MEDICAL GRAND ROUNDS
PARKLAND MEMORIAL HOSPITAL
December 12, 1957

[Metabolic Bone Disease]

Case I. [redacted] -- Osteoporosis

This 45 year old white woman was admitted with a chief complaint of recurrent ankle edema of three months duration. During this interval she also complained of weakness and some low back pain. Medical examination in Dallas failed to establish a diagnosis; but because of persistence of complaints, she was hospitalized for a work-up.

On physical examination slight rounding of face and some soft hair along lateral aspects of her cheeks were noted.

The most striking feature of the work-up was the finding of tremendous demineralization of the spine with three compression fractures. Na,K, CO2, Cl, BUN, Ca, P, proteins, alkaline phosphatase were normal. 17-hydroxycorticoids ranged from 12-15 mg/24 hrs. Glucose tolerance test was diabetic. 17-ketosteroids ranged from 11-16 mg/24 hrs. Sella turcica was enlarged.

The pituitary was irradiated. Within one month hypertension (160/110) and retinal hemorrhages supervened. Back pain became unbearable. For this reason, it was decided not to await possibility of remission from irradiation. Bilateral adrenalectomy was performed with marked clinical improvement. Back pain is reduced but still present.

Case II. [redacted] -- Osteomalacia

This 57 year old [redacted], an intermittent week-end alcoholic, entered the hospital with a chief complaint of severe weakness and weight loss for three years. For one year he had about three stools daily which were formed and appeared at times to be greasy. The stools were not voluminous, foul smelling, or remarkable in appearance. Other than the pain associated with a perforated peptic ulcer 18 years previously, he has had no abdominal pain. His diet during the present illness had been very poor. No other symptoms. Physical examination negative, same for malnutrition and emphysema.

Work-up revealed large amounts of fat and undigested muscle fibers in the stool. There was marked pancreatic calcification by x-ray and deformity with ulceration of the pyloric antrum. Bone marrow and glucose tolerance test were normal. Ser. Ca.: 8.1-8.5 mg%. Ser. P.: 2.0-4.0 mg%. Alk. phosphatase: 5.8. Liver function tests normal. No evidence of decalcification of the skeleton.

On a high protein-low fat diet, Vit. D., pancreatin, and calcium, there was recovery of strength and weight gain (21 lbs.). Ser. Ca. returned to normal (10.1 mg%).

Case III. [redacted]. Osteitis fibrosa -- manifested principally by renal stones.

This 36 year old woman had "kidney trouble" diagnosed as pyelitis with each of her seven pregnancies. Dysuria and frequency persisted after her sixth delivery in [redacted] 1952. These symptoms became more severe and were accompanied by right costovertebral and suprapubic pain in [redacted], 1952. I-V pyelograms revealed a right ureteral stone which was removed surgically. No studies of any kind were performed.

In [redacted], 1957, she was once again seen for pregnancy. She complained of severe constipation, malaise and fatigue. Following delivery she has had nausea with occasional vomiting, nervousness and some fatigue. Physical exam -- normal.

	Chemistry				
	Ca	P	Alk. Phosph.	Alb/Glob.	BUN
[redacted]-57	12.5	2.5	4.6		
[redacted]-57	12.8	3.3	-		8
[redacted]-57	11.6	2.3	3.7	4.8/2.5	
[redacted]-57	12.1	2.3	6.8	5.0/2.9	11
[redacted]-57	11.8	2.2	5.7		

X-rays of spine, pelvis, skull and lamina dura made in [redacted] and again in [redacted], 1957, revealed mild decalcification of the skeleton in [redacted] without any other findings. Lamina dura intact.

She is awaiting hospitalization.

Case IV. [redacted] Osteitis fibrosa -- manifested mainly by polyuria.
[redacted], a 22 year old white male, had urinary sp. gr. of 1.001 on Army discharge physical examination. After 18 hours of fluid restriction this was still 1.002. For several years he had imbibed and voided large volumes during the day and had obligatory nocturia once each night. He had never had dysuria, hematuria, pyuria, renal colic or calculi. Strength and stamina were normal, and history was negative for anorexia, N or V, constipation, fractures, bony or intra-oral tumors, and visual disturbance. His father had kidney stones.

