

Correspondence



**Retraction: Reconstitution of Hematopoiesis after High-Dose Chemotherapy by Autologous Progenitor Cells Generated ex Vivo**

*To the Editor:* Our 1995 paper on the reconstitution of hematopoiesis after high-dose chemotherapy<sup>1</sup> has been the subject of an investigation by the German Research Council. Since we wish the published data to be beyond dispute, we hereby retract the paper.

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**Malabsorption Due to Cholecystokinin Deficiency in a Patient with Autoimmune Polyglandular Syndrome Type I**

*To the Editor:* Högenauer and colleagues (Jan. 25 issue)<sup>1</sup> report on a patient with intermittent severe diarrhea and malabsorption, which lasted several months and “improved spontaneously.” There was no increase in serum cholecystokinin levels, and no endocrine cells could be demonstrated on one occasion by immunohistochemical studies in biopsy specimens of the duodenal mucosa. The authors concluded

that the diarrhea and severe malabsorption were caused by a deficiency of cholecystokinin-producing enteroendocrine cells in the mucosa of the patient’s proximal small intestine.

A deficiency of gut hormones can be experimentally induced by several means: the suppression of hormone secretion by somatostatin, the development of specific receptor antagonists, and the generation of receptor-deficient mouse strains by targeted gene disruption. All three approaches have been used to study the consequences of cholecystokinin deficiency in humans and animals. Subjects who received injections of the somatostatin analogue octreotide<sup>2</sup> or oral treatment with the cholecystokinin antagonist loxiglumide<sup>3</sup> had cholelithiasis but only slightly reduced secretion of pancreatic enzymes and mild steatorrhea (10 to 20 g of fat excreted). Mice with a deficiency of the cholecystokinin-A receptor have normal food intake and weight gain.<sup>4</sup> They are susceptible to gallstone formation but do not have diarrhea or malabsorption.<sup>5</sup>

Thus, the available data on cholecystokinin deficiency do not support the contention that the patient’s symptoms were due only to cholecystokinin deficiency. The immunohistologic finding reported by Högenauer et al. (an absence of chromogranin-positive cells) would mean a complete loss of all gut endocrine cells, or it might be a consequence of the methods used.

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INSTRUCTIONS FOR LETTERS TO THE EDITOR

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mice have increased susceptibility to cholesterol gallstones. *Hepatology* 1996;24:Suppl:246A. abstract.

*To the Editor:* We have previously reported the identification of tryptophan hydroxylase as an endogenous autoantigen in patients with the autoimmune polyendocrine (or polyglandular) syndrome type I.<sup>1</sup> Tryptophan hydroxylase is a rate-limiting enzyme in the synthesis of serotonin and is expressed in serotonin-producing enterochromaffin cells. The presence of tryptophan hydroxylase autoantibodies is correlated with malabsorption and loss of serotonin-producing enterochromaffin cells in patients with autoimmune polyendocrine syndrome type I.<sup>1,2</sup>

To determine whether there is a link between our earlier findings and the report by Högenauer et al., we performed immunohistochemical staining of serial sections from normal duodenal mucosa with the use of specific antibodies against serotonin (Medicorp, Montreal) and cholecystokinin (Sigma, St. Louis), as previously described.<sup>1</sup> Figure 1 shows mucosal enterochromaffin cells containing both serotonin and cholecystokinin. This finding suggests that serotonin and cholecystokinin can be synthesized by the same subpopulation of enterochromaffin cells. Both serotonin and cholecystokinin stimulate postprandial secretion of pancreatic enzymes,<sup>3</sup> and serotonin also affects the motility of the gut.<sup>4</sup> We postulate that malabsorption in autoimmune polyendocrine syndrome type I is caused by a depletion of enterochromaffin cells that

produce both serotonin and cholecystokinin, due to an autoimmune attack directed against tryptophan hydroxylase. Other, unknown functions of these enterochromaffin cells that are not mediated by serotonin or cholecystokinin cannot be ruled out.

