

Correspondence



Voriconazole versus Liposomal Amphotericin B for Empirical Antifungal Therapy

To the Editor: The report by Walsh et al. (Jan. 24 issue)¹ of a trial of voriconazole, as compared with liposomal amphotericin B, for patients with neutropenia and persistent fever and the accompanying editorial and letter to the editor^{2,3} leave many questions about what the trial actually demonstrated and how the findings should be applied. The abstract implies that the study showed equivalence and concludes, "Voriconazole is a suitable alternative to amphotericin B preparations." Yet the text and the accompanying editorial point out that the prespecified statistical criterion for equivalence was not met. To confuse the issue further, correspondents from the Food and Drug Administration provide alternative data, indicating that voriconazole was actually statistically inferior to liposomal amphotericin B with respect to overall success rates.³ Thus, whether the study showed equivalence, near equivalence, or frank inferiority remains unclear.

Even if equivalence had been demonstrated, the clinical implications of the findings would remain uncertain. Therapeutic decision making must take into account not just efficacy and safety, as emphasized in the editorial,² but also cost. Avoidance of toxic effects may allow a net cost savings despite higher drug acquisition costs,⁴ but that possibility requires empirical demonstration.

JAMES R. JOHNSON, M.D.

Minneapolis Veterans Affairs Medical Center
Minneapolis, MN 55417
johns007@tc.umn.edu

1. Walsh TJ, Pappas P, Winston DJ, et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med* 2002;346:225-34.
2. Marr KA. Empirical antifungal therapy — new options, new tradeoffs. *N Engl J Med* 2002;346:278-80.
3. Powers JH, Dixon CA, Goldberger MJ. Voriconazole versus liposomal amphotericin B in patients with neutropenia and persistent fever. *N Engl J Med* 2002;346:289-90.
4. Cagnoni PJ, Walsh TJ, Prendergast MM, et al. Pharmacoeconomic analysis of liposomal amphotericin B versus conventional amphotericin B in the empirical treatment of persistently febrile neutropenic patients. *J Clin Oncol* 2000;18:2476-83. [Erratum, *J Clin Oncol* 2000;18:3064.]

To the Editor: The trial by Walsh et al., which compared voriconazole with liposomal amphotericin B for the empirical treatment of neutropenic fever, presents a dilemma in conducting this type of study. Major goals in the empirical treatment of neutropenic fever include survival, defervescence, and the prevention of infections. Whether this composite end point is appropriate for the evaluation of an antifungal drug remains controversial. A previous trial reported by Walsh et al. underscores this problem. Numerous unknown additional variables in both studies probably account for the difference in the efficacy rates for liposomal amphotericin B despite a similar study design (effective in 129 of 422 patients [30.6 percent] in the current trial vs. 172 of 343 [50.1 percent] in the earlier trial).^{1,2} In our opinion, the main end points for this type of trial should focus only on the prevention of fungal infections, survival, and tolerance of the new drug.

ANDREW J. ULLMANN, M.D.
CLAUS PETER HEUSSEL, M.D.
Johannes Gutenberg University
55101 Mainz, Germany

OLIVER A. CORNELLY, M.D.
University of Cologne
50924 Cologne, Germany

1. Walsh TJ, Finberg RW, Arndt C, et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. *N Engl J Med* 1999;340:764-71.

INSTRUCTIONS FOR LETTERS TO THE EDITOR

Letters to the editor are considered for publication (subject to editing and abridgment) provided they do not contain material that has been submitted or published elsewhere. Please note the following: •Your letter must be typewritten and triple-spaced. •Its text, not including references, must not exceed 250 words if it is in reference to a recent *Journal* article and 400 words in all other cases (please provide a word count). •The letter must have no more than five references and one figure or table. •The letter must be signed by no more than three authors. •Letters referring to a recent *Journal* article must be received within four weeks of its publication. •Include your full mailing address, telephone number, fax number, and e-mail address. •Letters to the editor may be submitted over the Internet at <http://secure.nejm.org/letters>. You may also send us your letter by standard mail or fax.

Our address: **Letters to the Editor • New England Journal of Medicine • 10 Shattuck St. • Boston, MA 02115**

Our Web address: <http://secure.nejm.org/letters>

Our fax numbers: **617-739-9864** and **617-734-4457**

We cannot acknowledge receipt of your letter, but we will notify you when we have made a decision about publication. Rejected letters and figures will not be returned. We are unable to provide prepublication proofs. Financial associations or other possible conflicts of interest must be disclosed. Submission of a letter constitutes permission for the Massachusetts Medical Society, its licensees, and its assignees to use it in the *Journal's* various print and electronic publications and in collections, revisions, and any other form or medium.

2. Heussel CP, Kauczor HU, Heussel GE, et al. Pneumonia in febrile neutropenic patients and in bone marrow and blood stem-cell transplant recipients: use of high-resolution computed tomography. *J Clin Oncol* 1999; 17:796-805.

To the Editor: Walsh et al. used a composite scoring system similar to those validated in other studies.¹⁻³ However, they failed to point out or explain why the rate of response to liposomal amphotericin B in their study (30.6 percent) was much lower than the rates in previous studies in patients with febrile neutropenia (50 to 64 percent).^{1,4} Like itraconazole, voriconazole is metabolized by hepatic P-450 cytochromes, including CYP2C9, CYP2C18, and CYP3A4.⁵ Patients at risk for invasive fungal infections tend to receive multiple medications that could potentially interact with these cytochrome enzymes. Since the authors did not mention that patients with drug interactions were excluded from their study, we wonder whether the lower response rates in this study could be related to actual or potential drug interactions.

ANUCHA APISARNTHANARAK, M.D.
J. RUSSELL LITTLE, M.D.
PABLO TEBAS, M.D.

