Correspondence

Managed Care in the Crystal Ball

To the Editor: Ginzberg and Ostow (April 3 issue)[1] rightly predict that managed care's days are numbered. Less clear is whether others will acquire the authors' insights the easy way or the hard way (i.e., through foresight or through the forehead). If we do not take corrective action soon, but instead stand by until managed care has run its course, we may find ourselves bailing one more industry out of the financial crisis we have allowed it to create.[2] I expect Ginzberg and Ostow's crystal ball to be right, but I fear that many of the rest of us will find that only our hindsight is 20/20.

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1. Ginzberg E, Ostow M. Managed care — a look back and a look ahead. N Engl J Med 1997;336:1018-20.
2. Akula JL. Insolvency risk in health carriers: innovation, competition, and public protection. Health Aff (Millwood) 1997;16(1):9-33.

To the Editor: I'm with you in predicting that managed care is here to stay.[1] Ginzberg and Ostow convict managed care on the trumped-up charge of failing simultaneously to provide universal coverage, sustainable financing, and better care for all Americans. No health care system yet devised can meet this challenge. But for a substantial and growing number of Americans — who vote with their enrollments — managed care represents the best balance among competing objectives. . . .

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1. Kassirer JP. Is managed care here to stay? N Engl J Med 1997;336:1013-4.

To the Editor: Ginzberg and Ostow assert that managed care provided through health maintenance organizations (HMOs) has lowered the cost of medical care. An examination reveals that this reduction in cost is a mirage. The cost of medical services in the past included the costs of education of students and physicians, clinical research, some social services, and other services to maintain health and prevent disease. These costs are largely unfunded by most HMOs. The costs of liability insurance, which contribute to the rising cost of medical care, are as yet essentially negligible for HMOs and are borne by physicians. Furthermore, the compensation received by physicians has decreased while paperwork and administrative costs have increased dramatically.

Reducing medical education and medical research by decreasing funding has important Machiavellian consequences. Restricting education results in the emergence of physicians with knowledge hardly distinguishable from the knowledge of those with less formal education. HMOs are already replacing specialists with generalists, and generalists with nurse assistants. A second Machiavellian effect is that less-educated physicians may consider fewer differential diagnoses and thus less expensive evaluation and treatment of patients. Further "savings" are thus achieved.

The bell is tolling for the disappearance of educated physicians. For the maintenance of medical education, HMOs should be taxed at a percentage at least similar to

that provided by Medicare for education. A similar tax on pharmaceutical houses could be used to support research. Funds would then be available for education.

Apoptosis of medicine can be prevented.

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To the Editor: The Sounding Board article by Ginzberg and Ostow unfortunately fails to differentiate among the many types of HMOs. Unlike nonprofit HMOs such as Kaiser Permanente, whose mission is to spend the subscriber's premium optimally on direct patient care, community services, and medical education, the for-profit HMOs have the mission of maximizing the return to their investors.

In their historical review, the authors do not state that before 1960 health care insurance was uncommon. Paradoxically, it was the creation in the 1960s of third-party fee-for-service reimbursement, both private (through workplace benefits) and public (through Medicare and Medicaid), that led to the current dominance of managed-care programs. The third-party reimbursement system dissociated supply from demand so that the additional number of physicians and hospitals, instead of leading to reduced unit costs, led to increased utilization, higher prices, and increased total health care expenditures.[1,2] It was the inflated fee-for-service costs, as compared with competitive marketplace prices, that enabled Wall Street to invest in health care and extract profits for shareholders.

The unmanaged growth of the fee-for-service system from 1960 to 1990 led to the duplication of services in areas such as invasive cardiology and cardiac surgery. Not only has this duplication resulted in increased costs, but also the minimal volumes in many institutions have led to poor-quality outcomes. Opportunities exist for socially responsible programs to create centers of excellence and use economies of scale both to improve the health of subscribers and to limit the growth of their premiums. Although the excesses of health care programs that are driven by Wall Street should not be excused, nonprofit programs such as Kaiser Permanente, which spend more than 96 cents of the subscriber's dollar on direct patient care, can be a solution to the unmanaged, unorganized, and inefficient systems of the past. Unlike Ginzberg and Ostow, I believe that by making health care more affordable, well-managed HMOs increase the possibility of both universal coverage and an improved quality of care for the American people.

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1. Pearl RM. Health care — past, present, and future. Ann Plast Surg 1997;38:191-2.
2. Pearl RM, McAllister H, Pruzansky J. An economic analysis of health care reform and its implications for plastic surgery. Plast Reconstr Surg 1997;99:1-9.

The authors reply:

To the Editor: We agree with Dr. Barness that it is the funding for medical care that has been reduced by managed-care plans (which provide little or nothing for medical education and research) and that the efficiency of expenditures for patient care has not improved substantially. Moreover, we noted in our article that annual increases in health care costs, after declining, are once again heading upward.

