

## Correspondence



## Gene Therapy for Severe Combined Immunodeficiency Disease

*To the Editor:* Correction of X-linked severe combined immunodeficiency by infusion of autologous CD34+ stem cells transduced with retrovirus containing common  $\gamma$  chain, reported by Hacein-Bey-Abina et al. (April 18 issue),<sup>1</sup> is a milestone in medicine. We used a different therapy with a similarly good outcome.

X-linked severe combined immunodeficiency was diagnosed in two patients after the initiation of mechanical ventilation for pulmonary failure caused by infections. Immediately after the diagnosis had been made, haploidentical CD34+ peripheral progenitor cells mobilized with granulocyte colony-stimulating factor were isolated to a purity of more than 99 percent.<sup>2</sup> These cells were infused with no preparative regimen and no prophylaxis against graft-versus-host disease. Both patients showed signs of T-cell reconstitution beginning three weeks after the CD34+ infusion and were weaned from the ventilator. They are in excellent health, without graft-versus-host disease, 34 and 68 months after transplantation. Patient 1 does not need replacement immune globulin. Patient 2 received a "booster" infusion of CD34+ stem cells from the original donor one year later to improve B-cell function and now receives immune globulin every three months.

Our experience indicates that purified haploidentical CD34+ progenitor cells reconstitute the T-cell compartment and can correct the B-cell defect. Given the possibility of long-term risks<sup>3,4</sup> and the availability of effective alternatives, we think that broader application of gene therapy for the treatment of patients with severe combined immunodeficiency or strategies for the correction of persistent

B-cell deficiency after successful allogeneic transplantation<sup>5</sup> are premature and warrant longer follow-up.

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The authors reply:

*To the Editor:* Handgretinger et al. describe two cases of successful haploidentical hematopoietic stem-cell transplantation for X-linked severe combined immunodeficiency. It is indeed known that partially compatible hematopoietic stem-cell transplantation can provide T-cell reconstitution in 70 to 80 percent of cases.<sup>1,2</sup> Nevertheless, haploidentical hematopoietic stem-cell transplantation has a number of pitfalls. Despite low numbers of T cells in the graft, graft-versus-host disease does develop in some cases (5 to 10 percent). T-cell repopulation after haploidentical hematopoietic stem-cell transplantation is slow.<sup>1,2</sup> A period of more than three months is usually required before T cells can be detected.

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More important, Patel et al. have reported that after the performance of haploidentical hematopoietic stem-cell transplantation without myeloablation, T-cell immunity declines over time.<sup>3</sup> Finally, correction of B-lymphocyte immunity is infrequent in patients with X-linked severe combined immunodeficiency who undergo haploidentical hematopoietic stem-cell transplantation in the absence of myeloablation.<sup>1,4</sup> In contrast, so far all patients who have received gene therapy, with a follow-up of more than one year, in whom T-cell immunity has developed do not require intravenous immune globulin therapy. These observations justify further assessment of gene therapy as an alternative to hematopoietic stem-cell transplantation.

The potential risk of gene therapy must not be underestimated and must be balanced against the risk of alternative therapy. The concern of Handgretinger et al. is not entirely appropriate, since helper virus and the expression of a membrane receptor, which accounted for reported toxic effects, are irrelevant to our trial. In our opinion, gene therapy can be considered an option worth exploring for patients with severe combined immunodeficiency.

We would also like to note that on page 1185 of our article, author Lily Leiva's name was misspelled, and the affiliation for Dr. Leiva and author Ricardo Sorensen should have included both Louisiana State University Health Sciences Center and Children's Hospital, New Orleans.

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### Erythromycin-Resistant Group A Streptococci

*To the Editor:* Martin et al. (April 18 issue)<sup>1</sup> identified the emergence of a clone of macrolide-resistant group A streptococci among schoolchildren in Pittsburgh. We are concerned that, on the basis of this finding, physicians will unnecessarily choose even broader-spectrum antimicrobial agents for the treatment of pharyngitis caused by group A streptococci.

Our analysis of data collected in the National Ambulatory Medical Care Survey from 1989 to 1999 showed a significant increase in the use by primary care physicians of extended-spectrum macrolides (mostly clarithromycin and azithromycin) for adults with sore throat.<sup>2</sup> This increase probably provides the selective pressure necessary for the emergence

of clones such as that described by Martin et al. We also noted a low and decreasing rate of penicillin use among patients who received antibiotics: from 22 percent in 1989 to 13 percent in 1999 ( $P < 0.001$ ).

