Correspondence

Winning the War on Cancer

To the Editor: In their Special Article, provocatively entitled "Cancer Undefeated," Bailar and Gornik (May 29 issue)[1] acknowledge the substantial changes in mortality due to cancer during the past 20 years in men and women under the age of 55 years. The authors note that for this age group, there has been a 25 percent decrease in all cancer-related deaths, a 23 percent reduction in deaths from breast cancer, and a slight but definite decline in mortality from lung cancer; for persons of all ages, there has been approximately a 15 percent drop in deaths from colorectal cancer. Bailar and Gornik believe these changes reflect changes in the incidence of cancer or early detection, discount entirely the impact of therapeutic intervention, and argue that progress will occur only through a national commitment to prevention.

Nobody disputes the merits of cancer prevention. By now, eliminating the use of tobacco products — particularly among the young — has become a social and legislative issue; sufficient research has already been performed to justify the needed behavioral changes. Reducing exposure to known carcinogens such as ultraviolet light, hepatitis B and hepatitis C viruses, asbestos, and excess ethanol has received widespread attention, as has the importance of screening for breast, cervical, and colorectal cancers. The recent development of germ-line genetic-testing techniques will probably identify people at very high risk for breast, colorectal, and ovarian cancers in whom prophylactic medical or surgical interventions, or both, may be of value. A major component of the National Cancer Institute's budget is for cancer prevention, and in 1996, a distinguished panel of experts in this area was commissioned by the institute's director, Dr. Richard D. Klausner, to provide an external critique of this effort.

Bailar and Gornik reveal their underlying bias by choosing to ignore the influence of treatment on the reduction in cancer-related mortality among persons under the age of 55 years. During the past 25 years, previously fatal conditions, such as advanced testicular cancer,[2] Hodgkin's disease,[3] and childhood leukemia,[4] have become curable in more than 70 percent of cases, and up to 50 percent of patients with non-Hodgkin's lymphomas may now be cured.[5] Prospective, randomized trials have shown that postoperative (i.e., adjuvant) therapy leads to a 25 to 30 percent reduction in mortality among patients with locally advanced breast cancer[6] or colorectal cancer.[7] Reductions in cancer-related mortality clearly have multifactorial explanations, but for Bailar and Gornik to dismiss widely used, well-accepted advances in treatment is not only absurd but also potentially damaging to patients with newly diagnosed malignant conditions, who may be influenced by the publicity surrounding this extreme view to reject life-saving treatment. . . .

ROBERT J. MAYER, M.D.
LOWELL E. SCHNIPPER, M.D.
American Society of Clinical Oncology
Alexandria, VA 22314

1. Bailar JC III, Gornik HL. Cancer undefeated. N Engl J Med 1997;336:1569-74.
2. Williams SD, Birch R, Einhorn LH, Irwin L, Greco FA, Loehrer PJ. Treatment of disseminated germ-cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. N Engl J Med 1987;316:1435-40.
3. Canellos GP, Anderson JR, Propert KJ, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. N Engl J Med 1992;327:1478-84.
4. Pui C-H. Childhood leukemias. N Engl J Med 1995;332:1618-30.
5. Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 1993;328:1002-6.
6. Bonadonna G, Valagussa P, Moliterni A, Zambetti M, Brambilla C. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer — the results of 20 years of follow-up. N Engl J Med 1995;332:901-6.
7. Moertel CG, Fleming TR, Macdonald JS, et al. Fluorouracil plus levamisole as effective adjuvant therapy after resection of stage III colon carcinoma: a final report. Ann Intern Med 1995;122:321-6.

INSTRUCTIONS FOR LETTERS TO THE EDITOR

Letters to the Editor are considered for publication (subject to editing and abridgment) provided they do not contain material that has been submitted or published elsewhere. Please note the following: •Your letter must be typewritten and triple-spaced. •Its text, not including references, must not exceed 400 words (please include a word count). •It must have no more than five references and one figure or table. •It should not be signed by more than three authors. •Letters referring to a recent *Journal* article must be received within four weeks of its publication. •Please include your full address, telephone number, and fax number (if you have one). •You may send us your letter by post, fax, or electronic mail.

Our address: Letters to the Editor • *New England Journal of Medicine* • 10 Shattuck St. • Boston, MA 02115

Our fax numbers: 617-739-9864 and 617-734-4457

Our e-mail address: letters@nejm.org

We cannot acknowledge receipt of your letter, but we will notify you when we have made a decision about publication. We are unable to provide prepublication proofs. Please enclose a stamped, self-addressed envelope if you want unpublished material returned to you. Financial associations or other possible conflicts of interest must be disclosed. Submission of a letter constitutes permission for the Massachusetts Medical Society, its licensees, and its assignees to use it in the *Journal*'s various editions (print, data base, and optical disk) and in anthologies, revisions, and any other form or medium.

