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 Tables and figures will not be published.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.

Revising the Residency

TO THE EDITOR: The recent article by Schroeder and colleagues (1) provides a clear analysis and shows foresight in attempting to match the changing face of medicine and residency training needs in internal medicine.

I appreciate their acknowledging the experience of the specialty of family practice in providing ambulatory training in many of the areas noted by them as worthy of more attention in internal medicine residency training. Although it is correct to refer to family practice as a "new" specialty in a relative sense, your readers should recognize that this specialty recently celebrated its 17th anniversary. This is significant because many residency training programs in family practice have 10 to 15 years of experience in providing the kinds of ambulatory skills that Schroeder and colleagues are suggesting be available to residents training in internal medicine.

None of us needs to keep reinventing the wheel. Information and experience in teaching methods learned during this period by teachers in family practice need to be shared with colleagues in internal medicine. Ambulatory training experiences in model family practice centers are an excellent way to provide some of the training in decision management in chronic illness, office dermatology, gynecology, orthopedics, and behavioral medicine cited by Schroeder and colleagues.

Residents training in family practice have benefited over many years from excellent teaching available from faculty in internal medicine. Although my suggestion may cause some of my colleagues in family practice to bristle (not to mention many in internal medicine), it is time for family physicians to acknowledge their obligation to train residents in other disciplines, and for internists to acknowledge that faculty in family practice have something worthwhile to offer their residents. Cooperative ventures will enhance both specialties. A better trained physician is the goal of each of our graduate training programs.

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REFERENCE

1. SCHROEDER SA, SHOWSTACK JA, GERBERT B. Residency training in internal medicine: time for a change? *Ann Intern Med.* 1986;**104**:554-61.

TO THE EDITOR: As I read the article by Schroeder and coworkers (1) and the accompanying editorials (2, 3, 4) on residency training in internal medicine, I reflected on the reasons why I did not choose a residency position in internal medicine. I felt that an internal medicine residency would not prepare me for management of outpatient problems to the extent that I wished. I noticed that most of the time spent in such residency programs involved the care of acutely ill inpatients and that ambulatory medicine was a secondary interest. Because of the dichotomy between the education received during residency and my anticipated practice, I chose a residency in family practice.

My family practice program stressed increasing amounts of time spent in ambulatory settings as I progressed through the 3 years of the residency program. I encountered various outpatient problems and had an opportunity to direct patients' medical concerns under supervision by training in a model family practice center. Training in this setting taught me careful chart documentation, telephone medicine, time efficiency, practice management skills, appropriate use of consultants, and what I perceived as cost-reduced approaches to patient care. These were some of the many benefits that made me feel "marketable" as a new physician on completion of my training program.

Because I believe that outpatient training in the family practice center prepared me well for private practice, I propose an educational collaboration between family practice and internal medicine residencies. Each discipline could educate both groups of residents in the areas of their respective strengths. Educational strengths of family practice residencies include a defined population base for, and an interest in, ambulatory practice; the behavioral aspects of medical practice; and an exposure to problems in outpatient management of surgical and internal medicine subspecialties. The essentials for family practice residency programs (5) currently address educational objectives in the ambulatory rotations of ophthalmology, otolaryngology, orthopedics, dermatology, and gynecology.

Family practice residencies should allow internal medicine residents to participate in these rotations and to care for ambulatory patients in the family practice center under the supervision of its full-time faculty. In exchange, family practice residents would participate in general inpatient medicine rotations including subspecialties, as is currently practiced. Residents from each specialty could then appreciate the relative strengths of each discipline.

My recommendations require some risk taking by each discipline. However, as Schroeder and colleagues state, "Shifting some internal medicine training from hospital medical services to surgical services and ambulatory settings will not be easy." Schroeder and colleagues suggest that the time for change is now, and I agree. Collaborative education would only improve the training for residents in both disciplines and ultimately improve patient care, our primary goal.

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

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3. GELLHORN A. Graduate medical education in internal medicine [Editorial]. *Ann Intern Med.* 1986;**104**:569-70.
4. LEWIS CE. Training in internal medicine: time to retool the factory [Editorial]? *Ann Intern Med.* 1986;**104**:570-2.
5. *American Medical Association Directory of Residency Training Programs, 1986-7.* Chicago: American Medical Association; 1986:25.

TO THE EDITOR: Schroeder and colleagues (1) give an insightful analysis of current and future issues in the training (and even the definition) of the internist.

A recent document from the Residency Review Committee for Internal Medicine that will go into effect in July 1986 (2), however, shows the attitudinal changes in high places that must occur before changes recommended by Schroeder and colleagues can be contemplated. The Residency Review Committee's revised *Special Requirements,* a statement on the philosophical, organizational, educational, and physical requirements for an internal medicine residency, perpetuates the emphasis on the hospital-based training and consultative aspects of the medicine residency. It states, "Inpatient service assignments in which the resident has a meaningful responsibility must provide a substantial majority of the resident's clinical experience." On continuity of care experience, the document states that "the continuity experience should be sufficient to provide a meaningful learning opportunity (preferably 36 months), yet not interfere significantly with other assignments, e.g., one-half day per week when on inpatient rotations [and] possibly more during the elective subspecialty of consulting electives." Even for special educational tracks, such as those emphasizing primary care in the ambulatory setting, the statement says, "It is expected that the core experience of residents will be in the care of inpatients."

Despite the acknowledgment that internal medicine is a primary care specialty, the orientation of the revised *Special Requirements* towards traditional internal medicine training is unmistakable and contrasts sharply with Schroeder and colleagues' forward-looking commentary. That the document comes ultimately from the chairmen of internal medicine programs throughout the country underscores how far we are from meaningfully reorienting the training in internal medicine that is needed to accommodate the changing medical needs of our society.

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1. SCHROEDER SA, SHOWSTACK JA, GERBERT B. Residency training in internal medicine: time for a change? *Ann Intern Med.* 1986;**104**:554-61.
2. *Special Requirements for Residency Training Programs in Internal Medicine.* Chicago: Accreditation Council for Graduate Medical Education; September 1985.

TO THE EDITOR: The article on internal medicine residency training (1) in the April issue is squarely on target. It is a pretty easy target to hit. Whether this system, or any system so outmoded and so irrelevant, can or should long endure is an overdue question. Recruitment of a general internist from most internal medicine residency programs is similar to trying to find a piccolo player in the violin section.

Schroeder and colleagues' (1) emphasis on geriatric content in the programs is also clearly stated. The future of internal medicine, and most of the rest of medicine, is inextricably linked with the health care needs of our aging population. In my opinion, these needs should not be met by the establishment of a sequestered specialty of geriatrics, but rather by the inclusion of much geriatric medical training in the core program of residency, internal medicine or family medicine, training. Geriatric medicine has a different agenda and requires different strategies. Its algorithms and decision moments need the investment of inquiry, energy, and experience. Geriatric medicine should be "the fruition of the clinician."

It is my hope that all departmental chairmen of internal medicine programs read the sands correctly. The internists of the 21st century need relevancy as a prime credential.

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REFERENCE

1. SCHROEDER SA, SHOWSTACK JA, GERBERT B. Residency training in internal medicine: time for a change? *Ann Intern Med.* 1986;**104**:554-61.

TO THE EDITOR: "Residency Training in Internal Medicine," by Schroeder and colleagues (1) (with its three accompanying editorials [2, 3, 4]) offers an opportunity for others with concerns about residency training to contribute their ideas.

I agree with the authors' general premise but would emphasize other aspects of the problem. Obviously, the outpatient load is increasing, hospital patients are more acutely ill, and less time is available for reflection on diagnostic and treatment problems. This leads to such problems as superficial preoperative consultations just hours before major surgery and hurried arrangements for sick patients to be cared for at home. Many rehabilitation efforts are either being neglected or arranged under poor conditions. I wonder if the concentration on "inpatient" compared with "outpatient" experience may miss more important and humane considerations that sophisticated care should demand. No longer does the resident in medicine seem to have time to spend in experience outside internal medicine orientation when there are a dozen or more subspecialties of medicine with which to become acquainted. I have noticed that many recent graduates of medical residency programs have almost no appreciation of surgery, obstetrics, psychiatry, urology, and pathology. They are not sensitive to excellence in surgical judgment and technique.

