalciuria (presenting with kidney stones [47] or with rickets[48]), or can be part of a generalized defect in proximal tubular function (Franconi's syndrome, which is associated with varying combinations of glucosuria, aminoaciduria, uricosuria and bicarbonate wasting). It is the isolated defect, accompanied by inadequate production of $1,25\text{-}(OH)_2D$ that we are considering today. This disorder may be referred to as phosphate diabetes, hypophosphatemic rickets or vitamin D resistant rickets. It may occur as a familial X-linked syndrome or as an acquired form of vitamin D-refractory osteomalacia, often but not always associated with mesenchymal tumors. By this definition, our three patients all had adult-onset hypophosphatemic osteomalacia. Each patient manifested renal P wasting even in the presence of normal PTH levels. There was no evidence of a disturbance in renal tubular transport of glucose, aminoacids or uric acid. Serum $1,25\text{-}(OH)_2D$ levels were low and did not respond to appropriate stimuli (substrate loading, PTH). There was no family history of bone disease. In one case, there was association with a tumor with improvement following radiotherapy of the tumor. In the other two cases, tumor has not yet been found.

PATHOGENESIS OF ADULT-ONSET HYPOPHOSPHATEMIC OSTEOMALACIA

There have been two major hypotheses regarding the renal P wasting in this syndrome. The first posits a primary abnormality in vitamin D metabolism that results in decreased intestinal absorption of Ca and P with secondary hyperparathyroidism in turn producing the renal P wasting. In some respects, patient DM appears to fit this model, but even when her serum PTH level was normalized, the renal P wasting persisted. The second hypothesis postulates that the primary defect resides in the renal tubule itself and leads to deficient reabsorption of phosphate; hypophosphatemia is perceived as the cause of the skeletal abnormalities. Three lines of evidence favor an intrinsic renal tubular defect. Although earlier studies showed that calcium infusion could decrease P excretion in patients with vitamin D resistant rickets, implying that PTH played a pathogenetic role,[49] it is now clear that PTH levels are usually normal in untreated patients.[9] Phosphate transport does respond to manipulation of PTH secretion, however. Second, as shown in our own patients, treatment with large doses of vitamin D or its metabolites does not alter the phosphate transport defect despite a markedly positive Ca balance and normal levels of PTH.[50] In the hypophosphatemic mouse animal model for this syndrome, micropuncture studies demonstrated decreased proximal tubule P reabsorption. Even though P reabsorption increased after parathyroidectomy, the rate of transport remained low compared to that in controls.[51] Moreover, decreased phosphate uptake has been localized to the brush-border membrane vesicles from affected mice.[52]

Despite evidence that secondary hyperparathyroidism is not the proximate cause of the renal P wasting in vitamin D-resistant rickets, it is clear that a defect in vitamin D metabolism plays a role in some disease manifestations. Although levels of 1,25-$(OH)_2D$ are normal in humans with familial VDRR, the normal levels are inappropriately low for the prevailing level of serum P.[53]

Lyles and Drezner showed that intravenus administration of PTH, a potent stimulator of 25-(OH)D 1α-hydroxylase activity in normal humans, produced a much smaller increment in $1,25\text{-}(OH)_2D$ concentration in patients with X-linked hypophosphatemic rickets despite equivalent increases in urinary cyclic AMP excretion (Fig. 2).[54]

