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 Tables and figures will not be published.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.

Registry for Angiofollicular Lymph Node Hyperplasia

TO THE EDITOR: A registry of cases of localized and multicentric angiofollicular lymph node hyperplasia has been established at the University of Nebraska Medical Center. The localized form (Castleman's disease) is thought to be a benign process that occurs as solitary lymphoid mass in young patients (median age, 23.5 years). These patients are usually cured of the disorder by local excision of the mass.

Recently, a multicentric form of angiofollicular lymph node hyperplasia with significant patient morbidity and mortality has been reported (1, 2). Patients with the multicentric form are generally older (median age, 56 years) and frequently have constitutional symptoms, generalized lymphadenopathy, hepatosplenomegaly, anemia, polyclonal hypergammaglobulinemia, and bone marrow plasmacytosis. Patients with the multicentric form can be placed into three different clinical groups based on their presentation and course: stable disease, chronic relapsing disease, and aggressive disease (2). Patients with multicentric angiofollicular lymph node hyperplasia appear to be predisposed to the development of opportunistic infections, malignant lymphoma, and Kaposi's sarcoma (1, 2). The median survival of our patients with the multicentric form was only 26 months (2).

Enlistment of patients in the registry provides an opportunity to study the pathogenesis and natural history of angiofollicular lymph node hyperplasia and may provide a basis for developing treatment. A detailed multi-variable approach will include morphologic, immunologic, cytogenetic, and virologic studies. The registry will also provide clinical consultation to physicians attending these patients. Requirements for enrolling patients in the registry include sending clinical and laboratory records along with diagnostic microscopic slides. Additional studies on peripheral blood, serum, and processed and frozen tissues will be done when they are available. For registration of cases, please contact Dennis D. Weisenburger, M.D., Department of Pathology and Laboratory Medicine, University of Nebraska Medical Center, 42nd and Dewey Avenue, Omaha, NE 68105 (402-559-4186).

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Bilateral Breast Cancer and Radiotherapy for Asthma

TO THE EDITOR: Breast cancer occurs with greater frequency in women who have received breast irradiation during courses of radiotherapy or fluoroscopy for tuberculosis, mastitis, and acne (1). A recent patient of ours had been given radiation treatment at age 7 for "chronic asthmatic bronchitis." The radiation was administered with a 200 KV machine in two treatments given to anterior and posterior chest fields, with a total of 240 rad in air given anteriorly and 200 rad in air given posteriorly. The estimated total dose to each breast was 440 rad. At ages 28 and 32 she developed separate primary breast cancers of lobular type from which she died at age 33.

At age 28 the incidence of breast cancer in white American women is 30 per 100 000 per year (2). Second primary breast cancers occur at a rate of approximately 1 per 100 per year. Lobular breast cancer is uncommon in young women (3).

Although the induction of human breast cancer by radiation is well documented, the timing and doses are of particular interest. With longer follow-up of surviving women exposed to atomic bomb radiation, increased incidence of breast cancer has been found in those exposed, with prepubescent females up to 9 years of age at exposure showing the greatest increase in relative risk (4). The increases are seen in all age-specific incidence groups, which suggests that the temporal pattern of radiation-induced breast cancer follows that of nonradiation-related disease and that age-dependent factors influence disease expression (5). The breast cancers in our patient may be related to the radiation given, which was in the same dose range and during the same prepubescent period as in the young female survivors of the atomic bomb. If this association is real, two risk factors may have influenced disease expression: early age at menarche and nulliparity. These factors may have created a prolonged "promotional" environment for breast cancer cells initiated during prepubescence. Such a sequence places more emphasis on premenarchial exposures than has usually occurred.

How many patients with asthma were treated with radiation therapy is unknown; such therapy was recommended in the 1930s and 1940s but was unusual by the 1950s. In the absence of widespread public and familial discussion of such therapy, an accurate history of this radiation exposure is difficult to obtain. This experience suggests that clinicians should seek a history of radiation for asthma and evaluate breast abnormalities with this history in mind.

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

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Osler and "House Pupil"

TO THE EDITOR: I wish to compliment Dr. Hurst on his thought-provoking article (1) in which he uses a fictional visit by Sir William Osler as visiting professor to express his own views on the essential skills to be emphasized in training house officers. The fictional Osler states, "I like the name house pupil . . . *House* implies that you remain in the hospital as though it is your home, and *pupil* indicates that you must remain a student of medicine forever." Osler would have agreed with this statement in principal, as he resided within the Johns Hopkins Hospital for a number of years after its opening (2), and he admonished medical students that their course of study "was not a medical course, but a life course (3)." I doubt, however, that Osler would have used the term "house pupil" to refer to our modern house officers.

House pupil was first used in 1811 to refer to Harvard medical students visiting the Boston Almshouse and was later adopted in 1849 by the Massachusetts General Hospital to refer to young men selected in their final year of medical school to serve as "house physician" or "house surgeon." In 1922, the term "house officer" was adopted to replace "house pupil"(4).

