Correspondence

Spironolactone in Patients with Heart Failure

To the Editor: The study by Pitt and colleagues (Sept. 2 issue)[1] of the effect of spironolactone on morbidity and mortality in patients with severe heart failure addresses a very important issue. Spironolactone, a relatively inexpensive and safe agent, has not previously been shown to increase the value of triple therapy with an angiotensin-converting–enzyme (ACE) inhibitor, furosemide, and digoxin. We have not used it because of concern that it may precipitate serious hyperkalemia.

We are concerned, however, that the practical message of this study — that is, that spironolactone can decrease morbidity and mortality in patients with severe heart failure who are already receiving triple therapy — is undercut by the failure of the investigators to maximize the effect of triple therapy. For example, at base line, the mean daily doses of ACE inhibitors in the placebo and spironolactone groups were 62.1 and 63.4 mg of captopril, 16.5 and 13.5 mg of enalapril, and 13.1 and 15.5 mg of lisinopril, respectively. These doses are considerably lower than the target doses used in other studies and suggested by the American College of Cardiology and American Heart Association.[2]

Pitt et al. do not report the mean doses of digoxin or furosemide. They state that "the investigator was encouraged first to adjust the doses" of ACE inhibitors, digoxin, and diuretics before changing the dose of spironolactone. If so, what effect did this approach have? Could the favorable outcome with respect to morbidity and mortality be the result of maximizing the effects of these medications rather than adding spironolactone?

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1. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999;341:709-17.
2. Guidelines for the evaluation and management of heart failure: report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 1995;92:2764-84.

To the Editor: Caution may be necessary with respect to the broad use of spironolactone in the treatment of patients with congestive heart failure. The small but statistically significant elevation in serum potassium levels in the spironolactone group in the study by Pitt et al. must not be dismissed, since the prescribed doses of the ACE inhibitors were low in terms of the current standard of care. The fact that the average blood pressure was 122/75 mm Hg suggests that the dose of ACE inhibitors was less than optimal. The results of another recently completed study[1] provide evidence that higher doses of ACE inhibitors may result in larger reductions in combined end points and rates of hospitalization.

Patients with diabetes, who are prone to have hyporeninemic hypoaldosteronism, may be at particular risk for hyperkalemia when they are treated with the combination of spironolactone and a high dose of an ACE inhibitor. Half of patients with long-standing diabetes mellitus have subclinical abnormalities of the renin–aldosterone axis.[2] Treatment with ACE inhibitors alone can cause hyperkalemia in patients with diabetes,[3] and it is recommended that the serum potassium level be checked within 7 to 10 days after the initiation of such treatment.[4] Additional blockade of aldosterone receptors and subsequent down-regulation of the Na^+/K^+–ATPase pump could further increase this risk. Treatment with beta-blockers, which is now standard in many patients with New York Heart Association class III symptoms, also has the potential to increase the incidence of hyperkalemia.

Patients with diabetes mellitus were not excluded from the study, but they were not mentioned in the subgroup analysis. Since type 2 diabetes is common among patients with congestive heart failure, the data on potassium levels in the diabetic patients would be of considerable interest. Since the standard of care is to use high doses of ACE inhibitors in the treatment of congestive heart failure, we wish to reinforce that close monitoring of the serum potassium level after the initiation of spironolactone therapy is particularly

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important in patients with congestive heart failure that is complicated by diabetes.

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1. Hobbs RE. Results of the ATLAS Study: high or low doses of ACE inhibitors for heart failure? Cleve Clin J Med 1998;65:539-42.
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To the Editor: Pitt and coworkers report that blockade of aldosterone receptors by spironolactone, in addition to treatment with loop diuretics, ACE inhibitors, and other drugs, in patients with severe heart failure reduces the risk of both morbidity and death, with a minimal incidence of serious hyperkalemia. The authors warn about the risk of this complication in patients with an increased creatinine level and recommend a maximal dose of spironolactone of 25 mg.