I suspect this situation is also true for family practice residents. I have heard of family practice "gatekeepers" in health maintenance organizations who expect to manage patients with acute leukemia after one consultation with an oncologist. It cannot be done. A big challenge is to teach when and to whom to refer. Every general internist or subspecialist "in charge" should know when and when not to ask for outside help. How many know their own limitations, yet know also when a consultation is not needed? This challenge is not getting easier, with specialists in immunology, genetics, clinical pharmacology, dental surgery, iron metabolism, echo imaging, and so on.

Patients and physicians alike are grasping for straws when trying to determine where the best care can be found. Many who champion health maintenance organizations as the answer for better health care forget that these organizations developed in the 1950s when fewer physicians were able to cover most medical management. How many physicians can recognize and appreciate today's explosion of knowledge? Even the best informed physician cannot keep up. A chief of medicine is expected to ensure that the endoscopist or the cardiac catheter expert on his service knows what he or she is doing, for instance, but how can he when his own field may be nephrology? The chief easily finds himself with insufficient technical background to make proper judgments when setting priorities. We should not ignore this knowledge explosion while trying to respond to society's cost controls.

Will computer sources of data offer some hope? I can only hope that educators will review what is needed to train the internist to be an effective coordinator for difficult diagnostic and management problems. Will the graduate know when and to whom to refer for an opinion or management and be sensitive to whatever resources are available? Will the training include

the ever-increasing reservoirs of knowledge in multiple databases? Will the residents know how to use a computer or computer librarian and then know how to apply that information for a patient's welfare or benefit?

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Esophageal Pseudoworm: "Pasta, not Parasite"

TO THE EDITOR: Working at an international referral hospital, we have seen many exotic diseases among our well-traveled patients. It was with little excitement, therefore, that we agreed to see a patient with multiple serpiginous filling defects seen during an upper gastrointestinal tract series. Fully expecting the radiographic picture of ascaris infection, we were taught a valuable lesson by the ultimate endoscopic and histologic diagnosis: when one hears hoofbeats, do not assume you hear a member of the animal kingdom.

A 56-year-old Japanese woman was referred with solid-food dysphagia of 10 days' duration. She denied pyrosis, hematemesis, or ingestion of a caustic. Ten years earlier, she had had vagotomy, antrectomy, and Billroth I gastroduodenostomy for chronic peptic ulceration. Her diet was predominantly that of her native land and she liked uncooked seafoods (sushi and sashimi). She had recently returned to the United States after visiting family in Yokohama, Japan. Physical findings were unrevealing. After a 14-hour fast, the patient had an upper gastrointestinal tract series. Multiple serpiginous filling defects within the barium column were noted; a filling defect was apparent in the distal esophagus. We tentatively diagnosed parasitic infection, probably ascariasis.

In an attempt to extract the "worm" from the distal esophagus, endoscopy was done. Multiple gray-white vermiform structures were found within the esophagus, gastric remnant, and duodenum; they were 8 to 10 cm in length and approximately 0.5 cm in diameter. Of note to one observer was the absence of cuticular striations on the surface of the "worms." With some difficulty, one was grasped and extracted with biopsy forceps. The structure felt proteinaceous on palpation, but the cut ends failed to reveal any internal structures. Having considerable doubt at this point, we sent the specimen to the parasitology laboratory for examination. Their interpretation: "Pasta, not parasite." On recovery, the patient was questioned and related that she had eaten a meal 24 hours before that had included a particular type of Oriental noodle called shiritaki, made from a gummy Japanese tuber. Subsequent stool examinations for ova and parasites were negative.

The adult *Ascaris* has been found impacted in the appendix and larynx and traversing the nasopharynx, orbits, and external auditory meatus (1, 2). We have recently reported a case of pancreatitis due to an ascarid lodged in the ampulla of Vater (3). Dysphagia due to esophageal ascariasis has, to our knowledge, not been reported.

The radiographic differential diagnosis of serpiginous (vermiform) filling defects on barium study of the gastrointestinal tract has essentially been limited to ascarids or other parasites (*Strongyloides, Ancylostoma,* tapeworms) and vascular lesions (varices, phlebectasia, clots) (4). The case of this patient adds an item to that short list. After a prolonged fast (both by the patient and the parasite), the *Ascaris* worm has been seen to ingest barium, and the astute radiologist can then see a thin barium column through the worm's body. The absence of this finding and the appropriate history can lead to the correct diagnosis: pasta, not parasite.

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Alcohol, Acetaminophen, and Hepatic Necrosis

TO THE EDITOR: In your March issue, Seeff and coworkers (1) reported on 25 alcohol abusers who developed evidence of severe hepatic necrosis while taking acetaminophen for therapeutic purposes. Over the past 2 months, 2 young alcoholic men have been treated in our medical center for acetaminophen-induced severe hepatic necrosis. The doses ingested by each were far below those previously considered to be toxic for healthy adults.

Patient 1: A 39-year-old white alcoholic man was admitted to the Miami Veterans Administration Hospital with abdominal pain, nausea, and vomiting. He consumed 60 g of alcohol per day. Six days earlier, he had begun ingesting approximately 10 Extra-Strength Tylenol tablet (McNeil Consumer Products Co., Fort Washington, Pennsylvania) (5 g) per day for vague right inguinal discomfort. Physical examination showed mild pain in the right lower abdomen, where a small, reducible inguinal hernia was noted. Laboratory data revealed an hematocrit of 41%; leukocytes, 12 800/mm^3; platelets, 76 000/mm^3; prothrombin time, 21 s (control, 12); partial thromboplastin time, 52 s (control, <45); alanine aminotransferase (ALT), 6494 IU/L (normal, 5 to 40); aspartate aminotransferase (AST), >8270 IU/L (normal, 5 to 40); alkaline phosphatase, 166 IU/L; lactate dehydrogenase, 7054 IU/L (normal, 90 to 180); and total bilirubin, 4.2 mg/dL (normal, 0.2 to 1.2). No acetaminophen was detectable in the blood. With supportive care, the results of clotting studies and the platelet count became normal over the next week, and the AST level was 98 IU/L at discharge.

Patient 2: A 38-year-old black male ethyl alcohol abuser was admitted to Jackson Memorial Hospital with nausea, abdominal discomfort, and hematemesis. Sixty hours before, he had begun taking Regular-Strength Tylenol and Tylenol #3 (with codeine) for chronic back pain that had recently increased in intensity. He ingested 4400 mg/d of acetaminophen over 48-hours. The patient chronically drank about 100 g of alcohol per day.

On admission, the patient appeared very ill. Significant hypovolemia was evident. His liver span was 18 cm and a spleen tip was palpable. Laboratory data included an AST level of 13 496 IU/L; ALT, 4744 IU/L; alkaline phosphatase, 60 IU/L; total bilirubin, 6.1 mg/dL; total protein, 3.1 g/dL; albumin, 1.9 g/dL; creatinine, 3.2 mg/dL; sodium, 132 meq/L; glucose, 225 mg/dL; blood urea nitrogen, 22 mg/dL; hematocrit, 29%; leukocytes, 8400/mm^3; and platelets, 9000/mm^3. The disseminated intravascular coagulation screen was positive, with a prothrombin time of 30 s and a partial thromboplastin time of 60 s. The acetaminophen level 24 hours after the presumed last dose was 15.6 μg/mL, which was in the toxic range.

Therapy was begun with oral *N*-acetylcysteine along with transfusion of fresh frozen plasma, packed erythrocytes, and platelets. Endoscopy showed activie bleeding at a distal esophageal Mallory-Weiss tear which responded to intra-arterial vasopressin infusion. The patient improved clinically with conservative management and was discharged 3 weeks after admission. At

that time, results of clotting studies and aminotransferase levels were normal and his bilirubin level was 20 mg/dL.

Acetaminophen is a safe and effective analgesic and antipyretic if used judiciously. Hepatic necrosis occurring in alcoholics taking therapeutic doses is probably commoner than has been reported and is most likely unrecognized in its milder form. Because at least 200 over-the-counter products contain acetaminophen as a major ingredient (2), a careful history must be obtained in patients, particularly alcoholics, with hepatic necrosis. The public should be informed of the hazards of excessive acetaminophen intake, and chronic alcoholics must be cautioned about its potential serious adverse effects even with acceptable therapeutic doses.

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Topical Clonidine for Diabetic Diarrhea

TO THE EDITOR: I read with interest the article by Fedorak and associates (1) on treatment of diabetic diarrhea with clonidine. I recently used topical clonidine (Catapres TTs$_1$; Boehringer-Ingelheim, Ridgefield, Connecticut) to treat a 50-year-old woman who had diabetic diarrhea refractory to anticholinergic-opiate (Lomotil; Searle & Co., San Juan, Puerto Rico) and to kaolin-pectin (Kaopectate, The Upjohn Company, Kalamazoo, Michigan) treatment alone and in combination.

