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INSIDE

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How HAPE Happens

ABSTRACTS & COMMENTARY

Synopsis: *Recent studies suggest that high-altitude pulmonary edema (HAPE) is not primarily an inflammatory process, but that it might result from alterations in the sodium-driven clearance of alveolar fluid. In addition to gradual ascent, prophylactic salmeterol might be effective in travelers who are predisposed to HAPE.*

Sources: Swenson ER, et al. Pathogenesis of high-altitude pulmonary edema: Inflammation is not an etiologic factor. *JAMA*. 2002;287:2228-2235; Sartori C, et al. Salmeterol for the prevention of high-altitude pulmonary edema. *N Engl J Med*. 2002;346:1631-1636.

To determine whether inflammatory changes are important in the pathogenesis of high-altitude pulmonary edema (HAPE), Swenson and colleagues studied 10 subjects who had previously had HAPE and 6 similar alpinists who had not suffered from HAPE. Pulmonary artery pressure determinations and bronchoalveolar lavage (BAL) sampling were done at 490 m elevation prior to ascent and then again at 4559 m elevation before or at the onset of HAPE. HAPE-susceptible climbers had higher pulmonary artery pressures at altitude than did their HAPE-resistant counterparts. BAL fluid in HAPE-sensitive climbers had higher quantities of red blood cells and plasma-derived proteins than in HAPE-resistant subjects, but concentrations of white blood cells and inflammatory cytokines were similar in the 2 groups. Swenson et al concluded that inflammation is *not* a primary etiologic factor in HAPE but that HAPE is a form of hydrostatic pulmonary edema with altered alveolar-capillary permeability.

Sartori and associates studied similar mountaineers at the same Swiss site. In 33 HAPE-susceptible subjects, HAPE occurred more commonly with placebo (14 of 19, 74%) than with prophylactic salmeterol (6 of 18, 33%, $P = 0.02$). Understanding that beta-adrenergic agonists such as salmeterol affect sodium transport and the clearance of alveolar fluid, the nasal transepithelial difference (a marker for transepithelial sodium and water transport in distal airways) was found to be 30% lower ($P < 0.001$) in 33 HAPE-sensitive climbers than in 33 HAPE-resistant climbers. While providing evidence that alteration in the sodium-driven clearance of alveolar fluid might be important in the pathogenesis of HAPE, Sartori et al also provided initial evidence that salmeterol might be useful in preventing HAPE in hikers and climbers susceptible to this condition.

COMMENT BY PHILIP R. FISHER, MD, DTM&H

High-altitude recreation is increasingly accessible to adventurous individuals. In fact, on a single day (May 16, 2002), 54 individuals successfully reached the summit of Mt. Everest.[1] (In 1953, Tenzing Norgay and Sir Edmund Hillary reached Everest's summit for the first time.) Tenzing's grandson and Hillary's son were both among the dozens of people climbing Everest.

As travel medicine practitioners know, however, one need not climb Everest to suffer physical effects of high altitude. Acute mountain sickness (AMS) is a problem for 25% of travelers visiting destinations between 2000 and 3000 m above sea level and for more than 50% of people traveling to sites higher than 3000 meters.[2] Gradual ascent, acetazolamide, and, in selected cases, dexamethasone provide effective prophylaxis in AMS-susceptible individuals.[2] Treatment is by descent. High altitude cerebral edema (HACE) and HAPE are less common but can be fatal. Prevention of these serious complications has until now been limited to gradual ascent. Even in HAPE-susceptible travelers, gradual ascent can be preventive.[3] Treatment of symptomatic travelers with HAPE and/or HACE involves rapid descent, oxygen, dexamethasone (for HACE), and nifedipine (for HAPE).[2]

During the 4 decades since HAPE was characterized, there has been uncertainty as to the pathogenesis of this disorder. While pulmonary pressures and alveolar-capillary leaking seemed primary, there has also been concern that inflammation might play a key role in the pathogenesis of HAPE. This notion was supported by the finding that children with respiratory infections are more likely to develop HAPE[4] and by the suggestion that inflammatory mediators are increased in HAPE. The careful (and fairly aggressive interventional) study of Swenson et al provides compelling evidence that inflammation is not a major factor in leading to or initially mediating the development of HAPE. Previous findings of signs of inflammation in the alveolar fluid of patients suffering from HAPE were probably due to a later secondary result of HAPE rather than to a primary etiologic factor.[5]

