Letters and Corrections

Letters submitted for possible publication must be identified as such and submitted with a signed transfer-of-copyright form (see Table of Contents for location). Text length must not exceed 400 words. No more than five references may be used; reference format must be that specified in "Information for Readers and Authors." All parts of letters must be typed double-spaced, including references. Letters not typed double-spaced will not be considered for publication. Tables and figures will not be published.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, and space available; only about half of the letters submitted can be published. The Editor reserves the right to shorten letters and make changes to our style. Authors of letters to the published will be notified of their acceptance. Unpublished letters are returned only on request.

Life Expectancies: Population or Person?

To the Editor: We applaud Sox and colleagues' analysis (1) of the role of exercise testing in coronary artery disease. We are concerned, however, with the interpretation of the results, specifically, how one assesses the average change in the life expectancy for an entire cohort as opposed to a change for a single individual.

The authors state, for example, that for 60-year-old men with at least one risk factor, the average increase in life expectancy for the cohort is 17 days. However, given that the prevalence of disease is presumed to be 0.15, the average change in life expectancy for someone who actually has the disease is 17/0.15 or 113 days (and would be even higher for those with left main disease). This figure compares favorably with the 110 days of life gained by reducing diastolic blood pressure from 110 to 90 mm Hg in 60-year-old men with hypertension.

We believe that many people do not appreciate the meaning of marginal differences in life expectancy and that there is great variation among judgments of what constitutes trivial extensions of life expectancy (2). The population-based number of 17 days may have a different meaning to some than the 113-day figure.

A straw poll at our institution showed that several of the doctors, nurses, and medical students queried changed their opinion regarding screening depending on whether the benefit was presented as "15% will gain an average of 113 days of life expectancy and 85% will gain nothing" or "all will gain an average of 17 days." Almost all persons polled felt that the two vignettes presented different information.

Framing effects are well known (3), and the authors (1) include a section on other ways to express results using a variant of the number-needing-treatment method of Laupacis and colleagues (4). We believe, however, that the average life expectancy gain of the cohort is an outcome measure that obscures information needed by patients to make decisions. We suggest that life expectancy gains for those with the disease should also be represented. In that way doctors and patients can best use population-based life expectancy figures for decision-making.

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In response: Screening and other diagnostic strategies are invariably applied to heterogeneous populations. There are always at least two subgroups: those with and those without the disease. In our report (1), the summary estimate of 17 days of life is a weighted average of the therapeutic outcomes for members of each group, where the weights are the probabilities of being in each of the groups. It would be misleading to present the larger figure for life gained (113 days for the 15% who prove to have disease) without reference to the fact that this estimate is conditional upon being in the small subgroup of participants who have disease. These groups could be divided further–for example, into subgroups of diseased patients based on their coronary anatomy. Then the benefit in the highest-risk subgroup would be even greater. However, *all* who are screened, including the majority who do not benefit, bear the costs and risks of the strategy. As an extreme example, a strategy of monthly computed tomographic scans to detect lung cancer might yield large benefits for the few subjects who are spared death, but to assess

the value of such a strategy we must include the impact upon the many people who do not have disease and would not be saved (and, indeed, could be harmed) by the strategy.

We agree that the way results are presented can influence the way they are interpreted. Readers who prefer more detailed analysis or alternative presentations of results can find in our article (1) the probabilities and life expectancies associated with each branch of the decision tree. Because the results and assumptions of our analysis are described explicitly, our findings are subject to sensitivity analysis, review, revision, and debate. We feel that the cost-effectiveness ratio is the most informative, succinct summary of the results of the analysis. However, a summary estimate is just that: a summary. We hope that decision-makers will take advantage of the data presented in our analysis to inform their decision-making to the level of detail that best suits their own purposes.

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Cardiac Rehabilitation Services and Risk Reduction

To the Editor: The review by Drs. Greenland and Chu (1) on cardiac rehabilitation services and the accompanying position paper (2) developed by the Health and Policy Committee, American College of Physicians base their discussions of program components on a definition of cardiac rehabilitation that focuses on the restorative function of this intervention. Although programs for cardiac rehabilitation were originally based on a restorative model of care (3), subsequent epidemiologic research identifying specific risk factors associated with the development of coronary artery disease and the demonstration that the modification of those risk factors could alter cardiovascular morbidity and mortality (4) have shifted the focus of cardiac rehabilitation efforts towards prevention.