Washington University School of Medicine
St. Louis, MO 63110
anucha@gwu.edu

- Walsh TJ, Finberg RW, Arndt C, et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. *N Engl J Med* 1999;340:764-71.
- Winston DJ, Hathorn JW, Schuster MG, Schiller GJ, Territo MC. A multicenter, randomized trial of fluconazole versus amphotericin B for empiric antifungal therapy in febrile neutropenic patients with cancer. *Am J Med* 2000;108:282-9.
- Boogaerts M, Winston DJ, Bow EJ, et al. Intravenous and oral itraconazole versus intravenous amphotericin B deoxycholate as empirical antifungal therapy for persistent fever in febrile neutropenic patients with cancer who are receiving broad-spectrum antibacterial therapy: a randomized controlled trial. *Ann Intern Med* 2000;135:412-22.
- Prentice HG, Hann IM, Herbrecht R, et al. A randomized comparison of liposomal versus conventional amphotericin B for the treatment of pyrexia of unknown origin in neutropenic patients. *Br J Haematol* 1997;98: 711-8.
- Patterson BE, Roffey S, Jezequel SG, Jones B. UK-109,496, a novel, wide-spectrum triazole derivative for the treatment of fungal infections: disposition in man. In: Program and abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, September 17-20, 1995. Washington, D.C.: American Society for Microbiology, 1995:126. abstract.

The authors reply:

To the Editor: The overall response rate that Apisarntharak and colleagues cite is measured by a set of criteria that were formulated in 1994 and used in a study comparing liposomal amphotericin B with conventional deoxycholate amphotericin B,¹ and in subsequent studies.²⁻⁴ We included the resolution of fever as one of these criteria for a response in recognition of the time-honored use of this end point in previous studies of antibacterial and antifungal treatment in patients with febrile neutropenia. However, we have learned over time that although fever in this setting is a valuable marker for the risk of infection, the resolution of fever is not necessarily a reliable marker for a therapeutic response.

In the current study, patients were prospectively stratified as being at high or moderate risk of infection. The moderate-risk group included patients who received the study drug for a relatively short period. In our earlier study, the median period of treatment with the study drug was 10.4 days,¹ whereas in the current study, it was 7.0 days. A shorter period of treatment with the study drug allowed less time for the fever to resolve before recovery from neutropenia. This lower rate of defervescence resulted in a lower overall response rate in both groups. We included the resolution of fever as a criterion for success. However, if one removes this criterion, the overall response rate is substantially higher in both groups, and the 95 percent confidence intervals demonstrate non-inferiority (Table 1). The lower response rates in the current study were not related to plasma voriconazole concentrations, which were higher than the minimal inhibitory concentrations for most medically important fungal pathogens.

We concur with Ullmann et al. that the main end points for future trials of antifungal agents should exclude the resolution of fever and focus on the prevention of breakthrough invasive fungal infections, survival (in cases of invasive mycosis), and the response to treatment of base-line fungal infections. Fever can be assessed separately as a secondary end point.

In response to Dr. Johnson: our noninferiority trial of voriconazole as compared with liposomal amphotericin B demonstrated that the lower limit of the 95 percent confidence interval for the point estimate falls just outside the lower limit of -10 percentage points specified by the protocol (95 percent confidence interval, -10.6 to 1.6 percentage points). The point estimate and 95 percent confidence interval are presented in the abstract and text of our report. Examination of the individual elements of the composite score for success indicates that the two treatments are similar, with the prospectively defined stratum of high-risk patients having the greater benefit (95 percent confidence interval, -9.0 to 12.4 percentage points). In addition, voriconazole was superior in reducing documented breakthrough fungal infections, particularly in the high-risk cohort.

With regard to the type of analysis performed, the prospectively developed and approved statistical plan of the National Institute of Allergy and Infectious Diseases Mycoses Study Group was based on a primary analysis of raw

TABLE 1. EFFECT OF RESOLUTION OF FEVER AS A CRITERION OF SUCCESS ON THE OVERALL RATE OF RESPONSE TO EMPIRICAL ANTIFUNGAL THERAPY.

PRIMARY END POINT	OVERALL RESPONSE RATE		POINT ESTIMATE FOR THE PERCENT DIFFERENCE (95% CI)*
	VORICONAZOLE	LIPOSOMAL AMPHOTERICIN B	
	%		
Fever included	26	31	-4.5 (-10.6 to +1.6)
Fever excluded	82	85	-2.3 (-7.7 to +2.3)

*CI denotes confidence interval.

data. The corporate sponsor submitted a primary stratified analysis and a secondary analysis of raw data. With regard to the issue of cost effectiveness, a prospective analysis of resource utilization in the current study demonstrated a significant reduction in the number of hospital days among high-risk patients treated with oral voriconazole, suggesting potentially important cost savings. Pharmacoeconomic studies should be performed once the acquisition cost per unit of voriconazole is known.

THOMAS J. WALSH, M.D.
National Cancer Institute
Bethesda, MD 20892

PETER G. PAPPAS, M.D.
University of Alabama at Birmingham
Birmingham, AL 35294

DREW J. WINSTON, M.D.
University of California, Los Angeles
Los Angeles, CA 90049

- Walsh TJ, Finberg RW, Arndt C, et al. Liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Engl J Med* 1999;340:764-71.
- Prentice HG, Hann IM, Herbrecht R, et al. A randomized comparison of liposomal versus conventional amphotericin B for the treatment of pyrexia of unknown origin in neutropenic patients. *Br J Haematol* 1997;98:711-8.
- Winston DJ, Hathorn JW, Schuster MG, Schiller GJ, Territo MC. A multicenter, randomized trial of fluconazole versus amphotericin B for empiric antifungal therapy of febrile neutropenic patients with cancer. *Am J Med* 2000;108:282-9.
- Boogaerts M, Winston DJ, Bow EJ, et al. Intravenous and oral itraconazole versus amphotericin B deoxycholate as empirical antifungal therapy for persistent fever in neutropenic patients with cancer who are receiving broad-spectrum antibacterial therapy: a randomized controlled trial. *Ann Intern Med* 2001;135:412-22.

High-Dose Intravenous Immune Globulin for Stiff-Person Syndrome

To the Editor: Dalakas et al. (Dec. 27 issue)¹ report the efficacy of high-dose intravenous immune globulin for the treatment of stiff-person syndrome. Stiff-person syndrome is a devastating disorder, and evidence of the associated immunologic impairment began to emerge in the 1980s.² Over the next decade, it was confirmed that stiff-person syndrome was caused, in particular, by damage by an autoimmune mechanism.