Since inflammation does not seem to mediate HAPE, what might be the feature of susceptible travelers that prompts the development of life-threatening pulmonary edema at altitude? Sartori et al provide good evidence that the clearance of alveolar fluid is, at baseline, defective in HAPE-susceptible individuals. Perhaps the relative hypoxia seen at high altitude leads to increased pulmonary arterial pressures and increased alveolar-capillary leaking.[6] Many climbers can clear this increased leak, especially if given time during a gradual ascent and a gradual adaptation to increasing altitudes. Travelers with limited or defective alveolar clearance are much less likely to adequately handle the increased hydrostatic fluid shifts and can develop significant pulmonary edema. While the predisposing variation in salt and fluid equilibrium might not be amenable to full correction, it does appear that the added time and adaptation afforded by a gradual ascent allow the lungs to tolerate temporarily increased alveolar fluids. Even in HAPE-susceptible travelers who must reascend to high altitude, salmeterol now seems to offer promise as an additionally effective means of preventing HAPE. ■

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Yellow Fever Acquired in Amazonas, Brazil

ABSTRACTS & COMMENTARY

Synopsis: *An American traveler returning from Amazonas, Brazil, dies from yellow fever, which illustrates the importance of the yellow fever immunization in travelers going to endemic areas. In spite of the recent reports of rare and serious adverse events following yellow fever immunization, the vaccine has had a long safety record and still appears to be underused.*

Sources: Centers for Disease Control and Prevention. Fatal yellow fever in a traveler returning from Amazonas, Brazil, 2002. *MMWR Morb Mortal Wkly Rep*. 2002;51(15):324-325. Monath TP, Cetron MS. Prevention of yellow fever in persons traveling to the tropics. *Clin Infect Dis*. 2002;34:1369-1378.

A HEALTHY 47-YEAR-OLD MAN FROM TEXAS TRAVELED to Amazonas, Brazil, on a 6-day fishing trip in March 2002. He presented with abdominal pain, fever, and headache upon return, and subsequently developed intractable vomiting. His laboratory evaluation revealed

leukopenia, anemia, thrombocytopenia, abnormal coagulation profile, renal failure, and liver failure. His IgM and IgG titers for yellow fever were negative. However, serum and postmortem liver samples tested positive for yellow fever by polymerase chain reaction.

The patient had not received pretravel evaluation, yellow fever vaccine, or malaria prophylaxis. He had slept on an air-conditioned fishing boat and used DEET. Among the 15 US travelers on the fishing trip, no one else became ill with fevers. Eight (53%) of the travelers had appropriate yellow fever vaccination within 10 years and at least 10 days before arriving in Manaus. One traveler had been immunized 11 years prior to the trip; one traveler had been vaccinated 5 days before arrival, and one may have been immunized more than 30 years ago in the military. Four travelers had never been vaccinated against yellow fever, and 12 travelers did not take malaria chemoprophylaxis. According to the CDC report, the travel agent and outfitter appear to have underestimated the health risk for the group.

Monath and Cetron reviewed many of the issues regarding yellow fever in travelers. First of all, there is an increase in travel to areas where yellow fever is endemic. Secondly, the epidemiology of yellow fever in endemic countries is continually changing. Next, new concerns regarding vaccine safety have been raised since the report of severe multiorgan systemic failure in yellow fever vaccine recipients. Moreover, certified yellow fever vaccination centers tend to be located in urban areas, which requires motivation for travelers residing in rural areas who seek the vaccine. Finally, shortages in vaccine supply can contribute to inadequate vaccination.

Monath and Cetron estimated the risks associated with unvaccinated travelers. For someone visiting an area with yellow fever epidemic for 2 weeks, the risk of developing yellow fever infection is 1:267, and the risk of death is 1:1333. For the visitor to Africa, the risk of developing yellow fever infection is estimated to be 1:2000 for a 2-week trip, and the risk of death is 1:10,000. For the visitor to South America, the risk of yellow fever infection is estimated to be 1:20,000 and the risk of death is estimated to be 1:100,000. The highest risk occurs during the rainy season. In West Africa, the peak risk occurs from July to October, whereas in Brazil, it occurs from January to March.

Serious vaccine adverse reactions are also reviewed. These include hypersensitivity reactions (1 per 58,000-131,000 vaccinees), postvaccinal encephalitis (< 1 per 1,000,000), and multiorgan systemic failure (MOSF, 1 per 400,000).

Two other American and 2 European travelers died of yellow fever in recent years, 1996-1999, and none had received yellow fever immunization prior to their travel. Using a mathematical model, Monath and Cetron calculated yellow fever vaccine coverage in travelers, and estimated that vaccine coverage decreased by more than 50% from 1992 to 1998.