One of the first issues facing the Trustees after the opening of the Johns Hopkins Hospital in 1889 was the selection of house physicians and surgeons. Much of our current terminology and residency structure can be traced directly to Dr. Osler's comments at that time. Evidence that Dr. Osler would not have used the term house pupil comes from his report to the Medical Board on 30 January 1890 in which may be found the origin of the term "assistant resident." Furthermore, Osler recommended that "internes should be appointed indifferently from the entire country wherever we can hear of a man who wishes to do scientific work" and that they should remain in the department of their appointment "for their entire term of service and not rotate as is usually the case" (5). By selecting Dr. Osler as the vehicle through which to relay his own ideas about the modern residency system, Dr. Hurst pays homage to the man who first envisioned nearly 100 years ago our present day system of internship categories and a graded residency system, but by having his fictional Osler use the term house pupil, Hurst introduces an element that, for historical reasons, is incorrect.

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Abortion and the Ethics Manual

TO THE EDITOR: The Ad Hoc Committee on Medical Ethics of the American College of Physicians has dealt inadequately with the issues of abortion and contraception (1).

Although the Committee had no hesitation in deciding when life ends (2), it declined to confront the issue of when life begins. In four short paragraphs the Committee lumps the ethical issues of abortion and contraception under the same rubric. The manual repeats the cliched phrase "a physician should not impose his personal convictions upon the patient." Most seriously, the Committee imposes the duty "to assure that the patient is provided the option of receiving competent medical advice and care from a colleague who does not have these moral, religious, or ethical objections" on the physician who objects to abortion on moral, religious, or ethical grounds. To pro-life physicians, this statement is the equivalent of saying "I will not accept a contract for murder but will refer you to someone who might."

Clearly, the pregnant patient who desires to terminate a pregnancy is entitled to know if the physician's refusal to recommend an abortion is based on his or her judgment in the particular situation and what are the circumstances, if any, under which the physician would ever recommend an abortion. The patient then understands the context. The physician should be free to explain his or her view of the nature of the fetus and reasons for this policy. The patient is thus free to follow the physician's advice or not.

I propose the following statement as a substitute for the first two paragraphs on abortion and contraception:

> From its founding the American College of Physicians always held abortion to be unethical in the healthy woman who had not been raped. Following the 1973 U.S. Supreme Court decision of Roe versus Wade and subsequent decisions, abortion on request has been legal in the United States. Because many physicians, including some members of the College, concur in the Supreme Court decisions and others continue to adhere to the original view of the College, it is the duty of each physician to clarify to the patient his or her ethical commitment in this area so that the patient will have a clear basis for understanding a clinical recommendation.
>
> The issues with respect to contraceptive advice are less complex, because the question of a separate life is not at stake (unless the contraceptive measure is inherently abortifacient). Here again, however, the physician has a responsibility to clarify his or her ethical standards in this area so that the patient can appropriately understand the recommendation given.

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In response: The Ad Hoc Committee on Medical Ethics appreciates Dr. Gibson's comments about the statement on abortion and contraceptive advice that appeared in the American College of Physicians' Ethics Manual. It will be carefully filed for consideration when the manual is revised. The committee is not aware of any previous position of the American College of Physicians on the subject of abortion, as stated by Dr. Gibson. The present position is a "suggested guide to making ethical decisions," and is not binding on any member of the College.

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Solvent Intoxication with Parenteral Nitroglycerin

TO THE EDITOR: Several recent reports (1-4) have shown a potential for toxicity of solvents in most commercially available parenteral nitroglycerin products. Various concentrations of both propylene glycol and ethanol are found in four of five currently available commercial brands of this preparation. Such cosolvent systems provide greater solubility of nitroglycerin, resulting in an increased drug solution concentration (5 mg/mL). Because this drug is generally further diluted when administered intravenously, more dilute concentrations of the stock solution are acceptable.

In response to reports of solvent intoxication at our institution (1-3), we investigated potential alternatives to products containing ethanol and propylene glycol. Although our principal concern was to minimize the occurrence of toxicity, we also examined the cost effect of each option. Three different methods to obtain a completly aqueous nitroglycerin preparation (0.8 to 1 mg/mL) were identified. These methods include the purchase of a commercially available product (Nitrol IV; Kremers-Urban Company, Milwaukee, Wisconsin); the extemporaneous compounding of a suitable product in-house using one of many different methods reported in the literature (5); or the development of a contractual arrangement with a reputable small-volume pharmaceutical manufacturer to prepare a product for our use with "current good manufacturing practices" mandated by the Food and Drug Administration.

With present use, our institution spent $58 000 annually to purchase a product containing ethanol and propylene glycol. Through price negotiation with the Kremers-Urban Company, we projected an increase of $49 000 to convert to their product. There appeared to be a negligible cost difference between in-house compounding and outside contracting with a suitable manufacturing facility. However, the latter was capable of producing larger batches per unit time and already maintained the necessary quality control equipment. Therefore, a contractual agreement was developed. Through our current arrangement, we project an expense of $39 000 annually for an aqueous nitroglycerin product. This figure represents a 33% decrease from our expenditure for the nonaqueous product; and is 64% less expensive than the only commercially available equivalent product. This approach has eliminated our concerns about solvent toxicity and resulted in a substantial savings to the institution for parenteral nitroglycerin.