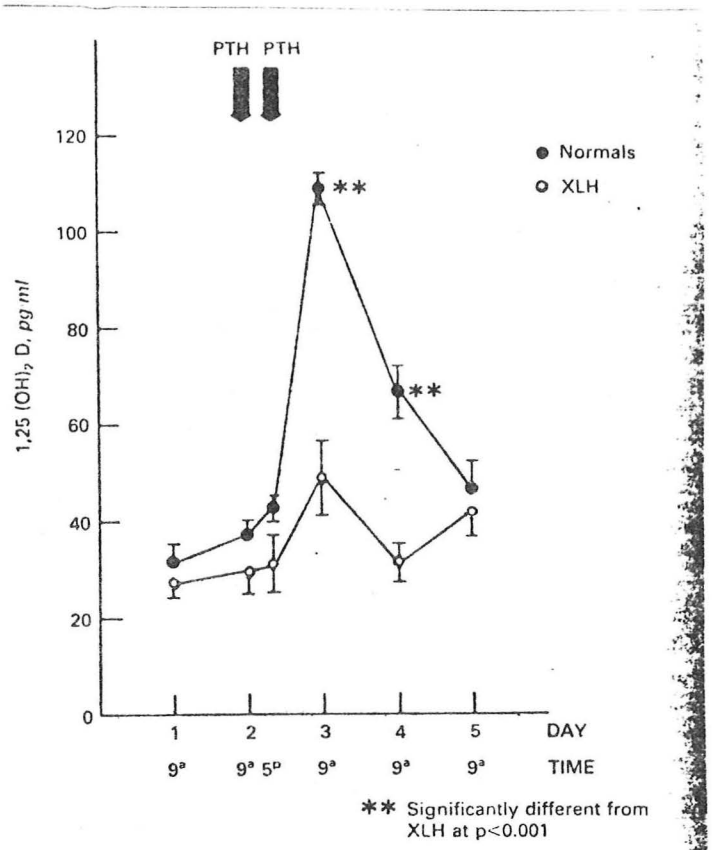

Fig. 2. *Effects of PTH on serum $1,25(OH)_2D_3$ levels in normal subjects and patients with X-linked hypophosphatemia* (XLH). Note that the levels increased significantly in both groups but were significantly greater in normals than in patients. (Reproduced from Ref. 37.)

Fig. 2

In addition to the defect in P excretion, patients with sporadic adult-onset vitamin D-resistant rickets and tumor-induced osteomalacia usually manifest low plasma levels of $1,25\text{-}(OH)_2D$. As we and others have shown, the decreased serum concentration of $1,25\text{-}(OH)_2D$ occurs despite decreases in serum P and normal levels of 25-(OH)D and PTH. Some have suggested that the decreased levels of $1,25\text{-}(OH)_2D$ in these patients, in contrast to the "inappropriately" normal levels in the patients with familial VDRR, might serve as a

marker for the presence of a tumor.[9]

TYPE OF TUMOR ASSOCIATED WITH ADULT-ONSET OSTEOMALACIA

Most of the tumors associated with adult-onset osteomalacia show a striking similarity. They tend to be mesenchymal tumors of bone or soft tissue. Mesenchyme is a mesodermally derived pleuripotential tissue capable of developing into fibrous, angiomatous, osseous or cartilaginous tissue and frequently containing 2 - 3 types. In this respect, the tumor of patient EW was fairly typical. However, most of the reported tumors were benign (only four were considered malignant).[8] Fifty-nine percent of the tumors were classified as hemangiomas, frequently hemangiopericytoma (21%). Other common tumor types were giant cell tumors and benign osteoblastomas. Some have considered the latter to be variants of hemangiopericytoma, but with focal collections of multi-nucleated giant cells.[17] The typical tumor involves prominent giant cells, spindle cells, and a high degree of vascularity. In the series of Ryan and Reiss, 44% of tumors were in the lower extemeties, 27% around the head, and 17% in the upper extremities.

Occasionally, adult-onset hypophosphatemic osteomalacia has been associated with other tumors. Multiple myeloma,[55] neurofibromatosis[56] and prostatic cancer[57] are three examples. When associated with multiple myeloma, the osteomalacia is generally part of the Fanconi syndrome. The presumed mechanism is renal tubular damage by one or more paraproteins. Neurofibromatous and prostatic cancer, on the other hand, may be akin to oncogenic osteomalacia. Recently, Lyles et al. transplanted tumor tissue from an affected patient with prostatic cancer into athymic nude mice.[58] The tumor bearing mice developed phosphate wasting, hypophosphatemia and defective 25-(OH)D 1α-hydroxylase activity. The phosphaturic substance has not been identified. In one interesting case report, the syndrome of oncogenic osteomalacia was described in a patient with oat-cell carcinoma of the lung, who also had SIADH.[59]

TUMOR FACTOR THAT INSTIGATES PHOSPHATURIA

The effectiveness of successful extirpation of tumors strongly suggests that tumor and osteomalacia are causally related. The simplest hypothesis is that these tumors secrete a substance that induces defective renal tubular transport of phosphate and interferes with renal 1α-hydroxylase. This mediator remains obscure. Three studies have suggested evidence of phosphaturic activity in saline extracts of such tumors,[27,35,60] and phosphaturia is transferable with tumor transplantation.[58] Isolation, identification, and characterization of the phosphaturic principle have not been accomplished.

