LETTERS AND CORRECTIONS

"The power and the beauty of science do not rest upon infallibility, which it has not, but on corrigibility, without which it is nothing."—HOWARD E. GRUBER*

Letters submitted for possible publication must be identified as such and submitted with a signed transfer-of-copyright form (see Contents page for location of form). Text length must not exceed 400 words. No more than five references may be used; reference format must be that specified in "Information for Authors" (page I-6). All portions of letters must be typed double-spaced, including references. Tables and figures will not be published. Acceptance of letters for publication depends on several factors: newness of information, relevance to current topics and recent content of this journal, clarity of statement, distribution of topics within this section, conformity to acceptable formats, space available. The Editor reserves the right to shorten letters and make changes to our style. Authors of letters to be published will be notified of their acceptance. Letters from U.S. correspondents not published will be returned if submitted with a stamped, addressed envelope; letters from persons outside the United States will be returned at our expense but without comment.

The Ethics Manual

TO THE EDITOR: I write to take exception to the paragraph on abortion and contraception in the American College of Physicians Ethics Manual (1). This section states that a physician who has moral, religious, or ethical objections to abortion has "the duty to assure that the patient is provided the option of receiving competent medical advice and care from a qualified colleague who does not have these moral, religious, or ethical objections." There is also the standard caveat about a physician's not imposing his personal convictions on the patient.

Does your ethics group feel that "pimping" an abortion makes one less culpable than engaging in the act personally? If your reply is yes, then I suggest that your group is sadly lacking in the basic tenets of ethics and morality.

Although I have no right to enforce my personal convictions on the patient, show me where the patient has an ethical right to enforce his or her convictions on me. (I come with the same moral, ethical, and legal rights as the patient.)

The patient has a perfect right to leave my office and find a person or group to do an abortion (they are not hard to find), but the patient has no right to expect me to breach my religious, moral, and ethical code to assist her or be a party to the abortion. This is really the basis of the disagreement between John J. O'Connor, Archbishop of New York, and the Cuomo-Ferraro branch of Catholicism.

If a person who is anti-abortion must follow your code of ethics to be in the American College of Physicians, then prepare to defend yourselves.

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REFERENCE

1. AD HOC COMMITTEE ON MEDICAL ETHICS, AMERICAN COLLEGE OF PHYSICIANS. American College of Physicians Ethics Manual. Part II: Research, other ethical issues, recommended reading. *Ann Intern Med.* 1984;101:263-74.

In response for the Ad Hoc Committee on Medical Ethics: I thank Dr. Currin for his comments, and point out that the Ethics Manual is by no means a set of rules for members of the American College of Physicians. This point is emphasized by the statement on page 2, "It is important to understand that this manual should serve only as a suggested guide to making ethical decisions." In such complicated ethical problems as those we face today, no group of physicians can possibly write rules that could or should completely satisfy all other physicians. Generally a physician is responsible for providing his or her patient with the best available medical care or advice, or to refer the patient to another physician who is knowledgeable in the field. Each physician, however, must make up his or her mind about how to deal with problems such as Dr. Currin discusses.

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TO THE EDITOR: The Ethics Manual published in the July and August issues (1, 2) fills an important need and advances the possibility of dialogue about central issues in the practice of medicine.

As an academic and clinical bioethicist, I can testify to the unqualified benefits of this document. Previously much of the material available for the dialogue between bioethicists and physicians has been generated by the bioethicists. Many physicians considered sources outside of medicine to be incomplete, if not untrustworthy. Now there is an incontrovertibly reliable document generated by a prestigious group of physicians that reflects the best bioethical thought available to all parties in the dialogue. This new common ground cannot help but benefit the welfare of patients.

The manual has numerous strengths. That the good of the patient must always be sought is articulated many times in the various concerns addressed in the manual. No matter what the situation, the good of the patient is paramount. The identification of the goals of medicine is as succinct, comprehensive, and accurate a description of the task of medicine as will be found anywhere. It emphasizes that the professional physician can fill many legitimate roles while serving patients. The emphasis on giving information to the patient and on how it is conveyed is important to preserving the patient's autonomy, and shows the commitment of the authors to the dignity that this autonomy confers on patients; it is appropriately coupled with the need for patients to participate in the decision-making process. The section on the care of the hopelessly ill is written with great sensitivity to the dignity of the person and the integrity of medical practice. The section on resuscitation is helpful because it addresses both theory and procedures. Viewing the living will as "instructive" confirms my long-standing perspective on these documents. The notion that "full discussion . . . nearly always results in a decision that is correct ethically" is an important moral and legal reminder for clinical professionals. Most malpractice originates in poor communication. Viewing the physician as the "patient's advocate" highlights the cooperative dimension of the clinical setting where the dignity and integrity of each participant is respected according to the proper ordering of the ends of medicine.

*GRUBER HE. The origin of the origin of species. Review of *Darwin and the Mysterious Mr. X. New Light on the Evolutionists.* By: EISELEY L. *The New York Times Book Review,* 1979, July 22:16.

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2. AD HOC COMMITTEE ON MEDICAL ETHICS, AMERICAN COLLEGE OF PHYSICIANS. American College of Physicians ethics manual: Part II. Research, other ethical issues, recommended reading. *Ann Intern Med.* 1984; **101**:263-74.

TO THE EDITOR: Congratulations are in order for the work and report of the Ad Hoc Committee of the American College of Physicians published in the July and August issues (1, 2). Although one can accept their view that research is an integral part of progress in medicine, the committee should have addressed the important question of the ethics of double-blind medical or surgical trials in which patients are randomly assigned to receive useful treatment and no treatment (placebo) to prove statistically that one group survived longer than the other.

In a double-blind trial, life-saving medications or procedures are denied to victims (who innocently sign informed consent forms) when they go on a placebo arm of a study; they could die early, to prove that the outcome for this arm was worse than for the treated arm. Do we have to double-blind the end result, "death," as a statistical phenomenon when dealing with life-saving medications or procedures? To the family of the victim there has been 100% mortality. One can understand comparing values of various medications as in scientific studies of treatments for hypertension or angina, or of antibiotics for severe infections, to get statistical results. But if one of this group is totally denied any medications to see the end results, this trial should be considered immoral.

The Hippocratic Oath states: "The regimen I adopt shall be for the benefit of my patients according to my ability and judgement and not for their hurt or for any wrong. . . ." This is true today as it was 2000 years ago, if we value precious human lives.

Double-blind clinical research can be valuable, but before it is done, any risk to life has to be weighed against the benefits as called for by the Ad Hoc Committee.

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1. AD HOC COMMITTEE ON MEDICAL ETHICS, AMERICAN COLLEGE OF PHYSICIANS. American College of Physicians ethics manual: Part I. History of medical ethics, the physician and the patient, the physician's relationship to other physicians, the physician and society. *Ann Intern Med.* 1984;**101**:129-37.
2. AD HOC COMMITTEE ON MEDICAL ETHICS, AMERICAN COLLEGE OF PHYSICIANS. American College of Physicians ethics manual: Part II. Research, other ethical issues, recommended reading. *Ann Intern Med.* 1984;**101**:263-74.