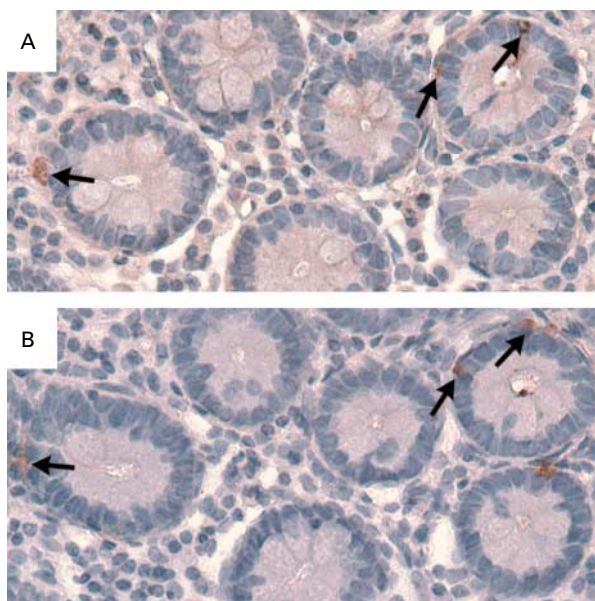
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1. Ekwall O, Hedstrand H, Grimelius L, et al. Identification of tryptophan hydroxylase as an intestinal autoantigen. *Lancet* 1998;352:279-83.
2. Ward L, Paquette J, Seidman E, et al. Severe autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy in an adolescent girl with a novel AIRE mutation: response to immunosuppressive therapy. *J Clin Endocrinol Metab* 1999;84:844-52.
3. Li Y, Hao Y, Zhu J, Owyang C. Serotonin released from intestinal enterochromaffin cells mediates luminal non-cholecystokinin-stimulated pancreatic secretion in rats. *Gastroenterology* 2000;118:1197-207.
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The authors reply:

*To the Editor:* Dr. Creutzfeldt suggests that cholecystokinin deficiency, no matter how severe, cannot cause severe steatorrhea. Although he may be correct, it also seems possible that in the studies in humans that he cites, cholecystokinin was not inhibited to the same extent and for the same period of time as may have been the case in our patient. In this regard, it is noteworthy that although octreotide causes only modest steatorrhea, patients with somatostatinoma have severe steatorrhea (up to 76 g of fat per day).<sup>1</sup> The cited findings in animals may not be completely relevant to people because of several species differences in the biologic characteristics of cholecystokinin.<sup>2,3</sup> Our patient had severe cholecystokinin deficiency, and in our opinion, this was the main cause of his steatorrhea. He also had deficiencies of peptide YY and gastric inhibitory polypeptide. The results of staining with antibodies against chromogranin A and Leu 7 suggest a deficiency of all enteroendocrine-cell subtypes and their products.<sup>4</sup> In addition to cholecystokinin deficiency, these other deficiencies probably accentuated the patient's steatorrhea and diarrhea.

Ekwall et al. demonstrate that cholecystokinin-producing enteroendocrine cells also synthesize serotonin and therefore contain the enzyme tryptophan hydroxylase. This important observation is supported by previous studies, which demonstrated the presence of serotonin in motilin- and secretin-producing enteroendocrine cells.<sup>4,5</sup> Ekwall et al. propose that the autoimmune attack in patients who have autoimmune polyendocrine syndrome type I with malabsorption could be targeting tryptophan hydroxylase in cholecystokinin-producing cells. This is an attractive explanation for the disappearance of cholecystokinin-producing cells in our patient. Since our immunohistochemical studies indicate an absence of all enteroendocrine cells in the small intestine, further studies would need to determine whether all such cells contained tryptophan hydroxylase. It would be interesting to test serum samples from our patient (obtained when he had severe steatorrhea and when he did not) for the presence of



**Figure 1.** Enterochromaffin Cells Containing Both Serotonin and Cholecystokinin in Consecutive Sections of Normal Human Duodenum ( $\times 200$ ).

Immunostaining (brown color) with antibodies against cholecystokinin (Panel A [1:5000 dilution, arrows]) and serotonin (Panel B [1:100 dilution, arrows]) was performed with the use of the avidin-biotin technique.

tryptophan hydroxylase or cholecystokinin-directed autoantibodies, or both, with the complementary DNA-library-based methods used by Ekwall et al.

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### Lack of Effect of Induction of Hypothermia after Acute Brain Injury

*To the Editor:* The study by Clifton et al. (Feb. 22 issue)<sup>1</sup> has two shortcomings. First, brain temperature was not monitored. Second, the types of injuries were neither described nor analyzed. Hypothermia might be beneficial in patients with specific types or areas of injury in the brain — for example, areas of edema or areas of focal contusions. In such injured but potentially viable areas, cerebral perfusion may be diminished or even absent. Cooling the blood in the systemic circulation to the predetermined level of 33°C (as measured by bladder temperature), as in the study by Clifton et al., may have a limited effect in lowering the temperature in areas of injured brain tissue.

