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Giles M. Robertson, Jr., M.D.

Edward W. Moore, M.D.

Virginia Commonwealth University, Medical College of Virginia

Donald M. Switz, M.D.

Glen W. Sizemore, M.D.

Herschel L. Estep, M.D.

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INADEQUATE PARATHYROID RESPONSE IN ACUTE PANCREATITIS

GILES M. ROBERTSON, JR., M.D., EDWARD W. MOORE, M.D., DONALD M. SWITZ, M.D.,
GLEN W. SIZEMORE, M.D., AND HERSCHEL L. ESTEP, M.D.

Abstract We studied nine consecutive hypocalcemic patients with acute pancreatitis to elucidate the mechanism of hypocalcemia. Mean serum ionized calcium, 0.97 mM, was below the normal mean of 1.16 mM ($P < 0.001$). Seven of eight patients tested had normal parathyroid hormone levels. All responded to parenteral parathyroid extract by increasing serum ionized calcium and urinary cyclic AMP, indicating parathyroid-hormone-responsive target organs. Calcitonin and glucagon concentrations were increased above normal in some patients, but there was no rela-

tion with serum ionized calcium. Parenteral glucagon had no significant effect on serum ionized calcium or calcitonin concentrations. These findings suggest that neither glucagon nor calcitonin was primarily responsible for the hypocalcemia, which did not produce expected increases in serum parathyroid hormone concentrations. Relative parathyroid insufficiency may account for the persistent hypocalcemia frequently observed in patients with acute pancreatitis. (*N Engl J Med* 294:512-516, 1976)

HYPICALCEMIA is frequently observed in patients with acute pancreatitis. Edmondson¹ called attention to this complication; in his series of 50 patients with hemorrhagic pancreatitis² 36 patients (72 per cent) had hypocalcemia, and all patients died who had a serum calcium below 7 mg per 100 ml. In 102 sequential episodes of acute pancreatitis in the Richmond Veterans Administration Hospital, 35 attacks (34 per cent) were associated with a serum calcium below 9 mg per 100 ml.³

The cause of hypocalcemia in acute pancreatitis has not been elucidated. Edmondson¹ proposed that the hypocalcemia is due to calcium deposition in and around the necrotic pancreatic tissue and estimated intra-abdominal calcium content to be 2.0 and 1.7 g in two patients so studied. Although deposition of calcium in the abdominal cavity or at other sites may occur in pancreatitis, this is not a likely explanation for the prolonged hypocalcemia, since induced hypocalcemia is normally followed by an increase in parathyroid hormone concentration and in serum calcium to normal levels within 12 hours.⁴⁻⁷

Other possible causes of hypocalcemia include increased secretion of glucagon or calcitonin (gastrin-stimulated), both of which have hypocalcemic effects.⁸⁻¹⁴ Finally, relative hypoparathyroidism, magnesium deficiency, and target-organ unresponsiveness to parathyroid hormone could each be a factor in initiating or maintaining the hypocalcemia. The present studies were undertaken to test the hypothesis that one or more of these mechanisms may be involved in the pathogenesis of the hypocalcemia that complicates acute pancreatitis.

MATERIALS AND METHODS

All patients entering the hospital with a clinical diagnosis of acute pancreatitis were asked to participate if their illness fulfilled the following criteria: the clinical diagnosis of pancreatitis was established by history, physical examination, and serum amylase greater than 200 Somogyi units per 100 ml; the creatinine was less than 2 mg per 100 ml on the day of the study; there were no signs of

From the Department of Medicine, Medical College of Virginia, the Veterans Administration Hospital, Richmond, VA, and the Department of Medicine, Mayo Clinic, Rochester, MN (address reprint requests to Dr. Moore at Box 908, MCV Station, Medical College of Virginia, Richmond, VA 23298).

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liver disease; and systolic blood pressure was above 100 mm Hg. No attempt was made to study patients with hypocalcemia selectively. Patient approval was obtained, and informed consent was given.

Studies were performed in nine consecutive patients whose clinical data are given in Tables 1 and 2. Note that serum magnesium, glucose, gastrin and tubular reabsorption of phosphate were all normal. All patients were men with chronic alcoholism except Case 2, a woman with a choledochal cyst. Serum amylase levels were elevated on the day of study in all patients except Case 4, who had hemorrhagic ascites and continuing symptoms on the day of the study and an amylase level of 2240 Somogyi units five days previously. No other patient had overt hemorrhagic pancreatitis.

