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Hypercalcmia in malignant neoplasms without osseous metatases: parathormone secretion as a possible mechanism

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HYPERCALCEMIA IN MALIGNANT NEOPLASMS WITHOUT OSSSEOUS METASTASES: PARATHORMONE SECRETION AS A POSSIBLE MECHANISM

A THESIS
Presented to
the Faculty of the College of Medicine
The University of Nebraska

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of the Requirements for the Degree
Doctor of Medicine

Advisor
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by
Robert Dunbar Sidner
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I. Introduction of Hypothesis and Possible Values of the Finding

It has been estimated that approximately 9% of people with cancer metastatic to bone develop a hypercalcemia sometime during the course of their disease. (1) This is seemingly rather easily explained on the basis of extensive osteolysis with mobilization of sufficient quantities of calcium to exceed the kidneys' excretory capacity.

Some malignancies, however, have been associated with a hypercalcemia without any evidence of bony metastasis. Furthermore the hypercalcemia increases with tumor size and decreases with surgical and chemotherapeutic extirpation of the tumor or soft tissue metastasis, and again increases with recurrence. Associated with the hypercalcemia there is often a hypercalcuria hypophosphatemia, and decreased tubular reabsorption of phosphate. These findings have been found most frequently in tumors of the lung, kidney, and breast as well as lymphomas and leukemia. Other tumors that have been associated with hypercalcemia include the stomach, cervix, bladder, uterus, tonsils, cartilage, and neuroblastomas. (1)

The above blood chemistry findings suggestive of hyperparathyroidism led Albright and Reiferstein, in 1948, (2) to propose that some tumors produced parathormone, or a parathormone like substance. Since that time there have been numerous reports of similar cases of hypercalcemia, hypercalcuria and hypophosphatemia without bony metastasis and normal
normal parathyroid glands. (3,4,5,6,7 & 8 & 14) In these patients other causes of hypercalcemia such as Vitamin D intoxication, prolonged immobilization, milk alkali syndrome, Boecks Sarcoid, and primary bone disease were adequately ruled out. Stone and Waterhouse, in 1961, (9) presented a similar case in which they found hyperplastic parathyroid glands and postulated that the tumor produced a trophic "substance X". This patient was also cured of her hypercalcemia by a subtotal parathyroidectomy. However this appears to be an isolated case and no similar ones can be found in the literature.

If some neoplasms do actually produce parathormone, the clinical importance of this finding is vast. Serum calcium levels may become an important screening test for malignancies as well as other more discrete methods of evaluating parathyroid activity. Also, since the apparent humoral activity parallels the tumor activity, these tests can be a good measure of the therapeutic effectiveness of antitumor drugs and surgery, and a measure of recurrence alerting the physician to the need of further and/or more drastic measures. Furthermore the hypercalcemia in itself is often a terminal factor in cancer deaths and an understanding of the nature of one of the causes of hypercalcemia can lead to more effective treatment of this problem. (10)
II. Typical Case and Other Reports from the Literature

It is germane to the thesis at this time to present a rather typical case which illustrates findings consistent with a parathormone secreting tumor: (4)

A forty-eight year old woman was admitted on June 27, 1950, because of 40 pound weight loss, anorexia and vomiting of four months' duration. On examination the striking findings were the cachexia and a soft, non-tender multilobular mass arising in the left adnexal region and extending halfway up to the umbilicus. She was anemic. The erythrocyte sedimentation rate was 117 mm. in one hour. The urine concentrated to 1.023 and was negative for albumin, sugar and Bence-Jones protein. The urea nitrogen was 16 mg. per cent. The serum calcium ranged between 15.7 and 17.9 mg. per cent, with serum phosphorus of 2.1 to 3.1 mg. per cent. The serum albumin was 3.6 gm. per cent and globulin 2.8 gm. per cent. X-ray of the chest was normal. Gastrintestinal X-ray study, barium enema and protoscopy were normal. Skeletal survey showed minimal demineralization with no changes suggestive of hyperparathyroidism or metastatic malignancy. The lamina dura of the teeth was intact. The electrocardiogram was normal except for a Q-T interval of 0.26 at a rate of 110.

It was thought that the patient had hyperparathyroidism and an ovarian neoplasm. Because of the immediate dangers of hypercalcemia it was decided to do an exploration of the neck first. This was done under pentothal, nitrous oxide, ether and cyclopropane. Shortly after induction and before insertion of the intratracheal tube, her heart stopped. The chest was opened and the heart was found in diastole. It was massaged and spontaneous contractions began. It was thought safe to continue the operation and exploration of the neck proceeded uneventfully. Two parathyroid glands on the left and one on the right were identified and appeared grossly normal. A small 0.5 cm. node was removed in the hope that this might be an adenoma but on section this proved to be a normal lymph node. Because of the previous cardiac arrest the sternum was not split. She made an uneventful recovery from these
procedures, but there was no change in her serum calcium which continued to range between 14.1 and 17.9 mg. per cent. It was felt that a reasonable effort had been made to exclude a parathyroid adenoma and that one should proceed against the ovarian neoplasm.