Physical examination was entirely normal; BP was 138/98. Urinalysis: sp. gr -- 1.002, trace reaction to Sulkowitch, 20 WBC per HPF. Maximal urine concentration was 1.005. Urea clearance was 64% and 60% of normal. BUN was 13.1 mg%. PSP excretion was 7% in 15 minutes, 23% in 2 hours. Urinary calcium excretion on low-calcium diet was 119, 94, and 810 mg. per day. Serum calcium was 19.2, 15.4, and 15.6 mg%. Serum phosphorus was 2.4, 3.2, and 2.5 mg%. Alkaline phosphatase was 6.9, 11.1, and 5.2 B.U. KUB film showed extensive bilateral nephrocalcinosis, but no renal calculi. An adenoma of the left superior parathyroid gland was removed. Tetany developed two days postoperatively, and subsided during the following week. Sixteen months after surgery, serum calcium is normal (10.2 mg%), but phosphorus is still sometimes slightly low (2.4 - 2.8 mg%). Alkaline phosphatase is normal (2.4 B.U.). Diffuse bilateral nephrocalcinosis persists, but BUN is 9.5mg% and PSP excretion has increased to 31% in 15 minutes. Urine now concentrates to 1.026 in 18 hours. Calcium excretion on 135 mg. calcium diet is 16 mg. per day. Tubular reabsorption of phosphorus is 90%.

Case V. [redacted] -- Osteitis fibrosa -- borderline hypercalcemia, no hypercalcuria when examined.

[redacted], 1950: First admission of [redacted], a 60 year old colored male, 12 hours after onset of gross hematuria. Previous health had been good, with normal strength and stamina, no urinary or gastrointestinal complaints, no fractures or skeletal lesions. BP was 140/90. Urinalysis showed gross hematuria, sp. gr. - 1.012, 3-plus albumin, occasional WBC. Serum calcium, phosphorus, and flat plate of abdomen were not done. Two large bladder calculi (calcium phosphate on analysis) were removed at cystotomy.

[redacted] 1952: Second admission, 5 days after acute onset of chills, fever, anorexia, and left CVA pain. BP was 140/80. Urinalysis: sp. gr. - 1.017, 1-plus albumin, 10 WBC and many RBC per HPF. BUN - 16 mg%. A single serum calcium was 10.6 mg%; no phosphorus was done. KUB showed an opaque calculus within the left renal pelvis.

[redacted] 1957: Third admission, complaining of weakness and vague joint pains of about 3 years duration. History was unreliable because of mental confusion (Truman is president) but apparently no weight loss, anorexia, constipation, thirst, polyuria or nocturia. Admission BP of 210/160 fell slowly to 140/80 during several weeks without treatment. Urinalysis: sp. gr. - 1.004, 1.011; 4-plus albumin; Sulkowitch - negative to 2-plus; many WBC and some RBC per HPF. Urea clearance: 28 and 32 cc/min. maximal. BUN - 16.9 mg%; serum creatinine - 1.2 mg%. A/G = 3.5/3.7. Nine serum calciums were between 11.6 and 12.7 mg%; eleven serum phosphorus values were between 2.2 and 2.7 mg%. Alkaline phosphatase - 4.0 B.U. Urinary calcium excretion on 135 mg. calcium diet was 87, 120, and 129 mg. per day. Tubular reabsorption of phosphorus was 60% and 52%. Serum calcium remained high (12.0-12.4 mg%) during five days of 1-M hydrocortisone hemisuccinate, 50 mg. q. 6 hours. IVP's showed left hydronephrosis secondary to an opaque calculus wedged in the left ureter. No bone disease by x-ray. A right superior parathyroid adenoma (1.2 x 1.6 cm) was removed. The next day serum calcium was 10.6 mg% and phosphorus was 3.7 mg%; subsequent values have remained normal. Left ureteral lithotomy was performed 3 weeks later. The patient's strength improved postoperatively and joint pains disappeared, but he still thinks Truman is president.

Case VI. [redacted] -- decalcification, etiology unknown.

[redacted] 1957: This 45 year old man, a chronic alcoholic, was admitted following an automobile accident and was found to have a cerebral contusion, aspiration pneumonia and Laenec's cirrhosis. He improved remarkably with treatment and was discharged after two weeks.