The infrequent use of penicillin is surprising, given that group A streptococci are universally susceptible to penicillin.<sup>3</sup> Inappropriate concern about resistance, the desire on the part of both patients and physicians for newer, "stronger" medications, and the active promotion of other antibiotics have probably contributed to the decrease in the use of penicillin.

With the emergence of antimicrobial-resistant bacteria, it is important to encourage the use of narrow-spectrum antimicrobial agents when appropriate. Martin et al. provide yet more evidence that, in the absence of penicillin allergy, the treatment of choice for pharyngitis caused by group A streptococci is still penicillin (or amoxicillin for children). These are effective, inexpensive, well-tolerated antibiotics to which the target pathogen is always susceptible.

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*To the Editor:* Martin and colleagues describe an unexpectedly high rate of macrolide resistance among pharyngeal isolates of endemic group A streptococci from asymptomatic and symptomatic children in Pittsburgh during the 2000-2001 respiratory-infection season. This high rate was due to a single *emm* 6 clone. In the accompanying editorial, Huovinen appropriately recommends nationwide assessment of the prevalence of macrolide-resistant group A streptococci.<sup>1</sup>

We established the U.S. Streptococcal Pharyngitis Serotype Surveillance Group in 2000 to assess systematically the serotype distribution of pharyngeal group A isolates from children in geographically diverse U.S. sites, in collaboration with the Centers for Disease Control and Prevention.<sup>2</sup> We collected 972 pharyngeal isolates from 9 sites during the 2000-2001 season and almost 1000 isolates from 10 sites during the 2001-2002 season. Our preliminary data for the 2000-2001 isolates indicate that the rate of macrolide resistance was approximately 7.4 percent. It is of particular interest that only 6 of 45 *emm* type 6 strains (13 percent), including 1 of 7 from our site in eastern Pennsylvania, were resistant to macrolides. This suggests that the *emm* 6 clone identified by Martin et al. had not become disseminated very widely in the United States in 2000-2001. It is important to continue national surveillance for resistance to macrolides

(as well as clindamycin) among pharyngeal isolates of group A streptococci and to evaluate the mechanisms of resistance.

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1. Huovinen P. Macrolide-resistant group A streptococcus — now in the United States. *N Engl J Med* 2002;346:1243-5.
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The authors reply:

*To the Editor:* The concern of Drs. Linder and Stafford about the use of broad-spectrum antibiotics for the treatment of pharyngitis caused by group A streptococci is completely appropriate. We continue to recommend the use of penicillin or amoxicillin for the treatment of streptococcal pharyngitis. Most patients who have an allergy to penicillin can safely take a first-generation cephalosporin. In the event of a serious penicillin allergy (type I hypersensitivity reaction), the macrolides can be used for susceptible isolates. Clindamycin may be a reasonable alternative, pending the results of antibiotic-sensitivity testing. Broad-spectrum antibiotics are not necessary for treatment, even when the group A streptococcal isolate is resistant to macrolides.

We agree with Shulman et al., as well as with Huovinen, that there is a pressing need to assess the prevalence of macrolide-resistant group A streptococcus in the United States. Preliminary reports from the surveillance study by Shulman et al. indicate a low rate of resistance to the macrolide antibiotics for the 2000–2001 respiratory-infection season. However, the generalizability of these results will depend on when and where the isolates were obtained. High rates of macrolide resistance were observed in our longitudinal study of schoolchildren and in community isolates during the 2001–2002 respiratory-infection season. The resistance emerged only during the latter part of our surveillance. Intermittent sampling may not reveal resistant isolates, which may be present only transiently. The nationwide prevalence of erythromycin-resistant group A streptococcus must be determined by examining representative isolates in multiple areas in the United States during an entire respiratory-infection season.

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### Sulindac in Familial Adenomatous Polyposis

*To the Editor:* Giardiello et al. (April 4 issue)<sup>1</sup> conclude that sulindac does not delay the occurrence or reduce the

number or size of colorectal adenomas in patients bearing a mutation of the adenomatous polyposis coli (*APC*) gene. The authors do not take into account two important factors: the position of the mutation in the germ-line *APC* gene and the level of expression of the wild-type allele in normal colonic mucosa and in adenomas. In familial adenomatous polyposis, there is a strong correlation between the location of the mutation in the *APC* gene and the age at onset and number and size of adenomas.<sup>2,3</sup> Moreover, polymorphism of the mutated allele also influences the phenotype.<sup>4</sup> This information is missing from the report by Giardiello et al.