To the Editor: Bailar and Gornik express gratitude to me "for kindly suggesting" the title of their article, "Cancer Undefeated." I did not suggest this title, and I respectfully decline the acknowledgment. I did, as part of a dialogue with Dr. Bailar, refer him to a 1960 article by Sir John Crofton, entitled "Tuberculosis Undefeated."[1] This article offers many parallels for our discussions about cancer today.

SAMUEL BRODER, M.D.
Miami, FL 33137

1. Crofton J. Tuberculosis undefeated. BMJ 1960;2:679-87.

To the Editor: The results of treatments for cancer may be better than Bailar and Gornik suggest. Any improvement in survival will increase the age at death. The number of deaths below any given age will therefore fall, and the number above it will rise. This will cause a divergence between the mortality rates for the old and those for the young. Indeed, Figures 2 and 3 in the article by Bailar and Gornik show a marked divergence in the rates at the age of 55 years — probable evidence of steadily increasing survival.

T.H. HUGHES-DAVIES, F.R.C.P.
Breamore Marsh
Fordingbridge, Hampshire SP6 2EJ, United Kingdom

To the Editor: Although Bailar and Gornik clearly demonstrate the failure of current treatment efforts in many areas, I fail to see how their article supports the conclusion that more money should be spent on prevention, since prevention has not been very effective either. . . .

TOM S. RAND, M.D.
Wilson Orthopaedic Surgery and Neurology Center
Wilson, NC 27895-3148

To the Editor: Bailar and Gornik report that the age-adjusted rate of mortality from all cancers in the United States declined by 1 percent from 1991 through 1994. Our estimate for the same interval[1] was 2.2 percent, and we also reported a 3.9 percent decline during the period from 1990 to 1995. The discrepancy in the data for the 1991–1994 period stems from the use of different populations for age adjustment. Bailar and Gornik used the relatively elderly 1990 U.S. population and by doing so, minimized striking reductions in mortality that occurred among young and middle-aged persons. We used the U.S. "standard million" population, the basis for all national reports. Use of this population, which is essentially the relatively young 1940 population, reveals the full downturn in cancer-related mortality. We used the standard million not for impact but of necessity to describe a current trend; the latest data are available only in this form. Thus, our 1996 report includes findings for 1995, whereas the report by Bailar and Gornik is limited to 1994. Data for the period from January to October 1996[2] show a further 0.7 percent reduction in mortality from cancer, bringing the decline for the period from 1990 to 1996 to 4.6 percent.

Our more important difference with Bailar and Gornik concerns their view that improvements in treatment resulted in little reduction in mortality from cancer. We reported that one half of the decline we observed reflected advances in medical care and access to it. This statement was based on data showing long-term gains in the survival of patients with cancer even after a correction had been made for the effect of earlier diagnosis.

There are three more reasons for our opinion. First, many aspects of the diagnosis and treatment of cancer have improved greatly, as Bailar and Gornik acknowledge. Second, virtually all oncologists believe that cures and long-term palliation of cancer are much more common now than previously. Finally, several national trends seem explicable only in terms of treatment gains. For example, the mortality rate for all cancers except lung cancer has declined since the mid-1970s, whereas the incidence has remained the same or increased.[3]

PHILIP COLE, M.D.
BRAD RODU, D.D.S.
University of Alabama at Birmingham
Birmingham, AL 35294

1. Cole P, Rodu B. Declining cancer mortality in the United States. Cancer 1996;78:2045-8.
2. National Center for Health Statistics. Births, marriages, divorces, and deaths for November 1996. Mon Vital Stat Rep 1997;45(11).
3. Devesa SS, Blot WJ, Stone BJ, Miller BA, Tarone RE, Fraumeni JF Jr. Recent cancer trends in the United States. J Natl Cancer Inst 1995;87:175-82.

To the Editor: . . . The cavalier attitude of Bailar and Gornik toward the remarkable reduction of deaths due to childhood cancer is wrong. Although the numbers of cured children may be small, each child's life affects many people — the family, the school, the community, and the parent's workplace. Moreover, without a cost–benefit analysis of curative childhood cancer effects, there can be no complete evaluation of the "war on cancer." The number of deaths from cancer is just one outcome to be reckoned with.

SETH COREY, M.D., M.P.H.
Children's Hospital of Pittsburgh
Pittsburgh, PA 15213

To the Editor: An analysis of the effect of the U.S. research effort on cancer that is based entirely on mortality rates, with no consideration of incidence rates, is flawed. Bailar and Gornik conclude that research funds should be diverted from treatment to prevention. They provide no analysis of the effectiveness of preventive strategies and summarily dismiss gains from nonpreventive approaches. Data from the Surveillance, Epidemiology, and End Results (SEER) study show that from 1973 to 1993, the increases in mortality and incidence rates for cancer were 5.8 and 27.3 percent, respectively.[1] Mortality rates decreased in 14 of the 23 cancer sites assessed. For six of the remaining nine sites, the increase in mortality was smaller than the increase in the incidence of cancer.