As geriatricians, we are concerned by the mean age of the study population (65±12 years), which is very different from that of the patients in our practice (mean, 83±8 years). Indeed, because the prevalence and incidence of heart failure increase exponentially with age, a high proportion of patients with heart failure are frail elderly persons. This proportion will further increase as a result of the doubling of the number of octogenarians in the next three decades. Therefore, if the warnings of the authors are appropriate for the population studied, we want to emphasize that for frail elderly patients, the combination of spironolactone with standard therapy including ACE inhibitors should be considered with more caution. This concern is based on clinical experience and on several physiologic factors.[1] Older patients have lower levels of aldosterone as well as impaired renal function, despite apparently normal levels of serum creatinine,[2] and hyperkalemia may develop in these patients after even a single use of ACE inhibitors or spironolactone.[3]

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To the Editor: The study by Pitt et al. demonstrating the importance of administering spironolactone and the consequent blocking of the action of aldosterone in the treatment of congestive heart failure is a major breakthrough in our understanding of the pathogenesis and therapy of this disease. In my view, the results of this study allow us to reevaluate our interpretation of many of the investigations of the effects of beta-adrenergic–receptor blockade in patients with congestive heart failure.[1,2]

The beneficial effects of beta-blockade that have been demonstrated in these studies have been attributed to blockade of the sympathetic nervous system, which produces harmful effects as a result of overcompensation. The tachycardia that is frequently present may well be an example of such overcompensation.

What does not seem to have been appreciated, however, is the fact that beta-blockade markedly reduces the secretion of renin from the juxtaglomerular apparatus of the kidney, an effect that has been known for several decades.[3] With the suppression of renin secretion, angiotensin levels fall and the stimulation of aldosterone production is minimized. Thus, in patients with congestive heart failure, the beneficial effects of spironolactone and beta-blockade are produced by means of the same final common pathway of suppressed aldosterone effects: spironolactone blocks aldosterone at its effector site, and beta-blockade decreases the production of aldosterone.

Such a formulation would help to explain the apparently counterintuitive finding that beta-blockade, which is a negative inotropic intervention, has salutary effects in patients with congestive heart failure.

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1. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure. Lancet 1999;353:2001-7.
2. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999;353:9-13.
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The authors reply:

To the Editor: In our study, we added spironolactone or placebo to the treatment regimen of patients with heart failure. Drs. Fernandez and Leipzig suggest that the use of maximal doses of ACE inhibitors might have negated the benefits of spironolactone. Although the mean daily doses of ACE inhibitors in our study were lower than target doses, they are reflective of current practice.[1] Furthermore, among all randomized patients, the final mean daily dose of enalapril used in the Studies of Left Ventricular Dysfunction (SOLVD)[2] was 11.2 mg, whereas in our study the mean daily dose was 15.0 mg at base line. A retrospective analysis of our data revealed no difference in the effect of spironolactone on mortality between patients who received higher doses of ACE inhibitors and those who received lower doses. In addition, there is no evidence that the use of either higher doses of ACE inhibitors or a combination of an ACE inhibitor and an angiotensin-receptor blocker effectively suppresses aldosterone production in the long term,[3] since factors other than angiotensin II, such as serum potassium, are important.[4]

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TABLE 1. RELATIVE RISKS OF DEATH AND HOSPITALIZATION AMONG THE SUBGROUPS OF 861 ELDERLY PATIENTS AND 389 PATIENTS WITH DIABETES.*

END POINT	RELATIVE RISK (95% CI)†		P VALUE	
	ELDERLY PATIENTS	PATIENTS WITH DIABETES	ELDERLY PATIENTS	PATIENTS WITH DIABETES
Death from any cause	0.68 (0.56–0.83)	0.70 (0.52–0.94)	<0.001	0.019
Death from cardiac causes	0.66 (0.53–0.83)	0.70 (0.50–0.98)	<0.001	0.04
Hospitalization for cardiac causes	0.72 (0.58–0.89)	0.68 (0.50–0.91)	0.003	0.01
Death from cardiac causes or hospitalization for cardiac causes	0.71 (0.59–0.84)	0.68 (0.53–0.89)	<0.001	0.004

*Elderly patients were defined as those who were 67 to 91 years old.

