Hypercalcemia in Critically Ill Surgical Patients

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Critical surgical illness, commonly accompanied by shock, sepsis, multiple transfusions, and renal failure, is usually associated with low total calcium and/or low or normal ionized calcium. A seminal case of hypercalcemia in a surgical intensive care unit (SICU) patient prompted the review of 100 patients with longer than average SICU days (>12) to determine the incidence, associated factors, and possible etiologies of this condition. Ten patients had elevated measured, and five others had elevated calculated, ionized calcium (5.9 ± 0.25 mg%), an incidence of 15%. Compared to the 85 patients who did not develop hypercalcemia, this population had a significantly higher frequency of the following: renal failure, dialysis, total parenteral nutrition (TPN) usage > 21 days, bacteremic days > 1, transfusions > 24 units, shock > 1 day, SICU days > 36, and antibiotics used > 7. In addition, this group had significantly more days of hypocalcemia early in their hospital course. There was no difference in sex, age, mortality, or incidence of respiratory failure. Two patients studied in depth had renal failure requiring dialysis and no malignancy, milk-alkali syndrome, hyperthyroidism, or hypoadrenalism. Parathormone (PTH) concentrations were high normal or elevated (N terminal 20 and 21 pg/ml; C terminal 130 μlEq/ml and 1009 pg/ml) at the time of elevated calcium (total 9.2 to 14.6 mg%; ionized 4.9 to 8.2 mg%). Immobilization does not increase PTH. In renal failure, PTH elevation is a consequence of hypocalcemia rather than hypercalcemia. Moreover, five patients did not have renal failure. Shock, sepsis, and multiple transfusions containing citrate may lower total and/or ionized calcium and thus stimulate PTH secretion. Whatever the mechanism, approximately 15% of critically ill surgical patients develop hypercalcemia, which may represent a new form of hyperparathyroidism.

CRITICALLY ILL surgical patients are at risk for developing hypocalcemia.[1] Renal failure, sepsis, and cardiovascular instability characterize this group of patients and are known to suppress serum concentrations of ionized calcium through a variety of mechanisms.[1-3] Hypercalcemia in this setting has been reported only once previously.[4]

A case of marked hypercalcemia (Case 1, below) in a critically ill surgical patient prompted the present review of 100 surgical intensive care unit (SICU) patients to determine the incidence and associated clinical features of this phenomenon. Through examination of the clinical course and the antecedent clinical factors of 15 patients who developed hypercalcemia, we hypothesize that the exposure of these patients to events that induce low concentrations of ionized calcium stimulates parathormone (PTH) secretion. Following repeated episodes of hypocalcemia, autonomous secretion of PTH may develop, producing a state of hyperparathyroidism. This report documents the review of these patients and the information supporting this hypothesis.

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Case Reports

Case 1. A 21-year-old white man was admitted on July 6, 1983, following a motor vehicle accident. He suffered severe closed head injury, received an intracranial pressure monitor, and was treated with Decadron®, Dilantin®, and mannitol. Four days later he developed staphylococcal pneumonia. Despite appropriate antibiotics, the pneumonia led to an empyema that required thoracotomy and decortication 12 days after admission. Subsequently, he developed renal failure requiring dialysis. Over the next 30 days, his neurological status improved, his renal failure resolved, and his temperature returned to normal. During his hospitalization, he had one bacteremic episode, received 12 antibiotics, had 2 days of hypotension < 90 mmHg, was transfused 50 units of red blood cells, and received total parenteral nutrition (TPN) for 54 days (Fig. 1).