▶ *Dr. Narasimhan has raised an important point. The ethical issues in double-blind trials are, however, complex. If a treatment of proved (by scientific standards) efficacy is available, the issues may be simpler. Unfortunately, the history of medicine is filled with "effective treatments" shown later to be no better or worse than no treatment.—The Editor.*

Diabetic Diarrhea and Lidamidine

TO THE EDITOR: Diabetic diarrhea is a rare but distinct complication of diabetes mellitus, characterized by watery stools often occurring at night, and frequently associated with incontinence. Extensive evaluation of these patients occasionally reveals a treatable cause, but usually it shows several abnormalities in concert causing the problem. A recent study has shown that these patients frequently have steatorrhea, voluminous stools, rapid whole-gut transit times, mild to moderate exocrine pancreatic dysfunction, or abnormalities of gastric emptying (1). Because these patients rarely have single problems that are treatable, such as sprue, pancreatic insufficiency, or small bowel bacterial overgrowth, the primary therapeutic goal is to find a drug or combination of drugs that will alleviate their symptoms. This often proves difficult even with potent antidiarrheal agents.

Chang and associates (2) have shown that alpha$_2$-adrenergic receptors on small bowel enterocytes are responsible for controlling fluid and electrolyte transport. Stimulation of alpha$_2$-adrenergic receptors results in fluid and electrolyte absorption and decreased small bowel motility. Through their work with streptozocin-treated rats Chang and colleagues (3) have provided evidence for the role of alpha$_2$-adrenergic receptors in diarrhea. These diabetic animals developed diarrhea that was caused by loss of adrenergic innervation.

Lidamidine hydrochloride, an experimental non-narcotic antidiarrheal agent which may be a partial alpha$_2$-adrenergic angonist, would seem to be an ideal agent to treat patients with chronic diabetic diarrhea. However, high doses of lidamidine hydrochloride may decrease blood pressure or raise blood glucose levels (4). Furthermore, clonidine, also an alpha$_2$-adrenergic agonist, has been shown to lower blood pressure in normal persons but to raise it in patients with autonomic neuropathy (5). Thus, the use of lidamidine hydrochlorie in diabetic patients, although theoretically beneficial for their diarrhea, could be potentially harmful.

To assess the clinical usefulness of lidamidine, three diabetic patients with long-standing poorly or partially controlled diarrhea were recruited from an extensively evaluated group of diabetic patients with diarrhea followed at the University of Colorado Health Sciences Center. The patients had three diverse but typical forms of diabetic diarrhea. One patient had voluminous non-steatorrheic stools, the second had voluminous steatorrheic stools, and the third had steatorrhea with small volume diarrhea.

The study protocol began with a 3- to 7-day observation period during which patients received no medications for diarrhea. Two of the three patients were admitted to the Clinical Research Center for more careful monitoring because of the severity of their diarrhea and diabetes, and the third was monitored as an outpatient. The baseline period was used to establish each patient's stool frequency and consistency. During the study blood pressure and weight were monitored daily in the hospital in the two more seriously ill patients and weekly thereafter as outpatients. The third patient was monitored weekly as an outpatient. All patients also had biweekly laboratory evaluations including complete blood count, urinalysis, and determination of electrolyte levels, blood urea nitrogen, creatinine, glucose, calcium, phosphorus, and serum enzymes.

The patients kept a daily diary recording the approximate time (day or night) of each bowel movement and its consistency throughout the study period. After the baseline period the patients were placed on oral lidamidine hydrochloride (open-label), 2 mg three times a day, with gradual increases as needed to a maximum of 20 mg/d. The drug treatment period lasted a total of 4 weeks.

The patients had a 30% to 60% decrease in bowel movement frequency from the baseline period with an associated improvement in stool consistency. No patient developed blood sugar problems. One patient complained of increased orthostatic dizziness but no objective worsening of his blood pressure could be shown. No drowsiness was reported by either patient who previously had drowsiness while using narcotic derivatives to treat their diarrhea.

Based on these preliminary clinical findings and the in-vitro work of Chang and associates (2, 3), it would appear that lidamidine hydrochloride may be a safe and effective alternative for the treatment of diarrhea in the diabetic patient.

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3. Chang EB, Bergenstal RM, Field M. Diabetic diarrhea: loss of adrenergic regulation of intestinal fluid and electrolyte transport [Abstract]. *Gastroenterology.* 1983;**84**:1121.
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Gastrointestinal Blood Loss in Runners

To the editor: McMahon and colleagues (1) studied faecal occult blood tests in runners before and after the 1983 Boston Marathon and concluded that runners' anemia is due at least in part to gastrointestinal blood loss.

The methods used in their fecal occult blood testing do not allow them to draw this conclusion. In their study, the Hemoccult (SmithKline Diagnostics Division, Sunnyvale, California) slides were developed after preliminary rehydration, a technique that increases slide sensitivity for blood and other peroxidase-containing substances, particularly red meat (2, 3). The runners were not asked to restrict red meat or other peroxidase-rich foods (4) either before or after the race. In our studies of normal volunteers eating a defined amount of red meat (250 g/d), the false-positive rate for rehydrated Hemoccult slides was 17% (3). This rate is close to the proportion (22%) of runners McMahon and associates found who were guaiac-positive after the marathon. It is possible that the runners had a generous intake of red meat after the marathon, accounting for the positivity. Furthermore, ferrous sulphate preparations caused 65% false-positive Hemoccult results in one study (5). This finding may account for the positive results in the runner taking Iberet-Folic-500 (Abbott Pharmaceutical Products, North Chicago, Illinois).

The report by Stewart and colleagues (6) in the same issue provides more compelling evidence for an association between occult gastrointestinal blood loss and marathon running.

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5. Lifton LJ, Kreiser J. False positive stool occult blood tests caused by non-preparations. *Gastroenterology.* 1982;**83**:860-3.
6. Stewart JG, Ahlquist DA, McGill DB, Ilstrup DM, Schwartz S, Owen RA. Gastrointestinal blood loss and anemia in runners. *Ann Intern Med.* 1984;**100**:843-5.

In response: We were aware of the fine work of Macrae and associates (1) in evaluating Hemoccult (SmithKline Diagnostics Division, Sunnyvale, California) testing under various dietary conditions. However, their criticism of our study fails to make adequate distinction between their study population and ours, and more importantly, the significant temporal associations in our study.

First, a comparison of their patients with positive Hemoccult results and our running population is not credible, as their patients were placed on diets high in both meats and foods containing peroxidase and kept on this diet for 3 days before Hemoccult testing (1). Second, they ignore the temporal relationship noted in our study between the occurrence of Hemoccult positivity within 36 hours of the race and its resolution in five of seven cases within 72 hours (2). Third, they also ignore the fact that those runners with Hemoccult-positive stools had significantly faster race times than those without. When our study results are evaluated in context, in light of these significant associations, occult blood loss is the most plausible explanation.

Because of the pilot nature of our study, it would have been inappropriate to exclude a runner for any reason, including iron ingestion. Therefore, we appropriately discussed this case at length in our report. Additionally, the removal of this one runner's data does not change the study's conclusions. Although one study does report that false positive Hemoccult results can be caused by ferrous sulfate (3), it is not clear that these positive Hemoccult tests are indeed "false," as they may be the result of gastrointestinal blood loss (4).

Finally, we agree with Macrae and associates that the study by Stewart and colleagues (5) provides additional evidence of the association between competitive running and gastrointestinal blood loss. We feel that our study, unlike that of Stewart and colleagues, has special value for the practicing clinician who must make clinical judgements using the available diagnostic tools such as the Hemoccult test, and agree that care should be taken in their interpretation.