POSTULATED MODEL OF PATHOPHYSIOLOGY OF ADULT-ONSET HYPOPHOSPHATEMIC OSTEOMALACIA

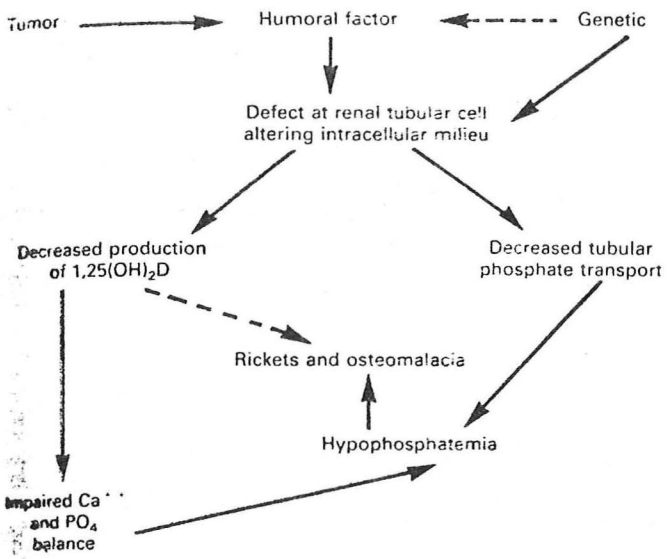

Fig. 3. *Model of the pathophysiology of vitamin D-resistant rickets.* Components of the model are speculative (see text). (Ref.9)

Fig. 3

THERAPEUTIC APPROACH

Recognition of oncogenic osteomalacia is important because 93% of patients with complete operative removal of a tumor had a cure of the osteomalacia.[8]

Occasionally, tumors are multiple or in unresectable locations, and complete removal of tumor is, therefore, impossible. Partial resection, however, has been associated with amelioration of clinical manifestations in 57%. When complete surgical excision can be achieved, the results are usually dramatic, with rapid improvement from a severely debilitated state to a normal active existence. Therefore, careful physical examination and roentgenographic surveys of the head and extremities should be performed, as well as special examination of the nose and mandible. Patients should be instructed to examine themselves for any unusual "lummps or bumps."

If no tumor can be found, the preferred treatment is $1,25\text{-}(OH)_2D$ combined with oral P supplements, as depicted in Fig. 4. The dosage must be determined by trial and error using symptoms, concentration of serum P, and serum alkaline phosphatase as end-points.

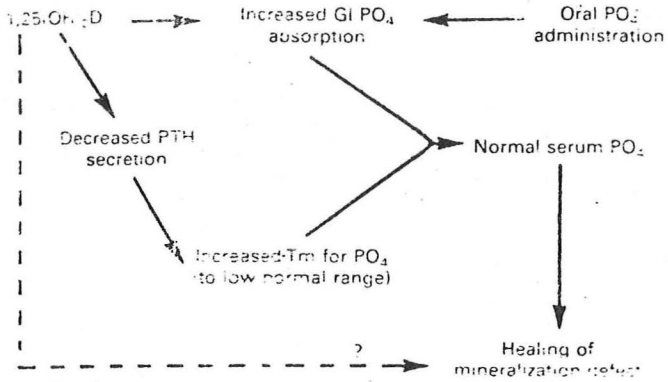

Fig. 4 *Therapeutic approach to vitamin D-resistant rickets.* (Ref. 9)

Fig. 4

TABLE I Biochemical, Histologic, and Clinical Characteristics of Patients with Oncogenous Osteomalacia