There are many points of attack in the effort to defeat

cancer, and we have seen valuable gains in the quality of life and knowledge of cancer biology, as well as reductions in mortality. For example, there have been major advances in preserving anatomy or function in treating cancers of the eye (uveal melanoma), esophagus, breast, larynx, anus and rectum, extremities, and prostate.

Significant improvement in survival has been demonstrated in recent phase 3 clinical trials for cancer of the testis, breast, rectum, colon, and esophagus, as well as osteogenic sarcoma and cancers in children. These improvements are largely due to the use of multidisciplinary treatment strategies (combinations of surgery, chemotherapy, and radiation therapy).

Finally, a remarkably rapid increase in our knowledge of cancer biology at the most basic level has occurred since 1970. Cancer is now known to be a genetic disease. We have gained great insight into the multistep process of cancer through research on tumor-suppressor genes, oncogenes, programmed cell death, DNA repair, angiogenesis, and the process of metastasis. These diverse research successes will make it possible for oncologists to begin using molecular diagnostics, individualizing management strategies, and planning gene therapy.

We support research on prevention, but it should not be undertaken at the expense of early detection and treatment.

HERMAN SUIT, M.D.
KURT ISSELBACHER, M.D.
BRUCE CHABNER, M.D.
Massachusetts General Hospital
Boston, MA 02114

1. Ries LAG, Kosary CL, Hankey BF, Harras A, Miller BA, Edwards BK, eds. SEER cancer statistics review, 1973–1993: tables and graphs. Bethesda, Md.: National Cancer Institute (in press).

To the Editor: As a practicing medical oncologist, I agree with Bailar and Gornik that the progress we have made in the treatment of cancer over the past number of years is disappointingly small. However, as both an oncologist and a patient with cancer, I vehemently disagree with the widely publicized opinion of the authors that "in an age of limited resources this may well mean curtailing efforts focused on therapy." Why? Are we putting up a white flag?

War is hell, including the war against the diseases called cancer. In war, progress may not be evident immediately. If the cause is just, one does not quit because of a few lost battles. Some wars last six days, others a hundred years. The war against cancer has been fought for a relatively short time and only very recently with the most modern laboratory techniques. Science is by nature a slow process with an occasional breakthrough. Twenty-five or 30 years is too short a period for a declaration of failure against such a difficult foe.

ALAN FELDMAN, M.D.
Coney Island Hospital
Brooklyn, NY 11235

To the Editor: Bailar and Gornik state, "35 years of intense effort focused largely on improving treatment must be judged a qualified failure," and they believe the emphasis should therefore be shifted toward a preventive approach. In truth, the effort has been far less than intense. As Donald Coffey, president of the American Association for Cancer Research, has noted, "A real war against cancer has never been mounted. To date, available federal funds have supported only a small, intense skirmish by a limited number of investigators."

Although political leaders pay lip service to stopping a disease that will attack one of every four Americans alive today, the fact is that the government's commitment has not changed substantially. During the past 10 years, federal funding for research on cancer, adjusted for inflation, has increased by just 1 percent. Today, research on cancer represents just 0.1 percent of the federal budget. . . .

RICHARD N. ATKINS, M.D.
PHILIP A. ARLEN
CHRISTOPHER L. NOXON
CaP CURE
Santa Monica, CA 90401

To the Editor: Cancer is "undefeated"; the "war against cancer" has not been won. These are military allusions, initially used by a political figure and too readily adopted as snappy media language by the medical and scientific communities in the United States and elsewhere.

In wars there are the victors and the vanquished (not always easily distinguished), and collateral damage is all too common. Wars delay and obfuscate problems but do not often solve them. Wars encourage simplistic and jingoistic attitudes — us versus them. But cancer is so much more complex than this. There is no invading army, no call to arms, no enemy — the trouble is within.

It is time to redefine the problem. Although we should continue our exploration of the biology of cancer, trials of new therapies, and population-based preventive strategies, we also need to face the inevitability of cancer. Cancer is the price we pay for being sophisticated organisms, and there are only so many times we can faithfully replicate the genome with each cell division before making a critical mistake. In addition, the rising incidence of some cancers needs to be seen in context: overall life expectancy in the Western world continues to increase. Although better prevention and early detection should reduce mortality, metastatic cancer will develop in many people and is likely to remain largely incurable. For these people, the emphasis should be on living with cancer rather than dying in battle.

The war-on-cancer metaphor distracts attention from the complexity of the disease and inevitably identifies winners and losers. We should tell the world that we are working at understanding cancer and that knowledge is power.

NICHOLAS WILCKEN, M.D., PH.D.
Westmead Hospital
Sydney, NSW, 2145, Australia

The authors reply:

To the Editor: Several letters and the Sounding Board article by Kramer and Klausner in this issue of the *Journal*[1] distort our position and divert attention from the critical issues. None of the authors, however, question the finding

that cancer-related mortality is higher now than at the time of the National Cancer Act of 1971, even after adjustment for aging in the population and declines in other lethal diseases.