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Wernicke's Encephalopathy and High-Dose Nitroglycerin

TO THE EDITOR: The long-recognized cause of Wernicke-Korsakoff encephalopathy has been thiamine deficiency, associated with poor nutrition in the alcoholic or nonalcoholic patient. Blass and Gibson (1) suggested a different cause, namely a genetic abnormality in transketolase, the thiamine-requiring enzyme. Even in their four patients, however, nutritional deprivation was necessary before the genetic expression appeared. Hence, nutritional deprivation has been a common theme in this disease.

Shorey and associates (2) propose that high doses of the diluent ethyl alcohol and propylene glycol given intravenously may produce this disease by a direct metabolic effect on thiamine metabolism. These authors should exclude the nutritional factor before proposing such a new idea. They do not clarify the nutritional status of their elderly patient. This man had chronic angina and received a carbohydrate load along with nitroglycerin and its diluents. One wonders, however, if the patient could have had a partial thiamine deficiency before admission and developed the syndrome after the carbohydrate challenge. This precedent has been reported by Phillips and associates (3).

There is a little doubt that the patient's symptoms probably represent Wernicke-Korsakoff syndrome because of the clinical picture and the reponse to intravenous thiamine. The rechallenge experiment does not, however, support their thesis without more data on the patient's nutrition. It only takes 18 days to become thiamine deficient when on a thiamine-free diet (4), and the Wernicke-Korsakoff syndrome has been precipitated in nonalcoholics receiving intravenous therapy alone. How many days elapsed between the patient's initial therapy and the rechallenge? Did the patient ever receive thiamine orally or parenterally during this period? These issues need to be clarified before one can accept the proposal that the diluent ethyl alcohol and propylene glycol can produce the Wernicke-Korsakoff syndrome.

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Captopril and Insulin Sensitivity

TO THE EDITOR: Captopril, an oral angiotensin converting enzyme inhibitor, is widely used in the treatment of patients with hypertension and chronic congestive heart failure, and to date no effect of this drug on carbohydrate metabolism has been reported.

We have recently seen three cases of unexplained hypoglycemia in insulin-dependent diabetic patients when captopril was used with their usual insulin dosage. Moreover, in a non-obese, non-insulin-dependent diabetic patient, hypoglycemia necessitated the withdrawal of hypoglycemic oral agents. To study a possible role of captopril on insulin sensitivity, we used the euglycemic glucose-clamp technique (1) in patients before and during treatment with captopril.

Three patients with non-insulin-dependent diabetes, one with insulin-dependent diabetes, and five nondiabetic patients were studied before and after they received captopril for 10 days (50 mg two times daily for two patients with hypertension, and 25 mg three times daily in seven patients with congestive heart failure). The euglycemia glucose-clamp studies were done after an overnight fast with a procedure adapted from the method of

De Fronzo and associates (1) that we successfully used in a previous study (2). All patients were treated with furosemide, and the patients with diabetes were treated additionally with hypoglycemic agents, for several months before the study began. These drugs were withdrawn the morning of the glucose clamp study.

The average blood-glucose levels were identical during the two sets of clamp studies: 4.66 ± 0.08 mmol/L before and 4.66 ± 0.11 mmol/L during treatment with captopril. The glucose disposal rate was higher during treatment with captopril in all the nondiabetic and in three of the four diabetic patients. The mean of the glucose disposal rate was significantly increased ($p < 0.01$) during treatment: 124.5 ± 9.3 and 162.3 ± 14.7 mg/m^2 body surface area · min before and during treatment respectively.

These results indicate an enhancement of insulin sensitivity by captopril. The mechanism of this effect remains hypothetical: a decrease of circulating catecholamines induced by captopril (3, 4) may explain this phenomenon, because epinephrine increases insulin resistance in humans (5). However, a direct action of captopril on insulin receptors, or on post-receptor events, or on both remains to be studied. Physicians should be alerted to the possible increasing risk of hypoglycemia in diabetic patients when captopril is used in association with hypoglycemic agents.

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Minoxidil in Breast Milk

TO THE EDITOR: Minoxidil is a potent vasodilator used in the treatment of severe hypertension (1). No pregnancies have been reported in patients receiving the drug. We report the case of a patient who became pregnant during minoxidil treatment and delivered a normal child whom she nursed. Excretion of minoxidil into breast milk in relation to plasma values was measured.

A 40-year-old hypertensive woman with bilateral intrarenal fibrodysplasia was successfully treated with minoxidil, 5 mg twice daily; propranolol, 40 mg twice daily; and furosemide, 40 mg twice daily. While being treated, she had an unplanned, uneventful pregnancy, delivering at 37 weeks a normal boy weighing 2880 g. Therapy with antihypertensive drugs was continued during breast feeding.

Two months later, the mother and child were hospitalized in our metabolic unit. Her blood pressure was 158/98 mm Hg and pulse rate was 72/minute. Results of her physical examination, serum electrolytes, SMA12 profile, complete blood count, and 24-hour creatinine clearance were all normal.