His total calcium was first noted to be elevated on hospital day 42. By hospital day 58, his total calcium was 14.2 mg%, associated with a measured ionized calcium (IC_{meas}) of 9.0 mg%, a phosphate of 3.2 mg%, a chloride of 106 mEq/L, a chloride/phosphate ratio of 33, and a total bicarbonate of 21 mEq/L. At about the same time, urine calcium and phosphate excretion were 763 mg/24 hr and 1196 mg/24 hr, respectively. On hospital day 46, carboxy-terminal (C-terminal) PTH was 130 μlEq/ml with IC_{meas} 5.6 mg%, a value abnormally elevated for the degree of hypercalcemia. On hospital day 60, amino-terminal (N-terminal) PTH was 20 pg/ml and IC_{meas} 8.2 mg% (also abnormally elevated). The hypercalcemia produced no symptoms and was treated by hydration, diuretics, oral phosphorous, calcitonin, mithramycin, and prednisone with varying degrees of success. A C-terminal PTH level 78 days after admission was 87 μlEq/ml with calculated ionized calcium (IC_{calc}) 8.7 mg%

(abnormally elevated). Total calcium remained elevated until the patient's discharge on hospital day 115.

Case 2. A 75-year-old white female was admitted on January 18, 1984, with abdominal distension and a history of multiple abdominal incisional herniorraphies. At laparotomy on January 19, 1984, a small bowel resection was performed for a strangulated and perforated segment. On hospital day 14, massive lower intestinal bleeding led to a subtotal colectomy. Subsequent sepsis, respiratory failure, and renal failure requiring dialysis led to her death on hospital day 210.

During this time, she suffered two bacteremic days, received 12 antibiotics, sustained a blood pressure < 90 mmHg on 16 days, and received 62 units of red blood cells and 91 days of TPN. SICU stay was 57 days. During these 57 days, total hypocalcemia was noted repeatedly and low IC_{calc} was present on 7 days. Subsequently, ionized calcium increased and remained elevated (4.5–5.5 mg%) the remainder of her hospital stay. C-terminal PTH measurements on hospital days 60 and 90 were 912 and 1009 pg/ml (normal: 50–330) with IC_{calc} of 5.6 and 5.3 mg%, respectively (abnormally elevated). N-terminal PTH measurements on those days were 21 and 35 pg/ml, respectively (abnormally elevated).

Methods

The records of the SICU were reviewed for 18 months from July 1, 1982, to December 31, 1983. During that time 1812 patients were admitted. The charts of 100 patients with an SICU stay greater than 12 days (approximately 5% of the total) were reviewed to determine age, sex, admitting diagnosis, SICU admitting diagnosis, operations, the presence of respiratory failure (mechanical ventilation for 72 hours or greater), the presence of renal failure (creatinine elevation of 2 mg% or greater), use of dialysis, episodes of shock (systolic blood pressure < 90 mmHg), bacteremic episodes, antibiotic administration, TPN administration, SICU stay, and serum biochemical data, recorded as close as possible to the time of a calcium measurement: total calcium (TC) (mg%), ionized calcium (IC_{meas}) (mg%), total protein (gm%), albumin (ALB) (gm%), phosphate (mg%), magnesium (mEq/L), alkaline phosphatase (IU/dl), bilirubin (mg%), creatinine (mg%), chloride (mEq/L), and arterial pH. Particular attention was directed to determine the presence of diseases known to be associated with hypercalcemia, including tuberculosis, sarcoidosis, Paget's disease, milk-alkali syndrome, metastatic carcinoma, and adrenal insufficiency.

When not measured, ionized calcium was calculated from the formula:

$$IC_{calc} = 0.9 + 0.55 \times TC - 0.3 \times ALB.$$

This equation was derived using linear regression analysis of 389 patient samples of IC_{meas}, TC, and ALB taken from the biochemistry laboratory of the Rhode Island Hospital. The relationship of IC_{meas} and IC_{calc} was verified and corrected with 45 samples of IC_{meas}, TC, and ALB from patients in this study. The line relating IC_{calc} to IC_{meas} had a slope of 0.8 and an intercept of 1.1 with a correlation coefficient of 0.95 (Fig. 2). Because the slope was not one and the error increased with increasing TC, we defined

