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Medical PROGRESS

Calcium and Skeletal Metabolism

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DURING THE past several years many new discoveries have been made in the field of calcium and skeletal metabolism. These discoveries have been of both fundamental importance and clinical relevance. The general theme that has emerged from this new knowledge is that calcium and skeletal metabolism is regulated by a complex and dynamic interaction of three hormones—parathyroid hormone (PTH), calcitonin (CT) and vitamin D (Table 1). These hormones exert their biological effects on the three organ systems that maintain calcium and skeletal homeostasis—bone, kidney and the gastrointestinal tract. In turn, the secretion and metabolism of these three hormones are influenced by these organ systems and others, such as the skin and liver, and by the concentrations of bone minerals which circulate in peripheral plasma. Finally, the hormones interact to influence each other's secretion, biological effects and metabolism.[1] Several recent reviews have considered these advances in bone mineral metabolism.[2-9] In this article, we shall emphasize those developments which seem to have the most clinical importance for each of the calcitropic peptide hormones. The emerging hormonal role of vitamin D has been thoroughly considered in recent publications, including one in this journal.[7-9]

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Parathyroid Hormone

Biosynthesis, Secretion and Metabolism

The process by which parathyroid hormone is produced by the parathyroid gland and delivered to its target organs has been discovered to be increasingly complex. There is at least one, and perhaps more, biosynthetic precursor to the 84 amino acid peptide which is the main hormonal constituent of the parathyroid glands.[10-14] The precursor(s), or prohormone(s), is converted into native hormone within the gland and then secreted into the circulation. Once in the circulation, the 84 amino acid peptide is broken down in plasma or at tissues or both into smaller peptide fragments.[15] Under some circumstances, hormonal precursors, hormone and perhaps hormone fragments may be secreted directly into the circulation from the parathyroid glands.[11-16] Therefore, there exist in plasma multiple forms of parathyroid hormones. These species of hormone have varying biological and immunological activity.[1-3,15,16] The latter observation is of practical significance since clinical measurements of the hormone are made by immunoassay systems which can react variously with different species of the hormones. Therefore, different immunoassay systems may give different results when applied to clinical measurements. *This emphasizes the importance of being familiar with the characteristics of any immunoassay system which one is using for clinical decisions.* If this precaution is taken, the immunoassay for parathyroid hormone can be very useful in the differential diagnosis of dis-

ABBREVIATIONS USED IN TEXT
CT = calcitonin
OAF = osteoclastic activation factor
PTH = parathyroid hormone

orders of calcium and skeletal homeostasis (Table 2).

Nonionic regulation of parathyroid hormone secretion. The importance of divalent cations, especially calcium, in the regulation of parathyroid hormone secretion is well-documented.[1] However, recent observations have suggested that other factors may also regulate hormonal secretion. A series of recent experiments has implicated other hormones, such as calcitonin and cortisol, and other organ systems, such as the gastrointestinal system and the central and peripheral nervous system (Figure 1), in the regulation of parathyroid hormone secretion.[17-20] Although many of these observations are preliminary and await further confirmation, their implications are of potential importance. They suggest that the control of parathyroid hormone secretion is more complex and multifactorial than previously appreciated.

Primary and Ectopic Hyperparathyroidism

Most patients with primary hyperparathyroidism have plasma levels of hormone which are absolutely or relatively (to blood calcium) elevated. By contrast, patients who have hypercalcemia not due to parathyroid gland neoplasia will have a suppressed parathyroid hormone level. However, it must be kept in mind that some nonparathyroid tumors are associated with excess parathyroid hormone production (pseudohyperparathyroidism, ectopic hyperparathyroidism).[1] Several controversies remain unresolved regarding the ectopic production of parathyroid hormone. How common is ectopic hyperparathyroidism in the differential diagnosis of hypercalcemia and is ectopically-produced PTH similar in molecular structure to glandular PTH?[21,22] The latter controversy is of obvious fundamental importance for molecular biology, but also important for clinical medicine. Some laboratories report that there are structural differences between

TABLE 2.—*Differential Diagnosis of Hypercalcemia*

Artifactual
- Hyperproteinemia
  - Venous stasis during blood collection
  - Hyperalbuminemia (e.g., hyperalimentation)
  - Hypergammaglobulinemia (e.g. myeloma)

Malignancy
- Solid tumors
- Hematological
  - Myeloma
  - Lymphoma
  - Leukemia

Endocrinological
- Primary hyperparathyroidism
  - Multiple endocrine adenomatoses, types I and II
- Inappropriate secondary hyperparathyroidism (renal failure)
- Hyperthyroidism
- Hypoadrenalism

Drugs
- Vitamin D intoxication
- Thiazides
- Calcium
  - Milk alkali syndrome
  - Dialysis

Granulomatous Disorders
- Sarcoidosis
- Tuberculosis
- Berylliosis

Pediatric Disorders
- Infantile hypercalcemia
- Hypophosphatasia

Immobilization
- Paget's disease
- Young patients

TABLE 1.—*Hormonal Regulation of Calcium and Skeletal Metabolism. The Effect of Each of the Calcitropic Hormones on Calcium (Ca^{++}) and Phosphate ($PO_4^{=}$) at the Three Critical Organ Systems and the Resulting Blood Concentrations Are Shown*

	Gastrointestinal Absorption		*Net Bone Mobilization*		*Renal Clearance*		*Blood Concentration*	
	Ca^{++}	$PO_4^{=}$	Ca^{++}	$PO_4^{=}$	Ca^{++}	$PO_4^{=}$	Ca^{++}	$PO_4^{=}$
PTH	I	I	I	I	D	I	I	D
CT	D	D	D	D	I	I	D	D
Vitamin D	I	I	D/I	D/I	D	D	I	I

CT = calcitonin
D = decreased
D = decreased, not firmly established
D/I = decreased or increased, not firmly established
I = increased
I = increased, not firmly established
PTH = parathyroid hormone

ectopic and glandular PTH and that these structural differences allow clinical distinctions to be made between ectopic and glandular PTH overproduction with radioimmunoassay and ancillary procedures.[21] Other laboratories have found only a small incidence of ectopic hyperparathyroidism in the differential diagnosis of the hypercalcemia of malignancy.[22] These laboratories emphasize that there may be other humoral factors associated with malignancy that resorb bone and produce hypercalcemia. Several such factors have been described in experimental studies. They include prostaglandins, osteoclastic activation factor (OAF) and other as yet uncharacterized substances.[23,24] The ultimate resolution of the etiological importance of parathyroid hormone and other bone resorbing factors in the hypercalcemia of malignancy will be of great clinical importance in diagnosis and management.