Kramer and Klausner[1] charge that we extrapolate the future from the past. A very long history of great effort by great scientists, marked by great ballyhoo and very spotty progress, *should* engender some skepticism about today's claims of wonderful things to come. We acknowledged that there are successes, but not enough, in palliation and treatment for childhood cancers and some adult cancers. Our argument is that new efforts should be made to advance cancer prevention, already shown to be fruitful, and the examples Kramer and Klausner cite actually support our conclusion. Fleming's discovery of penicillin was a product of acute observation, not basic science; iron lungs disappeared because of prevention, not treatment; tamoxifen is indeed useful in treatment but also has potential for prevention; the delay in federal efforts to reduce smoking (prevention again) was due to political pressures, not lack of knowledge or will at the National Cancer Institute; and the discovery of the roles of human papillomavirus, *Helicobacter pylori,* and nicotine addiction reinforces the need for greater attention to cancer prevention.

Kramer and Klausner ask whether cancer is sufficiently homogeneous to emphasize a single path. We do not claim so, but note that some preventive approaches, such as chemoprevention and strengthening of internal defenses, may have a broader spectrum of benefit than specific treatment regimens. We are not content with a 0.6 percent decrease per year in cancer-related mortality, since at that rate, it would take 115 years for mortality to decline to half the present level. Kramer and Klausner also dispute our contention that the present program is lopsided but fail to mention that prevention and control accounted for about 6 percent of the National Cancer Institute's budget from 1973 (the first year the budget was presented in the current form) until 1994 and that the recent expansion to 10 percent was at the direction of Congress. Furthermore, some of that money is for improved screening and treatment, not prevention.

Mayer and Schnipper say we ignore the influence of treatment on cancer-related mortality in people under the age of 55 years. This is not so; Figure 2 of our article shows trends for people 55 years or older and for those younger than 55, and we specifically mention improved treatment for Hodgkin's disease and childhood neoplasms. Whether adjuvant therapy for breast and colorectal cancer will have effects demonstrable at the population level is not yet known.

The point raised by Hughes-Davies applies to trends in crude rates. We presented only age-adjusted rates to avoid such problems.

We refer Rand to the substantial decline in tobacco use among adults; the effective control of asbestos, benzene, and many other industrial carcinogens; reductions in radiation doses per exposure; and the dietary changes adopted by increasing numbers of Americans — all initiated with little support from basic-science investigators or the government. We need to know how much more we could achieve with a vigorous program of prevention encompassing research and practice.

If cancer-related mortality rates for people of different ages were moving in parallel, the choice of a standard for age adjustment would make little difference, but the rates are not parallel. Declines are greatest at the youngest ages, and increases are greatest at the oldest ages, with a gradual change between these extremes and a crossover from declines to increases at about the age of 55 years. We chose the 1990 standard as the midpoint of the critical recent period; the National Cancer Institute chose the 1970 standard, with somewhat more favorable results; and Cole and Rodu prefer the even more favorable findings with the 1940 standard. If we had used a medieval population, with half the population under the age of 6 years and almost nobody over the age of 50, the trend would have looked wonderful. But only the 1990 standard is appropriate for comparisons of U.S. trends over a period centered on the year 1990.

In response to Cole and Rodu and to Suit et al.: we gave good reasons for not using incidence rates or case survival rates. Furthermore, the argument that better treatment is balancing the rapid increase in incidence supports our conclusion that prevention — reversing the increases in incidence — is crucial.

JOHN C. BAILAR III, M.D., PH.D.
HEATHER L. GORNIK, M.H.S.
University of Chicago
Chicago, IL 60637-1470

1. Kramer BS, Klausner RD. Grappling with cancer — defeatism versus the reality of progress. N Engl J Med 1997;337:931-4.

Anticoagulation and Elective Surgery

To the Editor: In their review of the management of anticoagulation before and after elective surgery, Kearon and Hirsh (May 22 issue)[1] assert that in patients with mechanical heart valves, anticoagulation should be discontinued perioperatively. They assume that the "temporary discontinuation of warfarin . . . exposes patients to a risk of thromboembolism equivalent to one day without anticoagulation before surgery and another day without anticoagulation after surgery." Although this may be possible when patients have an international normalized ratio (INR) between 2.0 and 3.0, it does not seem likely for patients with an INR between 2.5 and 3.5. At this higher level, patients will need a longer time without warfarin preoperatively and a longer time with warfarin postoperatively, thus increasing the length of their time at risk for thromboembolism.