COMMENT BY LIN H. CHEN, MD

Since the 1980s, yellow fever has reemerged. Outbreaks were reported predominantly in Africa: Cameroon, Ghana, Liberia, Nigeria, Sierra Leone, Gabon, and Kenya, but yellow fever has also resurged in South America, in Peru and Brazil.[1] Epidemics in Africa have affected the young, especially children younger than 15 years of age.[2] It is estimated that more than 200,000 cases occur annually in Africa, and less than 50% of the 34 African countries at risk have been able to finance some form of vaccination program for yellow fever.[2] Therefore, there are huge populations that are susceptible to the infection, and yellow fever epidemics can easily occur. Interestingly, 4 of the 5 American and European travelers who died of yellow fever since 1996 acquired their infections in South America.[3-5] This perhaps indicates an underappreciation of the risk of yellow fever to travelers who go there.

Recent reports of severe adverse events (MOSF) have renewed concerns regarding the yellow fever vaccine (See *TMA Update* 2001;11:35-36).[6-8] The estimated incidence is 1 case per 400,000 vaccine recipients. On the other hand, Monath and Cetron noted that 190 million yellow fever vaccine doses have been distributed since the initial recognition of the syndrome in 1996, since which time 10 cases have been reported. Thus, the true incidence of the severe adverse events needs further elucidation.

Monath and Cetron suggest that the MOSF can probably develop only in patients who are receiving their primary vaccination. This may reassure the many patients who need repeat yellow fever vaccination. Monath and Cetron also report on a patient with chronic lymphocytic leukemia for whom IVIG was given, which contained protective levels of yellow fever neutralizing antibody. This passive protection may prove to be a good option for patients with contraindications to the yellow fever vaccine (ie, immunosuppression).

The case of fatal yellow fever in a traveler to Amazonas, Brazil, illustrates that some travel agents understate or underestimate potential health hazards. There is little motivation on the part of the travel agent to mention the need to see a travel medicine specialist. Nonetheless, the consequences of illnesses such as yellow fever and malaria in a traveler are severe. Travel medicine specialists should work with the travel agents to portray accurate risks to the travelers. ■

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Tingling Away in Titusville, Florida

ABSTRACT & COMMENTARY

Synopsis: *Since January 1, 2002, there have been several cases of neurologic illness reported after ingestion of pufferfish caught in waters near Titusville, Fla.*

Source: Centers for Disease Control and Prevention. Neurologic illness associated with eating Florida pufferfish. *MMWR Morb Mortal Wkly Rep*. 2002;51:321-323.

Neurologic symptoms consistent with exposure to paralytic shellfish toxins are occurring with increasing frequency in persons after ingestion of pufferfish caught off the coast of Florida. Laboratory analysis determined the presence of saxitoxin in uneaten puffer fish. Titusville, Fla, is located south of Daytona Beach on the Atlantic Ocean.

One patient, a 34-year-old male, ate about 8 mouthfuls of pufferfish that had been caught in the waters near Titusville. His symptoms included numbness and tingling of his hands as well as vomiting and diarrhea. He was hospitalized for observation and hydration. His symptoms resolved and he was discharged after 48 hours.

A 50-year-old father and his 24-year-old son caught several pufferfish in Titusville and, upon return to their home in Virginia, cooked and ate the fish. They both began having numbness and tingling of their lips and tongues. After contacting the Richmond poison control center, they decided to monitor their symptoms at home. The son, who only had oral tingling, improved in 3-4 days. The father's numbness and tingling did extend to involve his face, neck, and shoulders. Within 2 weeks, his symptoms had also resolved.

In New Jersey, a 65-year-old female and her husband consumed a meal of pufferfish that a family member had caught in Titusville. Both persons developed tingling around their lips within minutes of eating the fish, but the woman began vomiting and she was later hospitalized. Her course was complicated by chest pain, tachycardia, ascending paralysis, and ventilatory failure requiring mechanical ventilation. Her paralysis and muscle strength gradually improved allowing her to be extubated and discharged after 3 days.

The uneaten pufferfish from the New Jersey case were sent to the Institute for Marine Sciences in Canada. Liquid chromatographic-tandem mass spectrometric analysis detected saxitoxin and 2 similar analogs, N-sulfocarbamoylsaxitoxin and decarbamoylsaxitoxin in the fish.