Mr. Piescik, drawing on his own experiences with managed care, is enthusiastic about what it has been able to do for him and for many others who prefer to rely on the marketplace to buy health care. No system is perfect, but competition is better than all the known alternatives. We wonder whether younger and older disabled persons and those with chronic diseases whom managed-care plans seek not to enroll would vote for the competitive marketplace.

Mr. Scofield warns that the United States had better address the managed-care issue before the country faces a bailout of many hundreds of billions of dollars if and when many of the current for-profit plans are forced into bankruptcy by a particularly strong reversal in the stock market. This point is worth raising and, what is more, is worth answering.

Dr. Pearl, of Permanente Medical Group in Santa Clara, has a much more positive view of nonprofit HMOs than Dr. David Lawrence,[1] the long-time chief executive officer of Kaiser Permanente. The fact that Kaiser spends such a high proportion of its revenue on patient services is commendable, but this fact provides no assurance that Kaiser is properly configured for the present, much less for the future — although it remains the leader among the nonprofit HMOs.

The crux of our assessment of managed care can be restated as follows. The easy "savings" have been made; these "savings" largely represent the unwillingness of managed-care plans to provide the substantial cross-subsidization funding that fee-for-service health insurance plans have long contributed for medical education, research, and charity care. The public is in active revolt against widespread undertreatment by managed-care plans without adequate processes of appeal and the right to sue for damages. The Congressional Budget Office estimates that by 2007, the United States will be spending over $2 trillion on health care annually and that 53 percent of the expenditures will be government dollars, not counting tax subsidies. Who is kidding whom about the competitive market?[2]

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1. Lawrence DK, Lowe JA. Cost and quality issues. In: Ginzberg E, ed. Critical issues in U.S. health reform. Boulder, Colo.: Westview, 1994:151ff.
2. Congressional Budget Office. The economic and budget outlook, 1998–2007. Washington, D.C.: Government Printing Office, 1997:126.

Solid Cancers after Bone Marrow Transplantation

To the Editor: Curtis et al. (March 27 issue)[1] conclude that patients undergoing bone marrow transplantation have an increased risk of new solid cancers later in life. The authors calculated the observed numbers of solid cancers on the basis of data from 19,229 patients who had received allogeneic or syngeneic transplants between 1964

and 1992 at 235 centers, with the expected numbers of solid cancers calculated on the basis of data obtained from selected registries in the United States, England and Wales, Europe, and Asia. The authors then calculated the ratios of observed to expected cases and the corresponding 95 percent confidence intervals, which suggested an elevated risk of new solid cancers among patients who had undergone bone marrow transplantation.

This comparison may be invalid, because the patients with cancers (such as acute lymphoblastic leukemia or acute nonlymphocytic leukemia) who underwent transplantation may have had a much higher risk of new solid cancers than the general population. Therefore, the correct comparison group for calculating the expected numbers of new cancers should be patients who had cancers (such as acute lymphoblastic leukemia or acute nonlymphocytic leukemia) and did not undergo bone marrow transplantation.

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1. Curtis RE, Rowlings PA, Deeg HJ, et al. Solid cancers after bone marrow transplantation. N Engl J Med 1997;336:897-904.

The authors reply:

To the Editor: Lai et al. question the validity of comparing the incidence of solid cancers after bone marrow transplantation with the risk of cancer in the general population. Since most of the transplant recipients in our study had an initial diagnosis of leukemia, Lai et al. speculate that such patients may have a higher risk of new solid cancers than the general population. Regrettably, little information is available on the risk of solid tumors after treatment for leukemia in the nontransplantation setting.[1-3] Data are particularly sparse for patients with acute or chronic myelogenous leukemia, the types that predominate among transplant recipients. These patients had a poor prognosis before the transplantation era, with very limited follow-up time in which to observe new cancers. Thus, we were not able to use as a comparison group patients with leukemia who had not undergone transplantation, as Lai and colleagues as well as others suggest.

We agree that factors associated with the primary disease may influence the risk of solid tumors among transplant recipients, especially the effects of treatment for the initial cancer before transplantation. For example, we reported that cranial irradiation before transplantation in patients with acute leukemia is likely to be related to the increased risk of solid cancers observed in our cohort, although the effect appears to be limited to cancers at certain anatomical sites (the brain and thyroid) and to younger age groups (<10 years).

Non–transplant-associated factors other than treatment for the primary disease, including shared genetic and environmental risk factors, could also influence the subsequent risk of cancer. However, if the results of previous studies of multiple primary cancers are generalizable, such factors are unlikely to result in the 5-to-10-fold elevation in risk after bone marrow transplantation. It should also be emphasized that a number of our major findings, including the dose–response relation between total-body irradiation and the risk of cancer, were based on comparisons within the transplantation cohort and did not rely on the use of the general population as a comparison group.