Before use of topical clonidine, she had 15 to 20 stools per day that were liquid to semisolid. While using clonidine she had well-formed stools, and unlike the patients described in the report by Fedorak and colleagues, she had a decrease in the frequency of stools to 1 to 2 daily. Topical clonidine treatment was well tolerated with no dryness of the mouth or hypotension (the patient was initially normotensive) and with only minimal drowsiness. Discontinuation of topical clonidine treatment resulted in recurrence of severe diarrhea, which rechallenge with topical clonidine again controlled.

The clustering of bowel movements seen by Fedorak and associates in their patients using oral clonidine might have coincided with trough serum levels of the drug, an occurrence which would be avoided by topical administration. Double-blind studies using a placebo patch and real tablet and vice versa are needed to determine whether topical clonidine really controls stool frequency better than oral clonidine and to determine whether topical clonidine controls diarrhea at a lower dosage and, by avoiding peak and trough levels, with fewer side effects.

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Cimetidine, Ranitidine, and Epstein-Barr Virus Infection

TO THE EDITOR: Patients with chronic Epstein-Barr virus infection (1) might be relieved to have their syndrome diagnosed but are usually discouraged when told there is no recognized effective therapy, because their symptoms are often disabling. I have treated ten such patients, who had dysfunction from 9 months to 15 years. All had antibody to Epstein-Barr early antigen in titers of 1:40 or greater. Because of my success in treating acute mononucleosis with cimetidine (2), I decided to try cimetidine or ranitidine on these patients.

In the usual doses prescribed for treatment of peptic ulcer disease, every one of these patients had a major or complete remission in 1 or 2 days. If treatment was stopped, the symptoms promptly returned. An unusual response to the H_2 blockers in these patients was stimulation and insomnia. These side effects resolved with time or reduction of dosage. Some patients have now been receiving this therapy for more than a year, and its efficacy has not diminished.

My hypothesis is that the suppressor T-cell hyperfunction induced by herpesvirus infections is responsible for much of the morbidity of these disorders, perhaps by secretion of lymphokines, although none of these patients have had an alteration of the helper/suppressor T-cell ratio. I submit these anecdotal findings so that other patients with this disorder may be helped and so that someone with a larger patient population might do a double-blind experiment.

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Danazol and Cholestatic Hepatitis

TO THE EDITOR: Danazol, used since 1971 for treatment of pelvic endometriosis, cystic disease of the breast, and hereditary angioneurotic edema, has recently been reported to be effective in idiopathic thrombocytopenic purpura (1). Because danazol is a C17 alkylated anabolic steroid, hepatic dysfunction and jaundice might be expected. We report a case of cholestatic hepatitis apparently induced by danazol.

A 73-year-old woman was referred with idiopathic thrombocytopenic purpura responding to prednisone. Treatment was stopped 6 months later with a good result. A moderate relapse occurred 1 year afterwards, and prednisone therapy was restarted. Because of iatrogenic Cushing's syndrome, prednisone was replaced by danazol, 600 mg/d. Before danazol was given, there had been no clinical or laboratory evidence of hepatic dysfunction.

After 4 weeks of therapy, her aspartate aminotransferase level had risen to 57 IU/L (normal, <17), and alanine aminotransferase, to 45 IU/L (normal, <23). Serum alkaline phosphatase, bilirubin, and albumin levels and prothrombin time remained normal. Despite withdrawal of danazol treatment, pruritus occurred, but there was no jaundice. Within 4 weeks, serum alkaline phosphatase levels rose to 619 IU/L (normal, <190) and gamma-glutamyltransferase levels rose to 553 IU/L (normal, <23). Serum aminotransferase levels returned to normal. The eosinophil blood count was normal throughout. Ultrasound showed normal intrahepatic and extrahepatic bile ducts. Tests for IgM anti-hepatitis A virus and anti-hepatitis B surface antigen antibodies were negative.

A transjugular liver biopsy sample, taken 6 weeks after drug withdrawal, showed intrahepatic cholestasis, Kupffer cell hyperplasia, portal and periportal lymphoplasmocytic infiltrate, and scattered fatty change. Pruritus disappeared within 2 weeks. Serum alkaline phosphatase and gamma-glutamyltransferase levels returned to normal within 3 months. Follow-up was uneventful.

The time course and histologic changes in this patient are compatible with drug-induced liver damage cause by danazol, the only drug being taken at the time. Only mild side effects have been reported previously with danazol, effects mainly related to its androgenic and antiestrogenic properties (2). Liver damage has been reported but consisted in most patients of isolated transient elevation of serum alkaline phosphatase values. Jaundice has been reported but without biochemical data (3). None of these reports included liver biopsy studies except

the report of a patient with peliosis (4) and one with hepatocarcinoma (5).

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Ranitidine and Hepatic Injury

TO THE EDITOR: Since our previous report (1) we have seen another case of ranitidine-associated hepatitis. It prompted a review of reports of hepatotoxicity associated with ranitidine and cimetidine that have been entered into the computerized filing system of the Division of Drug Experience of the Food and Drug Administration. The files encompassed a period of about 2 years for ranitidine and 8 years for cimetidine. There were 45 reports of hepatic injury for ranitidine, but a cause-and-effect relationship could not be established with certainty because of the frequent use of multiple drugs and the lack of rechallenge. We elected to review in detail the cases in which patients were taking no more than one additional drug.

Twenty-six such cases associated with ranitidine were available for review. We excluded 8 of these: 2 for lack of data, 2 for underlying chronic liver disease, 1 with recent blood transfusions, 1 with recent general anesthesia, 1 with cholelithiasis, and 1 with total parenteral nutrition. In the 18 remaining cases, the circumstantial evidence appeared strong despite lack of rechallenge. In contrast, in only 3 cases of cimetidine-associated hepatic injury was circumstantial evidence considered strong enough with the same guidelines.

The time from start of ranitidine treatment to onset of hepatic injury ranged from a few days to 2 months. It is possible that patients who developed reactions very early had been sensitized previously to ranitidine or another furan compound (for example, nitrofurantoin), but this hypothesis could not be verified. All patients recovered or their conditions improved on discontinuation of drug therapy. Several patients were anicteric at the time of the drug reaction, which underscores the importance of an alert clinician. The risk of underdiagnosing is that reexposure to the offending drug may lead to severe reactions.

Such retrospective analysis carries inherent flaws because of multiple external factors that may affect the data (2). However, a comparison of the data on the two currently available H_2-receptor antagonists may provide some insight of the true picture. Review of prospective studies may also be helpful. Unlike ulcers in average patients, ulcers in some study patients heal, under controlled conditions, in as little as 2 weeks, which may not be long enough for hepatic reactions to develop. When Ireland and colleagues (3) evaluated prospectively 102 patients receiving ranitidine (300 mg/d), one patient on the twice-daily regimen developed cholestatic jaundice. Barr and Piper (4) reported a possible case of ranitidine hepatitis in a patient during earlier clinical trials. In contrast, a recent multicenter trial evaluating the efficacy of single-dose cimetidine in over 1000 patients showed occasional mild elevations of aminotransferase values but no significant difference between the placebo and cimetidine groups (Sabesin S. Personal communication).

Only time and clinical experience can truly determine the safety profile of a pharmaceutical compound. The information outlined here suggests that a significantly higher incidence of hepatotoxicity occurs with ranitidine than with cimetidine, especially considering ranitidine's lifespan and smaller market share. The absolute incidence is not yet known. If there was a credit (such as continuing medical education credit) and an 800-number hotline for reporting adverse reactions, clinicians would have the incentive to report serious reactions without disruption of their practices and we could have a more accurate view of the incidence ratio for adverse events.

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Pentamidine and Pancreatitis

TO THE EDITOR: Among the adverse effects of pentamidine, fatal acute pancreatitis has never been reported. We have seen this complication in two patients with the acquired immunodeficiency syndrome treated with pentamidine for *Pneumocystis carinii* pneumonia. We report here the more illustrative case.