In clinic, x-rays of spine were taken because of backache of recent onset and revealed collapse of T-11.

[redacted] 1957: Having disappeared from clinic, patient was readmitted because of syncope. He had been drinking heavily. He complained of severe back pain. On physical exam, in addition to evidences of cirrhosis, he was markedly tender from T6 -- L3.

X-ray examination revealed collapse of two additional vertebrae and tremendous demineralization of the entire skeleton, including lamina dura and skull. On [redacted]57 x-rays revealed a 4th collapsed vertebrae.

Work-up: No fat in stools. Il serum Ca and P all normal. Alk. phosphatase elevated (4.8-7 I); liver function tests deranged. FBS, serum proteins, Na, K, CO_2, Cl, BUN normal. I7-ketosteroids 11.5 mg/24 hours. Normal bone marrow; antibodies for febrile agglutinins and blood groups present. TRP = 89%. Urinary Ca excretion on 150 mg. Ca diet -- 100 mg/day. Administration of 15 mg Ca/Kg body weight for 4 hours.

BIBLIOGRAPHY

Albright proposed that the phrase metabolic bone disease be confined to diseases of a systemic nature which influence the entire skeleton, although some bones were more susceptible than others.

Bone consists of a protein matrix (osteoid) and a mineral deposition therein consisting predominantly of calcium salts, apatite. Osteoblasts lay down matrix; osteoclasts destroy bone (both matrix and apatite). "Decalcification" alone, therefore, does not occur.

Metabolic bone disease is sometimes detected by x-ray evidence of decreased density of the skeleton. The terms "decalcification", "osteoporosis", etc., when used as synonyms for increased radiolucency, are incorrect. Rarefaction of bone is a more proper term. Albright distinguishes three forms of metabolic bone disease, all of which may be characterized in part by rarefaction:

A. Osteoporosis: a process in which the primary defect is impaired matrix formation. The trabeculae of bone are decreased in number and thickness and the cortex is thin; but all the bone which is present contains normal amounts of apatite.

B. Osteomalacia: deficient apatite deposition in bone matrix. The formation of the latter is normal or increased.

C. Osteitis fibrosa generalisata: excessively rapid bone destruction (osteoclastic activity).

Discussions of classifications:

(I.) Albright, F. and Reifenstein, E.C. The Parathyroid Glands and Metabolic Bone Disease, Williams & Wilkins, 1948.

(2.) Follis, R H., Jr A survey of bone disease. Am. J. Med., 1957, 22, 469.

Types of Osteoporosis

I. Inadequate osteoblastic activity

A. Immobilization of a part or all of skeleton -- e.g., nerve injury, immobilization after a fracture, extensive paralysis (e.g., poliomyelitis), etc. It has been suggested that disuse diminishes osteoblastic activity by causing a reduction of blood flow to bone;

(3) Stevenson, F.H. Osteoporosis of immobilization in recumbency. J. Bone & Joint Surg. 1952, 34B, 256. In normal subjects physical activity has a protein anabolic effect in association with which there is calcium retention:
(4) Deitrick, J.E., Whedon, G D., Shorr, E. Effects of immobilization upon various metabolic and physiologic functions of normal men. Am. J. Med., 1948, 4, 3.

B. Deficient estrogen -- post menopausal osteoporosis. Pan-hypopituitarism, artificially-induced or naturally-occurring menopause are associated with osteoporosis. Nine out of 17 patients between ages of 10 to 30 with Turner's syndrome had osteoporosis:
(5) Grunnback, M.M., et al. Gonadal dysgenesis. J. Clin. Endo. & Met. 1955, 15, 1161.

C. Congenital deficiency of osteoblastic activity -- osteogenesis imperfecta. Osteoblasts may be increased; alk. phosphatase may be elevated, but matrix is defective and does not calcify.