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### Transplantation of the Right Hepatic Lobe

*To the Editor:* We appreciate the valuable article by Trotter et al. (April 4 issue)<sup>1</sup> on living-donor liver transplantation, but we believe that it underestimates the psychosocial evaluation of donors and conveys an unduly narrow understanding of altruism. The decision to donate emerges from an interplay of developmental and sociocultural factors. Potential donors contemplate an act that is entirely altruistic in terms of their own physiologic health. They are supported or buffered by diverse interpersonal dynamics; they have unique psychological strengths and burdens, unique personality styles, and unique understandings of their roles vis-à-vis their fellow human beings.<sup>2</sup> We are skeptical that this profound and intricate psychosocial complex can be evaluated through a telephone conversation.

At our center, outcomes in donors indicate clearly that serious complications can result from inadequate psychosocial assessment. We therefore require that a psychiatrist and a social worker see each prospective donor independently; their respective assessments sometimes extend over several appointments. We feel strongly that a nuanced understanding of a donor's motivations and risks can be attained only through such intensive evaluation.

Furthermore, we disagree that donor acceptability must be predicated on a "long-term, significant relationship with the recipient." Altruistic motivations do transcend — however rarely — the limits of personal relationships. As we discuss elsewhere,<sup>3</sup> privileging an altruism that is based on genetic or emotional proximity risks devaluing one that is based on broader, humanitarian foundations. It is not self-evident that an inclusive, universal altruism is psychologically pathologic, simply because it is unusual. Many religions,

for example, extol such altruism as the very ideal of generosity. Again, the issue is complicated and demands thorough, individualized assessment.

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1. Trotter JF, Wachs M, Everson GT, Kam I. Adult-to-adult transplantation of the right hepatic lobe from a living donor. *N Engl J Med* 2002; 346:1074-82.
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*To the Editor:* The review article by Trotter et al. is timely and thorough. However, there is one factual error. The first successful adult-to-adult transplantation of a right hepatic lobe from a living donor was reported by us,<sup>1</sup> not by Yamaoka et al.<sup>2</sup> The patient treated by Yamaoka et al. was a nine-year-old child. Contrary to the view of Trotter et al. that living-donor liver transplantation has a limited role in the treatment of patients with acute liver failure, we found that this procedure is most valuable in patients who have acute liver failure or cirrhosis with acute deterioration.<sup>3</sup>

Some centers have reported that the results of living-donor liver transplantation in patients whose United Network for Organ Sharing (UNOS) status is 1 or 2A have not been satisfactory. We believe the reason is that the surgeons chose to use right-lobe grafts without the middle hepatic vein — a type of graft that is suboptimal in function and that cannot meet the metabolic demands of critically ill patients. To improve the results, more attention should be paid to improving the venous drainage of the right-lobe graft rather than to increasing the graft volume.

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*To the Editor:* Techniques for adult-to-adult living-donor liver transplantation have not been standardized, but we wish to point out our observations regarding the illustrations and the text concerning the operation in the article by Trotter et al. First, although the techniques used for all three of the major vascular reconstructions are critical, the establishment of unrestricted venous outflow is paramount. We perform

right-hepatic-vein cavoplasty, anastomosis of all posterior hepatic veins larger than 5 mm, and reconstruction of the venous drainage of segment 8 if its major venous outflow crosses the plane of parenchymal transection into the middle hepatic vein, together with the extensive use of fine, interrupted sutures. Figure 5 in the article depicts a vessel identified as the middle hepatic vein. This vessel might more correctly be identified as a segmental tributary of the middle hepatic vein. In our program, the true middle hepatic vein, identified intraoperatively by ultrasonography, is never divided and always remains with the left lobe. Our plane of parenchymal transection is always to the right of it — which brings us to our second observation regarding Figure 5. The plane of parenchymal transection depicted in the illustration is midway between a true right lobectomy and a right trisegmentectomy and goes right through liver segment 4. Again, it is our practice to ensure that all of segment 4 remains with the donor. We suspect that the authors present these illustrations as general representations rather than exact depictions of operative details, and we hope that others interpret them as such.

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*To the Editor:* The article by Trotter et al. on living-donor liver transplantation and the Perspective by Surman on the ethics of this practice<sup>1</sup> raise important issues concerning the complications donors have suffered, including death in two cases. Their discussion raises a fundamental question: Is it morally acceptable to remove organs from living donors?

