Global distribution of transfusion-transmitted virus

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Regression of Multivalvular Regurgitation after the Cessation of Fenfluramine and Phentermine Treatment

To the Editor: Treatment with the appetite-suppressant drugs fenfluramine and dexfenfluramine, alone or in combination with phentermine, has been associated with cardiac-valve abnormalities.\(^1\)\(^2\) Five echocardiologic surveys reviewed by the Food and Drug Administration suggested that the prevalence of cardiac-valve abnormalities is 30 to 88 percent among patients who have taken these drugs\(^2\) and led to the withdrawal of fenfluramine and dexfenfluramine from the U.S. market on September 15, 1997. Whether these lesions resolve, progress, or remain unchanged after discontinuation of the drugs is not yet known. We report the possibility of regression of multivalvular regurgitation associated with fenfluramine and phentermine in a patient who was followed for two years after she stopped taking the drugs.

A 44-year-old woman with morbid obesity was hospitalized in July 1996 for atypical chest pain. Myocardial infarction was ruled out, and an echocardiogram revealed normal chamber sizes and mildly reduced global systolic function. However, moderate-to-moderately-severe aortic regurgitation, mild mitral regurgitation, and moderate tricuspid regurgitation were present. The estimated pulmonary-artery pressure was mildly elevated (38 mm Hg). The patient had no history of cardiac disease. Her only medications were 60 mg of fenfluramine and 30 mg of phentermine daily, which she had taken for the previous 50 weeks, during which time she had lost 40 kg (87 lb). These drugs were discontinued, and the patient began taking 10 mg of lisinopril daily and 25 mg of metoprolol twice daily for borderline hypertension. In December 1997, an echocardiogram showed improved left ventricular function and a decrease in all regurgitant lesions, with no clinically significant change in the estimated pulmonary-artery pressure. In May 1998, physical examination revealed a weight of 198 kg (436 lb), blood pressure of 130/90 mm Hg, and a 1–2/6 systolic ejection murmur along the left sternal border. An echocardiogram obtained in June 1998 (two years after the initial study) demonstrated only trace aortic and tricuspid regurgitation without mitral regurgitation.

In this case, serial echocardiographic studies over a two-year period documented regression of multivalvular regurgitation first discovered while the patient was taking fenfluramine and phentermine. Although this patient was treated with lisinopril, the marked degree of improvement in all the regurgitant lesions is unlikely to be attributable to this medical intervention alone.\(^4\) Follow-up studies in all the affected patients are clearly needed to document the natural history of these lesions. This case report suggests, however, that mild-to-moderate valvular involvement associated with fenfluramine and phentermine may be at least partially reversible on discontinuation of these drugs.

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Fetal DNA and Cells in Women with Systemic Sclerosis

To the Editor: Artlett et al. (April 23 issue)\(^1\) put forward the provocative hypothesis that systemic sclerosis may be
caused by a graft-versus-host–like reaction induced by retained fetal cells in the mother. Although the hypothesis is intriguing, the occurrence of systemic sclerosis in men and nulliparous women clearly indicates that antimaternal reactions are not the sole basis of the disease. Furthermore, we believe that the similarities between graft-versus-host disease and systemic sclerosis are outweighed by considerable differences that make the two entities readily distinguishable.

Fibrosis occurs in only a minority of patients with graft-versus-host disease, develops late in the course of the disease, and is characterized by a central distribution, whereas fibrosis occurs in most patients with systemic sclerosis, develops early in the course of the disease, and is characterized by an acral distribution. Liver involvement is common in graft-versus-host disease but rare in systemic sclerosis. Raynaud’s phenomenon is unusual in patients with graft-versus-host disease but occurs in a majority of patients with systemic sclerosis. Histopathologically, graft-versus-host disease is characterized by fibrotic changes concentrated in the papillary (superficial) dermis, whereas systemic sclerosis is characterized by a sclerotic pattern throughout the reticular dermis, most prominently in the deep reticular dermis at the level of subcutaneous fat. Finally, graft-versus-host disease responds to several immunosuppressive drugs, whereas systemic sclerosis does not. Thus, the dissimilar clinical and histopathological features of graft-versus-host disease and systemic sclerosis raise questions about the use of graft-versus-host disease as a model for systemic sclerosis.