A 27-year-old woman was hospitalized with interstitial pneumonia. At admission she was afebrile; abdominal findings and results of hematologic studies were normal. Bronchoalveolar lavage was positive for *P. carinii* pneumonia, and therapy with trimethoprim-sulfamethoxazole (20 and 100 mg/kg body weight · d, respectively) was started. Despite initial improvement, her temperature rose to 40.5 °C after 3 weeks, and radiologic signs worsened. A second bronchoalveolar lavage revealed persistent *P. carinii* pneumonia. Therapy was changed to intramuscular pentamidine dimethane sulfonate (4 mg/kg·d). She became afebrile after 5 days, but from the 6th day hypoglycemic episodes occurred (2.2 mmol/L) and renal function deteriorated. On the 12th day severe abdominal pain occurred.

Her blood urea nitrogen level was 20 mmol/L; serum creatinine, 330 μmol/L; glucose, 40 mmol/L; and serum amylase, 1286 IU/L (normal, < 100). Ultrasonography showed a total enlargement of the pancreas. The patient died the next day from cardiovascular failure. An autopsy showed extensive pancreatic necrosis with hemorrhage. Special stains and postmortem cultures were negative for viruses, bacteria, and fungi.

The clinical course in this patient strongly implicates pentamidine in the development of acute pancreatitis, because trimethoprim-sulfamethoxazole treatment had been discontinued 2 weeks previously and no other risk factor could be identified (1). Our two patients shared many common findings. Both had progressive renal impairment associated with hypoglycemia that occurred after a week's therapy and preceded the clinical symptoms of acute pancreatitis. The cumulative dose of the salt used (pentamidine dimethane sulfonate) was also similar (2400 and 2520 mg).

Pentamidine is not a usual cause of drug-induced acute pancreatitis (2, 3). The occurrence of pancreatic toxicity is supported mainly by the hypoglycemic and diabetogenic effects of pentamidine (4). In-vitro studies show a direct cytolytic effect of pentamidine on pancreatic beta-cells with insulin release (4, 5). By a similar mechanism, acute pancreatitis may arise from intense acinar cell destruction. A cumulative effect of the drug is very likely in patients with renal impairment, since pentamidine is excreted unchanged in the urine.

Clinicians should be aware of pentamidine's potential for fatal pancreatic toxicity. We suggest that if hypoglycemia associ-

ated with progressive renal impairment develops, pentamidine therapy should be interrupted.

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Buccal Nitroglycerin Tablets in Heart Failure

TO THE EDITOR: A recent letter reported the application of nitroglycerin ointment to the buccal mucosa for relieving refractory pulmonary oedema (1). Sublingual nitroglycerin has also been used for the management of pulmonary oedema, and a comparative study of intravenous isosorbide dinitrate with furosemide has shown a better haemodynamic profile with nitrates in the management of acute heart failure occurring after infarction. Although buccal nitroglycerin ointment may have a prompt effect on left ventricular function, proper dose regulation may be difficult. Buccal-release nitroglycerin tablets which produce both rapid and sustained release of nitroglycerin are now available (2). We report here our experience in treating 10 patients with acute heart failure after acute myocardial infarction, in whom rapid improvement in left ventricular function and alleviation of symptoms were recorded after treatment with a single dose of buccal nitroglycerin tablets (5 mg).

Ten men (mean age, 60.2 years; range, 39 to 71) presented with breathlessness and radiologic evidence of pulmonary oedema within 72 hours after a documented acute myocardial infarction. Five patients had known ischaemic heart disease, and previous myocardial infarction had been documented in three. Five patients were taking furosemide, three were taking isosorbide dinitrate, two were taking digoxin, and one each was taking verapamil and propranolol. The other five patients were admitted with their first infarction.

Blood pressure and noninvasive radionuclide studies of left ventricular function were monitored, along with continuous electrocardiographic monitoring, before and for 30 minutes after the administration of buccal nitroglycerin (5 mg). The nonimaging nuclear probe (Bios Inc., Valhalla, New York) (3) was used to measure left ventricular ejection fraction, ejection rate, ejection time, and peak filling rate. Studies were done before and at 5, 15, and 30 minutes after administration of buccal nitroglycerin.

All patients tolerated the medication. Seven patients were continued on chronic therapy with buccal nitroglycerin. The mean $\pm$ SD heart rate and blood pressure did not change significantly when basal and 30-minute values were compared: 82 $\pm$ 11 to 86 $\pm$ 10 beats/min and 117 $\pm$ 12 to 112 $\pm$ 11 mm Hg, respectively. Basal and 30-minute values for other variables were compared: ejection fraction increased from 31 $\pm$ 14% (range, 6% to 45%) to 47 $\pm$ 18%, ejection rate increased from 1.19 $\pm$ 0.5 to 2.11 $\pm$ 0.9 end-diastolic volume (EDV)/s, and peak filling rate increased from 1.5 $\pm$ 0.4 to 2.6 $\pm$ 0.3 EDV/s ($p < 0.001$). Ejection fraction and ejection rate improved significantly within 5 minutes. Peak filling rate improved by 15 minutes. Ejection time did not vary significantly.

Three patients responded within 15 minutes, and five patients became less breathless by 30 minutes. In two patients the dose was doubled, with improvement in one and no change in one. One patient (aged 71 years), who had been unresponsive to treatment with 120 mg of furosemide intravenously, showed an increase in ejection fraction from 6% to 12% in 30 minutes and was maintained on chronic therapy with 10/mg of buccal nitroglycerin four times daily; however, he died of cardiogenic shock during contrast angiography after 4 months.

This study supports Shah's previous observations with buccal ointment (1). Buccal nitroglycerin has also been used for the management of chronic heart failure (4) and angina (5). This mode of delivery for nitrates produces rapid and salutary haemodynamic effects in patients with acute heart failure. An added advantage is its pharmacokinetic properties (2), which allow both acute and chronic use. Furthermore, this preparation provides more stable and graduated release, avoiding the large bolus release that may occur with nitroglycerin ointment.

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Alpha-Difluoromethylornithine Infusion and Cardiac Arrest

TO THE EDITOR: Alpha-difluoromethylornithine is an investigational antiprotozoal agent used to treat *Pneumocystis carinii* pneumonia in patients with the acquired immunodeficiency syndrome (AIDS) who are unresponsive to or intolerant of trimethoprim-sulfamethoxazole and pentamidine (1). We report the case of a patient who developed cardiac conduction disturbances leading to death during infusion of this agent.

A 31-year-old woman was admitted with AIDS, *P. carinii* pneumonia, and respiratory failure requiring mechanical ventilation. She initially received intravenous trimethoprim-sulfamethoxazole (20 and 100 mg/kg body weight·d, respectively) but developed a maculopapular rash after 3 days, and intravenous pentamidine (4 mg/kg·d) was substituted. Forty-eight hours later, the patient continued to have high fever, progressive infiltrates on a chest radiograph, and refractory hypoxemia. Therapy with trimethoprim-sulfamethoxazole was restarted in combination with pentamidine.

Because the patient showed no clinical improvement after 8 days of standard therapy, pentamidine and trimethoprim-sulfamethoxazole therapies were discontinued. After informed consent was obtained, intravenous alpha-difluoromethylornithine therapy was initiated at a dosage of 100 mg/kg to be infused over 1 hour. Thirty minutes after the infusion was started, the patient developed first-degree heart block and sinus bradycardia (48 beats/min). Ten minutes later she developed third-degree heart block and hypotension. Electromechanical dissociation ensued. Attempts at resuscitation failed. Immediately before cardiac arrest the electrocardiogram showed sinus tachycardia (124 beats/min) without other abnormalities and an arterial blood gas analysis showed pH of 7.38; arterial P_{CO_2}, 34 torr; and arterial P_{O_2}, 78 torr (fraction of inspired O_2, 0.5; post-end expiratory pressure, 10 cm H_2O). Permission for autopsy was denied.

The mortality rates in patients with AIDS who require mechanical ventilation range from 86% to 100% (2, 3), making this a lethal association. This report is the first of cardiac arrest after alpha-difluoromethylornithine therapy. Recently, sudden death has occurred after infusion of this agent in several other

critically ill patients with AIDS (Barlow JLR, Merrell Dow. Personal communication). Although the occurrence of cardiac arrest after infusion is alarming and suggests a causal relationship, it is clear that all of the affected patients were critically ill and that no solid link between their sudden death and therapy with this agent can be established at this time.

It has been reported that patients with AIDS have an extraordinary incidence of adverse reactions to several drugs, most notably trimethoprim-sulfamethoxazole (4, 5). Patients with AIDS appear to represent a subset who are at high risk for adverse drug reactions; cardiac toxicity from alpha-fluoromethylornithine may be one such reaction.