†The relative risk is for the comparison of the spironolactone group with the placebo group. CI denotes confidence interval.

Drs. Vanpee and Swine and Dr. Larkin and his colleagues are concerned about the risk of hyperkalemia in the elderly and in patients with type 2 diabetes mellitus. In our study, 9 percent of the patients were 80 years of age or older and nearly 25 percent of patients had a history of diabetes mellitus at base line. None of the patients who were randomly assigned to receive spironolactone died of hyperkalemia. Among elderly patients (age, 67 to 91 years) and patients with diabetes, the risk of death from any cause was reduced by 32 percent and 30 percent, respectively — values that were similar to those in the population as a whole. Similar reductions were also observed in the secondary end points (Table 1). Interestingly, an analysis of data from SOLVD revealed that mortality was lower among patients receiving a potassium-sparing diuretic than among those receiving a non–potassium-sparing diuretic.[5] Of the 24 patients in our study in whom serious hyperkalemia developed, 9 patients had diabetes (5 in the placebo group and 4 in the spironolactone group) and 4 (2 in each group) were at least 80 years old; there was no significant difference in the incidence of serious hyperkalemia between the treatment groups in either the study group as a whole or the subgroup of patients with diabetes. However, we recommend careful monitoring of the serum potassium level in patients who are receiving combination therapy.

Dr. Glick is correct that beta-blockers act on renin and that there may be an important additive or synergistic effect when a beta-blocker is combined with spironolactone in the treatment of heart failure. However, the benefits of the use of such a combination remain to be confirmed in large, well-controlled clinical trials.

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FOR THE RANDOMIZED ALDACTONE EVALUATION STUDY INVESTIGATORS

Editor's note: Dr. Pitt is a consultant for Searle, and Dr. Perez is an employee of Searle.

1. Consensus recommendations for the management of chronic heart failure. Am J Cardiol 1999;83(2A):1A-38A.
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Increased Mortality Associated with Growth Hormone Treatment in Critically Ill Adults

To the Editor: Takala et al. (Sept. 9 issue)[1] report that high-dose growth hormone therapy increased the mortality rate in a group of critically ill patients. Although the causes of death in the patients who died while receiving intensive care were given, the causes of later deaths, which accounted for approximately 20 percent of all deaths, were not. Furthermore, although the mean daily dose of growth hormone was similar in the patients who died and in those who survived, neither the duration of treatment nor the number of patients still receiving treatment at the time of death was given. Thus, the authors' speculation that modulation of immune function or insulin resistance was responsible for the higher death rate in the growth hormone group may be based on an incomplete analysis of the causes of death.

The authors state that growth hormone resistance may have resulted in decreased production of insulin-like growth factor I (IGF-I), but they do not examine this possibility further. Taking the hypothesis of reduced sensitivity to growth hormone and the administration of high doses of growth hormone into consideration, we propose another explanation for the increased mortality rate in the group of patients treated with growth hormone. Several studies have shown that IGF-I inhibits apoptosis in various cell lines.[2]

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In patients with acromegaly and high serum growth hormone and IGF-I concentrations, myocyte apoptosis is increased.[3] We suggest that growth signals to damaged cells may trigger cell death in some tissues. Thus, the effects of growth hormone appear to be organ-specific and dependent on local growth hormone and IGF-I concentrations. High doses of growth hormone lead to increases in the production of IGF-I, depending on the number and sensitivity of growth hormone receptors. Simultaneous stimulation of the growth hormone and IGF-I receptor pathways could trigger apoptotic signals in compromised cells, a fact that would explain organ failure in critically ill patients.

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1. Takala J, Ruokonen E, Webster NR, et al. Increased mortality associated with growth hormone treatment in critically ill adults. N Engl J Med 1999; 341:785-92.
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To the Editor: The patients studied by Takala et al. were assumed to have resistance to growth hormone on the basis of their low serum IGF-I and IGF-binding protein 3 concentrations and on the basis of the high serum growth hormone concentrations reported in patients after trauma and elective surgery; the resistance is due in part to the reduced expression of growth hormone receptors.[1] Very high doses of growth hormone were administered to overcome this resistance.

