

Correspondence



Therapeutic Cloning

To the Editor: In the May 16 issue, three articles deal with public policy on stem-cell research.¹⁻³ The authors of all three articles agree that reproductive cloning should be banned but that research on therapeutic cloning (i.e., nuclear transplantation to produce human embryos as sources of stem cells) should be permitted. Annas justifies this compromise politically as the only way to avoid the dangers of unrestrained research.¹ Evers thinks that abuses could be prevented if European and other models of regulation were globalized.² Weissman suggests that scientists are best qualified to make informed decisions on the matter because of their ability to understand fully the potential benefits of scientific and medical research.³

We find these articles seriously inadequate. Each fails to devote sufficient attention to the inevitable death of the human embryo when the embryo's stem cells are harvested. Millions of Americans do not accept the utilitarian argument that the potential benefits of research cloning justify the intentional destruction of the embryo. Yet Weissman and others seek to dispel concern about embryonic sacrifice with the simple protest that preventing embryonic destruction would impede medical research and thereby rob people of the means to improve and prolong their lives.³

Approaches to the formation of public policy that esteem scientific potential but fail to give sufficient weight to all basic ethical considerations are profoundly troubling, and attempts to dismiss those who oppose embryonic destruction simply by pointing to the good that may result are chilling. Although we applaud the desire to pursue therapies for human afflictions, a utilitarian perspective that allows science and medicine to trump ethics in the name of furthering medical benefits is exceedingly dangerous and will eventu-

ally have grave consequences. Any serious consideration of the issues raised by research cloning must engage all basic ethical arguments against such a prospect, rather than merely dismiss them or regard them as secondary in importance.

Inclusion in the *Journal* of material that grapples seriously with the often-neglected ethical issues raised by research cloning would have resulted in a better assessment of this highly contentious topic. The Center for Bioethics and Human Dignity and Georgetown's Center for Clinical Bioethics offer such material^{4,5} — not to hold back science but to encourage it to proceed in an ethical fashion. Our society must not subjugate basic ethical considerations to scientific and medical progress, lest we all become subjects mastered by our own technological prowess.

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1. Annas GJ. Cloning and the U.S. Congress. *N Engl J Med* 2002;346:1599-602.

2. Evers K. European perspectives on therapeutic cloning. *N Engl J Med* 2002;346:1579-82.

3. Weissman IL. Stem cells — scientific, medical, and political issues. *N Engl J Med* 2002;346:1576-9.

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4. CBHD home page. Bannockburn, Ill.: Center for Bioethics and Human Dignity, 2002. (Accessed October 11, 2002, at <http://www.cbhd.org>.)
5. Edmund Pellegrino's June 2000 testimony before the National Bioethics Advisory Commission. In: Ethical issues in human stem cell research. Vol. 3. Rockville, Md.: National Bioethics Advisory Commission, 2000:F3-F5.

To the Editor: As a member of the President's Council on Bioethics, I wish to note several problems with Dr. Weissman's treatment of the moral questions involved in research cloning. My comments are mine alone and are not made in the name of the council or its other members. First, as he did in his testimony before the council, Dr. Weissman makes wide-ranging claims about the nature of moral responsibility, especially responsibility for suffering if one opposes research cloning. These assertions are lacking in the complexities of moral theory.

Second, the attempt to characterize research cloning as the entirely different act of nuclear transplantation to produce stem cells is an astonishing example of what we try to teach students to avoid: winning arguments by manipulation of language. In his testimony before the council, Dr. Weissman was unable to defend this language in the face of critical questions, and it ill behooves one who is willing to manipulate language to wrap himself in the cloak of "objectivity."

Finally, I, for example, have no financial stake in this argument. Whether research cloning is permitted or prohibited will make absolutely no difference to my personal income. Those who cannot say the same are perhaps not in a position to lecture others on the moral meaning of objectivity.

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To the Editor: Annas says, "If no bill is enacted, cloning will remain unregulated." We may first observe that good moral reasons obtain for allowing nonprocreative cloning.¹ We may also observe that the Food and Drug Administration (FDA) has given force to a scientific consensus by declaring that "clinical research using cloning technology to clone a human being" may not proceed without an investigational-new-drug application, and that, given "unresolved safety questions," the FDA "would not permit any such investigation to proceed."² Notified of the FDA's policy, even mavericks have forsaken procreative cloning within U.S. borders. Someone might argue that the "cellular products" espied by the FDA in procreative cloning are not "biological products" or "drugs," and that the FDA therefore lacks jurisdiction, but unless a court adopts that argument, anyone who attempts procreative cloning risks prosecution.³ Hence the likely incidence of procreative cloning by U.S. providers seems nil.