Use of this earlier definition may explain why, in part, Greenland and Chu (1) emphasize the structured exercise efforts of a cardiac rehabilitation program, and give scant attention to or make no mention at all of the modification of the other risk factors such as smoking, obesity, and dyslipidemias, which are addressed in a modern-day program. Absent, by the authors' design, is a discussion of the primary-prevention candidate for whom both cholesterol-lowering programs and physical activity minimize risk for an initial cardiovascular event. The lack of discussion about this important subgroup of persons weakens the presentation and the subsequent position (2) based on it.

Also of concern are the conclusions regarding exclusion criteria reached by the Health and Public Policy Committee in the accompanying position paper (2), which was also authored by Drs. Greenland and Chu. With recent angiographic evidence of atherosclerotic regression in the coronary, carotid, and peripheral circulations of human subjects who have lowered their serum cholesterol levels dramatically (5), it seems limiting to suggest that only those persons with a demonstrated "cardiac-related disability in physical capacity" are appropriate candidates for cardiac rehabilitative effort (2). In its concluding remarks, the Committee proposes a judicious selection of candidates for the estimated $108 million spent annually on cardiac rehabilitation efforts. This sum is minimal, however, when compared with the billions of dollars spent on palliation of the vascular complications of atherosclerosis, which have been shown to be modified, if not avoided, by the risk-factor modification efforts of cardiac rehabilitation programs. All would agree that controlling the growth of the national health-care budget is long overdue, yet limiting the growth of cardiac rehabilitation programs rather than increasing programs to reduce risks for the population at large and for those already affected by coronary heart disease can only increase the burden of atherosclerotic diseases and the costs of their "high tech" treatments.

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In response: Dr. Downing suggests that the review by myself and Dr. Joyce Chu (1) fails to give adequate attention to the role of risk-factor modification for primary, secondary, or tertiary prevention of coronary artery disease. Several points in her letter are extremely well-taken. I agree that there is evidence, some of which Dr. Downing cites, that interventions such as cholesterol-lowering, smoking abstinence, or physical exercise may be effective in reducing one's risk for an initial or recurrent coronary event. The role of risk-factor modification after myocardial infarction has recently been reviewed by Siegel and colleagues (2); this article summarizes the potential benefits of cholesterol-lowering and other risk-factor interventions in that

population of patients. I concur with Dr. Downing that a rationale exists upon which physicians and other health-care professionals might offer services for risk-factor reduction to many groups of patients not covered specifically by our critique of cardiac rehabilitation services.

However, in the review (1) we stated clearly that our analysis was based on a "critical review of the published articles on the benefits and risks of cardiac rehabilitation *services* . . . with primary emphasis on the role of cardiac rehabilitation after myocardial infarction." We also stated that "many survivors of myocardial infarction could theoretically benefit from organized attempts to help them stop smoking, lower their blood lipids, and control hypertension or other standard risk factors." The question we intended to address in our review was whether the published medical literature supports the application of *specialized* cardiac rehabilitation services as an especially effective means of reducing cardiac risk factors in patients with coronary artery disease–not whether such treatments could be of theoretical benefit to this group of patients. As we noted, there is no body of published evidence to support the *routine* addition of treatments for risk-factor reduction to organized cardiac rehabilitation services for survivors of myocardial infarction. For that matter, I could find no evidence that routine efforts at risk-factor reduction in the form of *organized* programs are preferable to other forms of medical care for primary or secondary prevention of coronary artery disease. Consequently, our conclusions could not advocate or support the use of such treatments, even though, as Dr. Downing points out, such efforts have theoretical appeal.

I applaud the efforts of those interested in primary, secondary, or tertiary prevention of coronary artery disease and challenge clinical scientists to promote research that will support the addition of such clinical services on a more routine basis in the future.

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SI and Presently Conventional Units

To the Editor: Having grown up in the era of metric units, I am pleased to see that medical literature is finally adopting SI units (le Système internationale d'Unités). It is especially fitting now that research has clearly become more international, with workers from many countries often laboring on the same projects simultaneously.