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Heparin and Thrombocytopenia

To the editor: We read with interest the article by King and Kelton (1) on the clinical importance of heparin-associated thrombocytopenia. We wish to make two comments with regard to diagnosis of a platelet-aggregating factor using platelet aggregometry.

To avoid misinterpretation due to "spontaneous" aggregation induced by the heparin added to the test system as recommended by King and Kelton, we do a further control experiment. In addition to the control using saline instead of heparin, we use heat-inactivated (56 °C for 30 minutes) serum from a healthy group O donor instead of the patient's serum. Thereafter, heparin is added and the aggregation monitored. A positive result is defined as greater than 20% aggregation with no aggregation in either of the controls.

Because of the time-consuming nature of platelet testing in platelet-rich plasma, most patients with suspected heparin-associated thrombocytopenia will most likely not be tested. Using the impedance method for platelet aggregation testing in whole

blood (2) we offer a fast and simple technique for detecting the platelet-aggregating factor. In addition to the test serum from a patient, citrated whole blood and serum is collected from a healthy group O donor. After heat-inactivation of the sera, 0.5 mL of test serum is added to 0.5 mL of citrated blood in a siliconized glass cuvette. This mixture is placed in a whole blood aggregometer (Chrono Log Corporation, Havertown, Pennsylvania), stirred with a teflon-coated flea magnet (1200 revolutions per minute) at 37 °C and the electrical impedance is registrated after heparin (final concentration, 0.1 U/mL) has been added. Control experiments with saline instead of heparin and with control serum instead of test serum are done. A positive result is defined as an increase above the control values of more than 10 ohms in the test sample after 10 minutes.

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Vincristine and Kaposi's Sarcoma in the Acquired Immunodeficiency Syndrome

TO THE EDITOR: The acquired immunodeficiency syndrome and its complex of diseases has been seen among homosexual men, intravenous drug abusers, Haitians, and patients with hemophilia (1). This complex syndrome has been characterized by severe cellular immunodeficiency, opportunistic infection, and Kaposi's sarcoma (2). Although temporary control of infection has been possible in this disease, definitive control of Kaposi's sarcoma has not yet been achieved. A trial of the biological modifier alpha interferon (3) has been disappointing and etoposide (LAUBENSTEIN L. Post-graduate course on epidemic Kaposi's sarcoma and opportunistic infections in homosexual men. New York University Medical Center, March 1983), although active, is toxic and responses are short-lived. Because patients with Kaposi's sarcoma associated with the acquired immunodeficiency syndrome often present with leukopenia and lymphopenia, the administration of myelotoxic chemotherapeutic agents may be hazardous. Because vinblastine is active in classic Kaposi's sarcoma, it is appropriate to evaluate the non-myelosuppressive vinca alkaloid, vincristine, in Kaposi's sarcoma associated with this syndrome.

We treated five homosexual men with biopsy-proven Kaposi's sarcoma. Their median age was 33 years; the median leukocyte count was 4.9×10^9/L. All five patients had lymphopenia and inversion of the helper/suppressor T-lymphocyte ratio. The patients received vincristine, 1.4 mg/m^2 body surface area, administered weekly for 4 weeks and then every other week, as long as they responded. A total of 18 courses of vincristine were given. Complete response was defined by the disappearance of all measurable lesions. Partial response required a 50% decrease of indicator lesions and minor response, a 25% decrease in all indicator lesions. Stable disease was defined as no evidence or progression of an already established disease. Of the five patients treated, four achieved a partial response, one patient progressed while on therapy, and one died due to *Pneumocystis carinii* pneumonia. Two of the patients showed an increase in the number of lymphocytes. Treatment was well tolerated and none of the patients developed myelosuppression, neurotoxicity or gastrointestinal toxicity. The duration of response was short with a median of 10 weeks and a range of 3 to 14 weeks.

Vincristine is active in the treatment of patients with Kaposi's sarcoma associated with the acquired immunodeficiency syndrome. Although the duration of response to vincristine was short, no toxicity was encountered. Vincristine should be further evaluated for treatment of Kaposi's sarcoma; its lack of myelotoxicity makes it an ideal candidate for incorporation into combination chemotherapy regimens.

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Hodgkin's Disease and the Acquired Immunodeficiency Syndrome

TO THE EDITOR: In a letter to the editor, Robert and Schneiderman (1) note that during the present epidemic of the acquired immunodeficiency syndrome, the occurrence of non-Hodgkin's lymphoma in homosexual men was reported (2); however, they could not find in the literature reports on Hodgkin's disease in the same population at risk for this syndrome. The letter includes the report of a case in which Hodgkin's disease occurred in a male homosexual drug addict who later developed severe opportunistic infections. After this letter, a collaborative study of six medical institutions was published, reporting on 90 cases of non-Hodgkin's lymphoma in homosexual men (3). The article discusses the relation of non-Hodgkin's lymphoma with the acquired immunodeficiency syndrome and with the syndrome's related complex, but reports no cases and makes no comments on the occurrence of Hodgkin's disease in patients at risk for these syndromes.

We have studied 21 cases of lymphoma in homosexual men, diagnosed in one community hospital in New York City from February 1982 to September 1984. The patients' ages ranged from 26 to 55 years with a mean of 41 years, 8 years older than the mean age of homosexual patients with lymphadenopathies in our previous study (4). Of the 21 patients, 17 had non-Hodgkin's lymphoma and 4 had Hodgkin's disease, a reversed proportion of that usually seen in this age group. Lymphadenopathies of the complex related to the syndrome had been diagnosed 1 to 2 years earlier (5) in four cases of non-Hodgkin's lymphoma and one of Hodgkin's disease. The four cases of Hodgkin's disease were classified into mixed cellularity (3 patients) and nodular sclerosis (1 patient), and were diagnosed in 1982 (1 patient), 1983 (1 patient), and 1984 (2 patients). Two had initial bone marrow involvement; and the first patient died with extensive disease 3 months after diagnosis.

We agree with Robert and Schneiderman that the deregulation of the immune system that appears to initiate the sequence of events in the patients with this syndrome may be associated with a broader spectrum of lymphoid neoplasias than we originally suspected (5).

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Bone Marrow in the Acquired Immunodeficiency Syndrome

To the editor: The letter by Franco and associates (1) addresses the poorly understood phenomenon of bone marrow depression in the acquired immunodeficiency syndrome. We recently completed a cytologic and cytokinetic analysis of bone marrow from patients with the syndrome that supports and extends the findings by Franco and associates. Bone marrow biopsy samples from eight homosexual men meeting the Center for Disease Control's criteria for the syndrome were obtained, and differential cell counts and flow cytometry were done. Eleven patients were used as controls, ages 35 to 65, with localized solid tumors without histologic evidence of bone marrow involvement. As in the study by Franco and associates, patients with the syndrome had a relative marrow plasmacytosis as compared to controls ($3.1 \pm 1.7\%$ compared to $1.8 \pm 2.2\%$ [$\pm$ SD], $p = 0.19\%$). Patients with the syndrome also had a relative eosinophilia compared to controls ($4.5 \pm 3.6\%$ compared to $2.7 \pm 1.5\%$, $p = 0.22$). Dysplastic megakaryocytes were seen in five of eight patients with the syndrome, but in only 2 of 11 controls ($p = 0.31$).

