2. D'Amico AV, Loffredo M, Renshaw AA, Loffredo B, Chen MH. Six-month androgen suppression plus radiation therapy compared with radiation therapy alone for men with prostate cancer and a rapidly increasing pretreatment prostate-specific antigen level. J Clin Oncol 2006;24:4190-5.
3. Valicenti RK, Winter K, Cox JD, et al. RTOG 94-06: is the addition of neoadjuvant hormonal therapy to dose-escalated 3D conformal radiation therapy for prostate cancer associated with treatment toxicity? Int J Radiat Oncol Biol Phys 2003;57:614-20.
4. Sharifi N, Gulley JL, Dahut WL. Androgen deprivation therapy for prostate cancer. JAMA 2005;294:238-44.

Lost in Transcription

TO THE EDITOR: In the Clinical Problem-Solving article, "Lost in Transcription" (Oct. 5 issue),[1] Kalus and colleagues quickly home in on a medication error involving methotrexate overdosing as the likely cause of the patient's fever and presumed urosepsis. However, they do not discuss the fact that this patient, who was reportedly allergic to penicillin, received piperacillin–tazobactam as treatment for her urosepsis — an error that could be more deadly in the immediate future if she did have a true allergy.

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1. Kalus RM, Shojania KG, Amory JK, Saint S. Lost in transcription. N Engl J Med 2006;355:1487-91.

THE AUTHORS REPLY: Harris points out the potential risk of giving a beta-lactam antibiotic to a patient with a documented penicillin allergy. Although our patient did report a history of an allergy to penicillin, we explored this history in more detail before prescribing antibiotics. She described a nonspecific rash after receiving penicillin in the past, but a record review indicated that she had subsequently tolerated several courses of beta-lactams, including piperacillin–tazobactam, without incident. In many patients who report a history of penicillin hypersensitivity, penicillin-specific IgE antibodies are not detected on skin testing.[1] In this case, although we did not have information from skin testing, we considered the patient's tolerance of piperacillin–tazobactam on previous occasions to be reassuring. No adverse reaction to the beta-lactam was noted on this occasion, despite careful observation for signs and symptoms.

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1. Gruchalla RS, Pirmohamed M. Antibiotic allergy. N Engl J Med 2006;354:601-9.

Reversal of Type 1 Diabetes in Mice

TO THE EDITOR: Dr. Melton (July 6 issue)[1] misrepresents my study on the reversal of type 1 diabetes in mice and its implications for new treatment strategies in humans.[2] As in a previous study,[3] my colleagues and I discovered that an immune therapy triggered a permanent reversal of end-stage type 1 diabetes in mice. The treatment involved two components: injecting the mice with an immune adjuvant (to induce the production of tumor necrosis factor, which destroys autoreactive T cells) and injecting splenocytes from a donor mouse.

Dr. Melton writes that we ascribed the reversal of type 1 diabetes in a mouse model solely to the transplantation of spleen cells and that we claimed to have identified a stem cell among the donor splenocytes that contributed to regrowth of the islets in the recipient. It is true that we observed adult stem cells and that these cells can contribute, in part, to the regrowth of the islets. However, Dr. Melton does not acknowledge that we also observed regeneration of pancreatic islets and complete reversal of type 1 diabetes without the introduction of any live donor splenocytes.[2] Infusion of live splenic cells hastened the development of permanent normoglycemia in the mice but did not enhance the rate of cure. We did not claim that the regenerative process required

a stem cell, and we did not rule out other mechanisms, such as regrowth or rescue of host islets. Our research simply found regeneration of the pancreas once the autoimmune process was removed.

Instead of cheering the fact that our laboratory's immunomodulatory approach was replicated successfully by three recent studies,[4-6] Dr. Melton places emphasis on the failure of these cited studies to identify a splenocyte contribution to the observed regeneration of the pancreas. It is possible that methodologic differences between our protocol and theirs precluded finding a contribution of splenic stem cells to pancreatic regeneration in these studies. But since then, the optional splenic contribution has been replicated.[7]

From a clinical perspective, the existence of an adult stem cell in the spleen seems to be beside the point. Many studies have since shown that the regenerative process in the pancreas is likely to be intact and that targeted immune intervention may unleash the spontaneous regeneration of the pancreas. It seems reasonable to test the hypothesis that for end-stage diabetes, an immune intervention that destroys autoreactive T cells in the mouse can also work in the clinic.

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Dr. Faustman reports owning stock in General Electric, Pfizer, Microsoft, IBM, Keel, and Johnson & Johnson, all of which have research programs or products involving stem cells. Dr. Faustman's employer, Massachusetts General Hospital, owns patent applications on the nuclear factor-κB–tumor necrosis factor pathway for the treatment of autoimmunity. Should the hospital receive income from those applications, Dr. Faustman or her laboratory could receive income.

1. Melton DA. Reversal of type 1 diabetes in mice. N Engl J Med 2006;355:89-90.
2. Kodama S, Kuhtreiber W, Fujimura S, Dale EA, Faustman DL. Islet regeneration during the reversal of autoimmune diabetes in NOD mice. Science 2003;302:1223-7.
3. Ryu S, Kodama S, Ryu K, Schoenfeld DA, Faustman DL. Reversal of established autoimmune diabetes by restoration of endogenous beta cell function. J Clin Invest 2001;108:63-72.
4. Nishio J, Gaglia JL, Turvey SE, Campbell C, Benoist C, Mathis D. Islet recovery and reversal of murine type 1 diabetes in the absence of any infused spleen cell contribution. Science 2006; 311:1775-8.
5. Suri A, Calderon B, Esparza TJ, Frederick K, Bittner P, Unanue ER. Immunological reversal of autoimmune diabetes without hematopoietic replacement of beta cells. Science 2006;311: 1778-80.
6. Chong AS, Shen J, Tao J, et al. Reversal of diabetes in nonobese diabetic mice without spleen cell-derived beta cell regeneration. Science 2006;311:1774-5.
7. Faustman DL, Tran SD, Kodama S, et al. Comment on papers by Chong et al., Nishio et al., and Suri et al. on diabetes reversal in NOD mice. Science 2006;314:1243.

Amantadine-Resistant Influenza A (H3N2) Virus in Japan, 2005–2006

TO THE EDITOR: Strains of influenza A (H3N2) virus with a specific mutation (Ser31Asn) have recently shown a dramatic increase in resistance to amantadine in communities in Asia and North America. This resistance in 70 to 90% of strains has occurred despite the absence of sustained selective drug pressure.[1,2] We conducted a multicenter study to assess the prevalence of such resistance during the 2005–2006 influenza season in Japan. The study included molecular analysis of the hemagglutinin gene of resistant and sensitive influenza A (H3N2) viruses.

We examined a total of 415 isolates of influenza A virus, sampled from November 2005 to April 2006, for amantadine resistance. Of these samples, 231 of 354 influenza A (H3N2) viral isolates (65.3%) were amantadine resistant, with a Ser31Asn change in the M2 gene. The prevalence of resistance ranged from 36.8 to 100%, according to the area in Japan. However, none of 61 influenza A (H1N1) viral isolates were resistant. Analyses of the hemagglutinin gene in influenza A (H3N2) viral isolates showed two distinct clades: all amantadine-resistant viruses were in clade N, and all amantadine-sensitive viruses were in clade S.

The clinical presentation did not differ between patients shedding clade N virus and those shedding clade S virus. None of the patients had received previous treatment with amantadine. The numbers of patients with influenza at the medical facilities participating in the study were similar to those in the past, despite a high proportion of resistance. Clade N viruses were also found in other countries, suggesting that this strain predominated not only in Japan but also in other