II. Inadequate building-materials for matrix formation.

A. Protein deficiency. Simple starvation may be accompanied by osteoporosis. Nephrosis is sometimes responsible:
(6) Emerson, K., Jr. and Beckman, W.W. Calcium metabolism in nephrosis. J. Clin. Invest. 1945, 24, 564. Uncontrolled diabetes may result in osteoporosis--see ref. 1. Albright attributed rarefaction of bones in hyperthyroidism to the loss of protein because of excessive catabolism. This seems to be a minor factor. Increased amounts of Ca are in urine and stool in uncontrolled hyperthyroidism; occasionally alk. phosphatase is elevated; radioisotope data suggest increased flow of Ca into skeleton; microscopic examination reveals evidence of extensive bone destruction; and balance data reveal loss of Ca while in N equilibrium and retention of Ca, with treatment, in part independent of nitrogen. It has, therefore, been proposed that bone disease in hyperthyroidism is primarily the consequence of increased bone destruction (osteitis fibrosa) with secondary bone formation. Malnutrition may complicate the picture and cause some osteoporosis.
(7) Follis, R.H., Jr. Skeletal changes associated with hyperthyroidism. Bull. Johns Hopkins Hosp. 1953, 92, 905.
(8) Krane, S.M., et al. Effect of thyroid disease on Ca metabolism in man. J. Clin. Invest. 1956, 35, 874.
(9) Green, J. and Lyall, R. Ca metabolism in hyperthyroidism. Lancet, 1951, p.828.
Cushing's syndrome can lead to fulminant osteoporosis, particularly if activity is restricted. Mechanism is thought to be protein deficiency as a consequence of the anti-anabolic effect of hydrocortisone. Steroids, given for the treatment of rheumatoid arthritis over prolonged periods (up to 5 years), were associated with development of severe osteoporosis in 11 and compression fractures in 6 of 68 patients. Most of these patients were on restricted activity.
(10) Howell, D.S. and Ragon, C. Course of rheumatoid arthritis during 4 years of induced hyperadrenalism. Medicine, 1956, 35, 83.
Androgen deficiency -- long-standing eunuchoidism is often associated with osteoporosis. Presumably, androgens promote matrix formation by their anabolic effect -- not as a result of specific action on osteoblasts.

B. Ascorbic acid deficiency -- markedly diminished osteoblastic activity is noted microscopically. Alk. phosphatase may be diminished.

III. Osteoporosis of unknown etiology.

A. Acromegaly -- See ref. 1. Cause unknown. Best bet seems to be an associated deficiency of gonadotrophic hormone from which most acromegalics suffer.
(11) Reifenstein, E.C., et al. Endocrinol. 1946, 39, 71.

B. Senile osteoporosis -- cause unknwon -- may be connected with diminished activity, malnutrition, diminished andogen and estrogen secretion.
(12) Moldawer, M. Senile osteoporosis. Arch. Int. Med. 1955, 96, 202.

C. Tumor cells in bone marrow -- may give rise to osteoporosis:
(13) Follis, F.H., Jr. and Park, E.A. Bull. Hosp. Joint Dis. 1951, 12, 67.
(14) Wallerstein, R.S. Multiple myeloma without demonstrable bone lesions. Am. J. Med. 1951, 10, 325.

Special Features of Osteoporosis

I. Osteoporosis and hypercalcemia.

Osteoporosis is usually associated with normal values for serum Ca, P, and alkaline phosphatase. Fractures with immobilization sometimes result in acute hypercalcemia. Immobility is more important than the fracture in promoting Ca loss:
(15) Albright, F. et al. J. Clin. Endocrin. 1941, 1, 711.
Hypercalcemia is especially apt to develop following immobilization in children whose bones are rapidly metabolizing:
(16) Mason, A.S. Acute osteoporosis with hypercalcemia. Lancet, 1957, p.911.

II. Asymptomatic fractures in senile osteoporosis.

In homes for the aged, the incidence of asymptomatic vertebral fractures is 25-30%. T12 and L1 most vulnerable. In contrast to compression fractures in the young, these are usually asymptomatic. Immobilization aggravates osteoporosis and is unnecessary if pain is absent:
(17) Gershon-Cohen, J., et al. J.A.M.A. 1953, 153, 625.

III. Osteoporosis and hypercalciuria.

The rate of Ca loss may not be rapid enough to cause detectable hypercalcemia, but in pronounced osteoporosis increased Ca in urine and stool is common. Apart from skeletal rarefaction, the principal disorders are nephrocalcinosis and renal stones. Both of these occur in Cushing's syndrome. They are particularly common in any kind of paralytic disease where patients are bed-ridden. In severely paralyze patients with poliomyelitis hypercalciuria lasted more than one year:
(18) Dunning, M.F. and Plum, F. Hypercalciuria following poliomyelitis. Arch. Int. Med. 1957, 99, 716.