On day 1, basal milk and plasma samples were obtained for total and free minoxidil determinations. At 0800 h she received minoxidil, 7.5 mg orally; plasma and breast milk samples were again obtained at 0900, 1100, 1400, 1700 and 2000 over 2 days. Minoxidil was discontinued on day 2; propranolol and furosemide treatments were maintained. The patient was discharged on day 3.

Minoxidil levels were determined by radioimmunoassay (Clinical Research Laboratories, The Upjohn Company, Kalamazoo, Michigan). Breast milk specimens were centrifuged at 22 000 rev/min for 24 hours; the supernatant was assayed for total and free minoxidil (2). Minoxidil glucuronide concentration was determined by subtracting free minoxidil concentration from total minoxidil concentration.

Minoxidil was rapidly excreted into breast milk. The drug plasma concentration was slightly higher than the milk concentration at hour 1 (55 and 41.7 ng/mL); thereafter concentrations were similar (15.0 and 10.0 at hour 3, 3.1 and 2.9 at hour 6, 0.8 and 0.9 at hour 9, and 0.0 and 0.3 ng/mL at hour 12 in plasma and milk respectively). Glucuronide conjugate also appeared rapidly in plasma, but was barely excreted into milk, probably due to low liposolubility. Glucuronide conjugate in plasma was 62.5, 20.5, 4.2, 1.6, and 0.6 ng/mL at 1, 3, 6, 9, and 12 hours; and 3.4, 2.4, 1.1, 1.0, and 0.5 ng/mL for the same sampling periods in milk.

A lack of hypertrichosis and the other normal findings with the infant after 2 months of exposure to minoxidil suggests, but does not guarantee, that he did not suffer from secondary effects of the drug. Minoxidil does pass into breast milk, and prolonged exposure during breast feeding may be deleterious to the nursing infant.

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Dysomia, Dysgeusia, and Nifedipine

TO THE EDITOR: Nifedipine is a calcium channel blocker widely used in the treatment of angina. Its adverse effects include flushing, dizziness, headache, pedal edema, upper gastrointestinal distress, weakness, paresthesias, and transient hypotension. Uncommon serious adverse effects may include congestive heart failure, increased angina, and cerebral ischemia (1). We have recently encountered distortion of taste (dysgeusia) and smell (dysosmia) in two patients taking nifedipine.

A 71-year-old woman was hospitalized with unstable angina. She had been receiving nifedipine, 30 to 80 mg/d for 13 months, in addition to nitrates, digoxin, and furosemide. She also had a profound unexplained weight loss (27 kg) that had occurred over the past year; no malignancy could be identified. She had severe dysosmia and dysgeusia that had begun 1 year ago. She had developed an intense revulsion toward eating, complaining that food tasted and smelled like coffee. She was nauseated and, on rare occasions, vomited after eating. Dysgeusia had been noted previously by her local physician, who prescribed treatment with zinc and multivitamins without success. Results of laboratory tests, including SMA12 profile, complete blood count, urinalysis, cerebral computed tomographic scan, thyroid function tests, and VDRL, were all normal. There was no previous head trauma, hepatitis, or recent viral illness. On 13 January 1984, diltiazem was prescribed in place of nifedipine. By 15 January 1984, her symptoms were disappearing. Follow-up 2 months after discharge showed no recurrence of dysosmia or dysgeusia. She had received no more nifedipine.

A 45-year-old woman was hospitalized with unstable angina. She had been previously treated with nitrates and propranolol. Nifedipine was begun on hospital day 2. On hospital day 6, she began refusing meals. She complained that all food tasted "awful." There was no history of weight loss or disorders of taste or smell. The patient dated the onset of symptoms to the day she began receiving nifedipine. Nifedipine therapy was discontinued, and the dysgeusia disappeared in less than 24 hours. She received no more nifedipine and had no recurrence of symptoms.

Numerous disorders may produce dysosmia or dysgeusia, including chronic renal failure, hypothyroidism, viral hepatitis

and other infections, nutritional deficiencies, radiation therapy to the head and neck, head trauma, and reactions to various drugs (2). There are no published reports of nifedipine causing such symptoms. The rapid resolution of dysosmia and dysgeusia in our patients after discontinuation of nifedipine suggests that the drug was responsible. No other disorder causing abnormalities of taste or smell was evident in either patient. Rechallenge with nifedipine could have provided convincing evidence for causation, but was not possible with these two patients. The manufacturer has received reports of two other patients with dysgeusia who had received nifedipine, one of whom also had dysosmia (D'AMBROSIO G. Personal communication).

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Sarcoid Meningoencephalitis Treated with High-Dosage Steroids and Radiation

TO THE EDITOR: The incidence of neurologic involvement in sarcoidosis is reported as 5% to 7% (1, 2). Seizures occur in 5% to 18% of these patients and are associated with a combined morbidity and mortality of 75% (3). The response to steroid and anticonvulsant therapy is variable but generally poor, with most patients having chronic, poorly controlled seizures or progressing to death. We report the case of a patient with stage I pulmonary sarcoidosis complicated by sarcoid meningoencephalitis with seizures. The patient's course was progressive despite steroid treatments in high doses, and he began to show improvement only after receiving radiation to the central nervous system.