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1. Clifton GL, Miller ER, Choi SC, et al. Lack of effect of induction of hypothermia after acute brain injury. N Engl J Med 2001;344:556-63.

*To the Editor:* Clifton et al. reported that mild hypothermia (33°C) after traumatic brain injury had no effect on outcome. We believe that the study results were negative at least in part because hypothermia was not initiated soon after injury. Furthermore, in randomized clinical trials, numerous variables that can affect outcome cannot be accounted for in the randomization nor controlled during the trial. For example, in this study, patients with spontaneous hypothermia were included in the normothermia group. In addition, the beneficial effects of hypothermia can be offset by

suboptimal life support, and life support may have varied greatly among the participating hospitals.

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Dr. Clifton replies:

*To the Editor:* Devices approved by the Food and Drug Administration (FDA) that measure brain temperature concurrently with intracranial pressure were not available until the study was near completion. We did not think that we should use non-FDA-approved devices in a trial in which consent was waived for many patients. Although it would have been useful to measure brain temperature in the study, the limiting factor in the depth of hypothermia is the core temperature, because at core temperatures below 30°C there is a risk of ventricular arrhythmias.<sup>1</sup> As stated in the article, we used the standard classification system based on computed tomography to examine for subgroup effects and found none.<sup>2</sup>

Patients were not stratified according to the presence or absence of spontaneous hypothermia, and therefore the treatment groups were not balanced with respect to this variable. Spontaneous hypothermia was not known beforehand to affect outcome. There were no other imbalances between the treatment groups with respect to any variable known to affect the outcome of brain injury, and therefore there is no reason to believe that such imbalances could have affected the outcome. We agree that the overall negative results were probably due to the initiation of hypothermia too long after injury. This may account for the apparent benefit of the maintenance of hypothermia in patients with spontaneous hypothermia.

Although management of the patients' cerebral perfusion pressure varied among the hospitals within the boundaries defined by the protocol, there were no differences between the treatment groups with respect to cerebral perfusion pressure<sup>3,4</sup> (and unpublished data). There are no data to support the supposition that differences between the groups in management influenced the outcome of the study.

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### Vitamin D Intoxication Associated with an Over-the-Counter Supplement

*To the Editor:* As a group, fat-soluble vitamins are lifesaving at physiologic levels and dangerous at megavitamin lev-

els.<sup>1</sup> For many people the word “vitamin” implies something that is beneficial and essential, not potentially poisonous.<sup>2</sup> More than one third of people in the United States regularly use dietary supplements.<sup>3</sup> We describe a patient with hypercalcemia associated with the ingestion of an over-the-counter vitamin D supplement.

A 42-year-old man was hospitalized with symptoms of hypercalcemia of a few weeks' duration. For the past two years, he had been taking a supplement that contained vitamin D<sub>3</sub>. On admission his serum levels were as follows: 25-hydroxyvitamin D, 487.3 ng per milliliter (normal range, 8.9 to 46.7); calcium, 15.0 mg per deciliter (normal range, 8.8 to 10.1); creatinine, 2.4 mg per deciliter; and hemoglobin, 10.5 mg per deciliter (all measurements were performed at the Nichols Institute, San Juan Capistrano, Calif.). The patient had normal levels of 1,25-dihydroxyvitamin D, parathyroid hormone, angiotensin-converting enzyme, and thyroid hormone and had normal findings on radiography, computed tomography of the chest, neck, and abdomen, and bone

marrow-aspiration biopsy. He received intravenous hydration. The vitamin D<sub>3</sub> was discontinued, and he was advised to wear sunscreen at all times when he was outdoors. He was not treated with glucocorticoids. At discharge his serum calcium level was 9.8 mg per deciliter, his hemoglobin level was 11.2 mg per deciliter, and his creatinine level was 1.7 mg per deciliter. His creatinine level remained elevated for one year. Thirty months later, the results of all blood tests were normal, including serum levels of calcium and 25-hydroxyvitamin D (Fig. 1).