It is possible to imagine the emergence of procreative cloning technology that the FDA does not deem unsafe. In that event, a legislative ban would not be superfluous. But neither would a ban's justification be obvious. To beget a child is the quintessential liberty protected from governmental intrusion by the constitutional right of privacy. The proponent of a ban implies that even if other instances of impregnation are private in the sense of inviolable, cloning is not. The proponent's burden would be to adduce convinc-

ing nonsafety reasons — thus far we have heard mostly genetic deterministic and other speculations about clones' lives — that warrant this view of privacy.

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1. Guenin LM. Testimony before Subcommittee on Health, Committee on Energy and Commerce, U.S. House of Representatives, June 20, 2001. (Accessed October 24, 2002, at <http://energycommerce.house.gov/107/hearings/06202001Hearing291/Guenin452.htm>.)
2. Zoon KC. Letter to associations — cloning technologies. Rockville, Md.: FDA Center for Biologics Evaluation and Research, March 28, 2001. (Accessed October 24, 2002, at <http://www.fda.gov/cber/ltr/aacclone.htm>.)
3. FDA Associate Commissioner for Legislation. Letter to Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, U.S. House of Representatives, May 18, 2001.

To the Editor: Dr. Evers's review of European perspectives on therapeutic cloning gives the impression that the United Kingdom's controls are wholly based on the opinions of national ethics committees or research councils. This is incorrect. The United Kingdom has one of the most comprehensive sets of legislation on this matter in the world.

All human-embryo research is regulated by the Human Fertilisation and Embryology Authority under the Human Fertilisation and Embryology Act 1990. Such research is permitted only for the purposes set out in the 1990 act and then only if strict conditions are met and a license has been issued by the Human Fertilisation and Embryology Authority.

In August 2000, my expert group issued its report on stem-cell research.¹ The government of the United Kingdom subsequently introduced legislation — the Human Fertilisation and Embryology (Research Purposes) Regulations 2001 — in order to extend the permitted purposes of human-embryo research to include research into serious diseases.

Last year, the government of the United Kingdom specifically banned human reproductive cloning with the Human Reproductive Cloning Act 2001. It is now a criminal offense, punishable by up to 10 years in prison or an unlimited fine, to place in a woman an embryo created by any means other than fertilization.

The strong regulatory system in the United Kingdom, based on many years of discussion of the ethical issues, provides an appropriate balance, allowing medicine to gain the potential benefits of this technology while preventing its abuse through legislation.

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1. Chief Medical Officer's Expert Advisory Group on Therapeutic Cloning. Stem cell research: medical progress with responsibility. London: Department of Health, August 2000. (Accessed October 24, 2002, at <http://www.doh.gov.uk/cegc/>.)

To the Editor: Evers writes, "It is a fundamental tenet in many European cultures that humans shall not be treated merely as the means to an end but also as ends in them-

selves." I do not know of any Western culture where humans do not always have to be treated as ends in themselves. Under some special circumstances, humans are being abused as the means to an end, and some people accept the treatment of humans as such for a presumptive higher goal.

Concerning the issue of protection from abuse, Evers writes, "In order for such a regulation to be more than yet another . . . toothless declaration, the rules must be backed up by an internationally representative body with the mandate to issue sanctions." If science is to wait for this to happen before cloning commences — which is a *sine qua non* according to Evers — there is no need to be afraid. History teaches that this will never be the case.

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Dr. Weissman replies:

To the Editor: Pellegrino et al. claim that in my article on stem-cell research, I "suggest that scientists are best qualified to make informed decisions on the matter. . . ." I do not. I suggest that all parties in the debate should be sure of their facts, and I present four kinds of research that could not be done with the 64 approved human embryonic stem-cell lines or adult stem cells. There are many ways to view the relevant ethical, moral, political, legal, and religious issues. I say so in my Sounding Board article¹ and in the National Academies Panel I report.² In a pluralistic society, these issues need to be debated, especially when used for the determination of policy. But when groups make scientific and medical claims that are misleading, we have the obligation to clarify the facts. For example, the group Do No Harm, which includes Dr. FitzGerald, wrote to National Institutes of Health Director Ruth Kirschstein to state its opposition to human nuclear transfer, citing 228 reports on studies showing that adult stem cells of one tissue type could transdifferentiate to tissue of another type. None of the studies began with known human stem cells and proved transdifferentiation.