A 22-year-old previously healthy black man presented to another hospital in July 1982 with severe headaches. A diagnosis of aseptic meningitis was made and no specific treatment was given. In December 1982 he presented with diplopia and lethargy, bilateral papilledema, bilateral sixth nerve palsies, and mild meningismus. He had a major motor seizure. A computed tomographic scan of the head was consistent with a diagnosis of encephalitis, and a chest roentgenogram showed bilateral hilar adenopathy with clear lung fields. Results of a lumbar puncture were consistent with a diagnosis of aseptic meningitis, with negative spinal fluid culture, India ink stain, and cryptococcal antigen. The diagnosis of sarcoidosis was confirmed by transbronchial lung biopsy, and treatment was initiated with anticonvulsant agents and high-dose steroids. Over the subsequent 2 months, the patient continued to have frequent major motor seizures.

The patient was transferred to the Shands Hospital for further therapy. A repeat computed tomographic scan of the head showed extensive contrast enhancement of the brain throughout all regions with diffuse leptomeningeal enhancement and ventriculomegaly. Whole cranial irradiation was given totaling 2500 rad. Due to development of diffuse hyperreflexia and bilateral Babinski responses, he also received 1500 rad to the spinal column. After radiotherapy he began to show improvement with respect to his marked lethargy and memory deficit, and the progression of his extremity spasticity was halted. In April 1983, the patient had two additional major motor seizures. To confirm the diagnosis of sarcoid meningoencephalitis, he had a craniotomy with meningeal and right parietal brain biopsy. Pathologic studies were consistent with sarcoidosis and infection was excluded.

The patient has shown progressive improvement, with return of his mental status to his premorbid state. Prednisone has been gradually tapered to a current dose of 30 mg every other day and he has had no seizures for 18 months. A subsequent computed tomographic scan has shown decreased meningeal and parenchymal contrast enhancement with decreased but persistent mild ventriculomegaly.

Oppenheim and Pollack (4) have reported benefit from low-dose radiation to the mediastinum in patients with sarcoidosis. Grizzanti and associates (5) have reported the case of a patient with sarcoid meningitis and seizures with apparent improvement after cranial irradiation, but the patient died 7 months later of pulmonary emboli. Our patient has allowed more prolonged follow-up, with apparent significant benefit after radiation to the central nervous system.

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Transmission of Infection During Training for Cardiopulmonary Resuscitation

TO THE EDITOR: It has been estimated that there are 800 000 persons in the United States who are chronic carriers of hepatitis B surface antigen (HBsAg) (1). This antigen has been found in saliva. In guidelines published in 1984 (2) the National Research Council recommended that a person known to be seropositive to HBsAg should not participate in training for cardiopulmonary resuscitation. The Council further suggested that students be assigned in pairs and each pair have contact with only one manikin. As an additional means of reducing the change of spread of disease, it was recommended that the second student in two-rescuer resuscitation should only simulate ventilation of the manikin.

As part of the effort to prevent the spread of disease, a person with active, visible herpes simplex on or about the lips is not supposed to participate in cardiopulmonary resuscitation training. The possible transmission of herpes during such training still exists because studies have shown that up to 10% of adults periodically shed herpes virus in the saliva in the absence of clinically visible disease (3, 4). Except for periods of aborted recurrences, the amount of the herpes virus may be low but still sufficient to infect a nonimmune exposed person. Herpes virus has been shown to survive on inanimate objects—for example, 88 hours on dry gauze and up to 1.5 hours on a toilet seat (5).

We are concerned that the above viral diseases could be acquired during training for cardiopulmonary resuscitation despite the recommended precautions. Proper cleansing of the training manikin with hypochlorite solution or 70% isopropyl or ethyl alcohol may not be precisely done during the training session.

The use of an overlay mask designed to fit over a manikin's mouth and nose would help to further reduce cross-infection during training with manikins. A face shield is mentioned in the National Research Council's guidelines but has not yet received much publicity. Each participant should have exclusive use of a mask throughout the training session, and could retain the mask for use at subsequent training sessions. Several manufacturers produce and distribute such masks and we believe that their use will contribute to the safety of all participants during training for cardiopulmonary resuscitation.

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Levamisole, Immunostimulation, and the Acquired Immunodeficiency Syndrome

TO THE EDITOR: In addition to its antihelminthic and antianergic properties, levamisole is known to normalize the function of T lymphocytes in immunosuppressed patients without affecting B cells (1). We attempted to evaluate these properties in patients with the acquired immunodeficiency syndrome. Levamisole and other immunostimulants have been proposed as treatment for this syndrome but we are unaware of any clinical trials of levamisole.