Although there are probably multiple causes of the increased risk of solid cancers after transplantation, the conclusions of our report remain valid: survivors of allogeneic bone marrow transplantation have a substantially increased risk of new solid cancers, and lifelong surveillance is essential.

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1. Neglia JP, Meadows AT, Robison LL, et al. Second neoplasms after acute lymphoblastic leukemia in childhood. N Engl J Med 1991;325:1330-6.
2. Hawkins MM, Draper GJ, Kingston JE. Incidence of second primary tumours among childhood cancer survivors. Br J Cancer 1987;56:339-47.
3. Olsen JH, Garwicz S, Hertz H, et al. Second malignant neoplasms after cancer in childhood or adolescence. BMJ 1993;307:1030-6.

Radiotherapy for Rectal Cancer

To the Editor: In the Swedish Rectal Cancer Trial (April 3 issue)[1] more than 100 surgeons at 70 hospitals operated on 1168 patients in three years — fewer than 17 patients per hospital in three years, or fewer than 6 patients per hospital per year. With more than 100 surgeons participating, each on average performed fewer than four operations per year.

In this trial, the local-recurrence rate for Dukes' stage A cancers (4 percent after radiotherapy plus surgery and 12 percent after surgery alone) is unacceptably high and reflects less-than-adequate surgical techniques.

As noted in the discussion, it is possible to obtain "very low rates of local recurrence and good survival without radiotherapy." From 1980 to 1991, 666 patients with rectal cancer underwent surgery with curative intent at the Cleveland Clinic (unpublished data). Large bulky tumors were present in 18.2 percent of patients, who were selectively given preoperative radiotherapy. Two surgeons performed more than 60 percent of the operations. The mean and median follow-up times were 69.1 months and 64 months, respectively. The Kaplan–Meier estimates of rates of local recurrence and distant metastasis at five years were 10 and 20 percent, respectively. With respect to the stage of the tumor, the Kaplan–Meier estimates of the rates of local recurrence at five years for stage I, II, and III tumors were 1.6, 9.8, and 18.5 percent, respectively. Disease-free survival at five years was 71.6 percent. The survival rates for patients with stage I, II, and III tumors were 92, 75.8, and 50.3 percent, respectively. A Cox proportional-hazards model showed that the tumor–node–metastasis stage and the distance of the tumor from the anal verge were the

only significant and independent factors in the prediction of local recurrence. The Kaplan–Meier estimates of local-recurrence rates at five years for tumors 0 to 9 cm from the anal verge and those 10 to 15 cm from the anal verge were 12.9 and 4.7 percent, respectively ($P<0.001$).

Not all patients benefit from preoperative radiotherapy. With appropriate surgical techniques, stage I tumors at any level should not require radiotherapy. Tumors of any stage that are more than 10 cm from the anal margin have not been shown to benefit from radiotherapy. Any study performed to assess the efficacy of adjunctive radiotherapy must take into account variables that include the stage of the tumor, its distance from the anal verge, and the experience of the surgeon.

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1. Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med 1997;336:980-7.

To the Editor: The authors of the Swedish Rectal Cancer Trial did not address the very important issue of sphincter preservation. They did not state how many patients had abdominoperineal resection and how many had sphincter preservation. For patients in whom sphincter-preserving surgery is appropriate, a short course of preoperative radiotherapy now appears to be the treatment of choice, unless a subgroup analysis showed that complications were particularly high in this subgroup after preoperative radiotherapy. For patients in whom sphincter-preserving surgery is not appropriate, on the other hand, a short course of preoperative radiotherapy may eliminate an opportunity for down-staging of the tumor by a more protracted course of preoperative radiotherapy (with or without chemotherapy), followed by sphincter-preserving surgery.

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To the Editor: We would like to compliment the Swedish Rectal Cancer Trial investigators on their prospective, randomized, controlled trial. In his editorial in the April 3 issue, Minsky[1] compliments the investigators on the philosophy underlying the trial but observes that preoperative combination therapy with conventional radiation doses and techniques has far greater potential.