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Nifedipine and Ureteral Colic

TO THE EDITOR: After a report on the in-vitro effects of nifedipine on ureteral muscle (1) and an anecdotal report in your journal of its successful clinical use (2), we started a prospective clinical trial to test the therapeutic value of nifedipine in the treatment of ureteral colic.

So far, nine consecutive patients with definite evidence of urolithiasis and a clinical picture of ureteral colic have been studied. Informed consent was obtained from all patients, and the protocol was approved by the Ethical Committee of Tel Aviv Medical Center. Therapy consisted of a single dose of nifedipine, 10 or 20 mg. Patients were instructed to bite the capsules, keeping the liquid in the mouth for as long as possible before swallowing it.

In contrast to the report by Carol in this journal (2), we found no significant analgesic value for nifedipine in patients with ureteral colic, as evaluated with a standard method of pain assessment (3). We conclude that although nifedipine theoretically could be used as therapy for ureteral colic, its clinical value in this situation has not been proved.

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Antimicrobial Prophylaxis in Mitral Valve Prolapse

TO THE EDITOR: Dr. Kaye's recent update on prophylaxis against infective endocarditis (1) is well considered and practical. One suggestion therein deserves further exploration: the possible limiting of prophylaxis to those patients with mitral valve prolapse having a holosystolic murmur. Presumably, this proposal assumes that only holosystolic murmurs indicate mitral regurgitation and thereby the predisposition to infection (2). However, the literatures on physical diagnosis and on mitral prolapse (3-5) argue that mitral regurgitation occurs even in patients and cycles having only a late systolic murmur. In these instances, the valve is competent early in systole but "leaks" at end systole. Surely such leakage would produce the jet and Venturi effects requisite for endocarditis.

Therefore, although I concur that patients with mitral valve prolapse whose valves are competent may safely avoid prophylaxis, I submit that late systolic as well as holosystolic murmurs be taken in this context as evidence of valvular insufficiency and therefore of the need for prophylaxis.

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Diabetic Cutaneous Atrophy and Malignant Melanoma

TO THE EDITOR: Risk factors for the development of malignant melanoma include exposure to ultraviolet light, the degree of skin pigmentation (1), and the presence of dysplastic nevi, especially familial dyplastic nevi (2). Malignant melanoma has also been reported to develop in vaccination scars and a tattoo (3).

Vasculopathy due to involvement of both small and large blood vessels and neuropathy are the commonest causes of cutaneous abnormalities occurring in patients with diabetes mellitus. These cutaneous lesions progress with increasing duration of diabetes, and regression is uncommon despite optimal medical and surgical management. We report the case of a patient with multiple cutaneous malignant melanoma that appears to be related to chronic diabetes; no similar associations were detected on a MEDLINE search.

A 70-year-old Portuguese woman with diabetes mellitus of over 45 years' duration and associated cardiac, renal, and retinal complications was referred for evaluation of multiple black lesions on both of her legs. Her initial medical care was provided in Portugal, but she recalled the discolored patches of skin on her shins being present for over 40 years. The black lesions were self-detected 3 months before referral, and several nodules had been present for 1 month. She had bilateral reddish-brown atrophic patches involving the lower half of her anterior and lateral tibial surfaces. The skin was cold, pale, shiny, and atrophic. There was no palpable arterial pulse on the popliteal, dorsalis pedis or posterior tibial surfaces. Sensation to pinprick and light touch was decreased in a stocking distribution. There were a total of 25 black, slightly elevated papules, each less than 1 cm in diameter, confined to these atrophic areas; 13 were on the right leg and 12 on the left leg. In addition, on her right lateral tibial surface were 4 pink nodular lesions with patchy black pigmentation, each 1.5 × 1 cm. No similar papules, macules, or nodules suggestive of melanoma were seen on the remainder of her nonatrophic skin, and there was no suspicious popliteal, femoral, or inguinal lymphadenopathy. A thorough staging evaluation failed to detect evidence of distant metastases. Malignant melanoma, Clark's level IV and

depth greater than 3.5 mm, was diagnosed by punch biopsy. She received three courses of radiation, 800 cGy per treatment, over 6 weeks. The size of her nodules decreased by more than 50%, and she remains in partial remission 8 months after diagnosis.

This woman with long-standing cutaneous lesions from diabetes mellitus developed bilateral malignant melanoma disseminated diffusely within the patches of chronic atrophic epidermal lesions on her lower legs. This association is previously unreported and suggests that patients with chronic skin changes due to diabetes mellitus may be at risk for malignant melanoma.

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Heparin Flushes and Thrombocytopenia

TO THE EDITOR: Heparin-induced thrombocytopenia, with or without arterial thrombi, has been described as occurring with full-dose intravenous heparin treatment, as well as low-dose subcutaneous treatment (1, 2). We report a case of heparin-induced thrombocytopenia from heparin flushes (< 500 U/d).

A 73-year-old man was admitted for evaluation of anuric renal failure. A diagnosis of antiglomerular basement membrane disease was eventually made by renal biopsy. During the evaluation the patient became thrombocytopenic, with the platelet count decreasing from 541 000 to 50 000/mm^3 over 8 to 10 days. He had no evidence of sepsis, disseminated intravascular coagulation, or thrombotic thrombocytopenic purpura and was receiving no medication known to be associated with thrombocytopenia. He did receive heparin flushes through a heparin lock, 100 U every 8 hours, starting on admission. At the nadir of the thrombocytopenia, all heparin therapy was stopped. An immediate increase in his platelet count was noted, reaching greater than 100 000/mm^3 within 36 hours and greater than 200 000/mm^3 within 4 days of stopping the heparin flushes. Before the heparin infusion was stopped, the patient's plasma was analyzed with platelet serotonin release studies. Using donor platelets, in the presence of heparin, the studies showed markedly abnormal results.

No "gold-standard" test exists for diagnosing heparin-associated thrombocytopenia, so the diagnosis must be made by exclusion. However, Kelton and colleagues (3) have shown that heparin-induced platelet aggregation, in the presence of a patient's plasma, is a highly specific (95% to 100%), although poorly sensitive (36%), test for the disorder.

Our patient had a course consistent with this diagnosis. The onset of thrombocytopenia occurred within 5 days of the start of heparin therapy and resolved within 5 days after therapy was stopped. There was no evidence of other pathologic processes known to cause thrombocytopenia. In addition, the patient's plasma caused a markedly abnormal heparin-induced platelet serotonin release (4) (a test analogous to the aggregation study done by Kelton and colleagues [3]).

The mechanism responsible for heparin-associated thrombocytopenia is not fully understood but has many aspects of an immune-antibody reaction (4, 5). Investigators have shown that heparin, acting as a hapten, may induce an immune response against the platelet-heparin complex. If this is indeed the case, heparin-associated thrombocytopenia should not be dose dependent, and doses used in heparin flushes could conceivably produce thrombocytopenia. The diagnosis should therefore be considered in patients having thrombocytopenia on any dose of heparin.

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Obesity and the Erythrocyte Sedimentation Rate

TO THE EDITOR: The article in the April issue on the erythrocyte sedimentation rate (1) was a timely and well-written review. We write to comment on an additional condition that may significantly affect the erythrocyte sedimentation rate in certain population groups.

To determine if obesity was associated with an increase in the erythrocyte sedimentation rate, we prospectively compared 12 patients who were approximately 45 kg (100 lbs) over their ideal body weight (determined by the Metropolitan Height and Weight tables) to 13 patients who were normal weight and otherwise matched for sex and age. There were 2 men in each group. No patient had a history or physical evidence of an inflammatory process or significant anemia. Age, sex, and levels of alpha-I and alpha-II globulins, fibrinogen, albumin, total protein, and C-reactive protein were also measured. All patients had normal creatinine levels and were under age 40. The mean erythrocyte sedimentation rate in the obese group was 17 mm/h (range, 1 to 39), significantly higher ($p = 0.015$) than that in the control group, 4 mm/h (range, 1 to 10). Also, the C-reactive protein, cholesterol, fibrinogen, and triglyceride levels were significantly higher in the obese group ($p = 0.05$).