Treatment of Osteoporosis

(19) Bartter, F.C. Osteoporosis. Am. J. Med. 1957, 22, 197. In addition to treating specific cause of osteoporosis -- e.g. scurvy, diabetes, hyperthyroidism, Cushing's syndrome, -- several general points are always applicable:

A. Do not give Ca salts or Vit. D. Such measures increase hypercalciuria and therefore cause nephrocalcinosis and stones without serving to repair osteoporosis.
B. Mobilize patients. Disuse atrophy aggravates entire process. Needless braces about spine for asymptomatic compression fractures increases the osteoporosis. A rocking bed minimizes osteoporosis in paralyzed patients.
C. Generous protein intake -- especially if there is evidence of malnutrition.
D. Generous fluid intake -- to prevent stones.
E. Estrogens and androgens -- appear to be of benefit in all types of osteoporosis except osteogenesis imperfecta and certain idiopathic forms. Both cause diminished Ca and P excretion in urine and stool. Estrogens produce more Ca retention; androgens more N retention.

Dose of estrogens:
Diethylstilbesterol -- 1 mg. 1-3 times daily.
Premarin (water soluble conjugated strogenic substances) -- 1.25 mg 1-3 times daily.
Ethinyl estrodiol -- 0.1 mg 1-3 times daily.
-- estrogen is given for one month and omitted for one week in cycles

Dose of androgens:
Methyltestosterone -- 5-10 mg. daily by Linguet.
Nilevar -- still experimental --10 mg. t.i.d.

Combined estrogen and androgen therapy is of value in either sex. In women acne, hirsutism, deepening of voice, frontal baldness, hypertrophy of clitoris indicate excessive androgen. Estrogen produces tenderness of breasts and salt retention in both men and women and reduced libido in men.

In post-menopausal osteoporosis, although back pain responds after three weeks of estrogen, x-ray evidence of skeletal recalcification has not been forthcoming. However, further rarefaction is presumably prevented.

Bartter points out (ref. 19) that beneficial effects with methyl testosterone in osteoporosis have been shown only with doses of 40-100 mg/day. Small doses may be of value, but not clearly proved. Even small doses exert androgenic action in most women; dose usually reduced after 40 days.

Nilevar is a potent anabolic agent but exerts some androgenic effects in women. Still experimental.

Osteomalacia

Types of Osteomalacia:

A. Inadequate Ca or Vit. D. intake:
This is virtually never a cause of osteomalacia in adults in the U.S. It is important in China and India, where Vit. D. lack may contribute. Rarely, pregnant and lactating women or growing children on exceedingly poor diets may develop osteomalacia.

B. Steatorrhea.
All types of steatorrhea may give rise to osteomalacia. Mechanism is twofold: (1) loss of Vit. D. in fatty stools. (2) perhaps formation of Ca soaps. Steatorrhea may be occult, and present as a problem in bone disease without obvious G-I disturbance:
(20) Juergens, J.L., et al. Severe osteomalacia associated with occult steatorrhea due to non-tropical sprues. Arch. Int. Med. 1956, 98, 774.

Most severe osteomalacia in steatorrhea occurs in sprue where may have a specific defect in intestinal capacity to absorb Ca:
(21) Badenock, J. and Fourman, P. Osteomalacia in steatorrhea. Quart. J. Med. 1954, 23, 165.

Excellent review of steatorrhea.
(22) Valwiler, W. G-I malabsorptive syndromes. Am. J. Med. 1957, 23, 250.

C. Excessive renal excretion of Ca.
Acidosis of renal insufficiency. Renal disease causes acidosis with fixed acid (phosphate) retention. Urinary acid excretion is low. Azotemia present. Acidosis causes hypercalciuria which results in hypocalcemia. This stimulates parathyroids. Skeleton further depleted of Ca. But because of tubular disease, phosphate excretion is not increased. Bone findings are a mixture of osteomalacia and osteitis fibrosa.
(23) Albright, F. et al. Osteomalacia and late rickets. Medicine 1946, 25, 399.
Hyperchloremic renal tubular acidosis. High Cl, low CO_2, low P, normal BUN early, low K, striking nephrocalcinosis. Process attributed by Albright to impaired NH_3 production in kidneys (ref. 23). Alternative hypothesis: impaired proximal tubular bicarbonate reabsorption:
(24) Latner, A. and Burnard, E.D. Quart. J. Med. 1950, 19, 285.