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To the Editor: Artlett et al. have clearly demonstrated the presence of increased numbers of cells with a male chromosomal pattern in skin lesions and peripheral blood from women with a recent onset of systemic sclerosis. In their discussion, however, the authors do not consider the possibility that the persistence of fetal cells in tissues from women with this disease may reflect ineffective destruction of fetal cells entering the women’s circulation during pregnancy due to compromised immunologic function, instead of representing the stimulus for the development of sclerotic changes. An underlying immunologic abnormality would explain not only the persistence of fetal cells in women with systemic sclerosis but also the occurrence of the disease in men and nulliparous women.

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The authors reply:

To the Editor: We agree with Drs. Connolly and McCalmont that the hypothesis that systemic sclerosis may be caused by a graft-versus-host–like reaction induced by retained fetal cells in the mother would not explain the pathogenesis of systemic sclerosis in all patients. We suggested that the passage of maternal cells across the placenta to the fetus during pregnancy or the retention of cells from prior blood transfusions may be an alternative mechanism for the acquisition of foreign cells. We also agree that there are substantial clinical and histopathological differences between systemic sclerosis and graft-versus-host disease, but they are similar in that tissue fibrosis and certain immunologic abnormalities in host tissues can be induced by chimeric cells from a graft. If fetal cells retained in the maternal circulation and tissues can initiate an attack on maternal tissues that leads to systemic sclerosis, as suggested by the hypothesis, the resultant clinical manifestations may well be different from those of graft-versus-host disease. Numerous factors could explain such differences, including the genetic susceptibility to systemic sclerosis, the effects of immunosuppressive drugs given to patients receiving organ transplants, and the possible contribution of environmental exposure to the pathogenesis of systemic sclerosis.

In response to the comments of Dr. Daniell, we believe that there are no conclusive clinical or laboratory data to support the concept that patients with systemic sclerosis are chronically immunosuppressed, unless they have received treatment with glucocorticoids or other immunosuppressive drugs.

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The Nephrotic Syndrome

To the Editor: In their review article, Orth and Ritz (April 23 issue)¹ state that membranous nephropathy is the most common cause of idiopathic nephrotic syndrome in adults, citing as a source data from a book published in 1988.² According to these data, summarized in Table 1 of the article, minimal-change nephropathy is the second most common cause of adult nephrotic syndrome, and focal segmental glomerulosclerosis is third, accounting for fewer than 15 percent of such cases. However, recent data from three separate groups³-⁵ indicate that over the past 25 years and particularly during the past decade, there has been a marked increase in the incidence of primary focal segmental glomerulosclerosis in adults, both overall and as a cause of the nephrotic syndrome. In the renal-biopsy practice at my institution, which processes over 500 native renal-biopsy specimens a year from more than 30 hospitals in the midwestern United States, and in the similarly busy practice of D’Agati based in New York City, focal segmental glomerulosclerosis is now the leading cause of idiopathic nephrotic syndrome in adults.³ In a recent study of the underlying causes of 233 cases of adult idiopathic nephrotic syndrome diagnosed from 1995 to 1997, my colleagues and I found that focal segmental glomeruloscle-
The cause of this increase in the frequency of primary focal segmental glomerulosclerosis is not known, though it is not related to a change in the racial composition of our patient population, to changes in our ability as pathologists to diagnose focal segmental glomerulosclerosis, or to changes in the size or processing of renal-biopsy specimens.

To the Editor: Orth and Ritz provide a lucid and comprehensive review of the nephrotic syndrome. They recommend the use of ultrafiltration in particularly severe cases. However, they do not include metolazone among the noninvasive treatment options available as an adjunct to loop and potassium-sparing diuretics.

The addition of metolazone to furosemide therapy can be helpful in the treatment of refractory edema in infants and children, leading to greater natriuresis, urinary output, and weight loss than is induced by furosemide alone. The use of metolazone is based on the principle of sequential nephron blockade, in which metolazone acts synergistically with a loop diuretic by preventing compensatory sodium retention in the early distal tubule. Thus, we believe there is a place for metolazone in the management of severe edema resistant to loop diuretics before extracorporeal techniques are employed.