COMMENT BY MARY-LOUISE SCULLY, MD

Pufferfish, also known as swellfish, blowfish, or globefish, have the intriguing ability to inflate their bodies with air and/or water then and float upside down on the surface of the water discouraging potential attackers. Most puffers belong to the family Tertraodontidae ("four-toothed") but some include porcupinefish in the family Diodontidae ("two-toothed") as they are able to self-inflate as well. Neurotoxins (ie, saxitoxin or tetrodotoxin) can be found in several of the approximately 100 species of pufferfish. You may be familiar with the link between pufferfish and the deadly tetrodotoxin, associated with the Japanese fugu specialty. In Japanese, the word fugu is a general name for fish of the Tetraodontidae family but is also used more narrowly in that one type of puffer, *Fugu rubripes*, found only in the waters surrounding Japan.

These cases took place after patients ate pufferfish but are consistent with paralytic shellfish poisoning (PSP). PSP usually occurs in association with eating filter-feeding mollusks and shellfish. In the United States, about 10 cases a year of PSP are reported to the CDC. One of the best-characterized toxins involved is saxitoxin. Some freshwater cyanobacteria and dinoflagellates produce saxitoxin. Shellfish that filter to feed absorb these toxins, but nonfilter feeding shellfish, such as lobsters, crab, and shrimp, are usually safe to eat. Pufferfish, by eating mol-

lusks, are thought to accumulate and even amplify the saxitoxin.

Saxitoxin is heat and acid stable and is not destroyed by freezing or cooking. The presence of the toxin does not affect the taste or odor of the food. Saxitoxin is rapidly absorbed after ingestion and is felt to act by blocking the opening of the voltage-sensitive sodium channel needed for propagation of nerve impulses. Symptoms of PSP include tingling of the mouth and lips, facial paresthesias, vomiting, and in severe cases ataxia, muscle weakness, respiratory paralysis, and even death.[1] The time of onset and the severity of the symptoms are likely influenced by the amount of toxin ingested, though typically symptoms begin within 30 min to 2 h after ingestion.

Tetrodotoxin, also a sodium-blocking toxin, is felt to be produced by *Vibrio* species or other bacteria that bioaccumulate in the pufferfish. Tetrodotoxin is an *extremely* potent neurotoxin and is known for its association with the Japanese specialty fugu, as mentioned above. Tetrodotoxin ingestion is associated with a 60% mortality.[2] Tetrodotoxin intoxication has been associated with eating pufferfish, porcupinefish, horseshoe crab eggs, and even mollusks.[3] Although the symptoms begin similarly with numbness, paresthesias, and vomiting, the hallmark feature is the rapid onset of ascending paralysis, respiratory failure, and often death.

Treatment for either saxitoxin or tetrodotoxin intoxication are mainly gut decontamination and supportive care. Early intubation and mechanical ventilation can be life saving. With tetrodotoxin poisoning, there are 2 reports of reversal of motor and respiratory paralysis using edrophonium.[4]

Fish that are caught can often be transported to other areas. In this report, the pufferfish were caught in Titusville, Fla, but the victims of the illness were as far away as New Jersey. Until now, most pufferfish in US waters were not thought to be toxic. Now, at least 10 cases of presumed pufferfish poisoning have been reported in our waters. *Chemical analysis detected the presence of saxitoxin, the toxin associated with PSP, as the cause of the symptoms in these cases*. Health care providers need to be aware that the onset of neurologic symptoms after ingestion of pufferfish could be due to saxitoxin and ill persons should be advised to proceed immediately to a hospital facility. ■

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Lethal Irukandji Syndrome in Queensland, Australia

EDITOR'S NOTE

In a 1999 article that appeared in *Australian Family Physician*, Fenner and Carne noted an unusually high number of Irukandji victims who had required admission to intensive care facilities.[1] However, even in their report of events occurring in Australia between 1996 and 1999, *no* deaths had been noted. This recent newspaper account serves as a warning that Irukandji syndrome can be fatal, and that its incidence appears to be increasing. Why? And what is Irukandji syndrome anyway?

The stings from the tentacles of the *Carukia barnesi* jellyfish can result in severe sympathetic overdrive causing hypertension (responsive to α-blockers such as phentolamine), tachyarrythmias, profuse sweating, and shaking. This syndrome ultimately leads to pulmonary edema from hypokinetic cardiac failure that requires inotropic support and monitoring.