The initial concentrations of circulating immunoreactive calcitonin, gastrin, glucagon and parathyroid hormone were measured. Initial calcitonin and parathyroid hormone values are not available for Case 1. Target-organ responsiveness to exogenous parathyroid hormone was assessed by changes in the following indexes: serum ionized and total calcium; urinary cyclic adenosine 3'5' monophosphate (cyclic AMP) excretion; and phosphate excretion. Possible magnesium deficiency was estimated by measurement of serum total magnesium. Glucagon was administered to all patients to determine if it could be responsible for the hypocalcemia by stimulating calcitonin secretion^{12,13} or by its own hypocalcemic properties.¹⁴

On the day of the study, sodium chloride (0.15 M) was infused intravenously at a rate of 200 ml per hour. Initial blood and urine samples were collected, and then 200 units of bovine parathyroid extract (Eli Lilly lot 6TN67C) was given intravenously. Two hours later, 1 mg of glucagon (Eli Lilly lot 6WE16B) was given. In the

Table 1. Summary of Clinical Laboratory Data.

CASE No.	AGE	HOSPITAL DAY OF STUDY	GUARDING/ ILEUS	SERUM AMYLASE*	URINE AMYLASE*	WHITE-CELL COUNT*	COMPLICATIONS
	yr			SU/100 ml	SU/hr	$\times 10^3/mm^3$	
1	55	5	-/-	457	1260	27.5	Pneumonia, sepsis, stupor
2	19	2	+/-	1210	4116	16.0	Choledochal cyst
3	56	2	+/-	253	373	4.5	None
4	21	6	+/-	2240	5187	23.5	Hemorrhagic ascites
5	58	2	+/-	525	163	9.9	None
6	54	2	-/+	1680	1470	13.0	None
7	59	2	-/-	1050	742	17.8	Urinary-tract infection
8	52	2	+/+	1320	1325	9.6	Acute fatty liver
9	35	4	+/-	905	600	11.8	None

*Laboratory values indicated are highest value recorded during hospitalization.
*Somogyi units.

Table 2. Summary of Basal Laboratory Determinations.

CASE No.	SERUM AMYLASE	URINARY CYCLIC AMP	SERUM MAGNESIUM	SERUM ALBUMIN	URINARY TUBULAR REABSORPTION OF PHOSPHATE	SERUM GLUCOSE	SERUM PHOSPHORUS	SERUM GASTRIN
	Somogyi U /100 ml	μmoles/g of creatinine	meq/liter	g/100 ml	%	mg/100 ml	mg/100 ml	pg/ml
1	433	6.0	1.43	3.2	87	132	2.0	49
2	1210	6.3	2.10	4.7	92	100	2.5	196
3	233	7.3	2.53	3.4	94	90	3.4	53
4	75	5.4	2.80	3.3	94	100	1.8	46
5	202	9.3	2.14	3.5	87	84	2.1	88
6	855	8.3	1.80	4.3	70	79	1.6	74
7	735	11.0	1.47	2.7	92	115	1.8	44
8	304	6.6	1.90	4.6	79	104	3.1	64
9	240	11.0	1.70	3.0	97	108	3.3	127
Mean	476	7.9	1.99	3.6	88	101	2.4	82
SE	125	0.7	0.15	0.2	0.2	5	0.2	17
Normal mean	64	3.5	1.71	4.5	87.5	95	3.56	104
Normal range*	0-127	1.5-5.5	1.16-2.32	3.6-5.4	80-95	80-110	2.7-4.3	74-134
P value	<0.01	<0.001	NS†	<0.001	NS	NS	<0.001	NS

*95% confidence limit.

†Not significant.

first five patients, glucagon was given intramuscularly; when this step was found to be without apparent effects on serum ionized calcium or calcitonin concentration, an intravenous injection was employed in the last four patients. The first of five intramuscular injections of parathyroid extract, 200 units each, was given every four hours beginning two hours after the glucagon injection. Four hours after the last injection of parathyroid extract the study was terminated with the collection of serum samples. Blood was drawn without the use of a tourniquet at hourly intervals for four hours after time zero and at five, 15 and 30 minutes after glucagon administration. Urine was collected by indwelling catheter at hourly intervals for six hours. Urine samples were acidified with glacial acetic acid and aliquots frozen at -20°C .