TABLE 3.—*Classification of Nephrolithiasis*

Normocalciuric
Hypercalciuric
Idiopathic
Resorptive
Absorptive
Calciuric

Nephrolithiasis

There has been increased understanding of the several pathogenetic mechanisms that can be involved in the development of calcium-containing renal stones (Table 3). This has resulted in more rational management of affected patients. The association of primary hyperparathyroidism with hypercalciuria and nephrolithiasis is well-known (resorptive hypercalciuria) and in these patients, treatment of the nephrolithiasis is surgical treatment of the hyperparathyroidism.[1] However, evi-

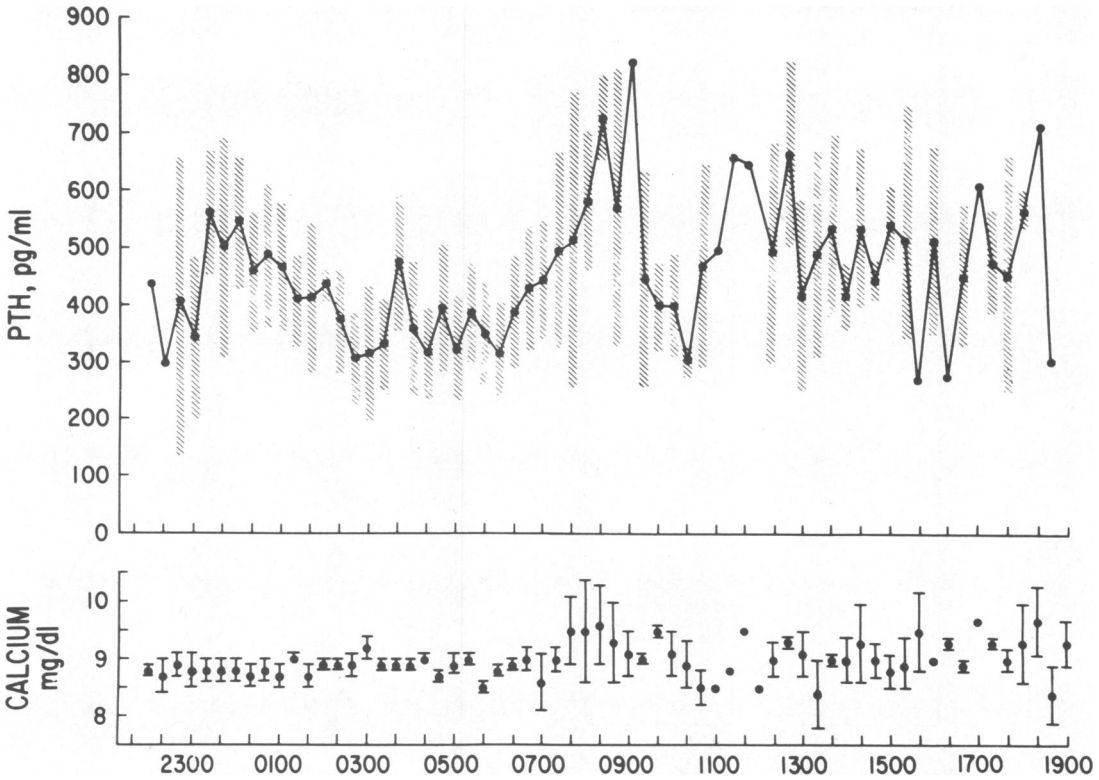


Figure 1.—Summary of the changes in plasma parathyroid hormone (PTH) and calcium in ten normal subjects obtained by frequent blood sampling through an indwelling catheter during continuous studies of up to 36 hours duration. The mean data were derived by dividing each hour into 20-minute segments and averaging the plasma PTH and calcium for each of the subjects during each of the 20-minute segments. Despite the fact that such data reduction tends to minimize and even obscure the changes seen in individual subjects it is evident that PTH concentrations, and less so calcium levels, change in an episodic or pulsatile manner. If the individual samples were normalized in a less arbitrary fashion and to a more relevant physiological measurement (such as, for example, electroencephalogram (EEG) changes during sleep), it is likely that a different pattern, but still pulsatile, would have resulted for PTH and calcium. The shaded areas and the bars represent the standard error for the indicated mean of each of the determinations.

dence has been presented recently to indicate that hyperparathyroidism in some patients with hypercalciuria may be a secondary rather than a primary phenomenon.[25] These patients have a primary renal hypercalciuria which results in calcium loss. To compensate for this loss, there is an increased secretion of parathyroid hormone which decreases the renal clearance of calcium. There is disagreement as to whether renal hypercalciuria and secondary hyperparathyroidism is a rare or common cause of nephrolithiasis and studies are in progress to establish the epidemiological significance of this disorder.[26] Controversies about incidence notwithstanding, the establishment of the presence of renal hypercalciuria for a given patient is therapeutically important. A patient with kidney stones who fits the diagnostic criteria established for renal hypercalciuria is a candidate for thiazide treatment since thiazides have been shown to decrease the renal calcium loss in such patients.[25]

Absorptive hypercalciuria is another clinical entity in the differential diagnosis of nephrolithiasis which has therapeutic significance. In contrast to a patient with primary hyperparathyroidism whose hypercalciuria results from the calcium release from bone by its increased resorption, the hypercalciuria in patients, usually males, with this form of nephrolithiasis results from the gastrointestinal absorption of an abnormal amount of dietary calcium (absorptive hypercalciuria).[27] Accordingly, in contrast to patients with renal hypercalciuria, rational treatment of these patients dictates a low-calcium diet.[28]