The recent trends, which are recounted in the following article from the Science section of *The New York Times*,[2] should alert travel medicine providers and their patients to the dangers associated even with apparently mild stings by small box jellyfish, such as *Carukia*. At the very least, swimmers and divers in endemic geographic regions must be aware of the possibility of jellyfish exposure and how to inactivate their stinging capsules with vinegar. Thirty minutes after an untoward sting they could be well on the path to cardiogenic shock. Specific antivenom is available in places like Cairns, Queensland, where its administration, coupled with appropriate life support measures, may be critical to survival. —**FJB**

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CME Questions

10. Which one of the following statements is true about high-altitude pulmonary edema (HAPE)?

a. All travelers to high altitude are equally at risk of HAPE.
b. Alveolar inflammation is a primary cause of HAPE.
c. Altered alveolar fluid clearance is associated with a risk of HAPE.
d. Albuterol is effective in treating HAPE.
e. Alveolar fluid clearance rates are not related to HAPE pathogenesis.

11. Which of the following statements is correct?

a. The epidemiology of yellow fever has not changed since the development of the vaccine.
b. Since the 1980s, yellow fever epidemics have occurred predominately in Africa.
c. The use of DEET and sleeping in air-conditioned accommodations should eliminate any risk of yellow fever.
d. None of the above

12. Which of the following statements about saxitoxin is *not* true? Saxitoxin:

a. is associated with paralytic shellfish poisoning (PSP).
b. gives fish a pungent peppery taste.
c. is a sodium channel blocking toxin.
d. is heat and acid stable.
e. is produced by some freshwater Cyanobacteria and dinoflagellates.

Readers are Invited

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PHARMACOLOGY WATCH

HRT: Position Paper Places Benefits in Question

A soon-to-be published position paper will call into question the benefits of hormone replacement therapy (HRT) for women. The "International Position Paper on Women's Health and Menopause" will go to press in June, but newspapers coast to coast are already publishing the recommendations of the document, which concludes that an evidence-based review of HRT does not support the use of HRT in preventing coronary artery disease, Alzheimer's disease, depression, or urinary incontinence. The position paper was the product of an international group of 28 doctors and scientists and was funded by the National Institutes of Health and the Giovanni Loren Zini Medical Science Foundation of Italy. The recommendations reflect a shift in opinion for most physicians and epidemiologists who feel that HRT's risks, which include increased risk of blood clots, cholelithiasis, and breast cancer do not outweigh the potential benefits. The thought process doctors must go through with patients when considering starting or discontinuing HRT is well laid out in a recent "Clinical Crossroads" paper in the *Journal of the American Medical Association*. Dr. Deborah Grady reviews the current literature, and dilemmas faced by both physicians and patients alike when trying to wade through conflicting studies. A self-avowed former proponent of HRT, Dr. Grady now feels that it should be reserved for treatment of vasomotor symptoms, and that it is second-line therapy to bisphosphonates for the treatment of osteoporosis (*JAMA*. 2002;287:2130-2137).

Alosetron Set for Comeback

Eighteen months after it was withdrawn from the US market, alosetron (Lotronex) GlaxoSmithKline's irritable bowel syndrome (IBS) drug, may be making a limited comeback. The FDA's Gastrointestinal Drugs and Drug Safety Advisory Committees approved the drug for patients with severe IBS symptoms. The drug was initially approved in February 2002 for the treatment of women with IBS characterized by diarrhea. However, soon after the drug was marketed, cases of severe constipation were reported along with several cases of ischemic colitis. Of the 7 deaths, alosetron was possibly a factor in all of them. The drug was effective in selected patients, however, and the FDA was inundated with requests to re-release the drug in a limited fashion. The current plan is to restrict the drug to patients with the most severe symptoms, and to require patients to sign a patient-physician agreement and to receive counseling about the potential risks of the drug. The FDA is also considering limiting the use of alosetron to gastroenterologists. GlaxoSmithKline is working out the plan for re-release of alosetron with the FDA and hopes the drug will be available before the end of the year.

Losartan Could Receive Expanded Indication

The angiotensin receptor blocker (ARB) losartan may soon be approved for prevention of renal disease in type 2 diabetes. The FDA is considering granting losartan the expanded indication based on a favorable vote by the FDA's Cardiovascular and Renal Drugs Advisory Committee early in April. Angiotensin converting enzyme inhibitors (ACEIs) have long been considered first-line treatment of hypertension in type 2 diabetics because of studies that suggested that blockade of the renin-angiotensin system delays progression to end-stage renal disease. Whether this benefit extends to ARBs was debatable until 3 articles were published in the

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. Telephone: (404) 262-5517. E-mail: robin.mason@ahcpub.com. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

Sept. 20, 2001, *New England Journal of Medicine* confirming the benefit of ARBs in protecting patients with Type 2 diabetes from developing renal disease.