We analyzed seven of the bone marrow specimens with flow cytometry (2). Samples were stained with either ethidium bromide and mithramycin to generate high resolution DNA histograms (mean coefficient of variation = 2.5%), or acridine orange for DNA and RNA histograms. In the high-resolution DNA histograms, no aneuploid clones, signifying a premalignant state, were seen. Acridine orange-determined RNA content of the bone marrow from patients with the syndrome did not differ from marrow of the controls.

Flow cytometric studies of the 11 control bone marrow specimens showed an average proliferative fraction (the percentage of cells in the S+G2/M compartments of the cell cycle) of $19.9 \pm 4.2\%$ Mean proliferative fraction of the bone marrow from patients with the syndrome was $16.9 \pm 6.4\%$ ($p = 0.3$). However, four of the seven marrows from these patients had proliferative fractions below 13%, whereas none of the normal marrow controls did ($p = 0.024$ by the chi-squared test).

The plasmacytosis and eosinophilia seen allows speculation as to whether there is an autoimmune inhibition of hemapoiesis (3), as has been hypothesized in Epstein-Barr virus aplastic anemia (4). Hassett and associates (5) in reporting their failure to reconstitute hemopoietic function in the acquired immunodeficiency syndrome with allogeneic bone marrow transplants postulated that the presence of a reactivated virus could have infected and suppressed donor stem cells. Or the marrow dysfunction could be a result of the malnutrition or multiple infections which occur in these patients. The phenomenon deserves more study because it can contribute significantly to the morbidity and mortality of these patients.

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Hematin-Induced Hemolysis in Acute Porphyria

To the editor: Although complications associated with the use of hematin have been rare, we report a case of hematin-related hemolysis in a woman with severe acute intermittent porphyria.

A 32-year-old woman who had had symptomatic acute intermittent porphyria for 18 months presented with her fourth monthly episode of porphyric neuropathy. She had severe, non-localized, lower abdominal pain requiring high-dose narcotics; resting tachycardia; fever without leukocytosis; hypertension (170/120 mm Hg); depression; urinary retention; the syndrome of inappropriate diuretic hormone secretion; and quadriparesis. An electromyogram 1 year before had shown a mild median neuropathy of the right hand with some delay in nerve conduction velocity. Serum porphobilinogen was 120 μg/100 mL (normal, 0-4.4 μg/100 mL), serum delta-aminolevulinic acid was 86 μg/100 mL (normal, 0-10 μg/100 mL), and 24-hour urine porphobilinogen was 68 mg/d (normal, less than 10 mg/d). Four weeks before this admission she had received six doses of hematin (4 mg/kg body weight · 12 h) with complete remission of abdominal pain, fever, tachycardia, and diffuse extremity pain. There was a corresponding biochemical response, and superficial phlebitis was the only complication.

Hematin was administered for the fourth monthly episode in the same fashion with marked improvement within 36 hours of therapy of all her neuropathic and psychiatric disturbances, but after 48 hours (four doses), the patient developed a Coombs' negative hemolytic anemia. The patient received no other medications before the onset of the hemolysis. Hematocrit fell from 0.36 to 0.18 in 24 hours. The leukocyte count was 6500/mm^3; platelets, 260 000/mm^3; reticulocytes, 16%; and lactic dehydrogenase, 940 U/L (normal, 80 to 240 U/L). Plasma-free hemoglobin was markedly elevated; haptoglobin non-detectable; the peripheral smear showed polychromasia, nucleated erythrocytes, and erythrocyte fragmentation. Fibrinogen, fibrin degradation products, and assays of glucose-6-phosphate dehydrogenase and pyruvate kinase were normal; prothrombin time, partial thromboplastin time, thrombin time, and anti-thrombin III were all normal. Complement, IgG, and IgM were not found on the erythrocyte membrane. With cessation of the hematin therapy, all variables reverted to normal within 72 hours. The patient has since received another successful course of hematin without hemolysis.

Thrombophlebitis (1), transitory oliguric renal failure (2), and a coagulopathy manifested by thrombocytopenia, a prolonged prothrombin time, partial thromboplastin time, and hypofibrinogenemia (3) have been reported as complications of hematin therapy. When examined in vitro, hematin has been shown to aggregate platelets, to induce the release of serotonin and adenosine triphosphate, and to inactivate thrombin (4). In addition, when mouse erythrocytes are incubated with ferriprotoporphyrin IX (hematin) for 2.5 hours at 37 °C and pH 7.4, dose-dependent hemolysis occurs, suggesting hematin-induced erythrocyte membrane destruction (5). Hematin is an effective and reasonably safe agent for the treatment of attacks of inducible porphyria when used in conjunction with a high carbohydrate intake, avoidance of all precipitating factors, and vigorous supportive care. However, we recommend careful observation for bleeding, coagulopathy, and hemolysis during and after its administration.

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Sulfasalazine and Ankylosing Spondylitis

To the Editor: We read with interest the review on sulfasalazine by Peppercorn (1). We write to suggest another indication for use of sulfasalazine.

We have evaluated the therapeutic effect of sulfasalazine in the treatment of ankylosing spondylitis. Eight patients (mean age, 29 years; 5 male, 3 female) with classic ankylosing spondylitis and peripheral arthritis (2), whose active disease was not adequately controlled by non-steroidal anti-inflammatory drugs, were included in an open trial. Two patients had transient diarrhea but no roentgenographic or sigmoidoscopic evidence of ulcerative colitis or Crohn's disease. None of the patients had psoriasis or Reiter's syndrome. Six of eight patients had the HLA-B27 antigen. Patients were treated for 16 weeks with sulfasalazine (2 g/d, four patients; 3 g/d, four patients). Non-steroidal anti-inflammatory drugs were continued in all patients. Clinical and laboratory variables of disease activity at 0 and 16 weeks were compared.

Sulfasalazine proved to be effective in six of eight patients. Sulfasalazine significantly decreased the duration of morning stiffness (mean, 10.7 minutes at 16 weeks compared to 94.3 minutes before treatment; $p < 0.05$); the number of painful joints (mean, 1.1 compared to 3.4, $p < 0.005$); and the erythrocyte sedimentation rate (16.3 mm compared to 48.0 mm, $p < 0.05$, Student's t-test). The mean decrease in the daily dose of non-steroidal anti-inflammatory drugs was 30.2% at 16 weeks. The mean global improvement assessed by the patient was 61% at the end of the trial. Improvement generally occurred in the first 4 to 8 weeks of the 4-month study. Patients had no significant adverse reactions to sulfasalazine.

This uncontrolled study suggests that over a 4-month period sulfasalazine is effective in the treatment of active ankylosing spondylitis with peripheral arthritis. A controlled double-blind study of sulfasalazine in ankylosing spondylitis is underway.

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Radiologic Methods for Estimation of Mineral Content of Bone

To the Editor: The American College of Physicians Position Paper (1) on radiologic methods to evaluate bone mineral content, does not give a balanced picture of the state of the art of bone mineral measurement from roentgenograms of the skeleton. The paper fails to distinguish between two different versions of measuring bone mineral mass from roentgenographic images of the phalanges. Photodensitometry is the name given to both methods. The older, inferior aluminum equivalency method (2-4) compares the optical density of the bone image with the optical density produced by an aluminum reference wedge. The mass of the flesh-covered bone is then reported in terms of an equivalent thickness of aluminum. As such, aluminum equivalency does not measure bone mineral mass, but rather mass of the entire limb including skin, fat, flesh, mineral, matrix, and body fluids. The paper would have been more correct if it had stated "... the aluminum equivalency version of photodensitometry has technical problems relating to radiologic technique and methods of film processing that limit its use." Although the literature is full of references to this outdated method, it is not used much today because it is plagued with inaccuracy and imprecision.