At laparotomy a large multicystic tumor was found arising from the pelvis and extending up to the umbilicus. No gross metastases were noted. A bilateral salpingo-oophorectomy and total hysterectomy were done. All of the right ovary could not be removed from the pelvis. The histopathologic diagnosis was papillary adenocarcinoma of the ovary. Careful search did not reveal parathyroid tissue, teratoma or unusual calcification. Tumor tissue was also found in the left ovary. The uterus showed no evidence of an estrogen effect. Postoperatively the patient did well. Three days postoperatively her serum calcium was 11.2 mg. per cent. Six days postoperatively it was 10.3 mg. per cent and the serum phosphorus was 3.1 mg. per cent. The serum alkaline phosphatase showed a transient rise to 7.1 Bodansky units (B.U.). Twelve days later radiotherapy was initiated to a total tumor dose of 4300 r. The patient gained sixteen pounds and her serum calcium remained at 10.5 mg. per cent with phosphorus of 3.4 mg. per cent.

Five months after the operation she lost a few pounds in weight (serum calcium 11.6, phosphorus 2.3 mg. per cent, sedimentation rate 110). Six months after the operation a mass became palpable in the lower right quadrant, and the serum calcium rose to 13.4, then 15.5 mg. per cent, the phosphorus to 3.4 mg. per cent, then 4.0 mg. per cent with spinal fluid calcium 5.4 and phosphorus 1.4 mg. per cent. After temporary improvement she began to fail and dependent edema and severe abdominal pain developed. The serum calcium then was 16.1 mg. per cent. At the patient's request, she was transferred to a hospital nearer her home. Skeletal X-ray studies there in July, 1951, failed to reveal bony metastases. She died suddenly one week later. Permission for autopsy could not be obtained.

Plimpton and Gellhorn (4) have a series of ten patients with malignant disease and normal bones. They all exhibited
symptomatology characteristic of hypercalcemia and blood chemistry consistent with hyperparathyroidism. Other causes of hypercalcemia were ruled out. Removal of the primary tumor in 3 of the patients was associated with prompt return to normal of the serum calcium and phosphorus and the alkaline phosphatase when elevated. The parathyroid glands were invariably found to be normal at the time of operation or autopsy. This series suggested to them that some humoral substance was produced by these tumors although they could not rule out the production of some substance which binds calcium and transports it in excessive amounts causing a secondary hyperparathyroidism.

Myers, in 1960, (11, 12, & 13) presented a series of 430 patients having hypercalcemia associated with malignant tumors. Of these, roentgenograms of the skeleton for metastasis were negative in 56 patients and not done in another 50. Therefore, 14% had hypercalcemia without bony metastasis. Included in his series were kidney, 17%; lung, 19%; cervix, 50%; and lymphoma, 38%; without bony metastasis. One particularly interesting presentation in his paper was a problem in differential diagnosis between primary hyperparathyroidism and hypercalcemia without bony metastasis:
<table>
<thead>
<tr>
<th></th>
<th>59 year old male</th>
<th>33 year old female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>carcinoma of the lung, 2 years</td>
<td>carcinoma of the cervix, 2 years</td>
</tr>
</tbody>
</table>

**History**

<table>
<thead>
<tr>
<th></th>
<th>Previous cancer treated</th>
<th>+</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>Thirst weight loss and polyuria</td>
<td>+</td>
</tr>
</tbody>
</table>

|                  | Evidence suggesting recurrent cancer | + |

**Laboratory**

<table>
<thead>
<tr>
<th>Value</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.2</td>
<td>Serum Ca++</td>
</tr>
<tr>
<td>2.2</td>
<td>Serum Phosphorus</td>
</tr>
<tr>
<td>141 B.U.</td>
<td>Alkaline Phosphatase</td>
</tr>
<tr>
<td>430</td>
<td>Urinary Ca++ mg 24h</td>
</tr>
<tr>
<td>12</td>
<td>BUN</td>
</tr>
<tr>
<td>3.7</td>
<td>Serum K+</td>
</tr>
<tr>
<td>29</td>
<td>Serum HCO 3-</td>
</tr>
</tbody>
</table>

| Normal | Bone Marrow | Hypocellular |

(6)
Demineralization | X-ray | Demineralization
---|---|---
Metastatic lung CA - Bone not invaded parathyroid, normal. | Diagnosis | No recurrence parathyroid adenoma.

Special tests - phosphate clearance, calcium tolerance and response to cortisone were not appreciably different.

This then shows how closely primary hyperparathyroidism can be mimicked and lends credence to the secretory theory. Myers (13) also noted that the rate of growth or functional capacity of a tumor may be reflected in serum and urinary calcium. He suggests that calcium studies may provide a precise way in which to measure changes in a tumor in response to treatment and this data may be useful in screening antitumor agents.

Connor, Thomas, and Howard, in 1956, (3) presented two cases of hypercalcemia and malignancy without skeletal metastasis. One was a 69 year old male who preoperatively had increased Ca++ and decreased $P_{0_{4}}$. A tumor of the lung was resected and the Ca++ returned to normal by the 4th postoperative day. Four months later the Ca++ increased and local tumor growth was noted. Shortly before death the Ca++ decreased and at autopsy the tumor was found to be
completely necrotic. The parathyroid glands and bones were normal.

Schatten, Ship, et al, in 1959, (14) reported a case of a patient with hypercalcemia and hypophosphatemia associated with squamous cell carcinoma of the vulva. There was a direct correlation between the presence of tumor and the serum abnormalities.

A fall of serum calcium and a rise of serum phosphorus followed excision of the tumor and a second rise in serum calcium with a fall of serum phosphorus followed its growth. The parathyroid glands were normal at autopsy and there were no osseous metastasis.