The fundamental goal of medicine is to help a sick person in need, from which stems the principle of nonmaleficence: “First, do no harm.” Removing an organ or a portion of an organ from a healthy person harms that person by subjecting him or her to anesthetic, surgical, and postsurgical risks. The altruism of the donor does not change this. It is one thing for a soldier to jump on a grenade thrown by an enemy to save his or her fellow soldiers; it is quite another for a person to donate a healthy organ. In the former case, an enemy is harming the soldier; in the latter, a physician is harming the patient, even if the harm is at the patient’s request, and even if the transplanted organ helps someone else. Public support for organ donation from living donors does not change this fact, nor does the popularity of a practice imply its moral rightness. Because the removal of organs from a living person does not benefit that person, but actually harms him or her, it violates the fundamental end of medicine to do no harm.

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*To the Editor:* Surman suggests that the risks of donation of the right hepatic lobe are unknown. Although donor experience is limited, the risk of death and other complications in association with right lobectomy should be familiar to the experienced surgeon. Right lobectomy has been performed in many cases for years, and late complications are exceedingly rare.

Surman asserts that transplantation of the right lobe of the liver began without discussion in the medical community. As the surgeon who performed the first such transplantation in the United States, I recall the detailed discussion that occurred before the first procedure. The ethical issues involved in living-donor liver transplantation in children were laid out. Following the model of the University of Chicago, my colleagues and I developed a program of adult-to-adult liver transplantation. The principles followed included assignment of an independent physician who served as a donor advocate, a multistep informed-consent process, exclusion of emergency transplantations, and inclusion only of recipients who were qualified to receive a cadaveric transplant. Each donor was informed of the experiences of previous donors and recipients. The safety of the donor was the paramount concern.

Although right lobectomy for transplantation is risky, it is not qualitatively different from kidney donation or left-lobe liver donation. We are a society that highly values autonomy. How can we decide how much risk is acceptable to one who freely chooses risk in order to save another person? Our role in transplantation is to inform donors of the risks involved. We should not set an arbitrary standard of risk beyond which no one may be permitted to step.

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*To the Editor:* Although the medical and psychiatric well-being of the donor is of paramount importance in the ethics of living-donor liver transplantation, so is an accurate portrayal of the medical risk, which we believe is overestimated by Surman. He reports seven deaths among all partial-liver donors in the United States and concludes that the incidence of death among right-lobe donors is "1 percent or more." To date, three donors have died during the course of approximately 1000 living-donor liver transplantations performed in the United States and recorded by UNOS. One donor died after providing a left lateral segment to a child, and two donors died after right-lobe donation to adults. Thus, the mortality rate among all partial-liver donors in the United States is approximately 0.3 percent, a rate similar to that reported worldwide and noted by Trotter et al. Unfortunately, the erroneous data presented by Surman are now being widely quoted as fact both in print and by the broadcast media and may have a deleterious effect on organ donation in general.

Many centers are considering initiating programs of living-donor adult-to-adult liver transplantation because of the apparently high success rates and the low morbidity rates in donors. However, enthusiasm must be tempered. Proper education and informed consent are mandatory, given the re-

ality that transplantation involving living donors is associated with a small but real possibility of death for the healthy donor.<sup>1</sup>

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1. Pomfret EA, Pomposelli JJ, Lewis WD, et al. Live donor adult liver transplantation using right lobe grafts: donor evaluation and surgical outcome. *Arch Surg* 2001;136:425-33.

Dr. Trotter replies:

*To the Editor:* My colleagues and I appreciate the comments of Drs. Dixon and Abbey. We agree that the psychosocial evaluation of donors cannot adequately be performed through a telephone conversation. In fact, all potential donors evaluated at our center are seen in person by a social worker affiliated with our transplantation team. These assessments frequently require several appointments with the potential donor or his or her family or friends. Currently, our program evaluates only potential donors who have a long-term relationship with the recipient. The evaluation of the good Samaritan donor — that is, a donor with no emotional relationship to the recipient — is extremely complex. As a result, it seems to us that good Samaritan donors will not substantially increase the number of donors available for living-donor liver transplantation.

Dr. Fan and colleagues are correct in stating that the first right-hepatic-lobe recipient was only nine years of age. However, the report of that transplantation, by Yamaoka et al.,<sup>1</sup> was published three years before the report by Lo et al.<sup>2</sup> and therefore is the first description of transplantation of the right hepatic lobe. Therefore, we should clarify our statement that the "first adult-to-adult transplantation of a right hepatic lobe was reported in 1994" by stating that the "first transplantation of a right hepatic lobe was reported in 1994." We agree that some patients with acute liver failure benefit from living-donor liver transplantation. However, the rapid nature of acute liver failure frequently precludes the evaluation of donors. In addition, the number of patients with acute liver failure is small relative to the number with chronic liver disease. As a result, acute liver failure will probably remain an uncommon indication for living-donor liver transplantation.