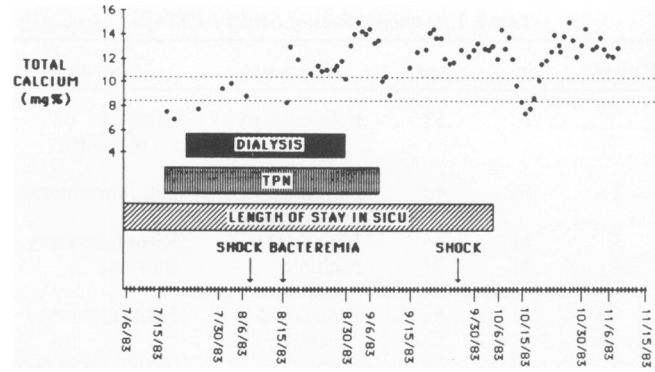

FIG. 1. Temporal sequence of total calcium and major clinical events in Case 1.

an elevated IC_{calc} to be one above the 95% confidence interval at IC_{meas} of 4.8 mg%, *i.e.*, >5.3 mg% and a low IC_{calc} one below the confidence interval at IC_{meas} of 4.2 mg%, *i.e.*, <4.1 mg%.

Ten patients had elevations in IC_{meas}, and five had elevations in IC_{calc} during their hospital course. Clinical variables in these 15 patients were compared to the remaining 85 with both the Student's t test and Chi square analysis, when appropriate. The simple and partial correlation coefficients between ionized calcium and clinical variables were determined using the statistical package in the APL language available at the Brown University Computer Center.

Results

As stated above, 15 patients were determined to have developed elevated ionized calcium levels during their hospital stay (Group 1); 85 patients did not (Group 2). The demographic features of the Group 1 patients are listed in Table 1. Only two patients suffered from pancreatitis. No patient had metastatic carcinoma, tuberculosis, Paget's disease, sarcoidosis, milk-alkali syndrome, or took thiazide diuretics.

The two groups were similar in age, sex, mortality, alkaline phosphatase, phosphate, magnesium, total protein,

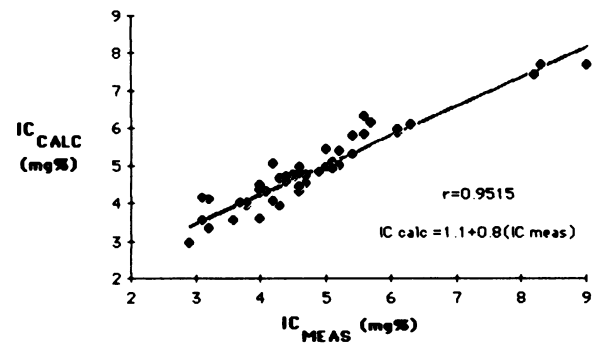

FIG. 2. Graph of measured ionized calcium (IC_{meas}) (mg%) *versus* calculated ionized calcium (IC_{calc}) (mg%).

TABLE 1. *Demographics of Group I Patients*

Patient	Sex	Age	Diagnosis	Operation
1	F	57	Inflammatory bowel disease	Subtotal colectomy
2	F	65	Perforated esophagus	Left thoracotomy
3	M	66	Lung cancer	Right lobectomy
4	M	21	Multiple trauma	Burrhole
5	M	65	Esophageal cancer	Esophagectomy
6	F	59	Sigmoid obstruction	Sigmoid resection
7	M	49	Exploratory laparotomy	Intra-abdominal sepsis
8	M	50	Renal failure/ sepsis	—
9	M	77	Esophageal cancer	Esophagectomy
10	F	43	Pancreatitis	Cholecystectomy
11	F	49	Pancreatitis	—
12	F	76	Lower GI bleed	Right colectomy
13	F	44	Tonsillar cancer	Radical neck
14	F	21	Acute abdomen	Exploratory laparotomy
15	F	75	Ischemic colitis	Right colectomy

chloride, and bilirubin at the time of calcium measurements (Tables 2 and 3). Group 1 patients demonstrated lower pH and higher serum creatinine concentration (Table 3).

