Staff Meeting Bulletin
Hospitals of the » » »
University of Minnesota

Calcium, Phosphorus, Phosphatase

Volume XVI | Friday, May 18, 1945 | Number 27

STAFF MEETING BULLETIN
HOSPITALS OF THE . . .
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INDEX

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I.

UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALENDAR OF EVENTS
May 21 - 26, 1945

No. 72

Monday, May 21

9:00 - 10:00 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 11:30 Allergy in Dermatology; Stephen Epstein, W-312, U. H.

9:00 - 11:00 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; Interns Quarters, U. H.

12:30 - ;L30 Pathology Seminar; Recent Advances and Future Possibilities in Radiation Therapy; H. W. Mixer, 104 I. A.

4:00 - Public Health Seminar; Health Education; Ruth Grout; Women's Lounge, Students' Health Service.

Tuesday, May 22

9:00 - 10:00 Roentgenology-Pediatrics Conference; L. G. Rigler, I. McQuarrie and Staff; Eustis Amphitheater, U. H.

11:00 - 12:00 Urology Conference; C. D. Creevy and Staff; Main 515 U. H.

12:30 - 1:30 Pathology Conference; Autopsies; Pathology Staff; 104 I. A.

12:30 - 1:30 Physiology-Pharmacology Seminar; Recent Developments in Cancer Biology; J. J. Bittner; 214 M. H.

4:00 - 5:00 Physiological Pathology of Surgical Diseases; Physiology and Surgery Staffs; Todd Amphitheater, U. H.

4:00 - 5:00 Obstetrics and Gynecology Conference; J. C. McKelvey and Staff; Station 54, U. H.

4:00 - 5:30 Pediatrics Grand Rounds; I. McQuarrie and Staff; W-205 U. H.

4:30 - 5:30 Ophthalmology Ward Rounds; Erling Hansen and Staff; E-534, U. H.

5:00 - 6:00 Roentgen Diagnosis Conference; A. Stenstrom, T. B. Merner; 515 U. H.

Wednesday, May 23

9:00 - 11:00 Neuropsychiatry Seminar; J. C. McKinley and Staff; Station 60; Lounge, U. H.

11:00 - 12:00 Pathology-Medicine-Surgery Conference; Cirrhosis of Liver; Common Duct Stone; E. T. Bell, C. J. Watson, O. H. Wangensteen and Staff; Todd Amphitheater, U. H.

12:30 - 1:30 Pediatrics Seminar; The Effect of Prenatal Nutrition of the Mother on the Condition of the New Born Infant; Dr. Mulholland; W-205 U. H.

12:30 - 1:30 Physiological Chemistry Literature Review; Staff; 116 M. H.

4:30 - 5:30 Neurophysiology Seminar; The Specific Function of the Occipital Cortex in Vision; A. J. Smith; 214 M. H.

Thursday, May 24

9:00 - 10:00 Medicine Case Presentation; C. J. Watson and Staff; Todd Amphitheater, U. H.

12:30 - 1:30 Physiological Chemistry; Intermediary Metabolism of Carbohydrates; M. F. Utter; 116 M. H.

4:00 - 5:00 Pediatric Journal Club; Review of Current Literature; Staff; W-205,U.H.

4:30 - 5:30 Ophthalmology Ward Rounds; Erling Hansen and Staff; E-534, U. H.

4:30 - 5:30 Roentgenology Seminar; Spondylolisthesis Cases of the Familial Origin; Captain Daniel Fink, M-515, U. H.

Friday, May 25

9:00 - 10:00 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U.H.

10:00 - 12:00 Medicine Ward Rounds; C. J. Watson and Staff; E-214 U. H.

10:30 - 12:30 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Otolaryngology Department, U. H.

11:45 - 1:15 University of Minnesota Hospitals General Staff Meeting; Erythrocyte Protoporphyrin in the Anemias; C. J. Watson; Powell Hall Recreation Room.

1:00 - 2:30 Dermatology and Syphilology; Presentation of Selected Cases of the Week; Henry Michelson and Staff; W-206, U. H.

1:30 - 3:00 Roentgenology-Neurosurgery Conference; H. O. Peterson, W. T. Peyton and Staff; Todd Amphitheater, U. H.

Saturday, May 26

8:00 - 9:00 Surgery Journal Club; O. H. Wangensteen and Staff; M-515 U. H.

9:00 - 10:00 Pediatrics Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater, U.H.

9:15 - 10:30 Surgery Roentgenology Conference; O. H. Wangensteen, L. G. Rigler and Staff; Todd Amphitheater, U. H.

9:00 - 10:00 Medicine Case Presentation; C. J. Watson and Staff; M-515 U. H.

10:00 - 12:00 Medicine Ward Rounds; C. J. Watson and Staff; E-221 U. H.

11:30 - 12:30 Anatomy Seminar; Mastoid Cells; C. H. Morningstar; Effects of Irradiation on Hematopoietic Tissues; Ruby M. Engstrom; 226 I. A.

II. CALCIUM, PHOSPHORUS, PHOSPHATASE. DIAGNOSTIC IMPLICATIONS.

G. T. Evans
E. B. Flink

The purpose of today's presentation is to review calcium, phosphorus, and phosphatase as they relate to clinical conditions. No attempt is made completely to characterize the individual diseases. A majority of bone diseases may be recognized by the x-ray and clinical examinations but in certain cases only by correlation of all the available data including laboratory criteria is it possible to arrive at the correct diagnosis. Frequently the laboratory procedures merely confirm the diagnosis but in some instances they are essential to it.

Normal Values: The serum calcium, phosphorus and phosphatase values vary with age. The normal serum calcium ranges from 9.5 to 10.5 mg. per 100 cc. for adults, 10.0 to 11.5 mg. for children and 10.5 to 12.0 for infants.[11] The serum phosphorus ranges from 2.5 to 4.0 mg. per 100 cc. for adults, 4.5 to 5.5 mg. per 100 cc. for children and 5.5 to 6.5 mg. per 100 cc. for infants; due to the high phosphorus content of cells it must be determined on serum which is completely free of hemolysis.

The serum calcium is composed of two fractions: the diffusible calcium (nearly all ionized) + the non-diffusible calcium; the latter constitutes about .45 per cent of total calcium and is bound to protein and hence the amount depends on the amount of protein or, somewhat more specifically, the amount of albumin. The effect of the protein concentration on total calcium has been emphasized by McLean and Hastings[13] and by Albright and his co-workers[2]. McLean and Hastings devised a graph for calculating the ionized fraction and the protein effect. When there is no renal insufficiency or hyperglobulinemia, one gram of protein binds approximately 0.75 mg. of calcium. (This is only an approximation but gives one an idea of the effect of lowering of serum protein by 1, 2, or 3 grams as in nephrosis or malnutrition.) Failure to recognize the protein effect sometimes obscures an actual hypercalcemia in hyperparathyroidism, or in other instance may lead to the false assumption of hypocalcemia. The cerebrospinal fluid calcium is equal to the diffusible fraction of normal serum; it is little affected by uremia, parathyroidectomy or parathyroid extract.

The phosphatase activity of serum has been extensively studied for many diseases. On the basis of activity at different pH ranges phosphatases may be divided into four types: (1) an alkaline type with optimal activity at about pH 9.3 found in bone, ossifying cartilage, intestine, kidney, mammary gland, lung, spleen, blood serum, leukocytes, adrenal cortex; (2) a phosphatase with optimum activity at pH6 found in mammalian erythrocytes; (3) a phosphatase with optimum activity at pH5 found in spleen, liver, pancreas, kidney, prostate and serum; (4) a phosphatase in certain yeasts with optimal activity at pH 3 to 4. There are two groups of phosphatases with which we are concerned clinically, namely, the alkaline at pH 8.6 to 9.3 and the acid at pH 5.0. The erythrocyte phosphatase can be dismissed with the statement that hemolysis free serum should be used for the determination of both phosphatases but specially the acid phosphatase. Unfortunately, many methods for determining phosphatase activity are being used each with a different set of standards. The ones in common use and the range of normal values is given in Table I.