There is reason to believe that the high growth hormone dose selected for these studies was based on inappropriate assumptions. Patients who have long stays in the intensive care unit, such as those in the studies reported by Takala et al., do not have overt resistance to growth hormone, if they have resistance at all.[2,3] Indeed, they have decreased pulsatile growth hormone secretion and low serum IGF-I concentrations, suggesting a relative deficiency of growth hormone. The relative growth hormone deficiency has a hypothalamic origin, because growth hormone secretion and serum concentrations of IGF-I and growth hormone–dependent binding proteins increase in response to infusions of growth hormone secretagogues, with preserved pulsatility and intact feedback inhibition preventing overtreatment. Treatment of patients in the chronic phase of critical illness may raise serum IGF-I concentrations into the range associated with acromegaly and can cause excessive fluid retention (up to 20 percent of body weight), pronounced insulin resistance, and hypercalcemia.[4] Thus, the high growth hormone doses administered by Takala et al. to sick but growth hormone–responsive patients may have had serious side effects, which were nonspecific and could easily have been mistaken for spontaneous deterioration associated with the underlying disease.

In addition, generalized hypothalamic–pituitary suppression occurs in patients with protracted critical illness, resulting in hypothyroidism, hypogonadism, and sometimes hypoadrenalism, as well as growth hormone deficiency.[2] These concomitant endocrine deficiencies may have amplified the side effects of growth hormone: hypothyroidism, for example, impairs free water clearance, and hypoadrenalism may mimic septic shock in patients in the intensive care unit.

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1. Hermansson M, Wickelgren RB, Hammarqvist F, et al. Measurement of human growth hormone receptor messenger ribonucleic acid by a quantitative polymerase chain reaction-based assay: demonstration of reduced expression after elective surgery. J Clin Endocrinol Metab 1997;82:421-8.
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The authors reply:

To the Editor: In response to Dr. Osterziel and colleagues, we did not include the causes of death for the patients who died after discharge from the intensive care unit because of incomplete records. Overall, 18 of the 108 deaths in the growth hormone–treated patients (17 percent) occurred after discharge from the intensive care unit. The median duration of growth hormone treatment in the patients who died was 14 days in the Finnish study and 7 days in the multinational study, and the median duration of treatment in the survivors was 15 days in the Finnish study and 17 days in the multinational study. Forty-two patients died during growth hormone treatment, and 43 patients died within one week after the last dose of growth hormone had been administered; 65 deaths in the intensive care unit (60 percent of all deaths) were due to multiple-organ failure and sepsis. Thus, we still believe that abnormal immune function is one of the more likely causes of increased mortality in the group of patients who received growth hormone. Among the many other possibilities, increased apoptosis is an interesting new suggestion. In both studies, however, serum IGF-I concentrations increased in response to growth hormone more frequently in the survivors than in the nonsurvivors, an observation that is inconsistent with the hypothesis of Dr. Osterziel and colleagues.

Dr. Van den Berghe's studies have indicated that patients who have long stays in the intensive care unit may not have resistance to growth hormone, and Dr. Van den Berghe suggests that the supraphysiologic doses of growth hormone used in our trials may have resulted in high serum IGF-I concentrations, excessive fluid retention, pronounced insulin resistance, and hypercalcemia, possibly worsened by generalized hypothalamic–pituitary suppression. However, the absence of resistance to growth hormone and the presence of generalized hypothalamic–pituitary suppres-

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sion have so far been demonstrated only after several weeks of intensive care,[1,2] whereas we studied patients who had been in the intensive care unit for only five to seven days. Nevertheless, we cannot exclude the possibility that alterations in responsiveness to growth hormone influenced our findings. However, most of the excess deaths in the multinational study and half the excess deaths in the Finnish study occurred within the first 10 days of growth hormone treatment, and neither hypercalcemia nor clinically evident excessive fluid retention was observed.