Despite this increased understanding of the pathogenesis of hypercalciuria and nephrolithiasis, many patients cannot be fit into the diagnostic categories of absorptive, resorptive or renal hy-

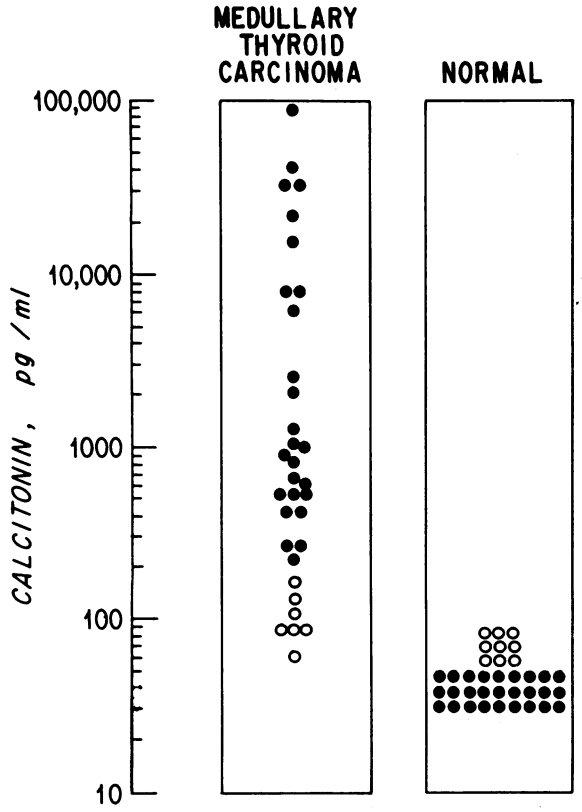


Figure 2.—Basal plasma calcitonin measurements in 33 subjects with histologically proved medullary thyroid carcinoma and in 36 normal subjects. At left (closed circles), patients with elevated basal concentrations of calcitonin; at right (closed circles), normal patients with undetectable concentrations of calcitonin. Some patients with thyroid tumors (open circles, at left) had basal calcitonin levels that could not be clearly distinguished from some normal subjects (open circles, at right). (Reproduced with permission from: Deftos LJ: Radio immunoassay for calcitonin in medullary thyroid carcinoma. JAMA 227:403-406, Jan 28, 1974. Copyright 1974, American Medical Association.)

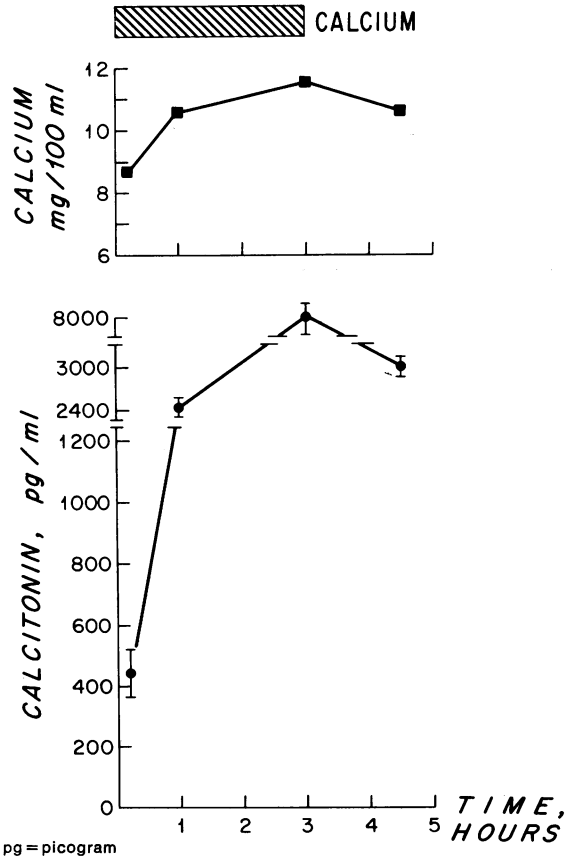


Figure 3.—Stimulatory effect of calcium (shaded area) infusion (12 mg per kg of body weight every three hours) on plasma calcitonin in a patient with medullary thyroid carcinoma (see Figures 4 and 5).

percalciuria.[1] Furthermore, many patients with calcium-containing renal stones do not have easily demonstrable hypercalciuria. Many of these previously-mentioned forms of therapy—dietary restriction of calcium, thiazide therapy, parathyroid surgical procedures—along with phosphate therapy, have been tried in such patients with varying degrees of success and newer forms of treatment are being introduced.[27,28] The intermittent nature of the nephrolithiasis makes it difficult to evaluate the effects of therapy. Although regimens that are apparently successful and do not harm the patient may be continued, a reasonably prudent regimen for all patients with hypercalciuria should include adequate hydration. The patients should be encouraged to drink as much (calcium-free) fluid as is manageable for them. Postprandial fluids are especially important and dehydration should be avoided.

Asymptomatic and Normocalcemic Hyperparathyroidism

The patient with the classical picture of hyperparathyroidism—significant hypercalcemia, bone symptoms, and osteitis fibrosa cystica and recurrent nephrolithiasis—is no longer commonly seen by physicians. Clinical and fundamental progress have greatly modified the clinical presentation of contemporary patients with hyperparathyroidism.[29] The progress has been in a better understanding of the gross as well as subtle manifestations of the illness and the greater availability of diagnostic procedures. A great impact has been made by the increased availability, especially as a part of screening procedures, of calcium determinations. More recently, direct PTH measurements by radioimmunoassay are now available to most physicians.[30] This progress has resulted in delineation of the syndromes of asymptomatic hyperparathyroidism and normocalcemic hyperparathyroidism. Close scrutinity shows that these appellations are probably misnomers for the large part, but they emphasize the evolution of the clinical presentation of primary hyperparathyroidism.