Stone, Waterhouse, and Terry, in 1961, (9) presented the case of a 34 year old woman with carcinoma of the cervix and hypercalcemia without bony metastasis. A subtotal parathyroidectomy was done which revealed a pathologic picture consistent with secondary hyperplasia. The serum Ca++ began a persistent fall until death. They felt that this represented production of a trophic substance by the tumor which stimulated the parathyroids. However a fourth parathyroid gland was found at autopsy and it is generally hopefully assumed by surgeons performing a total thyroidectomy that a single gland is adequate for normal parathyroid function. This would not appear to be due to high preoperative Ca++ causing temporary parathyroid suppression.
Abouav, Berkowitz, and Kolb, in 1959, (15) reported a case of masculinizing hypernephroid ovarian tumor associated with hypercalcemia and hypophosphatemia. Tubular reabsorption of phosphate was 85% and there was a hypophosphaturia. They believe that this is the usual finding in cases of this type and therefore argue that the humoral substance is not parathyromone because it lacks phosphaturic qualities. They believe that the hypophosphatemia in their case is due to the normal body homeostatic mechanisms which tend to maintain the physiochemical relationship $\text{Ca}^{++} \cdot \text{PO}_4^{-} = K$. In this belief then, they feel that the phosphate reabsorption can be used to differentiate between primary hyperparathyroidism and parathormomimetic tumors. The serum Ca++ fell and the phosphate rose following removal of the tumor.

In the CPC of the New England Journal of Medicine, October, 1963, (16) a case of adenocarcinoma of the transverse colon with extensive metastasis to the liver was presented. This patient had hypercalcemia, hypercalcuria and hypophosphatemia without evidence of metastatic bone disease. The parathyroid glands were normal at autopsy. The patient also had a high alkaline phosphatase. Dr. Armen Tashjian, by use of a quantitative complement fixation reaction and an antigen reacting with the specific antiparathyroid hormone, antigen to "parathyroid hormone" was detected, approximately 6 microgm. of antigen per gram of primary tumor and 1 microgram of antigen...
per gram of metastatic tumor. No antigen was found in surrounding tissues. He uses an antiserum to bovine parathormone which shows serologic cross reactivity with human parathormone (unpurified). That this is actually parathormone and not tissue components with antigenic cross reactivity has not been definitely established.

Goldberg and Tashjian, et al (8) have a series of 18 patients, with chemical abnormalities associated with tumors arising outside the parathyroid glands without bony metastasis. Seven are renal cell, 3 are bronchial, 2 ovarian carcinoma and 1 each of endometrium, bladder, vulva, generalized lymphoma plus reticulum cell sarcoma and hemangiosarcoma of the liver. In 10 of the 18 cases parathyroid examination was reported. One was adenomatous, one hyperplastic, and eight were normal. In all 10 cases in which the tumor was removed the serum calcium returned to normal but subsequently rose in 3 cases when the tumor recurred. The serum phosphate was consistently low in 11 of the 17 cases and the serum alkaline phosphatase was elevated in 7 of 15 cases.

Finally, for variety, Woolner, Keating, and Blank (17) presented a case of a woman who had primary hyperparathyroidism resulting from a parathyroid adenoma. One year previously an adenocarcinoma of the breast had been surgically removed. Operation disclosed a parathyroid tumor that was the site of metastasis from the adenocarcinoma of the breast.
III. Mechanism of Action of Parathormone

If parathormone is indeed produced by some neoplasms, an understanding of its action and effects is necessary to derive any clinical benefits from this finding.

The parathyroid hormone has recently been isolated by Rasmussen and Craig (18). It is a polypeptide with a molecular weight of approximately 9,500 and is homogeneous by counter current distribution, paper and column chromatography and ultra centrifugation and possesses calcium mobilizing and phosphaturic activity. It can be partially hydrolysed without complete loss of biologic activity and this is probably the explanation for some false results obtained with cruder extracts.

Parathormone has been found to have effects at four target organs. These include bone, the kidney, the gastrointestinal tract and the lactating breast. The main biochemical effect of this hormone seems to be associated with the transport of calcium across a variety of membranes (intestinal epithelium, renal tubule, bone cells and mammary epithelium), and it also seems to be involved in the uptake and turnover of phosphate in the kidney and possibly other organs.

Peripheral Effects of Parathormone on the Kidney

It seems well established that parathyroid hormone controls
the renal excretion of phosphate (19, 20, 21) but the manner in which it does this is a subject of controversy, either by increasing the glomerular filtration rate or by its control over the tubular reabsorption or excretion. However from the work of Jacobs (22) and Hint and Thomas (23, 24) it appears that the more significant is the control of tubular reabsorption or secretion of phosphate. The bulk of the proof is derived from experiments which show a rapid and sustained increase in the urinary phosphate excretion with no change in the clearance of inulin following adequate doses of parathormone. Unilateral perfusions of dog kidneys have given similar results and retrograde infusions in the chicken which has a renal portal system whereby only the tubule is perfused have given similar results, i.e. increased phosphate excretion without an increased GFR.