Intravenous immune globulin is extraordinarily costly; thus, the current focus of interest among clinicians is not on the efficacy of this approach but, rather, on the timing of the treatment and its long-term outcome, including the duration of the effect and any adverse consequences. Dalakas et al. failed to address this issue, because they terminated their comparative observation one month after the end of the double-blind study, even though in the group that received immune globulin first, titers of antibodies against glutamic acid decarboxylase (GAD65) had increased significantly four months after the completion of the study, whereas in the group given placebo first, the titers were monitored for only

one month. We believe that the authors should provide further follow-up information.

KAZUMASA SUDO, M.D.
YASUTAKA TAJIMA, M.D.
AKIHISA MATSUMOTO, M.D.
Sapporo City General Hospital
Sapporo 060-8604, Japan
sudo@med.hokudai.ac.jp

- Dalakas MC, Fujii M, Li M, Lutfi B, Kyhos J, McElroy B. High-dose intravenous immune globulin for stiff-person syndrome. *N Engl J Med* 2001;345:1870-6.
- Piccolo G, Cosi V, Zandrini C, Moglia A. Steroid-responsive and dependent stiff-man syndrome: a clinical and electrophysiological study of two cases. *Ital J Neurol Sci* 1988;9:559-66.

To the Editor: Dalakas et al. report the efficacy of intravenous immune globulin for treating stiff-person syndrome. They did not report whether cerebrospinal fluid was analyzed in order to determine whether anti-GAD65 antibodies were being synthesized intrathecally. As shown recently by Dalakas et al. in another study,¹ the production of antibodies within the central nervous system seems to have an important role in the pathogenesis of the disorder, by affecting the synthesis of a neurotransmitter, γ -aminobutyric acid (GABA),² within the central nervous system. Immune globulin should work in the periphery, since its hypothesized mechanism of action is to reduce the levels of circulating antibody against an antigen target that accelerates IgG catabolism or to induce an anti-idiotypic antibody response. Does the activity in the periphery reflect what is happening in the cerebrospinal fluid?

Dalakas et al. also report that the reduction in anti-GAD65 antibody titers after immune globulin therapy did not correlate with the degree of clinical improvement. Can we suppose that a correlation exists between the clinical outcome and the level of the antibodies in cerebrospinal fluid or the anti-GAD65 antibody index in cerebrospinal fluid?

CLAUDIO SOLARO, M.D.
Ospedale P.A. Micone
16153 Genoa, Italy
csolaro@neurologia.unige.it

- Dalakas MC, Li M, Fujii M, Jacobowitz MD. Stiff person syndrome: quantification, specificity, and intrathecal synthesis of GAD65 antibodies. *Neurology* 2001;57:780-4.
- Dinkel K, Meinck HM, Jury KM, Karges W, Richter W. Inhibition of gamma-aminobutyric acid synthesis by glutamic acid decarboxylase auto-antibodies in stiff-man syndrome. *Ann Neurol* 1998;44:194-201.

Dr. Dalakas replies:

To the Editor: Contrary to the contentions of Sudo et al., the main concern of clinicians caring for patients with stiff-person syndrome is not when to treat but how best to treat the disease; hence, the need for controlled studies to determine the efficacy of the various proposed therapies. My colleagues and I demonstrated that intravenous immune globulin improves or reverses even the long-standing disabling symptoms in most patients with stiff-person syn-

drome. Furthermore, we monitored the anti-GAD65 antibody titers not for one month, as Sudo et al. suggest, but for up to three months. Immune globulin is an immunomodulating (not an immunosuppressive) agent that modifies but does not permanently suppress various immune factors. Consequently, the rebound in the antibody titers after the end of treatment is not unexpected. Although the purpose of our study was to establish the efficacy of immune globulin and not to assess its long-term effectiveness, we reported long-term follow-up data that were collected for at least two years after the completion of the study.

Dr. Solaro refers to our previous study of the intrathecal synthesis of IgG antibodies¹ and wonders whether immune globulin acts in the periphery or directly within the central nervous system to suppress antibody production. This pertinent question also relates to the pathogenic role of anti-GAD65 antibodies. GAD65 is a cytoplasmic antigen that may not be easily recognized by the immune system, and the antibody titers do not correlate with disease severity. Thus, the relation between the suppression of anti-GAD65 antibody titers and the magnitude of clinical benefit after immune globulin therapy is unclear. Immune globulin probably suppresses anti-GAD65 antibodies in the periphery through an idiotypic-anti-idiotypic interaction.^{2,3} However, the IgG molecules within the immune globulin cross the blood-cerebrospinal fluid barrier⁴ and may enter the brain; whether they also exert an effect in situ is unknown. Although high titers of anti-GAD65 antibodies in serum and cerebrospinal fluid are highly specific for stiff-person syndrome, another target antigen or surface receptor, in conjunction with GAD65, may be more directly involved in GABAergic transmission and may correlate better with the severity of symp-

toms. Our search for other target antigens in affected patients continues.

MARINOS C. DALAKAS, M.D.

National Institutes of Health
Bethesda, MD 20892-1382
dalakasm@ninds.nih.gov

1. Dalakas MC, Li M, Fujii M, Jacobowitz DM. Stiff person syndrome: quantification, specificity, and intrathecal synthesis of GAD65 antibodies. *Neurology* 2001;57:780-4.
2. Kazatchkine MD, Kaveri SV. Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. *N Engl J Med* 2001;345:747-55.
3. Dalakas MC. Intravenous immunoglobulin in the treatment of autoimmune neuromuscular diseases: present status and practical therapeutic guidelines. *Muscle Nerve* 1999;22:1479-97.
4. Sekul EA, Cupler EJ, Dalakas MC. Aseptic meningitis associated with high-dose intravenous immunoglobulin therapy: frequency and risk factors. *Ann Intern Med* 1994;121:259-62.