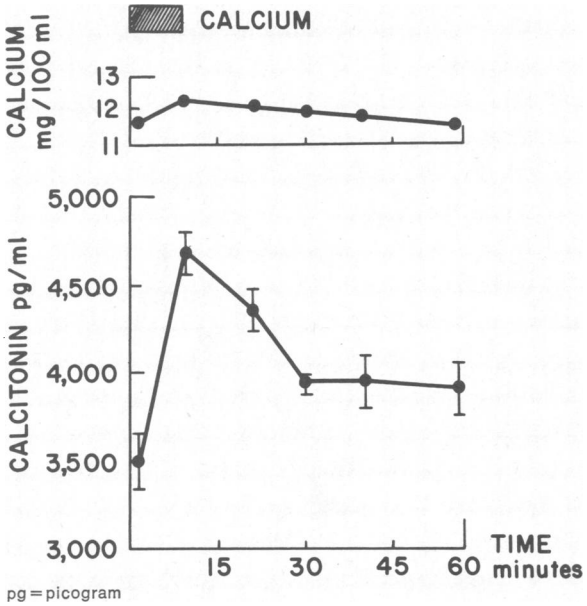


Figure 4.—Stimulatory effect of a short calcium (150 mg) infusion (shaded area) on plasma calcitonin in medullary thyroid carcinoma. The mean calcitonin and calcium changes for seven patients are shown. Bars represent standard errors (see Figures 3 and 5).

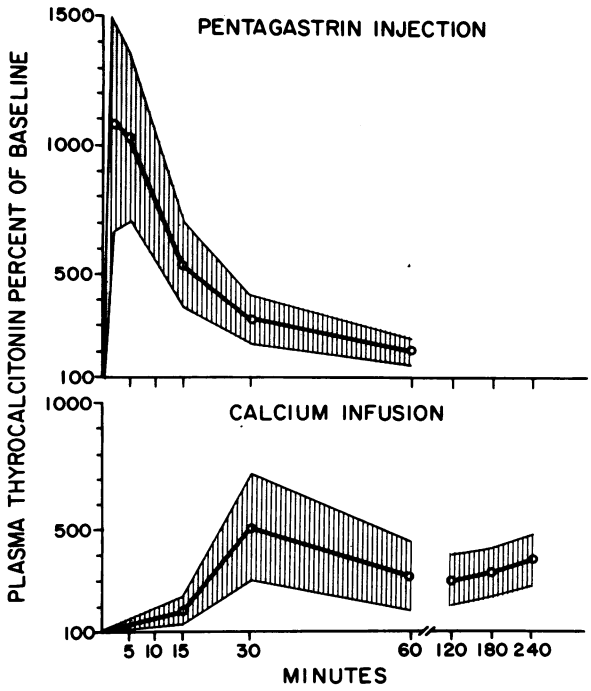
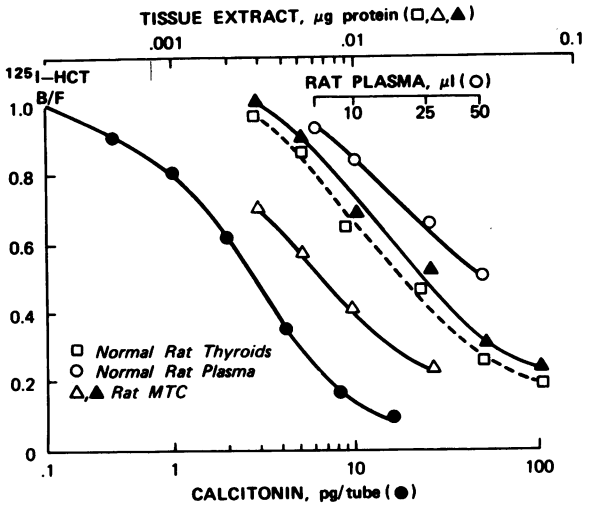


Figure 5.—Combined responses of seven patients with elevated baseline levels of plasma thyrocalcitonin (TCT) to pentagastrin injection and calcium infusion. Each patient received both tests on separate days wih pentagastrin injection being the initial test in four of the patients and calcium infusion being the initial test in three of the patients. Responses are expressed as the percent increase in immunoreactive TCT above initial baseline levels. Open circles and solid lines represent the mean responses and the shaded areas indicate the range of the standard errors. (Reproduced with permission from the authors and publisher from: Hennessy JF, Wells SA Jr, Ontjes DA, et al: A comparison of pentagastrin injection and calcium infusion as provocative agents for the detection of medullary carcinoma of the thyroid. J Clin Endocrinol Metab 39:487-495, 1974.)



^{125}I-HCT = human calcitonin MTC = medullary thyroid carcinoma
B/F = bound/free

Figure 6.—Measurement by radioimmunoassay of the calcitonin in peripheral rat plasma (during induced hypercalcemia), normal rat thyroid and rat medullary thyroid carcinoma (MTC). The two tumors represented are third and fourth transplantation generations, respectively (see references 60, 61).

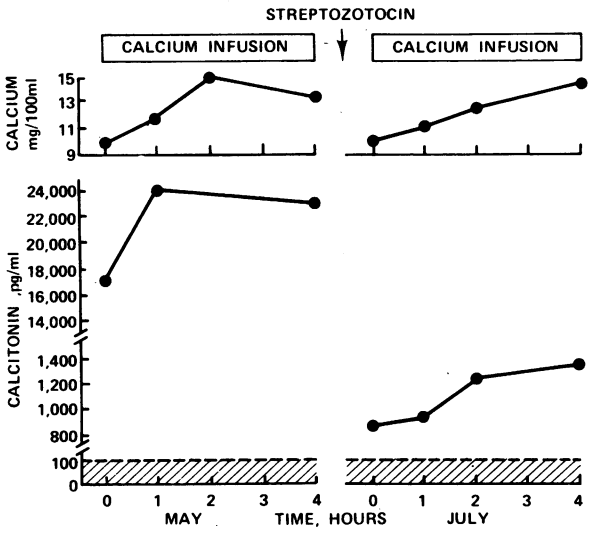


Figure 8.—Ectopic calcitonin production by an islet cell carcinoma of the pancreas. The tumor cells were shown to contain calcitonin by an immunoperoxidase procedure. Calcium infusion (15 mg per kg of body weight every three hours) stimulated calcitonin secretion by the tumor before and after streptozotocin therapy. There was a pronounced decrease in plasma calcitonin following streptozotocin therapy.