We believe there is an alternative interpretation of the data. Preoperative radiotherapy with conventional doses of radiation (between 40 and 50 Gy) and an interval to allow for down-staging of the tumor before surgery has been demonstrated to reduce local recurrences of potentially operable, locally advanced tumors[2] but has failed to show a survival advantage. The Swedish Rectal Cancer Trial group focused on operable rectal tumors, using a short course of preoperative high-dose radiotherapy to improve the outcome rather than affect operability. This is the first trial to demonstrate a survival advantage of radiotherapy in the treatment of rectal cancer rather than solely a reduction in local recurrences, and as the main difference from previous trials is the use of accelerated fractionation, this is likely to be the important factor. Use of a multiple-field technique averted the increased mortality associated with the anterior–posterior irradiation technique, and the demonstrated survival advantage is equivalent to that associated with conventional postoperative radiochemotherapy.[3]

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1. Minsky BD. Adjuvant therapy for rectal cancer — a good first step. N Engl J Med 1997;336:1016-7.
2. Medical Research Council Rectal Cancer Working Party. Randomised trial of surgery alone versus radiotherapy followed by surgery for potentially operable locally advanced rectal cancer. Lancet 1996;348:1605-10.
3. Krook JE, Moertel CG, Gunderson LL, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med 1991;324:709-15.

The authors reply:

To the Editor: We agree with Lavery and colleagues that the rate of local recurrence for Dukes' stage A tumors in our study is unacceptably high. The figure reflects the standard surgery that was used at most centers. Today, most of us consider this surgery suboptimal, but the rates of local recurrence in this trial are similar to those in all the other randomized trials.[1] There were, however, participating centers in Sweden with rates of local recurrence in the surgery-alone group that were as low as those at the Cleveland Clinic. Surgical skill is not only a matter of numbers but also a matter of education.[2] Since the closure of the trial, several workshops in rectal-cancer surgery have been organized, and patients are now referred to one or a very few surgeons at each hospital in Sweden. Ongoing nationwide registration will tell us whether these efforts improve the results.

It is also our belief that with optimized surgery, high lesions in a favorable stage (Dukes' stage A), provided that they can be reliably identified before surgery, probably do not require radiotherapy. However, data from the trial showed the same recurrence rate and relative reduction with radiotherapy irrespective of the distance of the tumor from the anus.

With regard to Dr. Vikram's comment, the data on immediate adverse effects have been published.[3] There was no increase in anastomotic leakage or other complications among the patients who underwent surgery with sphincter preservation. The only adverse effect was an increased risk of a perineal wound infection among the patients in the radiotherapy-plus-surgery group who underwent surgery with an abdominoperineal excision. The rationale of achieving down-staging, and thus performing more sphincter-saving procedures, by using prolonged preoperative radiotherapy or chemoradiotherapy in patients with low rectal tumors was also pointed out by Minsky in his editorial. This was not an aim of our trial. Although the approach is theoretically attractive, we are hesitant to use it. The sur-

gical procedure may appear easier because the tumor bulk is smaller, but can the bowel be resected at a higher level without increasing the risks associated with a radical procedure? The most commonly used preoperative dose (about 50 Gy in five weeks) kills only subclinical tumor cells (five fractions of 5 Gy each in one week may be as effective). Ongoing trials in Europe and the United States can answer this question. With higher doses, the goal may be reached without an increased risk of local recurrence, but the risk of late effects on bowel function may be unacceptably high.[4]

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1. Påhlman L, Glimelius B. The value of adjuvant radio(chemo)therapy for rectal cancer. Eur J Cancer 1995;31A:1347-50.
2. Påhlman L. Surgery for rectal cancer: the relationship between treatment volume and results. In: Söreide O, Norstein J, eds. Rectal cancer surgery. Berlin, Germany: Springer, 1997:364-70.
3. Swedish Rectal Cancer Trial. Initial report from a Swedish multicentre study examining the role of preoperative irradiation in the treatment of patients with resectable rectal carcinoma. Br J Surg 1993;80:1333-6.
4. Graf W, Ekström K, Glimelius B, Påhlman L. A pilot study of factors influencing bowel function after colorectal anastomosis. Dis Colon Rectum 1996;39:744-9.

Transmission of the Human Immunodeficiency Virus and the Hepatitis C Virus

To the Editor: Ridzon et al. (March 27 issue)[1] report a case of the transmission of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) from a single source, followed by unusually long times to seroconversion for both viruses. We report a similar case, but one in which transmission was followed by seroconversion times similar to those previously described for HIV[2] and for HCV.[3]

In a suicide attempt, a 27-year-old man injected himself in the brachial vein with 0.1 ml of blood that he had obtained, using the same insulin syringe, from a drug addict seropositive for HIV and HCV. Thirteen days after the injection, the man had a temperature of 40°C, sweating, and erythematous pharyngitis. These symptoms lasted 10 days. On day 17 the concentration of p24 antigen was 250 ng per liter, the HIV Western blot assay had no positive band, and an enzyme immunoassay for antibodies to HIV was negative. The test for HIV antibodies first became positive on day 31, when the HIV Western blot assay revealed only weak bands for gp160, p55, p24, and p18. The full HIV-positive Western blot pattern was obtained on day 73. The assay for antibodies to HCV became positive on day 123. Zidovudine treatment began on day 51 and was continued for seven months. Four years later, with only the seven months of zidovudine treatment, the patient was free of symptoms.