Octreotide for Tumor-Induced Osteomalacia

To the Editor: Seufert et al. (Dec. 27 issue)¹ describe a man with tumor-induced (oncogenic) osteomalacia, in which the subcutaneous administration of octreotide abolished renal tubular phosphate wasting. The authors suggest that in patients who cannot undergo surgery, phosphate wasting may be relieved by treatment with somatostatin analogues, provided that the tumor expresses somatostatin receptors. We believe that this statement is a misleading generalization. We observed a case of oncogenic osteomalacia in which total-body octreotide scintigraphy detected the tumor. We therefore intravenously administered octreotide at a dose

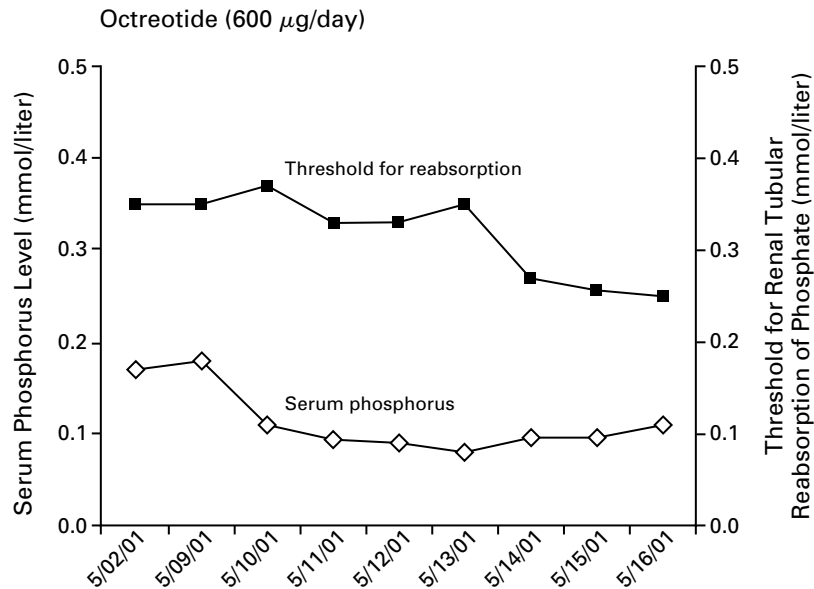


Figure 1. Serum Phosphorus Level and Threshold for Renal Tubular Reabsorption of Phosphate during Intravenous Octreotide Therapy in a Patient with Tumor-Induced Osteomalacia. The normal range for the serum phosphorus level is 0.8 to 1.4 mmol per liter; the normal range for the threshold for renal tubular reabsorption of phosphate is 0.8 to 1.6 mmol per liter.

of 600 μg per day for six days — a dose in the same order of magnitude as the dose administered subcutaneously by Seufert et al. We did not observe any effect on the biochemical variables (Fig. 1).

The lack of response in our patient could be attributed either to the heterogeneous distribution of somatostatin receptors among tumor cells^{2,3} or to the prevalence of cells lacking somatostatin receptors, as has been documented in some neuroendocrine tumors.³ In the latter case, it is possible that treatment with the analogues of somatostatin affects only some areas of the tumor. In fact, octreotide binds with high affinity to somatostatin receptor subtypes 2 and 5 and with moderate affinity to subtype 3 but does not bind to subtypes 1 and 4. Finally, it is unclear whether the secretion of phosphaturic factors by the tumor cells is modulated by somatostatin receptors. In any case, we do not support the widespread use of somatostatin analogues, especially considering their cost.

FEDERICA PAGLIA, M.D.

SIMONA DIONISI, M.D.

SALVATORE MINISOLA, M.D.

Università degli Studi di Roma La Sapienza
00193 Rome, Italy
salvatore.minisola@uniroma1.it

1. Seufert J, Ebert K, Müller J, et al. Octreotide therapy for tumor-induced osteomalacia. *N Engl J Med* 2001;345:1883-8.
2. Wynick D, Anderson JV, Williams SJ, Bloom SR. Resistance to metastatic pancreatic endocrine tumours after long-term treatment with the somatostatin analogue octreotide (SMS 201-995). *Clin Endocrinol (Oxf)* 1989;30:385-8.
3. Lamberts SWJ, van der Lely A-J, de Herrder WW, Hofland LJ. Octreotide. *N Engl J Med* 1996;334:246-54.

The authors reply:

To the Editor: Paglia et al. point out that octreotide therapy does not affect phosphate wasting in all patients with tumor-induced osteomalacia. We have become aware of similar cases characterized by the obvious contradiction of positive results on octreotide scintigraphy and little therapeutic effect of the compound. By reporting our single case, we certainly did not mean to imply that the findings could be generalized to all tumors. The two findings we wanted to stress are that tumors can be diagnosed with the use of octreotide scans if conventional localization procedures fail and that a therapeutic trial of octreotide may be worthwhile in individual patients. Furthermore, this case might be considered as a paradigm for the novel concept of secretory control of phosphaturic substances in humans. We notice differences between the two patients such as the route of octreotide administration and the basal phosphate reabsorption threshold — differences that can be evaluated only if one has the opportunity to analyze more patients. However, fibroblast growth factor 23 was recently reported to suppress 25-hydroxyvitamin D₃ 1 α -hydroxylase activity in the kidney,¹ which may, in part, explain the low levels of 1,25-dihydroxyvitamin D₃ in patients with tumor-induced osteomalacia.² This finding could contribute to the low renal tubular threshold of phosphate reabsorption. Concomitant 1,25-dihydroxyvitamin D₃ treatment in our patient may have had

a permissive effect on normalization of phosphaturia. The relative heterogeneity of underlying histologic entities^{3,4} may serve as an alternative explanation for the lack of an effect of octreotide in octreotide-positive tumors. Although tumor-induced osteomalacia is a rare disorder, we propose that systematic analysis of somatostatin-receptor expression has relevance to tumor-derived phosphatonin secretion.

In Table 1 of our article, the threshold for renal tubular reabsorption of phosphate before octreotide therapy should have been 0.2 mmol per liter, not 0.6 mmol per liter.

JOCHEN SEUFERT, M.D.

FRANZ JAKOB, M.D.

University of Würzburg
97070 Würzburg, Germany
j.seufert@mail.uni-wuerzburg.de

1. Shimada T, Mizutani S, Muto T, et al. Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. *Proc Natl Acad Sci U S A* 2001;98:6500-5.
2. Strewler GJ. FGF23, hypophosphatemia, and rickets: has phosphatonin been found? *Proc Natl Acad Sci U S A* 2001;98:5945-6.
3. Crouzet J, Mimoune H, Beraneck L, Juan LH. Hypophosphatemic osteomalacia with plantar neurilemoma: a review of the literature (100 cases). *Rev Rhum Engl Ed* 1995;62:463-6.
4. Park YK, Unni KK, Beabout JW, Hodgson SE. Oncogenic osteomalacia: a clinicopathologic study of 17 bone lesions. *J Korean Med Sci* 1994;9:289-98.