That this is primarily a secretory rather than a decreased reabsorption response is supported by Nicholson (25) who suggests that the hormone controls the rate of phosphate excretion at the distal tubule. This is supported by the work of deVerdier (26) who has shown an increased turnover of P32 in the renal tissues of animals treated with parathyroid extract, which is more consistent with an increased secretion rather than a reabsorption of phosphate. Thus the effect of parathormone on the kidneys in regard to phosphate is primarily an increased secretion of phosphate in the distal tubule. This subject has not been thoroughly resolved, however.
Parathormone also seems to influence the rate of calcium reabsorption by the renal tubule. This is supported by data from Albright and Ellsworth (2) that shows the initial effect of administration of parathormone to a hypoparathyroid animal is a fall in urinary calcium presumably due to an elevation of the Tm for calcium in the renal tubule. It is only after the plasma Ca++ becomes elevated that the hypercalcuria develops. Likewise following parathyroidectomy there is an increased excretion of calcium and this is followed by hypocalcuria only after the plasma Ca++ has fallen significantly. This suggests that there is a decreased rate of tubular reabsorption in the hypoparathyroid state. Although these actions upon the renal handling of Ca++ and \( \text{PO}_4^- \) are the most striking effects which follow the administration of parathormone, other effects have been observed which may be refined and also used as indicators of excessive parathormone activity.

Following rapid infusion of a purified parathyroid extract in hypoparathyroid patients, Rich (27) found a rapid onset of increased citrate excretion, an elevation in urinary pH and an increase in total solute excretion. Possible these can be attributed to an increased tubular phosphate secretion resulting in increased Na+ excretion and decreased \( \text{Na}^+ \leftrightarrow \text{H}^+ \) exchange, an elevation of pH with resultant increased citrate excretion.
Na+ and H+ excretion. The increased solute excretion is of interest in view of the suggested diurectic effect of parathormone.

**Peripheral Effects of Parathormone on Bone**

The effects of parathormone on bone may be theorized as follows: (28) The primary action of the hormone is to convert potentially osteogenic cells from osteoblastic into osteolytic cells, either multinucleated giant cells or an osteolytic fibroblast which elaborates an argentophil fibrous tissue. This results in increased bone resorption possibly by increasing acid production and increasing acid phosphatase activity, resulting in the destruction of both matrix and bone mineral. The release of the latter tends to elevate the level of both $\text{Ca}^{++}$ and $\text{HPO}_4^{2-}$. This fall of ion product is buffered by the withdrawal of calcium and phosphate from the exchangeable calcium of bone. Since the kidney is more sensitive and responds more rapidly to the hormone, the first effect upon bone is probably withdrawal of calcium and phosphate. However, as soon as bone resorption is increased, and the $\text{Ca}^{++} \cdot \text{HPO}_4^{2-} = K$ is returned to normal, calcium and phosphate leave the extracellular fluid and return to the exchangeable bone mineral. Thus this compartment serves a buffering function. Although this buffering function superficially appears to be a simple
physiochemical process, there is much to suggest that the
exchange is controlled by the cellular activity of the osteo-
blasts. Although the initial effect of the hormone is to
decrease osteoblastic activity, the increased bone resorption
leads to a weakening of the bone, which leads to mechanical
stress and compensatory activation of resting osteogenic cells
into active osteoblasts, resulting in an increased rate of
bone growth and mineral accretion. In mild hyperparathyroidism
this compensatory change may be sufficient to maintain a
nearly normal amount of total bone tissue. However, with
more severe degrees of hyperparathyroidism the compensatory
increase in osteoblastic activity is insufficient, an
imbalance between osteogenesis and osteolysis develops, and
bone density as observed radiologically decreases, leading
to the classic picture of hyperparathyroidism with rarefaction
of bone and fractures. In this process the trabeculae and
certain areas of cortical bone appear to be more sensitive to
the action of the hormone and exhibit the pathologic changes
sooner and to a greater degree than the major part of cortical
bone.

Peripheral Effects of Parathormone on the Gastrointestinal
Tract

Parathormone seems to increase the rate of absorption of
Ca++ by the G.I. tract (28). This has been shown by taking
loops of bowel from normal and parathyroidectomized rats. The loops from the hypoparathyroid rats had a decreased ability to develop and maintain a concentrated gradient of calcium between serosal and mucosal fluid. Thus parathyroid hormone is necessary along with Vitamin D for adequate calcium absorption.

For the purpose of this paper, the most important effect of the hormone is that on the kidney, because the earliest effects of hypersecretion would be manifest in changes of function in the organ most sensitive to its action, that is the kidney. The best explanation for this seems to lie in the fact that in the dog kidneys, as estimated by Copp (29), roughly 20-26% of the resting cardiac output perfuses the kidneys in contradistinction to 3-7% total blood flow to the bone. Also Neuman and Neuman (30), by the use of isotopes (deuterium), showed that injected deuterium equilibrates almost immediately with soft tissues but is only 90% complete in bone at the end of 4 hours. Since parathyroid hormone is a relatively large molecule it would diffuse slowly through the bone and depend on local blood flow to get to its site of action, the bone cells. This system has an inherent stability tending to smooth out slight changes in circulating hormone and would be slow to respond to larger variations in hormone concentrate. The kidney, on the other hand, would have all cells reached essentially simultaneously and would be more sensitive to small changes in the concentration of circulatory
hormone. By using phosphate excretion as a test of renal response and an increase in serum calcium as an indicator of osseous response, the difference between the onset of action of parathormone can be shown. If adequate doses of parathormone are given the maximal renal response is obtained in 15-45 minutes; whereas, the increase in serum calcium occurs in six or more hours (31). Also if serum Ca++ is decreased by the use of EDTA a change in the urinary excretion of phosphorus occurs within 20 minutes.