Group 1 had more patients with one or more bacteremic days (14/15 *vs.* 48/85, $p < 0.025$) and more treated with seven or more antibiotics (12/15 *vs.* 29/85, $p < 0.005$). Group 1 had more days with episodes of shock (11/15 *vs.* 33/85, $p < 0.05$) and received 24 or more units of red cells more frequently (11/15 *vs.* 29/85, $p < 0.025$.). Renal failure and dialysis were also more common in Group 1 (10/15 *vs.* 26/85, $p < 0.025$; 9/15 *vs.* 14/85, $p < .001$, respectively).

During the entire hospital stay, Group 1 patients had significantly more episodes of measured or calculated low serum ionized calcium (5.0 ± 1.9 *vs.* 2 ± 0.5 days, $p < 0.025$).

More Group 1 patients had a SICU stay greater than 36 days than did Group 2 patients (10/15 *vs.* 21/85, $p < 0.050$). TPN was administered more frequently for

TABLE 2. *Clinical Features Comparison*

	Group I (N)	Group II (N)
Age (mean ± SEM)	54 ± 4.5 (15)	59 ± 2.3 (85)
Sex (per cent male)	40 (15)	76 (85)
Died (per cent)	60 (15)	45 (85)
Respiratory failure (per cent)	100 (15)	94 (85)

TABLE 3. *Laboratory Data Comparison**

	Group I (N)	Group II (N)
Alkaline phosphatase (IU/dl)	28 ± 6.3 (13)	22 ± 1.8 (77)
Phosphate (mg %)	3.6 ± 0.70 (13)	3.6 ± 0.14 (81)
Magnesium (mEq/L)	1.8 ± 0.071 (13)	1.7 ± 0.049 (78)
pH	7.37 ± 0.014 (10)†‡	7.42 ± 0.007 (71)
Total protein (gm %)	6.4 ± 0.30 (15)	6.0 ± 0.12 (85)
Albumin (gm %)	3.1 ± 0.16 (15)	2.8 ± 0.07 (85)
Chloride (mEq/L)	97 ± 2.1 (15)	97 ± 1.3 (85)
Bilirubin (mg %)	4.6 ± 1.9 (13)	4.0 ± 0.81 (76)
Creatinine (mg %)	4.0 ± 0.74 (15)†	2.3 ± 0.30 (85)

* Mean ± SEM.
† $P < 0.05$.
‡ pH was converted to $[H^+]$ for statistical analysis and then reconverted to logarithmic form.

greater than 21 days (11/15 *vs.* 26/85, $p < 0.005$). The usual amount of vitamin D administered in our TPN protocol at that time was 1000 IU per day.

The seven factors listed above that were found to differ significantly between Groups 1 and 2 were evaluated using simple and partial correlation coefficients (Table 4). Ionized calcium correlated with all seven factors; however, the partial correlation coefficients are significant only for TPN and antibiotics.

Discussion

This study suffers from some of the problems inherent in a retrospective review, including limited data, incomplete data collection, preselection of patients, and bias in data analysis. Although the causal sequence proposed (see below) is plausible, it is not necessarily true. The corre-

TABLE 4. *Correlation Coefficients with High Ionized Calcium*

Simple	
Surgical intensive care unit	0.45*
Shock	0.35*
Transfusions	0.41*
Bacteremia	0.38*
Antibiotics	0.45*
Renal failure	0.34*
Dialysis	0.35*
Total parenteral nutrition	0.53*
Partial	
Total parenteral nutrition	0.27†
Antibiotics	0.24†

* $p < 0.001$.
† $p < 0.05$.

lations detailed above are significant, but other, possibly more important, factors may not have been tested.