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HIV-Protease Inhibitors

To the Editor: In his review of inhibitors of human immunodeficiency virus (HIV)—encoded protease (April 30 issue), Dr. Flexner states that ritonavir causes hypertriglyceridemia in no more than 5 percent of patients and has not caused pancreatitis. However, we found that of 52 patients treated with ritonavir for six months, 41 (79 percent) had caused pancreatitis. However, we found that of 52 patients treated with ritonavir for six months, 41 (79 percent) had

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hypertriglyceridemia (serum triglyceride concentration, >160 mg per deciliter [1.8 mmol per liter]), with values higher than 500 mg per deciliter (5.6 mmol per liter) in 22 patients (42 percent) and higher than 1000 mg per deciliter (11.3 mmol per liter) in 8 (15 percent). The risk varied as a function of the base-line serum triglyceride concentration. Among the 24 patients who had normal base-line concentrations, 5 (21 percent) had concentrations higher than 500 mg per deciliter (in at least one determination at month 1, 3, or 6), whereas 17 of the 28 patients (61 percent) with high concentrations before treatment had further increases during treatment. The risk of a serum triglyceride concentration higher than 1000 mg per deciliter during treatment was 4 percent in the group with normal base-line values and 25 percent in the group with elevated base-line values. Acute pancreatitis developed in two patients in the latter group (serum triglyceride concentrations, 1980 and 1880 mg per deciliter [22.4 and 21.2 mmol per liter]); it resolved with conventional medical management and the withdrawal of ritonavir. In both patients, the serum triglyceride concentration was less than 500 mg per deciliter within 10 days after the withdrawal of ritonavir.

We believe that serum triglyceride concentrations should be monitored in patients receiving ritonavir, especially those not in compliance (the average compliance rate was 69 percent of the person-years in the study were covered by screening, only about 50 percent of the cases detected among subjects in compliance with the requirements of the test, only about 10 percent were missed at the time of the screening. Although only half the cancers diagnosed during the trial were detected by screening, only about 50 percent of the person-years in the study were covered by screening. The majority of interval cancers occurred in those not in compliance (the average compliance rate was about 75 percent) or during a four-year hiatus when no screening was conducted. A screening test does not necessarily have to be highly sensitive to be effective, as long as its repetitive use reliably detects a neoplasm before it becomes incurable. Second, Simon states that the specificity of fecal occult-blood testing results in unnecessary colonoscopies and that modification of the tests has not improved their performance. However, it is important to maximize the sensitivity of screening tests in order to detect most potentially fatal cancers, even if it causes false positive results. Unlike screening for some other cancers, a false positive fecal occult-blood test is not without value. It results in a colonoscopy — a test many now promote for primary screening; it provides reassurance about the risk of this common cancer; and it obviates the need for further screening for up to 10 years. Third, Simon concludes that screening by fecal occult-blood testing is not cost effective. Although the cost of screening everyone would be high, it must be compared with the cost savings derived from detecting curable cancers and preventing cancers by resecting polyps. Using data from the Minnesota trial, economists calculated the cost of annual screening by fecal occult-blood testing to be $13,581 per year of life gained (not $35,000 to $40,000, as claimed by Dr. Simon).
Finally, Simon criticizes screening by fecal occult-blood testing because current compliance is low. It is not surprising that the studies he cites showed poor compliance, since they preceded the publication of the randomized studies showing efficacy. Now that virtually all guidelines in the United States recommend screening, educational campaigns to improve compliance are under way. Of all the options for screening, compliance with fecal occult-blood testing may be the easiest to achieve. In the Minnesota trial, for example, compliance with both repetitive screening and diagnostic evaluations exceeded 75 percent over a period of 15 years.

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Dr. Simon replies:

To the Editor: Bond and his colleagues raise important and valid points, but our perspectives on fecal occult-blood screening still differ.