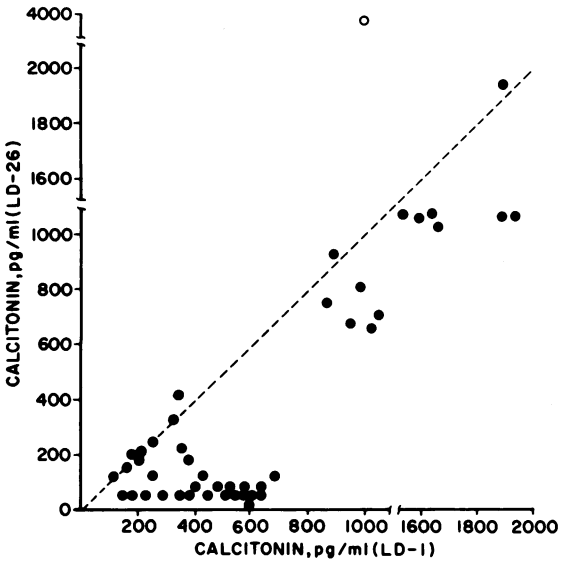
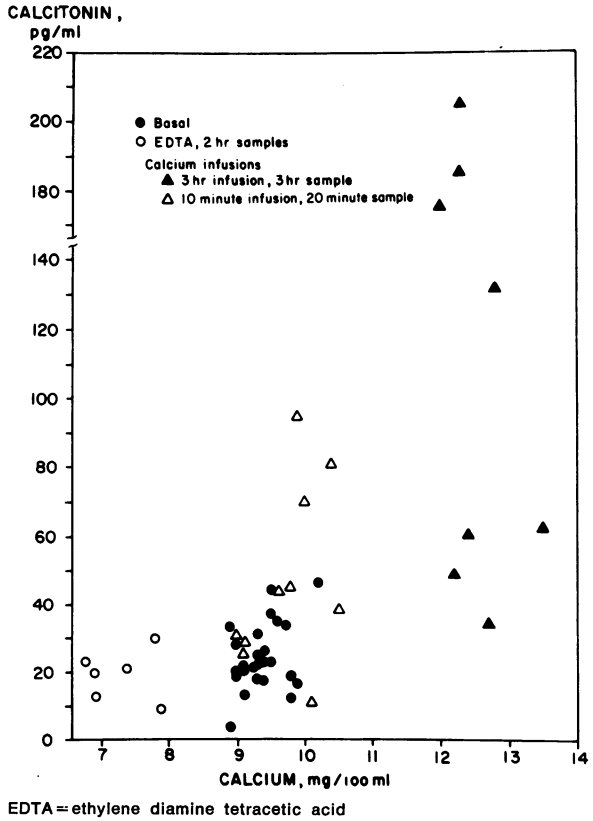


Figure 7.—Stimultaneous determination using two antisera (LD-1 and LD-26) of calcitonin in 44 plasma samples from 13 patients with medullary thyroid carcinoma (●), and one patient with a calcitonin-producing islet cell carcinoma of the pancreas (o). LD-1 gives a generally greater (or equal) estimate of calcitonin concentration in all of the samples than does LD-26 except for the patient with the pancreatic tumor and ectopic calcitonin production (o). Dashed line represents the relationship between the two calcitonin measurements which would exist if both of the antisera give indistinguishable results. (Assay limits 100 picograms per ml.)



EDTA = ethylene diamine tetracetic acid

Figure 9.—Immunoassayable calcitonin concentrations in normal subjects during the basal state (●) and during functional tests of hormone secretion (o, △, ▲).

TABLE 4.—*Principal Feature of Multiple Endocrine Adenomatosis*

TYPE II	
Medullary thyroid carcinoma	Hyperparathyroidism
Pheochromocytoma	Mucosal neuromata

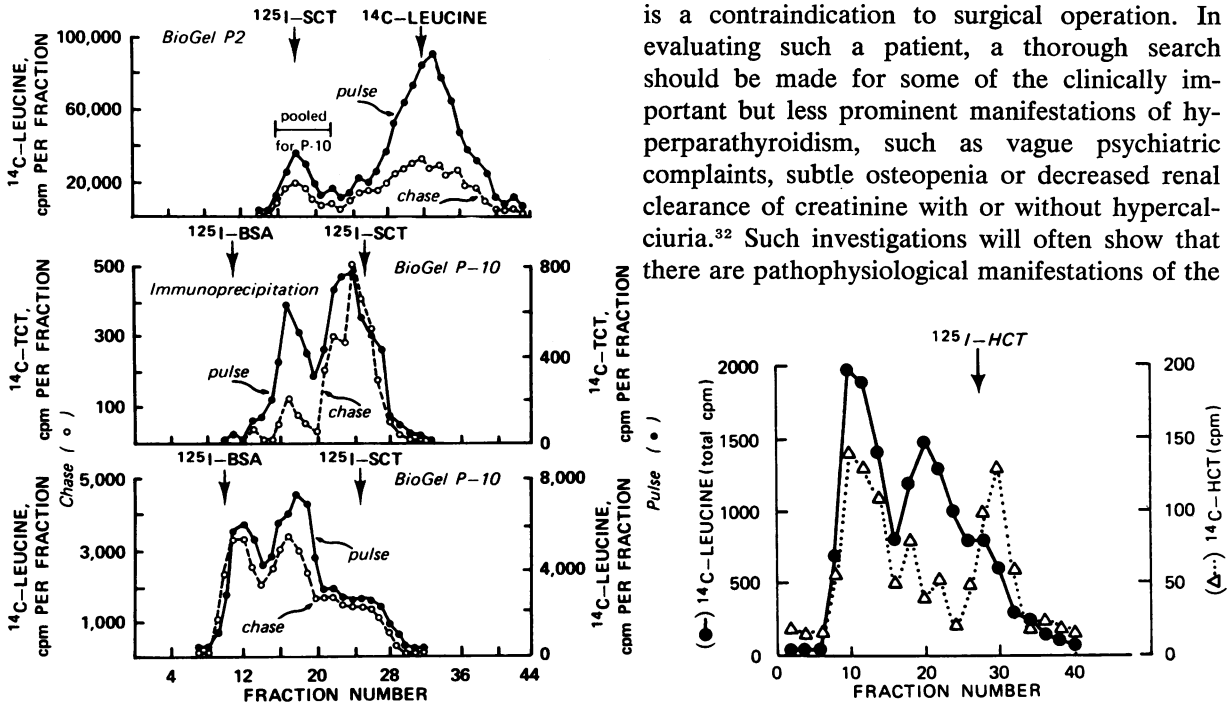
TABLE 5.—*Malignancies Associated with Calcitonin Production**