Disease is acquired (pyelonephritis most common) or inherited.
Vitamin D resistant rickets or phosphate diabetes. Osteomalacia develops about age of 2. Serum Ca usually normal (may be low); ser. P very low; marked phosphoturia. Primary defect appears to be inability of tubules to absorb P. Absorption of Ca and P from gut is normal. Defect is partially corrected by massive doses of Vit. D. Mechanism not clear. Secondary hyperparathyroidism plays a role in skeletal depletion. Although Vit. D can partially correct the disturbance, it is probably not a result of a primary deficiency of the vitamin:
(25) Engfeldt, B., et al. Primary Vit. D resistant rickets. J. Bone & Joint Surg. 1956, 38-A, 1323. There is a strong familial tendency.

Phosphoturia may be accompanied by renal glycosuria: syndrome called glycosuric-rickets.

Fanconi syndrome: phosphoturia, glycosuria, amino-aciduria, ketonuria and organic aciduria. Cystinosis is an essential feature only of the infantile type. Hyperchloremic or hypochloremic acidosis is usually present, but this is not invariable. Nephrocalcinosis is absent. Hypophosphotemia is regularly present. Osteomalacia due to excessive P excretion and acidosis:
(26) Milne, et al. Quart. J. Med 1952, 21, 61.
(27) Anderson, et al. Quart. J. Med. 1952, 21, 33.
(28) Jackson, et al. Quart. J. Med. 1953, 22, 133.
Idiopathic hypercalciuria. Primary disturbance is excessive Ca excretion at any given level of serum Ca. No acidosis. Serum Ca is normal or low. Serum P is usually normal, but may fall as a result of secondary hyperparathyroidism. Renal stones are marked. See ref. 23.
Uretero-enterostomy with hyperchloremic acidosis.

D. Excessively rapid bone calcification.
Osteomalacia following removal of parathyroid tumor.
Osteomalacia following correction of scurvy.
New bone is rapidly laid down; ser. Ca and ser. P fall to low values and matrix is not calcified.

Treatment of Osteomalacia

A. In steatorrhea with osteomalacia.
Vitamin D -- 50,000-300,000 units/day.
Ca lactate -- 5 gm. t.i.d. or more.
To prevent Vit. D intoxication: Hypercalcemia will not be present if urine Ca is low. Therefore, do Sulkwitch test for rough index of Ca. Follow serum Ca. See ref. 21.

B. For Vit. D resistant rickets:
May need as much as 600,000 units of Vit. D daily.
Must be careful to prevent Vit. D intoxication as osteomalacia recedes.

C. In osteomalacia due to acidosis:
Shohl's solution:
Na citrate 98 gm.
Citric acid 140 gm.
Water 1000 cc.
Take 50-100 cc. daily in divided doses. Can substitute K citrate in part or in whole if K deficiency or edema is present. Watch for alkalosis, edema, K intox. when renal function is poor.
If osteomalacia is severe, large amounts of Ca salts and Vit. D must be given.

Osteitis fibrosa generalisata

I. Causes of primary osteitis fibrosa generalisata.
Single parathyroid adenoma -- about 82%.
Multiple parathyroid adenomas -- about 4%.
Multiple parathyroid adenomas associated with adenomata of pancreas, adrenal, pituitary -- about 4%.
Primary diffuse Wasserhelle hyperplasia -- 9%.
Carcinoma of parathyroid -- < 1%.

II. Clinical syndromes.

A. Renal or bladder stones -- 5% of all patients with renal stones have hyperparathyroidism (Albright). Figure is probably low.

B. Nephrocalcinosis -- may be manifested only by polyuria. Occasionally get renal diabetes insipidus with dilute urine. Ultimately renal failure may dominate picture.

C. Bone disease -- rarefaction, cysts, tumors, path. fractures and deformity. Absence of lamina dura; decalcification of skull. Complaints of bone pain.