Patients with mechanical valves in the mitral position are considered to have a high risk of thromboembolism and therefore require an INR between 2.5 and 3.5. Two studies, both retrospective reviews, have examined how these patients fare without anticoagulation in the perioperative period. In their report of patients with prosthetic valves who required surgery, Katholi et al. noted that 2 of 10 patients with mitral or combined mechanical valves had fatal strokes when anticoagulation was discontinued three to five days preoperatively.[2] Tinker and Tarhan noted that among 74 patients with mitral or combined mechanical valves, none had embolic events in the absence of anticoagulation.[3] But interpreting the results of the latter study

is difficult, because it is not clear for how many days patients with mitral valves did not receive anticoagulants.

An alternative approach for patients who have mechanical mitral valves or who are otherwise at high risk for thromboembolism is to stop warfarin five days before surgery and start intravenous heparin or low-molecular-weight heparin once the INR becomes subtherapeutic. Heparin may then be restarted on the second postoperative day. This technique permits the patient to be without anticoagulants for only one day. Waiting until the second day to start anticoagulation should decrease postoperative bleeding.

JOHN SPANDORFER, M.D.
GENO MERLI, M.D.
Jefferson Medical College
Philadelphia, PA 19107

1. Kearon C, Hirsh J. Management of anticoagulation before and after elective surgery. N Engl J Med 1997;336:1506-11.
2. Katholi RE, Nolan SP, McGuire LB. Living with prosthetic heart valves: subsequent noncardiac operations and the risk of thromboembolism or hemorrhage. Am Heart J 1976;92:162-7.
3. Tinker JH, Tarhan S. Discontinuing anticoagulant therapy in surgical patients with cardiac valve prostheses: observations in 180 operations. JAMA 1978;239:738-9.

To the Editor: Kearon and Hirsh suggested that it was safe to stop anticoagulation in patients with nonvalvular atrial fibrillation who were scheduled for elective surgery and that the risk of thromboembolism did not justify the use of either preoperative or postoperative intravenous heparin. As the authors noted, the average risk of thromboembolism in this population is 4.5 percent per year without anticoagulation, but the risk is variable and depends on the presence of certain factors.[1] The risk of thromboembolism is considerably higher among patients who have had a transient ischemic attack or stroke within the previous three months (12 percent per year),[2] and even higher (17.6 percent per year) among patients who have two or three risk factors (a history of thromboembolism, hypertension, or recent congestive heart failure).[3] Patients with nonrheumatic atrial fibrillation are therefore not a homogeneous population in terms of their risk of thromboembolism, and a one-rule-fits-all approach to the perioperative management of anticoagulation may not be appropriate. Management should be stratified according to an individual patient's risk of thromboembolism as compared with the risk of surgical bleeding. Given that a stroke in patients with atrial fibrillation is fatal or is associated with a severe neurologic deficit in over 60 percent of cases,[4] there is a persuasive argument for a more aggressive approach to prophylaxis against thromboembolism, including the use of both preoperative and postoperative intravenous heparin, in high-risk patients.

STUART M. LOWSON, M.B., B.S.
ERIC W. HANSON, M.D.
University of Virginia Health Sciences Center
Charlottesville, VA 22906-0010

1. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials. Arch Intern Med 1994;154:1449-57. [Erratum, Arch Intern Med 1994; 154:2254.]
2. European Atrial Fibrillation Trial Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. Lancet 1993;342:1255-12.
3. The Stroke Prevention in Atrial Fibrillation Investigators. Predictors of thromboembolism in atrial fibrillation. I. Clinical features of patients at risk. Ann Intern Med 1992;116:1-5.
4. Fisher CM. Reducing risks of cerebral embolism. Geriatrics 1979;34: 59-61, 65-6.

To the Editor: Drs. Kearon and Hirsh recommend that perioperative intravenous heparin not be used in patients with mechanical valves except during the first month after systemic embolism, when, they conclude, the use of only preoperative heparin appears justified. The authors fail to take into consideration the relative risk associated with the various types of mechanical valves (caged ball vs. tilting disk) and the position of the valve (mitral vs. aortic). Nor is it apparent that they account for coexisting cardiac conditions (e.g., left ventricular dysfunction, atrial fibrillation, or recent myocardial infarction). The fourth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy recommends perioperative heparin therapy for patients at high risk for thromboembolism, such as those with mechanical mitral-valve prostheses who are undergoing major surgery.[1] In a recent review, Vongpatanasin et al.[2] recognized the importance of such factors and recommended perioperative heparin therapy in patients with "caged-ball prosthetic valves, mechanical mitral valves, atrial fibrillation, left atrial thrombus, previous systemic embolization, or severe left ventricular dysfunction."

Although we agree that there is certainly room for the strategy described by Kearon and Hirsh in selected patients, we wish to emphasize the importance of using clinical judgment and risk assessment in individual patients.

ALAA SHALABY, M.D.
SYED M. MOHIUDDIN, M.D.
Creighton University
Omaha, NE 68131-2044

1. Stein PD, Alpert JS, Copeland J, Dalen JE, Goldman S, Turpie AG. Antithrombotic therapy in patients with mechanical and biological prosthetic heart valves. Chest 1995;108:Suppl:371S-379S. [Erratum, Chest 1996; 109:592.]
2. Vongpatanasin W, Hillis LD, Lange RA. Prosthetic heart valves. N Engl J Med 1996;335:407-16.