This patient differed from the one described by Ridzon et al.[1] in that concomitant transmission of HIV and HCV was followed by normal seroconversion times for both viruses.[2,3] Four years after the dual contamination, the patient remained symptom-free. Thus, simultaneous acquisition of the two viruses is not always followed by a rapid progression of HIV or HCV disease. We do not know whether the zidovudine treatment slowed the progression of HIV disease, as has been suggested.[4,5] We also do not know whether that treatment interfered with the progression of HCV disease by reducing the HIV-related immunodeficiency.

The use of combination therapy against HIV has been proposed after exposure to that virus. Interferon alfa can be given to prevent HCV infection, but nothing is known about its efficacy as prophylaxis.[3] These two cases of simultaneous exposure to HIV and HCV raise the question of whether interferon alfa therapy should be administered with combination therapy for HIV after such exposures or only after HCV infection has been documented.

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1. Ridzon R, Gallagher K, Ciesielski C, et al. Simultaneous transmission of human immunodeficiency virus and hepatitis C virus from a needle-stick injury. N Engl J Med 1997;336:919-22.
2. Tindall B, Cooper DA. Primary HIV infection: host responses and intervention strategies. AIDS 1991;5:1-14.
3. Iwarson S, Norkrans G, Wejstål R. Hepatitis C: natural history of a unique injection. Clin Infect Dis 1995;20:1361-70.
4. van Der Poel CL, Cuypers HTM, Reesink HW, et al. Confirmation of hepatitis C virus infection by new four-antigen recombinant immunoblot assay. Lancet 1991;337:317-9.
5. Kinloch-de Loës S, Hirschel BJ, Hoen B, et al. A controlled trial of zidovudine in primary human immunodeficiency virus infection. N Engl J Med 1995;333:408-13.

The authors reply:

To the Editor: Biron et al. describe another case of simultaneous transmission of HIV and HCV. There are two notable differences between that case and the one we described. In their patient, the times to seroconversion were shorter, and the course of the illness was much less aggressive. The reasons for these differences are unclear. Because the groups at risk for these two blood-borne pathogens overlap, it is likely that more such dual infections will occur. Additional studies will be needed to determine the range of seroconversion times, the continuum of immune responses, and the clinical outcome in such cases.

The care of patients with percutaneous or mucosal exposure to blood from an HCV-infected person is problematic, because prophylaxis with immune globulin after the exposure does not appear to be effective,[1] and no data are available for use in assessing the postexposure efficacy of interferon or other antiviral agents. Given the rate of transmission of HCV as a result of exposure to blood, clinical trials to assess the efficacy of postexposure prophylaxis against HCV infection will be difficult because of the large sample needed for the study to have sufficient power. As has been done in the case of exposure to HIV through blood, surveillance data on exposures to HCV-infected

blood may be helpful and provide additional information about the potential efficacy of various types of postexposure prophylaxis. Although the mechanisms of the effect of interferon in patients with hepatitis C are poorly understood, the antiviral mechanisms of the drug may require the presence of an established infection.[2] Interferon must be administered parenterally, and its side effects can be severe. On the basis of these considerations, postexposure prophylaxis against HCV infection is not currently recommended.[3]

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2. Peters M, Davis GL, Dooley JS, Hoofnagle JH. The interferon system in acute and chronic viral hepatitis. Prog Liver Dis 1986;8:453-67.
3. What is the risk of acquiring hepatitis C for health care workers and what are the recommendations for prophylaxis and follow-up after occupational exposure to hepatitis C virus? Hepatitis surveillance report no. 56. Atlanta: Centers for Disease Control and Prevention, 1995.

The Management of Hypertrophic Cardiomyopathy

To the Editor: With regard to the excellent review article by Spirito et al. (March 13 issue),[1] we wish to report data on percutaneous transluminal septal myocardial ablation, which Sigwart introduced in 1995 as a new option for the treatment of highly symptomatic patients with hypertrophic obstructive cardiomyopathy.[2] Since January 1996,[3] we have used this technique of nonsurgical myocardial ablation by alcohol-induced occlusion of the first septal perforation in 56 highly symptomatic patients (mean [±SD] New York Heart Association functional class, 2.7±0.6). The left ventricular outflow tract gradient was reduced in 93 percent of patients (eliminated in 27 percent, reduced by at least 50 percent in 52 percent, and reduced by 20 to 49 percent in 7 percent; mean reduction with the patient at rest, from 68.1±32.7 to 18.2±21.6 mm Hg; after an extrasystole, 141.6±40.7 to 63.6±49.1 mm Hg). In four patients whose primary treatments failed, the ablation technique was repeated successfully when the target septal branch was identified by myocardial contrast echocardiography.[4]