I recognize that my opinions outside my scientific and medical expertise are no better and no worse than those of any other self-described bioethicist. I presented information about the medical and scientific issues largely ignored in this debate. What if we had banned recombinant-DNA research because many bioethicists believed it was not our right to create a new form of life? By now thousands of patients have benefited from the products of that research.

Meilaender claims from his position as a moral philosopher and theologian that I would not pass muster in his field but cites no specific examples of my failures. It is clear that he is using arguments only about me, not about the issues. I did not make wide-ranging claims about the nature of moral responsibility, especially responsibility for suffering if one opposes research cloning, nor did I manipulate the language beyond the accepted terminology of two independent panels of the National Academies. My comments concerned the scientific and medical aspects of these issues, and I tried to point out what would be lost if a research ban were imposed. I refer readers to the transcripts of my testimony to the

President's Council on Bioethics to judge the merits of the arguments and facts. Finally, as I disclosed to Meilaender and the council, if research cloning is permitted, it will not increase my personal income; I have interests only in adult-stem-cell companies.

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1. Weissman IL. Stem cells — scientific, medical, and political issues.

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2. Committee on Science, Engineering, and Public Policy. Scientific and medical aspects of human reproductive cloning. Washington, D.C.: National Academy Press, 2002.

Dr. Evers replies:

To the Editor: Pellegrino et al. warn that societies should not "subjugate basic ethical considerations to scientific and medical progress" and "allow science and medicine to trump ethics in the name of furthering medical benefits." I am not under the impression that any of the articles discussed recommends any such thing. From their different viewpoints, the articles suggest that it may be more ethical to proceed with therapeutic cloning than not to proceed with it. In so doing, they put forward various ethical arguments, which is not to trump ethics. Pellegrino et al. may not agree with these arguments, but they fail to offer substantial objections from which an interesting discussion could ensue. They use emotionally laden expressions such as "embryonic sacrifice" with "chilling" results and refer to "grave consequences" that are "exceedingly dangerous" and unacceptable to "millions of Americans," but no further details are provided. It is important to remember that in order to ensure that science and medicine proceed in an ethical manner, ethics must be based on sound, substantial, and rational arguments.

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Professor Annas replies:

To the Editor: The key point made in my article was that enacting legislation on cloning in the United States would politically require treating the use of research cloning to make drugs differently from the use of asexual reproductive cloning to make children. The President's Council on Bioethics has since also come to this conclusion, with the majority of the council recommending a ban on reproductive cloning but only a moratorium on research cloning.¹ President George W. Bush has not yet commented publicly on his council's recommendation. None of the competing bills outlined in my article reached the floor of the U.S. Senate this summer, and even if the President strongly encourages a compromise along the lines suggested by his Council on Bioethics, no cloning law is likely to be enacted this year.

Guenin apparently disagrees that this leaves reproductive

cloning unregulated, because he thinks the FDA has jurisdiction over it. I think he is wrong about this, for three reasons. First, babies are not medicine, drugs or devices, or even “cellular products,” and the FDA has no jurisdiction over either human reproduction or the practice of medicine. Second, the FDA, as its foray into tobacco regulation demonstrates, does not obtain jurisdiction simply by asserting it. Third, there is no practical way to separate safety from efficacy in reproductive cloning: tests of both would require the birth of a cloned child. Rules for phase I drug-safety trials have no meaning in the context of human reproduction. You can inject a small amount of an investigational drug; you cannot be just a little pregnant.

Finally, Guenin’s suggestion that reproductive cloning would be constitutionally protected if the FDA found it safe is unpersuasive not only because safety could never be ethically demonstrated, but also because asexual reproduction is so different from sexual reproduction that the U.S. Constitution need not protect it, even though the Constitution continues to protect sexual reproduction.² Those who want to protect children by outlawing asexual human reproductive cloning are not the genetic determinists; rather the determinists are those who believe that the only child likely to be worthy of their aspirations is a genetic duplicate of an existing person.

I agree with Pellegrino et al. that their ethical arguments deserve serious consideration. But agreement with them would require, among other things, that in vitro fertilization itself be banned, at least unless no “spare embryos” were created that might ultimately be destroyed. I think this goes too far and, like the majority of the President’s Council on Bioethics, cannot agree that human embryos must be treated the same as human children.¹ Protecting children, however, does require an effective international treaty banning human reproductive cloning, and the United States will have to outlaw reproductive cloning before it can assume a leadership role in this effort.²

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1. Human cloning and human dignity: an ethical inquiry. Washington, D.C.: President’s Council on Bioethics, July 2002. (Accessed October 24, 2002, at <http://www.bioethics.gov/cloningreport/>)

2. Annas GJ, Andrews LB, Isasi RM. Protecting the endangered human: toward an international treaty prohibiting cloning and inheritable alterations. *Am J Law Med* 2002;28:151-78.