All determinations were performed in duplicate. Serum and plasma samples were frozen at -20°C until analysis. Serum was re-equilibrated with carbon dioxide before measurement of ionized calcium by the Orion flow-through electrode as previously described.^{15,16} Cyclic AMP was determined by a protein-binding displacement radioassay.¹⁷ Pancreatic glucagon values were determined by radioimmunoassay using antibody 30K and methods provided by Dr. Roger Unger, University of Texas Health Science Center, Dallas, Texas. Serum gastrin, parathyroid hormone and plasma calcitonin were measured by radioimmunoassay.^{18,19} The calcitonin assay used a new anti-human calcitonin antiserum, G1701, that has major recognition for the region containing residues 11-28 of human calcitonin monomer. The highest calcitonin concentration measured in 34 normal adults in our laboratory is 87 pg per milliliter.

Total protein was determined by the biuret method,²⁰ albumin by paper electrophoresis, amylase by a modified Somogyi technic,²¹ total calcium and magnesium by titration,²² and phosphorus and creatinine by AutoAnalyzer methods. Statistical analysis was performed with Student's *t*-test.²³

The normal range for all laboratory tests had previously been determined in normal subjects in each respective laboratory performing the analyses. The normal range for calcitonin, glucagon and parathyroid hormone concentrations is defined as the range of observed values in normal subjects; in the remainder of the determinations the normal range is defined as the mean ± 2 standard deviations (95 per cent confidence limit).

RESULTS

In the nine consecutive patients with acute pancreatitis, ionized calcium was reduced in all patients, and the mean, 0.97 ± 0.02 mM was significantly ($P < 0.001$) below the

normal mean of 1.16 mM (Fig. 1). Mean serum total calcium, 8.68 ± 0.2 mg per 100 ml, was also significantly reduced below the normal mean of 9.88 mg per 100 ml ($P < 0.001$). In Cases 4 and 7, ionized calcium concentrations were reduced in the presence of normal total calcium concentrations.

Plasma calcitonin and glucagon levels are shown in Figure 2. It can be seen that six of eight patients tested had calcitonin levels above the highest normal concentration. In three patients, both calcitonin and glucagon levels were elevated. As shown in Figure 3, no relation could be demonstrated between ionized calcium and calcitonin concentrations.

To test the hypothesis that glucagon might reduce ionized calcium, either directly or by stimulating calcitonin secretion, glucagon was administered to all patients. Figure 4 shows the maximal measured change for each patient in ionized calcium and calcitonin after the intramuscular or in-

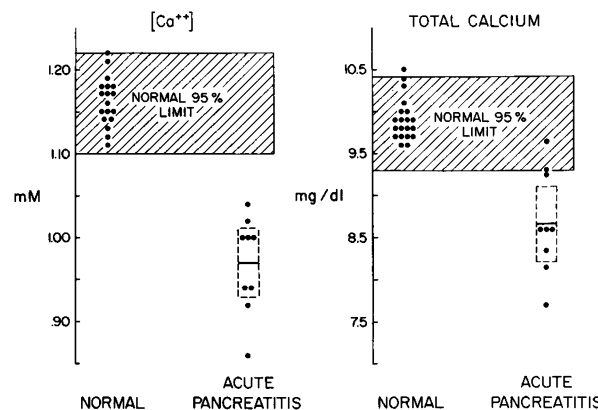


Figure 1. Serum Ionized Calcium $[\text{Ca}^{++}]$ and Total Calcium in Normal Subjects and in Patients with Acute Pancreatitis ($P < 0.001$).

The horizontal line and enclosed boxes represent the mean ± 2 S.E.

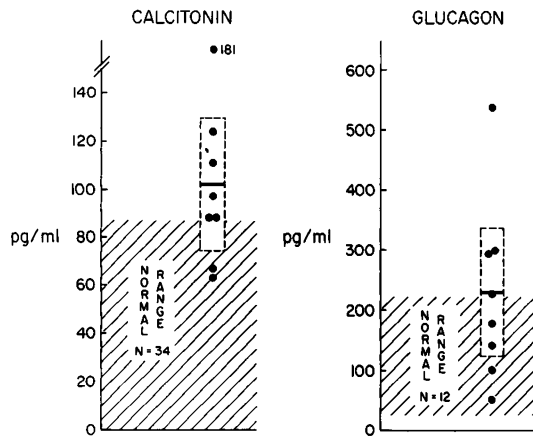


Figure 2. Plasma Calcitonin and Glucagon Concentrations in Patients with Acute Pancreatitis.
The concentration range in normal subjects is shown by the shading.

travenous administration of glucagon. No significant effect was obtained.