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Enoxaparin for the Prevention of Venous Thromboembolism

To the Editor: Samama et al. (Sept. 9 issue)[1] compared enoxaparin with saline placebo for the prevention of venous thromboembolism in acutely ill medical patients. I was surprised that the study drug was compared with a placebo, since venous thromboembolism is a potentially life-threatening illness and since those receiving the placebo would have a higher incidence of morbidity. The authors state, "The use of a placebo group was considered to be ethically justifiable because the incidence of venous thromboembolism among such patients had not been established, there was no established method of thromboprophylaxis for these patients, and patients with a very high risk of venous thromboembolism were excluded." This statement does not make sense to me.

First, with regard to the incidence of thromboembolism, Samama et al. state that they assumed an incidence of 15 percent, and the results in their placebo group confirm this assumption. Thus, they knew very well what the incidence of thromboembolism was. Second, use of unfractionated heparin is a standard method of prophylaxis against this disease, so it would have been better to compare enoxaparin with this standard and to prevent any harm to patients in a placebo group. Indeed, one of the authors' references[2] is a meta-analysis of comparisons of low-molecular-weight heparin with unfractionated heparin, placebo, and dextran for the prevention of venous thromboembolism. The conclusions were that both forms of heparin were better than dextran or placebo and that a clear decision as to which form of heparin was better could not be made. Unfortunately, because of the use of a placebo group in the study by Samama et al., approximately 27 more patients had deep-vein thrombosis than would have if all groups had received prophylaxis, 14 more had hemorrhage, and 4 more died during the treatment period. This is a high price to pay to avoid a direct comparison with the standard therapy.

Moreover, Samama et al. state that of 1102 patients enrolled in the study, 1073 were included in the analysis of safety. What happened to the others? They should have been included since the authors mention in the Methods section that they applied the intention-to-treat principle. The authors also state that "one patient in the 40-mg group died, but the hemorrhage was not considered to be related to treatment (it was characterized by massive hemoptysis due to bronchial carcinoma)." All bleeding must be considered a complication of the study drug.

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1. Samama MM, Cohen AT, Darmon J, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. N Engl J Med 1999;341:793-800.
2. Leizorovicz A, Haugh MC, Chapuis FR, Samama MM, Boissel JP. Low molecular weight heparin in prevention of perioperative thrombosis. BMJ 1992;305:9913-20.

To the Editor: In the sole figure included in their report on the efficacy and safety of prophylactic enoxaparin in acutely ill, hospitalized medical patients, Samama et al. imply with their graph and explicitly state in their figure legend that 40 mg of enoxaparin reduced the risk of death relative to the risk associated with placebo. According to the authors' own statistical analysis, this conclusion is not true. The authors report a relative risk of death in the 40-mg enoxaparin group of 0.83, with a 95 percent confidence interval of 0.56 to 1.21 and a P value of 0.31. Therefore, no reduction in the risk of death was identified. To be correct, the authors should have stated that there was no statistically significant difference between the 40-mg group and the placebo group in the risk of death.

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To the Editor: Samama and colleagues concluded that prophylactic treatment with 40 mg of enoxaparin per day, given subcutaneously, safely reduces the risk of venous thromboembolism in patients with acute medical illnesses. Analysis of the primary outcome shows that the number of patients who would need to be treated[1] to prevent one venous thromboembolic event by using 40 mg of enoxaparin per day rather than placebo (number needed to treat) was 11. However, 62 percent of the prevented events were instances of distal deep-vein thrombosis. The absolute reduction in the risk of pulmonary embolism was 1.1 percent, and the number needed to treat to prevent one episode of pulmonary embolism was 90. Analysis of the incidence of severe hemorrhage (major or fatal) in both the 40-mg enoxaparin group and the placebo group shows that the number needed to harm (the number of patients who would have to receive enoxaparin for 1 patient to have severe hemorrhage) was 125. Thus, about 300 hospitalized medical patients would need to be treated with 40 mg of enox-

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aparin per day to prevent three cases of pulmonary embolism, but two cases of severe hemorrhage would result.