The position paper gives only a passing reference to the newer method, radiographic absorptiometry (4). A glance at Table 1 of the paper shows that "photodensitometry" (actually radiographic absorptiometry) compares favorably with all of the other methods listed there as to precision (1% to 4%), reliability (6%) and radiation exposure (local tissue, up to 100 mrad; gonads, negligible), as well as cost (up to $65).

The only true area of controversy is whether the phalanges mirror conditions in the axial skeleton. The paper says "Radiogrammetry, photodensitometry, and single-energy absorptiometry are used to measure the mineral content of the appendicular skeleton, but are not useful for the axial skeleton. Therefore, these methods of quantifying bone mineral content may be of limited clinical use in assessing those metabolic bone diseases that usually involve areas of proportionately greater trabecular bone content, such as the spine."

I think it should be made clear that the three methods mentioned do not measure the same quantity (that is, mineral mass, mineral density, and bone volume), the same site, or even the same kinds of bone. Lumping these methods together by implying that all appendicular skeleton measurements are unlikely to mirror the spinal condition may be unwarranted. In particular, phalangeal bones are quite a fair mix of spongiosa and compacta, and may be better indicators of the axial skeletal status than the hard compact bone of the forearm.

Because the radiographic absorptiometric version of photodensitometry is having significant clinical impact in chronic renal failure and osteoporosis detection, whereas the aluminum equivalency method is little used, it is unfortunate that the paper did not clearly delineate these two methods.

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To the Editor: In a recent position paper (1) on radiologic methods for evaluating bone mineral content, there was a marked error. On page 909, it is stated that "neutron activation analysis requires higher radiation doses, generally on the order of 300 to 5000 mrad." These figures were for mrem; the actual dose should have read 30 to 500 mrad.

I should also mention that two key references were omitted from this report (2, 3).

An important point missed in this position paper is that total body neutron activation, although not available in many centers, is the only direct measure of bone mass (total body calcium). This measure, therefore, is important as a standard by which the indirect density measurements of photon absorptiometry and computed tomography need to be validated.

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In response: We have tried to stress that recent technical advances such as absorptiometry have enhanced the efficacy of photodensitometry. The figures for "photodensitometry" in Table 1 are ranges for both the aluminum equivalency method and the radiographic absorptiometry method. Dr. Krumholz is correct in that the figures in Table 1 include both old and new techniques. The new technique does indeed have better sensitivity and selectivity. However, the crux of the controversy, as Dr. Krumholz points out, rests in whether the techniques that measure bone mineral content in the appendicular skeleton accurately reflect the changes that occur in the axial skeleton. There is ample evidence that changes in total skeletal bone mineral content may be heterogenously distributed (1-4). Most studies suggest that measurement of bone mineral content should probably be determined at the site of anatomic interest.

Dr. Cohn refers to the quality factor analysis for conversion of mrem to mrad. The figures for neutron activation analyses in Table 1 are incorrectly given in mrem, rather than mrad. The range of exposure for neutron activation analyses in Table 1 should read 30 to 3000 mrad, depending on the neutron energy used (5). We have noted that "photon absorptiometric methods tend to correlate better with results from neutron activation analysis, the 'gold standard' for total skeletal calcium measurement." Further studies are needed to correlate radiologic methods for evaluating bone mineral content with data from regional neutron activation analyses.

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Cardiac Function in Septic Shock

TO THE EDITOR: Parker and colleagues (1) noted a paradox in their study of 20 patients with documented septic shock. Ten of thirteen survivors but none of seven nonsurvivors had an initial ejection fraction less than 0.4. Survivors' ventricular end systolic and end diastolic volumes were substantially increased (160 and 120 mL) with a normal stroke volume index (40 mL) but ejection fraction of only 0.32 at the end of the first day of sepsis. The end systolic and end diastolic volumes in the nonsurvivors were about 80 and 32 mL (ejection fraction of 0.55). The authors ascribe the better nonsurvivor ejection fraction to lower nonsurvivor vascular resistance (1200 compared to 1500 dyne · 5 · cm^{-5}/m^2 for survivors). The large differences in end diastolic and end systolic volumes in spite of pulmonary capillary wedge pressures, maintained at 12 to 15 mm Hg, remain unexplained. If the wedge pressure was maintained as stated, either ventricular compliance differed markedly for unclear reasons, or ventricular filling pressure was consistently dissociated from wedge pressure in one of the groups.

Two other observations, in which wedge pressure was higher than ventricular filling pressure, may be relevant. Mammana and associates (2) found that wedge pressure averaged 10 mm Hg higher than left atrial pressure in patients receiving nitroprusside 4 hours after cardiac surgery. Lefcoe and colleagues (3) reported wedge pressure to be 30 mm Hg higher than left ventricular end diastolic pressure in five septic patients. These observations could be integrated with those of Parker and colleagues by the following postulate: vasodilation may occur related to depression of hypoxic pulmonary vasoconstriction by sepsis, administration of nitroprusside or other vasodilators, or the recruitment of pulmonary vessels associated with an elevation of cardiac index. Any of these factors could cause sufficient increase in collateral circulation to the vascular bed distal to the occluding pulmonary artery catheter balloon, sufficient to maintain wedge pressure higher than left atrial pressure. In the series of Parker and colleagues, it could be that collateral pulmonary blood flow elevated wedge pressure above left atrial pressure in the nonsurviving patients. Pulmonary vascular resistance in nonsurvivors could have undergone greater septic depression of hypoxic pulmonary vasoconstriction, and been decreased by higher cardiac index. The lower end diastolic volume of the nonsurviving group may have been due, therefore, simply to a lower left atrial pressure.

If this dissociation occurs in septic patients, there are several implications. Ventricular filling pressure may be considerably less than is suggested by the wedge pressure. To assure adequate ventricular filling in septic patients, greater reliance would have to be placed on volume challenge, measurement of end diastolic volume, or direct measurement of left atrial or left ventricular end diastolic pressure (2, 3) in lieu of wedge pressure. Pulmonary microvascular pressure and the risk of pulmonary edema would be higher for any given ventricular filling pressure. The use of vasodilators to maintain oxygen transport with minimal pulmonary microvascular pressure (4) may inherently maintain pulmonary microvascular pressure higher than left atrial pressure.

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Digitalis in Congestive Heart Failure

TO THE EDITORS: We read the interesting review by Mulrow and associates (1) and wish to clarify a few points, particularly with regard to our own study (2). Although we did not explic-

itly state so, our double-blind, placebo-controlled study of digitalis in patients with stable congestive heart failure was in fact randomized. Indeed, after designing a placebo-controlled crossover study, it would make little sense not to randomize. Randomization was done by our hospital pharmacy.