Plasma parathyroid hormone concentrations are shown in Figure 5. Patients with chronic hypocalcemia (malabsorption or osteomalacia) with serum total calcium values similar to those observed in the present patients are shown for comparison. It can be seen that serum parathyroid hormone concentrations were normal in seven of the eight patients with pancreatitis, but were elevated in most of the patients with comparable hypocalcemia without pancreatitis. Mean parathyroid hormone was significantly less in the patients with pancreatitis ($P < 0.01$).

Since serum ionized calcium was significantly reduced in our patients (Fig. 1), the finding of normal parathyroid hormone levels suggests the possibility of target-organ unresponsiveness to parathyroid hormone. This possibility was evaluated by administration of parathyroid extract. As

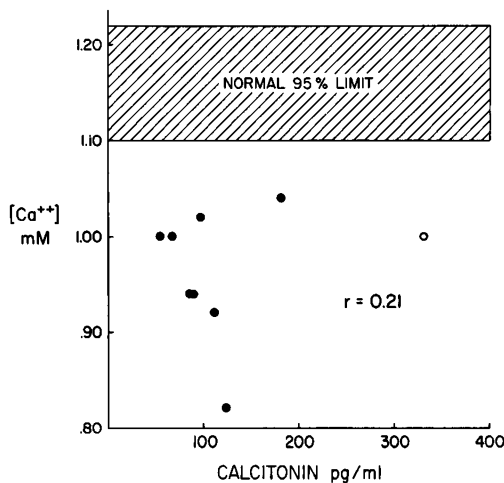


Figure 3. Relation of Ionized Calcium [Ca⁺⁺] to Plasma Calcitonin.

The open circle represents this relation in Case 1 on sample obtained four days after the day of study. Note lack of correlation indicated by the correlation coefficient of 0.21 ($P = 0.53$).

shown in Figure 6, intramuscular administration of 1200 U of parathyroid extract was followed by a significant ($P < 0.001$) increase in serum ionized calcium, an increase occurring in all patients. Similarly, 200 U of intravenous parathyroid extract resulted in a significant ($P < 0.001$) increase in urinary cyclic AMP excretion in all patients.

DISCUSSION

Hypocalcemia in patients with acute pancreatitis has been studied by means of two recent advances in the field of calcium metabolism: electrode measurement of serum ionized calcium — the biologically active species; and radioimmunoassay of parathyroid and other hormones (calcitonin, gastrin, and glucagon) that may influence serum calcium levels. The present studies have thus examined both the major biologic (ionized calcium) and immunologic (plasma parathyroid hormone) measures of parathyroid hormone activity.

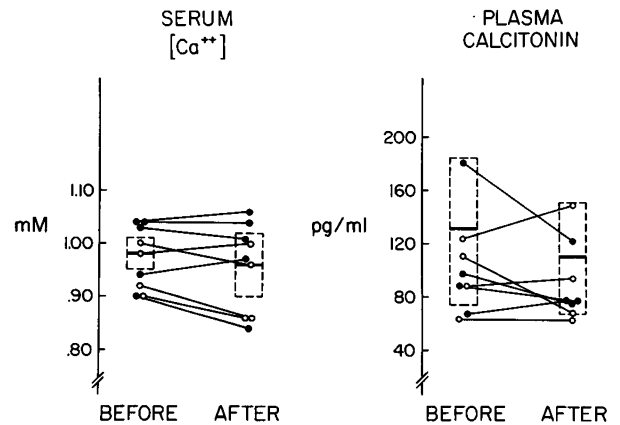


Figure 4. Effects of Glucagon Given Intramuscularly (●—●) or Intravenously (○—○) on Ionized Calcium [Ca⁺⁺] and Calcitonin.

The maximal change for each patient is shown. The horizontal line and enclosed boxes represent the mean \pm 2 S.E. Differences before and after glucagon are not significant.

