Correspondence

Authors' Conflicts of Interest: A Disclosure and Editors' Reply

To the Editor: My recent article in the *Journal* (Sept. 23 issue)[1] has received some attention from the media, and I would like to clarify the facts.

In February 1998, Dr. Alastair Wood, editor of the *Journal*'s Drug Therapy series, invited me to submit a review article on the treatment of hair loss. He asked me to inform him of any equity interest I held in companies whose products would be discussed in the article and any consultancies or other financial support I had from such companies. I responded in writing to Dr. Wood that I was a consultant to two pharmaceutical companies whose products would be mentioned in the article (Merck and Company and Pharmacia & Upjohn), that I had no equity interest in either company, that I had never been an employee of either company, and that I would terminate my consultancy agreements with them immediately. At no time did I have a retainer from either company, and I was compensated on a per diem basis only.

In answer to Dr. Wood's question about financial support, I responded that I was an investigator in multicenter, double-blind clinical trials of finasteride for androgenetic alopecia and of topical minoxidil solution for androgenetic alopecia and alopecia areata, and that funds for conducting these trials were provided by the pharmaceutical companies to the University of California. I was told that this support did not disqualify me from writing the article.

Dr. Wood asked me to inform him if any outside person or organization was to be involved in the preparation of the manuscript. I was the only person involved in the preparation of the manuscript and, except for the reviewers chosen by the *Journal,* no one saw the manuscript before publication.

When I was invited to write the review article in February 1998, 1-mg finasteride and 5 percent topical minoxidil solution had been available as drugs approved by the Food and Drug Administration for approximately one month. At that time, in my view, the clinical investigators who conducted the double-blind trials and therefore had first-hand knowledge of the efficacy, limits, and side effects of the two drugs were those who could best write about them.

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1. Price VH. Treatment of hair loss. N Engl J Med 1999;341:964-73.

Editors' reply:

The *Journal*'s conflict-of-interest policy prohibits authors of editorials and review articles from having "current, recent past, or planned future financial associations (such as equity interest, consultancies, or major research support) with a company that stands to gain from the use of a product (or its competitor) discussed in the editorial or review article." At the time Dr. Price was asked to write her review article, she was consulting for Merck and Upjohn and received the majority of her research support from them.

The discrepancy between policy and practice in this case was not the fault of Dr. Price. As she explains, she informed Dr. Wood, the editor of our Drug Therapy series, whose office is in Nashville, of her consultancies with Merck and Upjohn and of her research support from them. Dr. Wood assured Dr. Price that it would be permissible for her to write a review article for the *Journal* if she discontinued her consultancy arrangements, and they exchanged letters to that effect. Those letters were reviewed in our Boston office, and we did not question them — which, to conform with our written policy, we should have done.

As for research support, Dr. Wood has not routinely

considered support from companies that is given through researchers' institutions to constitute a conflict of interest, nor has he routinely tried to distinguish between major and minor research support. In this case, he ascertained that Dr. Price had research support from Merck and Upjohn given through her institution.

Dr. Price signed our standard form attesting that she had no major financial associations with relevant companies, but she understandably assumed that her assurances from Dr. Wood took precedence.

In view of the differences between our stated policy and the way it has been interpreted with respect to Drug Therapy articles, both in Nashville and in Boston, we are now looking into the possibility that authors of other published articles in this series may have had financial associations with pharmaceutical companies that were incompatible with our stated policy. We will disclose the facts when we have reviewed them. In addition, it is possible that authors of Drug Therapy articles in preparation may have major research support from relevant companies or recent consultancy arrangements. Since it would be unfair to reject those articles after their authors acted in good faith, we will simply disclose such support at the time of publication.

Authors of newly solicited and all future review articles will be held strictly to our stated policy. We will continue to decide whether research support is major on a case-by-case basis. Minor research support will not preclude authorship but will be disclosed to readers at the time of publication.

Our conflict-of-interest policy for editorials and review articles is the most stringent of any medical journal, and it is stricter than our policy for original research articles, which requires only disclosure. For reasons made clear in earlier editorials,[1-3] we believe it is important that authors of editorials and review articles have no significant financial associations with companies that make products they discuss in those articles. It is a difficult policy to maintain, because of the increasing connections between clinical researchers and the companies that make the products they study. Nevertheless, it is our intention to continue the policy and to redouble our efforts to bring our practice into conformity with it.

We regret the recent confusion about this matter and apologize to Dr. Price for any difficulty it has caused her.

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ALASTAIR J.J. WOOD, M.D.

1. Relman AS. New "Information for Authors" — and readers. N Engl J Med 1990;323:56.
2. Kassirer JP, Angell M. Financial conflicts of interest in biomedical research. N Engl J Med 1993;329:570-1.
3. Angell M, Kassirer JP. Editorials and conflicts of interest. N Engl J Med 1996;335:1055-65.