The effect on the kidney is thus more rapid, but also limited in magnitude. During prolonged administration of the hormone the serum calcium will continue to increase until death occurs. However after a certain dosage level no further effect upon urinary phosphate excretion can be obtained (26) and despite an increased Tm for calcium, when a significant hypercalcemia occurs, hypercalcuria ensues. The effect of parathyroid hormone can be summarized thusly:

<table>
<thead>
<tr>
<th>Response</th>
<th>Bone</th>
<th>Kidney</th>
<th>G.I. Tract</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Slow</td>
<td>Rapid</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>Insensitive</td>
<td>Sensitive</td>
<td>?</td>
</tr>
<tr>
<td>Magnitude</td>
<td>Unlimited</td>
<td>Limited</td>
<td>Limited</td>
</tr>
</tbody>
</table>
From the above then it is possible to conceive the regulation of parathyroid activity by regulation of $A_{Ca^{++}}$. The kidneys are a rapid and sensitive regulator which respond to small hormone concentration and in a limited capacity; whereas, the bone is slow to respond and insensitive, but of nearly unlimited capacity. Thus, a fall in the $A_{Ca^{++}}$ of the plasma stimulates the parathyroid glands to secrete more hormone. The hormone acts upon at least three peripheral tissues, the kidney, the bone, and the gastrointestinal tract. Its effect upon the kidney is to increase the tubular resorption of calcium; upon the bone to increase resorption; and upon the gastrointestinal tract to increase absorption. All these effects tend to elevate directly the $A_{Ca^{++}}$ of plasma, which in turn shuts off the further production of hormone by the gland. In addition, an increased rate of bone resorption leads to an increased release of phosphate into the plasma. However, the hormone has an additional action upon the kidney, that of increasing distal tubular secretion of phosphate. This effect results in a lowering of $A_{HPO_{4}^{--}}$ which usually more than offsets the rise produced by the resorption of bone. The net result is a decrease of $A_{HPO_{4}^{--}}$ which leads to an increase of $A_{Ca^{++}}$, due to their interrelationship ($A_{Ca^{++}}A_{HPO_{4}^{--}} = K$).
IV. Symptoms of Hypercalcemia

Since hypercalcemia is often the cause of the presenting complaints of these patients, and the symptoms are a rough guide to the therapy, it is imperative that one be familiar with the effects of hypercalcemia. (32)

The various manifestations of hypercalcemia may be categorized by their effect on the nervous system, gastrointestinal tract, kidney, heart and metabolic alterations.

A high calcium level results in a diffuse disturbance in the electrical activity of the brain which can be demonstrated by an electroencephalogram. The resultant symptoms are lassitude, somnolence and stupor which progress eventually to coma and death. There also may be occasional convulsions and variable changes in the deep tendon reflexes.

The gastrointestinal symptoms are prominent and include anorexia, nausea, vomiting and constipation although occasionally diarrhea. There may also be duodenal ulcer disease and pancreatitis.

The effect on the kidney is the inability to concentrate urine with a resultant polyuria and polydipsia. There also seems to be a direct effect on the distal tubule with loss of potassium, sodium, and magnesium and subsequent hypokalemic alkalosis.

The effects on the heart are usually changes in electrical activity of the myocardium with a shortened QT interval,
lowering of the T waves and lowering or sagging of the P waves.

The effect on skeletal muscle seems to be depressant with resultant muscle weakness.
V. Differential Diagnosis of Hypercalcemia

In order to qualify for the category of a "parathormone secreting neoplasm" it is mandatory that all other possible causes of hypercalcemia be ruled out.

The first thing that comes to mind in these days of generalized usage of nonprescription vitamins is hyper-vitaminosis D. Since D is a fat soluble vitamin it cannot be excreted by the kidney and thus is cumulative. The clue here is usually the history. Also in Vitamin D intoxication there is usually a hyperphosphatemia which is not characteristic of the syndrome under consideration. (33) A more refined test is a trial of therapy with cortisone which is said to be antagonistic to Vitamin D and would thus lower serum calcium.

About 10% of patients with sarcoidosis have hypercalcemia and they may have hypercalcuria with or without hypercalcemia. Many investigators (34, 35) (37) feel this is due to an endogenous hypervitaminosis D and cortisone treatment will indeed reduce the hypercalcemia and can thus be used as a diagnostic adjuvant. Calcium balance studies will show increased uptake of calcium with decreased fecal calcium. Blood phosphate and alkaline phosphatase may be normal or elevated. Other aids in the diagnosis of sarcoidosis include the Kveim reaction, and tubercle biopsy. Findings of pulmonary lesions, hilar and
general lymphadenopathy, uveoparotid fever, skin lesions, erythema nodosum, rheumatoid-like arthritis and granulomatous uveitis should make one suspicious of sarcoidosis. (33)

The so-called Milk Alkali syndrome may present a problem in the differential diagnosis. There is usually a history of excessive milk and absorbable alkali ingestion for the treatment of peptic ulcer disease. In addition there is hypocalcuria and hypophosphaturia, and azotemia as opposed to the findings in excessive parathormone secretion. Marked renal insufficiency with alkalosis, azotemia and nephrocalcinosis are also findings. (16) (38)

Immobilization is another cause of hypercalcemia. (40) Especially in the first 3-4 weeks when bone reabsorption is at a height and osteoporosis is developing. However, the serum phosphate is normal or elevated and tubular phosphate reabsorption is normal. Also a trial of therapy (ie) mobilization will cause a drop in serum calcium even to the point of hypocalcemia. This cause of hypercalcemia can usually be elicited by history, but it is an important point to remember in the treatment of people with Pagets disease and hypercalcemia of other causes.