The inter-relation between serum ionized calcium and parathyroid hormone concentrations is complex. Parathyroid hormone secretion is influenced by existing ionized calcium levels through a negative feedback mechanism. Acute elevations in ionized calcium decrease secretion and plasma of parathyroid hormone levels.²⁴⁻²⁶ Acute reduction of ambient calcium in vitro or plasma calcium in vivo leads to increased secretion^{24,25} and plasma levels of the hormone.^{4,5} In these acute experimental situations in normal man, there is an inverse relation between total calcium and parathyroid hormone concentrations.¹⁹ In contrast, a direct relation between ionized calcium and parathyroid hormone²⁷ or total calcium and parathyroid hormone¹⁹ has been observed in patients with hyperparathyroidism.

The data in Figure 1 clearly show that the major biologic indicator of parathyroid hormone activity, ionized calcium, is significantly decreased, whereas the data in Figure 5 indicate that the immunoreactive parathyroid hormone concentration was normal in seven of the eight patients tested. The significant decrease in serum calcium was thus not ac-

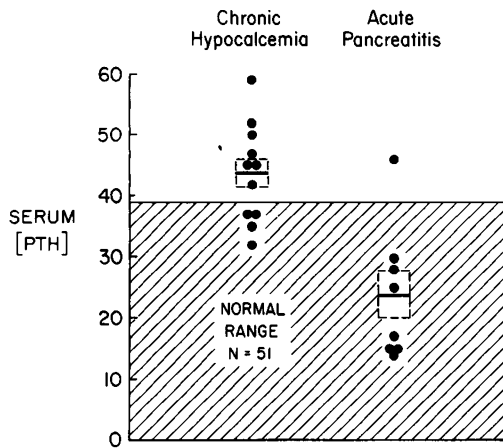


Figure 5. Parathyroid Hormone (PTH) Concentration in Patients with Chronic Hypocalcemia¹⁹ and Acute Pancreatitis. The measurements are made in microliter equivalents per milliliter. The horizontal line and enclosed boxes represent the mean \pm 2 S.E. The concentration range in normal subjects is shown by the shading.

accompanied by increased parathyroid hormone immunoreactivity. This observation is in marked contrast to the findings of Arnaud et al.,¹⁹ who reported an inverse relation between serum total calcium and parathyroid hormone concentration in normal and hypocalcemic subjects. Chronic hypocalcemia in their patients with malabsorption or osteomalacia (Fig. 5) was associated with a significant increase in parathyroid hormone levels. The hypocalcemia was comparable in both our patients and theirs, and the parathyroid hormone levels were measured in the same laboratory with the same assay. Because of the inverse relation between calcium and parathyroid hormone levels in hypocalcemic man, an increased parathyroid hormone concentration would have been predicted. Thus, the concentration in response to hypocalcemia was inadequate in our patients; these findings suggest that relative hypoparathyroidism

may be an important factor in the persistent hypocalcemia in patients with acute pancreatitis.

The cause of the relative hypoparathyroidism is not known, but at least three possibilities merit consideration. The first is that the relatively low serum parathyroid hormone values may reflect diminished secretion by the parathyroid cells. In this respect, magnesium may be of importance since decreased parathyroid hormone secretion has been observed in patients with magnesium depletion.²⁸ Although serum magnesium concentrations may not necessarily reflect total body magnesium, the finding of normal serum magnesium values in all of our patients suggests that magnesium deficiency was not the major factor responsible for the low parathyroid hormone levels. Secondly, it is conceivable that excessive circulating proteolytic activity in patients with pancreatitis directly affects the surface of the parathyroid cell, altering its secretion of parathyroid hormone in response to ionized calcium. Thirdly, excessive proteolytic activity could result in accelerated degradation of secreted parathyroid hormone, with loss of both biologic and immunologic activity. The antibody employed for measurement of parathyroid hormone in the present studies is reactive with the carboxy-terminal region of the molecule and has a positive correlation with biologic activity.²⁶ Since this fragment has a very long half-life (about 20 hours²⁹), excessive secretion and degradation might be expected to yield high immunoreactive parathyroid hormone levels. Thus, excessive turnover of the hormone is not a likely explanation of the observed decrease in biologic activity (ionized calcium) and relative decrease in serum parathyroid hormone unless proteolytic destruction of the parathyroid hormone molecule is so extensive that small, inactive fragments are present. Further studies are needed to assess this possibility. In any case, the result is relative hypoparathyroidism.