The comments by Dr. Shackleton and colleagues are important. The illustrations in our article are accurate, but they are general representations and therefore do not depict the critical details of the operative procedure. The review was intended for a general medical audience, and for this reason and reasons of space limitations the details of the operative procedure could not be included. My colleagues and I have previously published a full description of the operative technique used at our center.<sup>3</sup>

The comments by Dr. Potts are very interesting, especially because he speaks as a nonclinician. We obviously disagree with his opinion that living-donor liver transplantation lacks

“moral rightness.” Having observed the remarkable long-term clinical improvement in our recipients and the apparent absence of major injury to donors, we believe that this procedure is ethical. However, the events surrounding a recent death of a donor in New York have forced liver-transplantation physicians to reexamine their own personal views on living-donor liver transplantation. Shaw has written a very thoughtful and cautionary editorial about living-donor liver transplantation, one that outlines critical ethical issues from the standpoint of a transplantation doctor.<sup>4</sup>

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3. Bak T, Wachs M, Trotter J, et al. Adult-to-adult living donor transplant using right-lobe grafts: results and lessons learned from a single-center experience. *Liver Transpl* 2001;7:680-6.
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Dr. Surman replies:

*To the Editor:* Dr. Seek and colleagues are right in noting that the number of deaths I described in my Perspective is incorrect. Eight deaths are now known to have occurred in worldwide experience with partial-liver donation (the seven mentioned by Dr. Seek and colleagues as well as an additional, recent death).<sup>1</sup> Three of these deaths occurred in the United States, two of them in right-lobe donors. Compare this with the results of a survey of member centers of the Organ Procurement Transplant Network between January 1, 1999, and June 30, 2001. In the course of 10,000 living-donor kidney transplantations, at least two donors died from perioperative complications, and another donor entered a persistent vegetative state. These 3 donors were among the 5000 who underwent laparoscopic nephrectomy.<sup>2</sup>

Mortality is greater among right-hepatic-lobe donors than among kidney donors or those undergoing left-hepatic-lobe resection. A high relative rate of complications after right-lobe donation has also been well documented, and the effect on quality of life is still being defined.<sup>3</sup> Busuttil recommends a reimbursement-linked certification process for centers performing living-donor liver transplantation.<sup>4</sup> He suggests that requirements include demonstration of the need to perform this type of transplantation as well as extensive experience with hepatobiliary surgery and liver resection and expert capacity and resources for surgery in the donor. There should also be an established means of recording outcomes and a comprehensive process of informed consent that ensures autonomy.<sup>4</sup>

Dr. Howard's contribution is important. Stringent criteria for right-hepatic-lobe donation are needed until other means of treatment, such as tissue engineering, are available. Unlike kidney or left-lobe donation, right-lobe donation depends on subsequent hepatic regeneration. Its use creates an ethical slippery slope. In 1989, the University of Chicago group made public their intent to perform parent-to-child

liver transplantation after a six-month period for national discussion.<sup>5</sup> I am unaware of any such moratorium before right-lobe transplantation, which entails higher risk. Dr. Howard states that our society values autonomy, but this ethical principle is in ultimate conflict with a utilitarian focus on the greatest good for society.<sup>6</sup>

Dr. Potts's concern about harm to living donors was a source of controversy in the 1960s but yielded to an appreciation of substantial psychological benefits, both personal and altruistic. Organ donors typically find great meaning in this life-sustaining experience. Emotionally related donors may also benefit personally when the recipient becomes socially productive and is relieved of suffering. There is an ethical conundrum, however, when the risks are high and when the surgeon's acceptance of those risks causes potential donors to feel obligated.

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## Luxury Primary Care

*To the Editor:* The article by Brennan on luxury primary care (April 11 issue)<sup>1</sup> was of particular interest to us as patients of a physician who notified us only two weeks in advance that he would eliminate us from his practice unless we joined MDVIP at a fee of \$1,500 per person per year.

Our reaction went from surprise to shock to indignation. For the most part, the services being offered were no different from those we have been receiving — that is, prompt responses to our telephone calls, timely appointments, and adequate examinations and consultation times.

We cannot believe that this kind of medical practice is legal. As Medicare patients, we are entitled to access to our physicians with nothing more than a 20 percent copayment. Without a doubt, if this practice is allowed to continue, we will have a two-tiered medical system in our country. How sad.

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1. Brennan TA. Luxury primary care — market innovation or threat to access? *N Engl J Med* 2002;346:1165-8.