Merck supplied additional data to the FDA in April, which eventually led to the recommendation. The FDA is expected to endorse the committee's recommendation, granting losartan the indication for reno-protection in type 2 diabetes, the first drug to receive such approval.

Viagra Shown Beneficial in Intensive Care Unit

Viagra (sildenafil) in the ICU? It may not be so far-fetched, and the benefit may be lifesaving for those with severe pulmonary hypertension. Sildenafil has been shown to cause pulmonary vasodilation along with its other well-known effects. German researchers looked at 30 patients with severe pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension, or pulmonary hypertension due to aplasia of the left pulmonary artery. Patients were randomized to receive sildenafil alone or in combination with iloprost, a long-acting inhaled prostacyclin analogue. Maximum pulmonary vasodilatory potency (maximum reduction of pulmonary vascular resistance and increase in cardiac index) occurred with the combination of sildenafil 50 mg plus inhaled iloprost (-44.2%, 95% CI, -49.5% to -38.8%). This compared with a drop of 14.1% with inhaled nitric oxide. The combined effect of sildenafil with iloprost lasted longer than 3 hours and had minimal effect on systemic arterial pressure and arterial oxygenation. It was concluded that sildenafil is a potent pulmonary vasodilator that acts synergistically with inhaled iloprost (*Ann Intern Med*. 2002;136:515-522).

Smallpox Vaccination Needs Consideration

Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases, has kicked off "an open and public dialogue" on the need for a national preemptive smallpox vaccination program (*N Engl J Med*. 2002;346:1319-1320). Nearly unthinkable a year ago, the events of Sept. 11 have focused the national health-care community on the real possibility of bioterrorism. And of all the potential bioterrorism pathogens, which include anthrax, plague, and even tularemia, it is smallpox that stands out as a true threat. Declared eradicated from the world in mid-1970s, routine vaccination for smallpox in this country was discontinued 30 years ago. As a result, more than half the American population is susceptible to smallpox infection. Samples of variola virus, the cause of smallpox, were stored at the CDC and were actually produced and stored in the former Soviet Union as part of a biologic warfare program. Those stores were reported destroyed by the current Russian government, but it is unknown whether samples of the deadly virus may have fallen into the hands of potential bioterrorists. Smallpox is a uniquely deadly bioterrorist weapon. Once infected, victims are most contagious prior to the development of symptoms, thus becoming unwitting agents of the bioterrorist, especially in our highly mobile society. Plus smallpox infection carries a relatively high mortality rate, from 5 to 20% based on 30-year-old data. Current CDC policy for an attack focuses on a "ring-vaccination" strategy in which suspected or confirmed cases and their contacts are isolated and immediately vaccinated. This is the method that successfully eliminated smallpox 30 years ago. The CDC currently is advocating the strategy in the event of a bioterrorists attack. But critics, such as William J. Bicknell, MD, from Boston University School of Public Health, argue that ring-vaccination was effective against natural outbreaks of the virus but may not be effective against a deliberate bioterrorist attack. He makes the case for widespread voluntary smallpox vaccination, which would achieve protection for the majority of Americans and also act as a deterrent to attack (*N Engl J Med*. 2002;346:1323-1325). There is a risk to the vaccine including encephalitis and vaccinia, and vaccination of the majority of Americans would be expected to result in approximately 180 deaths. This debate would have been moot 2 months ago because it was felt that CDC did not have enough vaccine for a nationwide vaccination program. However, researchers from the National Institute of Allergy and Infectious Diseases Smallpox Vaccine Study Group have tested dilutions of a recently discovered cache of smallpox vaccine produced in 1982. The randomized single-blind trial of 680 adult volunteers showed that both 1:5 and 1:10 dilutions of the vaccine were as effective in conferring immunity as the full strength vaccine, with at least 97% of those vaccinated developing protective antibodies (*N Engl J Med*. 2002;346:1265-1274). The common side effects from the vaccine included formation of satellite skin lesions, regional lymphadenopathy, fever, headache, nausea, and other signs of a viral infection. But the true upshot of the study was the realization that as a nation, we suddenly have the ability to vaccinate the entire population. But with this realization comes the debate as to whether we should. The turning point in this deliberation may depend on our government's ability to truly characterize the risk of a bioterrorist attack. ■