Age at Time of Study	Age at Onset	Duration of Postoperative Follow-up (years)	Sex	Serum Phosphorus (mg/dl)			Urine Phosphorus		Site/Histology of Tumor	Symptoms	Comments
				Preoperative	With Medical Therapy	Postoperative	Preoperative	Postoperative			
24	15	29	F	2.1	1.8	4.7	—	—	Femur/"degenerate osteoid"	Muscle weakness	Original case, relation of tumor and disease not appreciated, complete cure
11.5	10.5	1	F	1.9	—	4.1	77 μM/minute*	166 μM/minute*	Rib/giant cell granuloma	Fatigue, leg pain	Apparent cure
54	48	1	F	0.9	—	5.4	−5.6–+59%†	90+%†	Popliteal region/cavernous hemangioma	Leg pain; unable to sit up	Apparent cure
56	53	2	M	1.4	3.3	3.2	28%†	—	Hip/giant cell tumor	Pain	Apparent cure, possibly malignant tumor
38	34	5	M	1.4	2.1	4.6	23%†	81%†	Groin/sclerosing hemangioma	Bone pain, weakness	Complete cure
30	27	0.5	M	1.2	—	3.3	46%†	84%†	Lower thigh/sclerosing hemangioma	Pain; unable to walk	Apparent cure
45	43.5	1.5	F	1.2–2.2	2.8–4.2	3.6	53%†	—	Femur/"unusual type of primary bone tumor, possibly of vascular origin"	Fractured femur; weakness, pain and tenderness	Improvement during therapy with vitamin D, tumor incompletely removed, osteomalacia persisted
40	30	3	M	1.1	2.7	3.5	29%†	—	Lateral pharynx/benign tumor, giant cells, sheets of bland fibroblasts, many blood vessels	Severe bone pain, confined to bed	Postoperative hypercalcemic hyperparathyroidism,
9	7.5	1.5	M	1.7	2.0	4.8	58%†	88%†	Radius/nonossifying fibroma; giant cells, few blood vessels	Difficulty in standing, waddling gait	Apparent cure
54	53	1	M	1.7	"Normal"	"Normal"	72%†	—	Great toe/"microscopic appearances identical to those described by Olefsky"	Pain in multiple joints	Good response to medical treatment, apparent cure
11.5	7–8	0.25	F	1.7	—	4.4	—	—	Distal ulna/benign ossifying mesenchymal tumor; "osteoid and a few giant cells"	Delayed growth, genu valgum	Abstract, apparent cure
30	25	1.9	M	0.7	—	3.5	195 mg/24 hr	499 mg/24 hr	Mid-thigh/fibrous xanthoma; "spindle and round-shaped cells, many giant cells, proliferation of blood vessels"	Bone pain, muscle weakness, unable to walk	Rapid postoperative improvement
53	48	0.1	F	1.2	—	—	—	—	Ethmoid/hemangiopericytoma	Unable to walk	Tumor partially excised two years earlier, relation to osteomalacia not recognized then
58	44	None	M	1.6	2.2	—	—	—	Abdominal wall/benign hemangiopericytoma; "fibroblastic and giant cell reaction"	Pain, bone tenderness, unable to walk	Tumor found accidentally 14 years after diagnosis of osteomalacia
43	41	8.0	F	1.1–1.8	—	1.8	—	—	Femur/hemangiopericytoma; "spindle-shaped cells, vascular spaces"	Painful feet, knees, shoulders	Incomplete excision of tumor, not cured
36	27	0.5	M	1.4	—	4.0	63%†		Medial malleolus/hemangiopericytoma	Back pain, unable to walk	Apparent cure
54	50	1.0	M	0.9	—	1.6	42–63%†	87–92%†	Knee/angiosarcoma	Back pain, muscle spasms, unable to walk	Persistent hypophosphatemia after amputation
44	39	3.0	M	0.8–1.6	1.6	1.6–4.3	960–1,180 mg/24 hr	96 mg/24 hr	Tibia/spindle cells, abundant collagen, some giant cells, pleomorphic, muscle invasion	Pain in feet, shoulders, ankles, proximal muscle weakness	Transient postoperative increase of serum phosphorus and more prolonged postoperative mild hypercalcemia, clinical course uncertain

* Tubular maximum of phosphate resorption.
† Tubular resorption of phosphate.
‡ Tubular maximum of phosphate resorption/glomerular filtration rate.
$1,25(OH)_2D_3$ = 1,25-dihydroxycholecalciferol.