*To the Editor:* I have been practicing “luxury” primary care for many years, since I am accessible to all my patients 24 hours a day, 7 days a week, and I do not even charge an annual fee. I allow such access because I strongly believe in practicing patient-centered medicine with joint decision making.

Granted, my practice is small. I am not part of any health maintenance organization, because I do not fit into the mainstream of contemporary medicine. My annual well-woman examination with a pap smear may take up to one and a half hours because I discuss with the patient any health-related concerns she may have. I want my patients to leave my office with all their questions satisfactorily answered and all concerns addressed.

Financially, I am not a huge success. Even as a practicing obstetrician-gynecologist many years ago, my largest gross annual income was less than \$200,000. Today, I supplement my income from my office by working elsewhere, and my gross income is about \$100,000 per year. But what is money? Serving my patients well is very important to me. Surely, I am not in the minority. I do not want to be in the rat race.

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*To the Editor:* Brennan inadequately addresses the association of many luxury primary care programs with teaching hospitals, where new doctors learn professional ethics and where standards of evidence-based medicine are developed and taught. The general public contributes substantially, through state and federal taxes, to the education and training of new physicians. Should those physicians limit their practices to the wealthiest fraction of our citizenry, when 43 million Americans lack health insurance, our country ranks near the bottom among Western nations in life expectancy and infant mortality, and racial and wealth-based disparities in access to care and outcomes abound?<sup>1</sup> For teaching institutions to promote luxury primary care in the face of these problems is to erode fundamental ethical principles of medicine, such as equity and justice, and such promotion will engender cynicism among trainees and the public.

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*To the Editor:* As physicians in the center of the controversy over luxury primary care, we were particularly struck by the absence of the patient’s voice in the review by Brennan. The current system of primary care is the creation not of doctors and patients, but of those who pay for care — in general, insurance intermediaries acting on behalf of employers or governments. Since this system is not designed by or for the patients we serve, it is not surprising that there

has been widespread dissatisfaction with the results it delivers. When those who pay for services are different from those who receive those services, problems arise. Some patients want something different, and we have responded to that desire.

Our practice is not an answer to the problems of the uninsured, nor is it offered as a solution for all patients or all doctors. Our practice is an answer to the needs of specific persons — patients and doctors — who have felt inadequately served by the system as it exists. We have risked our livelihoods and our reputations in an effort to prove that a better and different way of practicing medicine is possible. We believe that free choice and the marketplace of services and ideas are better alternatives than the status quo. Our success will be measured by our ability to deliver on our promises, as determined by the patients who choose our care.

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*To the Editor:* Brennan sets out to “examine the . . . ethical issues that arise with [luxury primary care] practices.” His chief concern is access, and he concludes with the prescriptive (as opposed to descriptive) statement that “as physicians we have a commitment to the equitable distribution of health care.” What is the basis for this statement? Certainly, most people believe that food and shelter are more important than medical care, yet there is no expectation that builders have an obligation to provide for the equitable distribution of housing or that supermarket chains have an obligation to provide for the equitable distribution of food. The origin of Brennan’s assertion lies in the concept, beloved by certain policy makers and health economists, of medical exceptionalism. Again, however, beyond the assertion that “medicine is different,” there is no argument to sustain such a belief. The distribution of resources belongs in the political arena, and ethical physicians of all stripes can advocate for whatever scheme they are committed to, but clearly equitable distribution is not a problem for the individual physician, no matter how guilty he or she can be made to feel.

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*To the Editor:* I take issue with the definition of luxury care given in Brennan’s article. Luxury is a subjective term that hints at extravagance, exclusivity, and exclusion. It troubles me when this term is used to describe activities that until recently were considered to be quite ordinary — in fact, the standard of care. The half-hour office visit may be a thing of the past, but it seems wrong to regard it as a luxury. In many instances, particularly in the case of an elderly patient with multiple medical problems, more than 15 minutes of a physician’s time is a necessity and not a luxury.

I think that the problem that is leading to plans such as “luxury primary care” is the woeful inadequacy of reimbursement for office-based medical care. The current standard for office visits of 15 minutes or less is not a matter of choice, but rather a matter of financial survival. With reimbursement rates as low as they are, a physician has to keep patient turnaround time short in order to keep a practice financially viable. The situation is made worse by the tendency of government to balance its budget at the expense of the medical practitioner. This year, Medicare cut payments to doctors by 5.4 percent, and additional cuts totaling 17 percent are anticipated during the next three years.<sup>1</sup> Meanwhile, overhead costs for medical practices continue to climb. For instance, medical-malpractice insurance premiums throughout the country are rising at an average annual rate of 30 percent.<sup>2</sup> Where will it all lead? Nowhere good, I’m afraid.

