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### Global distribution of transfusion-transmitted virus

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## Correspondence



### 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.<sup>1-3</sup> Five echocardiologic surveys reviewed by the Food and Drug Administration suggested that the prevalence of cardiac-valve abnormalities is 30 to 38 percent among patients who have taken these drugs<sup>2</sup> 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 document 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.<sup>4</sup> Follow-up studies involving larger numbers of 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.

LAURALYN B. CANNISTRA, M.D.

ANTHONY J. CANNISTRA, M.D.

Brown University School of Medicine  
Providence, RI 02912

1. Connolly HM, Crary JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med* 1997;337:581-8. [Erratum, *N Engl J Med* 1997;337:1783.]
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### Fetal DNA and Cells in Women with Systemic Sclerosis

*To the Editor:* Artlett et al. (April 23 issue)<sup>1</sup> put forward the provocative hypothesis that systemic sclerosis may be

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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,<sup>2</sup> whereas systemic sclerosis does not.<sup>3</sup> Thus, the dissimilar clinical and pathological 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.

M. KARI CONNOLLY, M.D.  
TIMOTHY H. MCCALMONT, M.D.  
University of California, San Francisco  
San Francisco, CA 94143-0517

1. Artlett CM, Smith JB, Jimenez SA. Identification of fetal DNA and cells in skin lesions from women with systemic sclerosis. *N Engl J Med* 1998; 338:1186-91.
2. Sullivan KM, Witherspoon RP, Storb R, et al. Alternating-day cyclosporine and prednisone for treatment of high-risk chronic graft- $\nu$ -host disease. *Blood* 1988;72:555-61.
3. Pope JE. Treatment of systemic sclerosis. *Rheum Dis Clin North Am* 1996;22:893-907.

*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.

HARRY W. DANIELL, M.D.  
2626 Edith Ave.  
Redding, CA 96001

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.

CAROL M. ARTLETT, PH.D.  
J. BRUCE SMITH, M.D.  
SERGIO A. JIMENEZ, M.D.  
Thomas Jefferson University  
Philadelphia, PA 19107-5541

## The Nephrotic Syndrome

*To the Editor:* In their review article, Orth and Ritz (April 23 issue)<sup>1</sup> 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.<sup>2</sup> 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 groups<sup>3-5</sup> 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.<sup>3,5</sup> In a recent study of the underlying causes of 233 cases of adult idiopathic nephrotic syndrome diagnosed from 1995 to 1997,<sup>5</sup> my colleagues and I found that focal segmental glomeruloscle-

rosis was the cause in 35 percent of cases, membranous nephropathy in 33 percent, and minimal-change disease in 15 percent. Our data are similar to those of Korbet and coworkers.<sup>4</sup> Focal segmental glomerulosclerosis is particularly common in blacks, accounting for 56 percent of cases of idiopathic nephrotic syndrome in black adults and two thirds of such cases in black adults under the age of 45 years. In white adults, although membranous nephropathy remains the most common cause of idiopathic nephrotic syndrome (frequency, 38 percent), the relative frequency of focal segmental glomerulosclerosis as a primary nephropathy has more than doubled since the late 1970s, and it is now the second most common cause of idiopathic nephrotic syndrome in this group, accounting for 25 percent of cases.<sup>5</sup> 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.<sup>5</sup>

MARK HAAS, M.D., PH.D.  
University of Chicago  
Chicago, IL 60637-1470

1. Orth SR, Ritz E. The nephrotic syndrome. *N Engl J Med* 1998;338:1202-11.
2. Lewis EJ. Management of the nephrotic syndrome in adults. In: Cameron JS, Glasscock RJ, eds. *The nephrotic syndrome*. New York: Marcel Dekker, 1988;461-521.
3. D'Agati V. The many masks of focal segmental glomerulosclerosis. *Kidney Int* 1994;46:1223-41.
4. Korbet SM, Genchi RM, Borok RZ, Schwartz MM. The racial prevalence of glomerular lesions in nephrotic adults. *Am J Kidney Dis* 1996;27:647-51.
5. Haas M, Meehan SM, Karrison TG, Spargo BH. Changing etiologies of unexplained adult nephrotic syndrome: a comparison of renal biopsy findings from 1976-1979 and 1995-1997. *Am J Kidney Dis* 1997;30:621-31.