The patient sent us two bottles of his vitamin D<sub>3</sub> supplement (Prolongevity, Markham, Ont., Canada), and we purchased one from the manufacturer. All supplements were from different lots. The vitamin D<sub>3</sub> supplement was extracted with methanol and analyzed by high-performance liquid chromatography.<sup>4</sup> The supplements from each of the three lots that we analyzed contained a mean of  $1.3 \pm 0.1$  mg,  $12.8 \pm 0.1$  mg, and  $21.7 \pm 0.2$  mg of vitamin D<sub>3</sub> per gram of powder, respectively, or about 26 to 430 times the amount listed by the manufacturer (2000 IU or 50  $\mu$ g of vitamin D per gram of powder). The patient consumed one teaspoon (or 3 g) of powder daily, or 156,000 to 2,604,000 IU of vitamin D<sub>3</sub> per day. This amount was 78 to 1302 times the recommended safe upper limit of 2000 IU per day.

To diagnose vitamin D intoxication, one must consider it in the differential diagnosis and obtain a history of vitamin D intake in patients with hypercalcemia, azotemia, and anemia of obscure origin.<sup>1</sup> The renal disease is reversible if the use of vitamin D is stopped. Hypervitaminosis D is characterized by high serum levels of 25-hydroxyvitamin D, hypercalcemia, hypercalciuria, and hyperphosphatemia.<sup>5</sup> In severe cases of vitamin D intoxication, glucocorticoids are used for short-term management. Renal and hematologic abnormalities may persist despite striking symptomatic improvement.<sup>1</sup>

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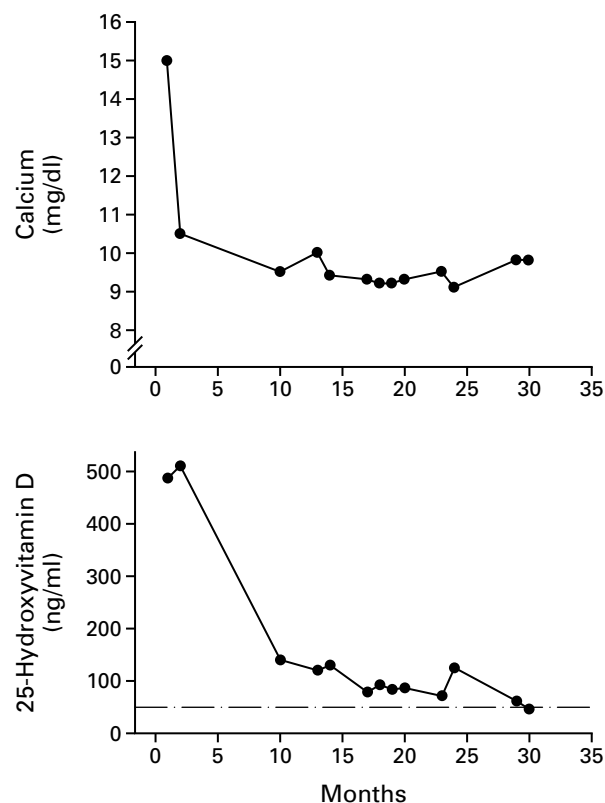
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**Figure 1.** Serum Levels of Calcium and 25-Hydroxyvitamin D in a Patient Who Had Vitamin D Intoxication after the Ingestion of an Over-the-Counter Vitamin D Supplement.

Month 0 represents the time of hospitalization. The patient subsequently stopped taking the supplement and wore sunscreen before going outside. The dashed-and-dotted line in the lower panel represents the upper limit of the normal range for 25-hydroxyvitamin D (46.7 ng per milliliter).

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*Editor's note:* The above letter was submitted to Prolongevity, the manufacturer of the vitamin D<sub>3</sub> supplement, which declined to respond.

### Preventing Upper Gastrointestinal Bleeding in Patients with *Helicobacter pylori* Infection

*To the Editor:* Chan et al. (March 29 issue)<sup>1</sup> sought to determine whether eradication of *Helicobacter pylori* is “equivalent to maintenance treatment with omeprazole” in the

secondary prevention of upper gastrointestinal bleeding in patients taking low-dose aspirin or other nonsteroidal anti-inflammatory drugs. Unfortunately, their data do not make clear in how many of the patients with recurrent bleeding the attempted eradication of *H. pylori* was successful. The authors report an eradication rate of 91 to 93 percent among those who completed the study. This leaves a substantial number of patients who remained positive for *H. pylori*. What percentage of the patients who had recurrent bleeding were persistently infected?