Medullary thyroid carcinoma	Carcinomas
Carcinoids	Maxillary antrum
Pheochromocytomas	Tongue
Melanoma	Pharynx
Pancreatic islet cell carcinoma	Parotid
Lymphoma	Tonsil
Seminoma	Prostate
Liposarcoma	Ovary
Astrocytoma	Rectum
Carcinoid Tumor	Uterus
Bronchial	Bladder
Intestinal	Stomach
Gastric	Cervix
Hodgkin's disease	Breast
	Lung

*Prepared from references 63-67 and authors' experience.

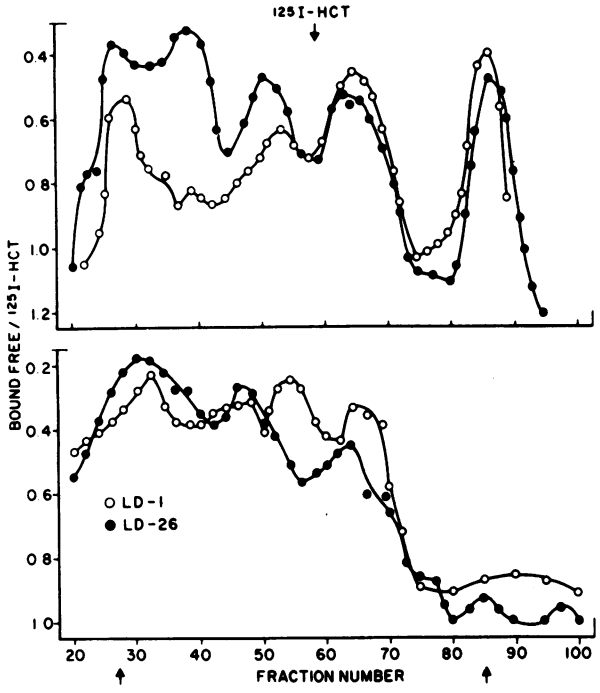
Asymptomatic Hyperparathyroidism

The clinical situation of asymptomatic hyperparathyroidism occurs when a patient is discovered to have a blood calcium level that is elevated, usually minimally, during a screening panel of blood chemistries. Further evaluation—such as x-ray studies (on industrial film) of the hands and clavicles (areas that are most sensitive radiographically to an excess of parathyroid hormone), blood PTH and phosphate determination, and lack of evidence for any other cause of the hypercalcemia—establishes the presence of hyperparathyroidism. But the diagnosis is made so early in the course of the illness that the patient is apparently asymptomatic. This situation presents a physician with a therapeutic dilemma—should he recommend surgical operation or follow the course of the patient? A prospective study is in progress to attempt to answer this question.[31] Until conclusive data are compiled, it is probably prudent to operate in most patients, unless there is a contraindication to surgical operation. In evaluating such a patient, a thorough search should be made for some of the clinically important but less prominent manifestations of hyperparathyroidism, such as vague psychiatric complaints, subtle osteopenia or decreased renal clearance of creatinine with or without hypercalciuria.[32] Such investigations will often show that there are pathophysiological manifestations of the



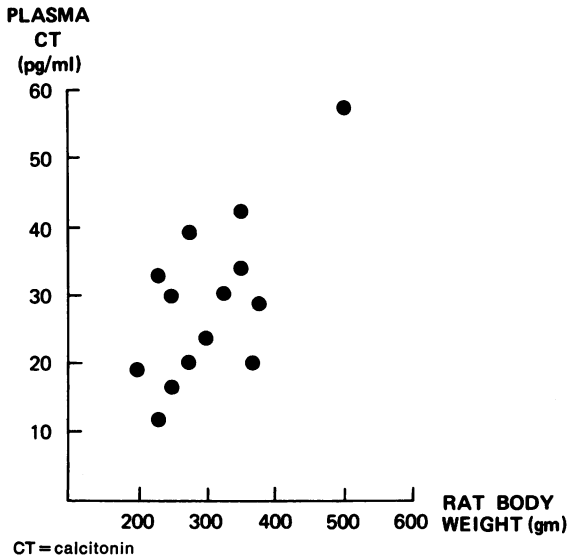
^{14}C-TCT = trout calcitonin
^{125}I-BSA = bovine serum albumin
μc = microcurie
^{125}I-SCT = salmon calcitonin
^{125}I-HCT = human calcitonin
cpm = counts per minute
C-cell = calcitonin cell

Figure 10.—Left Panel, Gel chromatography of acid soluble C-cell proteins obtained from pulse-chase experiments. After 14-hour preincubation, duplicate tubes of trout C-cell suspensions (10^6 cells/tube) were labelled with [^{14}C] leucine (7.5 μc/ml) for five hours. At this time 0.10 ml of 50 mM [^{12}C] leucine in Hank's salt solution was added to the "chase" tube, while the "pulse" tube received 0.10 ml of Hank's salt solution containing no leucine. Incubations were continued for an additional eight hours before homogenization and extraction of acid-soluble proteins. The pulse (•) and chase (o) samples were separately chromatographed on Bio Gel® P-2 and total [^{14}C] radioactivity of each column fraction was determined **(top panel).** The excluded volume from the P-2 column was then chromatographed on Bio-Gel P-10 and total [^{14}C] radioactivity **(bottom panel)** and immunoprecipitable, radiolabelled trout calcitonin ([^{14}C]TCT) **(middle panel)** was determined for each fraction. The **Right Panel** shows similar findings for monolayer tissue cultures of calcitonin-producing cells derived from medullary carcinomas of the thyroid.