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*To the Editor:* I think you should comment on some other losses in the population of physicians who are practicing standard medicine. Could you comment on the ethics of physicians who choose to leave clinical medicine to earn master’s degrees in business administration and become physician-executives? Could you comment on physicians who subsequently attend law school and practice law? Could you comment on physicians who retire before becoming enfeebled or incompetent or 65 years of age? Finally, could you comment on the 13th Amendment to the U.S. Constitution and its applicability to persons holding the M.D. degree?

When I attended medical school, the teachers repeatedly articulated the concept that my fellow students and I acquired a special responsibility to society by attending a state-subsidized medical school. In exchange for life-and-death responsibility and hard work, society would offer us respect and remuneration substantially higher than that afforded the average worker.

My perception is that lawyers and bureaucrats have dismantled the implied social contract that was described to me when I was a medical student. Production pressure has diminished “the calling” of being a physician. It comes as no surprise to me that some physicians have found novel ways to support themselves.

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Dr. Brennan replies:

*To the Editor:* Bohan and I disagree sharply. I believe that our ethical commitment to patients does create a responsi-

bility to address the distribution of health care resources in the political arena. Medicine is different from other forms of commerce — we adhere to an explicit set of moral principles that give rise to professional responsibilities, including, I believe, the responsibility to address policy issues.

Unlike Flier et al., I do not believe that luxury primary care is a simple matter of choice for patients and doctors. I see it as part of what I believe is a long-term trend toward segmentation of the medical market into the haves and the have-nots. I think that the profession simply cannot tolerate structural inequalities in the ways in which sick people are treated and must resist libertarian, market-driven changes that create such inequities.

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### Botulinum Toxin, Sweating, and Body Odor

*To the Editor:* Since our description of the anhidrotic effect of injections of botulinum toxin A in humans,<sup>1</sup> there have been several studies confirming the efficacy and safety of botulinum toxin injections in several forms of focal hyperhidrosis, including the study reported in the *Journal* by Heckmann et al. (Feb. 15, 2001, issue).<sup>2</sup> The injections have been shown to be particularly useful in axillary hyperhidrosis and are now used widely.<sup>2,3</sup> The excellent response of axillary hyperhidrosis to botulinum toxin injections is due to the fact that the hyperactive sweat glands are usually localized in one or two small areas within the hair-bearing axillary skin. Since the toxin diffuses, causing a dose-dependent anhidrotic circle, two to three injections are usually sufficient to denervate the oval hair-bearing area of the axilla without decreasing the efficacy of the toxin.<sup>4</sup> However, in most published studies, as many as 14 injections were used, which makes the procedure unnecessarily painful. We recommend the use of only two to four injections in each axilla in order to minimize discomfort and risk.

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The authors reply:

*To the Editor:* Bushara et al. deserve credit for showing that as few as two injections of botulinum toxin A per axilla suffice to produce anhidrosis in healthy volunteers.<sup>1</sup> The rate of axillary sweat production is typically below 25 mg per minute in normohidrotic persons but can reach 1000 mg per minute in patients with hyperhidrosis. In view of this difference, it seems appropriate to adhere to injection protocols that have proven efficacy for treating severe axillary hyperhidrosis. When 30-gauge needles were used for 10 injections, 98.6 percent of our patients rated their tolerance of treatment as excellent or good.

There is a second difference between normohidrotic persons and those with hyperhidrosis: the former often report having unpleasant axillary odor, whereas the latter typically do not.<sup>2</sup> Body odor is attributed to the production by apocrine axillary sweat glands of a turbid secretion that has a pungent smell when it is degraded by microbes that are resident in the skin.<sup>3</sup> It has been suggested that apocrine activity in persons with hyperhidrosis does not parallel the activity of eccrine and apoecrine glands.<sup>2</sup> Some patients with hyperhidrosis become more aware of their body odor after botulinum toxin injections. In contrast, a substantial reduction in body odor was found in normohidrotic healthy volunteers in whom one axilla was injected with botulinum toxin A and then compared with the other axilla.<sup>4</sup> This finding further supports the concept that normohidrotic persons and those with hyperhidrosis differ in the quantity and quality of sweat secretion. Both the extent of moisture and the extent of odor of the axillary milieu differ. Therefore, the effects of botulinum toxin injections on the two variables are not the same in healthy volunteers and patients with hyperhidrosis.