The authors reply:

To the Editor: We agree with Drs. Spandorfer and Merli that patients who have a targeted INR of 2.5 to 3.5 may need a longer time without warfarin before surgery, depending on what the measured INR is about five days preoperatively. If the INR is greater than 3.0, it may mean that an additional daily dose of warfarin has to be withheld, but that should not increase the amount of time preoperatively during which the INR is less than 2.0, since it will take commensurably longer for the initially high INR to return to 2.0. The situation is similar when warfarin is restarted after surgery. If, as Drs. Spandorfer and Merli propose, such patients have an increased risk of thromboembolism while their INR is 2.0 to 2.5, the magnitude of this effect would be extremely small and would not alter our recommendations.

Drs. Spandorfer and Merli, Lowson and Hanson, and

Shalaby and Mohiuddin all expressed concern that our recommendations were based on calculations that use the average risk of thromboembolism in patients with mechanical heart valves or atrial fibrillation who are not receiving anticoagulants. We acknowledged this point in our article; however, even in patients with the highest individual risk of arterial embolism (excluding those with embolism within one month after surgery), the argument in favor of administering intravenous heparin preoperatively remains weak, and after major surgery, intravenous heparin is still likely to do more harm than good. As an example, with a base-line risk of arterial embolism of 25 percent per year, one day without anticoagulation is associated with a risk of major embolism of approximately 1 in 2000 (0.05 percent). After major surgery, we estimate that the risk of arterial embolism needs to be about 9 percent per month (108 percent per year) just to offset morbidity from heparin-induced bleeding. Delaying the initiation of intravenous heparin until 24 hours after operation will lessen but not eliminate the associated morbidity. We do recommend the postoperative use of subcutaneous heparin in doses used as prophylaxis against venous thromboembolism in high-risk patients, including patients with arterial indications for anticoagulation.

Randomized, controlled trials assessing the perioperative use of intravenous heparin in patients with different indications for long-term anticoagulation would provide better data on which to base management decisions. Until such trials are performed, debate continues to be appropriate. However, until more reliable data than those on which our analysis is based become available, we stand behind our recommendations.

CLIVE KEARON, M.D., PH.D.
JACK HIRSH, M.D.
McMaster University
Hamilton, ON L8V 1C3, Canada

Fatal Intoxication with 1,1-Dichloro-1-Fluoroethane

To the Editor: Hydrochlorofluorocarbons are being developed as alternative solvents for use instead of chlorofluorocarbons, which deplete stratospheric ozone and increase ultraviolet radiation at the earth's surface.[1] The metabolism and toxicity of these new hydrochlorofluorocarbons in humans and animals have been only very partially studied.[2,3] They are considered to have low toxicity. Among them, 1,1-dichloro-1-fluoroethane is a potential substitute for trichlorofluoromethane (also known as CFC-11) in foam-blowing operations and as a cleaning agent in the computer industry.[2,4] We report a fatal intoxication involving 1,1-dichloro-1-fluoroethane.

A 40-year-old man was found collapsed in a factory workroom where he had been cleaning a degreasing tank. The solvent used in the degreasing process was pure 1,1-dichloro-1-fluoroethane (Genosolv 2000, Allied Signal, Morristown, N.J.). The man was found inside the degreasing tank, which was free of liquid. He wore no protective clothes except a surgical mask. His body and clothes were free of any liquid. At postmortem examination there was evidence of violaceous coloration and edema of the face. He had no history of cardiac or respiratory diseases, but there was evidence of chronic alcoholic intoxication. No macroscopic abnormality was found at the autopsy except slight pulmonary edema.

High concentrations of 1,1-dichloro-1-fluoroethane were found in the man's blood (14 mg per liter) and tissues by gas chromatography. The concentrations in the liver and the heart were nearly identical and were twice that in the blood (29 μg per gram). The levels in the lungs and the spleen were lower. No urinary metabolite was found. Structurally related halogenated hydrocarbons, such as 1,1,1-trichloroethane, depress heart rate, contractility, and conduction. They sensitize the heart to the arrhythmogenic effects of endogenous beta-agonists and may induce sudden death.[5] The high level of 1,1-dichloro-1-fluoroethane in the heart raises the possibility of a particular tropism for the cardiac tissues and supports the potential cardiotoxicity of the compound. Considering the potential for exposure in humans as the use of this solvent increases, laboratory studies are urgently needed to determine the toxicity profile of 1,1-dichloro-1-fluoroethane and propose guidelines for its safe handling.