Reimbursement for Evaluation and Management Services

To the Editor: Lasker and Marquis (July 29 issue)[1] offer a simple scheme to deal with the complexities of reimbursement for medical services, but it suffers from two major flaws, which the authors themselves point out. First, the system can easily be "gamed." Because payment rates decline as more time is spent with a patient, income can be maximized by fragmenting care — treating two problems in two short visits rather than in one long one. More seriously, this payment scheme provides a very strong disincentive to treat difficult or time-consuming conditions, further aggravating the trend in managed care toward preferential treatment of patients with minor problems.

Stripped to its essence, the proposed scheme is to pay physicians on a piecemeal basis — so many dollars for so many visits per hour. It is a payment system that was tried by industry earlier in the century and largely abandoned because it was considered ineffective in a modern society. The system, which is still used to pay minimally skilled laborers in some Third World countries, rewards quantity over quality, speed over skill.

Lasker and Marquis's scheme is certainly a solution for the evaluation and management–coding morass, but the price will be further degradation in the quality of the medical care provided to our most seriously ill citizens.

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1. Lasker RD, Marquis MS. The intensity of physicians' work in patient visits — implications for the coding of patient evaluation and management services. N Engl J Med 1999;341:337-41.

To the Editor: We have a strong sense of *déjà vu*. We analyzed the resource costs of evaluation and management services as a fundamental part of the resource-based relative-value scale (RBRVS) study. In 1988, we reported that regardless of the type of evaluation and management service, the site at which it is performed, or the specialty of the physician performing it, the level of work per unit of time varied only slightly.[1] By 1992, we had surveyed more than 4000 physicians in 31 specialties on roughly 400 evaluation and management services, using vignettes that panels of clinicians had drafted. Multiple regression analyses showed that intraservice time (encounter time for office visits and consultations and time on the unit for hospital visits) predicted 90 percent of the variation in the level of work. Objective criteria, including the site of the service, whether the patient was new or established, and referral status, predicted a portion of the remaining 10 percent.[2] We therefore recommended using time and these other criteria to bring *Current Procedural Terminology* (CPT) codes for evaluation and management services into closer accord with resource costs.[1,2]

Lasker and Marquis support our finding that intraservice time is a powerful predictor of physicians' perceptions of the work involved in evaluation and management services. Furthermore, whereas Lasker and Marquis surveyed 399 urologists, rheumatologists, and general internists about actual consultations and office and hospital visits and Iezzoni, in an accompanying editorial, noted that "calibrating their system would require new data on diverse specialties,"[3] we had surveyed 10 times that number of physicians in every specialty and major subspecialty, using vignettes involving office, hospital, consultative, nursing home, critical care, and emergency services, according to established RBRVS study methods.

In its 1989 annual report to Congress, the Physician

Payment Review Commission stated, "The coding system for evaluation and management services should be revised so that visits are classified on the basis of time as well as site of service, type of patient and referral status."[4] Indeed, the Health Care Financing Administration (HCFA) set the relative-value units for the work involved in evaluation and management services by selecting an intraservice time for each code and taking the level of work directly from our curves for work and time. Unfortunately, the American Medical Association's CPT Editorial Panel has defined evaluation and management services increasingly on the basis of content. Moreover, the resource costs of evaluation and management services performed according to current, content-based CPT documentation guidelines have, to our knowledge, not been studied.

The empirical evidence that time is an excellent predictor of physicians' work and the principle of avoiding needless administrative interference in how physicians practice lead us to urge again that intraservice time be used as a criterion for determining and documenting the CPT codes for evaluation and management services.

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1. Braun P, Hsiao WC, Becker ER, DeNicola M. Evaluation and management services in the Resource-Based Relative Value Scale. JAMA 1988; 260:2409-17.
2. Braun P, Dernburg J, Dunn DL, Cohen W. Predicting the work of evaluation and management services. Med Care 1992;30:Suppl:NS13-NS27.
3. Iezzoni LI. The demand for documentation for Medicare payment. N Engl J Med 1999;341:365-7.
4. Annual report to Congress, 1989. Washington, D.C.: Physician Payment Review Commission, 1989.

To the Editor: The most appropriate code for evaluation and management services is a dollar sign followed by the appropriate digits and decimal points. We now have sufficient information about what is involved in various medical services to establish the validity of such a code by having an experienced clinician evaluate the medical record. Everything from patients' complaints to statistical outliers could be used to trigger such inspections. Physicians found to have charged low fees could be given a gold star; in the case of ordinary fees, nothing would happen. Physicians whose fees were a little too high would receive a warning, those whose fees were very high would be thoroughly investigated and might have to refund money, and those whose fees were exorbitant or were for services that had not been performed would be charged with fraud and put in jail. The possibility of such an investigation would be just as effective as the possibility of an audit by the Internal Revenue Service in the case of an income tax return.