Sophisticated analyses of the Minnesota trial have reached disparate conclusions about sensitivity1,2; in part, this reflects the conceptual distinction between the sensitivity of the individual test and the overall sensitivity of the screening program. Although I agree that even a relatively insensitive test can be effective if used repetitively, the broad literature clearly indicates that fecal testing misses a substantial proportion of cancers and the vast majority of neoplastic polyps.3

Furthermore, enhanced sensitivity comes at the price of weak specificity. In the Minnesota program, a mere 2 percent of positive hydrated occult-blood tests were positive owing to cancer (i.e., 98 percent were false positives).4 This extreme inefficiency imposes on the public an inordinate number of needless invasive colonic workups and is a huge waste of both human and economic resources. It is true that a normal colonoscopy precipitated by a false positive test obviates further screening for up to a decade, but surely it is much better not to have a false positive result in the first place. Bond et al. argue that it is important to maximize sensitivity, but I think it is equally or even more important to maximize specificity. I hope that technical advances will narrow the gap between us.

Cost effectiveness is a complex issue, and estimates of cost differ. Regardless of whether true costs are at the low or the high end of published estimates, a broad societal program of fecal occult-blood screening would require either a major shift of current medical resources or a major infusion of new resources—most of which would be consumed by invasive colonic evaluations based on false positive results. Whether this is justified is as much a philosophical issue as an economic one.

Compliance in the Minnesota trial was indeed relatively good, but this cannot be extrapolated to the general public, because the subjects in Minnesota were all recruited from volunteers for the American Cancer Society and other organizations.4 I acknowledged new educational campaigns to improve compliance, but the outcome of such efforts remains to be seen. The literature to date is generally pessimistic.

Bond and his colleagues have made landmark contributions, and I greatly respect their opinions. Their work and that of others make a strong case in favor of occult-blood screening. But there are also compelling contrary arguments—arguments that have not received the attention they deserve.

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or euthanasia, physicians said that they “believed that the request reflected the patient’s wishes.” This safeguard presumably refers to the stipulation in the Oregon law that the patient’s decision be voluntary and uncoerced. The survey did not determine, however, what efforts the physician made to find out whether this was so. Simple belief is not enough.

Belying such belief, and perhaps most disturbing in the survey, is the fact that, in 79 percent of cases, physicians who gave lethal injections to patients had received no direct request from the patients to do so. Meier has written elsewhere that the likelihood that such practices would increase with legalization and the fact that these practices cannot be regulated have led her to cease to favor legalization of assisted suicide or euthanasia.

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To the Editor: According to the survey by Meier et al., 97 percent of those who received prescriptions for a lethal dose of medication were men. This rate contrasts with that of the group who received a lethal injection, of which only 57 percent were men. For lethal injection, the request was more likely to be somewhat indirect or made by a family member, and the doctor–patient relationship was, in some cases, of very short duration. Although statistical probabilities are not reported, the differences based on sex are likely to be statistically significant and, at least for feminists, clinically significant; they should give us pause as we debate legalizing assisted suicide. How do the authors interpret these findings?

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The authors reply:

To the Editor: Contrary to Hendin’s assertion, nowhere in our article did we claim that Oregon’s Death with Dignity Act requires evidence of suffering by a patient as a safeguard. We did list (as a footnote to Table 4) that the law requires that a patient be an adult with a terminal illness and a life expectancy of less than six months, that the request be made by the patient, and that the request be voluntary. Our data suggest that the majority of patients who received a prescription for a lethal dose of medication met these requirements. Our national survey was conducted before the passage of the Oregon legislation; at that time, physician-assisted suicide was illegal in all 50 states. The fact that procedural safeguards (such as getting a second opinion) were not followed is not surprising. Since lethal injections are not permitted under the Oregon law, it is not appropriate to assess the conformit of the use of lethal injection with the legislation.

We do not know the reasons for the disparity between men and women in the proportions of patients receiving prescriptions for a lethal dose of medication (a weighted 97 percent were men). The survey contained data on only 36 patients who received such a prescription for whom sex was reported. The raw (unweighted) numbers show that two thirds (24 patients) were men. The weighted proportions are considerably more lopsided because the seven prescriptions written by general internists or family practitioners (groups of physicians whose responses were weighted more heavily to reflect their preponderance in the population of U.S. physicians) were all written for men. Given the low prevalence of such prescriptions in our study, it is uncertain whether the sex differences found were in fact true differences or whether they were an artifact of the statistical weighting necessary to analyze the survey. The raw data suggest that both assistance with suicide from a physician and euthanasia are more commonly requested and received by men, with men making up 60 to 66 percent of the patients described. Most, but not all, previous surveys have found a similar sex distribution. Possible explanations for this disparity are that women are less inclined to seek to hasten their own deaths, that they are uncomfortable asking their physicians (most of whom are men) for help, or some other factor or combination of factors.