Problems always emerge with any attempt at modernization, however, including the chance that those unfamiliar with the new systems will be left behind. This particular problem surfaced for me after reading the article (1) on methylprednisolone therapy in alcoholic hepatitis by Carithers and colleagues. The study design, methods, eligibility criteria, and results were clearly stated, and the article was well worth clipping and saving. As I was putting it in my file, however, I tried mentally to compare the patients featured with my own. Just how severe was the hepatitis described? Was the bilirubin concentration 5 times normal? 20 times normal? No normal values were given in the new SI units.

It is a simple matter to convert miles to kilometers, and pounds to kilograms, but to convert SGOT levels from international units per litre to microkatals per litre, bilirubin concentrations from micromoles to milligrams per decilitre, and so on, requires the memorization of molecular weights and catalytic constants. It simply discourages the comparison of pre-SI with post-SI patients. To make matters worse, the patients featured in this article (1) were accrued from 1979 to 1984, a period in which no one in American medicine used SI units. Thus, the data must have been converted to SI format for publication, and the conversion factors then removed from the manuscript.

There is no reason to close off the literature from those readers whose laboratory slips may still express values in milligrams per decilitre. Simply print the normal ranges for the new units when they are first mentioned in the article, and even the most Neanderthal of medical readers will have some point of reference from which to begin counting on his (opposable) thumbs.

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Disclaimer: The opinions expressed in this letter are my own and do not necessarily reflect those of this command, the Department of the Army, or the Department of Defense.

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We do offer authors the option of including present metric units with SI units, and only a fraction of authors ask for it. Dr. Giacoppe's view is reasonable, and we shall suggest to authors that they include non-SI units, at least for measurements that are central evidence for a paper's main conclusion.–The Editor

The Metaraminol Test and Adverse Cardiac Effects

To the Editor: Familial Mediterranean fever (FMF) is a hereditary disorder of unknown cause. The diagnosis is not difficult when a family history is relevant and diagnostic criteria are met (1, 2). Barakat and colleagues (3) have proposed a metaraminol provocation

test for diagnosis of familial Mediterranean fever. They found that this test had a 100% sensitivity and specificity and did not provoke any serious side effects; only headache and transient palpitations were reported during metaraminol infusion. We report a case of bigeminal rhythm and angina pectoris secondary to the metaraminol test.

A 38-year-old woman had a family history of familial Mediterranean fever and occasionally had diffuse abdominal tenderness. She reported no history of fever, chest pain, arthralgia, or skin manifestations, and she did not have hypertension or cardiac disease. In view of a possible diagnosis of familial Mediterranean fever, and with informed consent of the patient, a metaraminol test was done.

A baseline, standard electrocardiogram (ECG) was obtained, and supine blood pressure, pulse rate, and temperature were recorded. Throughout the test period the patient was monitored. An intravenous infusion of normal saline, 500 mL, to which was added a 10-mg dose of metaraminol bitartrate, was given for 4 hours. Thirty minutes after beginning the test, the patient had chest pain with coronary characteristics and palpitations. An ECG showed a bigeminal rhythm. The metaraminol infusion was discontinued, and 5 minutes later the patient was asymptomatic, and the ECG was normal. A week later, an exercise ECG was negative.

Although Barakat and colleagues (4) did not report any serious side effects in their experience with metaraminol tests (80 cases), we agree with Cattan and colleagues (5) that this test is not harmless and that it should not be used unless absolutely necessary, possibly in patients with paucisymptomatic forms of late-onset familial Mediterranean fever who do not have a relevant family history. We think the criteria established by Sohar and colleagues (1) and Eliakim and colleagues (2) and a family history are sufficient for the diagnosis of most cases.

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Collagenous Colitis and Histiocytic Lymphoma

To the Editor: Collagenous colitis is a relatively rare cause of watery diarrhea and abdominal pain and is characterized histologically by a thickened band of collagen beneath the colonic mucosa epithelium. I report a case of collagenous colitis associated with diffuse histiocytic lymphoma, which responded to sulfasalazine and steroid enemas, even as lymphoma progressed.