*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.<sup>2</sup> 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.

ZOHAR BARZILAY, M.D.  
GIDEON PARET, M.D.  
Chaim Sheba Medical Center  
Tel-Hashomer 52621, Israel

1. Garin EH. A comparison of combinations of diuretics in nephrotic edema. *Am J Dis Child* 1987;141:769-71.
2. Arnold WC. Efficacy of metolazone and furosemide in children with furosemide-resistant edema. *Pediatrics* 1984;74:872-5.

The authors and a colleague reply:

*To the Editor:* We are aware of the report by Haas et al.<sup>1</sup> and similar reports<sup>2-4</sup> of a trend toward an increase in the frequency of focal segmental glomerulosclerosis in recent decades. The report by Haas et al. was published after our article had been completed, and we thought that without some comment and discussion, it might have been misleading to make a global statement about focal segmental glomerulosclerosis as the number-one cause of the nephrotic syndrome. Haas et al.<sup>1</sup> reported that in the past two decades the proportion of patients with focal segmental glomerulosclerosis and IgA glomerulonephritis among patients undergoing renal biopsy for the nephrotic syndrome has increased. Among black adults with the nephrotic syndrome, 56 percent had focal segmental glomerulosclerosis, whereas the respective value among white adults was 25 percent.<sup>1</sup> The findings of Haas et al.<sup>1</sup> are in agreement with our observation that among patients who underwent renal biopsy for the nephrotic syndrome in 1997, 30.5 percent had membranous glomerulonephritis, 19.4 percent had focal segmental glomerulosclerosis, and 11.1 percent had minimal-change glomerulonephropathy.

Drs. Barzilay and Paret correctly point out that natriuresis is enhanced by sequential blockade of the nephron — i.e., of the ascending thick loop of Henle with loop diuretics and the distal tubule with thiazides, possibly in combination with potassium-sparing diuretics. We could show this effect even in patients with advanced renal failure.<sup>5</sup> Metolazone, although chemically not characterized by a thiazide ring system, is a diuretic acting at the thiazide-sensitive distal site and thus fits into the scheme of sequential nephron blockade that we had proposed. We thank Drs. Barzilay and Paret, however, since this simple method of increasing diuretic potency is not widely known and is even less widely used.

STEPHAN R. ORTH, M.D.  
IVAN RYCHLIK, M.D.  
EBERHARD RITZ, M.D.  
Ruperto Carola University  
69115 Heidelberg, Germany

1. Haas M, Meehan SM, Karrison TG, Spargo BH. Changing etiologies of unexplained adult nephrotic syndrome: a comparison of renal biopsy findings from 1976-1979 and 1995-1997. *Am J Kidney Dis* 1997;30:621-31.
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4. Braden G, Mulhern J, O'Shea M, Germain M, Nash S, Ucci A. Changing incidence of idiopathic glomerular diseases in adults. *J Am Soc Nephrol* 1995;6:413. abstract.
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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),<sup>1</sup> 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

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 who have elevated concentrations at base line, and that the drug should be discontinued if the value exceeds 1000 mg per deciliter.

GIOVANNI DI PERRI, M.D., D.T.M.&H., PH.D.  
PAOLA DEL BRAVO, M.D.  
ERCOLE CONCIA, M.D.  
University of Verona  
37126 Verona, Italy

1. Flexner C. HIV-protease inhibitors. *N Engl J Med* 1998;338:1281-92.

*To the Editor:* Flexner's review of HIV-protease inhibitors clearly explains how these drugs work and describes the properties of the various protease inhibitors. However, the references to the protease inhibitor saquinavir do not explicitly differentiate between the two available formulations of saquinavir: Fortovase and Invirase. Fortovase, a new, soft-gel formulation of saquinavir, is more potent than Invirase. Physicians treating their patients with saquinavir should prescribe Fortovase.