^{125}I-HCT = human calcitonin

Figure 11.—Gel (Bio Gel® P-30) filtration pattern of immunoreactivity in the plasma calcitonin from a patient with medullary thyroid carcinoma **(bottom)** and islet cell carcinoma of the pancreas **(top)** as measured by two anticalcitonin antisera, LD-1 and LD-26. The thyroidal **(bottom)** and nonthyroidal **(top)** calcitonin have different elution patterns. In addition, within each sample the two different antisera also yield different elution patterns of immunoreactivity. Arrows at bottom define void and salt volumes of column, respectively. Elution position of labelled calcitonin is also shown by arrow.



CT = calcitonin

Figure 12.—Immunoassayable calcitonin in the peripheral plasma of Wistar rats of varying weight (age).

hyperparathyroidism present and therefore provide a clear indication for surgical operation. But, the final judgment must be made by considering all of the clinical features in the patient.

Normocalcemic Hyperparathyroidism

Although similar in some respects, the case of a patient with normocalcemic hyperparathyroidism is likely to be the obverse in many ways to that of a patient with asymptomatic hyperparathyroidism. A common presentation is a patient who has repeated episodes of renal stones which are refractory to treatment. Most calcium determinations are within normal limits but the patient comes to surgery, the decision perhaps supported by an elevated plasma PTH, where abnormal parathyroid tissue may or may not be found.[33,34] While it is possible that some cases of normocalcemic hyperparathyroidism exist, it is equally likely that they are rare and that alternative explanations exist for the clinical course. In many of the cases of reported normocalcemic hyperparathyroidism, the patients had calcium levels that were continually near or at the upper limit of normal or even intermittently above the normal range.[33-35] The normal range of blood calcium is subject to age- and sex-related constraints which are not usually applied routinely by most clinical laboratories. The total blood calcium level is also subject to artifacts introduced by venous stasis during blood drawing and changes in blood protein concentrations.[1] Limited comparisons of total calcium measurements (usually by atomic absorption spectrophotometry) and ionic calcium measurements have shown the superiority of the ionic method for identifying abnormal values.[36] However, this procedure is not yet suitable for routine clinical application.[37]

All of these technical considerations would suggest that most patients who are diagnosed as having normocalcemic hyperparathyroidism actually have hyperparathyroidism with a minimally or intermittently elevated blood calcium level—or both. The identification of such patients is another result of the better appreciation of the manifestations of primary hyperparathyroidism and of its earlier diagnosis. Parenthetically, it is unlikely that normocalcemic hyperparathyroidism can produce hypercalciuria and nephrolithiasis. The hypercalciuria of hyperparathyroidism is due to the hypercalcemia which produces an increased filtered load of calcium. In fact, parathyroid hormone acts to *decrease* renal calcium clearance.

Therefore, in order to explain hypercalciuria in the face of a normal total calcium concentration and an elevated PTH, one would have to postulate that there is an increase in the filtered load of calcium without an increase in total blood calcium. Future studies of the importance of endogenous calcitonin secretion in nephrolithiasis may help to clarify the importance of this hormone in pathogenesis and it is of course possible that some of these patients have renal hypercalciuria and secondary hyperparathyroidism.[25,33]

Osteoporosis

Osteoporosis is a common disease that continues to be frustrating to physicians. No significant advances have been made in its treatment, and its pathogenesis remains obscure.[1] Some recent studies suggest that parathyroid gland dysfunction may play a role in a small percentage of patients with osteoporosis but the data are conflicting.[38,39] However, parathyroid hormone determination may be of some clinical value in osteoporotic patients. An increase in hormone concentration may offer a clue to the presence of complicating osteomalacia. If the presence of osteomalacia can be confirmed, the osteomalacic component of the osteopenic state could then be treated with vitamin D.

Calcitonin

Calcitonin can be considered to be in many ways the physiological antagonist of parathyroid hormone.[1] The biochemistry and biology of this hormone and its usefulness in the treatment of some hypercalcemic states are thoroughly considered in several reviews.[1,4,5,40,43] This discussion will focus on the importance of calcitonin in the treatment of Paget's disease and in the diagnosis of medullary thyroid carcinoma and other neoplastic disorders.

Paget's Disease

Significant progress has been made in the management of patients with Paget's disease.[1,42] Several forms of therapy are now available for effective treatment of the illness.[1] The regimen that seems to offer the greatest therapeutic effect in combination with the fewest untoward effects is the use of calcitonin. Clinical trials with calcitonin are now over and the salmon form of the drug is commercially available as Calcimar®. Calcitonin acts to reverse the primary pathological defect in Paget's disease—increased bone resorption. Treatment with calcitonin reverses the increased plasma alkaline phosphatase and the increased urinary hydroxyproline and has been reported to produce histological and x-ray changes in bone toward normal.[44] Not all patients with Paget's disease who are treated with calcitonin respond to the drug. Furthermore, some patients respond only partially and some patients become refractory to its effects after several months of therapy. The development of antibodies to salmon calcitonin may account for some treatment failures.[1,42] The availability of human calcitonin may be useful in some patients. It has also been suggested that chronic calcitonin administration may result in secondary hyperparathyroidism.[45] However, contrary reports have also appeared and the resolution of this controversy awaits further study.[46] Calcitonin is relatively safe with its major side effect being nausea. A disadvantage of the drug is that it has to be taken parenterally. But, most patients receive sufficient symptomatic benefits from its administration that they readily learn to administer calcitonin to themselves.

Medullary Thyroid Carcinoma

It has become well-established during the past several years that plasma calcitonin measurement by radioimmunoassay offers an accurate and reliable test for the diagnosis of medullary thyroid carcinoma.[47-53] This tumor is a malignancy of the calcitonin-producing cells of the thyroid gland.[1] It can occur sporadically or in a familial pattern which is transmitted with an autosomal dominant inheritance pattern.[54] As a familial tumor it is part of one of the multiple endocrine adenomatoses, MEA Type II (Table 4).