The coding industry has become a fraud itself. It is wasteful and abusive in the extreme.

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To the Editor: . . . If 10 percent of health care dollars are lost to fraud and abuse, that means that 90 percent of the claims are appropriate. Most health care providers do the right thing even with perverse incentives built into the system, so we should not be afraid of the flaws in Lasker and Marquis's proposal. As Iezzoni points out, "their general framework is . . . reasonable, straightforward, and consistent with clinical practice." I believe we should adopt it now, while calibrating it to current data and working out the problems, rather than wait for it to be perfected. Their proposed system is no worse than the system we have today, it is much simpler to use, and I suspect it represents the way in which many physicians really do their coding in the privacy of their offices. Physicians should pressure HCFA to adopt a time-based system now and spend its money on evaluating and refining it rather than trying to fine-tune the current arcane and cumbersome system.

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To the Editor: Reading the article by Lasker and Marquis, I was reminded of the Gary Larson cartoon in which, after covering a blackboard with sophisticated and arcane mathematical equations, Einstein discovers that time equals money.

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To the Editor: Lasker and Marquis's attempt at solving the problem of reimbursement for medical services is courageous and daring. Yet it does not take into account a vital part of care involving complex situations: the research and paperwork required for a large number of patients as part of their health care. I shall call it the after-office-hours work, which is often as important as the face-to-face encounter. This work includes but is not limited to telephone consultations with patients and other physicians, completion of insurance forms, and written requests for nonformulary medications. All other professionals who have a consulting role (accountants, lawyers, engineers, marketing experts, and others) charge a fee for time that is real but does not involve face-to-face encounters. In a primary care setting, a large portion of the day, and often the night, is spent reviewing charts, studying cases, reviewing recent literature, filling out forms, and making multiple calls about patients' problems. Is this time to be considered a free service when it comes to medical care?

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To the Editor: . . . Life would be simpler if all physicians were paid according to a fixed formula based on the worldwide standard for measuring labor: actual time spent

working with the patient. The following formula appears reasonable: $50 for the first 20 minutes, $35 for the next 20 minutes, and $30 for each additional block of 20 minutes. To prevent the dehumanization of medical care, provision of low-quality care, and assembly-line economics, there should be no reimbursement for seeing more than three patients in an hour.

Minor adjustments will be necessary to account for differences in overhead and malpractice costs, length of subspecialty training, and differences in the cost of living. But in the long run, a fixed formula for paying physicians will prevent medicine from degenerating into a branch of science that is preoccupied with irrelevant documentation, bizarre codings, and artful billing.

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To the Editor: Primary care physicians face coding dilemmas every day. How do I code for the visit of a patient who presents for periodic follow-up of stable diabetes, hypertension, and hyperlipidemia but who also wants me to evaluate a new skin lesion and a newly sore knee and to suggest a treatment for periodic constipation? Not uncommonly, this same patient will have contracted an upper respiratory infection two days before the visit and will expect me to evaluate and treat it, too — all in a 15-minute visit. I face this type of scenario multiple times a day. The "oh, by the way's" that patients with stable chronic conditions save up for their regular visits to their doctors are a financial disaster for primary care physicians.

Lasker and Marquis's proposed coding scheme suffers from the same deficiency that the current CPT evaluation and management guidelines do. Both approaches assume that the physician is dealing with only one problem at a time or, with the CPT guidelines, up to three stable chronic problems. Until a coding scheme is developed that encompasses a mix of chronic, acute, and subacute problems, primary care physicians are left with four bad options for dealing with these visits. We can bend the guidelines and bill at the next higher level, bill for each service separately with the CPT code "-25" modifier (and usually not get paid for the extra services), bill for the service with the highest charge and give away the rest of the care, or require the patient to come back on a separate day for each problem. Obviously, all these options are less than satisfactory.

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To the Editor: Lasker and Marquis's proposal for simplifying coding for physicians' services is certainly "reasonable, straightforward, and consistent with clinical practice," as Iezzoni notes in the accompanying editorial. It is also familiar.

Long before the current enthusiasm for increasingly complex documentation, the general internal medicine department in our large multispecialty group practice used simple guidelines to charge for outpatient care. They were based on time with fees weighted in favor of shorter visits, and distinctions among visits involving new, returning, and referred patients were made.

As far as I can make out, this arrangement was just what Lasker and Marquis now propose. And it worked well. Since current coding policies seem to satisfy no one, it may be time for HCFA to go "back to the future" and adopt a plan that is simple, fair, and cheap.

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The authors reply:

To the Editor: We appreciate the support by Drs. Goldman, Kelwala, and Gutknecht for the simple reimbursement framework we proposed. Their comments are in accord with the feedback we have received directly from the medical community.