In multiple myeloma, Woodard (1) has a series of 80 patients in which the average serum Ca++ is 11.44 mg and 21% had a serum Ca++ greater than 12.1 mg% and another 15% had serum Ca++ greater than 13.1 mg%. That this is not due to
increased plasma protein is attested to by the fact that it is the globulins that are increased and the albumin is normal or usually decreased. The albumin fraction is responsible for the majority of calcium binding. Also in the Woodard (1) series the alkaline phosphatase was greater than 5.1 BU in 20% of his patients. The plasma phosphate is usually normal or elevated in multiple myeloma. This disease can usually be ruled out by skeletal roentgenograms and appropriate marrow aspirations, electrophoresis, and detection of Bence Jones protein in the urine.

Osteoporosis and osteomalacia are not usually a problem in the differential diagnosis since serum Ca++ and P_{4} are either normal or decreased. (33)

Paget's Disease can present a problem in the differential diagnosis between it and primary hyperthyroidism with Brown tumor formation. However the serum phosphate is normal or increased and the phosphate reabsorption test will usually make the distinction. (36)

Since estrogen therapy has been shown to cause hypercalcemia, it may be contraindicated in certain cases of breast and prostate carcinoma. (1, 39) (45) It has also been postulated that some mechanism is present in the body which can convert androgens to estrogens and thus produce a hypercalcemia.

Cancer metastatic to bone presents a problem in the differential diagnosis. It is generally accepted that in about 9% of all cancers metastatic to bone there is a hypercalcemia

(23)
during the course of the disease. (1) This is apparently true in all neoplasms except that of the thyroid. In extensive studies of serum phosphorus the results have always been equivocal. (1, 12, 13) This leads one to believe that these series may be mixed, that is they may contain both tumors causing hypercalcemia by excessive osteolysis and exceeding the renal excretory capacity and also hormone-producing tumors. There is nothing to prove that these so-called hormone-producing tumors cannot metastasize to bone and thus cannot be considered as a factor in the muddled results of phosphorus metabolism in metastatic bone disease. Therefore it seems unlikely that marrow aspiration for tumor cells and skeletal roentgenograms can decide whether or not one is dealing with a hormone-producing tumor or not. Rather the answer would lie in the phosphorus metabolism or some other more discrete indicator of excess hormone activity.

The differential diagnosis between primary hyperparathyroidism and parathormone secreting tumors will be covered in the section titled "discussion".

Other causes of hypercalcemia such as thyrotoxicosis, Gaucher's disease, Nieman Pick disease, Hand Schuller Christian Syndrome, Hodgkin's disease, osteogenesis imperfecta, osteomyelitis, xanthomatosis, chronic radium poisoning, polycythemia vera, etc. must of course be considered. Idiopathic hypercalcuria more recently has often been found to be primary hyperthyroidism by more sensitive tests. (41)
VI. Discussion

At this point there have been enough well documented cases presented to show the extreme likelihood of the presence of certain tumors capable of producing a picture very similar if not identical to primary hyperparathyroidism.

Some argue that the hypercalcemia is due to skeletal metastasis which are so minute that they are undetectable by radiographic and microscopic means. This would seem to be refuted by the observance of these patients over a long period of time without development of observable metastasis. To maintain high enough serum Ca++ levels to supersede to the kidneys' ability to excrete over a long period of time, especially in anorectic hypercalcemic cancer patients without some bony change is inconceivable. The serum Ca++ also seem to fall rapidly following surgical removal of the tumor. Some may argue that this is a phenomenon similar to choriocarcinoma of the uterus where the metastases seem to disappear following removal of the primary tumor. That is, the satellite cancers are dependent on the primary. However, small metastases in soft tissue do not seem to regress following the removal of the primary tumor. Also the presence of the hypophosphatemia cannot be explained on the basis of unobservable skeletal metastases. In almost all cases of bone destruction by a
neoplastic process that is widespread enough to cause hypercalcemia there is normal or slightly increased serum phosphorus. Myers (12), in one report, shows a serum phosphorus which roughly parallels the rise in serum calcium in an exacerbation of metastatic bone disease, although the serum phosphorus never reaches abnormal levels. When treatment is begun the serum phosphorus falls along with serum calcium and a concomitant rise in alkaline phosphatase which signals the beginning of osteoblastic activity. Thus in pure metastatic bone disease one sees normal or slightly increased serum phosphorus levels but not hypophosphatemia. Although the serum calcium does rise a phosphate diuresis is not observed as an attempt to maintain $A_{CA^{++}} \cdot A_{PO_{4}^{2-}} = K$.

One theory that has been advanced is that there is increased production of an endogenous Vitamin D like substance such as in sarcoidosis. However, calcium balance studies done by Stone and Waterhouse (9) showed that their patient was in a negative calcium balance of 286 mg per day over a 6 day measurement period when Ca++ intake was 341 mg per day and fecal Ca++ was 307 mg per day. This was in spite of 200 mg per day cortisone acetate therapy.

Another explanation that has been advanced is the presence of an abnormal substance which binds calcium and transports it in excessive amounts, thus accounting for the hypercalcemia by production of a secondary hyperparathyroidism.
Studies, however, by Plimpton and Gellhorn, (4) on Howe fractionation of plasma proteins and electrophoretic patterns have shown no abnormal protein. Also studies to isolate a circulating mucopolysaccharide have failed, and no calcium binding lipid or cephalin has been found in adequate amounts to explain the abnormalities observed.