The five patients who participated in this study were homosexual men with the syndrome (ages, 29 to 37 years) who had recovered from *Pneumocystis carinii* pneumonia. All five patients had other opportunistic infections such as oral candidiasis. One patient had Kaposi's sarcoma. The patients were given either levamisole, one 5-mg tablet per week, or placebo (Janssen Pharmaceutica, Incorporated, Piscataway, New Jersey) in a double-blind manner. Physicians' evaluations and blood counts were done biweekly. Skin testing was done with *Candida,* mumps, *Trichophyton,* tetanus, and purified protein derivative antigens before and at the end of the study. Lymphocyte proliferative responses to mitogens were also assayed before and at the end of the study.

Two of three patients who received levamisole developed leukopenia 1 week and 3 weeks after the start of treatment. A third patient developed skin rash and fever within hours of receiving levamisole. There was no significant change in the clinical course of the two patients who received placebo tablets, although one discontinued the medication.

The study was discontinued because of possible drug toxicity and the lack of apparent efficacy. There was no improvement in immune status: cutaneous anergy persisted, T-helper cell members declined, and lymphocyte proliferative responses to phytohemagglutinin and pokeweed mitogen decreased. Two of three patients treated with levamisole had a slight increase in responsiveness to concanavalin A.

Other immunomodulatory agents have been studied in the acquired immunodeficiency syndrome. Grieco and coworkers (2) found some enhancement of mitogen-induced (particularly concanavalin A-induced) proliferation in patients given isoprinosine. Although our study was small, we conclude that the risks of levamisole outweighed the benefits. All the patients with this syndrome who received levamisole had one or more drug-related problems. There was no evidence of stimulation of the immune system.

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Pneumocystis carinii Pneumonia

TO THE EDITOR: Kovacs and associates (1), in their comparative analysis of *Pneumocystis carinii* pneumonia in patients with the acquired immunodeficiency syndrome and other immunodeficiencies, report differences in the clinical behaviour of the pneumonia between the two groups of patients: those with the acquired immunodeficiency syndrome had a more insidious onset. We believe, however, that the clinical data they offer can be interpreted differently. Their Table 2 shows clinical data from both groups of patients. The main differential features are a lower mean respiratory rate, higher median oxygen tension (with room air) and a longer median duration of symptoms at presentation in the patients with the syndrome than in patients with other immunodeficiencies. That the group without the syndrome is composed of patients with malignant tumors and systemic vasculitis is noteworthy. It is well known that these patients often have respiratory insufficiency secondary to chemotherapy or anemia, and as a consequence of the primary diseases themselves.

The early detection of *Pneumocystis carinii* pneumonia in the group without the syndrome compared to the patients with the syndrome could be attributed to other reasons: patients without the syndrome were known to have serious diseases and therefore were in close contact with medical care. The development of nonspecific respiratory symptoms in these patients may have been found earlier than in those of patients with the syndrome, particularly the patients being treated on cancer services by physicians familiar with the diagnosis of opportunistic infections. The patients with the syndrome were previously healthy, young, and more reluctant to seek medical attention, and were treated on an ambulatory basis for a longer time.

We believe that the evidence presented by these authors is not enough to explain the differences in clinical behaviour of the two groups of patients with *Pneumocystis carinii* pneumonia.

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REFERENCE

1. KOVACS JA, HIEMENZ JW, MACHER AM, et al. *Pneumocystis carinii* pneumonia: a comparison between patients with the acquired immunodeficiency syndrome and patients with other immunodeficiencies. *Ann Intern Med.* 1984;**100**:663-71.

TO THE EDITOR: We read with interest the article by Kovacs and associates (1) on *Pneumocystis carinii* pneumonia. In a recent prospective study we compared pneumocystis infection in ten patients presenting with the acquired immunodeficiency syndrome and in ten patients with other immunodeficiencies.

The diagnosis of pneumocystis infection was made either by bronchoalveolar lavage (14 patients) or by open lung biopsy (6 patients). All patients with the syndrome fit the Centers for Disease Control (2) criteria for the acquired immunodeficiency syndrome. The patients with other immunodeficiencies presented with non-Hodgkin's lymphoma (7 patients), acute lymphoblastic leukemia (1 patient), or renal cancer (1 patient), or had had a kidney transplant (1 patient). All patients were receiving chemotherapy (5 patients) or steroid therapy (6 patients).

The pneumocystic disease in the patients with the syndrome differed from that in the patients with other immunodeficiencies in several ways. Clinical manifestations were delayed (72 days compared to 18 days) in patients with other immunodeficiencies. Chest roentgenographic opacities were discrete and in seven cases interstitial in distribution; in contrast, in patients with other immunodeficiencies chest roentgenographic immunodeficiencies were alveolar and diffuse. Hypoxia was less intense (70 mm Hg compared to 50 mm Hg in patients with other immunodeficiencies). Side effects due to trimethoprim-sulfamethoxazole were more frequent (three compared to none in the patients

with other immunodeficiencies). The appearance of normal findings on roentgenograms was delayed in surviving patients (20 days as compared to 8 days in patients with other immunodeficiencies).

On the whole, the pneumocystis pneumonia seemed to have a more insidious course in patients with the acquired immunodeficiency syndrome than in patients with other immunodeficiencies. The radiologic abnormalities persisted in patients with the syndrome despite the absence of *Pneumocystis* in bronchoalveolar lavage during treatment.