Dr. Bystryn is concerned that our scheme is a piece-rate system, which rewards quantity rather than quality. Although all fee-for-service reimbursement systems have incentives to provide more services (and none, to our knowledge, reward a good outcome or high quality), the system we propose is intended to achieve equity by paying physicians in proportion to their work. The scheme uses easily measured proxies for total work — face-to-face encounter time, new or established patient, new or ongoing problem, and referral or nonconsultative care — thereby reducing the burden of documentation. It reflects the work involved in treating patients by providing higher payments for longer visits than for shorter visits and by paying more per unit of time for types of visits that are more complex or that require more intensive care. Yet the scheme also rewards physicians who are efficient in delivering care — that is, those who deliver care that is similar to the care provided by other physicians but in a shorter period of time.

We agree with Dr. Gutman that "after-office-hours" work is as important as the face-to-face encounter. Indeed, the system we propose explicitly recognizes, and pays for, this effort. Although the coding in our scheme is based on blocks of encounter time, physicians would be paid according to the total amount of their work (i.e., the work they perform before, during, and after the face-to-face encounter with the patient). One reason that our scheme does not increase the payment in proportion to the amount of time spent in a face-to-face encounter is that shorter visits were shown to involve more time before and after the encounter than were longer visits.

Our finding that face-to-face encounter time is correlated with physicians' work in a study of actual visits substantiates the findings of Braun and his colleagues, who studied hypothetical visits. Moreover, the actual visits we studied included the full range of problems that physicians address during a single visit. Thus, contrary to Dr. Reynolds's concern, our scheme does not assume that the physician is dealing with only one problem, but instead reflects the mixture of problems in actual practice. Despite this mixture, we find that much of the variation in total work can be accounted for by a few easily measured and documented

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characteristics, and it does not require detailed and complex coding of the content of the visit.

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To the Editor: In their totality, the letters confirm impressions of recent years: that debates about the coding of evaluation and management services engender strong emotions; that considerable energy is being expended on this topic, diverting attention from more pressing matters related to patient care; and that consensus about an optimal coding scheme is impossible to achieve. These letters largely reinforce my plea that HCFA move expeditiously to a straightforward approach for coding evaluation and management services that is consistent with clinical practice. In an increasingly electronic environment for medical-records documentation, it is unreasonable to expect the coding system to be the bulwark against Medicare fraud. Time — that vanishing commodity — should be spent on patient care, not on needless documentation and complex decision algorithms for quantifying that care.

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Neostigmine for Acute Colonic Pseudo-Obstruction

To the Editor: Ponec et al. (July 15 issue)[1] reported that treatment with neostigmine rapidly decompresses the colon in patients with acute colonic pseudo-obstruction who have not had a response to conservative therapy. Symptomatic bradycardia, however, developed in two patients.

Because bradycardia is a well-recognized and important complication of neostigmine therapy, use of neostigmine for reversal of neuromuscular blockade in the operating room is always accompanied by administration of an antimuscarinic anticholinergic agent such as atropine or glycopyrrolate. Although the authors recognized that administration of glycopyrrolate has not been shown to decrease colonic motility, they did not administer it prophylactically. Vital signs were monitored before the injection of neostigmine and 5 and 30 minutes after injection. Since vital signs were not continuously monitored, asymptomatic bradycardia might not have been detected, and thus the true incidence of important bradycardia might have been underestimated. Moreover, even if bradycardia is treated, the effects of neostigmine may outlast those of glycopyrrolate or atropine.

We recommend that patients who are given neostigmine for colonic pseudo-obstruction also receive either atropine or glycopyrrolate prophylactically and that they be monitored continuously by electrocardiography and blood-pressure measurement for one hour after neostigmine administration.

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1. Ponec RJ, Saunders MD, Kimmey MB. Neostigmine for the treatment of acute colonic pseudo-obstruction. N Engl J Med 1999;341:137-41.

To the Editor: We have been using neostigmine to treat patients with acute colonic pseudo-obstruction for more than six years and have found it to be extremely effective and safe.[1] However, we are concerned that some patients in the study by Ponec et al. — specifically, those with air in the rectosigmoid colon on plain abdominal radiography — did not receive radiographic contrast enemas to rule out a mechanical obstruction. In our experience and that of others,[2] the presence of air at the presumed rectosigmoid junction in association with dilatation of the proximal colon can be misleading and can wrongly imply the absence of an obstructing lesion. Such a false sense of reassurance can lead to incorrect diagnosis and treatment of a patient with a potent colonic stimulant such as neostigmine.[3] This can have severe adverse consequences.