Condon³⁰ and Weir et al.³¹ have also measured parathyroid hormone concentrations in hypocalcemic patients with pancreatitis. In the former study 75 per cent of hypocalcemic patients had undetectable concentrations, and the authors considered hypoparathyroidism to be the cause of the hypocalcemia. In the latter study, three of eight hypocalcemic patients had undetectable concentrations of parathyroid hormone, suggesting relative hypoparathyroidism. Differences in concentrations in the various studies may reflect differences in the antisera used to measure the hormone.

Elevation in plasma glucagon concentration is an unlikely explanation of the hypocalcemia for the following reasons: glucagon levels were increased in only four of nine patients; there was no apparent relation between glucagon and ionized calcium concentrations; and acutely administered parenteral glucagon did not decrease serum ionized calcium in these patients. It might be argued that exogenous glucagon would have no additional hypocalcemic effect in the presence of increased endogenous glucagon concentrations. However, no consistent hypocalcemic effect of exogenous glucagon was noted regardless of the pre-existing glucagon concentration.

We examined the possibility that calcitonin induced the hypocalcemia because elevated calcitonin levels have been observed in patients with pancreatitis.^{32,33} Six of eight patients tested in our study had elevated calcitonin concentra-

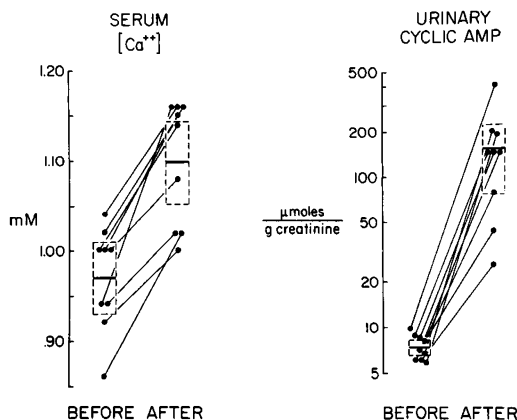


Figure 6. Effects of 1200 U of Parathyroid Extract (PTE) on Serum Ionized Calcium ($P < 0.001$) and 200 U of PTE on Urinary Cyclic AMP Excretion ($P < 0.001$, after as Compared with before Administration).

The horizontal line and enclosed boxes represent the mean \pm 2 S.E.

tions. As noted in Figure 3, no apparent relation between calcitonin and serum ionized calcium concentrations could be demonstrated. These data and the known minimal hypocalcemic effects of calcitonin in normal man³⁴ and in patients with medullary thyroid carcinoma³⁵ suggest that the elevated calcitonin levels were not the cause of the hypocalcemia observed in our patients.

A possible defect in bone metabolism, target-organ unresponsiveness, has been suggested as the cause of the hypocalcemia.³¹ To test this possibility, the effects of exogenous parathyroid extract were evaluated. A significant increase in serum ionized calcium and urinary cyclic AMP excretion was observed in all patients after administration of parathyroid extract, indicating that the target organs were capable of responding³⁶ to parathyroid hormone under the conditions of this study. However, the possibility of decreased responsiveness cannot be completely excluded since a pharmacologic dose of parathyroid extract was employed.

Three other points deserve further study. First of all, the cause of initial lowering of calcium is obscure. This study has not disproved the original hypothesis that the cause of the initial decrease in calcium is calcium sequestration secondary to formation of intra-abdominal calcium complexes. Secondly, the source of the increased urinary cyclic AMP excretion before parathyroid extract administration is also obscure. Glucagon or catecholamines may elevate urinary cyclic AMP excretion through increased renal clearance.^{37,38} Thirdly, the reduction in serum phosphorus is unexplained. This decrease might be due to an inadequate diet³⁹ or prolonged vomiting⁴⁰ before admission to the hospital.

The present studies indicate that there is an inadequate parathyroid hormone concentration in response to hypocalcemia associated with acute pancreatitis. More detailed studies will be necessary to determine the defect (or defects) responsible for this relative parathyroid insufficiency.

We are indebted to Dr. V.L.W. Go, Mayo Clinic, Rochester, Minnesota, for the gastrin assays, Dr. C. Arnaud, Mayo Clinic, Rochester, Minnesota, for the parathyroid hormone assays, Dr. G. Makhlof, Medical College of Virginia, Richmond, Virginia, for the glucagon assays, Lilly Research Laboratories for the donation of parathyroid extract and Mr. Jay Meek for some of the statistical analyses.

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