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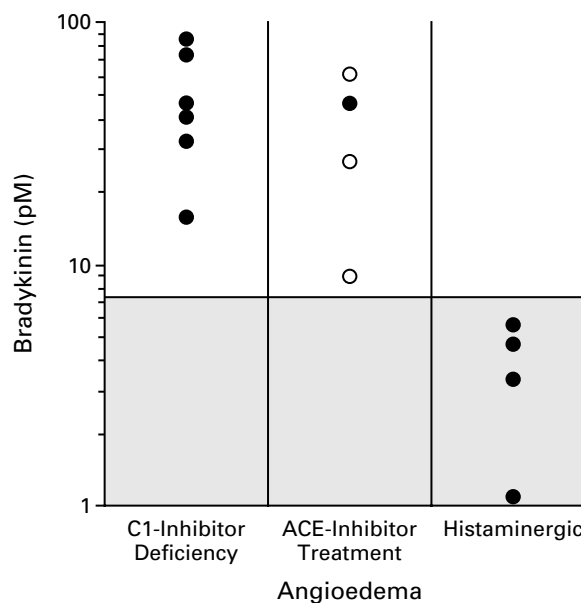
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### Bradykinin-Mediated Angioedema

*To the Editor:* Angioedema is a nonitchy, pale swelling of subcutaneous or submucosal tissue that tends to recur chronically and can become life-threatening if the swelling occurs in the upper airways or can be very painful if it oc-

curs in the gastrointestinal tract. Angioedema presenting together with urticaria<sup>1</sup> usually responds well to antihistamines and corticosteroids, whereas angioedema without urticaria is frequently resistant to such therapy but may respond to a C1 esterase inhibitor, tranexamic acid, or both<sup>2</sup> — therapies that can reduce bradykinin generation. These findings raise the question of whether bradykinin mediates angioedema.

We measured plasma bradykinin in patients with angioedema, with or without urticaria, during acute attacks, periods of remission, or both (Fig. 1).<sup>3</sup> Six patients with hereditary C1-inhibitor deficiency had very high bradykinin levels during attacks of antihistamine-resistant angioedema. This finding confirms previous data showing that bradykinin clearly increases during acute angioedema in such patients but is normal or marginally increased during remission.<sup>3</sup> Previous studies in two other patients with C1-inhibitor deficiency showed that bradykinin levels in blood draining from an angioedematous site were three and eight times as high as the levels in systemic circulation.<sup>4</sup> In three patients with a history of angioedema related to the use of angiotensin-converting-enzyme (ACE) inhibitors, bradykinin levels were high during ACE-inhibitor treatment. In a fourth, previously described patient,<sup>3</sup> the bradykinin level



**Figure 1.** Plasma Bradykinin Levels in Six Patients with Angioedema Due to Hereditary C1-Inhibitor Deficiency, Four Patients with Angioedema Related to Angiotensin-Converting-Enzyme (ACE) Inhibitors, and Four Patients with Urticaria and Angioedema That Responded to Antihistamines (Histaminergic Angioedema).

Plasma bradykinin-(1-9)nonapeptide was measured by radioimmunoassay after extraction by high-performance liquid chromatography. Solid circles denote bradykinin levels during acute attacks of angioedema, and open circles denote levels during remission. Each circle represents one patient. The shaded area indicates the normal range of venous plasma bradykinin levels (0.2 to 7.1 pM).

was 47.0 pM during an attack of angioedema and decreased to 3.2 pM after withdrawal of the ACE inhibitor.

In contrast, four patients with urticaria and angioedema that responded to antihistamines had normal levels of bradykinin during acute attacks of angioedema. In one of these patients, who had angioedema of one arm, venous bradykinin levels were normal in both arms.

Bradykinin appears to be involved in angioedema related to hereditary C1-inhibitor deficiency and in angioedema related to ACE inhibitors; both conditions are resistant to antihistamines. In contrast, bradykinin is minimally involved in urticarial angioedema that is responsive to antihistamines.

Hereditary or acquired deficiencies of C1 inhibitor, which lead to overproduction of bradykinin, are rare. However, nonurticarial angioedema is most frequently related to the use of ACE inhibitors. ACE, which is identical to kininase II, metabolizes bradykinin to its breakdown products. When ACE inhibitors are administered, ambient bradykinin levels increase. Angioedema is a complication of ACE-inhibitor therapy, with an incidence of 0.1 to 0.7 percent.<sup>5</sup> Given that approximately 35 million persons with hypertension or heart failure are currently being treated with ACE inhibitors, one might anticipate more than 100,000 cases of angioedema per year. An awareness of this issue and an understanding of the pathophysiology of angioedema — as suggested by

Osler in 1888 — can guide clinicians in providing appropriate therapy and can save lives.

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