We believe that a water-soluble contrast enema should be used for all patients with possible acute colonic pseudo-obstruction when pharmacologic treatment with neostigmine is considered. Also, over the past four years, we have used a combination of glycopyrrolate and neostigmine (Robinul-Neostigmine, Wyeth Laboratories) (500 μg and 2.5 mg, respectively) to good effect in seven consecutive patients in the intensive care unit who had acute colonic pseudo-obstruction.[4] None had even a transient bradycardia.

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ALISON EVANS, M.B., B.CH.
BRIAN M. STEPHENSON, F.R.C.S.
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1. Stephenson BM, Morgan AR, Drake N, Salaman JR, Wheeler MH. Parasympathomimetic decompression of acute colonic pseudo-obstruction. Lancet 1993;342:1181-2.
2. Stewart J, Finan PJ, Courtney DF, Brennan TG. Does a water soluble contrast enema assist in the management of acute large bowel obstruction: a prospective study of 117 cases. Br J Surg 1984;71:799-801.
3. Trevisani G, Hyman N, Church J. Neostigmine: a new treatment for Ogilvie's syndrome. Dis Colon Rectum 1998;41:A29. abstract.
4. Stephenson BM, Morgan AR, Salaman JR, Wheeler MH. Ogilvie's syndrome: a new approach to an old problem. Dis Colon Rectum 1995;38: 424-7.

To the Editor: I was surprised by the enrollment of an obviously very sick patient in the study by Ponec et al. The authors stated that "one patient, who was subsequently randomly assigned to the placebo group, was enrolled after only 18 hours of conservative therapy, when the consulting gastroenterologist determined that urgent decompression was warranted." I wonder how they justify their disregard of the patient's consultant, who obviously as-

sessed the situation as urgent. What was the outcome for this patient?

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To the Editor: In 1948, Ogilvie described two cases of large-intestine colic due to sympathetic deprivation associated with abdominal carcinoma.[1] No massive distention was found. To refer to massive distention of the colon without mechanical obstruction as "Ogilvie's syndrome" is not appropriate.

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1. Ogilvie H. Large-intestine colic due to sympathetic deprivation: a new clinical syndrome. BMJ 1948;2:671-3.

The authors reply:

To the Editor: We appreciate the comments of Abbasakoor and colleagues and acknowledge that the report by Stephenson et al.[1] was one of the reasons we performed our controlled study. We also are concerned about the use of neostigmine in the presence of mechanical obstruction and agree that contrast radiography should be used to rule out obstruction if plain abdominal radiographs do not have the classic appearance of acute colonic pseudo-obstruction. We cannot agree, however, that contrast radiography must be performed in all cases, since in the right clinical setting, plain abdominal radiographs with classic findings are seldom incorrect.

Vavilala and Lam discuss the importance of monitoring patients when they are given neostigmine. We agree with this and monitor all our patients continuously with portable electrocardiographic and automated blood-pressure equipment for 30 minutes after infusion of neostigmine. Our protocol called for atropine for patients who had symptomatic bradycardia. We are very interested in the potential application of glycopyrrolate as a means of avoiding this adverse effect of neostigmine, as suggested by both Abbasakoor et al. and Vavilala and Lam, and look forward to the results of a controlled trial to prove its efficacy.

Pierach raises an important point with regard to the use of neostigmine. Patients whose cardiovascular or respiratory condition is unstable should probably not receive neostigmine. Thus, we adhered to the strict inclusion and exclusion criteria listed in the Methods section of our article. With regard to the specific patient mentioned, he was offered entry into the study early because the consulting gastroenterologist did not believe that he should wait for an additional 6 hours to allow the 24 hours of conservative therapy otherwise required before study entry. According to our protocol, patients who did not have decompression three hours after infusion of the study drug were offered open-label neostigmine, as was this particular patient, who had a response to open-label treatment. The protocol was designed in this manner specifically to avoid the ethical dilemma described by Pierach.

Finally, as Nicholson points out, it may be a misnomer to use the term "Ogilvie's syndrome" to refer to acute colonic pseudo-obstruction. In his original report of two patients with widespread cancer, Ogilvie called attention to the importance of a balanced autonomic nervous system for maintenance of colonic function. His patients, however, actually presented with chronic symptoms. Ironically, today we would probably not diagnose acute colonic pseudo-obstruction in his two patients.

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1. Stephenson BM, Morgan AR, Drake N, Salaman JR, Wheeler MH. Parasympathomimetic decompression of acute colonic pseudo-obstruction. Lancet 1993;342:1181-2.

DNA Vaccines

To the Editor: Indeed, vaccines are among the triumphs of medical science. However, the enthusiasm of Seder and Gurunathan (July 22 issue)[1] must be tempered with prudent restraint. They understate the potential harm to the patient evoked by "a strong cellular immune response not only against the microbial antigen but also against the host's own antigens." Producing immunity by genetically engineered vaccines should not involve a risk of producing disease by immunostimulatory nucleotide sequences contained in plasmid vectors.