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Leukopenia, Trimethoprim-Sulfamethoxazole, and Folinic Acid

TO THE EDITOR: After several reports of the high incidence of leukopenia in patients with the acquired immunodeficiency syndrome after the use of high-dose trimethoprim-sulfamethoxazole (1, 2), Kinzie and Taylor (3) suggested that all patients should receive prophylactic folinic acid. Although the biochemical basis of this recommendation is sound, in practice this has not been efficacious. The unusual sensitivity of these patients' bone marrow to various antibiotic agents is borne out by a recent report of severe leukopenia seen during therapy with pentamidine, the other accepted treatment for *Pneumocystis carinii* pneumonia (4). These cytopenias are commonly seen in conjunction with rash, fever, and hepatocellular dysfunction (1), suggesting an immunologically mediated rather than metabolic cause for these abnormalities. The absence of megaloblastic changes in bone marrow or erythrocyte macrocytosis also argues against significant folate deficiency (5). Finally, Jaffe and colleagues (5) saw that in several patients the prophylactic use of folinic acid neither prevented nor reversed the leukopenia. This has been our experience as well.

The mechanism of leukopenia in this population differs from that described by Kinzie and Taylor, making the prophylactic use of folinic acid unwarranted. Although nutritional status should be carefully monitored in patients with the acquired immunodeficiency syndrome, drug-induced leukopenia is rarely reversible on the basis of folate deficiency and will resolve only with cessation of the offending agent.

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5. JAFFE HS, AMMANN AJ, ABRAMS DI, LEWIS BJ, GOLDEN JA. Complications of co-trimoxazole in treatment of AIDS-associated *Pneumocystis carinii* pneumonia in homosexual men. *Lancet.* 1983;**2**:1109-11.

Fungal Peritonitis and Peritoneal Catheters

TO THE EDITOR: Cecchine and Panarello (1) in differing with Kerr and coauthors (2) suggest that a protracted course with an appropriate agent may be useful for the treatment of patients with fungal peritonitis without necessitating removal of a permanent peritoneal catheter.

If not promptly treated, peritonitis, manifested by abdominal pain, tenderness, fever, cloudy dialysate, elevated leukocyte count in the dialysate, and positive dialysate cultures, remains a significant and potentially life-threatening complication. In many cases peritonitis can be successfully treated with intraperitoneal or intravenous plus intraperitoneal antibiotic agents.

Between 1980 and 1983, of 47 patients with peritonitis secondary to indwelling peritoneal catheters, 5 were treated for fungal peritonitis (3). These patients were maintained on chronic peritoneal dialysis and 4 had previous episodes of bacterial peritonitis. The commonest fungal organism cultured was *Candida albicans.* All patients initially received intraperitoneal and systemic amphotericin B or systemic ketoconazole and flucytosine. Medical management was uniformly unsuccessful in these patients and all catheters had to be removed to eradicate the infection, whereas only 8 of 42 catheters were removed in patients with bacterial peritonitis.

Our experience, similar to that of Kerr and coauthors, shows that the removal of indwelling peritoneal catheters is indicated for patients with fungal peritonitis.

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Nitrofurantoin and Peripheral Neuropathy

TO THE EDITOR: The review by Snavely and Hodges (1) provides a clear discussion of the neurotoxic potential of commonly prescribed antimicrobial agents. However, in the section describing agents capable of causing peripheral nerve toxicity, nitrofurantoin was omitted. Indeed, a major problem associated with nitrofurantoin has been the occasional development of polyneuropathy (2).

Nitrofurantoin polyneuropathy may develop in patients with normal renal function, if prolonged courses of nitrofurantoin are used. In addition, changes in nerve conduction have been found without clinical features of neuropathy after a 2-week course of nitrofurantoin, 400 mg/d, in healthy volunteers. This complication has also been reported in patients with normal blood urea nitrogen levels who have had marginal renal functional impairment shown by low creatinine clearance values. The polyneuropathy, however, usually develops in patients who have renal insufficiency and has been ascribed either to progression of subclinical uremic neuropathy or to neurotoxic effects of the drug. The improvement in neural function experienced by many patients when the administration of the drug is stopped suggests the drug, not renal failure, is responsible for this condition.

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2. JACKNOWITZ AI, LEFROCK JL, PRINCE RA. Nitrofurantoin polyneuropathy: report of two cases. *Am J Hosp Pharm.* 1977;**34**:759-62.

In response: The association of nitrofurantoin use with the development of peripheral neuropathy was inadvertently overlooked in our recent review of neurotoxicity associated with the use of antibacterial agents (1). We appreciate Dr. Jacknowitz's bringing this omission to our attention.

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REFERENCE

1. SNAVELY SR, HODGES GR. The neurotoxicity of antibacterial agents. *Ann Intern Med.* 1984;**101**:92-104.

Vitamin B_{12} Deficiency After Gastric Surgery

TO THE EDITOR: Schilling and associates (1) are to be commended for their fine study showing vitamin B_{12} deficiency and the probable need for B_{12} supplementation after gastric bypass surgery for obesity.