The units are different primarily because of differences in the substrate used. In the Bodansky method the phosphorus (actually phosphate ion) liberated during incubation of serum with B-glycerophosphate is determined. In the King-Armstrong method the amount of phenol liberated during incubation of seryn with di-sodium phenylphosphate is determined. There is an approximate ration of 1 to 3 between the molecular weights of P and the molecular weight of phenol. This difference of molecular weights accounts chiefly for the difference between the range of normal values for the two methods.

Disturbed Serum Phosphatase. A list of diseases in which the alkaline phosphatase is elevated regularly or frequent-

Table I

NORMAL VALUES FOR SERUM PHOSPHATASE[20]
Units per 100 cc. Serum

	Acid(pH 5.0)	Alkaline(pH 8.6-9.3)	
	Adults	Adults	Children
Bodansky*	0.0-0.4	1.5- 4.0	5.0-12.0
King-Armstrong**		3.7-13.1	15.0-20.0
King-Armstrong** (Gutman's Modification)	0.0-3.25		

*Substrate -- sodium B-glycerophosphate (unit is based on 1 mg. P)
**Substrate -- di-sodium phenylphosphate (unit is based on 1 mg. Phenol)

- - -

ly enough to be of importance in the differential diagnosis is given in Table 2.

Table 2

DISEASES IN WHICH ALKALINE PHOSPHATASE MAY BE ELEVATED[20]

Rickets
Osteomalacia
Paget's disease of bone
Renal Rickets (or renal osteodystrophy)
Hyperparathyroidism with osteitis fibrosa cystica generalisata
Neurofibromatosis of bone or osteitis fibrosa cystica diffusa
Osteogenic sarcoma
Carcinomatous metastases to bones
Hodgkin's (and other lymphoblastoma) involving bone
Boeck's sarcoid
Carcinoma of the prostate with metastases
Jaundice of regurgitation type
Extensive fractures in healing phase
Last trimester of pregnancy

DISEASES WITH ABNORMALLY LOW PHOSPHATASE

Cretinism
Scurvy

- - -

indications that increases phosphatase activity depends on the presence of osteoid tissue or osteoblastic activity. In Paget's disease of bone, particularly the osteoblastic activity predominates over the osteoclastic process, and the phosphatase is uniformly elevated when sufficient bone is involved.

If one excludes regurgitation jaundice, there are many direct and some indirect

In hyperparathyroidism the height of the phsophtase is correlated with the extent of bone disease. At first

glance it is correlated then with the degree of decalcification as evidenced by x-ray. A case has been reported from this hospital in which the phosphatase was normal in the face of extensive osteitis fibrosa cystica generalisata. Biopsy of a bone in this patient revealed chiefly inactive bone with fibrous tissue replacement of bone. Phosphatase is increased in rickets and osteomalacia where there is attempted bone repair and an abundance of osteoid tissue. Multiple myeloma is characterized primarily by destruction of bone with minimal attempt at repair, and the phosphatase is usually normal. It is reasonable then to state that phosphatase activity depends on osteoblastic activity in the non-jaundiced individual.

Because of the large number of conditions in which it is elevated, the phosphatase is not pathognomonic of any single condition but when correlated with other findings it is of great usefulness. The significance of acid phosphatase is very special and relates only to carcinomatous metastases from the prostate.

Calcium Excretion. Careful and laborious calcium balance studies are necessary to determine whether or not the patient has a net gain or loss of calcium in a given period. Furthermore, the ratio of stool to urine calcium is of importance. Normally about 2/3 of calcium is excreted in the feces and 1/3 in the urine. This ratio changes most markedly in diseases of the parathyroid gland. The ratio is shifted in hyperparathyroidism so that a larger percentage is excreted in the urine and in a quantity which leads to a negative calcium balance. The ratio is shifted in all hypocalcemic states so that a larger portion or often all the calcium is excreted in the feces. Determination of the quantity of urine calcium has proved to be of use clinically. When a patient is on a restricted calcium, neutral ash diet, the calcium excretion can be measured reasonably accurately by an adaptation of the Sulkowitch test to the Evelyn photoelectric colorimeter[15]. A normal individual excretes less than 100 mg. per day. In hyperparathyroidism and hyperthyroidism especially patients excrete larger amounts of calcium, - usually over 200 mg. per day. The excretion may be increased in any disease with rapid decalcification of a portion of the whole skeleton. When correlated with other laboratory tests as indicated in Table III, observation of the renal excretion of calcium under controlled conditions is important.

The action of parathyroid hormone has been the subject of many investigations and debates. There are two chief theories: (1) The parathyroid hormone causes a phosphate diuresis and thus secondarily causes elevation of serum calcium; (2) It causes absorption of calcium by direct effect on bone. It is possible that both mechanisms are operating. A review of current experimental evidence is given by Pope and Aub[17].

The action of dihydrotachysterol and vitamin D is not known definitely. Dihydrotachysterol has little antirachitic activity. Both have some effect on calcium and phosphorus absorption and excretion of phosphorus by the kidneys. Elaborate theories have been advanced comparing the action of the three substances but there is no need to recite them at this time.

Calcium, Phosphorus and Phosphatase in Disease Pictures.

An attempt will be made to review diagnostic and other interesting features of some bone diseases. Case histories will be reported, and their differential diagnosis discussed.

Hyperparathyroidism.

For purposes of illustration two cases of primary hyperparathyroidism observed recently will be given in detail. Table III includes the laboratory findings in six cases of hyperparathyroidism, but only cases 3 and 6 are given in detail.

Case 3.-- . This 57-year old female patient had noted a mass in the left side of her neck for 5 or 6 years. Eructations of food began in April, 1942, and vomiting after meals with serious dehydration developed in July, 1942. After a period of hospitalization elsewhere her condition improved symptomati-

Table III

HYPERPARATHYROIDISM[7]

	Preoperatively					Postoperatively			
Case No.	Serum Calcium mg./100cc.	Serum Phosphorus mg./100cc.	Serum Protein gm./100	Serum* Phosphatase units/100cc.	Urine** Calcium mg./day	Serum Calcium mg./100cc.	Serum Phosphorus mg./100cc.	Serum* Phosphatase units/100cc.	Urine Calcium mg./day
1	12.4 12.8	2.3 2.0		38 B.U.*		7.1 9.7 *** 10.1(25)	2.3 4.5 3.7(25)	20 13.5(25)	5.7 65.0 17.0(9)
2	12.5 16.0 15.2	1.8 2.6 2.3	 6.2 	77 89 	525 387 311 259	11.2 9.4 10.2(14)	2.1 3.6 2.4(14)	54 8 7.7(14)	0 52
3	15.7 11.8 9.6 9.8 11.0	4.0 3.4 1.9 3.4 3.4	5.5 5.0 	8 10 	491 431 269 308 274 269	10.7 11.0 9.6 8.5 8.5 11.1(22)	3.3 2.9 3.4 3.4 3.4 2.9(22)	 8.9(22)	225 193 56 63 75 58
4 1st admission	12.8 13.8 12.1 11.6	2.9 2.1 2.0 	6.6 	39 50 	246 321 392 	8.4 12.7 	2.7 2.3 	 	198 164
2nd admission	14.1 11.7 13.7	2.7 1.6 2.7	7.0 	67 	237 184 263 	10.7 9.1 9.6 8.1(2)	2.3 2.8 2.4 1.5(2)	53 59 45(5)	57 190 236(5)
5	12.5 13.0	1.7 1.9	7.0	104	248 180 180 228	 10.1(8)	 4.7(8)	 14(8)	
6	17.6 16.5 14.5	 4.2 2.2	 6.7 	 50 	 256 208 161	10.8 9.7 7.5 7.0 9.8(1) 8.5(3)	1.6 2.8(1) 3.6(3)	 40(3)	+ 0 0 0 trace

*Serum alkaline phosphatase units are expressed as King-Armstrong units/100cc. serum in all instances except the first marked B.U. - Bodansky Units.