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1. Seder RA, Gurunathan S. DNA vaccines — designer vaccines for the 21st century. N Engl J Med 1999;341:277-8.

The authors reply:

To the Editor: We appreciate the thoughtful comments of Dr. Freis regarding the potential danger of inducing an autoimmune disease after inducing a cellular immune response by DNA vaccination. Indeed, in our concluding paragraph we wrote, "We must also keep in mind that DNA vaccines could provoke a strong cellular immune response not only against the microbial antigen but also against the host's own antigens, thereby causing more harm than good." We believe that this warning clearly and unequivocally states the potential dangers of inducing a strong cellular immune response by DNA vaccination.

Autoimmune diseases can be devastating, but the clinical course of disease in patients with malaria, tuberculosis, or human immunodeficiency virus infection is equally if not more devastating. Because of the enormity of the morbidity and mortality caused by these diseases, the benefits of successful DNA vaccines against them would have to be carefully weighed against the potential dangers. The potential risks, however, should not impede the careful use in scientific and clinical studies of DNA vaccines

against diseases for which current vaccines have not been successful.

Finally, although it is still early, clinical studies in which DNA vaccines are used in humans have not shown any deleterious side effects.

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The Effects of Vancomycin and β-Lactam Antibiotics on Vancomycin-Resistant *Staphylococcus aureus*

To the Editor: First Sieradzki et al.[1] and then Climo et al.[2] presented evidence that combinations of vancomycin and β-lactam antibiotics were synergistic in vitro and in vivo against vancomycin-resistant *Staphylococcus aureus*. We performed population analyses to examine the effectiveness of combinations of vancomycin and β-lactam antibiotics against *S. aureus* strains with various levels of vancomycin resistance: Mu 3 and Mu 50[3] (provided by Keiichi Hiramatsu, Juntendo University) and wound isolates Fu 10 and Fu 18, which were recovered from a patient receiving combination therapy with β-lactam antibiotics and vancomycin in our hospital.

Figure 1A shows the results of the population analysis of Fu 10, Fu 18, Mu 3, and Mu 50, plus a reference strain, FDA 209P (American Type Culture Collection 6538P). Fu 10 and Mu 3 had similar levels of resistance to vancomycin, and Fu 18 had a higher level of resistance, although not as high as that of Mu 50. Figures 1B, 1C, 1D, and 1E show the effects of combinations of oxacillin and vancomycin on Fu 10, Mu 3, Fu 18, and Mu 50, respectively. The population-analysis profiles indicate that a high concentration of oxacillin (8.0 μg per milliliter) induced a reduction in the number of subpopulations resistant to vancomycin, as Sieradzki et al.[1] and Climo et al.[2] indicated. However, at a low concentration of oxacillin — 0.05 μg per milliliter — the number of surviving colonies increased. For example, in the presence of 8.0 μg of vancomycin per milliliter and 0.05 μg of oxacillin per milliliter, the numbers of surviving colonies of Mu 50 were about 200 times as high as those exposed to vancomycin alone. Hence, an antagonistic effect was seen (arrow in Fig. 1E).

It is likely that the vancomycin concentration at which the most prominent antagonistic effect of oxacillin is observed increases in proportion to the degree of vancomycin resistance (e.g., 2.0 and 3.0 μg per milliliter for Fu 10, 4.0 and 5.0 μg per milliliter for Fu 18, and 8.0 and 9.0 μg per milliliter for Mu 50). Such antagonistic activity was also demonstrated with another β-lactam antibiotic, ceftizoxime (Fig. 1F). Such low concentrations of β-lactam antibiotics are present in tissues or plasma of patients during treatment. Our data on the effect of combination therapy with vancomycin and β-lactam antibiotics on *S. aureus* with low or intermediate levels of resistance to vancomycin suggest that these combinations should be used with caution to avoid precipitating greater resistance to vancomycin.

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1. Sieradzki K, Roberts RB, Haber SW, Tomasz A. The development of vancomycin resistance in a patient with methicillin-resistant *Staphylococcus aureus* infection. N Engl J Med 1999;340:517-23.
2. Climo MW, Patron RL, Archer GL. Combinations of vancomycin and β-lactams are synergistic against *Staphylococci* with reduced susceptibilities to vancomycin. Antimicrob Agents Chemother 1999;43:1747-53.
3. Hiramatsu K, Aritaka N, Hanaki H, et al. Dissemination in Japanese hospitals of strains of *Staphylococcus aureus* heterogeneously resistant to vancomycin. Lancet 1997;350:1670-3.