D. Combined bone and renal disease.

E. Chemical hyperparathyroidism -- no x-ray evidence of bone disease and no calcinosis or calculi May be:
(1) asymptomatic -- chance findings in blood establish diagnosis.
(2) syndrome referable to elevated serum calcium:
(a) hypoirritability of peripheral nerves (hypotonia, muscular weakness, hypermobility of joints, diminished reflexes)
(b) hypoirritability of splanchnic autonomic system (severe constipation, abdominal distension with nausea and vomiting)
(c) hypoirritability of central nervous system (impaired hearing, drowsiness, frank coma, psychosis)
(d) disturbance of cardiac muscle (arrhythmias, short Q-T interval)
(e) dry mouth and pruritus
(f) metastatic calcification (band keratitis and calcification at sclero-corneal junction, calcification of media of arteries of leg with eschemic leg ulcers and intermittent claudication, calcification bilaterally in brain and basal ganglia, calcification of pancreas with pancreatitis, calcification in lungs and thyroid)

III. Important types of presenting features.

A. Gastro-intestinal syndrome -- anorexia, nausea, vomiting, constipation, cachexia, and abdominal pain In addition to direct effects of hypercalcemia on autonomic nerves, this syndrome is due to the increased incidence of peptic ulcer and pancreatitis in hyperparathyroidism:
(29) Rogers, H.M , et al. Primary hypertrophy and hyperplasia of parathyroid glands associated with duodenal ulcer. Arch. Int. Med. 1947, 79, 307.
(30) Cape, O., et al. Pancreatitis: a diagnostic clue to hyperparathyroidism. Ann. Surg 1957, 145, 857.

B. C.N.S. disturbances -- depresion and psychosis:
(31) Fitz, T E and Hallman, B L. Mental changes associated with hyperparathyroidism Arch. Int. Med. 1952, 89, 547.

C. Renal--- polyuria, low specific gravity of urine; sometimes hyposthenuria and renal diabetes insipidus. For a long time, concentrating power of kidney is depressed out of all proportion to azotemia or impaired PSP excretion:
(32) Hellström, J. Primary hyperparathyroidism. Acta endocrinol. 1954, 16, 30.
If polyuria and polydipra are present due to nephrocalcinosis, stones are not likely to form.

D. Hyperparathyroidism associated with other endocrine adenoma, especially islet cell adenoma (hypoglycemia).

E. Acute parathyroid intoxication -- coma, fulminant renal failure, cardiac arrhythmias (heart stops in systole).

F. If chronic renal failure occurs, ser Ca may fall toward normal and P rises to high values. Usually, Ca is higher than would be expected from degree of azotemia and Pretentine.

IV. Laboratory diagnosis.

A. Repeated determinations of serum Ca, P, and alkaline phosphatase. This is by all odds the most critical lab. aid.
Normal values for Ca: 9.2-10.4 mg%.
Normal values for P : 2.8-4.5 mg%.
If serum proteins are altered, must correct for estimated ionized Ca:

B. X-ray: rarefaction of skeleton; bone cysts and tumors: absent lamina dura; granular decalcification of skull; renal stones; nephrocalcinosis; metastatic calcification (vessels esp. of lower extremities, pancreas, etc.).

C. Demonstration of hypercalciuria: Bauer-Amb diet (135 mg Ca daily for 3 days; then collect urines while still on diet for several days thereafter). 125-150 mg/day is borderline. > 150 mg Ca/day — hypercalciuria.

D. Phosphate reabsorption test:
(33) Schaaf, M. and Kyle, L.H. Measurement of % renal P reabsorption in diagnosis of hyperparathyroidism. Am. J. Med Sci. 1954, 228, 262. Creatinine clearance used to estimate glomerular filtration rate.

$$\% \text{ TRP} = \frac{\text{tubular reabsorption of P}}{\text{filtered P}} \times 100$$

Normal subjects % TRP = 91.3 ± 3.3%
Hyperparathyroidism = 58%

If serum creatinine is normal, can use a shortened formula which eliminates urine volume and timing errors:

$$\% \text{ TRP} = 100 \left\{ 1 - \frac{\text{urine P conc. x serum creatinine conc.}}{\text{urine creatinine conc. x serum P. conc.}} \right\}$$

All concentrations are in mg/ml.
Values of % TRP = normal 85% ± 1.
osteoporosis 84% ± 0.6
hyperparathyroidism 65% ± 1.