**Preoperative values on successive days were obtained when the patient was eating a low calcium neutral ash diet and the postoperative values were obtained when the patient was eating a general diet often with extra calcium.

***Numbers in parentheses indicate number of months after operation.

cally but she was an invalid most of the time until her admission to this hospital in December, 1942. Vomiting after meals and marked anorexia continued until this time. She lost about 30 pounds of weight in all, was unusually nervous and irritable, and so weak that she could not work at all. She had been constipated for many years. For five years she had noted polyuria and polydipsia but no renal colic at any time. Only on direct questioning did she admit having had some aching pains in the extremities and back. On examination, her pulse was 100 and her temperature was normal. The blood pressure was 196/114. She was tall and very malnourished, weighing 87 pounds on admission. The retinal arterioles were attenuated and there were moderate arteriosclerotic changes. A small nodular mass was located just below the thyroid cartilage on the left side in the region of the medial portion of the left lobe of the thyroid. The heart was moderately enlarged to the left. There was some thoracic kyphosis. Slowly moving peristaltic waves were visible over the stomach and small intestine. Neurological examination was essentially negative. Laboratory examinations: Hemoglobin 9.0 grams per 100 cc.; erythrocytes 4,400,000; normal leukocyte and differential counts. The blood urea nitrogen obtained during the period of dehydration and eventual oliguria from fluid restriction and polyuria rose from 22 mg. per 100 cc. to 56 mg. per 100 cc. but returned to normal in 12 days. Her basal metabolic rate was plus 3%. (For other data see Table III) X-rays: Films of the skull, hands, mandible, spine and long bones showed only osteoporosis consistent with her age and sex. The urogram revealed poor excretion and stippled areas of calcification throughout the cortical portions of both kidneys. Chest films showed metastatic calcification in the bronchi. The gastrointestinal tract was negative for intrinsic lesions but there was definite hypomotility of both stomach and intestine with very slow emptying time. Course: During preliminary investigation fluids were restricted for various reasons on four successive days. The polyuria was so marked that the patient lost eight pounds of weight in that period and exhibited definite dehydration phenomena. On December 29, 1942, Dr. Richard Varco removed a chief cell adenoma composed of four lobules and weighing four grams. Three normal appearing parathyroid glands were identified. The postoperative course was uneventful. The patient developed a moderate amount of edema during the subsequent month, but this subsided following simple salt restriction, and has not recurred. In four months she gained 20 pounds in weight, was much stronger, was able to be up all day, was able to eat without vomiting and was no longer constipated. She has no polydipsia now. She is able to work as a maid all the time and her only symptom is the occurrence of an occasional severe headache. Her blood pressure was 220/120 at last clinic visit 21 months after operation.

Case 6. . - The 59-year old male patient was admitted to the hospital on April 2, 1944. Two years before that he fell and injured his left knee. The injury was treated by the application of a cast, but it was not certain whether he had a fracture. Since that time he had pain in the lower back, in his hips and both lower extremities. The pain was deep-seated, often shooting in character, and severe enough to require opiates for relief. He had been weak for 12 years and for 3 years the weakness had been progressively interfering with his work. For 25 years he had had polydipsia of varying intensity. He had had to drink as much as two gallons of water some days. There were no other renal symptoms. He lost 30 pounds in weight during the past several years in spite of a good appetite. On examination, he was a well-developed but very poorly nourished male weighing 120 pounds. His blood pressure was 113/72. A small mass was palpable below the right sternomastoid muscle at the level of the lower pole of the right lobe of the thyroid. This mass moved on swallowing. He had a lumbar lordosis and a slight thoracic kyphosis. There was slight inequality of the tendon reflexes, but sensory examination was normal. Laboratory examinations: Hemoglobin 12.1 grams per 100 cc.; erythrocytes 3,760,000; leukocytes and differential counts normal. The blood urea nitrogen was 45 mg. per 100 cc. and the creatinine 2.3 mg. per 100 cc. before surgery. Several weeks after surgery the blood urea nitrogen had decreased to 17 mg. per 100 cc. An

electrocardiogram revealed a PR interval of 0.20 seconds. (For other data see Table III. X-rays: The skull showed an extremely granular appearance. Some rarefaction of the mandible was evident as well as a marked osteoporosis of the hands with thinning of the cortices of the small bones, erosion of many of the distal phalanges and fracture of some of the terminal tufts. Both tibiae and fibulae showed extensive decalcification with some granularity and thinning of the cortex. There was evidence therefore of a severe form of osteitis fibrosa cystica generalisata. Course: In May 1944, Dr. Richard Varco removed a parathyroid tumor weighing 20 grams from the region of the lower pole of the right lobe of the thyroid and the subclavicular area. The adenoma was composed of chief cells predominantly. In some areas there was a tendency to rosette formation and gland formation. Normal parathyroid glands were identified on the left side.

On the 7th postoperative day the patient had definite but mild symptoms of tetany. For several days the Chvostek and Trousseau signs were positive and remained positive for four or five days thereafter. He received 1.0 gram of calcium gluconate on three occasions with satisfactory response. During the whole postoperative period and for the day of surgery he received 3.75 mg. of dihydrotachysterol and 6.0 to 24 grams of calcium lactate orally every day. In the three month period from operation to the last clinic visit he had gained 15 pounds, was stronger, was practically free of pain, and his morale was much better. There had been a remarkable increase in the calcification of the skull and skeleton in general but not a complete return to normal.

Discussion: Primary hyperparathyroidism is an important starting point for any discussion because the pathological physiology is understood as well as that of any bone disease. It occurs more frequently in females than males in a ratio of 2 to 1. The symptoms are referable to the musculo-skeletal, genito-urinary and gastrointestinal systems. There are two types of pathology of the parathyroid glands. Primary hyperplasia of all the glands of the "Wasserhello" cells and adenoma formation of one or rarely two glands[3]. It is important to differentiate the types of pathology at operation so as not to overlook other hyperplastic glands when one enlarged gland is found and thought to be a solitary adenoma.

Hyperparathyroidism is frequently a hidden disease and its consistent recognition will depend upon: (1) X-ray examination of all patients who have musculo-skeletal symptoms. This fact is so well known that the statement seems to be trite, but it is surprising how many patients with definite chronic musculo-skeletal symptoms are not given the benefit of x-ray examination. (2) Investigation of every patient who has symptoms of renal calculi and of mild polyuria and polydipsia, particularly by the very simple Sulkowitch test, will lead to a positive diagnosis of hyperparathyroidism in a number of patients who would otherwise be unrecognized and go untreated.

The bone lesions in this disease have received enough emphasis and the matter is fixed in all of our minds. What is less well known is the serious renal damage which occurs in untreated hyperparathyroidism even if it be relatively mild. Renal stones are frequent and can cause hydronephrosis, pyelonephritis, etc., with all the attendant sequelae of calculi. Ot the parenchyma of the kidney may become calcified causing serious or irreversible renal insufficiency and eventually uremia. The renal lesions have been classified by Albright and co-workers[2] and will not be discussed further. To give a little better insight into the seriousness of the renal pathology, 4 out of 6 cases given in Table III have definite renal insufficiency and 2 of these have severe hypertension.

The phosphatase activity has a special significance aside from its diagnostic value. The probability of developing tetany after removal of a parathyroid adenoma or hyperplasia is much greater in patients with very high values than in patients with normal values. In fact, the tendency to tetany can serve as a measure of the completeness of surgery.

The reason, of course, is that phosphatase is a measure of osteoblastic activity and this in turn is a determinant of the avidity with which the bone takes up calcium.

There is only one adequate form of treatment once a diagnosis has been made and that is by surgical removal. Cope[6] reviews the surgical principles including the location and treatment of mediastinally-placed parathyroids.