A 78-year-old woman with a 1-year history of diarrhea was admitted in February 1988 for a presumed stroke with mild aphasia. In the past year she had had four to five loose stools per day. At admission, cultures of the stool and examination for ova and parasites were negative. Colonoscopy was done and was remarkable only for decreased haustral markings. A random biopsy sample showed thickened subepithelial collagen deposition consistent with collagenous colitis. Staining of the biopsy sample was negative for iron and amyloid. She was treated with sulfasalazine and steroid enemas with resolution of her diarrhea. Magnetic resonance imaging of her head showed a parietal lesion, a biopsy specimen of which showed diffuse histiocytic lymphoma. She was not considered a candidate for chemotherapy and had skin-flap closure with palliative cranial radiation therapy. Progression of her lymphoma was manifested by increased cervical lymphadenopathy. She died, and an autopsy was not done.

A patient with Hodgkin lymphoma and collagenous colitis has been described (1). In this case, collagenous colitis was thought to reflect a paraneoplastic phenomenon. The patient's diarrhea showed significant improvement after both treatment with prednisone-based chemotherapy and clinical improvement of her lymphoma. Collagenous colitis can have a variable course (2), and spontaneous resolution without therapy has been reported (3). Therefore, it is difficult to assess treatment success in patients with collagenous colitis. The patient with Hodgkin lymphoma had been treated with a corticosteroid, which has been used successfully in the past for treating collagenous colitis (2, 4, 5). It is unclear whether the collagenous colitis improved because of the prednisone or because of the improvement of the lymphoma after chemotherapy.

A paraneoplastic phenomenon, however, would not be a consideration in my patient because her diarrhea resolved after treatment with sulfasalazine and local steroid enemas. Sulfasalazine has not been shown to have any effect on lymphomas. Although there may be systemic absorption of the steroid from the enemas, the patient's diarrhea improved even as lymphoma progressed. Collagenous colitis is a rare disease and its exact incidence has yet to be determined. The finding of lymphoma in two patients with collagenous colitis may suggest that an association exists.

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Pancytopenia and Methotrexate with Trimethoprim-Sulfamethoxazole

To the Editor: Kozarek and colleagues (1) found a dramatic clinical improvement in patients treated with methotrexate who had refractory Crohn colitis and an incomplete remission of chronic ulcerative colitis. Of 21 patients, 14 were also receiving either sulfasalazine or metronidazole (exact number of patients not mentioned).

The risk of bone marrow suppression is increased when other antifolate drugs (derivatives of sulfonamides, trimethoprim) are used simultaneously with methotrexate. Besides additive folate antagonism, other pharmacologic mechanisms, such as competition with tubular secretion and displacement from albumin binding sites, play an important role in interactions of sulfonamides and methotrexate. Moreover, it was shown that sulfasalazine inhibits the hydrolysis of polyglutamyl folate and the intestinal transport of folate in patients with ulcerative colitis (2). Pancytopenia due to the combined use of methotrexate and trimethoprim-sulfamethoxazole has been reported in two patients with rheumatoid arthritis (3, 4). We report two additional cases of this severe side effect.

In case 1, an 81-year-old woman had refractory rheumatoid arthritis and impaired renal function (creatinine, 166 μmol/L) and was treated with methotrexate, 5 mg weekly for 6 weeks. Cystitis (*Escherichia coli*) was treated with trimethoprim, 300 mg daily. One week after starting trimethoprim, bone marrow suppression developed (leukocytes, 1.9×10^9/L; platelets, 15×10^9/L; hemoglobin, 6.3 mmol/L). Both methotrexate and trimethoprim were discontinued. Blood cell counts returned to normal in 2 weeks. One month after discharge she died of severe bronchopneumonia (determined at autopsy).

In case 2, a 75-year-old woman with refractory rheumatoid arthritis and impaired renal function (estimated creatinine clearance, 40 mL/min) was receiving methotrexate, 5 mg weekly. A recurrent cystitis was treated with trimethoprim-sulfamethoxazole. Shortly after beginning trimethoprim-sulfamethoxazole, bone marrow suppression developed (hemoglobin, 5.6 mmol/L; leukocytes, 1.6×10^9/L; platelets, 23×10^9/L). A bone marrow biopsy specimen showed hypocellularity. Both drugs were discontinued, and therapy with leucovorin was begun; she recovered in several weeks.