Osteoprotegerin Deficiency and Juvenile Paget’s Disease

To the Editor: Whyte et al. (July 18 issue)¹ report that homozygous deletion of the gene encoding osteoprotegerin is a potential cause of juvenile Paget’s disease in some Navajo patients. A deficiency of osteoprotegerin leads to unopposed effects of its ligand, receptor activator of nuclear factor κ B (RANK) ligand, resulting in enhanced osteoclastic bone resorption and profound bone loss. Since osteoprotegerin also serves as a receptor antagonist for tumor necrosis factor–related apoptosis-inducing ligand (TRAIL),²

one cannot rule out the possibility that excessive TRAIL effects contributed to the skeletal phenotype.

Increased susceptibility to infectious and cardiovascular diseases in patients with juvenile Paget’s disease — Patient 2 died from pneumonia and heart failure — may reflect the crucial role of RANK ligand and osteoprotegerin in immune³ and vascular⁴ function. In support of this hypothesis, one must note that serum osteoprotegerin levels have been shown to correlate with cardiovascular mortality in elderly women.⁵ The increased prevalence of cardiovascular diseases in the Navajo population may, at least in part, be due to abnormalities of the RANK ligand–osteoprotegerin system.

Finally, the findings of elevated levels of soluble RANK ligand in Patient 1 (Fig. 4 of the article) might be explained by the characteristics of the assay that was used (that of Biomedica Gruppe), which specifically detects free soluble RANK ligand but not any soluble RANK ligand that is bound to osteoprotegerin. Thus, in these patients with homozygous deletion of osteoprotegerin, no osteoprotegerin protein interferes with the measurement of soluble RANK ligand, which results in a false elevation of soluble RANK ligand protein levels.

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1. Whyte MP, Obrecht SE, Finnegan PM, et al. Osteoprotegerin deficiency and juvenile Paget’s disease. *N Engl J Med* 2002;347:175-84.

2. Emery JG, McDonnell P, Burke MB, et al. Osteoprotegerin is a receptor for the cytotoxic ligand TRAIL. *J Biol Chem* 1998;273:14363-7.

3. Kong Y-Y, Boyle WJ, Penninger JM. Osteoprotegerin ligand: a regulator of immune responses and bone physiology. *Immunol Today* 2000;21:495-502.

4. Hofbauer LC, Schoppet M. Osteoprotegerin: a link between osteoporosis and arterial calcification? *Lancet* 2001;358:257-9.

5. Browner WS, Lui LY, Cummings SR. Associations of serum osteoprotegerin levels with diabetes, stroke, bone density, fractures, and mortality in elderly women. *J Clin Endocrinol Metab* 2001;86:631-7.

The authors reply:

To the Editor: Unequivocal evidence now shows that osteoprotegerin deficiency causes juvenile Paget’s disease. After our article was published, Cundy et al.¹ reported an in-frame, 3-bp, homozygous deletion in exon 3 of *TNFRSF11B* in siblings of Iraqi origin whose parents were consanguineous and who manifested a hyperphosphatasia phenotype. Furthermore, we discovered deactivating, homozygous *TNFRSF11B* defects in three more inbred families with juvenile Paget’s disease (unpublished data).

Regarding the points made by Drs. Hofbauer and Schoppet, we speculated that phenotypic variation among the extremely rare heritable disorders that activate the osteoprotegerin/osteoclast differentiation factor (RANK ligand)/RANK/nuclear factor- κ B signaling pathway reflects the effect of additional factors. If osteoprotegerin does indeed act as a decoy for TRAIL,² excessive TRAIL effects could influence the juvenile Paget’s phenotype.

Although there is evidence that osteoprotegerin and RANK ligand act in the immune and vascular systems, pro-



Figure 1. Anteroposterior Radiograph of Patient 2 at 15 Years of Age (11 Years before Death) Showing Profound Osteopenia and Marked Skeletal Deformity.

gressive skeletal deformity probably explains the pneumonia and cardiopulmonary collapse that led to the death of Patient 2 (Fig. 1). Furthermore, it is unlikely that a deficiency of osteoprotegerin accounts for any significant predisposition of the Navajo population to cardiovascular disease. We hope to investigate the prevalence of heterozygotes among Navajos directly by searching for the *TNFRSF11B* deletion in representative samples of DNA. However, on the basis of census information for Native Americans,³ Hardy-Weinberg equilibrium⁴ predicts that only approximately 1 percent of Navajos are carriers of juvenile Paget's disease.