Idiopathic steatorrhea and osteomalacia

Illustrative case: , a 28 year old male, stopped growing at age of 12. For the last six years he had aching pains in the arms and legs, numbness and paresthesia in the hands and feet, during winter months especially, progressive deformity of the sternum and ribs, tenderness of the ribs, and pain on weight bearing in the left hip. He had never been able to do very much work because of weakness. He was an amateur entertainer. He had had a diarrhea with passage of 2-4 fatty bulky stools daily since early childhood. On examination he was obviously dwarfed; he weighed only 60 pounds and was 46 inches tall. He had marked kypo-scoliosis, pegeon-breast deformity of the chest, and coxa vera deformity of both hips. He was unable to walk without use of a crutch. There was a bilateral chronic otitis media. He had positive Trousseau and Chvostek signs. His abdomen was distended and tympanitic. Laboratory tests: Urinalysis and the phenolsulfonphthalein test were normal. The blood urea nitrogen was normal. Serum calciums were 6.9, 7.8 and 7.6 mg. per 100 cc. (when the serum protein was normal), and serum phosphorus levels were 2.5, 2.3, and 3.3 mg. per 100 cc. The serum alkaline phosphatase was 46 King-Armstrong units. A secretin test revealed normal pancreatic function. After use of high Ca diet and vitamin D in the dose of 10,000 units a day, the calcium increased to 9.2 and 10.3 and symptoms of tetany disappeared. X-ray examination of his skeleton revealed very striking osteomalacia with extreme decalcification of all the bones of the body. The cortex of the long bones was paper thin and there were horizontal lines of compression. The pelvis was extremely contracted. A diagnosis of osteogenesis imperfecta was briefly entertained particularly because of the appearance of the long bones.

Discussion: Osteomalacia, reported elsewhere in the world as the result of frank calcium and vitamin D deprivation, has been recognized in this country chiefly as the result of chronic mild steatorrhea.[16] When steotorrhea begins in adult life, osteomalacia may not occur, but hypocalcemia and tetany may be very bothersome and sometimes the presenting symptoms.

Paget's Disease

Illustrative case: , a 63 year old man, suffered a fracture of the left femur November 1, 1931. He had deepseated pain in the left thigh for 6 months. He had gradually lost his hearing over a 10-year period. He had noted pain and tenderness of the skull intermittently since 1929. He was admitted to the University Hospitals in February 1932 because of failure of proper healing of the fracture after 12 weeks of immobilization. On admission to this Hospital in 1932, he had shortening and bowing of the left femur. The left thigh was larger than the right. Very few laboratory tests were carried out, but serum calcium and urinalysis were normal. X-ray examination revealed marked subperiosteal decalcification and a pathological fracture with partial union of the left femur. There was typical Paget's disease of the pelvis, skull and whole left femur. A walking caliper was supplied and in 4 months remarkable improvement occurred as evidenced by recalcification of the femur.

Discussion. Reifenstein and Albright[18] have reported similar acute atrophy of bone in Paget's disease. When there is immobilization of fractures in extremities involved in Paget's disease, acute atrophy of the bone occurs. Their cases had hypercalcemia, polydipsia, polyuria and renal disturbances during the height of the decalcifying process.

Paget's disease is never generalized. It is chronic and tends to be progressive. Pain in part of the skeleton is

frequent and may be disabling, but often the disease is discovered accidentally when other x-ray examinations are obtained. There is 10% incidence of renal stones in patients with Paget's disease[19]. Deformities, particularly of the skull, may be disfiguring. A pathological fracture may be the first symptoms. When fractures do occur, it has been demonstrated that as little immobilization as possible should be allowed because of the probability of acute atrophy. No etiology has been discovered as yet. It is not endocrine in origin for the disease is localized to certain bones leaving some normal skeleton uninvolved[18].

Multiple Myeloma

Illustrative Case: ... , a 60 year old white woman, had been ill for 6 months. She had severe pains in the back, in the flanks and extremities on weight bearing. She had lost 30 pounds weight because of severe anorexia. On examination she was emaciated and pale. She had so much bone tenderness that she would cry out whenever she was moved in bed. No viscera were palpable. Laboratory examinations: Hemoglobin 7.0 mg. per 100 cc. Blood urea nitrogen was 60 mg. per 100 cc. Sedimentation rate was 142 mm. in 20 minutes. Total protein was 7.3 gm. per cent, albumin 3.3 gm. per cent and globulin 3.5 to 3.7 gm. per cent. Serum calcium was 11 mg. to 15 mg. per 100 cc. Phosphorus was 5.6 and 5.76 mg. per cent. Bence-Jones protein was positive and phosphatase was 8.3 and 5. K.A. units. X-ray examination of the pelvis, spine, skull and chest revealed an extreme grade of osteoporosis with multiple rarefied areas throughout all the bones examined. There was collapse of two vertebral bodies. The findings were interpreted as indicating widespread carcinomatous metastases or multiple myeloma. She remained approximately the same during two months of hospitalization. She has not been followed after discharge from the hospital but undoubtedly has succumbed by this time.

Discussion: There are certain features of multiple myeloma which are of utmost importance. Aside from the calcium, phosphorus and phosphatase findings, there are several very important clues to the diagnosis. Any time an erythrocyte sedimentation rate is extremely rapid as in the above instance, multiple myeloma should be suspected; the sedimentation rate is not always markedly elevated. The blood smears often have a greasy appearance because of tendency to rapid rouleau formation. Accurate red blood cell counts are difficult, too, for the same reason. Bence-Jones protein appears in the urine in a majority of cases, but it is not pathognomonic of multiple myeloma. In the case cited above, it was found only after repeated careful testing, using nitric acid as originally discussed by Bence-Jones. Hyperglobulinemia occurs frequently and may be extreme. Snapper reported a case with 11.0 gm. globulin per 100 cc. Accurate pathologic diagnoses are possible during life by means of sternal marrow aspiration or by sternal biopsy and should be carried out routinely.

The laboratory findings in a group of cases of multiple myeloma studied by Jaffe and Bodansky[11] is given in Table IV. Note particularly the phosphatase activity which is normal or only slightly elevated and the serum calcium values most of which are elevated. Also take note of the incidence and extent of hyperglobulinemia and the presence of Bence-Jones protein in the urine.

Hyperthyroidism with osteoporosis.

Illustrative case: ., a 64 year old white female, developed classical symptoms of hyperthyroidism and had a subtotal thyroidectomy in 1927. She had a recurrence and another operation in 1928. She was never completely symptom-free nor was her basal rate normal until first observations in this hospital in 1935. She took Lugol's solution continuously until 1935. She first developed pain in the back in 1935 and became quite stooped in a few years. She began drinking extra milk and taking viosterol in 1936 and her pain decreased. A gradual increase in kyphosis occurred from 1936 to 1943. On examination, she had a hypertension, moderate tachycardia, was malnourished and had marked kyphosis of the thoracic spine. She had exophthalmos, stare and lid-lag at the time of each of four hospital admissions from 1935 to 1943. Laboratory examinations:

Table IV

MULTIPLE MYELOMA[11]

	Ca	P	Ptase	NPN	ALB	GLOB	EUG	TP	BJP
MM	10.3	2.8	2.4	35	3.3	6.9	5.5	10.2	Neg.
AR	11.7	3.8	3.5	22	2.8	3.4		6.2	Pos.
MH	12.3	4.2	1.8	31	3.0	6.3	0.2	9.3	Neg.
PL	12.5	5.2	2.3	51	2.7	10.1	7.1	12.8	Pos.
CJ	16.6	4.5	5.1	82	4.8	1.9	0.5	6.7	Neg.
EC	17.8	4.4	2.5	61	4.1	2.8	0.9	6.9	Neg.
JM	14.1	5.3	2.6	57					Pos.
JB				107	2.0	14.0	11.3	16.0	

This table shows blood chemistry values in 8 individual cases of multiple myeloma. Phosphatase activity value (Bodansky) (ptase), euoglobulin value (EUG), Bence-Jones protein (BJP).