Additionally, the concentration of ionized calcium had to be calculated for several patients. The calculation of ionized calcium or the correction of total calcium for serum proteins has been shown to be inaccurate in predicting the calcium status.[5] We derived an equation relating IC_{meas} to TC and ALB, using data from the biochemistry laboratory. Because IC_{calc} was not a perfect predictor of IC_{meas}, *i.e.*, the slope was not one and the error was a function of TC, we defined normal values of IC_{calc} on the basis of 95% confidence intervals. The latter were obtained from the least squares analysis of IC_{calc} and IC_{meas}, using simultaneous measurements of IC_{meas}, TC, and ALB from our patient group. Thus, the derived limits for normal IC_{calc} of 4.1 and 5.3 mg% are conservative estimates of hypocalcemia and of hypercalcemia.

From this analysis, approximately 15% of long-term SICU patients (stay > 12 days) will develop elevated serum ionized calcium. These patients were clearly critically ill. The episodes of bacteremic days and the use of multiple antibiotics illustrate the frequency of documented or suspected sepsis. The more frequent hypotension and greater use of blood transfusion demonstrates the recurrent resuscitation requirements. Renal failure requiring dialysis bears a poor prognosis.[6] The increased SICU stay and TPN use speak to the prolonged efforts to treat these patients. Our data demonstrate an association between these factors and the appearance of elevated ionized calcium levels, possibly through the effect of these conditions on serum calcium concentration.

The correlation coefficients between Group 1 and these clinical factors are significant and demonstrate an association between the presence of high concentrations of ionized calcium and the factors. The values of the correlation coefficients are small, implying a loose association. Partial coefficients between Group 1 and the seven factors are significant only for TPN and antibiotics. Again, the values are small, suggesting that most of the variation in the variables is explained by factors other than those measured.

Septic shock is known to reduce serum ionized calcium.[2,7] In the toxic-shock syndrome, hypocalcemia is a well-known feature and has been thought to be secondary to reduced serum albumin. However, a recent study found low ionized calcium as well. PTH was slightly elevated, and calcitonin was markedly elevated. In fact, the log of calcitonin concentration correlated inversely with ionized calcium, suggesting that calcitonin may be in part responsible for the fall in ionized calcium.[2]

Shock alone may result in reduced ionized calcium,[3,8,9] although this has not always been reported.[7] Explanations for this phenomenon vary and include depressed parathormone function, failure of calcium mobilization from bone secondary to abnormal blood flow, intracellular movement of calcium, hypomagnesemia, and altered renal excretion of phosphate.[3] A recent paper has related primary aldosteronism to low concentrations of ionized calcium and elevation of PTH.[10] Aldosterone is elevated in shock and may remain so until resuscitation is complete.[11]

The citrate in transfused blood has been implicated as the etiology of low ionized calcium following blood transfusion.[12] Citrate binds calcium, increases unfiltrable calcium, and thereby decreases ionized levels.[13] In fact, PTH elevations have been reported during reduction of ionized calcium by infusion of citrate.[14]

Renal failure results in hypocalcemia. In renal failure, phosphate excretion is limited by the reduction in glomerular filtration. As phosphate accumulates, ionized calcium decreases. The decrease in calcium is enhanced by a defect in the synthesis of Vitamin D_3, thereby reducing intestinal absorption of calcium.[15]

A retrospective study at the Naval Medical Center demonstrated a 64% incidence of hypocalcemia in 259 intensive care unit patients.[1] The hypocalcemic group had lower albumin levels, more blood transfusions, longer ICU stay, higher mortality, and a greater likelihood of renal failure, sepsis, and heart failure compared to the normocalcemic group. In a prospective study of total and ionized calcium concentration in patients resuscitated from shock, the calcium levels fell and correlated inversely with the amount of blood transfused and the duration of shock. Ionized calcium correlated directly with mean arterial pressure and serum protein concentration.[8]

In the present study, the patients who developed elevated ionized calcium levels had a significantly higher incidence of sepsis, shock, and renal failure as well as days when low ionized calcium was present. The data, therefore, support these other reports associating critical illness with hypocalcemia. The prospective study mentioned above also demonstrated the elevation of C-terminal PTH in the hypocalcemic patients, which correlated directly with the duration of shock and inversely with the ionized calcium level.[16]