A deficiency of osteoprotegerin and high levels of RANK ligand were detected in the serum of Patient 1 with the use of the enzyme immunoassays from Biomedica. The kit we used measures soluble RANK ligand that is not in complex (not bound to osteoprotegerin). The procedure did not give a "false elevation" of the RANK-ligand level in our osteoprotegerin-deficient patient, but rather correctly quantitated a marked increase in free RANK ligand that could contribute to the skeletal disease of Navajos with juvenile Paget's disease.

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2. Emery JG, McDonnell P, Burke MB, et al. Osteoprotegerin is a receptor for the cytotoxic ligand TRAIL. *J Biol Chem* 1998;273:14363-7.
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4. Holsinger KE. Hardy-Weinberg law. In: Brenner S, Miller JH, eds. *Encyclopedia of genetics*. Vol. 2. San Diego, Calif.: Academic Press, 2002: 912-4.

Lansoprazole for the Prevention of Recurrences of Ulcer Complications from Long-Term Low-Dose Aspirin

To the Editor: Lai et al. (June 27 issue)¹ report that lansoprazole after the eradication of *Helicobacter pylori* was significantly better than eradication alone in decreasing the risk of recurrence of ulcer complications in patients with long-term low-dose aspirin use. In their study, 61 patients were randomly assigned to receive placebo after therapy to eradicate *H. pylori*, and 9 of these patients had further ulcer complications. It appears, however, that four of the nine patients were reinfected with *H. pylori*, and an additional two patients took other nonsteroidal antiinflammatory drugs. If these 6 patients are excluded from the analysis, is there still a statistically significant difference (3 of 61 vs. 1 of 62 patients) in the recurrence of ulcer complications between the two treatment groups? If not, then the findings of Lai et al. are in keeping with the data published by Chan et al.,² who reported that eradication of *H. pylori* is equivalent to treatment with omeprazole in preventing recurrent ulcer complications in patients with long-term low-dose aspirin use.

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1. Lai KC, Lam SK, Chu KM, et al. Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. *N Engl J Med* 2002;346:2033-8.
2. Chan FKL, Chung SCS, Suen BY, et al. Preventing recurrent upper gastrointestinal bleeding in patients with *Helicobacter pylori* infection who are taking low-dose aspirin or naproxen. *N Engl J Med* 2001;344:967-73.

The authors reply:

To the Editor: We found in our study that 14.8 percent of patients receiving placebo had a recurrence of ulcer complications. This high rate may have resulted in part from reinfection with *H. pylori* or a recrudescence of the original infection. Relapse of ulcer in our patients with persistent *H. pylori* infection confirms that such infection is also important in the pathogenesis of aspirin-related peptic ulcers.¹ Despite this fact, it may be inappropriate to exclude these patients from the analysis, as Drs. Maiden and Harris suggest. Our patients had reinfection or recrudescence despite apparent initial eradication of *H. pylori*. Failed eradication or recrudescence of the *H. pylori* infection is not uncommon

in clinical practice. Moreover, it is unknown whether frequent monitoring for relapse of *H. pylori* can be helpful in further reducing the risk of recurrent ulcer complications. Indeed, two of the four patients with recurrence of *H. pylori* had only a positive urea breath test (with negative results on both histologic analysis and urease testing of a biopsy specimen) when recurrent ulcer complications developed. Initial *H. pylori* eradication is not sufficient to prevent relapse of ulcer complications in patients receiving low-dose aspirin. To reflect real-life clinical practice, patients with a relapse of *H. pylori* infection should be included in the analysis.

On the other hand, only a small proportion of patients had a recurrence of ulcer when a proton-pump inhibitor was added to the regimen. Besides being useful in patients in whom *H. pylori* has been eradicated, it is very likely that a proton-pump inhibitor is useful in patients with a relapse of *H. pylori* infection (or even in those in whom an initial attempt at eradication has failed).

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1. Lanas A, Fuentes J, Benito R, Serrano P, Bajador E, Sainz R. *Helicobacter pylori* increases the risk of upper gastrointestinal bleeding in patients taking low-dose aspirin. *Aliment Pharmacol Ther* 2002;16:779-86.