The incidence of medullary thyroid carcinoma has not been carefully established since its existence as a distinct pathological entity has only been appreciated for one decade. Although the tumor is now being diagnosed with increased frequency, it is not likely to be a common tumor in a general epidemiological sense. However, its general epidemiological importance is far outweighed by the dominant inheritance pattern of the familial form of the tumor. Once the diagnosis is made in a given patient, a careful family search is likely to turn up affected relatives. This becomes a therapeutically important consideration since the application of the calcitonin assay can establish the presence of the tumor very early in its course[1,55,56]—so early that there may be no

clinical manifestations of the tumor and it may be confined to the thyroid and, therefore, curable by thyroidectomy. This can often be done by the relatively simple measurement of calcitonin by radioimmunoassay in a peripheral plasma sample of the patient. In most patients with medullary thyroid carcinoma, the basal level of the hormone will be diagnostically elevated. However, a significant percentage of patients may have basal levels of calcitonin which are indistinguishable from normal (Figure 2). In these patients, provocative tests of calcitonin secretion may be used to establish the diagnosis. Three procedures are currently being used for provocative testing: long (two to four hour) calcium infusion, gastrin infusion and short (ten minute) calcium infusion.[48,50,56,57] The long calcium infusion has been most extensively used and experience with it has established its reliability (Figure 3). The shortened (10 minute) calcium infusion also seems reliable but experience with it is less extensive (Figure 4). The short infusion is more convenient and less likely to cause any untoward consequences of induced hypercalcemia.

Gastrin also appears to be a reliable provocative test for calcitonin secretion (Figure 5). Its disadvantages are that its administration produces chest discomfort and that it is still considered an experimental agent for this indication and, therefore, is not as readily available. The immunoassay can also be used in conjunction with selective venous catheterization for diagnostic purposes.[58] This procedure can help to define the extent and location of the malignancy and can perhaps lead to even earlier diagnosis than is offered by provocative testing.

The recent development of an immunoassay for rat calcitonin[59-61] and the identification of a rat form of medullary thyroid carcinoma[60-62] will provide an experimental model for the systematic study of this tumor (Figure 6).

Ectopic Calcitonin Production

As important as the calcitonin immunoassay has become in the early and reliable diagnosis of medullary thyroid carcinoma, recent observations indicate that the clinical value of this procedure may become even more important. It has been observed during the last several years that tumors other than medullary thyroid carcinoma may be associated with excess calcitonin production.[63-67] It was first considered that this represented a common embryological origin for the calcitonin-producing cells, since these tumors—like medullary thyroid carcinoma—were usually of neural crest origin.[63] However, the large variety of tumors that have been now reported in association with elevated plasma calcitonin are not consistent with this explanation (Table 5). In fact, there is some evidence to suggest that the nonthyroidal calcitonin produced by some tumors is immunochemically distinct from thyroidal (medullary thyroid carcinoma) calcitonin (Figure 7).

Not all tumors associated with hypercalcitoninism have been shown to produce excess calcitonin; in fact this has only been directly shown for a few (Figure 8). Therefore, other explanations may exist for this hypercalcitoninism of malignancy. The tumor may be secreting a calcitonin secretagogue or it may have metastasized to bone where it is stimulating the secretion of thyroidal calcitonin by (1) destroying bone and producing an autoinfusion of calcium or (2) causing the release of an endogenous bone factor which stimulates the secretion of calcitonin in order to counteract the increased resorption produced by the metastases. Whichever of these explanations pertains, an increased plasma calcitonin can be the signal for a variety of metastatic disorders. It is to be hoped that hypercalcitoninism will be as early a signal for these other tumors as it has been for medullary thyroid carcinoma.

Calcitonin in Physiology and Pathophysiology

In contrast to the events that attend the discovery of many new hormones, the discovery of calcitonin was followed by an appreciation of its importance in pathology (medullary thyroid carcinoma) and pharmacology (treatment of Paget's disease and hypercalcemia) rather than its role in normal physiology. In fact, the role of calcitonin in normal physiology has not been well-defined. Progress in such studies was limited by the difficulties of measuring the low concentrations of this potent hormone which circulate in human plasma. However, improved assay techniques are now available for these experiments. Preliminary clinical studies indicate that circulating levels of calcitonin are responsive to pertubations of calcium and bone mineral homeostasis (Figure 9) and gastrointestinal physiology and that secondary as well as primary disorders of calcitonin secretion exist.[17,68-73] These studies indicate that the biosynthesis, secretion and metabolism of calcitonin may be as complicated as for

parathyroid hormone. A biosynthetic precursor (procalcitonin) for calcitonin has been identified (Figure 10) and multiple immunoreactive forms of the hormone have been shown in both human (Figure 11) and rat[60,74,75] plasma. There is even some evidence that calcitonin may have a biological role not directly related to bone mineral metabolism. And, the development of an immunoassay for rat calcitonin has already produced some unanticipated findings in this animal model for calcitonin physiology (Figure 12). These preliminary observations will serve as a framework for clinical and experimental studies conducted in the next several years to identify the physiological and pathophysiological significance of calcitonin.

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Prophylactic Antibiotics

One part of prophylactic antibiotics that is the biggest myth that has ever been perpetrated is the value of antimicrobial bowel prep. Every chapter that is written in standard American textbooks about surgical operation on the colon starts out with an erroneous, but well-intentioned, statement that all of the good things come as a result of the frequent use of antimicrobial bowel preparation with sulfa and neomycin and whatnot. You will remember that Edgar Poth's initial experiments with these drugs showed benefit only in a situation in which the blood supply to the bowel was impaired. Now, if you want to do your colon anastomosis with faulty blood supply, you can, but I think I can beat you any day of the week by using good blood supply. There is no place for intraluminal antimicrobial agents in surgical operation on the large intestine unless one is going to deal with impaired blood supply. Now, there is one clinical setting where we regularly do this and that is with patients who have aortic aneurysms resected in which we suspect or think that the inferior mesenteric artery is patent. That is an induced form of intestinal ischemia. And there are good data, largely from the Mayo Clinic, that show about a 4 percent incidence of clinical ischemic colitis if you do not use a bowel preparation, and that this largely disappears if you do. But for a person in whom colon resection is being done, bowel prep contributes nothing.

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