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1. 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.

Dr. Chan replies:

*To the Editor:* None of the patients with recurrent bleeding who received eradication therapy were infected with *H. pylori*. In contrast, all patients with recurrent bleeding who received omeprazole remained positive for *H. pylori*.

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### The Cost Effectiveness of Antiretroviral Therapy for HIV Disease

*To the Editor:* The study by Freedberg et al. (March 15 issue)<sup>1</sup> compared a three-drug regimen with no antiretroviral therapy in patients infected with the human immunodeficiency virus (HIV) and found the regimen to be effective. One weakness of this study is that no treatment was chosen as the reference category. There were no comparisons between triple therapy and double therapy or between triple therapy and monotherapy. Studies of cost effectiveness should be guided by clinical research, and the controlled studies in the analysis by Freedberg et al. did not include untreated groups. Since withholding treatment is unethical, the design of the study is incorrect and its results are misleading.

We estimated the quality-adjusted life expectancy with zidovudine monotherapy as 2.03 years with an annual discount rate of 3 percent.<sup>2</sup> The quality-adjusted gain in life expectancy found by Freedberg et al. was 1.38 years, which was calculated, with an annual discount rate of 3 percent, as the difference between 2.91 additional years with triple therapy and 1.53 additional years with no treatment. This gain was large because the reference category was no treatment. If monotherapy is used for comparisons, the gain in life expectancy becomes a much less impressive 0.88 year (2.91 minus the 2.03 years from our estimate), and the analysis of cost effectiveness will yield quite different results. The gain be-

comes even smaller if double therapy is used as the reference category.

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1. Freedberg KA, Losina E, Weinstein MC, et al. The cost effectiveness of combination antiretroviral therapy for HIV disease. *N Engl J Med* 2001;344:824-31.

2. Messori A, Becagli P, Berto V, et al. Advanced HIV infection treated with zidovudine monotherapy: lifetime values of absolute cost-effectiveness as a pharmacoeconomic reference for future studies evaluating antiretroviral combination treatments. *Ann Pharmacother* 1997;31:1447-54.

*To the Editor:* The cost effectiveness of combination antiretroviral therapy for HIV-infected patients in the United States, as reported by Freedberg and associates, was important to document. However, over 90 percent of HIV infections occur elsewhere, in the developing world. Recently, attention has focused on the cost of antiretroviral drugs and their distribution; these economic analyses will need to be considered by those advocating widespread use of antiretroviral therapy in the developing world. As Freedberg et al. noted, current antiretroviral therapy extends the lives of HIV-infected patients by only a few years. Viral resistance and adverse effects of the drugs undermine their utility.

Strategies to mitigate the failure of antiretroviral therapy, such as testing for resistance and monitoring of compliance, were not included in their survey. Because of the public health consequences, such procedures should be an integral part of the discussion of the economic aspects of HIV and AIDS. The recent calls for wide distribution of antiretroviral therapy, in Africa and other parts of the world being decimated by HIV, could be acted on without adequate oversight.

A total of 5.8 percent of patients newly infected with HIV in the United States and Canada have strains resistant to two classes of anti-HIV drugs, as compared with just 0.4 percent six years ago.<sup>1</sup> One in seven newly infected persons in the United States now acquires a strain resistant to at least one class of antiviral agents.<sup>1</sup> Many factors may facilitate such resistance, but noncompliance of patients and drug interactions are key and, given existing economic limitations, can only exacerbate the situation in the developing world.

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1. Stephenson J. 20 Years after AIDS emerges, HIV's complexities still loom large. *JAMA* 2001;285:1279-81.

The authors reply:

*To the Editor:* We agree with Messori and colleagues that all relevant and available alternatives should be included and compared incrementally in a cost-effectiveness analysis and that the choice of those alternatives should be guided by

clinical research.<sup>1</sup> In our study, the efficacy of antiretroviral therapy was based on data from clinical trials, and we assessed the costs and effects of all treatments studied in each trial. For example, in our analysis of the AIDS Clinical Trials Group 320 Study, we compared triple therapy with double therapy, as well as with no therapy. As we stated, we found that double therapy was both less effective and less cost effective than triple therapy; the quantitative results of this analysis were not included because of space constraints. If triple therapy is not a viable option (e.g., because of limited resources), then double therapy would be cost effective as compared with monotherapy or no therapy. Further details are available through the National Auxiliary Publications Service. (See document no. 05582 for 6 pages of supplementary material. To order, contact National Auxiliary Publications Service, c/o microfiche Publications, 248 Hempstead Tpke., West Hempstead, NY 11552.)