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1. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. N Engl J Med 1988;318:1728-33.

The authors reply:

To the Editor: We cannot agree with Dr. Sosis's comment that unfractionated heparin is a standard treatment. At the time we planned our study, some physicians were using thromboprophylaxis in general medical patients, but there was no solid scientific evidence to support this practice. Controlled studies of unfractionated heparin have been small, and on the basis of their results it is difficult to make recommendations about its use. Studies of mortality have had various methodologic limitations, and the results are conflicting, as we indicated in our article. Consensus in this area is not definitive, and recommendations are controversial.[1,2]

Also in response to Dr. Sosis: the frequency of venous thromboembolism was not precisely known and was anticipated to be 15 percent on the basis of the hypothesis that our population would be at moderate risk, according to venographic data from studies of surgical patients (these data are unavailable for medical patients). We wanted to evaluate whether the response to therapy would be the same as it is for surgical patients, and indeed, for the lower dose of enoxaparin (20 mg), it was not. Hence, we included a group that received placebo rather than low-dose unfractionated heparin. In contrast to Dr. Sosis's contention, we considered it unethical to treat patients with a potentially harmful treatment such as anticoagulants when the benefit had not been clearly established. We agree that analysis according to the intention to treat is the primary method of analysis, but to evaluate unwanted events, an analysis of data on all patients who received at least one dose of therapy was legitimate. Although treatment may have contributed to the massive hemoptysis in the patient with bronchial carcinoma, the investigator who performed the blinded assessment reported that this episode was unrelated to the study treatment. Autopsy findings were consistent with neoplastic vessel erosion.

In response to Dr. Hynson: the legend to Figure 1 neither implies nor states that enoxaparin reduced the risk of death relative to that associated with placebo. However, we agree that this issue could have been clarified by adding a P value, consistent with the legend and the Results section, to the figure. Although data on the risk of death constituted neither a primary nor a secondary efficacy outcome, this was a major prespecified safety outcome.

In response to Dr. Calderon and colleagues: the number needed to treat and the number needed to harm are other ways to express absolute differences, but they should be presented with confidence intervals. They are meaningful only for statistically significant end points. In the calculations of Dr. Calderon and colleagues, the confidence intervals would include a negative number of patients to treat.

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1. Nicolaides AN. Prevention of venous thromboembolism: European Consensus Statement. Int Angiol 1997;16:3-38.
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Genetic and Phenotypic Correlates of Colorectal Cancer in Young Patients

To the Editor: Colorectal cancer in young patients (age, 21 years or younger) is rare and has a well-recognized aggressive, often fatal course, but the genetic origin and developmental biology of this disease are poorly understood.[1] We analyzed data from Memorial Sloan-Kettering Cancer Center on young patients with colorectal cancer to assess the hereditary basis of this disease. We used pedigree analysis and molecular assessment to identify microsatellite instability and other genetic markers. Microsatellite instability is a characteristic pattern of genetic instability seen in microsatellite DNA that occurs in most hereditary nonpolyposis colorectal cancers (more than 95 percent).[2]

Twenty-nine patients with adenocarcinoma of the colon who were 21 years of age or younger at diagnosis were identified over a 30-year period. The median age at diagnosis was 19 years. Pedigree analysis revealed only seven patients with a family history of colorectal cancer (one patient had hereditary nonpolyposis colorectal cancer according to the Amsterdam criteria, and six patients had family histories of the disease, some stronger than others). The majority of patients had sporadic colorectal cancer (22 of 29 patients, or 76 percent). Therefore, most patients had no clinical features suggestive of hereditary colorectal cancer other than a young age at onset. Slides and paraffin blocks were available in the case of 13 patients; microsatellite instability was found in specimens from 6 of these 13 patients (46 percent). As compared with cancers without microsatellite instability, cancers with microsatellite instability were not associated with distinct clinical, histologic, or familial features. However, they did have a significantly lower prevalence of K-*ras* mutations and of loss of heterozygosity at 17p or 18q (Table 1).