In addition, two statements in the article concerning saquinavir need to be clarified. In Table 1, the dose of saquinavir is given as 600 mg three times a day. That dose is for Invirase. The dose of Fortovase is 1200 mg three times a day. (Fortovase, like other protease inhibitors, is recommended for use in combination with two nucleoside analogues.) The same table lists saquinavir's bioavailability as less than 4 percent, a figure that also applies only to Invirase. The bioavailability of Fortovase is substantially higher than that of Invirase. For physicians who want more information about Fortovase, Hoffmann-LaRoche has a toll-free information number (800-526-6367) staffed by health care experts knowledgeable about all aspects of the drug's use.

SANDRA PALLEJA, M.D.  
Hoffmann-LaRoche  
Nutley, NJ 07110-1199

Dr. Flexner replies:

*To the Editor:* I appreciate the report by Di Perri and colleagues about the prevalence of hypertriglyceridemia in patients treated with ritonavir. It would be helpful to know whether the two patients in whom pancreatitis developed had other risk factors for it. Although the authors recommend that ritonavir be discontinued in all patients with serum triglyceride concentrations exceeding 1000 mg per deciliter (11.3 mmol per liter), in some patients, hypertriglyceridemia may be tolerated and the benefit of continued ritonavir therapy may outweigh the risk of pancreatitis.

I acknowledge Dr. Palleja's comments on the difference between the two commercially available formulations of saquinavir. The Fortovase formulation became available while the article was in press and therefore was not included in the table of pharmacokinetic properties.

CHARLES W. FLEXNER, M.D.

Johns Hopkins University School of Medicine  
Baltimore, MD 21287-5554

### Role of Fecal Occult-Blood Testing

*To the Editor:* Simon's argument against population screening for colorectal cancer by fecal occult-blood testing (April 16 issue)<sup>1</sup> contains inaccurate conclusions related to our Minnesota screening trial.<sup>2</sup> First, he concludes that the fecal occult-blood test has limited sensitivity. An analysis of the sensitivity of individual screening tests and of repetitive screening in our trial shows that 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.<sup>3</sup> 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.<sup>3</sup>

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).<sup>4</sup>

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.

JOHN H. BOND, M.D.  
JACK S. MANDEL, PH.D.  
TIMOTHY R. CHURCH, PH.D.  
University of Minnesota, Minneapolis  
Minneapolis, MN 55455

1. Simon JB. Should all people over the age of 50 have regular fecal occult-blood tests? Postpone population screening until problems are solved. *N Engl J Med* 1998;338:1151-2.
2. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. *N Engl J Med* 1993;328:1365-71. [Erratum, *N Engl J Med* 1993;329:672.]
3. Church TR, Ederer F, Mandel JS. Fecal occult blood screening in the Minnesota study: sensitivity of the screening test. *J Natl Cancer Inst* 1997;89:1440-8.
4. Wagner JL, Tunis S, Brown M, Ching A, Almeida R. Cost-effectiveness of colorectal cancer screening in average-risk adults. In: Young GP, Rozen P, Levin B, eds. *Prevention and early detection of colorectal cancer*. London: W.B. Saunders, 1996:321-56.

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 sensitivity<sup>1,2</sup>; 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.<sup>3</sup>

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).<sup>4</sup> 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.<sup>4</sup> 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.

JEROME B. SIMON, M.D.  
Queens University  
Kingston, ON K7L 5G2, Canada

1. Church TR, Ederer F, Mandel JS. Fecal occult blood screening in the Minnesota study: sensitivity of the screening test. *J Natl Cancer Inst* 1997;89:1440-8.
2. Pignone M, Ransohoff DE. New concepts to understand sensitivity in fecal occult blood testing. *Gastroenterology* 1997;112:A639. abstract.
3. Simon JB. Fecal occult blood testing: clinical value and limitations. *Gastroenterologist* 1998;6:66-78.
4. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. *N Engl J Med* 1993;328:1365-71. [Erratum, *N Engl J Med* 1993;329:672.]