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Global Distribution of Transfusion-Transmitted Virus

To the Editor: Transfusion-transmitted virus has recently been identified as a potential cause of post-transfusion non-A, non-B, non-C hepatitis. The virus has a single-stranded DNA genome whose organization is similar to those of the Paroviridae. Transient viremia due to transfusion-transmitted virus was detected by the polymerase chain reaction (PCR) in three patients six to eight weeks after the transfusion of blood components and coincided with modest elevations of alanine aminotransferase. It has been proposed that transfusion-transmitted virus is the chloroform-resistant non-A, non-B agent shown to cause transient alanine aminotransferase elevations in chimpanzees.
To understand more about the distribution of transfusion-transmitted virus infection, we investigated the prevalence of infection in a wide range of geographically separated human populations and among chimpanzees in Africa. Blood samples were obtained from people inhabiting equatorial forests in Ecuador, northern Brazil, and Papua New Guinea (Karkar Island) and from people living in predominantly rural, farming communities in Gedaref in eastern Sudan, the Lower River Division in the Gambia, around Lagos in Nigeria, and the Kinshasa region in the Democratic Republic of the Congo. Samples were obtained from blood donors in Karachi, Pakistan, and from wild animals in an area extending from Central Africa to West Africa. The samples had originally been collected for studies of other viruses and parasites.

Sequences of transfusion-transmitted virus were amplified by heminested PCR according to previously described conditions. Full precautions were taken to prevent contamination of the PCR, with primary and secondary reactions performed in separate laboratories and negative controls included with each set of samples.

We found high frequencies of viremia due to transfusion-transmitted virus in most of the study populations, with values ranging from 16 percent in Pakistan to 83 percent in the Gambia (Table 1). Transfusion-transmitted virus DNA sequences were also detected in one of the chimpanzees. Although Nishizawa et al. reported that infection with transfusion-transmitted virus was transient among blood recipients, the high frequencies of viremia that we found indicate that the infection can also be persistent. The mechanism by which infection can be maintained at such high frequencies and the routes of transmission are unclear. It is also difficult to assess the clinical significance of the infection and whether it causes disease without detailed clinical assessment or prospective longitudinal studies. However, the finding of transfusion-transmitted virus infection in such a large proportion of the study groups highlights the need for further investigations.

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Reforming Medicare: The Gramm Plan

To the Editor: Under the plan proposed by Gramm et al. (April 30 issue), uninsured workers would pay for current Medicare recipients and their own future benefits, but they still would have no current medical insurance. Why not have an investment-based Medicare system for all (“Americare”), so those who pay for the health care of others will be covered as well? As the most prosperous society in the world, we have the resources to provide universal health care. Do we have the wisdom and the will?

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that may well exceed 35 percent and a total tax burden on the younger generation in excess of 60 percent. If the younger generation is unwilling to give up that much to help their elders, any promises we have made to the baby boomers will remain just that—promises.

To gain control over this problem, we must accomplish two things. First, we must slow the continued increase in per capita health care expenditures; second, we must introduce a financing system that allows each generation to pay for its own retirement health care. These two parts of the problem are separable, and although converting Medicare to an investment-based system can hardly be called tinkering, no one would argue that rising health care costs are unimportant or that the existing system is not without its inefficiencies.

However, a reform effort with only a traditional focus on per capita costs is doomed to failure if Medicare’s basic financial structure is not put on a sound footing. The generational transfer system now used reduces the nation’s wealth and income. By moving to a system in which each generation prepay its retirement health care insurance, we will set in motion rising national wealth that will ultimately produce the additional national income that provides the doctors, nurses, pharmaceuticals, hospital beds, and other medical equipment that will be required by the baby-boom generation.

As for the currently uninsured, investment is the ideal method of preparing to pay for a large known future expense such as health care during retirement, but you do not earn compound interest when the principal is spent on the current consumption of health care. These are two separate problems and should be treated as such. The most important thing we can do to help the uninsured is to provide persons seeking to buy individual health insurance with the same tax break General Motors gets when it buys health insurance for its employees. This would reduce the cost of health insurance for such persons by as much as a third.

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