Urinalysis negative. Hemoglobin 14 gm. per 100 cc. Normal leukocyte counts with tendency to lymphocytosis most of the time. B.M.R. was +41% to +3% (always over +20% until 1943). Serum calcium 10.4 mg.+ in 1936, 10.1 mg.% in 1939, and 8.8 and 12.2 in 1932. Serum phosphorus ranged from 2.9 to 2.7 mg. per 100 cc. No phosphatase determinations were carried out. X-ray examination: Osteoporosis of extreme grade with multiple compression fractures of the thoracic and lumbar vertebrae were present on the first examination in 1935. All parts of the skeleton studied showed osteoporosis. There was an increase in degree of kyphosis in 1943 but the osteoporosis was about the same. She received three courses of x-ray therapy to the thyroid - one in 1935 and two in 1943. Apparently the hyperthyroidism was finally controlled in 1943.

Discussion: Hyperthyroidism is a very important cause of osteoporosis because of the increased excretion of calcium and phosphorus in the urine and feces. It is difficult to maintain a positive calcium balance during the active phase of hyperthyroidism. Patients do not develop osteoporosis if the hyperthyroidism is treated promptly and cured. However, in patients like this one, with chronic hyperthyroidism, a continued negative calcium balance eventually manifests itself as extreme osteoporosis. Another factor, namely, post- menopausal osteoporosis undoubtedly contributed to the osteoporosis in this patient. A careful study of post-menopausal osteoporosis has been made by Albright and co-workers[3].

Carcinoma of the Prostate with Metastases to the Skeleton.

Illustrative case: , a 70 year old man, had been extremely weak for 3 or 4 months. He had so much pain in the back that he had been bedridden. Nausea and vomiting with hematemeses began the day before hospital admission. He had nocturia for two years and frequency for a month. On examination he was cachectic, extremely pale, in constant agony and appearing practically moribund. He had arthritic deformities of his hands and feet and had ecchymoses in the epigastrium and on the left leg. The landmarks of the prostate were completely obliterated and the prostate was firm and irregular. Laboratory examinations: Urinalysis - specific gravity 1018, albumin 0, occasional W.B.C. Hemoglobin 3.6 gm. per cent. B.U.N. 48 mg. per cent on admission but 14 mg. per cent ten days later. The reticulocyte counts were 13% and 18% on the 3rd and 5th days after starting therapy with stilbestrol. The serum calcium was 9.3mg. per cent and the serum phosphorus 2.3 mg. per cent. The phosphatase values were as follows:

	Before therapy	9 days after	5 mo. later*	12 mo. later
Acid phosphatase	10.4 K.A.	3.1	4.8	2.3
Alkaline phosphatase	8.7 K.A.	20.0	14.6	12.9

*No therapy for 2-3 months.

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X-ray examination: Extensive osteoblastic metastases in lumbar spine, pelvis, and ribs and evidence of an old ankylosing spondylitis. At 5 months the process was not very different, but the osteoblastic metastases were somewhat less dense. He was given 5 mg. stilbesterol daily orally and improved remarkably. Only one blood transfusion was given and yet his hemoglobin rose from 3.6 to 8.3 gm. per cent in 2 weeks. His pain was controlled so well that he was able to be up and about again in a week. He has been symptom free for a year. He voluntarily stopped stilbesterol for 2½ months, and though he had no recurrence of pain his acid phosphatase increased slightly. For 6 months he has been taking 1 mg. of stilbesterol regularly and has no pain. He demonsrates a typical course following estrogen therapy.

Discussion: Carcinoma of the prostate with skeletal metastases has a unique place among bone diseases. Elevated values of serum acid phosphatase occur in about 85% of the cases of prostatic carcinoma[9]. Prostatic tissue has very high acid phosphatase content, and, unless it is very undifferentiated, carcinoma of the prostate also has a high acid phosphatase content. Huggins and Hodges[10] were the first to demonstrate clearly the effectiveness of castration or estrogen therapy in these cases and also the dramatic change in acid phosphatase as improvement occurred. Acid phosphatase is markedly elevated only in metastatic carcinoma of the prostate; however, slight elevations may be seen in patients with very high alkaline phosphatase such as in Paget's disease, hyperparathyroidism, and metastatic carcinoma from the breast. One more interesting item of evidence is the effect of testosterone proprionate which causes an increase in an already high acid phosphatase and an exacerbation of symptoms of carcinoma of prostate with metastase[10].

Renal Osteodrystrophy (Renal Rickets or Renal Dwarfism).

Illustrative Case: , a 12 year old boy, began to limp in January 1944. He had had pain in the bones and joints for 2 years. His physical development was retarded so that he was the size of a 7 year old boy. He had urinary frequency and poor bladder control until 3-4 years ago. Dysuria and frequency began again 1 year and hematuria occurred 6 months before admission. At age 3 albumin was found in the urine. On examination he was obviously dwarfed. He had a coated tongue and a uriniferous breath. His skin and mucous membranes were pale. His B.P. was 106/80 to 110/70. Laboratory examinations: Urinalysis - specific gravity 1005-1011, albumin 0 to +, 0 to occ. R.B.C. P.S.P. test 7.5% in 2 hours. Hemoglobin 7.5 gm., R.B.C. 2,600,000; blood urea nitrogen 66 mg. %, creatinine 5.1 mg.%, CO_2 combining power 39, 42, and 43 volumes per cent. B.U.N. was 132 mg. per cent 6 months after initial value. Cholesterol, 269 to 311 mg. %. Serum calcium 9.1 to 12.4 mg. per 100 cc.; serum phosphorus 6.2 to 8.8 mg. per 100 cc.; serumphosphatase 58 K.A. units per 100 cc. Serum protein 6.4 gm. per 100 cc. with normal fractional proteins. X-ray examinations: There is marked diminution in the development of the epiphyses of long bones, deformity of the costo-chondral junction of all ribs. The appearance at the elbow and shoulder was that of a 6 or 7 year old child. All the bones had a granular decalcified appearance. Marked changes characteristic of rickets in the ends of the metaphyses at the epiphyseal line are present in all the bones. Both kidneys were small. There was marked saucering of the ends of the bones of the lower extremities, flaring of the epiphyseal line and ragged and irregular bone formation

in the zone of calcification. His condition has not improved. He weighs two pounds less now, i.e., eight months after initial examination.

Discussion: It is clear that this is a case of renal osteodystrophy (or renal rickets). He probably also has secondary hyperparathyroidism. Renal osteodystrophy occurs in children with chronic renal insufficiency from any cause (usually developmental anomalies) which is severe enough to cause retention of non-protein nitrogeneous substances and inorganic acid radicals, namely phosphate and sulfare. Mild acidosis is the rule. The most important feature of the chemical findings is a retention of phosphorus. The kidney is unable to excrete phosphates in normal amounts. One plausible theory for the parathyroid hyperplasia is that the high phosphate stimulates them to hypertrophy and this in turn causes secondary hyperparathyroidism. Hypertension usually does not occur in these children.

Renal osteodystrophy can occur in adults, but, of course, the changes at the epiphyses do not occur. Actually secondary hyperparathyroidism with osteitis fibrosa occurs[1]. The uremia has to be of long duration and there always is a moderate acidosis. Metastatic calfication of subcutaneous tissue is common and has been found in arteries, soft tissues in the neighborhood of joints, subcutaneous tissues, lungs, stomach, liver, and heart muscles[19].

The pathology of the parathyroid gland in this condition must be sharply differentiated from that of primary hyperplasia of the parathyroids which is characterized by "Wasserhelle" cell hyperplasia. In secondary hypertrophy the chief cells are the predominant cells.