Unfortunately, only two of our patients had PTH measured, but, in both, PTH was higher or increased in relation to their ionized calcium. Although three of the six PTH measurements were in the high normal limits of the laboratories performing them, they should have been lower in respect to the elevated calcium.[17,18] This suggests autonomous PTH secretion. These levels were obtained well into each patient's hospital course. Thus, in the Group 1 patients, a pattern is suggested of repeated shock, sepsis, and renal failure accompanied by hypocalcemia. Recurrent episodes of hypocalcemia may result in PTH secretion, which in some cases persists despite subsequent hypercalcemia.

Other etiologies of hypercalcemia to consider are immobilization, vitamin D intoxication, and acute renal failure. Hypercalcemia has been reported in a critically ill patient once before.[4] In this case, a patient with an enterocutaneous fistula, supported on TPN, was immobilized for the entire hospital course (9.5 months) until death. Hypercalcemia developed without symptoms and with an N-terminal PTH of 46 pg/ml at the time of a total calcium of 11.2 mg%. Further evaluation was unrevealing, and immobilization and vitamin D toxicity were considered etiologic.

Immobilization is associated with increased calcium. In 1941, Albright failed to find a parathyroid adenoma or hyperplasia in a patient with hypercalcemia and a fractured femur.[19] The features of this cause of hypercalcemia are healing fractures, immobilization for several weeks, increased urinary calcium, and low or normal PTH.[20–24] Calcium returns to normal within weeks of resuming activity.[25] Patients with this disorder often manifest symptoms of hypercalcemia—nausea, vomiting, anorexia, altered mental state—and will markedly improve with normalization of levels.[20,21,25–28] Although certainly possible, immobilization appears an unlikely etiology of hypercalcemia in Group 1 patients because few had symptoms or fractures, and, when measured, PTH levels were high. Vitamin D toxicity secondary to TPN administration is also unlikely since hypercalcemia in this setting is seen only after many months (6–73) of TPN and usually in home TPN programs. In addition, PTH levels in these cases are low.[29] Acute renal failure may be followed by hypercalcemia, a phenomenon of short duration and associated with low PTH.[30–33] Therefore, immobilization, vitamin D toxicity, and acute renal failure are unlikely etiologies for the elevated ionized calciums seen in our patients.

It is unreasonable to presume that the two patients with PTH measurements obtained had undiagnosed primary hyperparathyroidism preceding their illness or that 15% of critically ill patients have undiagnosed primary hyperparathyroidism. The two patients with measured PTH levels were no different from the remaining 13 in their overall clinical features.

The phenomenon of parathyroid autonomy following hypocalcemia is well recognized in chronic renal failure and has recently been described following hypocalcemia induced by primary aldosteronism. Therefore, it is tempting to speculate that a small group of SICU patients suffering a protracted illness, repeated bouts of sepsis and shock, and multiple episodes of hypocalcemia similarly contract hyperparathyroidism. In fact, primary hyperparathyroidism has been proposed to develop in just such a manner.[34]

The data in this manuscript support the hypothesis presented in the introduction:

(1) Depressed serum ionized calcium follows sepsis, shock, multiple transfusions, and renal failure.
(2) Low ionized calcium stimulates the parathyroid glands.
(3) PTH levels increase.
(4) Repeated insults continue to stimulate the parathyroids.
(5) Autonomous secretion of PTH then follows even into the resolution phase of illness.

This hypothesis is attractive in its simplicity. Further investigation is required to determine the magnitude and duration of hypocalcemia required to produce autonomous PTH release if, indeed, this occurs. Further longitudinal studies may also determine if PTH secretion continues to the point of producing symptomatic hypercalcemia requiring surgical intervention.