Schatten, Ship, et al (14) observed that the spinal fluid calcium was lower than what would be expected from the total serum calcium values and total serum protein. However by rapid infusion of human albumin they produced a prompt rise in total serum calcium which suggested that the calcium was normally bound. Also evidence of ultracentrifuged studies indicated a normal relationship of bound calcium to serum protein. Howard and co-workers (42) have also found that in primary hyperparathyroidism spinal fluid calcium is lower than one would predict. In his case of apparent parathormone activity, Connor (3) found that the spinal calcium was lower than expected. Thus this is another parallelism between primary hyperthyroidism and parathormone secreting tumors.

It would seem fairly well substantiated that a humoral substance is produced by some neoplasms. The problem now is to decide whether it is: (1) A parathyrotrophic substance, (2) A substance resembling parathormone but not containing phosphaturic qualities, (3) Breakdown products of tumor with production of substances with phosphaturic attributes, or
Actually parathormone.

Stone and Waterhouse (9) believe that some trophic substance is produced because they seemingly cured the hypercalcemia by removal of 3 out of 4 parathyroid glands thus showing that the hypercalcemia was dependent on the presence of intact parathyroids. Secondly, the glands removed by them were described as resembling secondary hyperplasia of the parathyroids. This is, however, the only case reviewed in which the parathyroids have been described as abnormal. Their patient progressed rapidly to death following the operation with hypocalcemia being a prominent factor in the decline. A 4th gland was removed at autopsy and also found to be hyperplastic.

Abouav, et al (15) believes that the hypercalcemia is due to elaboration of a humoral substance by the tumor which has an action on bone like parathormone but lacks phosphaturic qualities. Their patient had normal phosphorus reabsorption studies (85%), but also a hypophosphatemia and increased urine 24 hour phosphate excretion. They account for the hypophosphatemia on the basis of the body's tendency to maintain $A_{Ca^{++}} \cdot A_{P0_{4}} = K$. Thus they claim that the hyperphosphaturia is due to an "attempt by the body to maintain this constant," but in fact, one of the major methods of maintaining this constant is by phosphaturia which is mediated through the parathyroid glands.
If there is a substance produced by some neoplasms which resembles parathormone in its activity on bone then it is logical to assume that there would be an increase in both serum calcium and phosphorus in direct proportion to their concentration in bone. This would then exceed the solubility product of $A_{Ca^{++}} \cdot A_{PO_{4}^{2-}} = K$ and there would be metastatic calcification. This however does not happen, but rather there is a decrease in serum phosphate. Assuming that the system is receiving an adequate intake of calcium and phosphorus and that the glomerular filtration rate remains constant, then the only way for the body's homeostatic mechanisms to lower serum phosphorus would be through increased tubular activity. Thus when the body is presented with an increased load of calcium and phosphorus it responds by increasing phosphorus excretion. Therefore per cent tubular reabsorption studies should show a decrease.

Schaff and Kyle (47) have also shown that increasing serum calcium in normal subjects has no effect on phosphate per cent tubular reabsorption, but the addition of parathormone lowers the percentage of phosphate reabsorption. Another possible source for the difference claimed by these investigators is that their report deals with a masculinizing ovarian tumor and studies done by them showed increased serum androgens. Experimental work has shown nonspecific effects of adrenal hormones on the parathyroid gland. (43, 44)
Stewart and Bowen (46) have demonstrated a phosphaturic action of spleen and thymus extracts. This can thus raise the possibility that the phosphaturic activity of some of these tumors is not due to parathormone, but simply tissue breakdown products. Sufficient work has not been done in this field to reach any definite conclusions.

Finally, there is the theory that these tumors secrete parathormone. If this is the case then the symptoms and laboratory findings should be the same as in functioning parathyroid adenoma because there would be continued release of parathormone unrelated to serum $A_{\text{Ca}^{++}}$. The laboratory findings in hyperparathyroidism are hypercalcemia, hypercalicuria, hypophosphatemia, hyperphosphaturia, as well as some ancillary findings of hyperuricemia, (16) hypokalemic alkalosis, increased solute excretion, increased serum citrate and decreased RBC magnesium. The symptoms of primary hyperparathyroidism are due mainly to the hypercalcemia. The laboratory diagnosis can be most readily made on the basis of phosphate reabsorption studies. Schaaf and Kyle (47, 48) showed that in control subjects per cent renal phosphate reabsorption demonstrated a mean value of $91.3 \pm 3.3\%$. Three instances of primary hyperparathyroidism averaged $58\%$.

Elevation of serum calcium in normal subjects failed to alter the normal per cent renal phosphorus reabsorption; however, addition of parathyroid hormone to the calcium infusate produced a fall in per centage to levels similar to those seen
in primary hyperparathyroidism. These results were reproducible even in the presence of azotemia. Goldman and Bassett (49) indicate that phosphate clearance is well preserved until G.F.R. is less than 25 ml/min. Goldsmith and Ceccarelli (41) have further refined this test and have been able to justify surgical exploration in primary stone formers with hypercalcuria and normal serum calcium and phosphorus. They have found a high percentage of parathyroid adenomas in the so called idiopathic hypercalcurias. They demonstrated the presence of a morning increase in phosphorus excretion in normal and hyperparathyroid subjects. Rapid infusion of calcium causes a reversal of this spontaneous phosphateric rhythm in normal subjects but not in hyperparathyroid subjects. Surgical correction of this disease was followed by a normal response to calcium infusion. These results may help to explain controversial phosphate reabsorption studies and provide better means of control.