Solid tumors in young patients are extremely likely to have a genetic cause. In colorectal cancer, germ-line mutations associated with a young age at onset include mutations in the adenomatous polyposis coli (*APC*) gene, which are the basis of familial adenomatous polyposis, and in the

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TABLE 1. CLINICAL SIGNIFICANCE OF MICROSATELLITE INSTABILITY IN YOUNG PATIENTS WITH COLORECTAL CANCER.

CHARACTERISTIC	MICROSATELLITE INSTABILITY (N=6)	NO MICROSATELLITE INSTABILITY (N=7)	P VALUE*
Age at diagnosis — yr			
Mean	18.2	18.7	
Range	11–21	15–21	NS
Family history of colorectal cancer — no. (%)	2 (33)	2 (29)	NS
Colorectal cancer proximal to splenic flexure — no. (%)	2 (33)	4 (57)	NS
Poorly differentiated colorectal cancer — no. (%)	4 (67)	5 (71)	NS
Mucinous histologic appearance — no. (%)	2 (33)	3 (43)	NS
Stage IV cancer at presentation — no. (%)	3 (50)	5 (71)	NS
Three-year survival — no. (%)	2 (33)	1 (14)	NS
p53 Immunostaining — no. (%)	3 (50)	5 (71)	NS
Loss of heterozygosity at 17p or 18q — no. (%)	1 (17)	4 (57)	0.05
K-*ras* mutation — no. (%)	0	3 (43)	0.02

*The chi-square test was used. NS denotes not significant.

DNA mismatch-repair genes (*MSH2, MLH1, PMS1,* and *PMS2*), which are the basis of hereditary nonpolyposis colorectal cancer. Because the clinical diagnosis of hereditary nonpolyposis colorectal cancer has many pitfalls, genetic testing plays an important part in diagnosis.[3,4] Our data indicate that the presence of microsatellite instability in tumor specimens from young patients with colorectal cancer can be used to identify a distinct pathway of genetic development in which loss of heterozygosity at 17p or 18q and K-*ras* mutations are rare. Microsatellite instability is not, however, predictive of a family history of colorectal cancer or of unique phenotypic features.

Sporadic colon cancer in young patients is an aggressive disease whose morphology and natural history differ from those of familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, and adult colon cancer. The tumors appear to develop by means of either of two pathways: one involving a tumor suppressor or loss of heterozygosity and the other involving a mutation. However, it is likely that other genetic or developmental factors account for the aggressive course and poor prognosis of this disease.

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Clinician-Educators in Academic Medical Centers

To the Editor: In describing the failure to integrate clinician-educators into the traditional academic milieu, Levinson and Rubenstein (Sept. 9 issue)[1] have focused on the symptom, an outmoded promotions process, and not the underlying disease, the fact that excellence in teaching is undervalued and not the primary mission of most academic medical centers. Our data from one institution with a long-standing non-tenure track showed that winners of a "Teacher of the Year" award left the department sooner than nonwinners, even after adjustment for age, rank, and career track.[2]

Although medical education is the mission that sets academic medical centers and medical schools apart from other health care and research entities, the primacy of research is too much ingrained to be repaired by modification of the promotions process alone. Most, if not all, academic medical centers would point to their mission statements citing the importance of all three missions. The reality, however, is quite different, particularly at institutions whose deans and department chairs measure their quality according to the center's ranking in terms of funding by the National Institutes of Health. Members of medical-school faculties are socialized into a value system in which scholarship, narrowly defined as research, especially if it is funded by the National Institutes of Health, is more highly valued than teaching or clinical work. Moreover, the costs of both research and medical education have been subsidized by clinical income; much teaching consists of unreimbursed contributions of time and effort by those who will not receive recognition in the current system.

Establishing organizational systems that support clinical care and teaching, as suggested by Levinson and Rubenstein, would require a major change in both the financial underpinnings and the value system of academic medicine. We question whether those who have benefited from the current system and continue to have a stake in its preservation are willing to cede its perquisites, much less provide the leadership necessary for the transformation of academic culture.