Hypoparathyroidism

Hypoparathyroidism is a disease which may occur spontaneously but is more commonly secondary to surgical trauma or removal during the course of thyroidectomy. There is a rare type called pseudo-hypoparathyroidism in which the patient apparently has normal or even hyperplastic parathyroids but with typical symptoms and signs of hypoparathyroidism. These individuals do not respond normally to parathyroid hormone administered parenterally and probably do not respond to their own parathyroid hormone[4]. The diagnosis is easily made when manifest tetany occurs but patients have been treated for years as epileptics and have even had exploratory craniotomies before the right diagnosis was established. Papilloedema may occur and certainly is misleading. It is more difficult to recognize latent tetany (the cardinal symptoms are paresthesia, stiffness of the muscles, muscle cramps on moderate exertion and development of carpo-pedal spasm without tetany). Patients are often treated as neurotics or malingerers. The Trousseau and Chvostek signs are very helpful. Erb's sign is also positive and is useful particularly in children. Delirium occurs in acute hypoparathyroidism frequently so that any patient who becomes delirious after thyroidectomy should be carefully examined for signs of hypocalcemia. It is very important to exclude chornic renal insufficiency in the differential diagnosis. See the Table V, for means of differentiating various types of tetany.

Hypocalcemic Tetany

The simplest and quickest way to determine presence of hypocalcemia is the performance of the qualitative Sulkowitch test.* Absence of precipitate usually means a serum calcium (with normal protein) of 8.0 mg. per 100 cc. or less.

When tetany occurs, it must be treated immediately. Laryngeal spasm or diaphragmatic spasm may be fatal. The intravenous administration of calcium

*The Sulkowitch test is performed by adding 5 cc. of the reagent (oxalic acid 2.5 gm., ammonium oxalate 2.5 gm., glacial acetic acid 5.0cc., aqua dist.q.s. 150 cc.) to 5 cc. of urine which is acid (or acidified with 5% acetic acid). Absence of any precipitate indicates no calcium. A heavy turbid precipitate indicates a large amount of calcium.

as the lactate, gluconate or chloride is very satisfactory treatment. Separate injections of 10 gm. should be repeated as needed to relieve the symptoms. The surgery staff has recently demonstrated the efficiency and probable superiority of the continuous intravenous injection of glucose solution containing 6.0 to 8.0 gm. of calcium gluconate daily for treatment of acute tetany until dihydrotachysterol or vitamin D have begun to take effect. From 1 to 3 cc. of parathormone a day may be given in this acute phase, but parathormone is very very satisfactory for use chronically.

The treatment of chornic hypoparathyroidism consists of administration of large excess of calcium ion over phosphate ion, limitation of phosphorus intake, and administration either of dihydrotachysterol or vitamin D (calciferol). Phosphate ingestion can cause a latent tetany to become manifest. When a high phosphorus diet is given to these patients larger doses of specific medications must be given. Therefore, moderate restriction of phosphorus in the diet is useful. It should be borne in mind that milk with advantage of high Ca content, also, has high P content, useful for growth but not for use in hypoparathyroidism.

One means of decreasing phosphorus absorption is by administering aluminum hydroxide gel (amphogel). Albumin forms a relatively insoluble compound with phosphorus and is eliminated in the feces. Iron salts will do the same thing as has been demonstrated by Liu and Chu[12] in cases of renal osterdystrophy. The usefulness of aluminum hydroxide or ferrous sulfate has not been extensively exploited.

Calcium should be given in large doses; 12 to 20 gm. of calcium lactate, calcium gluconate or calcium chloride. Calcium lactate is inexpensive when given as the powder and is not unpleasant to take ($CaCl_2$ is rather unpleasant).

Dihydrotachsterol (A.T.10) in doses of 0.625 mg. to 1.875 mg. is required as a daily maintenance dose, and the initial doses for 3 to 5 days should be 3.75 to 5.0 mg. daily. It is supplied in capsules containing 0.625 mg. and in glycerin solution with 1.25 mg. pure substance per cc. Inferences are made that this substance is a specific medication to the exclusion of Vitamin D_2 (or calciferol). This is not true.[14]

It has been amply demonstrated that vitamin D_2 or calciferol has a marked calcemic effect when given in large enough doses. One mg. of calciferol is equivalent to 40,000 units. For strictly comparable effects larger doses of vitamin D are necessary than for dihydrotachysterol. From 50,000 units to 200,000 units (or 1.25 mg. to 5 mg.) are required as daily maintenance dose[14]. No difference can be seen between Vitamin D. treated and the dihydrotachsterol treated patients. Larger doses are required during pregnancy and during periods of nervous and physical strain, etc. Calciferol is available in capsules containing 50,000 units. For equal metabolic effects, the cost of calciferol is approximately $\frac{1}{4}$ to $\frac{1}{2}$ that of dihydrotachysterol (A.T.10).

The Sulkowitch test is very useful in prescribing an adequate dose of either of the activated sterols. Hypercalcemia must be avoided. If too much sterol has been administered a heavy cloudy precipitate is formed. If no turbidity forms, it is safe to conclude that insufficient therapy is being given. The patient can be taught to do this simple test himself. An occasional serum calcium determination should be used to check the Sulkowitch test.

The same principles can be applied to the treatment of idiopathic steatorrhea when hypocalcemia is present. Because of poor fat absorption, much material is necessarily wasted, but doses comparable to those used in hypoparathyroidism are usually effective. A very useful adjunct is ultra-violet light (either natural or artificial) and must not be forgotten.

Rickets and certain other conditions are not discussed separately but are included in the summarizing, Table V. In rickets it should be emphasized, however, that the serum phosphatase activity is uniformly increased and is the most constant biochemical finding as well as the

best guide as to progress of healing of rickets[11].

Senile osteoporosis, not included in the table, is characterized by normal Ca, P and phosphatase in the serum. The structural effect on the skeleton is the main feature.

Differential Diagnosis of Bone Diseases

Table V gives a schematic representation of specific disturbances in the various diseases of bone. It is not possible to cover every possibility in a given disease. Calcium and phosphorus are reciprocally related in most instances so that when calcium is elevated the phosphorus is low and vice versa. When there has been calcium, phosphorus, and vitamin deprivation in rickets, steotorrhea, etc. both calcium and phosphorus in solution depends on the solubility product $(Ca^{++}) \times (PO_4^{=})$ unless there has been deprivation of either calcium or phosphorus.

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Table V

DIFFERENTIAL DIAGNOSTIC FEATURES OF DISEASE WITH DISTURBED CALCIUM AND PHOSPHORUS METABOLISM

CONDITION	SERUM			URINE		FECES	REMARKS
	Ca	P	P tase	Ca	P	Ca	
Hyperparathyroidism	OXX	XX.	OXX	.XXX	.XXX	O	
Hyperthyroidism	O	O	OX	.XXX	.XXX	.XX	
Paget's Disease	O	O	.XXX	OX	O	.	
Multiple Myeloma	OX	O	O	OX	OX	.	
Rickets	O	XXO	.XXX	X.	X.	.	
Osteomalacia	XO	X.	.XX	X.	X.	X.	
Idiopath.Steatorrhea	XXO	XO	OX	X.	X.	.XX	
Renal Rickets	XO	.XX	.X	X.	X.	.	
Osteogenic Sarcoma	O	O	OX	O	O	.	
Metastatic Carcinoma	OX	O	OX	.X	.X	.	
Prostatic Carcinoma	OX	O	.XX	.	.	.	Acid P tase UP
Neurofibromatosis	OX	XO	OX	.	.	.	
Uremia	XX.	.XX	O	.	XX.	.	
Regurgit'n Jaundice	.	.	.XXX	.	.	.	
Hyperproteinemia	.X	O	.	.	.	.	Ca function
Hypoproteinemia	X.	O	.	.	.	.	normal
Acidosis	O	O	.	.	.	.	Ca ions up
Alkalosis	O	O	.	.	.	.	Ca ions down
Hypoparathyroidism	XXX.	.XX	O	XXX.	X.	.	
High Vit.D.Therapy	.XX	.XX	O	.XX	.XX	.	

Schema: O - normal. XX. decreased. .XX increased The number of X's indicates roughly the extent of increase or decrease.