Childhood Infections and Autoimmune Diseases

To the Editor: The article by Zinkernagel (Nov. 1 issue)¹ and the accompanying editorial² discuss the attractive and popular notion that the occurrence of fewer infectious diseases during childhood leads to an increase in the incidence of autoimmune diseases. This idea, however, is not soundly based. The apparently increased incidence of autoimmune diseases in industrialized countries may well be attributable to the use of improved diagnostic tools and widespread awareness of these diseases. Large-scale epidemiologic studies have been done only with regard to type 1 diabetes. Moreover, there is evidence that the prevalence of autoimmune diseases in underdeveloped countries is much higher than previously suspected.³ This would be in keeping with the findings in Sardinia, which has the highest prevalence of autoimmune diseases in Europe (similar to that in Finland), despite having, until recently, a high incidence of infectious diseases.⁴ Finally, the idea that coxsackievirus B can lead to type 1 diabetes is unproved, and the proposal that molecular mimicry (i.e., the presence of viral antigenic determinants that resemble those of the host) may explain the disease in humans has been challenged.⁵

SANDRO VENTO, M.D.

FRANCESCA CAINELLI, M.D.

University of Verona
37138 Verona, Italy
ventosandro@yahoo.it

1. Zinkernagel RM. Maternal antibodies, childhood infections, and autoimmune diseases. *N Engl J Med* 2001;345:1331-5.
2. Rosen FS, Mackay I. The immunology series comes to an end. *N Engl J Med* 2001;345:1343-4.

3. Molokhia M, McKeigue PM, Cuadrado M, Hughes G. Systemic lupus erythematosus in migrants from West Africa compared with Afro-Caribbean people in the UK. *Lancet* 2001;357:1414-5.
4. Stroffolini T, Franco E, Mura I, et al. Age-specific prevalence of hepatitis A virus infection among teenagers in Sardinia. *Microbiologica* 1991; 14:21-4.
5. Cainelli F, Manzaroli D, Renzini C, Casali F, Concia E, Vento S. Cox-sackie B virus-induced autoimmunity to GAD does not lead to type 1 diabetes. *Diabetes Care* 2000;23:1021-2.

To the Editor: Zinkernagel describes the function of maternal antibodies as passive protective mediators that help to generate immunity to invading microbes during early ontogeny. We believe that his view neglects a large body of evidence demonstrating that maternal antibodies also exert a variety of active stimulatory functions on the nascent immune system of the newborn.^{1,2} Maternal antibodies stimulate T-cell-dependent idiotypic responses that have long-term effects, and they are involved in the establishment of the T-cell repertoire. In addition, in animals, they may substantially enhance immune responses and can transfer a carrier sensitivity (a T-cell-dependent function) from mothers to offspring. In mice, maternal immunization with antigen or anti-idiotypic antibodies induces the production of antigen-reactive IgM antibodies in nonimmunized first-generation offspring. A further argument against the view that maternal antibodies provide only passive protection is the fact that even antibodies that do not react with the antigen — namely, anti-idiotypes — are able to transfer antimicrobial protection from mothers to offspring. Finally, maternally derived IgG antibodies induce long-lasting, allergen-specific suppression of IgE responsiveness in offspring.

We believe that maternal antibodies indeed exert a variety of important active stimulatory functions. These depend on idiotypic interactions among B and T cells, which thus form a physiologically active idiotypic network.^{3,4}

HILMAR LEMKE, PH.D.

HANS LANGE, PH.D.

Christian Albrechts University at Kiel
D-24098 Kiel, Germany
hlemke@biochem.uni-kiel.de

1. Lemke H, Lange H. Is there a maternally induced immunological imprinting phase *à la* Konrad Lorenz? *Scand J Immunol* 1999;50:348-54.
2. *Idem*. Generalization of single immunological experiences by idiotypically mediated clonal connections. *Adv Immunol* (in press).
3. Jerne NK. The Nobel Lectures in Immunology: the Nobel prize for physiology or medicine, 1984: the generative grammar of the immune system. *Scand J Immunol* 1993;38:1-9.
4. Janeway CA Jr. How the immune system works to protect the host from infection: a personal view. *Proc Natl Acad Sci U S A* 2001;98:7461-8.

Dr. Zinkernagel replies:

To the Editor: My article is not comprehensive, and there are many host and environmental factors that influence autoimmune disease.¹ Better epidemiologic data in different human populations would clearly be very valuable. I do not want to push the notion that infants with fewer infections have a higher incidence of autoimmune disease than other infants; rather, I would like to argue that infants with insufficient maternally transmitted immunoglobulins, or “clean

kids,” either are not sufficiently protected or become infected too late to benefit from maternal antibody protection. I propose that the transfer of maternal antibodies offers a mechanism for “natural,” or “physiologic,” vaccination by attenuating early infections in infants. This mechanism balances decreasing passive maternal protection with active infection and with the maturing immune system of the baby. It explains why vertebrates transfer antibodies to offspring and why emerging infections are generally more severe in the first few generations of new hosts than in subsequent generations.

I agree that mimicry, though possible, is rare and that in many cases, this possibility is supported only by poorly specific assays in vitro. Therefore, the overall role of mimicry in autoimmune disease remains elusive.² HLA-disease associations have been observed particularly frequently in patients with autoimmunity, which may indicate that chronic or subclinical infections can induce autoimmune disease, even though they are often not recognized as triggering events.³ I propose that during the phase of protection provided by maternal antibodies, favorable, physiologic immunizations of offspring limit early infections, including those that eventually lead to chronic immunopathologic conditions (or autoimmunities). Factors such as increased hygiene and the absence of breast-feeding or the use of breast-feeding for short periods influence the time and dose kinetics of some infections unfavorably, shifting them toward autoimmunity. Such shifts may also be found in developing countries; the increase in the incidence of diabetes in adults between 20 and 40 years of age in southern India is perhaps an example.⁴

In theory, the postulated active effects of maternal antibodies on the immune system of the offspring by way of idiotypic networks cannot be ruled out. But I am unaware of solid evidence of a survival advantage or disadvantage with respect to infections or autoimmune diseases. Although anti-idiotypic responses may be demonstrated in selected experimental or clinical conditions,⁵ such evidence does not prove that idiotypic networks have active regulatory roles, either in general or as a result of the influence of maternal antibodies on B-cell or T-cell responses of the offspring. Examination of the cited references suggests that these effects are probably dwarfed in importance by the evolutionary selection pressures exerted by infections that kill offspring early.