These two patients were not treated with the combination of sulfasalazine and methotrexate; however, other antifolate drugs were used in conjunction with methotrexate. Additive folate antagonism, independent of which antifolate drug was used simultaneously with methotrexate, seemed to play a central role in inducing bone marrow suppression in these patients. We do not recommend prescribing other drugs with antifolate action simultaneously with methotrexate. The toxicity of and the possibility of adverse drug interactions with methotrexate are increased in the presence of other risk factors such as old age, hypalbuminemia, impaired renal function, and decreased bone marrow reserve (5).

Acknowledgment: We thank Drs. J. Rasker, W. Hissink Muller, and J. Haverman for allowing us access to their patients.

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Lyme Carditis in the Netherlands

To the Editor: A recent article by McAlister and colleagues (1) included an extensive review of 54 cases of Lyme carditis in the world literature. We bring to attention two cases (2, 3) of Lyme carditis reported in the Netherlands and not included in the review. In one case (2), a previously healthy 33-year-old man was hospitalized on 12 August 1987 after several days of exertional dyspnea and lightheadedness followed by a syncopal episode. An electrocardiogram showed a 2:1 atrioventricular block. A chest roentgenogram was normal. After intravenous infusion of atropine, a first-degree atrioventricular block developed. Three days later, an electrocardiogram was normal. A few weeks later, he developed severe arthralgia and arthritis of his first left metatarsophalangeal joint. At this time, he recalled an insect bite on his left leg followed by erythema chronicum migrans and malaise occurring in June 1987. He also recalled a period of severe low back pain with radiation of pain into his left leg occurring in July 1987. A clinical diagnosis of Lyme borreliosis was supported by a positive test for antibodies

(indirect immunofluorescence IgG, 1:320; normal, < 1:80). He has been treated with oral tetracycline, 250 mg every 6 hours for 4 weeks. To this point (May 1989), no further symptoms of Lyme borreliosis have occurred.

In the second case (3), a previously healthy, 40-year-old woman was hospitalized in August 1986 after having had increasing fatigue and palpitations for 10 days. She had no symptoms of a systemic illness. Her pulse rate was 42 beats/minute and her blood pressure was 130/90 mm Hg. There was no cardiac murmur. General examination was otherwise unremarkable. Laboratory results showed slightly abnormal liver function. Her electrocardiogram showed a complete atrioventricular block with a junctional escape rhythm of 50 beats/minute. Chest roentgenogram and echocardiography were normal. A DDD (on demand) pacemaker was inserted; afterwards she felt well.

In June 1987, a friend suggested she might have Lyme disease. A test for antibodies against *Borrelia burgdorferi* was positive (1:1280, immunofluorescence assay). At that time she recalled erythema chronicum migrans on her right leg and symptoms suggesting meningoradiculitis preceding her complete atrioventricular block in August 1986. To prevent further complications of Lyme borreliosis she was treated with intravenous penicillin, 5 million units every 6 hours for 10 days. Her pacemaker could be removed without difficulty in December 1987. She has remained well to this point (May 1989).

Clearly, in countries such as the Netherlands, Lyme borreliosis deserves more attention. We found recently that in the most southern part of the Netherlands 15% of *Ixodes ricinus* ticks carry *Borrelia* spirochetes. We strongly suspect that Lyme carditis and other manifestations of Lyme borreliosis are being under-reported, at least in the Netherlands.

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Lupus Anticoagulant

To the Editor: In their recent review, Rao and colleagues (1) reported one case of bilateral adrenal hemorrhage associated with the lupus anticoagulant (Patient 3). We describe three patients who had adrenal hemorrhage associated with the lupus anticoagulant or anticardiolipin antibodies, or both.