We did not use phonocardiography routinely because only one patient had an S_3 gallop heard on auscultation. We agree that a sample size calculation beforehand may provide useful estimates for study design; however, the high degree of uncertainty regarding the endpoint frequency—that is, clinical deterioration after digoxin withdrawal—limits the overall usefulness of such calculations. Although none of our 30 patients deteriorated clinically over the 3-month placebo phase, it is conceivable that an occasional patient with seemingly well-compensated heart failure may have such deterioration. Our intent was not to precisely quantify this "withdrawal failure rate" but merely to emphasize that it is small. Among our ten patients who dropped out, one had an exacerbation of heart failure; even if he is included and considered a withdrawal "failure," the withdrawal failure rate becomes only 2.5%. Perhaps more important, our numbers and techniques were sufficient to detect a 3% increase in echocardiographic end diastolic left ventricular size and a 10% decline in velocity of circumferential fiber shortening associated with withdrawal from digoxin. That the clinical compensation was maintained in these patients over a follow-up period averaging 19 months emphasizes that these echocardiographic changes are probably clinically unimportant. Nearly identical changes in these echocardiographic variables were shown by Griffiths and associates (3) after digoxin withdrawal in 11 patients, only 1 of whom decompensated. Finally, a study by Gheorghiade and Beller (4) published in 1983, although unblinded, has confirmed our success in withdrawing digoxin therapy from a well-defined subset of 24 predominantly older men with coronary artery disease.

We heartily concur with Mulrow and associates (1) that further long-term studies with specific clinical endpoints involving well-defined patient subjects are crucial to determining the role of digitalis in the management of chronic congestive heart failure. The well-known toxicity of digitalis and the rapidly expanding number of diuretic agents and vasodilators only heighten the need for such studies.

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Precipitation of Verapamil in an Intravenous Line

To the editor: In a letter in the October 1982 issue, Bar-Or and associates (1) reported a case in which an intravenous line of 0.45% NaCl was established. Sodium bicarbonate had been added to the primary intravenous solution and verapamil, 5 mg, was injected through the intravenous line. An immediate precipitate was seen in the line distal to the point of injection.

We wish to report a similar incident with verapamil injection in a patient at our institution with the antibiotic nafcillin sodium (Unipen; Wyeth Laboratories; Philadelphia, Pennsylvania). Precipitation occurred on three occasions involving three different nurses in the coronary care unit on different days. Dopamine was being infused at the same time during one of the three incidents. When verapamil was pushed through the intravenous line when dopamine was being infused alone, there was no precipitation. This phenomenon occurred only when the nafcillin was being passed via a buretrol system into the primary intravenous line of 5% dextrose and 0.33% NaCl with potassium chloride in a 1-litre bag. This occurrence may also be related to a pH problem as mentioned by Cutie (2) in her evaluation of the verapamil-sodium bicarbonate incompatibility.

Cutie (3) has published a comprehensive review of compatibilities with verapamil HCl in which she used verapamil HCl, 80 mg, in 1 litre of normal saline solution and 5% dextrose; her findings showed that nafcillin, 2 g, and verapamil in the study concentration were physically compatible. From our experiences with verapamil intravenous push and nafcillin, we do not recommend adding verapamil to any line that has nafcillin being infused through it. A thorough flush of the line with the primary solution should be done at the conclusion of the administration of the added nafcillin to insure complete delivery of the nafcillin dose to the patient and to avoid verapamil precipitation to the primary intravenous line. Our nursing staff was concerned with this incompatibility. The patient had only one central line in place and it was difficult to change lines and drug administration times because the patient went into supraventricular tachycardia spontaneously and needed verapamil immediately for conversion to normal sinus rhythm.

We could not find any documentation in the literature of this intravenous incompatibility. Because it was quite troublesome to our nursing staff, we believe that this problem should be brought to the attention of all personnel involved in preparing and administering medications, especially in critical care units of hospitals.

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Vancomycin and Cardiac Arrest

To the editor: Neither a recent review of the neurotoxicity of antibacterial agents (1) nor the *Physician's Desk Reference* (2) includes vancomycin as a drug that can cause neuromuscular blockade or cardiac arrhythmia. We recently saw a patient in whom inadvertent rapid intravenous administration of this drug resulted in apparent cardiopulmonary arrest.

A 57-year-old diabetic woman undergoing peritoneal dialysis developed enterococcal peritonitis. Vancomycin, 1 g, was mistakenly administered as an intravenous bolus over 2 minutes. Within 1 minute after receiving the bolus, the patient suddenly slumped back and stopped breathing; her pulses were unobtainable. External cardiac compression and bag ventilation were immediately started. Within 2 minutes the patient began to breathe spontaneously; an electrocardiogram showed only normal sinus rhythm, and her blood pressure was 130/70 mm Hg. The patient became alert 5 minutes later. The possibility of acute myocardial infarction was excluded and the patient's condition remained stable thereafter.

The exact mechanism of our patient's transient apnea and lack of pulse was not identified. But we suggest that vancomycin given rapidly as an intravenous bolus may cause transient neuromuscular blockade or ventricular arrhythmia. This possibility strengthens current recommendations (2) to administer this drug intravenously over 20 to 30 minutes.

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Paradoxical Diaphoresis in Cyclobenzaprine Poisoning

TO THE EDITOR: Cyclobenzaprine (Flexeril; Merck Sharp & Dohme, West Point, Pennsylvania) is a central-acting skeletal muscle relaxant structurally related to the tricyclic antidepressant amitryptiline. Severe cyclobenzaprine poisoning from intentional overdose has been reported in only three previous cases (1). These patients presented with anticholinergic signs, including dry skin and mucous membranes, and an organic brain syndrome that reversed with treatment with physostigmine. We report the case of a patient with cyclobenzaprine poisoning who presented atypically with profound diaphoresis.

A 22-year-old man ingested an unknown quantity of "yellow stop sign-shaped pills" in a suicide attempt approximately 1 hour before admission. Vital signs included: blood pressure, 160/84 mm Hg; pulse, 160/minute and regular; respiratory rate, 28/minute; and temperature, 37 °C. The skin was profusely diaphoretic but of normal color and temperature. The mucous membranes were moist. The pupils were midposition and sluggishly reactive. Bowel sounds were normoactive, and the bladder was not enlarged. The patient was initially lethargic but became progressively more agitated and confused, requiring restraint. Naloxone, 2 g, and dextrose, 25 g, were administered intravenously, without benefit. Orogastric lavage could not be done because of extreme patient combativeness. Laboratory data, including complete blood count, electrolytes, glucose, and arterial blood gases were within normal limits. The electrocardiogram showed sinus tachycardia with a rate of 160/minute; the QRS interval was 100 milliseconds. Over the next several hours, his agitation diminished and he became stuporous. The skin was now warm and dry. A urine drug screen showed pyrilamine (an antihistamine), but no tricyclics, amphetamines, cocaine, or phencyclidine. He made an uneventful neurologic recovery over the next 48 hours. Upon regaining full consciousness, he identified 10-mg tablets of Flexeril as the pills he had taken.

Although paradoxical sweating has been recognized as an uncommon side effect of therapeutic doses of cyclobenzaprine (2) (and, indeed, of tricyclic antidepressants in general [3]), anhidrosis with hot, flushed skin is considered a classic sign of anticholinergic poisoning that accompanies cyclobenzaprine overdose (1, 4). However, our patient presented with profuse diaphoresis, initially causing us to reject the possibility of acute tricyclic poisoning. Because the neurologic complications of tricyclic overdose, including agitated delirium and seizures, are rapidly reversible with physostigmine (1, 5), early diagnosis is essential. Diaphoresis, as well as anhidrosis, must be considered part of the dermatologic spectrum of cyclobenzaprine poisoning, and perhaps of tricyclic antidepressant poisoning as well. The cause of the diaphoresis is unknown (3).