Varicella Vaccine in Recipients of Hematopoietic-Cell Transplants

To the Editor: Hata et al. (July 4 issue)¹ report that inactivated varicella vaccine given before and after hematopoietic-cell transplantation reduces the risk of zoster. The primary end point of their study was the development of zoster within 12 months after transplantation. We believe, however, that the follow-up is too short to support a definite conclusion concerning the effect of vaccination. Offidani et al.² reported that the actuarial probability of varicella-zoster virus infection in 164 recipients of autologous hematopoietic-cell transplants was 10 percent at one year, 17 percent at two years, and 24 percent at three years. In the study by Hata et al., the incidence of zoster was increasing during the 12 months after transplantation.

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1. Hata A, Asanuma H, Rinki M, et al. Use of an inactivated varicella vaccine in recipients of hematopoietic-cell transplants. *N Engl J Med* 2002; 347:26-34.
2. Offidani M, Corvatta L, Olivieri A, et al. A predictive model of varicella-zoster virus infection after autologous peripheral blood progenitor cell transplantation. *Clin Infect Dis* 2001;32:1414-22.

To the Editor: Herpes zoster after hematopoietic-cell transplantation results in considerable morbidity.^{1,2} Acyclovir is virtually 100 percent effective in preventing reactivation of herpes simplex virus³ and varicella-zoster virus⁴ early after hematopoietic-cell transplantation, during the period of the greatest immunosuppression, when complications from infections are higher. The protection lasts as long as acyclovir therapy is continued. Therefore, routine prophylaxis with acyclovir for a variable period of time after hematopoietic-cell transplantation has become standard practice.

Thus, the fact that recipients of hematopoietic-cell transplants enrolled in the study by Hata et al. did not receive prophylactic acyclovir may be controversial. How many of the patients in whom zoster developed — especially within the first three to four months, when they would otherwise have been protected by acyclovir — had clinically significant sequelae (cutaneous or visceral dissemination, postherpetic neuralgia, secondary opportunistic infections, or death) related to reactivation of the virus?

Since zoster that is clinically mild can occur after the discontinuation of acyclovir in these patients, it is possible that the researchers could have achieved their objective by administering acyclovir prophylactically to all patients for three months and comparing the incidence of late zoster in vaccinated patients with that in unvaccinated patients. This approach would have allowed the researchers to avoid exposing immunocompromised patients to unnecessary risk. Presumably, patients were warned about the risks associated with infection as well as about the alternative of using prophylactic acyclovir with near-certain protection against reactivation of the virus.

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1. Locksley RM, Flournoy N, Sullivan KM, Meyers JD. Infection with varicella-zoster virus after marrow transplantation. *J Infect Dis* 1985;152: 1172-81.
2. Schuchter LM, Wingard JR, Piantadosi S, Burns WH, Santos GW, Saral R. Herpes zoster infection after autologous bone marrow transplantation. *Blood* 1989;74:1424-7.
3. Wade JC, Newton B, Flournoy N, Meyers JD. Oral acyclovir for prevention of herpes simplex virus reactivation after marrow transplantation. *Ann Intern Med* 1984;100:823-8.
4. Perren TJ, Powles RL, Easton D, Stolle K, Selby PJ. Prevention of herpes zoster in patients by long-term oral acyclovir after allogeneic bone marrow transplantation. *Am J Med* 1988;85:99-101.

The authors reply:

To the Editor: In response to Kami and colleagues: Figure 2 of our article depicts cumulative episodes of zoster. It does not show an increasing frequency over time. We designed our study on the basis of our experience that most cases of zoster occur within 12 months after transplantation for relapsed lymphoma or leukemia,^{1,2} which is consistent with reports from other centers indicating that approximately 80 percent of recurrences of varicella-zoster virus are diagnosed during this interval. Offidani et al. had found that 65 percent of cases of zoster developed during the first 12 months in their more heterogeneous population of transplant recipients. Identifying the period of peak frequency

differs from determining the actuarial risk of zoster in the first 12 months, which was 10 percent in their cohort and 33 percent in our unvaccinated group. Recipients of hematopoietic-cell transplants do remain at some risk for later zoster. However, the enhanced reconstitution of immunity to varicella-zoster virus in vaccinees at 12 months and the correlation between virus-specific CD4 T-cell responses and reduced risk of zoster suggest the possibility of longer-term protection. Vaccine regimens also have the advantage that booster doses can be given.