The most frequent complication was permanent trifascicular block in 14 percent of the patients, which required the implantation of a DDD pacemaker. A new bundle-branch block developed in 50 percent of the patients. During the injection of the alcohol, neither ventricular fibrillation nor septal perforation was seen in this cohort. Two patients (4 percent) died in the hospital from complications unrelated to the procedure. At the three-month follow-up visit, 35 patients had excellent clinical improvement (New York Heart Association class, 1.3±1.1; $P<0.001$); there was ongoing reduction of the outflow gradient in 56 percent of the patients. No septal perforation or noncardiac complications were seen during follow-up.[5]

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2. Sigwart U. Non-surgical myocardial reduction for hypertrophic obstructive cardiomyopathy. Lancet 1995;346:211-4.
3. Gleichmann U, Seggewiss H, Faber L, Fassbender D, Schmidt HK, Strick S. Kathetertherapie der hypertrophen obstruktiven Kardiomyopathie. Dtsch Med Wochenschr 1996;121:679-85.
4. Faber L, Seggewiss H, Fassbender D, Strick S, Bogunovic N, Gleichmann U. Guiding of interventional myocardial ablation in obstructive hypertrophic cardiomyopathy by myocardial contrast echocardiography (MCE): first experiences. Presented at the 8th Essen–Mayo–Mainz-Symposium, Essen, Germany, October 25–27, 1996. abstract.
5. Seggewiss H, Gleichmann U, Faber L, Fassbender D, Schmidt HK, Strick S. Catheter treatment of hypertrophic obstructive cardiomyopathy: acute and mid-term results. J Am Coll Cardiol 1997;29:Suppl A:388A. abstract.

The authors reply:

To the Editor: Seggewiss et al. address the potential role of nonsurgical partial septal ablation in hypertrophic obstructive cardiomyopathy. In this procedure, absolute ethanol is injected into a septal perforator artery to produce a localized myocardial infarction. This novel approach is being offered experimentally at a few selected centers as an alternative to ventricular septal myotomy–myectomy.[1-3] However, a number of important considerations pertaining to the technique deserve emphasis.

First, although much of the clinical experience with septal ablation in patients with hypertrophic obstructive cardiomyopathy is still unpublished, the mortality and morbidity associated with the procedure (including complete atrioventricular block requiring the permanent implantation of a pacemaker) are unacceptably high at some centers and may in fact exceed those associated with septal myotomy–myectomy. Indeed, standard surgical intervention for hypertrophic obstructive cardiomyopathy is now performed with low operative risk (less than 1 to 2 percent mortality) at selected centers, and it has long-term benefits, with substantial reduction or abolition of the outflow gradient in more than 90 percent of patients and marked improvement in symptoms in 70 percent.[4]

Second, a substantial proportion of patients with hypertrophic obstructive cardiomyopathy have a benign clinical course, with only mild symptoms or none, and they may have a normal life span.[4] Such patients do not require a profoundly aggressive procedure that is designed to produce a controlled myocardial infarction (with its associated risks) to reduce an outflow gradient that in itself may not necessarily influence prognosis. Consequently, septal ablation would theoretically be justified only in patients with severe symptoms refractory to drug therapy (New York Heart Association functional class III or IV), as an alternative to surgery. Unfortunately, up to 40 percent of patients who have undergone alcohol ablation at selected institutions were not severely symptomatic but, rather, had only mild symptoms or were even asymptomatic.[1]

Third, although the preliminary data suggest that partial

septal ablation may reduce the outflow gradient in many patients with hypertrophic obstructive cardiomyopathy (as Seggewiss et al. point out), there are no data to substantiate that the procedure improves symptoms or enhances exercise capacity. Indeed, we have already observed the substantial placebo effect that may be produced in symptomatic patients with this condition by experimental techniques focused on reducing the outflow gradient, such as dual-chamber pacing.[5]

Furthermore, the high rate at which permanent or temporary pacemakers are implanted for complete heart block after alcohol ablation (up to 33 percent in some centers) represents an important complication that is rare with myotomy–myectomy and is also a confounding factor in assessing whether ablation itself benefits left ventricular hemodynamics (since the pacemaker may contribute to reducing the gradient). Obviously, the long-term hemodynamic and functional consequences of alcohol-induced septal ablation are unknown at this early stage.