ALAIN ASTIER, PH.D.
Henri Mondor University Hospital
94010, Créteil, France

FRANÇOIS PARAIRE, M.D.
Raymond Poincaré University Hospital
92000, Garches, France

1. Molina MJ, Rowland FS. Stratospheric sink for chlorofluoromethanes: chlorine atomc-atalysed destruction of ozone. Nature 1974;249:810-2.
2. Dekant W. Toxicology of chlorofluorocarbon (totally awesome!) replacements. Environ Health Perspect 1996;104:75-83.
3. Turnbull D, Machado RJ, Boberg RE. Safety assessment of HCFC-141b: use as a blowing agent for insulation in building construction and refrigeration. Regul Toxicol Pharmacol 1994;19:282-96.
4. Anders MW. Metabolism and toxicity of hydrochlorofluorocarbons: current knowledge and needs for the future. Environ Health Perspect 1991;96:185-91.
5. Jones RD, Winter DP. Two case reports of deaths on industrial premises attributed to 1,1,1-trichloroethane. Arch Environ Health 1983;38:59-61.

Clinical Problem-Solving — Where Did Good Old Clinical Diagnosis Go?

To the Editor: In their recent Clinical Problem-Solving article (May 15 issue),[1] Rozenman et al. suggest that the delayed diagnosis of endocarditis was the result of a failure to follow up on an appropriate initial diagnostic hypothesis that the patient had anemia due to iron deficiency. I challenge the appropriateness of the belief that iron deficiency is common in this setting. The anemia that occurs after bypass surgery is due to acute blood loss. Average adult iron stores of about 1 g are equivalent to four to five units of blood. The net operative blood loss is less than this because of transfusion, so most patients should be able to correct the postoperative anemia without supplemental iron. In fact, elderly adults have been shown to tolerate iron losses of up to 1.5 g by phlebotomy.[2] In addition, a randomized, controlled trial of iron supplementation after bypass surgery showed no benefit of iron therapy.[3]

Without such a high suspicion of iron deficiency, there

would be no reason for an empirical trial of iron, and the results of the iron studies in this patient (though compatible with iron deficiency) might have been more appropriately interpreted as most consistent with anemia of chronic disease. The anemia would then have suggested the presence of an undiagnosed inflammatory disease in a patient with known valvular disease and symptoms of worsening heart failure, making endocarditis an obvious consideration. My experience has been consistent with this case in that it is common to label patients with anemia inappropriately as iron-deficient, occasionally causing another important diagnosis to be missed and frequently resulting in an extensive, unnecessary search for a source of bleeding.

EDWARD W. GREENO, M.D.
Hennepin County Medical Center
Minneapolis, MN 55415

1. Rozenman Y, Gilon D, Fuchs S. Where did good old clinical diagnosis go? N Engl J Med 1997;336:1435-8.
2. Conrad ME, Crosby WH. The natural history of iron deficiency induced by phlebotomy. Blood 1962;20:173-85.
3. Crosby L, Palarski VA, Cottington E, Cmolik B. Iron supplementation for acute blood loss anemia after coronary artery bypass surgery: a randomized, placebo-controlled study. Heart Lung 1994;23:493-9.

To the Editor: The discussant in the article by Rozenman et al. refers to the patient's elevated sedimentation rate and indicates that it concerns him because, as he states, "cardiac failure is usually associated with a low sedimentation rate." As long ago as the 1940s, when I was a medical student and a house officer, I often heard that statement in the course of ward rounds but found very little substantiating evidence in the literature. Accordingly, I invited two fourth-year medical students to join me in studying the sedimentation rate in 38 patients with acute congestive heart failure; we determined the rates during the acute stage, as well as after recompensation. Twenty-six of the 38 patients in acute cardiac failure had elevated sedimentation rates, and by and large the elevations persisted after recompensation.[1]

The February 7, 1991, issue of the *Journal* included a more extensive study of this topic by Haber et al.[2] They studied patients with chronic heart failure and concluded that the sedimentation rate was "of limited value in the clinical management of this disorder."

ROBERT J. GLASER, M.D.
525 Middlefield Rd.
Menlo Park, CA 94025

1. McGinnis AE, Lansche WE, Glaser RJ. Observations on the erythrocyte sedimentation rate in congestive heart failure. Am J Med Sci 1953;225:599-604.
2. Haber HC, Leavy JA, Kessler PD, Kukin ML, Gottlieb SS, Packer M. The erythrocyte sedimentation rate in congestive heart failure. N Engl J Med 1991;324:353-8.

To the Editor: I enjoyed the article by Rozenman et al., but I broke into a profuse sweat when I came across the word "diaphoresis" in the first paragraph. Although I am proud of the contribution of the Greek language to the vocabulary of medicine, I have strong antibodies against some words. "Diaphoresis" is one of them.