ROLF M. ZINKERNAGEL, M.D.

University Hospital
CH-8091 Zurich, Switzerland
rolf.zinkernagel@pty.usz.ch

1. Bach JF. Protective role of infections and vaccinations on autoimmune diseases. *J Autoimmun* 2001;16:347-53.
2. Benoist C, Mathis D. Autoimmunity provoked by infection: how good is the case for T cell epitope mimicry? *Nat Immunol* 2001;2:797-801.
3. Haddad J, Deny P, Munz-Gothel C, et al. Lymphocytic sialadenitis of Sjogren's syndrome associated with chronic hepatitis C virus liver disease. *Lancet* 1992;339:321-3.
4. Ramachandran A, Snehalatha C, Kapur A, et al. High prevalence of diabetes and impaired glucose tolerance in India: National Urban Diabetes Survey. *Diabetologia* 2001;44:1094-101.
5. Levy R, Miller RA. Therapy of lymphoma directed at idiotypes. In: The lymphomas: current concepts in pathogenesis and management. *Journal of the National Cancer Institute monographs*. No. 10. Bethesda, Md.: National Cancer Institute, 1990:61-8. (NIH publication no. 90-1930.)

Case 1-2002: *Loa loa*

To the Editor: The case discussion by Nutman and Kradin (Jan. 10 issue)¹ triggered the recollection of a case of *Loa loa* infection that I saw years ago as a Peace Corps physician in Cameroon, West Africa. A healthy young man noted migratory arthralgia of the joints. He had few, if any, constitutional symptoms. One wrist was red, warm, and swollen but fully mobile and mildly tender. We diagnosed infection with *L. loa* and began treatment with diethylcarbamazine.

Some weeks later, he reappeared with two gracile white worms preserved in ethanol. He reported that after a day or so of therapy, the worms had crawled out of his anterior chest wall. Being resourceful and unflappable, he preserved them and brought them in for identification. The worms were sent to the Centers for Disease Control, which confirmed that there was one male and one female *L. loa*.

The cause-and-effect response to therapy was so dramatic and striking that the case remains unforgettable decades later. Would that all our patients' infestations so definitively and resolutely declared their response to our ministrations. One teaching point that was not mentioned in the case report is that this predilection of the worm to get out when challenged is the basis for the admonition not to treat patients when the worm makes its classic traversal of the sclera.

HENRY GREENBERG, M.D.

St. Luke's-Roosevelt Hospital Center
New York, NY 10019
hmg1@columbia.edu

1. Case Records of the Massachusetts General Hospital (Case 1-2002). *N Engl J Med* 2002;346:115-22.

Dr. Nutman replies:

To the Editor: Dr. Greenberg emphasizes several salient and often dramatic clinical features of loiasis in long-term visitors to (or temporary residents of) regions of the world where *L. loa* is endemic: Calabar swellings, the subconjunctival migration of the adult parasite (eye worm), and the appearance of adult worms after treatment with diethylcarbamazine. In our experience, however, the parasites rarely emerge from the skin spontaneously after treatment but, rather, are found as subcutaneous papular or vermiform eruptions. When these eruptions are examined by biopsy¹ or nicked with a scalpel while the patient is under local anesthesia, adult *L. loa* worms are found. Indeed, my colleagues and I found, in our initial study of 20 temporary residents of West and Central Africa with loiasis,² many of whom were Peace Corps volunteers, that 13 (65 percent) had such a finding after the administration of diethylcarbamazine, typically within the first 48 hours.

When access to ophthalmologic services is available, the adult *L. loa* worm can be removed during its subconjunctival migration, thus allowing the definitive diagnosis of loiasis to be made. Because of the velocity of the worm, extraction is not very common, and it is unusual to have the administration of diethylcarbamazine coincide with the presence of a worm under the conjunctiva. Moreover, to my

knowledge, emergence of adult worms through the conjunctiva after therapy with diethylcarbamazine has not been reported. The real concern with treatment is the precipitation of severe, life-threatening adverse reactions, such as encephalitis or encephalopathy, which can occur in patients with increased parasite burdens (high-grade microfilaremia).³ Although apheresis to reduce microfilarial burdens,⁴ graded diethylcarbamazine dosing schedules, and concomitant administration of corticosteroids have been used successfully to prevent some of the serious post-treatment reactions, in heavily infected patients — particularly in West and Central Africa — there are few treatment options. Fortunately for the traveler or temporary resident who acquires loiasis, parasite burdens are low, and severe post-treatment reactions, though dramatic, are infrequently a cause for concern.

THOMAS B. NUTMAN, M.D.

National Institutes of Health
Bethesda, MD 20892-0425
tnutman@niaid.nih.gov

1. Van Dellen RG, Ottesen EA, Gocke TM, Neafie RC. *Loa loa*: an unusual case of chronic urticaria and angioedema in the United States. *JAMA* 1985;253:1924-5.

2. Nutman TB, Miller KD, Mulligan M, Ottesen EA. *Loa loa* infection in temporary residents of endemic regions: recognition of a hyperresponsive syndrome with characteristic clinical manifestations. *J Infect Dis* 1986;154:10-8.

3. Carme B, Boulesteix J, Boutes H, Puruehnce ME. Five cases of encephalitis during treatment of loiasis with diethylcarbamazine. *Am J Trop Med Hyg* 1991;44:684-90.

4. Chandener J, Pillier-Loriette C, Datry A, et al. Intérêt de la cytophèrese dans le traitement des loases à fortes microfilarémies: résultats à propos de sept cas. *Bull Soc Pathol Exot Filiales* 1987;80:624-33.