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1. Knight C, Kurbaan AS, Seggewiss H, et al. Nonsurgical septal reduction for hypertrophic cardiomyopathy: outcome in the first series of patients. Circulation 1997;95:2075-81.
2. Lakkis N, Kleiman N, Killip D, Spencer WH III. Hypertrophic obstructive cardiomyopathy: alternative therapeutic options. Clin Cardiol 1997; 20:417-8.
3. Seggewiss H, Gleichmann U, Faber L, Fassbender D, Schmidt HK, Strick S. Catheter treatment of hypertrophic obstructive cardiomyopathy: acute and mid-term results. J Am Coll Cardiol 1997;29:Suppl A:388A. abstract.
4. Spirito P, Seidman CE, McKenna WJ, Maron BJ. The management of hypertrophic cardiomyopathy. N Engl J Med 1997;336:775-85.
5. Nishimura RA, Trusty JM, Hayes DL, et al. Dual-chamber pacing for hypertrophic cardiomyopathy: a randomized, double-blind, crossover trial. J Am Coll Cardiol 1997;29:435-41.

Familial Atrial Fibrillation

To the Editor: Brugada et al. (March 27 issue)[1] reported the mapping of familial atrial fibrillation in three kindreds to a locus on chromosome 10q, but they did not discuss the locus on 10q for dilated cardiomyopathy with mitral-valve prolapse, which they and others have previously described.[2] Supraventricular dysrhythmias and dilated cardiomyopathy often segregate within the same family, apparently as a result of variable expression of a single trait.[3] Mitral-valve prolapse itself is associated with ventricular and supraventricular dysrhythmias.[4] Interestingly, two of the affected family members in the study of familial atrial fibrillation had evidence of ventricular dilatation and systolic dysfunction.

Many clinical entities in cardiovascular disease are so heterogeneous that they confound investigation. It would be central to the message of this paper to know whether or not the loci for atrial fibrillation and dilated cardiomyopathy are genetically distinct. In addition, was there any clinical information — for example, from endomyocardial biopsy — to link the two phenotypes? Clinical genetics and molecular genetics offer at least some insight into the inadequacies of current nosology.

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1. Brugada R, Tapscott T, Czernuszewicz GZ, et al. Identification of a genetic locus for familial atrial fibrillation. N Engl J Med 1997;336:905-11.
2. Bowles KR, Gajarski R, Porter P, et al. Gene mapping of familial autosomal dominant dilated cardiomyopathy to chromosome 10q21-23. J Clin Invest 1996;98:1355-60.
3. Kass S, MacRae C, Graber HL, et al. A gene defect that causes conduction system disease and dilated cardiomyopathy maps to 1p1-1q1. Nat Genet 1994;7:546-51.
4. Kligfield P, Hochreiter C, Kramer H, et al. Complex arrhythmias in mitral regurgitation with and without mitral valve prolapse: contrast to arrhythmias in mitral valve prolapse without mitral regurgitation. Am J Cardiol 1985;55:1545-9.

Dr. Roberts replies:

To the Editor: My colleagues and I appreciate Dr. MacRae's comments about a possible relation between the locus for dilated cardiomyopathy and the locus for atrial fibrillation, since the two are in overlapping regions of chromosome 10q (10q21–23 and 10q22–24, respectively). We do not think there is any relation between dilated cardiomyopathy and atrial fibrillation in the family with atrial fibrillation that we studied. We have now identified several other families with atrial fibrillation with members as old as 70 and 80, and there is no evidence of dilated cardiomyopathy in these patients. It is also noteworthy that in the family with atrial fibrillation studied by us, the condition began in some members when they were as young as two or three years old. In the family with dilated cardiomyopathy, there was no atrial fibrillation. We have no evidence to indicate that the locus for atrial fibrillation at 10q22–24 is in any way related to the locus for dilated cardiomyopathy at 10q21–23, even though they are on the same chromosome. The actual physical distance between these two loci (as opposed to the estimated genetic distance) is potentially several million base pairs and represents hundreds of genes. However, the possibility that these diseases are due to different alleles of the same gene cannot be ruled out until the gene or genes have been identified.

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Anaphylaxis with *Anisakis simplex* in the Gastric Mucosa

To the Editor: Anisakis simplex is a nematode (Anisakidae family, Ascaridoidea superfamily) that parasitizes sea mammals. Common intermediary hosts include the cod-