With regard to acyclovir prophylaxis, we challenge Dr. Mehta's position that this approach is standard practice and that our study design raises ethical questions. The guidelines of the Centers for Disease Control and Prevention for preventing opportunistic infections in recipients of hematopoietic-cell transplants state that long-term prophylaxis to prevent recurrent varicella-zoster virus infection (e.g., during the first six months after hematopoietic-cell transplantation) "is not routinely recommended" and suggest instead that this approach "could be considered for those patients with severe, long-term immunodeficiency."³ Antiviral prophylaxis is not a recommended or uniform practice because zoster can occur during the administration of acyclovir or after it is discontinued, resulting in no overall decrease in the rate of reactivation of the virus.^{4,5} Perren et al.⁵ concluded only that oral acyclovir may be of value in selected patients. Finally, all decisions about the administration of antiviral agents to participants in our study were made solely by their attending physicians, and as we reported, some patients were given acyclovir prophylaxis. The hypothesis that a regimen of inactivated varicella vaccine might be combined effectively with an initial short course of acyclovir prophylaxis is of interest and could be pursued in future clinical investigations.

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Long-Term Care after Hematopoietic-Cell Transplantation in Adults

To the Editor: In his Clinical Practice article (July 4 issue),¹ Antin does not discuss an important cause of late death af-

ter hematopoietic stem-cell transplantation: invasive fungal infection. Several centers have reported that such infections (such as invasive aspergillosis) occur in up to 15 percent of recipients of allogeneic hematopoietic stem-cell transplants and are most commonly encountered in the late phase.² Chronic graft-versus-host disease and therapy with corticosteroids are important risk factors for these infections.² With increasing treatment options that include azole antifungal agents, aggressive diagnostic workup and treatment should be pursued; prophylaxis with azoles in patients at highest risk is under investigation.

Although Antin endorsed the use of valganciclovir for the treatment of cytomegalovirus infection, we caution against its use for preemptive therapy or treatment of cytomegalovirus disease in patients with graft-versus-host disease of the gut, since absorption has not been demonstrated in these patients and since the viral-replication time in vivo is likely to be short. Induction treatment with intravenous ganciclovir should be considered for patients with high levels of immunosuppression or gastrointestinal graft-versus-host disease until ongoing pharmacokinetic and phase 3 efficacy studies better define the role of valganciclovir in recipients of stem-cell transplants.

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Editor's note: Drs. Boeckh and Nichols have reported that they have received honorariums from Roche for speaking and consulting.

1. Antin JH. Long-term care after hematopoietic-cell transplantation in adults. *N Engl J Med* 2002;347:36-42.
2. Grow WB, Moreb JS, Roque D, et al. Late onset of invasive aspergillus infection in bone marrow transplant patients at a university hospital. *Bone Marrow Transplant* 2002;29:15-9.

Dr. Antin replies:

To the Editor: I appreciate Boeckh and colleagues' comment that invasive fungal infections may occur after transplantation. Certainly, anyone who is immunocompromised, especially during long-term corticosteroid therapy, is at risk for invasive fungal infections. The risk of invasive fungal infections is highest early after transplantation and declines with time. For instance, in the study by Grow et al. that is cited by Boeckh and colleagues, there were nine documented cases and five suspected cases, and the median time to the development of invasive fungal infection was 92 days (range, 31 to 459). In addition, one must consider nocardia, actinomyces, and a variety of other unusual organisms in these patients. The use of agents such as voriconazole and posaconazole with activity against filamentous fungi is an important subject for study but not a recommendation that can be made on the basis of available data.

I agree with Boeckh and colleagues' comments regarding the treatment of cytomegalovirus infection, but I would also underscore, in this context, my previous recommendation

that patients with clinically significant graft-versus-host disease be cared for by physicians experienced in transplantation.

Finally, in Table 2 of my article, an error regarding the timing of immunizations after transplantation should be corrected. Each “or” in the second column of the table should be replaced by “and” (such that the entries read “12, 14, and 24 months” and “12 and 24 months”).

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Anxiety and Genetically Engineered Mice

To the Editor: Freedman’s conclusions about the stability of timidity in genetically engineered mice (July 18 issue)¹ are not supported by longitudinal studies in children. It is unjustifiable to suggest that temperamentally inhibited children are destined to a life of anxiety disorders.

In their landmark study, Chess and Thomas followed a cohort of children from shortly after birth into their 20s.² They found that what matters to the adjustment of children is not just the children’s personality traits themselves, but also their interaction or “fit” with the attitudes and management of the caregivers. Moreover, there is ample evidence that the brain remains a plastic organ that is responsive to environmental influences even in adulthood.³

Freedman states, “It is worthwhile to treat each episode [of anxiety], in order to minimize the psychosocial damage of each.” We read this statement as a not-so-subtle message to medicate children with psychiatric drugs at an earlier and earlier age. We fear that Freedman’s speculations will simply fuel further bioreductionistic initiatives, supported by the pharmaceutical industry, to medicate children for their emotional and behavioral challenges. On the basis of available evidence, we do not think it is “Pollyannaish” to counsel parents that, with the proper parenting interventions, their children can usually “grow out” of their symptoms or at least master them.