In case 1, a 42-year-old man presented with progressive lethargy, malaise, and weight loss. He was hyperpigmented and hypotensive (blood pressure 80/60 mm Hg). Two months before, he had had acute pain in his left loin followed by rightsided back pain, for which no cause had been found. Serum sodium was 125 mmol/L; potassium, 6.6 mmol/L; creatinine, 150 μmol/L; and glucose, 5.1 mmol/L. Adrenal insufficiency was confirmed by a basal serum cortisol of 89 nmol/L, rising to only 249 nmol/L 60 minutes after intravenous infusion of tetracosactrin, 250 μg (RR rise, < 200 nmol/L to > 500 nmol/L). A random serum adrenocorticotropin (ACTH) was 290 ng/L (RR, 10 to 85 ng/L). He responded promptly to glucocorticoid and mineralocorticoid replacement. Computed tomographic scans showed left adrenal calcification and an enlarged right adrenal gland, findings consistent with past hemorrhage (1). He later developed a right-popliteal-vein thrombosis. Before heparin therapy, activated partial thromboplastin time was 66 seconds (control, 33 seconds). Anti-adrenal antibodies were absent but the lupus anticoagulant was detected.

In case 2, a 27-year-old man presented with rightsided abdominal pain, fever, nausea, progressive malaise, and hypotension. His history included recurrent deep venous thromboses, pulmonary emboli, presence of the lupus anticoagulant and anticardiolipin antibodies (titer, 1:100; NR < 1:25). No heparin-dependent antibodies were present. Computed tomographic scans showed inferior vena caval thrombosis and enlargement of the right adrenal gland; the left adrenal gland was not visualized. His basal serum cortisol was 15 nmol/L, with no rise after tetracosactrin (250 μg, intramuscularly). He responded to steroid replacement therapy.

In case 3, a 67-year-old woman with a history of discoid lupus of the mouth presented with abdominal pain, anorexia, nausea, and mild hyponatremia (sodium, 129 mmol/L). Computed tomographic scans showed bilateral adrenal masses. Serum cortisol was 90 nmol/L, with no response to tetracosactrin, and anticardiolipin antibodies were detected (titer, 1:70). Although she responded to steroid replacement therapy, her course was complicated by a hypertensive crisis associated with mildly elevated urinary vanillylmandelic acids. At laparotomy, bilateral adrenal hemorrhage was found with no evidence of pheochromocytoma. Histologic examination confirmed adrenal hemorrhagic infarction with thrombosed vessels at the margins.

The lupus anticoagulant is more commonly associated with thrombosis than hemorrhage (2). Anticardiolipin antibodies show a similar thrombotic action (3) and may recognize similar antigens (4). For anatomical reasons (1), adrenal hemorrhage may follow multiple thromboses in the capsular adrenal vein (5). We suggest that lupus anticoagulant or anticardiolipin

antibodies predispose to adrenal hemorrhage, perhaps by causing adrenal vein thrombosis.

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GM-CSF Treatment and Hypokalemia

To the Editor: Granulocyte-macrophage colony-stimulating factor (GM-CSF) is currently proposed as a means for accelerating hematopoietic recovery after aplasia-inducing chemotherapy (1, 2) and as an agent for treating myelodysplasias (3). The various side effects described are rarely of a metabolic nature. We report a case of severe acute hypokalemia in a patient treated with GM-GSF.

A 79-year-old woman was hospitalized for GM-CSF treatment (GM-CSF obtained from Cho-Cell, Sandoz Pharmaceuticals, Basel, Switzerland) because of refractory anemia with excess blast cells as defined by the FAB (French American British Cooperative) requiring erythrocyte transfusions every 4 weeks (randomized study of the Leukemia group of the European Organization for Research and Treatment of Cancer for the myelodysplastic syndromes, protocol no. 06885, Dr. R. Willemze, coordinator). Complete blood counts showed leukocytes, 6.6 $\times 10^9$/L (neutrophils, 65%; blasts, 7%; monocytes, 4%); hemoglobin, 114 g/L; platelets, 230 $\times 10^9$/L; lactate dehydrogenase (LDH), 392 U/L. The serum chemistry profiles were normal, and, in particular, serum potassium was 3.6 mmol/L.