Case 4-2002: Cancer-Associated Obstruction and Glomerular Damage

To the Editor: Case 4-2002 (Jan. 31 issue) described a 75-year-old man with acute renal failure five months after cystoprostatectomy and urethrectomy for carcinoma.¹ Recently, we cared for a 52-year-old woman who had acute renal failure after surgery for an obstructing transitional-cell carcinoma of the bladder. The follow-up serum creatinine concentration was 1.5 mg per deciliter. Two months after surgery, she presented with acute oliguric renal failure. No obstruction was present, and hemodialysis was initiated. Findings on a biopsy of the kidney were consistent with the presence of anti-glomerular basement membrane antibody disease: light microscopy revealed an acute necrotizing, crescentic glomerulonephritis, and immunofluorescence was strongly positive for linear deposition of IgG in the glomerular basement membrane. Hemoptysis later developed, and treatment with plasmapheresis, corticosteroids, and cyclophosphamide was begun. The titer of anti-glomerular basement membrane was 191 U per milliliter before therapy, as assessed by enzyme-linked immunosorbent assay. Hemoptysis resolved, but there was no recovery of renal function.

These case reports suggest that obstructions associated with cancer may result in glomerular damage, triggering anti-glomerular basement membrane disease. Of interest in this regard are three reports of patients in whom anti-glo-

merular basement membrane disease developed after lithotripsy.²⁻⁴

ALFREDO BLAS III, M.D.
 RITA MCGILL, M.D.
 STEPHEN SANDRONI, M.D.
 Allegheny General Hospital
 Pittsburgh, PA 15212
 sandroni@pol.net

1. Case Records of the Massachusetts General Hospital (Case 4-2002). *N Engl J Med* 2002;346:353-60.
2. Guerin V, Rabian C, Noel LH, et al. Anti-glomerular-basement-membrane disease after lithotripsy. *Lancet* 1990;335:856-7.
3. Umekawa T, Kohri K, Iguchi M, Yoshioka K, Kurita T. Glomerular-basement-membrane antibody disease and extracorporeal shock wave lithotripsy. *Lancet* 1993;341:556.
4. Xenocostas A, Jothy S, Collins B, Loertscher R, Levy M. Anti-glomerular basement membrane glomerulonephritis after extracorporeal shock wave lithotripsy. *Am J Kidney Dis* 1999;33:128-32.

Vaccination with HPV-18 E7–Pulsed Dendritic Cells in a Patient with Metastatic Cervical Cancer

To the Editor: The management of disseminated carcinoma of the cervix that is no longer amenable to control with surgery or radiation therapy has not improved significantly with the advent of modern chemotherapy. The one-year survival rate remains between 10 percent and 15 percent.¹ Studies have provided a rationale for using dendritic cells as natural adjuvants for human immunotherapy.²⁻⁴

We describe a 52-year-old woman with multiple lung metastases secondary to recurrent human papillomavirus type 18 (HPV-18)–associated adenocarcinoma of the uterine cervix. In 1997 she underwent external irradiation and intracavitary brachytherapy combined with weekly intravenous infusions of cisplatin and followed by an adjunctive hysterectomy for stage IB2, grade III, cervical cancer. The patient did well until January 2000, when a chest x-ray film

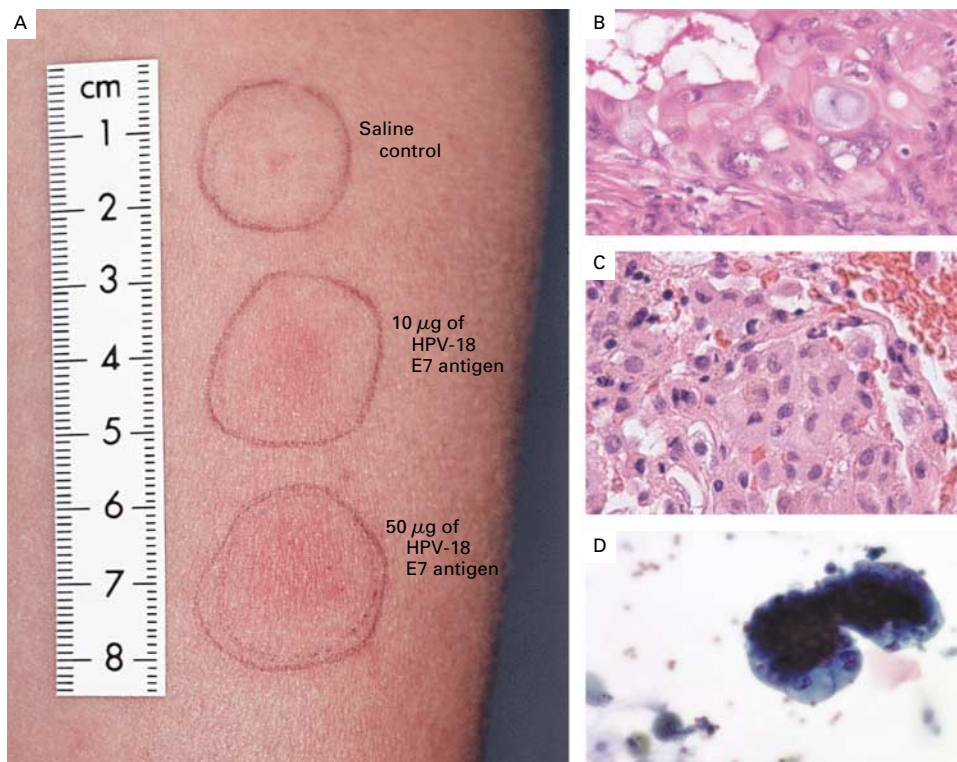


Figure 1. Immunologic and Histologic Findings in a Woman with Metastatic Cervical Cancer.

Delayed-hypersensitivity skin tests were performed at the time of the third vaccination with HPV-18 E7–pulsed dendritic cells. HPV-18 E7 antigen induced an erythematous reaction with induration (Panel A). Large tumor cells were clearly evident in biopsy specimens of the primary lesion obtained before vaccination (Panel B; hematoxylin and eosin, $\times 400$). After 10 months of treatment, examination of bronchoscopic-biopsy tissue revealed a predominant mononuclear-cell infiltrate in the pulmonary cavity lesion (Panel C; hematoxylin and eosin, $\times 600$). The presence of macrophages was confirmed by immunohistochemical staining for CD68 (KP-1), whereas there was no staining for epithelial-cell cytokeratin or tumor-associated mucin (not shown). Twenty months after the initiation of vaccine treatment, recurrent adenocarcinoma was evident in a bronchoscopic-biopsy specimen (Panel D; hematoxylin and eosin, $\times 400$).

and computed tomographic (CT) scans revealed metastatic lesions in both lungs and bilateral pleural effusions.