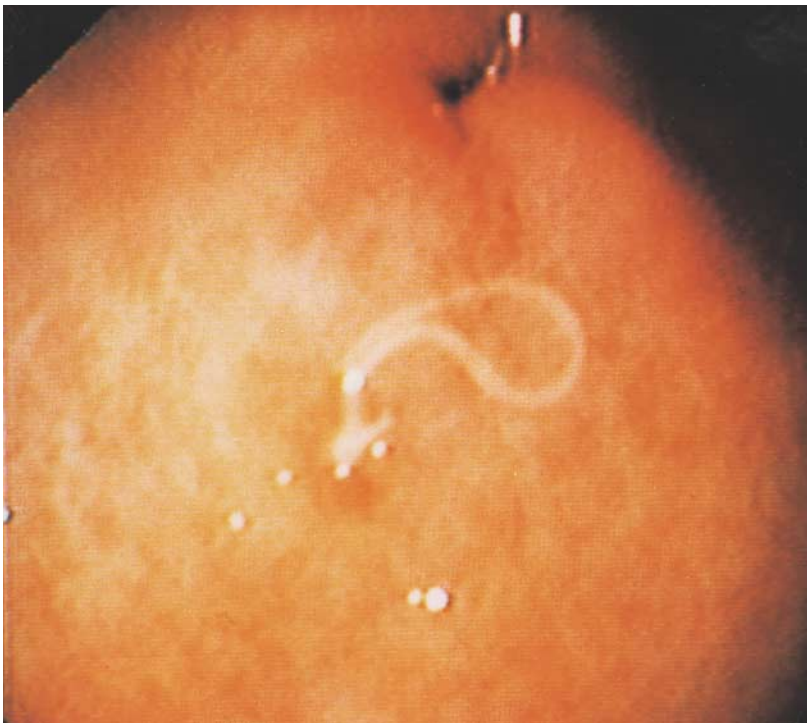

Figure 1. *Anisakis simplex* Larva in the Gastric Mucosa.

fish, hake, sardine, anchovy, salmon, tuna, mackerel, and squid.[1] Humans acquire the larvae by eating raw or undercooked seafood.[2] Anisakis larvae can be invasive, penetrating the host's stomach or intestinal wall,[3] but it is very unusual to find the nematode in the gastric mucosa. We have seen three patients with allergic reactions and clinical findings that led us to suspect acute gastric anisakiasis.

A 47-year-old woman had anaphylaxis, vomiting, and gastric pain two hours after eating raw anchovy in vinegar sauce. Gastroscopy showed a gastric erosion. The symptoms disappeared after 12 hours. A 51-year-old man had urticaria, bronchospasm, and gastric discomfort 90 minutes after eating raw anchovy in vinegar sauce, and a 34-year-old woman had gastric discomfort, urticaria, and angioedema 60 minutes after eating undercooked hake. Gastroscopy in each of these two patients showed a live worm in the gastric mucosa (Fig. 1). The worms were removed, and the symptoms disappeared. Sensitization to anisakis was demonstrated by positive skin-prick tests (International Pharmaceutical Immunology, Madrid), the presence of specific IgE in serum (CAP system, Pharmacia, Uppsala, Sweden), or both. Sensitization to seafood was not detected. The worms were identified as *A. simplex*.

In Western countries it is uncommon to find patients with nematodes in the gastric mucosa, but gastroscopy is rarely performed in patients who have allergic or gastric symptoms after eating seafood. In patients with allergic reactions who also have gastric symptoms after eating raw or undercooked seafood, endoscopy can be used to prevent the penetration of live larvae into the gastric mucosa. We think our three patients had systemic IgE-mediated reactions (caused by their sensitization to anisakis) and local gastric reactions, which may also have been mediated by IgE,[3] to the parasite in the gastric mucosa. The two events, allergic reaction and infestation, can occur together, and allergic reactions with gastric symptoms may be clues to the presence of acute gastric anisakiasis.

The best treatment for anisakiasis is prophylaxis. Larvae cannot survive a temperature higher than 60°C for 10 minutes or lower than −20°C for 24 hours. However, the ingestion of safely cooked but parasitized seafood can cause an allergy.[4,5] Allergic reactions after the ingestion of seafood, without evidence of IgE against the implicated food (negative skin tests and the absence of specific IgE in serum), may be due to anisakis allergy in sensitized patients.[5]

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1. *Nematodos secernenta*. In: Cheng TC. Parasitología general. Superfamilia heterocheloidea. Madrid: Editorial AC, 1978:649-51.
2. Ishikura H, Kikuchi K, Nagasawa K, et al. Anisakidae and anisakidosis. In: Sun T, ed. Progress in clinical parasitology. Vol. 3. New York: Springer-Verlag, 1993:43-102.
3. Asaishi K, Nishino C, Ebata T, Totsuka M, Hayasaka H, Suzuki T. Studies on the etiologic mechanism of *Anisakiasis*. 1. Immunological reactions of digestive tract induced by *Anisakis* larvae. Gastroenterol Jpn 1980;15:120-7.
4. Kasuya S, Hamano H, Izumi S. Mackerel-induced urticaria and Anisakis. Lancet 1990;335:665.
5. Moreno-Ancillo A, Caballero MT, Cabañas R, et al. Allergic reactions to Anisakis simplex parasitizing sea food. Ann Allergy Asthma Immunol (in press).