Cyclobenzaprine is not among the tricyclic compounds routinely assayed in gas chromatographic analysis of the urine. Therefore, it is not surprising that the results of our patient's toxicologic studies were negative for tricyclic antidepressants. Linden and associates (1) reported that in two of their patients with cyclobenzaprine overdose in whom toxicologic screens were negative, two unclassified peaks in the tricyclic-antidepressant retention time range were subsequently identified. Reevaluation of our patient's gas chromatographic studies did not show any similar peaks.

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Cellulitis at Vein-Donor Sites

TO THE EDITOR: Donor-site cellulitis after saphenous venectomy for coronary artery bypass has been previously reported (1, 2). We report a case of cellulitis involving two distinct vein donor sites after a dental procedure.

A 61-year-old Latin American man had triple coronary artery bypass surgery in July 1980. Two months after surgery he developed spontaneous cellulitis involving both donor sites of the right leg. The infection responded to intravenous nafcillin therapy. In 1984 he developed fever, chills, and malaise 1 day after a dental extraction. The next day cellulitis of the right leg became apparent, and he was admitted to the hospital. There was no history of recent trauma to the leg or foot.

At examination the patient had a temperature of 37.5 °C; heart rate, 70/minute; respiratory rate, 16/minute; and blood pressure, 130/80 mm Hg. His pulmonary, cardiovascular, abdominal, and neurologic findings were all normal. All peripheral pulses were 2+ and symmetrical. He had an 18-cm well-healed surgical scar on the medial side of the right thigh and a 19-cm surgical scar on the medial aspect of the right leg. Separated by 10 cm, each scar was surrounded by areas of erythema that were separate and distinct. Both areas were warm and tender to palpation and trace edema was seen. No evidence of infection or trauma to the right foot was found. The right inguinal nodes were slightly enlarged and tender.

The leukocyte count was 8900/mm^3 with 81% polymorphonuclear forms, 2% band forms, 16% lymphocytes, and 1% monocytes. Electrolytes and SMA-12 were normal. Two sets of blood cultures were negative. The ASO titer was negative. Nafcillin was administered intravenously, and the cellulitis resolved within 24 hours. The patient was discharged and given oral dicloxacillin.

The exact pathogenesis of vein-donor-leg cellulitis is not known. Group A streptococcus has been proposed as the causal agent (1). The major predisposing factor is probably local compromise of lymphatic and venous drainage. Concurrent *Tinea pedis* infection (2) and hypersensitivity to streptococcal exotoxin (1) have also been implicated as causative factors. The relation in time of our patient's cellulitis to the dental extraction may suggest that a transient bacteremia seeded the vein-donor leg leading to recurrent cellulitis in this patient. *Streptococcus pyogenes*, however, is an unlikely organism to cause bacteremia after dental extraction, and the pathogenesis of the soft tissue infection remains obscure (3, 4). Patients who have recurrent episodes of vein-donor-leg cellulitis may benefit from antimicrobial prophylaxis similar to those regimens used in the prevention of rheumatic fever (5), but definitive therapy recommendations await further experience with this syndrome.

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Schistosomiasis and Praziquantel

TO THE EDITOR: Last year, in commenting on a review article on praziquantel published in your journal (1), we reported excellent results obtained by treating *Schistosoma haematobium* infection in children with a single oral dose of 30 mg/kg body weight (2). Indeed, this low dose was subsequently also found to be adequate in relieving urinary obstructive lesions caused by *S. haematobium* infection (3). In the same letter, we emphasized the unsuccessful treatment of *S. mansoni* infection in Egyptian children with praziquantel, even when using a higher single dose of 40 mg/kg body weight; instead, we suggested treating them with three doses of 20 mg/kg body weight given in 1 day.

We have now completed treatment of a similar group of 20 children infected with *S. mansoni* (mean age, 14 years; mean stool egg count, 261 per gram of feces; mean follow-up period after treatment, 6 weeks). All of the children were cured; in none were eggs found in the stool or rectal tissue biopsy specimens obtained 6 weeks after completing therapy. No adverse reactions were reported in any patient.

We conclude that a three-dose 1-day regimen of orally administered praziquantel is effective therapy for *S. mansoni* infection in Egyptian children.

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Cimetidine in Recurrent Genital Herpes Simplex Infection

TO THE EDITOR: Recurrent genital infection with herpes simplex virus is a common clinical problem associated with considerable morbidity. A large number of different therapeutic regimes have previously been reported. The use of immunomodulatory agents, such as cimetidine, has not been comprehensively assessed; however, experience with this agent in the treatment of other herpes viral infections indicates a possible beneficial effect (1, 2). The mode of action of cimetidine in this context has not been fully elucidated but may relate to the effect of the drug on suppressor T-cell function (3).

Over a 6-month period, six patients (three men and three women) with severe, recurrent culture-proven herpes simplex virus II genital infection were treated on a prophylactic basis with cimetidine, 400 mg twice a day. The mean age for the women was 33 years and for men 37 years (range, 27 to 49 years). The mean frequency of attacks of genital herpes before the use of this drug was 1.6 attacks per month, and the patients had had the disease an average of 32.5 $\pm$ 25.3 months (range, 5 to 84 months). After a 3-month course of cimetidine, the frequency rate of recurrent genital lesions fell to 0.4 attacks per month. In two patients the treatment was stopped and after a 3-month follow-up, attack rates had returned to pretreatment levels. There have been no serious side effects and the treatment is well tolerated, with all but one patient on continuous treatment. Treated patients who developed recurrent herpes simplex virus infections had less pain and a shorter time course of the local lesion than before the use of prophylactic cimetidine.

The results of this small uncontrolled trial show a significant effect with the use of cimetidine on a prophylactic basis in recurrent severe genital herpes. The results are similar to the recent reports on the use of acylovir (4, 5) in the treatment of this disease, and cimetidine may provide an alternative or supplementary agent in the treatment of severe recurrent genital herpes viral infection. The advantages of cimetidine in this context may relate to the greater clinical experience with the prophylactic use of this agent, and the possibility that its use may not result in the development of viral stains resistant to antiviral agents. A double-blind controlled trial to further assess the efficacy of this new form of treatment is underway.

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Cytomegalovirus Infection or Disease

TO THE EDITOR: I read with interest the informative report by Stover and associates (1) on bronchoalveolar lavage and diffuse pulmonary infiltrates in immunosuppressed hosts. I agree that bronchoalveolar lavage is safe and useful, and our own experience corroborates its high yield, especially in certain patient groups such as patients with the acquired immunodeficiency syndrome and *Pneumocystis carinii* pneumonia (2).

One question that occurred to me on reviewing this report is how to differentiate between cytomegalovirus infection and disease. Previous reports imply the frequent finding of both *Pneumocystis carinii* pneumonia and cytomegalovirus infection in immunosuppressed patients. In our first 20 patients with this syndrome and *P. carinii* pneumonia, 17 had coexistent cytomegalovirus lung infection. All but 3 of these first 20 patients did well on therapy for *P. carinii* pneumonia alone with resolution of symptoms, hypoxia, and abnormalities seen on chest roentgenogram and gallium lung scan. This therapeutic response to *P. carinii* pneumonia makes less likely a pathologic role for cytomegalovirus in terms of disease, that is, cytomegalovirus pneumonia. I am wondering if Dr. Stover has also seen coexistent *P. carinii* pneumonia and cytomegalovirus in patients with the syndrome who do well on therapy for *P. carinii* pneumonia alone. It is possible that the lung is a reservoir for cytomegalovirus and finding this virus does not imply disease but simply infection.