Priming with Human Chorionic Gonadotropin before Retrieval of Immature Oocytes in Women with Infertility Due to the Polycystic Ovary Syndrome

To the Editor: Women who have infertility due to anovulation in association with the polycystic ovary syndrome are particularly difficult to treat. A substantial proportion have no response to the induction of ovulation, and those who do have a response are at increased risk for the ovarian hyperstimulation syndrome. This syndrome is characterized by massive ovarian enlargement, ascites, pleural effusion, oliguria, hydrothorax, hemoconcentration, electrolyte disturbances, and in the most severe cases, thromboembolic phenomena related to coagulation disturbances. A woman with the polycystic ovary syndrome who became pregnant after in vitro maturation of oocytes and in vitro

Figure 1. Results of Population Analyses of Strains of *Staphylococcus aureus* with Various Levels of Resistance to Vancomycin.

Panel A shows the results for Mu 50, Fu 18, Mu 3, Fu 10, and FDA 209P, a reference strain. Fu 10 and Fu 18 had identical phenotypes (confirmed by analysis with API-Staph Trac, Bio-Merieux) and identical banding patterns on pulsed-field gel electrophoresis. The minimal inhibitory concentrations of vancomycin for these strains were as follows: Mu 3, 2.0 μg per milliliter; Mu 50, 8.0 μg per milliliter; Fu 10, 2.0 μg per milliliter; and Fu 18, 4.0 μg per milliliter. In Panels B through F, cultures of Fu 10 (Panel B), Mu 3 (Panel C), Fu 18 (Panel D), and Mu 50 (Panels E and F) were incubated overnight and plated at different concentrations on four sets of brain–heart infusion agar plates: the first set contained various concentrations of vancomycin alone (open circles); the second and third sets contained the same concentration of vancomycin as well as 0.05 μg of oxacillin per milliliter (open triangles), 0.5 μg of oxacillin per milliliter (solid triangles), or 0.05 μg of ceftizoxime per milliliter (squares); and the fourth set contained the same concentration of vancomycin with 8.0 μg of oxacillin per milliliter (inverted open triangles) or 16.0 μg of ceftizoxime per milliliter (solid circles). The arrow in Panel E indicates the antagonistic effect on vancomycin resistance of a high concentration of oxacillin (8.0 μg per milliliter).