Primary hyperparathyroidism has to be differentiated from multiple myeloma, neurofibromatosis with osteitis fibrosa cystica disseminata, Paget's disease, hyperthyroidism with osteoporosis, senile osteoporosis and renal calculi without endocrine origin. No comment need be made regarding the chemical findings except to emphasize the fact that a correlation of all findings is important in studying any single case.

Other features of bone diseases need comment. Hyperparathyroidism causes

diffuse and generalized bone disease as that x-ray of any portion of the skeleton will reveal changes. Paget's disease never is generalized as that x-rays reveal normal bone in part of the skeleton at least and in fact one part of a single bone may be normal and another part have typical osteitis deformans. Multiple myeloma may be generalized so that its appearance may be confusing but the adjunct to diagnosis, namely, Bence-Jones protein in the urine, hyperglobulinemia, bone marrow study by aspiration or biopsy, and sedimentation rate are very helpful.

Carcinomatosis is apt to be confused with multiple myeloma or even hyperparathyroidism. Recognition of metastases to the lung or regional lymph nodes is very helpful. Discovery of a primary tumor or biopsy of a lymph node aids considerably. From the table it is evident that the biochemical findings in multiple myeloma and carcinomatosis overlap so that differentiation has to be made on other grounds.

The osteitis fibrosa cystica disseminata of neurofibromatosis is never generalized, there are stigmata of neurofibromatosis such as "cafe' au lait' spots, neurofibromata, precocious puberty in some girls, occurrence at a very early age, and the absence of the generalized musculo-skeletal symptoms and genito-urinary symptoms so characteristic of hyperparathyroidism. Because of its superficial resemblance to the latter condition it has been erroneously diagnosed and unnecessary operations have been performed. Thannhauser[22] maintains that von Recklinghausen included cases of neurofibromatosis with bone involvement in his original description of hyperparathyroidism.

Secondary hyperparathyroidism such as occurs in renal insufficiency may lead to an osteitis fibrosa cystica generalisata which is identical with the primary disease[1]. The biochemical findings are the important differential feature particularly the high phosphorus and low or normal calcium. When renal insufficiency is due to primary hyperparathyroidism, the characteristic high Ca, low P, may become normal Ca., high P, and it becomes difficult to differentiate the two conditions; however, it is usually possible to do so from the chronology of the symptoms and other manifestations. Moderate or severe skeletal changes are rare in primary renal disease, and renal insufficiency severe enough to cause a considerable hyperphosphatemia is rare and late in primary hyperparathyroidism. Occasionally the pathology of the parathyroid glands are crucial in making this differential diagnosis[5].

The patient with idiopathic steatorrhea and osteomalacia does not have osteogenesis imperfecta. In this latter disease serum calcium, phosphorus and phosphatase are normal, whereas patient E.W. had findings typical of steatorrhea given in Table V. Hypophosphatemia and an abnormal skeleton by x-ray excluded idiopathic hypoparathyroidism.

Chronic hyperthyroidism causes osteoporosis and increased excretion of both calcium and phosphorus, but there usually are normal serum calcium and phosphorus levels. Other evidences of hyperthyroidism are present. Hyperthyroidism should be considered as a possible cause of osteoporosis when it occurs before senility. Patient A.S. was considered to have a toxic thyroid adenoma and treated as such for a number of months before the diagnosis of hyperparathyroidism was made and confirmed. It is noteworthy that renal insufficiency and renal calculus formation does not occur as a result of hyperthyroidism in spite of increased calcium and phosphorus excretion in the urine.

Carcinoma of the prostate with metastasis to the skeleton has a unique place among the bone diseases because of the increased serum acid phosphatase activity of a great majority of cases. See the discussion following the case report. One must not exclude this diagnosis from consideration just because of a normal acid phosphatase activity.

In conclusion, emphasis should again be placed on the importance of a careful study of all patients with skeletal complaints by x-ray examination of the

part causing symptoms (and others as indicated on consultation with the radiologist) and by obtaining chemical determinations, especially serum calcium, phosphorus, phosphatase and protein.

* * * * *

The authors wish to express their thanks and appreciation to Dr. C. J. Watson, Dr. O. H. Wangensteen, and Dr. I. McQuarrie for the privilege to study cases on their respective services and for many helpful suggestions. Dr. L. G. Rigler has given much time in discussing various cases and in stimulating one of us to undertake this study originally. He has generously supplied slides of x-rays for use today.

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III. GOSSIP

Help:

The Chinese Government plans to establish 5 Training Centers which will train some 34,000 persons of various technical categories for medical relief and rehabilitation in China. Of these 5 centers, it is hoped that 3 may be inaugurated about 1 July 1945. Since the number of qualified Chinese teachers is insufficient, the Chinese Government hoped that some teachers could be recruited from the various United Nations through UNRRA to fill this deficiency. It has submitted a specific request for 30 teachers of the following categories to be recruited and sent to China as soon as possible:

1 of each: General Surgeon
General Physician
Otolaryngologist
Epidemiologist
Bacteriologist
Pathologist
Public Health Administrator
Nurse

2 of each: Orthopedic Surgeons
Genito-urinary Surgeons
Dermatologist & Syphilologists
Ophthalmologists
Radiologists
Sanitary Engineers
Maternity & Infant Care Specialists
Tuberculosis Specialists
Hospital Administrators
Dentists
Mental Diseases

These 30 persons should have as high qualifications as possible for teaching. Their salaries will be paid by UNRRA, and would not be less than what they may be receiving in their present positions up to a limit of $8,800 per annum. Teachers who were Officers with the Public Health Service would have their salaries reimbursed to the Service as with other Officers so detailed. Regarding the method of operation, it is the intention of the Chinese Government to assign each teacher to one of the 3 training centers, with possible transfer to the other 2 centers for short periods as a visiting lecturer; teaching will be either in Chinese or in English. The Chief Medical Officer at the UNRRA Chungking Office would act as liaison officer between these teachers and the Chinese Government. Their period of employment wouldbe preferably for 18 months, but at least for 1 year, with the possibility of renewal at the end of that period. See Dean Diehl about details...Note: Address of the 31st Station Hospital has been changed from A.P.O. 502 to 1054, % Postmaster, San Francisco....Paul H. Fesler, Secretary, Oklahoma State Medical Association, former Superintendent, University of Minnesota Hospitals is back in the type of work which he does best. In his final legislative bulletin from Oklahoma, he points out that the legislature has set up a Board of Health which will appoint the state health commissioner, and will be responsible for the new post-war health program. This will include (1) a survey of all medical facilities in Oklahoma, (2) development of health centers in each community with subsidy of $3000 per year for each one, (3) plan for development of community hospitals, (4) hospital licensing law, (5) an appropriation of $1,680,000 for the Medical School and University Hospitals. Mr. Fesler was here during our period of greatest expansion, and is tops in doing this kind of a job....Sister Loretta of Duluth supplies the following information: in the early days, Boston Dispensary classified patients as follows: Bostonians, Americans, Hiberinco-Americans and other people...Annual meeting of the Minnesota Radiological Society will be held on Saturday, May 26 at 2:00 P.M. in the Century Room of the Lowry Hotel in St. Paul. Scientific session at 2:00 P.M., dinner at 6:30 P.M. Speakers are Leo G. Rigler, T. Borden Morner, K. Wilhelm Stenstrom, of the Medical School, C. Allen Good, David G. Pugh, and Harry M. Webber, Mayo Foundation. Dinner speakers will be either Major Ajack, or Captain Washako. This is one of the best state societies of its kind, thanks tothe energetic influence of radiologists from the University of Minnesota, in the Medical School and the Mayo Foundation...

IS ANIMAL EXPERIMENTATION JUSTIFIABLE?

Armand J. Quick, M.D.

The question "Is animal experimentation justified?" must be answered dispassionately and logically without fanaticism or undue emotionalism. In preface then I wish to state that the term we hear so often, "vivisection", at one time did mean pain and gruesomeness. That was before the age of anesthesia and probably the human that underwent vivisection, which means cutting into the living, suffered much more than the animal. Today with anesthesia, vivisection no longer means horror or torture. Some of our members in the medical profession practice human vivisection daily, for every surgical operation is in fact a vivisection.