Treatment consisted in a subcutaneous injection of GM-CSF twice a day (108 μg glycoprotein = 75 mg protein). On the fifth day of treatment, laboratory findings were leukocyte count 70.3 $\times 10^9$/L (blast cells, 3%; neutrophils, 71%; monocytes, 9%); hemoglobin, 110 g/L; platelet count, 260 $\times 10^9$/L; LDH, 539 U/L; potassium, 2.8 mmol/L. A urinalysis did not reveal any potassium leak. The patient was not taking any other hypokalemia-inducing medication and she did not have diarrhea. Oral potassium supplementation was started. The treatment with GM-CSF was continued according to the protocol. On day 11, the leukocyte count was 165 $\times 10^9$/L (blast cells, 6%; neutrophils, 60%; monocytes, 22%); hemoglobin, 102 g/L; platelet count, 50 $\times 10^9$/L; LDH, 1044 U/L; potassium, 1.7 mmol/L. Discrete alkalosis was detected. This hypokalemia was accompanied by intense asthenia, with muscle weakness but no cardiac arrhythmia. Arthralgia (knee) occurred but regressed rapidly. There was still no urinary or gastrointestinal potassium leak.

Renal function, evaluated by serum creatinemia, was normal and remained stable. The GM-CSF therapy was stopped and potassium supplementation was initiated (intravenously for 3 days, then orally) with success. The leukocytosis regressed progressively, with the leukocyte count 79.5 $\times 10^9$/L on day 22 and 46.5 $\times 10^9$/L on day 29.

Treatment with GM-CSF has various adverse effects including low-grade fever, myalgias, phlebitis, flushing, and bone pain. Administration of high doses (32 μg/kg body weight per day) can induce a capillary leak syndrome (1) similar to that described in connection with treatment by interleukin-2. However, to our knowledge, hypokalemia has never been reported.

The absence of a serum potassium leak or an intercurrent gastrointestinal abnormality and the very rapid development of hypokalemia that paralleled the rise in the leukocyte count suggests intracellular potassium uptake in this patient who probably had a low potassium pool. Serum chemistry monitoring thus appears advisable during GM-CSF treatment, and particular attention should be paid to kalemia. Serial assays should be done in case of an "explosive" response of the leukocytosis, as in our patient.

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Toxic Shock Syndrome and Estrogen Therapy

To the Editor: Estrogen administration may play a role in the treatment of the toxic shock syndrome. I recently treated a woman with the toxic shock syndrome who did not respond to conventional therapy

until her menstrual period was stopped with an injection of estrogen.

A 34 year-old white woman presented with a 3-day history of myalgias, diarrhea, nausea, vomiting, and weakness. Her menstrual period had started 4 days before admission; she used a hyperabsorbent tampon and changed it every 8 hours. Her blood pressure was 60/0 and temperature was 39.5 °C. She had diffuse lower abdominal pain, tender cervix with purulent discharge, and a diffuse erythematous skin rash with conjunctival hyperemia. A culture of the vagina grew *Staphylococcus aureus* sensitive to cefazolin. The tampon was removed, and she received a vaginal douche. She was given 6 litres of normal saline the first 5 hours; methylprednisolone, 750 mg every 8 hours; and cefazolin, 2 g every 8 hours. The rash improved by the second hospital day. Five days into her hospitalization, however, she still had a low-grade fever, diarrhea, malaise, low blood pressure (90/0), nausea, and anorexia. Her menstrual period continued. On day 9 of her menstrual period (day 5 of her hospitalization), the patient was given 3 mg of depoestradiol in oil. The next day her menses stopped, and she almost jumped out of bed and asked to be discharged. Her diarrhea had cleared, her blood pressure stabilized (115/75), her malaise subsided, and her appetite returned.

The clinical response of this patient to estrogen was dramatic. The mechanism of estrogen therapy in this case is unknown. It is possible, however, that estrogen administration helps diminish the surface area of a bleeding, raw uterine lining to exposure to the toxic shock syndrome toxin. The estrogen helps to end the period and promote a thickened "protective" proliferative endometrium that acts as a barrier to the toxin. It is also possible that the pathogenic toxic shock syndrome staphylococcus itself is inhibited by an estrogen milieu. Another infectious disease, South American blastomycosis, typically flares during the menstrual period. It is thought that the low estrogen levels associated with the menstrual period alter steroid hormone receptors on the fungi, permitting pathogenic yeast conversion and tissue invasion (1).

Regardless of the mechanism, it seems prudent to terminate menstruation as rapidly as possible in this life-threatening disease associated with a woman's menstruation.

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