The erythrocyte sedimentation rate, as well as the level of C-reactive protein, appeared to be significantly higher than the rate in a matched control group. The cause is unknown but may be due to nonspecific stimulation of the liver by factors such as interleukin-1 (2). Hypercholesterolemia was directly correlated with obesity in our patients. The elevation of the erythrocyte sedimentation rate in obese patients may be independent of cholesterol levels and deserves further study. Morbid obesity may be associated with a significant increase in erythrocyte sedimentation rates in normal persons under age 40 and needs to be considered in the clinical setting.

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Sarcoidosis and Hypercalcemia

TO THE EDITOR: Although the exact pathogenetic mechanism of hypercalcemia in sarcoidosis remains unknown, several studies (1-3) have suggested that the basic disturbance is an increase in circulating levels of 1,25-dihydroxyvitamin D. Increased levels of this substance are thought to be due to excessive synthesis, reflecting aberrant 1-alpha-hydroxylase activity (3). Sarcoid tissue may be the locus of this ectopic 1-alpha-hydroxylase activity (4). We present a clinical observation supporting the involvement of sarcoid tissue.

A 47-year-old woman was hospitalized in May 1982 for persistent cough and wheezing due to extrinsic asthma. Chest roentgenograms showed an enlargement of the superior mediastinum, and a computed tomographic (CT) scan of the thorax revealed a 15-mm, isolated, heterogeneous, nodular mass. The level of serum calcium was 11.2 mg/dL (normal, 8.5 to 10.2); plasma albumin, 4 g/dL; and serum phosphorus, 4.2 mg/dL. Parathyroid hormone was moderately suppressed by the hypercalcemia. After common causes of hypercalcemia were excluded, the existence of a granulomatous disorder was considered, but no further evaluation of the hypercalcemia or mediastinal mass could be done.

In November 1984 the patient was readmitted because of acute asthma. The superior mediastinal mass was more pronounced and now had a diameter of 50 mm on CT scan. Fiberoptic bronchoscopy showed normal bronchi, and several bronchial and five transbronchial biopsy specimens were normal. The serum calcium concentration was still elevated, considering seasonal variations (5), to 10.2 mg/dL; serum phosphorus was 3.8 mg/dL and plasma albumin was 3.5 g/dL. A right lateral thoracotomy was done, and the isolated mass was removed totally with no abnormal tissue remaining. No other abnormalities (that is, lymph node enlargement) were found. Anatomopathologic examination of the mass showed a lymph node structure filled with noncaseating sarcoid granulomas. Immunocytologic examination showed a normal T-lymphocyte and polyclonal B-lymphocyte population.

Direct examination and cultures for *Mycobacterium tuberculosis* were negative. Extensive investigation of kidney, liver, skin, eyes, and abdomen did not reveal sarcoid involvement elsewhere. The diagnosis of sarcoidosis, presenting as an isolated mediastinal mass without pulmonary or other organ involvement, was withheld. After surgery, serum calcium concentrations fell significantly to normal levels (8.4 to 8.8 mg/dL), without changes in plasma albumin levels.

This clinical observation of correction of hypercalcemia by removal of all sarcoid tissue from patient supports the experimental evidence for sarcoid tissue as the site of excessive 1-alpha-hydroxylase activity in sarcoidosis-related hypercalcemia.

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Naproxen and Acute Renal Failure in a Runner

TO THE EDITOR: We recently treated a 41-year-old male marathon runner who developed acute renal failure after taking a nonsteroidal anti-inflammatory drug.

The patient was an advertising writer in excellent condition, and his prior history was remarkable only for borderline hypertension. For 1 week before the marathon he had been taking naproxen, 250 mg three times daily, until 36 hours before the race.

During the 17th mile of the race he dropped out with severe cramping, nausea, and fever. Two days later he was hospitalized with oliguric acute renal failure. He appeared well nourished and well hydrated. His temperature was 37.6 °C; blood pressure, 170/100 mm Hg; pulse, 60 beats/min; and respiration, 16/min. There was mild periorbital edema but no muscle tenderness. His hematocrit was 36.3%; leukocyte count, 7400/mm^3; blood urea nitrogen, 62 mg/dL; serum creatinine, 11.6 mg/dL; sodium, 133 meq/L; potassium, 4.8 meq/L; chloride, 94 meq/L; bicarbonate, 21 meq/L; calcium, 8.9 mg/dL; phosphorus, 7.8 mg/dL; uric acid, 10.9 mg/dL; and creatine kinase, 83 U/L (normal, < 225 U/L). The scant urine was clear yellow with 3+ proteinuria, 1+ hematuria, scattered renal tubular cells, and a few erythrocytes; myoglobinuria was absent. Renal sonography showed two normal kidneys without evidence of obstruction.

The oliguria persisted, and on the fifth day after the race the serum creatinine level was 15.8 mg/dL. Acute hemodialysis was done because of uremic symptoms. On the tenth day a diuresis occurred, and by the 26th day the serum creatinine was 1.2 mg/dL and there were no residual urinary abnormalities.

Fifteen cases of patients developing acute renal failure after running in a marathon have been reported, mostly after extended marathons of 90 km (56.25 mi) (1, 2). All but two patients developed oliguria, eight required acute dialysis, nine recovered completely, and one died (3). During the week before the race, eight had taken an analgesic for injuries sustained during training.

As inhibitors of renal prostaglandin synthesis, nonsteroidal anti-inflammatory drugs may interfere with the autoregulation of renal blood and the maintenance of the glomerular filtration rate during states of volume depletion and high renin activity (4), such as after intense exercise. It is more than likely that the naproxen taken by our patient interfered with the compensatory mechanisms responsible for preserving his renal function and directly contributed to the onset of acute renal failure. Because nonsteroidal anti-inflammatory drugs may have extended serum half-lives (17.7 hours for naproxen [5]) and sustained inhibition of renal prostaglandin synthesis, we caution marathon runners to avoid use of these drugs for several days before the race.

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Reports of DHPG Treatment of Cytomegalovirus Retinitis

TO THE EDITOR: In the *Annals'* January issue, Masur and colleagues (1) reported on the effect of 9-(1,3-dihydroxy-2-propoxymethyl) guanine (DHPG) on serious cytomegalovirus disease in 8 immunosuppressed homosexual men. The data outlined in that article bear some resemblance to data included in their paper published in the January issue of the *American Journal of Ophthalmology* (2). I was unable to tell whether these papers included data on some of the same patients or whether they represented two entirely different studies on separate patient groups. If these articles do represent different studies, then the amount of information regarding the authors' use of DHPG in treating cytomegalovirus retinitis is more extensive than a single report would indicate. Because 7 of the 8 patients in the report in *Annals* had retinitis, the data in that study appear quite similar to those in the report in the *American Journal of Ophthalmology*. If separate patients were used for the two studies, a total of 15 patients would have received DHPG for treatment of cytomegalovirus retinitis under the authors' protocol. I would appreciate any comments by the authors as to the exact number of patients with cytomegalovirus retinitis treated to date and whether the two reports represent different patient populations.

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2. Palestine AG, Stevens G Jr, Lane HC, et al. Treatment of cytomegalovirus retinitis with dihydroxy propoxymethyl guanine. *Am J Ophthalmol.* 1986;**101**:95-101.

In response: At the Clinical Center, we have used 9-(1,3-dihydroxy-2-propoxymethyl) guanine to treat 18 patients with serious cytomegalovirus disease. Nine patients were treated with drug obtained from Syntex Corporation (Palo Alto, California), and 9 patients were treated with drug obtained from Burroughs-Wellcome Company (Research Triangle Park, North Carolina).

The report in *Annals of Internal Medicine* (1) described our experience in treating serious cytomegalovirus retinitis, colitis, and pneumonitis. The report in the *American Journal of Ophthalmology* (2) focused on treatment of retinitis. Details of the ophthalmologic presentation, funduscopic photographs, and response to therapy could not be presented in *Annals* because of space limitations. The authors thought that these ophthalmologic details were important enough to warrant publication, particularly in a journal directed at ophthalmologists.

The report in *Annals* included three patients who were also included in the report in the *American Journal of Ophthalmology.* The methods section of the latter article (page 96) describes this overlap: "Some aspects of the treatment of Patients 3, 5, and 6 have been reported by Masur and associates" (with the appropriate citation).

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2. Palestine AG, Stevens G, Lane HC, et al. Treatment of cytomegalovirus retinitis with dihydroxy propoxymethyl guanine. *Am J Ophthalmol.* 1986;**101**:95-101.

▶ *Real or potential ambiguities in the identity of cases could be avoided by assigning a unique identification to each case; see the editorial comment by Dr. Abrutyn on pages 131-132.*—The Editor.