(34) Chambers, E.L, Jr., et al. Tests for hyperparathyroidism. J. Clin. Endocrinol. & Met. 1956, 16, 1507.
Others have not confirmed this work. Part of the difficulty is that as serum P rises, P clearance increases. A new formula, phosphate excretion index (P.E I.) has been proposed to correct for this:

$$\frac{\text{Clearance P}}{\text{Clearance Cr}} - \frac{\text{P}}{20} + 0.05 = 0 \pm 0.12 \text{ in normal people.}$$

Values above 0.12 should be obtained in hyperparathyroidism:
(35) Norden and Fraser. Indirect assessment of parathyroid function in Bone Structure and Metabolism. Ciba Foundation Symposia, Little Brown, 1956.
Even this correction has not been found reliable: high values found in patients with stones; normal values in hyperparathyroidism.
(36) McGeown, M G. Normal standards on renal phosphate clearance. Clin. Sci. 1957, 16, 297.

E. Calcium infusion test.
Low values of serum Ca stimulate parathyroid secretion; high values inhibit it. Therefore, in normal subjects ser. P should rise, urine P should fall, Ca excretion should be fairly brisk.
Patient placed on low Ca and low P diet. After 3 days, collect control 24 hr. urine on 4th day. On 5th day give an infusion of Ca gluconate, 15 mg Ca/Kgm body wt. in 1 liter of saline over 4 hrs:
(37) Norden and Fraser. Ca infusion test. Lancet 1956, 823 & 827.
If urine is collected 8-24 hrs. after infusion is begun, results are better:
(38) Heatt, H.H. and Thompson, D.D. J.C.I. 1957, 36, 573.
Test is no good for hyperparathyroidism. Magnitude of Ca retention may be of some value in osteomalacia.

F. Phosphate deprivation test.
Low P diet for 5 days. Ser. Ca rises in hyperparathyroidism, not in normal subjects. Ser. P and urine P falls in both. Of minor value.
See ref. 34.

G. Response to hydrocortisone
Hypercalcemia of all types disappears on large doses of hydrocortisone except in hyperparathyroidism and some forms of metastatic cancer.

V. Causes of hypercalcemia other than hyperparathyroidism.

A. Milk-alkali syndrome.
No hypercalciuria on low Ca diet. Metabolic alkalosis. Usually K deficiency. Renal insufficiency prominent.
(39) Burnett, C.H , et al. N.E. J. M. 1949, 240, 1.

B. Vitamin D intoxication.
Serum P usually normal. Renal insufficiency prominent.

C. Hypercalcermia in adrenal insufficiency (crisis):
(40) Leeksma, C.H.W., et al. Hypercalcemia in adrenal insufficiency. Acta Med. Scand. 1957, p. 455.

D. Idiopathic hypercalcemia of infancy. May be a form of hypersensitivity to Vit. D.
(41) Daeschner, G.L. Ped. 1957, 19, 362.

E. Sarcoidosis -- may be due to endogenous Vit. D. intoxication.
(42) Henneman, P.H., et al. J C.I. 1956, 35, 1229.
May get high Ca, low P, elevated alk. phosphatase.

F. Berylliosis.

G. Acute osteoporosis especially with immobilization.

H. Paget's disease with fracture and immobilization.
(43) Reifenstein adn Albright N.E.J.M. 1944, 231, 343.

I. Multiple myeloma (alk. phœphatase normal or low.)

J. Lymphoma.
(44) Kabakow, B. et al. Hypercalcemia in Hodgkin's disease. N.E.J.M. 1957, 256, 59.
Nephrocalcinosis and renal stones are important causes of death in lymphoma even with normal serum Ca.

K. Malignancy.
Osteolytic lesions of bone are associated with hypercalcemia. Breast and prostate are most common.
Recently, hypercalcemia, low P, elevated alk. phosphatase has been observed in patients with malignancy without bone destruction. Removal of turmor corrects disorder. If tumor reappears, disturbance reappears. Tumor seems to secrete a parathormone-like substance Cortisone has no effect on hypercalcemia.
(45) Plimpton, C.H. and Gellhorn, R. Am. J Med 1956, 21, 750.