## Physician-Assisted Suicide and Euthanasia in the United States

*To the Editor:* The article by Meier et al. (April 23 issue)<sup>1</sup> on physician-assisted suicide and euthanasia in the United States contains somewhat misleading information about the Oregon law on assisted suicide. The authors say that the majority of patients to whom physicians gave prescriptions to assist them in suicide would have met the criteria of the Oregon law's regulatory safeguards for this practice. They list such criteria as the patient's age and prognosis, the presence of a repeated request, the physician's belief that the request reflected the patient's wishes, consultation with another physician, and the presence of a group of clinical symptoms such as severe discomfort, pain, dependence on others, and being bedridden.

The Oregon law, unlike Dutch law, does not regard suffering as a requirement for assisted suicide and refers to no clinical symptoms. That the patient must be over 18 years of age and have a terminal illness with a prognosis of less than six months' survival are statutory requirements of the law, not safeguards. A repeated request is such a safeguard, but only half the patients receiving prescriptions in the survey by Meier et al. met that requirement. Obtaining a second opinion is another safeguard, but fewer than 1 percent of physicians who assisted in suicide obtained such an opinion.

Euthanasia is prohibited by the Oregon law, so none of the 4.7 percent of physicians who gave lethal injections were in compliance with the law. In all cases of assisted suicide

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<sup>2</sup> and the fact that these practices cannot be regulated have led her to cease to favor legalization of assisted suicide or euthanasia.<sup>3</sup>

HERBERT HENDIN, M.D.

American Foundation for Suicide Prevention  
New York, NY 10005

1. Meier DE, Emmons C-A, Wallenstein S, Quill T, Morrison RS, Cassel CK. A national survey of physician-assisted suicide and euthanasia in the United States. *N Engl J Med* 1998;338:1193-201.
2. Hendin H. Seduced by death: doctors, patients, and assisted suicide. New York: W.W. Norton, 1998.
3. Meier D. A change of heart on assisted suicide. *New York Times*. April 24, 1998.

*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?

SUSAN DORR GOOLD, M.D.

University of Michigan  
Ann Arbor, MI 48109-0376

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<sup>1</sup> 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 conformity 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,<sup>2-4</sup> but not all,<sup>5</sup> 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.

DIANE E. MEIER, M.D.

R. SEAN MORRISON, M.D.

SYLVAN WALLENSTEIN, PH.D.

Mount Sinai School of Medicine  
New York, NY 10029

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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.<sup>1</sup> The virus has a single-stranded DNA genome whose organization is similar to those of members of the Parvoviridae.<sup>2</sup> 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.<sup>3</sup>

**TABLE 1.** VIREMIA DUE TO FREQUENCY OF TRANSFUSION-TRANSMITTED VIRUS ON PCR TESTING IN VARIOUS GROUPS.

COUNTRY*	SUBJECTS	VIREMIA	
		NO. POSITIVE/ TOTAL NO. TESTED	PREVALENCE (%)
Scotland	Blood donors	19/1000	1.9
Japan	Blood donors	34/290	12
Pakistan	Blood donors	25/45 pools of 5	16†
Sudan	Rural people	5/70	7
Nigeria	Rural, periurban people	32/63	51
The Gambia	Rural people	63/76	83
Congo	Rural people	32/72	44
Papua New Guinea	Indigenous rural people	51/69	74
Ecuador	Indigenous rural people	57/96	59
Brazil	Indigenous rural people	18/91	20
Central and West Africa	Chimpanzees	1/31	3

\*Data on subjects from Scotland and Japan have been reported previously.<sup>2,4</sup>

†The samples were mixed in pools of five and tested by PCR. To allow for the possibility that some pools might contain more than one positive sample, the prevalence was calculated from the adjusted frequency  $f$ , according to the following Poisson relation:  $f = -\ln(f_0)$ , where  $f_0$  is the frequency of negative pools.