Reiter's Syndrome in Homosexual Men

To the editor: The relative infrequency of Reiter's syndrome in homosexual men is puzzling since the distribution of the HLA-B27 antigen is the same in this group as in the population at large and the frequency of chlamydial and shigella infections is apparently increased. The study by Melbye and colleagues (1) suggests a possible explanation: infection by the human T-lymphotropic virus type III may so alter the immunologic profile that these men do not respond to those infections by developing this reactive form of arthritis.

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Asymptomatic Esophageal Candidiasis in the Acquired-Immunodeficiency- Syndrome-Related Complex

To the editor: Esophagitis caused by *Candida albicans* is a criterion for diagnosing the acquired immunodeficiency syndrome (AIDS) in persons at risk for this syndrome (1). Twenty-four such patients (23 addicts to intravenous heroin and 1 homosexual) with generalized lymphadenopathy, antibodies to the human T-lymphotropic virus type III/lymphadenopathy virus, and a mean T4/T8 ratio of 0.93 (range, 0.13 to 2.2) were examined endoscopically at admission as a staging procedure for a research protocol.

No patient had oral thrush or symptoms of esophageal disease. In four of them, esophagoscopy showed dense plaques of white exudate. Cytologic examination of esophageal brushings showed candidiasis in all four. Seven patients had fever on admission, due to staphylococcal endocarditis in three, bacterial pneumonia in two, gonococcal sepsis in one, and urinary tract infection in one. Esophageal candidiasis was found in three of seven febrile patients and in one afebrile patient with idiopathic thrombocytopenic purpura. The median T4/T8 ratio in the group with esophageal candidiasis was 0.4 (range, 0.13 to 0.87). In patients without this disorder, the median T4/T8 ratio was 1.04 (range, 0.4 to 2.2) ($p < 0.05$).

The follow-up of all patients (median, 14 months; range, 8 to 28) has not shown the development of other opportunistic infections or tumors. In our group, esophageal candidiasis has not conferred the bad prognosis found for oral candidiasis in high-risk patients (2). Esophageal candidiasis could be related to the infectious process or antibiotic therapy, although esophagoscopy was done at a maximum of 48 hours after the start of antibiotic treatment, a period that probably does not allow the development of this disorder.

Some patients at risk for AIDS may present with asymptomatic esophageal candidiasis, and when it is the only opportunistic infection, it should not be considered a criterion for AIDS unless the infection is shown to be invasive by biopsy. These patients should be considered as having the AIDS-related complex.

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Immune Thrombocytopenia Gammaglobulin, and Seropositivity to the Human T-Lymphotropic Virus Type III

To the editior: Walsh and colleagues (1) and Abrams and colleagues (2) recently described the successful treatment of immune thrombocytopenia with steroids or splenectomy in patients with antibodies to the lymphadenopathy-associated virus/human T-lymphotropic virus type III (LAV/HTLV III).

We report our experience with intravenous gammaglobulin in such patients.

Immune thrombocytopenia occurred in 17 patients (12 hemophiliacs, 4 intravenous drug users, 1 homosexual man) out of 248 LAV/HTLV-III-seropositive patients seen in our hospital since 1981. The presence of these antibodies was assessed by an enzyme-linked immunosorbent assay (ELAVIA; Diagnostics Pasteur, France) and was confirmed by Western blot analysis. Thrombocytopenia was severe ($< 50 \times 10^9$ platelets/L) in 12 patients and moderate ($< 100 \times 10^9$/L) in 5. Data obtained from either bone marrow smears (15 patients) or studies of in-vivo survival of ^{111}In-labeled autologous platelets (13 patients) supported the peripheral origin of thrombocytopenia. Elevated platelet-bound IgG levels were detected by direct radioactive Coombs' test or a Dixon test in all patients.

Intravenous infusion of gammaglobulin (Veinoglobuline; Institut Mérieux, France) at a dosage of 0.4 g/kg body weight · d for 5 days was followed by an increase in platelet counts from $22 \pm 16 \times 10^9$/L (mean $\pm$ SE) to a peak of $151 \pm 54 \times 10^9$/L in 10 of 11 treated patients. Platelet counts remained over 50×10^9/L for 6 to 21 days. Steroid therapy was transiently effective in 9 of 10 patients. Splenectomy was done in 8 patients and resulted in sustained elevation of platelet counts ($> 100 \times 10^9$/L) in 6. No opportunistic or bacterial infections or the acquired immunodeficiency syndrome has yet occurred in any patient (follow-up, 1 to 51 months).

Treatment with steroid (1, 2) or vincristine (3) has been shown to be effective in patients with thrombopenia seropositive for LAV/HTLV-III, but these treatments have deleterious metabolic and immunologic side effects that hamper their use in patients with or at risk for severe immunodeficiency. Late effects of splenectomy, a more radical and definitive procedure, are unknown in this condition. Intravenous immunoglobulin therapy has been reported to be effective in two patients (4) but ineffective in two others (3). Because late spontaneous remission of thrombocytopenia may occur (1) and severe bleeding is rare (2), "no treatment" has been advocated as a viable alternative (1, 2). Our data confirm that intravenous gammaglobulin is a safe and frequently effective therapy that can be used as an alternative to steroids or splenectomy when severe bleeding occurs or if a surgical or invasive procedure is needed. We suggest that the efficacy of intravenous gammaglobulin infusions should be assessed at presentation in each LAV/HTLV-III-seropositive patient with immune thrombocytopenia in view of the management of future bleeding events.

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Pentamidine and Hematuria

TO THE EDITOR: A recent review on the use of pentamidine (1) outlines the frequent, though usually reversible, renal toxicity associated with this agent. We write to report the occurrence of gross hematuria associated with the administration of pentamidine.

A 35-year-old man with the acquired immunodeficiency syndrome presented in August 1985 with fever and massive lymphadenopathy. Lymph node biopsy samples revealed disseminated histoplasmosis. He was treated with a 2-g course of intravenous amphotericin B and placed on maintenance therapy with ketoconazole. At the end of his therapy, symptoms and adenopathy were completely resolved and renal function was normal.

The patient returned in December 1985 with fever and dyspnea. Bronchoscopy established the diagnosis of *Pneumocystis carinii* pneumonia, and therapy was begun with pentamidine isethionate, 4 mg/kg body weight · d intravenously. After 3 days of treatment, the patient was afebrile and his symptoms had improved. He received no additional medications other than oral ketoconazole, 400 mg/d. From days 4 to 6 of pentamidine therapy, the blood urea nitrogen and creatinine levels rose from a baseline of 13 and 1.1 mg/dL, respectively, to 39 and 2.4 mg/dL. On day 6, the patient developed gross hematuria and transient abdominal pain. Results of urinalysis were otherwise negative for pyuria, fungal elements, or eosinophils, and cultures were negative. A ^{99}Tc renal scan showed normal perfusion with mild isotope retention. Cytoscopic examination showed normal bladder mucosa with bloody efflux from both ureteral orifices. Intravenous pyelography several days later showed no evidence of nephrolithiasis, papillary necrosis, or other lesions. Results of hematologic studies including hemoglobin electrophoresis were normal, as were coagulation variables with the exception of a mildly prolonged bleeding time. A serum autoantibody panel which included glomerular basement membrane antigen had negative findings. Pentamidine therapy was discontinued, the hematuria cleared over a 72-hour period, and the blood urea nitrogen and creatinine levels returned to baseline.

Renal toxicity is found in about 25% of patients given pentamidine (2, 3). As seen with our patient, azotemia is usually mild and reversible. Hematuria has not been previously identified as a consequence of pentamidine use. We found no other apparent cause for this patient's acute renal dysfunction and associated gross hematuria, and we believe that this complex is a newly described complication of pentamidine administration.

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Legionella bozemanii and Empyema

TO THE EDITOR: Parry and colleagues (1) recently reported five cases of nosocomial pneumonia due to *Legionella bozemanii* in immunosuppressed patients. We report a case of an empyema due to this organism occurring in a patient with an underlying lymphoma.

A 65-year-old man with a 12-year history of non-Hodgkin's lymphoma was hospitalized because of left-sided pleuritic chest pain and fever of 5 days' duration. He denied having headache, abdominal pain, nausea, diarrhea, or difficulty in walking. His medications included chlorambucil and prednisone (for 2 months).