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1. Freedman R. Long-term effects of early genetic influences on behavior. *N Engl J Med* 2002;347:213-5.

2. Chess S, Thomas A. Origins and evolution of behavior disorders: from infancy to early adult life. New York: Brunner/Mazel, 1984:96-100.

3. Schwartz JM, Stoessel PW, Baxter LR Jr, Martin KM, Phelps ME. Systematic changes in cerebral glucose metabolic rate after successful behavior modification treatment of obsessive-compulsive disorder. *Arch Gen Psychiatry* 1996;53:109-13.

Dr. Freedman replies:

To the Editor: My article did not advocate any particular treatment. I suggested that parents not simply be reassured that their shy child will grow out of his or her symptoms.

Dr. Diller and Carey suggest that parents be told that “with the proper parenting . . . children can usually ‘grow out’ of their symptoms or at least master them.” It is certainly reasonable to help both parents and children with psychoeducational treatments for anxiety. Pharmacologic treatments are also part of the therapeutic armamentarium for behavioral disorders, and their use in well-selected cases need not be interpreted as a personal or family failure. Moreover, for the person who becomes one of the 15 percent of adults with symptoms of anxiety, it does not seem appropriate to attribute the symptoms to lack of proper parenting or personal mastery.

Current studies of childhood behavioral disorders demonstrate that both genetic factors and family environment have important roles.¹ The provocative feature of the genetically engineered mouse model is that perinatal effects of genes persist into adulthood, even if the genetic defect itself has been reversed. The well-documented persistence of symptoms of anxiety from early childhood into later life in many persons is a phenomenon whose explanation is not yet clear.² Progress in its elucidation may challenge a number of strongly held beliefs about the nature of behavioral disorders and their treatment.

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Nipple Piercing and Hyperprolactinemia

To the Editor: A healthy 20-year-old woman presented with breast pain and bilateral purulent nipple discharge three weeks after having her nipples pierced. She received a course of antibiotics (cephalexin), and her infection resolved. Two weeks later, she returned because of bilateral spontaneous galactorrhea. Evaluation at that time showed a prolactin level of 218 μg per liter, with a negative urine test for pregnancy and normal concentrations of serum thyrotropin (0.22 μU per milliliter), blood urea nitrogen (8 mg per deciliter [2.9 mmol per liter]), and serum creatinine (0.6 mg per deciliter [53 μmol per liter]). Three weeks later, the patient noted a decrease in galactorrhea; her prolactin level was 82.7 μg per liter. Two months later, she became pregnant and had an uneventful termination of the pregnancy. Her menses remained normal throughout this time, except during the pregnancy. Two months after the pregnancy, she had the nipple rings removed, and she has had no further galactorrhea. By a month after the removal of the rings, her prolactin level had returned to normal, at 11.3 μg per liter. Since cephalexin therapy was completed, the patient has not received any medications. Magnetic resonance imaging of the pituitary was normal.

This young woman had a dramatic increase in prolactin

and associated galactorrhea that coincided with the placement of bilateral nipple rings. *Harrison's Principles of Internal Medicine*¹ notes that hyperprolactinemia in which the prolactin level is greater than 100 μg per liter "almost invariably is indicative of a prolactin-secreting pituitary adenoma." *Williams Textbook of Endocrinology*² comments that "a single prolactin measurement may be sufficient to diagnose a prolactinoma if the value is greater than 200 μg [per liter]." The online version of *UpToDate*³ notes that serum prolactin concentrations "may increase slightly," reaching the range of 21 to 40 μg per liter, with "intense breast stimulation" and that serum prolactin values above 200 μg per liter "usually indicate the presence of a lactotroph adenoma." In an older study,⁴ nipple stimulation did not elevate serum prolactin levels in nonlactating women. Other studies have shown lower levels of hyperprolactinemia (less than four times the upper limit of normal) even with the intense stimulation of afferent pathways from severe chest burns or rib fracture or immediately after thoracotomy.⁵ In the case we report, marked hyperprolactinemia (prolactin level, >200 μg per liter) was associated with the intense stimulation of nipple rings (probably with the added stimulation of the asso-

ciated infections), and the prolactin level returned to normal with removal of the rings.

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