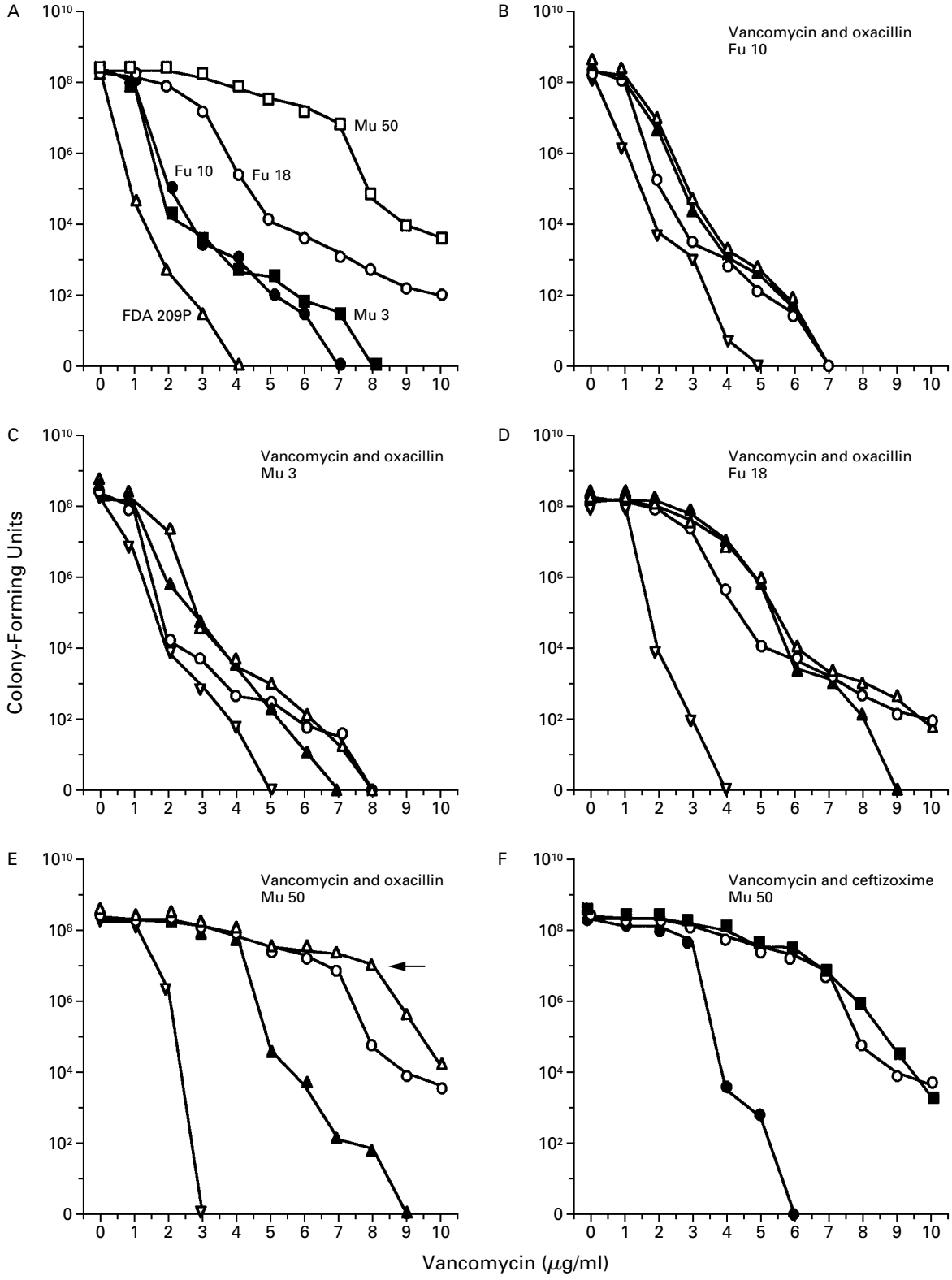

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TABLE 1. RESULTS OF IN VITRO MATURATION AND FERTILIZATION OF OOCYTES FOLLOWED BY EMBRYO TRANSFER IN 20 WOMEN WITH THE POLYCYSTIC OVARY SYNDROME.*

VARIABLE	VALUE
Cycles of in vitro fertilization	25
Age — yr	35.4±4.7
Oocytes retrieved — no.	
Total	249
Mean	10.3±5.4
Oocytes matured — no. (%)	209 (84)
Oocytes fertilized — no. (%)	182 (87)
Embryos cleaved — no. (%)	173 (95)
Embryos transferred — no.	
Total	73
Mean	2.9±0.6
Clinical pregnancies — no. (%)	10 (40)
Implantation — no. (%)	8 (32)

*Plus–minus values are means ±SD.

fertilization was described in 1994.[1] Subsequently, very few pregnancies have been reported in such women, largely because the maturation and fertilization rates of these immature oocytes have been low.[2] We report the results of 25 cycles of in vitro fertilization in 20 women with the polycystic ovary syndrome. There was in vitro maturation of immature oocytes retrieved from all 20 women after priming with human chorionic gonadotropin.

The patients were less than 41 years of age (mean age, 35.4) and had not become pregnant after at least six cycles in which either clomiphene citrate or menotropins were given to induce ovulation. To initiate the treatment cycle, the patients received intravaginal progesterone suppositories at a dose of 300 mg for 10 nights to induce withdrawal menstrual bleeding. Retrieval of immature oocytes was scheduled on day 10 to 14 of the cycle, and 10,000 IU of human chorionic gonadotropin was administered 36 hours before the retrieval. Immature oocytes were cultured in an organ–tissue culture dish (60 by 15 mm) containing 1 ml of maturation medium, TC-199 medium supplemented with the patient's own serum at a concentration of 20 percent (inactivated by incubation at 56°C for 30 minutes), 25 mM pyruvic acid, and 75 mIU of menotropins per milliliter (follicle-stimulating hormone and luteinizing hormone; Humegon) for 24 or 48 hours at 37°C in an atmosphere of 5 percent carbon dioxide and 95 percent air with high humidity. The mature oocytes were then inseminated by intracytoplasmic sperm injection, and the embryos were transferred two or three days later.

The results are shown in Table 1. The oocyte-maturation rate of 84 percent (209 of 249 oocytes) was higher than previously reported rates.[3,4] Ten women became pregnant, three of whom had not conceived during previous cycles of conventional in vitro fertilization. As of September 1999, three of the women had given birth, two had had miscarriages, and five were still pregnant. A total of four healthy infants have been born (one set of twins and two singletons). These results provide evidence that priming with human chorionic gonadotropin before the retrieval of immature oocytes has a role in the treatment of women with infertility due to anovulation in association with the polycystic ovary syndrome.

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1. Trounson A, Wood C, Kausche A. In vitro maturation and the fertilization and developmental competence of oocytes recovered from untreated polycystic ovarian patients. Fertil Steril 1994;62:353-62.
2. Cha KY, Chian RC. Maturation in vitro of immature human oocytes for clinical use. Hum Reprod Update 1998;4:103-20.
3. Barnes FL, Crombie A, Gardner DK, et al. Blastocyst development and birth after in-vitro maturation of human primary oocytes, intracytoplasmic sperm injection and assisted hatching. Hum Reprod 1995;10:3243-7.
4. Barnes FL, Kausche A, Tiglias J, Wood C, Wilton L, Trounson A. Production of embryos from in vitro-matured primary human oocytes. Fertil Steril 1996;65:1151-6.