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.<sup>2</sup> 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,<sup>1</sup> the high frequencies of viremia that we found indicate that the infection can also be per-

sistent. 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.

LINDA E. PRESCOTT, PH.D.  
PETER SIMMONDS, M.R.C.PATH.  
University of Edinburgh  
Edinburgh, EH8 9AG, United Kingdom  
AND INTERNATIONAL COLLABORATORS

(The international collaborators were Professor D.I. Pritchard, University of Nottingham, Nottingham, United Kingdom; Dr. D.E. Arnot and Dr. E.M. Riley, University of Edinburgh, Edinburgh, United Kingdom; Dr. B.M. Greenwood, Medical Research Council Laboratories, Fajara, the Gambia; Dr. S. Hamid, Aga Khan University, Karachi, Pakistan; Dr. M.O. McClure, St. Mary's Hospital, London; Dr. J.C.M. Lewis, International Zoo Veterinary Group, Keighley, United Kingdom, and Dr. J. Mokili, University of Edinburgh, Edinburgh, United Kingdom.)

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## Reforming Medicare: The Gramm Plan

*To the Editor:* Under the plan proposed by Gramm et al. (April 30 issue),<sup>1</sup> 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?

GERALD FRANKEL, M.D.  
1441 Redbud Blvd.  
McKinney, TX 75069

1. Gramm P, Rettenmaier AJ, Saving TR. Medicare policy for future generations — a search for a permanent solution. *N Engl J Med* 1998;338:1307-10.

*To the Editor:* Senator Gramm's proposed health care policy is flawed because it is based on three false assumptions. The first false assumption, shared by many, is that the goal is to save Medicare. Medicare began as a stopgap



political compromise and has become a patient-provider obstacle course that encourages profit taking with one hand and ratchets down revenues with the other. The policy makers' goal should not be to save such a system. Rather, the goal should be to preserve health care benefits for people now turning 65 whose contributions to Medicare have already been spent in the current transfer-payment financing model. The best way to do that is not simply to tinker with a system begging to be fundamentally changed.

The second false assumption is that health care policy is a unidimensional issue. There is much more to reforming health care than just finding a financing mechanism agreeable to a variety of interests. For example, it is time to "follow the money" spent on health care. If one runs water through one end of a hose at a steady high pressure and only a trickle of water comes out the other end of the hose, one knows to look for a hole in the hose. There is such a leak in Medicare. The current system is characterized as much by expenditures on financial, legal, and political maneuvering as by spending what it takes to provide dependable, affordable health care services to an aging population.

The third false assumption is that health care is the right only of Medicare beneficiaries and insurance beneficiaries. In every other major nation in the world, health care is considered a customary right of citizenship, however flawed the systems by which those countries try to fulfill that principle. The common mistake is to believe that this is because other countries have more of a social conscience than we do in the United States. But the economic reality is that those countries appreciate what we have apparently not yet discovered — that is, like it or not, failing to meet the needs of entire populations results in increased health care costs for the entitled few.

RICHARD E. THOMPSON, M.D.  
1975 Orange Ct.  
Palm Harbor, FL 34683

The authors reply:

*To the Editor:* Providing health care for the aged involves real resources, and because we have elected to finance the purchase of these resources by transferring income from the working generation to the retired generation, we are at the mercy of demographics. The tax rates that will be required to allow the baby boomers to consume health care at the current per capita rate will result in payroll taxes

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 prepays 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.

PHIL GRAMM  
U.S. Senate  
Washington, DC 20510

ANDREW J. RETTENMAIER, PH.D.  
THOMAS R. SAVING, PH.D.  
Texas A&M University  
College Station, TX 77843

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