I do not think it is necessary for me to explain to you that we scientists are not ghouls or sadistic vampires as so often pictured in the movies and in such comic strips as "Superman." One of the greatest triumphs of which medicine boasts is its conquest of pain, and it certainly does not sound logical that we who hold this conquest of pain so highly should turn around and inflict needless pain and torture on helpless animals. It does happen that we who are working in the medical sciences are compelled to use animals in our work just as other scientists use the materials of their specialty--the botanist plants and the geologist minerals.

I thought it probably would be interesting to you if I outlined very briefly the various purposes and ways in which these animals are used in a medical school. I take my material from our own school. The first use that I might mention is animals for experimental demonstration. In courses as pharmacology and physiology, demonstration experiments are exceedingly valuable. In such experiments the animal is first completely anesthetized before any work is done. Then of course in some experiments either the chest or the abdomen is opened and the internal organs exposed. But this occurs only after the animal is completely unconscious and insensitive to pain. You can well imagine that if somebody would happen to watch the experiment and not know that these animals are under deep anesthesia he might take offense, though these experiments are no different from a human surgical operation in which the abdomen is opened and organs removed or intestines exposed. When the experiment is completed the animal is worthwith killed. A second use of animals is to teach surgical technique. The first practice or experience that the student has is on animals. Again, these animals are completely anesthetized and the same care is taken as in human operations. After the operation is completed the abdomen is carefully closed and then the animal is killed. The third use of animals is in what we might call research surgery. If a surgeon wants to develop a new technique he does not feel justified to try it first on human beings. He therefore carries it out on an animal and I wish to emphasize that he uses the same precision, care and precautions that are essential for successful human surgery. When the operation is completed and the would dressed the animal is returned to warm, clean surroundings. This is necessary not only because the surgeon is humane but because the success of the experiment which takes valuable time may be lost by any carelessness.

Value in Drug Testing

Surgery is also carried on to produce various physiological changes in an animal in order to get information concerning the various processes within the living animal. I might mention for instance, that much valuable information has been obtained by what is called the Eck fistula operation in which the blood vessels which carry the food from the intestine directly to the liver are shunted into the big blood vessel, the vena cava - so that the blood goes directly to the heart instead of to the liver. By that simple procedure much valuable information concerning the liver has been obtained. Nearly all of the information concerning the glands of internal secretion such as the thyroid, the parathyroids, the pancreas and the adrenal has been obtained by the surgical removal of these glands from animals.

In recent years there has been an ever increasing use of animals for studies that do not involve any surgery whatsoever. As you well know there has been a tremendous development in drug therapy. Every new drug has to be tested on animals before it can be used in human medicine. All these valuable drugs that are now so well known as the sulfonamides, the antisyphilitic drugs, penicillin and the great drug against malaria, atabrine, all had to be tested laboriously and extensively on animals before they could be given with safety to man. Likewise, the developments of our chemical industry, which have multiplied greatly the toxic substances with which man comes in contact, have necessitated animal experimentation. I might mention merely synthetic rubber. When that process was developed it was found that the workmen were exposed to the important intermediates, butadiene and styrene, and the question arose "How toxic are these to man?" The answer could only come from animal experimentation. I might elaborate further but I want to get on to the fifty use, namely, the employment of animals for nutritional studies and particularly for vitamin investigation. That has become an exceedingly important development within the last two or three decades.

Diabetes Conquered

The question naturally arises "Is this employment of animals for experimentation of real value? Could we have gotten along without it?" I can probably answer that best by citing from the numerous achievements three outstanding examples to show what animal experiments have yielded for the welfare of mankind: Diabetes. This disease, of which there are probably a million or more cases in the United States, was a short time ago not only an incurable but a fatal disease. In children it was onvariably fatal within a very short time. By the use of animal experimentation, and I might emphasize that in this work only the dog was found suitable, the discovery of insulin was made possible. With the short time at my disposal I cannot elaborate on the significance of that discovery except to say that a disease which not only kills but maims by causing gangrene which necessitates amputation of limbs, blindness, hardening of the arteries and other complications is now under perfect control, thanks to insulin. Pernicious anemia, likewise a fatal disease, was by means of animal experimentation brought under complete control. Whipple's studies on the regeneration of blood in dogs after severe hemorrhage furnished the key to effective therapy in pernicious anemia. The simple finding that feeding liver hastened the restoration of the red blood cells, has led to the highly potent liver extract of today. A third example, of particular interest to us because it took place in our own State University, is Elvehjem's studies of black tongue in dogs, a disease which very closely resembles pellagra in humans. He found that nicotinic acid prevented or cured this mysterious disease. No sooner had he made his discovery when another scientist, Dr. Spies, applied the discovery to human pellagra and found that it cured the disease. It should be mentioned that pellagra is one of our greatest nutritional problems in the United States and that the use of nicotinic acid in the prevention and cure of this deficiency has a social significance that cannot easily be over-emphasized.

I could enumerate numerous other examples of benefits derived from animal experimentation but I must now turn to the important issues that we have to face. The first is, is it moral to kill animals for the benefit of mankind? Before answering this question hastily, it might be well to remember that meat is one of our stable articles of diet; that leather is an essential part of our clothing; and that fur is hardly considered a luxury in this climate. Before we give too definite an answer let us also remember that hunting is a sport in which many of our best citizens engage, that often there is no other motive in hunting than the pleasure of killing an animal. It is well to remember too that in this sport a wounded animal often crawls away to die in pain and misery.

The second important issue is, if animal experimentation is wrong, then we must forbid experimentation on all

animals for all purposes. I am unalterably opposed to saying that we can use all except one particular species. It happens that most of us are sentimentally attached to dogs. Therefore many feel that a law should be passed forbidding the use of dogs. But is it just to our dogs in one class? Are there not citizens who would protest and say "we are fond of cats and we also want cats excepted." And I see no reason why the union of Italian organ grinders should not want monkeys exempted. If that happens all research on poliomyelitis or infantile paralysis would come to an end since that particular animal is found most suitable for that type of work. We often hear that the dog is man's best friend. But when we consider how many babies are dependent upon cows' milk I believe the cow can be considered a runner-up in this contest for man's friendship. Volumes could be written on horses as friends of man. I think there is a distinct danger in elevating any one class or species of animal above the others because that was done in India and the sacred cow now helps to consume the scant food supply in competition with the starving millions whereas that cow could probably serve best be being used as food. Are we going to elevate the dog to a position where that animal becomes more or less sacred?

It is up to us to decide whether we want all experimentation stopped, but let us realize that when this happens we are stopping progress and going backwards. We depend upon animals for many of our biological drugs: insulin, liver extract and adrenalin. Many of our very important drugs such as digitalis are standardized with animals. No new drug can be introduced without animal experimentation. As I said, pernicious anemia and diabetes once were fatal diseases; but now are completely under our control. Innumerable diseases, cancer, myelogenous leukemia, and we may include various forms of insanity, are still unsolved problems. If you are unfortunate enough to get one of these diseases the diagnosis is often a death warrant. Research with animals ultimately will give the answer to the question of handling many of those diseases. Before we can decide whether animal experimentation should be stopped or not, we must consider that it is not only what we think but we must hear the voices of helpless children that have a right to the fruits of science.

I want to leave with you this thought -- you see a house on fire. You know that in that house there is a dog in the basement and a sleeping child on the second floor. Time will permit you to rescue only one. Which one will you choose? Now to be sure that fire is allegorical. The real fire is rheumatic fever, infantile paralysis and innumerable other diseases which cripple, maim and kill. We scientists are faced with this problem and we have chosen to rescue the child.

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SPECIAL MEETING

ALPHA OMEGA ALPHA

May 24, 1945 - - - 8:00 P. M.
15 Medical Science.

Speaker: Paul R. Cannon, University of Chicago.

Subject: Some Clinical Aspects of Immunology.

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