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Discussion

DR. CHARLES E. LUCAS (Detroit, Michigan): Dr. Forster has very nicely pointed out that the acute shock or septic insult is associated routinely with a fall in calcium, and this fall is due primarily to relocation of proteins into the extravascular space. This supports some of our previous studies related to the severely sick patient and also supports some of our studies showing that this fall in ionized calcium is associated with a rise in PTH. They have taken it a step further, suggesting that in the patient who is in a seriously ill state for a long period of time the persistent falls in the serum calcium will lead to the PTH rise being autonomous.

There are a couple of problems with this study as it relates to the methodology. One has to do with the use of measured ionized calciums.

Our own data suggest that the calculated ionized calcium is thrown off by the administration of albumin. I suspect that the normal ratio of ionized to total calcium is also thrown off by the use of long-term TPN. I suggest, therefore, that part of the elevations in the measured calciums may be due to this artifact.

The authors have described some associated problems with this hypercalcemia, but most importantly they have postulated that this becomes autonomous. Like any postulate, it must stand the test of time, and I am sure that they are currently trying to determine whether this postulate will do so. As they do their future determinations, I am sure that they will have a calcium machine in their intensive care unit for the interested nurse or resident who is involved with the project to measure calcium on a daily basis and correlate it with the progressive changes in PTH over a period of many weeks and months. Only by doing this type of prospective analysis can they provide data to support their postulate that this truly represents autonomous parathyroid function even in the presence of high calcium.

Finally, when they do their prospective studies, they should also look at the role of calcium blockers on this response.

DR. ALDEN HOOD HARKEN (Denver, Colorado): I appreciate the opportunity to review this interesting study. I am delighted, although not surprised, to see the continued productivity of the metabolic and surgical unit from Brown.

This study reminds me of some posters that were in Dr. Moore's laboratory at the Brigham. Right beside the poster that said, "Facts are kiels that winna-ding," was the poster that said: "We see what we look for and we look for what we know." Clearly, Dr. Forster was prepared to see this patient and then followed up looking for the problem.

I think of intensive care unit patients and sick folks as being hypocalcemic, and what we probably should do now is think of all patients that have calcium problems and look at the specific end organ. We all appreciate the fact that hypercalcemia and hypokalemia are potent regulators or influence muscle membrane potential.

We see in patients that are hypokalemic and hypercalcemic substantial automatic cardiac arrhythmias, and this leads me to my first question.

In this group of patients, did they see more supra and ventricular ectopy and was this more difficult to deal with?

I am reminded of an interesting study recently by Mitchell in which dogs were made hypokalemic and hypercalcemic. They were then taken to the surgical laboratory, their endotrachial tube clamped, and ventricular fibrillation produced. In the normokalemic, normocalcemic group, all of these animals were easily resuscitated. In the hypokalemic, hypercalcemic group, a third of them could not be resuscitated.

My second question relates to gastric physiology. We think of calcium as stimulating gastrin and producing and being a potent gastric secretagogue.

In this patient population that is hypercalcemic—indeed, 15% of our intensive care unit patients that are fairly sick are—should we, or did they, evaluate gastric or acid production and were the gastrointestinal complications in this group greater?

DR. FRANCIS D. MOORE (Boston, Massachusetts): I just wondered if the authors did any calcitonin measurements. It is hard to figure out what is going on with the calcium concentration if you do not measure calcitonin. The other thing is that I noticed in the abstract—this was not emphasized quite so much in the paper—that these patients had a very much longer, two- or threefold longer period on TPN.

In the early days of TPN when we were looking at amino acid combinations, we found that some patients given a mixed set of amino acids chosen by someone else rather than their own gut would develop hypercalcemia and sometimes outlandish levels of parathyroid hormone and calcitonin. We thought it was quite remarkable. It was evidently a response to the infusion of large amounts of amino acids into peripheral veins. That very abnormal metabolic situation occasionally produced hypercalcemia. When the infusions were stopped, the levels returned to normal.