The other question relates to the recommendation that bronchoscopy not be delayed more than 48 hours after beginning therapy for *P. carinii* syndrome for fear of leading to a false negative biopsy or lavage. In our experience, even patients who resolve clinically and roentgenographically after a 3-week course of treatment still have *P. carinii* cysts and *P. carinii* pneumonia on bronchoscopic examination after treatment. More than half of our patients with *P. carinii* pneumonia in the context of the acquired immunodeficiency syndrome have persistent organisms even with a clear positive clinical response to therapy and a subsequent course that rules out persistent disease. I certainly agree that bronchoscopy should be done as early as possible and empiric use of therapy for *P. carinii* pneumonia should be discouraged without the appropriate evidence for lung infection by *P. carinii*. I would ask Dr. Stover if bronchoscopic examination after treatment in her experience has not been positive for pneumocystis cysts or *P. carinii* pneumonia. It may be that cysts after treatment are not viable but to date this dilemma of persistent organisms despite clinical resolution of pneumonia has not been adequately studied or resolved.

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2. BROADDUS C, DAKE M, STULBARG M, GOLDEN J, HOPEWELL P. Bronchoalveolar lavage in the diagnosis of opportunistic infections in patients with the acquired immune deficiency syndrome [Abstract]. *Am Rev Respir Dis.* 1984;**129**:A35.

In response: We appreciate Dr. Golden's remarks about our recent paper (1). First, we wish to emphasize that this paper dealt with immunosuppressed patients without the acquired immunodeficiency syndrome. *Pneumocystis carinii* pneumonia has recently been reported to have significant differences in patients with the syndrome and those without (2). Cytomegalovirus infection, although not reported, may also be different in these two patient populations.

To address the comment about distinguishing cytomegalovirus infection versus disease, we would agree that the differentiation is often difficult. We have found, however, that the presence of cytopathologic changes suggestive of cytomegalovirus on bronchoalveolar lavage specimens has a high correlation with active disease (unpublished data). More cases, however, will be needed to obtain sensitivity and specificity data. Contrary to Dr. Golden's data, in our experience when *P. carinii* pneumonia and cytomegalovirus were found simultaneously on bronchoscopic specimens, patient outcome was dismal (3). In the 13 original patients with this finding, mortality was 92%. Mortality remained high whether cytopathologic changes were present or cultures were positive for cytomegalovirus in the presence of pneumocystis pneumonia. More recent data suggests mortality is lower than 92% with the combined infection but certainly worse than with pneumocystis pneumonia alone (unpublished data).

To answer the second question about timing of bronchoscopic examination after specific treatment for *P. carinii* pneumonia has begun, we have not systematically reexamined these patients. There are reports that cysts remain for long periods of time after treatment, especially in patients with the acquired immunodeficiency syndrome (4). However, there is no study that delineates the shortest period of time that total clearance of cysts can take place. Therefore, once therapy has begun, a diagnostic procedure should not be unduly delayed.

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Listeria monocytogenes Bacteremia in the Acquired Immunodeficiency Syndrome

TO THE EDITOR: Patients with the acquired immunodeficiency syndrome are highly susceptible to a number of opportunistic infections. *Listeria monocytogenes* frequently causes bacteremia and meningitis in patients with T-cell defects, most commonly immunosuppressed cancer patients (1). Although listeria infections would be anticipated in patients with this syndrome, there have been no reports of such infections to date. We have followed 2 patients with listeria bacteremia in a group of 226 patients with the acquired immunodeficiency syndrome seen at this center as of March 1984.

The two patients presented with high temperatures and constitutional symptoms. Blood cultures showed *L. monocytogenes*. Neither a focus of infection nor neurologic abnormalities were found. Although one patient showed pleocytosis in the cerebrospinal fluid, bacteria were not isolated from it. Both patients were treated with intravenous ampicillin, 12 g/d for 2 weeks, and both developed a generalized skin rash, treated with antihistamines. Neither patient developed a documented recurrence of listeria infection.

Bacteremia is one of the several manifestations of listeria infection. In adults, bacteremia most often presents in immunosuppressed patients, particularly in patients with lymphoma, in patients receiving corticosteroids and, less often, in patients with solid tumors receiving chemotherapy (1). Evidence of central nervous system infection is commonly found, sometimes in the absence of any clinical symptoms or signs. When *Listeria* produces meningoencephalitis, findings in the cerebrospinal fluid are extremely variable. In a large series, *Listeria* was the commonest cause of meningitis in patients with underlying neoplastic disease (2). Neither of our patients developed signs suggestive of central nervous system involvement.

There is considerable evidence that resistance to *Listeria* depends on the presence of intact cellular immune mechanisms. Mackaness (3) showed that in mice resistance to listeria infection depends on the activation of macrophages, and that passive protection was obtained only by transfer of viable peritoneal exudate cells from immune animals. As processing of listeria antigens by macrophages is necessary for induction of specific T-cell immunity (4), gamma interferon, a potent macrophage activator, may play a key role. Patients with the acquired immunodeficiency syndrome have been shown to be deficient in producing gamma interferon (5), and this may have contributed to the development of listeria bacteremia in the two patients reported here. Overall, it is surprising that listeria infections have not been seen more often in patients with this syndrome. Nevertheless, as shown by our observation of two cases, it is likely that listeria infections will be encountered in some of these patients. As the duration of antibiotic treatment should be extended to 4 weeks in patients with central nervous system involvement (1), cultures of cerebrospinal fluid should be done as part of the evaluation of patients with listeria infections.

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Correction: Review of Videotapes on Endoscopy

TO THE EDITOR: In your August issue you published a review (1) of a series of videotapes on endoscopic procedures produced by Grandview Hospital. Although I appreciate most of the criticism provided by the reviewer and the exposure that your journal provides, I would like to clarify a few points concerning our tapes.

First, the correct name of our organization is Grandview Hospital and Medical Center. Although we are an osteopathic institution, "Grandview Osteopathic Hospital," as the review states, is not the appropriate name for our facility. Second, neither the review nor the list of tapes that describes the series indicates that these tapes are available individually and can be purchased separately. In light of the reviewer's criticism of the series as being "overpriced," a clarification of this point may be helpful to your readers.

Lastly, your reviewer states that a "special projector" is required to view the tapes. Although the videotapes are available in various formats, once a customer has ordered the appropriate tape, no special arrangements are necessary. One advantage of the videocassette format is that it is "user-friendly." Your reviewer somehow implies that we have made this advantage a disadvantage.

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1. KUIPER DH. Endoscopic procedures series [Audiovisual review]. *Ann Intern Med.* 1984;**101**:285-6.

Correction: Author's Academic Degree in Letter on Cytomegalovirus

In a letter in the August issue (1) the academic degree of one of the authors was incorrectly given as M.D. The letter should have read Richard C. Hunt, M.S.

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1. HUGHES GS JR, HUNT R. Cytomegalovirus infection with rhabdomyolysis and myoglobinuria [Letter]. *Ann Intern Med.* 1984;**101**:276-7.

Correction: Figure in Article on Theophylline Overdose

In an article in the October issue (1) on theophylline overdose, an error appear in Figure 1. In the left hand panel, the equation for y should read $y = 3.44 - .007\ x$.

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