The close correlation between primary hyperparathyroidism and parathormone producing tumors is evident. If this is the case then a differential diagnosis between the two should be impossible unless luckily a parathyroid adenoma was palpated or picked up on a barium swallow. An especially difficult problem would be the presence of a known malignancy, since the two diseases could both be present.

Numerous questions are still in need of answering before
the presence of a parathormone secreting tumor can actually be stated with certainty. One would expect if there were excessive secretion of parathormone the parathyroid glands themselves would be suppressed and exhibit atrophy. This however, has never been the case in the cases reviewed (3,4,5,6,7,8,14). This area could definitely use some detailed pathologic study by a single investigator.

Another problem is that one would expect these tumors to show some likeness to each other regarding cellular patterns and structure. So far no common structure has been found. However, Abouav, et al (5) stated that their tumor with apparent parathormone activity morphologically resembled parathyroid carcinoma. Also Schatten, Ship, et al (14), found that neither their primary carcinoma of the vulva nor the first metastasis was associated with hypercalcemia. The picture was one of a well differentiated squamous cell carcinoma with pearl formation. The second episode of metastasis had a hypercalcemia and this tumor was extremely anaplastic. The apparent change in function of the tumor was thus accompanied by an unmistakable change in its histological appearance.

Another interesting observation regarding secretory activity of neoplasms has been made in regard to excessive production of ACTH and ADH (51,52,53). These two substances are also polypeptides and secretory activity seems to be
correlated with the degree of anaplasia. Thus if breakdown products of tumors can resemble these two products closely enough to function in an endocrine capacity then it is logical to assume that parathormone can be also produced by a neoplasm.

To date there have been no reports of osteitis fibrosa cystica from the influence of the tumors, but rather the main bone change is just demineralization. (3,4,6,8,14). One would seemingly expect to see this. (28) However, if one bears in mind that these cells are subjected to many influences other than the changing levels of parathyroid hormone, it is possible to imagine that under proper conditions osteoclastic activity will be followed by a compensatory increase in osteoblastic activity. Actually in marked hyperparathyroidism, in spite of compensatory osteoblastic activity, the osteoclastic activity predominates, resulting in the decreased bone density observed radiologically and the fractures observed clinically. In other words, the reason for the development of bone weakness and fractures is not due to any abnormality of the calcification mechanism but due to the fact that the predominant cellular activity is osteolysis and such a large percentage of all bone cells are in this state that, despite all the compensatory physiologic adjustments, osteoblastic activity is insufficient to maintain the normal balance between accretion and resorption.

(33)
In less severe cases it seems likely that the initially increased osteolysis leads to compensatory increased osteoblastic activity with a resulting increased rate of bone turnover. This being the case it is misleading to classify hyperparathyroidism as occurring with or without bone disease. Changes in bone metabolism undoubtedly occur in all cases of the disease. However, the generally used indices of such changes are so gross that only in moderately severe or long-standing cases of hyperparathyroidism are abnormalities recorded. Also in view of the facts (1) that the availability of phosphate is an important factor in the rate of deposition of bone matrix, and (2) that the calcium: phosphorus ratio in the diet will influence the levels of $\text{Ca}^{++}$ and $\text{HPO}_4^{2-}$ in the plasma of hyperparathyroid subjects (and therefore influences the supply of phosphate available for bone matrix formation), it is important to point out the role which diet may play in the rate of progression of the signs of bone disease.

One field in which further developments should elucidate the hormone producing tumor controversy, is the development of sensitive assay tests for parathyroid hormone. To date attempts at using extracts from tumors have been unsuccessful in showing any parathyroid activity in experimental animals (3). Tashjian (16), however, has demonstrated the presence of "parathyroid hormone" in extracts of these tumors by use of an antibody to bovine parathormone. Also Berson, et al (50) have found that parathyroid hormone concentration in plasma is

(34)
in the range of .1 to 1.0 millimicrogram per milliliter. This assay technique will surely be sensitive enough to determine if these tumors do indeed secrete parathormone.
VII. Summary and Conclusions

A series of patients from the literature with malignant neoplasms without bone metastasis has been presented in which a syndrome resembling primary hyperparathyroidism has been found. It is postulated that these tumors secrete parathyroid hormone and that the excess hormone is responsible for the hypercalcemia, hypercalcuria, hypophosphatemia and hyperphosphaturia found in these patients. The signs of excess hormone production are reduced by surgical removal or chemotherapeutic treatment of the neoplasms. They also tend to recur with recurrence of the neoplasm. There is no typical histological pattern on these neoplasms and they arise from numerous primary sites. However, there is some correlation between changes in the histologic pattern of the tumor and amount of hormone production.

One investigator has found parathyroid hormone in the neoplasm and this is the area where further research will probably either refute or solidify the subject of this thesis.

The work being done in this area is valuable for many reasons. It may be used as a screening agent for occult neoplasms. It can be used as a guide to therapy and also in the screening of the effectiveness of various anti-cancer drugs. Also it can help to develop effective treatment for the hypercalcemia which complicates the therapy of many terminal cancers.
No definite conclusions can be reached, but it is this writer's opinion that such neoplasms do exist and that this will eventually be confirmed by pathologic histology and hormone assay studies.
VIII. Bibliography


51. Ware, Fredrick: Personal communication.