Physical examination showed the patient to be chronically ill but alert and oriented. His temperature was 39.5 °C; pulse, 88 beats/min; and respirations, 18/min. Decreased breath sounds and dullness were found in the lower third of the left lung. Abdominal examination revealed an enlarged liver and spleen.

The patient's hematocrit was 42%; hemoglobin, 14 g/dL; and leukocytes, 5900/mm^3 with 63% polymorphonuclear cells, 31% band forms, 2% lymphocytes, 3% monocytes, and 1% eosinophils. Liver function tests were all normal. His creatinine level was 1.5 mg/dL. Chest radiographs revealed a large, loculated, left pleural effusion. No infiltrates were seen.

Therapy with carbenicillin and gentamicin was started. The next day, thoracentesis yielded yellow, cloudy pleural fluid. The protein level was 4.7 g/dL; glucose, 110 mg/dL; and leukocytes, 80/mm^3 with 90% polymorphonuclear cells and 10% mononuclear cells. Gram's stain and cultures for aerobic, anaerobic, fungal, and acid-fast organisms were negative. Cultures for legionellae were not done. The patient defervesced and his chest pain resolved. His therapy was switched to cefoxitin.

On the 20th hospital day, his temperature rose to 39.5 °C. A repeat thoracentesis yielded purulent fluid. Gram stain showed sheets of neutrophils and many small gram-negative rods. Cultures for aerobic, anaerobic, acid-fast, and fungal organisms were negative. Culture on buffered charcoal-yeast extract (BCYE) medium was positive for *L. bozemanii* and this finding was confirmed by specific direct immunofluorescence. After a drainage procedure, the patient rapidly defervesced. Cefoxitin therapy was continued until the patient was discharged on the 29th hospital day. He has done well with no further antibiotic therapy.

Several confirmed or suspected cases of pneumonia due to *L. bozemanii* have been reported (1-4). Our case represents an empyema due to *L. bozemanii* without an apparent underlying pneumonia. We could not determine whether the *L. bozemanii* was the original cause of the empyema or whether it was a nosocomial pathogen. One other case of empyema without apparent underlying pneumonia due to a *Legionella* species was found in the literature (5). *Legionella* species should be considered in the evaluation of "culture-negative" infections of the pleural space, particularly in immunocompromised hosts.

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Efficacy of Pneumococcal Vaccine

TO THE EDITOR: In your January issue, Bolan and coworkers (1) argue for the efficacy of pneumococcal vaccine, continuing work first reported 4 years ago (2). They describe current difficulties in mounting a prospective randomized trial and present an analysis of available data on serotype prevalence in vaccinated and unvaccinated populations. Their report does not include the full description of methods found in the original paper (2).

Briefly restated, those methods state that in a vaccinated population (size N_1), let a equal cases of pneumococcal disease caused by serotypes included in the vaccine, and let b equal cases due to nonvaccine serotypes. Similarly, for an unvaccinated population (size N_2), let c equal vaccine-type cases and d equal nonvaccine-type cases. Vaccine efficacy (proportion of vaccine-type disease prevented) can be calculated as $1 - (a/N_1)/(c/N_2)$ or $1 - (aN_2/cN_1)$, where a/N_1 and c/N_2 equal the incidence of vaccine-type disease in vaccinated and unvaccinated populations, respectively. Calculating incidence requires that one begin with a defined population (N_1 or N_2) and identify all cases of disease (a or c). Bolan and colleagues avoid this difficulty by assuming that vaccination will not affect the incidence of disease caused by nonvaccine serotypes (in the above scheme, $b/N_1 = d/N_2$). By substitution and algebraic manipulation, efficacy can be determined as $1 - ad/bc$; one need not begin with a defined population, as N_1 and N_2 may remain unknown.

The method above depends critically on the assumption that vaccination will reduce the incidence of vaccine-type disease without a compensatory increase in incidence of disease caused by other serotypes. The original report (2) cites data to support this assumption. At least one recent trial, though, finds the opposite result (3), that the decrease in incidence of vaccine-type disease is balanced by an increase in other serotypes.

These discrepant results correspond to different models of pneumococcal disease. In one model, many persons are susceptible to disease but few are exposed; each exposure would result in clinical infection. In such a system, vaccination would prevent transmission after each exposure to vaccine serotypes, eliminating that portion of disease. In the other model, susceptibility would be rare and the infectious agent ubiquitous. Susceptible persons would eventually develop disease regardless of vaccination, because, through repeated exposure, they would eventually encounter nonvaccine serotypes. Any decrease in incidence of vaccine-type disease would accompany a corresponding increase in incidence of disease due to other types.

Reality surely lies between these two poles. Bolan and coworkers (1), however, depend on one of these extreme positions. Their recent data are actually consistent with vaccine efficacy anywhere between 64% and 0%, depending on the range of possibilities described above. Only studies that begin with defined at-risk populations will determine to what degree pneumococcal vaccination actually prevents disease or simply shifts it to different serotypes.

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In response: The points raised by Dr. Simon are important theoretical considerations in determining the effectiveness of pneumococcal vaccine. We agree that data on whether vaccine-type disease in vaccinated persons is replaced by disease due to other pneumococcal serotypes or organisms other than the pneumococcus are necessary to evaluate the effect of vaccination on overall morbidity and mortality. These data are not currently available, and we have recommended that further studies are needed (1). To date, however, available data are consistent with the assumptions that we propose, including the study Simon cites on the use of pneumococcal vaccine in the institutionalized elderly by Bentley and colleagues (2). The rate of nonvaccine-type disease in vaccinated persons, 29.3/1000, is not significantly different from the rate of 24.8/1000 in the unvaccinated persons. In addition, these data are based on small numbers of respiratory isolates in a nonrandomized trial.

The models proposed by Simon assume that non-vaccine-type pneumococci are as invasive as vaccine-type organisms. Data from carriage studies (3) showing that some serotypes of pneumococci may be more invasive than other types contradict this assumption. In general, the types included in the vaccine were selected for their invasive potential, and the frequency with which carriage results in disease appears to be substantially higher for the vaccine types. Our approach to estimating efficacy uses a model including variable invasiveness, which is consistent with known data. However, we do agree that further studies in well-defined, high-risk populations are essential to ascertain the effectiveness of pneumococcal vaccine in reducing overall respiratory morbidity and mortality.

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Co-trimoxazole Desensitization in Bone Marrow Transplantation

TO THE EDITOR: Co-trimoxazole (trimethoprim sulfamethoxazole) is a safe and effective oral anti-infective agent commonly used in recipients of bone marrow transplants for prophylaxis against infection, particularly *Pneumocystis carinii* pneumonia. Since the institution of co-trimoxazole as a prophylactic agent, the morbidity of *P. carinii* interstitial pneumonia has decreased (1, 2). However, the occurrence of a hypersensitivity reaction to co-trimoxazole can prevent its administration. Penicillin V may be substituted for bacterial prophylactic coverage after transplantation, but it is not effective against *P. carinii*. Successful desensitization to co-trimoxazole would permit continued use of this most effective agent for prophylaxis or treatment of pneumocystis infections.

Desensitization procedures have been successfully carried out with penicillin, insulin, aspirin, and sulfasalazine (3-5). A literature search, however, revealed no specific guidelines for co-trimoxazole desensitization, thus necessitating the development of a protocol for use in our marrow transplantation unit. We report the cases of two patients in whom a successful inpatient desensitization procedure was carried out, allowing the continued use of co-trimoxazole.

A 22-year-old white man with acute lymphoblastic leukemia, who took co-trimoxazole for prophylaxis before marrow transplantation, developed skin rash, fever, and difficulty in breathing after ingesting the initial dose of two single-strength tablets. A similar reaction occurred 2 months later when the patient was rechallenged with one single-strength tablet. The desensitization procedure consisted of the oral administration of an initial dose of co-trimoxazole suspension equal to 0.04 mg of sulfamethoxazole that was progressively increased over a 5-hour period to a dose equal to 400 mg. There were no adverse effects during the desensitization procedure. The second patient, a 28-year-old white man with chronic myelogenous leukemia, also developed a skin rash without fever after ingesting the initial dose of prophylactic co-trimoxazole before marrow grafting. This patient was also successfully desensitized, with no adverse effects, by the same procedure.

The conclusions that may be derived from two case reports are somewhat limited. We believe, however, that these two cases show the possibility of inducing tolerance to co-trimoxazole through a desensitization procedure. Because tolerance induction through desensitization was safe and effective for these two patients, this procedure may have a broader application in patients who develop allergic manifestations to co-trimoxazole.

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