18	13	0.25	M	1.5	—	3.5–4.5	58–83%†	90+%†	Metacarpal/benign osteoblastoma	Difficulty in walking, profound weakness	Dramatic postoperative improvement, apparent cure
18	13	0.3	F	1.2	—	4.5–5.5	78–94%†		Humerus/benign osteoblastoma	Unable to walk, profound weakness	Dramatic postoperative improvement, from wheelchair to unassisted walking in one month
12	5	1.0	M	2.0	1.3	3.9	35%†	72%†	Skin, especially face and lower limb/ fibroangioma	Muscle weakness, unable to walk	Incomplete resection with some clinical improvement and healing
42	34	0.1	F	1.3	3.2	3.2	0.82 mg/dl	2.55 mg/dl‡	Iliac wing/"fibroblasts, multinuclear cells and giant cells"	Fatigue, muscle weakness, back pain	Impressive response to $1,25(OH)_2D_3$
62	59.5	4.0	F	1.0; recurrence 1.75	1.4–2.5	3.6	60.0 mg/24 hr	436 mg/24 hr	Radius/"benign connective tissue, no secretory granules"	Lumbar pain, unable to walk	Remission for 20 months postoperatively, followed by relapse
49	45	2.0	F	1.5	—	1.5	1.29 mg/dl‡	—	Nose/mesenchymoma	Muscle weakness, bone pain, unable to walk	Tumor resected twice, "drastic" improvement with $1,25(OH)_2D_3$
—	—	—	—	1.9	"Normal"	"Normal"	79%†	—	Hand/atypical chondroma	Diffuse bone pain, myopathy	Abstract, apparent cure
56	48	—	F	"low"	—	"Normal"	—	—	Foot/cavernous hemangioma	Bone pain	Apparent cure
34	33.25	—	M	1.8	3.8	—	49%†	—	Multiple skeletal sites/ hemangioma	Back pain, muscle weakness, malaise	Improvement with medical treatment
27	"Several years"	0.5	F	1.5	2.6	3.1	75%†	90%†	Tibia/benign osteoblastoma	Proximal muscle weakness	Apparent cure
--	—	—	—	1.3–2.7	1.1–2.5	4.1	31–41%†	68%†	Unknown/sclerosing hemangioma	—	Abstract
37	28	0.5	M	1.6	1.8–3.0	3.4	47%†	92%†	Frontal bone/ hemangiopericytoma	Vertebral compression fracture, ankle pain	Apparent cure
37	36	0.5	F	2.2	—	3.2	75%†	83%†	Rectum/benign hemangioma	Bone pain	Apparent cure
72	71.6	0.1	M	1.8	—	3.4	66%†	74%†	Nerve root/neuroma	Lumbar pain, sciatica	Previous gastrectomy and possibly malabsorption with secondary hyperparathyroidism
37	31	0.5	M	1.7	1.7–3.2	3.4	47–84%†	92%†	Frontal bone/ hemangiopericytoma	Bone pain, fracture of femur	History of epilepsy
25	24	5 days	F	1.5	—	2.7	0.9 mg/dl‡	2.8 mg/dl‡	Middle turbinate/ hemangiopericytoma	Painful feet, muscle weakness	Two operations, serum $1,25(OH)_2D_3$ increased after first resection, decreased on recurrence of tumor, and increased to normal after curative second resection
56	51	—	F	1.7	1.5	1.2	1,240 mg/24 hr	134 mg/24 hr	Nostril/hemangiopericytoma	Back pain, unable to walk	Incomplete resection, died of epistaxis
26	24	0.3	M	1.5	—	3.1	920 mg/24 hr	—	Brown-tumor of jaw/ "many giant cells"	Pain, muscle weakness	Dramatic clinical improvement
15	14	0.1	M	1.8–2.5	—	3.3–5.0	47–58%†	90%†	Distal radius/benign nonossifying fibroma	Bone pain and muscle weakness	Apparent cure
14	13	0.25	F	1.7	—	3.8	160 mg/dl	4 mg/dl	Lower femur/"red-brown nonossifying fibroma with spindle cells, giant cells, and hemorrhage"	Pain in knees and heel	Apparent cure
65	—	—	F	—	—	—	—	—	Quadriceps/cavernous hemangioma	—	Abstract, apparent cure
69	—	—	M	—	—	—	—	—	Nose/Angiofibroma	—	Abstract, initial improvement followed by relapse on tumor recurrence
44	41	0.1	F	1.3	—	3.3–5.0	824 mg/24 hr	660 mg/24 hr	Foot/fibroangioma	Bone pain, muscle weakness, unable to walk	Abstract, apparent cure
29	27	—	M	1.0–1.6	2.1	3.0–4.2	47–58%†	80–85%†	Mandible/osteosarcoma	Lumbar pain, muscle weakness	Improved after two resections and chemotherapy
64	60	7	M	1.8	2.6	2.1			Lower femur/"spindle cells, round cells, giant cells, very vascular"	Bone pain, muscle weakness, unable to walk	Minimal response to surgery, fair response to $1,25(OH)_2D_3$
66	63.5	—	F	1.3	1.8–2.4	—	39%†	—	Frontal bone and cerebral cortex	Bone pain	Good response to $1,25(OH)_2D_3$

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