Laurence states that antiretroviral therapy extends life by only a few years. However, the analysis to which he refers focuses on patients with advanced HIV disease; gains in life expectancy with earlier treatment are greater. We also argue that a few additional years of life is a substantial clinical benefit relative to gains in life expectancy associated with other well-accepted clinical interventions. For example, gains in life expectancy associated with combination antiretroviral therapy are greater than those resulting from other widely used treatments, such as coronary-artery bypass graft surgery and treatment of both moderate hypertension and hypercholesterolemia.<sup>2</sup>

We share Laurence's concern about viral resistance and adverse effects of drugs. The effects of resistance, noncompliance, and drug toxicity were all included in our analysis. Moreover, the flexibility of the model has allowed us to evaluate specific strategies that enhance the efficacy of antiretroviral therapy, such as genotypic resistance testing and interventions to improve compliance.<sup>3,4</sup>

Finally, we agree with Laurence that effects of HIV disease are largest in low-income countries. Providing antiretroviral therapy in these settings will present formidable challenges, including linking treatment with prevention programs, developing approaches to facilitate compliance, and monitoring for drug resistance. However, as recently outlined by over 130 members of the faculty of Harvard University,<sup>5</sup> with sufficient scientific and financial efforts to advance HIV care in low-income countries, these challenges can be overcome.

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5. Individual Members of the Faculty of Harvard University. Consensus statement on antiretroviral treatment for AIDS in poor countries. April 2001. Accessed June 15, 2001. (See [http://www.cid.harvard.edu/cidinthenews/pr/consensus\\_aids\\_therapy.pdf](http://www.cid.harvard.edu/cidinthenews/pr/consensus_aids_therapy.pdf).)

## The Disposition of Unused Frozen Embryos

*To the Editor:* The disposition of unused embryos is a pressing problem for in vitro fertilization programs.<sup>1,2</sup> Although cryopreservation of embryos gives couples the chance to make additional attempts at pregnancy, unused frozen embryos create a storage problem and require couples to make difficult decisions regarding their disposition. Divorcing couples have had contentious disputes over embryos.<sup>3</sup> In addition, interest in the use of these omnipotent cells for genetic research raises concern about unauthorized or inappropriate use.

In vitro fertilization clinics offer these disposition options: continued cryopreservation, uterine transfer, donation to an infertile couple, donation to research, and disposal. In a study of the experience at our in vitro fertilization program, 107 of 404 couples (26 percent) had embryos remaining in the freezer after the three-year storage deadline. Sixteen of these 107 couples were still in treatment. Attempts were made to contact the other 91 couples with the use of information from charts, directory assistance, and birth announcements and with the use of forwarding addresses. Over a three-month period, only 52 of the 91 couples (57 percent) could be located. At the time of contact, 17 of the 52 couples (33 percent) chose to dispose of the embryos, 7 (13 percent) chose to donate them to an infertile couple, 5 (10 percent) wanted to donate them to research, 15 (29 percent) chose to continue storage, 6 (12 percent) decided to undergo another transfer cycle, and 2 (4 percent) were undecided.

A comparison of the initial and current disposition choices of 41 couples for whom both initial and current information was available indicated that only 12 of these couples (29 percent) kept their initial disposition choice; 29 couples (71 percent) changed their preferences. Thirteen of 22 couples who had initially opted for disposal now wanted either to use or to donate the embryos. Nine of 11 couples who had initially opted for donation to an infertile couple no longer chose that option: 2 couples now decided to use the embryos, 2 chose to thaw them, 3 continued storage, and 2 donated the embryos to research. Seven of eight couples who had initially planned to donate the embryos to research now chose either to use the embryos or to dispose of them. Having a child was not significantly associated with the final choice regarding disposition.

The American Society for Reproductive Medicine recommends that couples indicate their preferences for embryo disposition in many potential scenarios, including abandonment, so that programs are not required to cryopreserve embryos indefinitely.<sup>4</sup> Improved systems for embryo disposition require appropriate counseling of couples, documentation of disposition choices, and clear definition of time limits for storage. The current findings highlight the need for ongoing contact between programs and couples to facilitate reassess-

ment and confirmation of decisions regarding embryo disposition.

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