This term is nowhere to be found in Greek dictionaries or British textbooks of medicine. Its use appears to be almost exclusively American. *Dorland's Illustrated Medical Dictionary* defines the term as "perspiration, especially profuse perspiration."[1] In Greek the word literally means "trans-carriage" or "carrying through" (cf. "electrophoresis"). It bears no etymologic relation to sweating, for which the correct Greek term is "ephidrosis." We already use "anhidrosis" to denote the absence of sweating, so it would be only appropriate to use the correct word for its presence.

I realize, of course, that established terms are difficult to change. Until this happens, people will continue to earn their daily bread by the sweat of their brows (and not by the diaphoresis of their supraorbital ridges), and my antidiaphoretic antibodies will continue to give me a paradoxical sweaty reaction.

ANTHONY PAPAGIANNIS, M.D.
Gregoriou E' 42
GR 542 49 Thessaloniki, Greece

1. Dorland's illustrated medical dictionary. 25th ed. Philadelphia: Saunders, 1974.

To the Editor: The article "Where Did Good Old Clinical Diagnosis Go?" could more aptly have been titled "Whatever Happened to the Problem List?" The value of carefully delineating all the problems and searching for the unifying syndrome that explains them all cannot be overestimated. In the patient described, the formulation of a problem list — unexplained anemia, worsening congestive heart failure, and increasing mitral regurgitation after open-heart surgery — should have prompted a systematic differential diagnosis that included infectious as well as neoplastic causes before the lytic bone lesion developed.

Unfortunately, in the day-to-day practice of medicine, the problem list exists but is often relegated to the front of the chart as a document intended to satisfy administrative requirements. Instead of consulting the list and searching for a syndrome with each new problem, we tend to apply imprecise algorithms widely — for example, anemia equals gastrointestinal blood loss; lytic bone lesion equals cancer — rather than to assess accurately how the new problem fits into the patient's overall clinical findings.

CATHERINE REINIS LUCEY, M.D.
Washington Hospital Center
Washington, DC 20010-2975

To the Editor: Until I read "Where Did Good Old Clinical Diagnosis Go?" I believed that most physicians guided their diagnostic thinking by some variation of a clinical pearl I received from one of my medical school professors, a pediatric nephrologist. I wish to share it, because it has served me well by saving time, money, and, I believe, a life or two:

> There are three diagnoses for every disease: the one that pulls all the history together; the one you can't afford to miss; and the one that it actually is. Sometimes, if you are lucky, the first two and the third are the same, but usually they are not.

Grammatical incorrectness aside, this earthy statement embodies the practical essence of applied differential diagnosis. When one checks the "all-the-history" diagnosis against the "can't-afford-to-miss" diagnosis, their common and contradictory points emerge. As a next check, the "common-things-being-common" rule is applied to distinguish among multiple "can't-afford-to-miss" choices. As a next step, the "can't-afford-to-miss" diagnoses are eliminated, in the order of their acuity and temporal danger to the patient, by definitive diagnostic testing. Finally, a skeptical mind is maintained, even in the face of elegant thinking, for what is probable and what is possible are never really the same thing.

VINCENT J. KOPP, M.D.
University of North Carolina at Chapel Hill
Chapel Hill, NC 27599-7010

The authors reply:

To the Editor: We agree that iron supplementation does not have to be routinely prescribed to patients after coronary-artery bypass surgery. However, because transfusion practices are highly variable,[1] iron deficiency should be considered in patients who received few, if any, blood products after surgery, and especially when (as in our patient) aspirin therapy is started despite a history of peptic ulcer disease.

Since the classic paper of Wood[2] suggested that the erythrocyte sedimentation rate is low in patients with uncomplicated chronic heart failure, this observation has become part of medical lore.[3] The study by Dr. Glaser and his colleagues is interesting, but most of their patients had acute, rather than chronic, heart failure. Even though Haber et al.[4] concluded from their study of chronic heart failure that the "lack of discriminatory power [of the sedimentation rate] greatly limits the value of the test in the routine management of this disorder," they also state that their data "provide objective evidence . . . that depression of the sedimentation rate reflects a state of severe cardiac decompensation."

We agree with Dr. Lucey that a careful formulation of a problem list and a search for a unifying diagnosis might have led to an earlier diagnosis. In fact, this was one of the main messages of our article.

YOSEPH ROZENMAN, M.D.
DAN GILON, M.D.
SHMUEL FUCHS, M.D.
Hadassah University Hospital
91120 Jerusalem, Israel

1. Goodnough LT, Johnston MF, Toy PT, Transfusion Medicine Academic Award Group. The variability of transfusion practice in coronary artery bypass surgery. JAMA 1991;265:86-90.
2. Wood P. The erythrocyte sedimentation rate in diseases of the heart. Q J Med 1936;29:1-20.
3. Kassirer JP, Kopelman RI. A man with severe valvular heart disease. Hosp Pract 1985;20:56, 61-3.
4. Haber HL, Leavy JA, Kessler PD, Kukin ML, Gottlieb SS, Packer M. The erythrocyte sedimentation rate in congestive heart failure. N Engl J Med 1991;324:353-8.