Internists should be cautioned, however, that these results apply only to patients who have had the original gastric bypass procedure and not the gastroplasties now in vogue (the latest variation of which is the vertical banded gastroplasty). These gastroplasties are thought to be more physiologic and therefore less likely to lead to the complications some foresaw with the earlier gastric bypass procedure (2-4). The newer procedures remain to be studied for vitamin B_{12} deficiencies as sequelae.

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Dapsone and Aplastic Anemia

TO THE EDITOR: There are several reports of agranulocytosis and erythrocyte aplasia after administration of dapsone for treatment of leprosy and for prophylaxis against falciparum malaria (1, 2). We report what we believe is the first reported case of aplastic anemia due to administration of dapsone.

A 18-year-old man from the island of Ponape (Eastern Caroline Islands) was diagnosed as having lepromatous leprosy on the basis of a hypoestetic macule on his chest. (A subsequent biopsy showed only tinea versicolor.) The patient was started on dapsone, 50 mg/d. Two weeks later, he developed a headache, runny nose, sore throat, dry cough, and low-grade fever followed 2 days later by a generalized maculopapular rash. The patient himself decided to stop taking dapsone, and 1.5 to 2 weeks later all his symptoms had resolved. One week later, he resumed taking medication and within 2 to 3 days, he developed sore throat, productive cough, high fevers, and chills, followed by periorbital edema and a diffuse scaling eruption. The patient was admitted to a South Pacific hospital, dapsone treatments were stopped, and the patient was started on intravenous gentamicin, cephapirin, and chloramphenicol. The next morning the patient's leukocyte count was found to be 2000/mm^3 with an absolute neutrophil count of 300/mm^3; hematocrit, 27%; and platelet count, 45 000/mm^3. The chloramphenicol was discontinued, the patient having received only one dose.

The patient was immediately transferred to our institution. On admission he was afebrile, and results of his physical examination were normal except for the diffuse eruption, a few aphtous ulcers on the buccal mucosa, and oral candidiasis. Hemoglobin was 9.3 g/dL; hematocrit, 25.8%; leukocyte count, 2200/mm^3; neutrophil count, 528/mm^3; reticulocyte count, 11 000/mm^3; and platelet count, 14 000/mm^3. Peripheral smear showed no evidence of hemolysis and Coombs' test results were negative. Although no focus of infection was found, the patient was kept in isolation and on gentamicin and cephapirin until his neutrophil count was over 1000/mm^3.

Bone marrow aspiration and biopsy showed markedly decreased megakariocytes, and erythroid and myeloid elements, the latter two accounting for less than 10% of the total population, thus compatible with aplastic anemia. The patient improved and his laboratory values gradually returned to normal. At the time of discharge, the hemoglobin was 11.3 g/dL; hematocrit, 31.7%; leukocytes, 5000/mm^3; neutrophil count, 1900/mm^3; and platelet count, 147 000/mm^3. The patient was discharged 17 days after admission; a follow-up bone marrow biopsy was not obtained.

In our review of the literature, we could find no cases of aplastic anemia due to dapsone. Direct toxicity to the bone marrow as shown by aplastic anemia is postulated. Dapsone is widely used throughout the world. We recommend that frequent hematologic monitoring be done and the drug discontinued at first sign of toxicity.

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Correction: Sulfasalazine Dose

TO THE EDITOR: I would like to bring to your attention an error in sulfasalazine dosing in the article by Peppercorn (1). On page 384, the article reads "These authors now advocate discontinuance of sulfasalazine treatments for 1 to 2 weeks in patients who have nausea, vomiting, abdominal pain, headache, reticulocytosis, and mild rash; treatment then can be restarted at a dose of 0.125 to 0.25 g/d for 1 week, with a gradual increase by 0.125 g/wk to a maintenance dose of 2 g/wk." The doses given as g/wk should both read g/d with substitution of the word weekly for gradual.

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REFERENCE

1. PEPPERCORN MA. Sulfasalazine: pharmacology, clinical use, toxicity, and related new drug development. *Ann Intern Med.* 1984;**101**:377-86.

▶ *A reviewer of the Peppercorn review article informs us that the only error is a misprint: the maintenance dose is 2 g/d, not 2 g/wk.—The Editor.*

Correction: Baylor University and Baylor College of Medicine

TO THE EDITOR: I write with reference to Dr. Thomas' editorial (1) on extracorporeal shock-wave lithotripsy. Baylor University is in Waco, Texas. Baylor College of Medicine is in Houston, Texas. There is a distinct and widely maintained separation between these two similarly named institutions.

The lithotripter, however, is located at the Methodist Hospital in Houston, which is a teaching hospital for Baylor College of Medicine with physically distinct funding and its own separate governing board.

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REFERENCE

1. FINLAYSON B, THOMAS WC JR. Extracorporeal shock-wave lithotripsy. *Ann Intern Med.* 1984;**101**:387-8.

In response: My error in not correctly identifying Baylor College of Medicine and the affiliated Methodist Hospital is regrettable. The fact that there is a lithotripter in Houston is the information we wanted to provide for readers.

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