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To the Editor: The recommendations of Levinson and Rubenstein regarding integrating clinician-educators into academic medical centers fail to address the changing role of tenure in academic medical centers. Eliminating requirements for a regional or national reputation and publication in peer-reviewed journals for clinical-track promotion will send the not-so-subtle message that nontenured clinicians have less value than their tenured research-track colleagues, despite the observation that the degree of financial risk to an institution is probably less with respect to clinicians than to scientists.

Although expectations for clinician-educators and investigators may reasonably be different, a two-tiered system with different rewards promotes elitism and conflict. Clinicians as well as investigators may be intimidated by the lack of academic security. It is time to level the playing field: either tenure should be available to clinicians, or investigators should share the same risks of continued performance on a nontenured basis as their clinical colleagues.

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To the Editor: Levinson and Rubenstein make a plea for strengthening the clinician-educator track by eliminating the need for a regional or national reputation and the need to publish. My own institution was one of the first to be founded on the premise of training doctors who "not only sail by the old charts, but who can make new and better ones for the use of others."[1] To do so, one ideally should submit written evidence that bears up under public scrutiny and trial. To do so by local oral tradition may inadvertently perpetuate outdated parochial landmarks. Students find important validation in knowledge derived from clinician-educators who can profess not only at the bedside, but also to the world at large.

Levinson and Rubenstein, however, rightly decry the overemphasis on the making of charts that increasingly seem to be designed more for self-promotion than for the use of others. For it is in the clinical use of knowledge that its effectiveness and accuracy can be tested, mid-course corrections made, and once again another newer and better way found. Moreover, only appropriately charted care can lead to the relief of human suffering, which should be a major goal of all academic medical centers. Ultimately, institutions that promote the science and not the teaching of the art of medicine will train doctors who care little about the use of charts by others. Therefore, a resolution to the current economic pressure to deliver more care is not to relax high academic standards, but rather to strengthen our commitment to clinical scholars, who test the current charts so that new and better ones can be made.

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1. John Shaw Billings' dedication address, Johns Hopkins Hospital, May 7, 1889.

To the Editor: Traditionally, promotion has been the reward for excellence in whatever one does at an academic institution. Because research has tangible results, in the form of papers, it has always been easy to document the progress and evaluate the excellence of those involved in research. Though it is harder to do this for teaching, it can and should be done. Teaching portfolios and teaching awards definitely have their place in documenting activity and, one hopes, excellence. Developing new and innovative ways of teaching are clearly important, but these methods must be disseminated. It is here that I disagree with Levinson and Rubenstein that a national reputation should be unnecessary. Going to meetings and presenting ideas is the only valid way of discerning whether or not new methods can actually have useful, long-term effects. Writing book chapters, books, and articles and speaking at meetings are all ways to teach. Even presenting old ideas in new ways is a form of teaching. To look at it from a researcher's point of view, what good is discovering something new if no others hear about it or try to use it themselves?

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The authors reply:

To the Editor: We agree with the correspondents that the clinical and teaching missions of academic medical centers should be valued equally with the research mission. Changing promotion criteria for clinician-educators is necessary to evaluate the contributions of these faculty members properly. The result will be two sets of expectations, each tailored to the job descriptions of different and complementary faculty members — investigators and clinician-educators. We believe that two tracks for promotion can be equally valued rather than present a situation in which one track is less prestigious than the other. Alternatively, these two sets of clearly defined expectations can be incorporated into a single-track system. Commitment on the part of leaders will be necessary to make this happen.

Dr. Curry raises the important point that scholars should develop new teaching methods and study their effectiveness. She suggests that these scholars should disseminate their work nationally. We agree that rigorous scholarship pertaining to medical education is needed to advance the science of the field. However, faculty members conducting research on medical education will need to devote the majority of their time to this research and will not be able to spend 80 percent of their time on clinical care and teaching, as clinician-educators do. Innovative science in any field, including medical education, requires a major commitment of time and effort.

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