To inhibit tumor progression, we subcutaneously administered autologous mature, monocyte-derived dendritic cells pulsed with HPV-18 E7 oncoprotein. The first five injections were given at intervals of 10 to 14 days (3 million to 5 million dendritic cells per injection). To increase the number of T cells potentially responsive to disease, the first, second, and fourth vaccinations were followed 72 hours later by the adoptive transfer of autologous T cells (1.5×10^7 cells) that had been stimulated in vitro with HPV-18 E7-pulsed dendritic cells. Low-dose interleukin-2 (1 million U per square meter of body-surface area per day for three days, infused over a six-hour period) was concomitantly administered. Vaccinations 6 to 14 were administered at intervals of 30 to 60 days.

The patient had minor side effects, including tender induration at the site of the injections and an influenza-like syndrome at the time of interleukin-2 infusion. After the third vaccination, we assessed whether delayed hypersensitivity had occurred by intradermally injecting the patient with HPV-18 E7 oncoprotein (Fig. 1A) or lethally irradiated autologous tumor cells. There was swelling and induration, indicating a strong local reaction to the HPV antigen and tumor cells. A skin biopsy of both injection sites, used to assess whether delayed-type hypersensitivity had occurred, revealed marked CD4+ and CD8+ T-cell infiltration. Serial CT scans showed no evidence of tumor progression during 13 months of therapy. Cavities developed in the majority of lesions. In contrast to results obtained before vaccination (Fig. 1B), after 10 months of treatment, CT-guided fine-needle biopsy revealed fibrosis and macrophage infiltration but no viable tumor cells (Fig. 1C).

After the initiation of dendritic-cell immunotherapy, the patient resumed her normal activities. Twenty months later, she became short of breath. CT showed that her pulmonary masses had increased in size. Bronchoscopic biopsy confirmed that metastatic disease had recurred (Fig. 1D). Delayed-hypersensitivity status against HPV-18 E7 oncoprotein was not reassessed at this time. The patient died 23 months after the beginning of the dendritic-cell immunotherapy. Although this approach did not result in permanent remission, it inhibited disease progression and markedly improved the patient's performance status for an extended period without clinically significant adverse effects.

ALESSANDRO D. SANTIN, M.D.
STEFANIA BELLONE, PH.D.
MURAT GOKDEN, M.D.
MARTIN J. CANNON, PH.D.
GROESBECK P. PARHAM, M.D.

University of Arkansas for Medical Sciences
Little Rock, AR 72205
santinalessandro@uams.edu

1. DiSaia PJ, Creasman WT. Clinical gynecologic oncology. 5th ed. St. Louis: Mosby-Year Book, 1997:1-106.
2. Banchereau J, Steinman RM. Dendritic cells and the control of immunity. *Nature* 1998;392:245-52.
3. Schuler G, Steinman RM. Dendritic cells as adjuvants for immune-mediated resistance to tumors. *J Exp Med* 1997;186:1183-7.
4. Santin AD, Hermonat PL, Ravaggi A, et al. Induction of human papillomavirus-specific CD4+ and CD8+ lymphocytes by E7-pulsed autolo-

gous dendritic cells in patients with human papillomavirus type 16- and 18-positive cervical cancer. *J Virol* 1999;73:5402-10.

Acute Dystonic Reactions to "Street Xanax"

To the Editor: Acute dystonic reactions have been reported after the ingestion of numerous medications that alter dopaminergic tone in the basal ganglia or antagonize dopamine D2 receptors. At the emergency department of an urban community hospital, we have recently treated six patients presenting with acute dystonia. All patients reported the ingestion of what street sellers had assured them was Xanax (alprazolam). In five of these patients, the ingested drug was actually proved to be haloperidol.

Three teenage boys presented to the emergency department with symptoms consistent with torticollis, oculogyric crisis, and opisthotonos. Each reported the ingestion of "one or two" tablets of "Xanax" 12 to 16 hours before admission. Two of these patients specifically described blue tablets bearing the inscription "GG126," and the third supplied an unused pill with the same markings. The drugs were identified as 10-mg tablets of the Geneva brand of generic haloperidol. All three patients had rapid resolution of their symptoms after the administration of intravenous diphenhydramine.

We also treated three additional patients with more subtle clinical presentations. A child presented with intermittent mouth puckering and sedation, followed by torticollis and involuntary tongue movements. A 32-year-old woman presented with mild, intermittent bruxism. And a teenage boy presented with a feeling of weakness and spasm in his back and a sensation of swelling in his tongue, followed by dysarthria, buccolingual spasm, and diaphoresis. In all three of these patients, the symptoms resolved rapidly after the administration of intravenous diphenhydramine. In the first patient, a serum assay that used gas chromatography-mass spectroscopy identified haloperidol and detected no alprazolam. The second patient's unused pills were identified as haloperidol. The third patient reported that he had ingested a pill that was identical in appearance to the Geneva brand of generic haloperidol, although the person who supplied the drug to him insisted that the pill in question was generic alprazolam.

The substitution of haloperidol for the benzodiazepine diazepam ("street Valium") was common on the street in the 1970s and 1980s. Both these pills were blue and had a central hole.^{1,2} Physicians today should be aware that haloperidol is being substituted for alprazolam ("street Xanax"), even though the pills have different shapes and colors.

ROBERT G. HENDRICKSON, M.D.
ANTHONY P. MOROCCO, M.D.
MICHAEL I. GREENBERG, M.D., PH.D.

Medical College of Pennsylvania-Hahnemann University
Philadelphia, PA 19129
rob.hendrickson@drexel.edu

1. Demetropoulos S, Schauben JL. Acute dystonic reactions from "street Valium." *J Emerg Med* 1987;5:293-7.
2. Bryant SG. Street drug misrepresentation. *JAMA* 1980;244:2160.

Correspondence Copyright © 2002 Massachusetts Medical Society.