

presenting cells is a costimulatory signal for T-cell activation (Fig. 1). LFA-1 also binds to CD54 and other ligands expressed by endothelial cells and keratinocytes. Thus, the rationale for using hu1124 in patients with psoriasis is to inhibit the interaction between LFA-1 and its ligands, in order to decrease the activation of T cells and their movement into psoriatic plaques. Other agents that inhibit T-cell activation include CTLA-4-Ig, a fusion protein that binds to CD80 (B7-1) and CD86 (B7-2) on antigen-presenting cells, preventing their costimulatory interaction with CD28 on T cells.<sup>10</sup>

In addition to agents that block the activation of T cells, there are immunomodulators that inhibit the activity of proinflammatory cytokines. Two such agents are infliximab and etanercept, which are directed against tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ). Both drugs have been approved by the Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis<sup>11</sup> and ulcerative colitis<sup>12</sup> and are undergoing clinical testing for psoriasis. A trial of infliximab (a human–mouse monoclonal antibody against TNF- $\alpha$ ) showed that patients with plaque psoriasis had considerable improvement when they were treated with this agent.<sup>13</sup>

With each of these strategies, there is a risk of toxic effects, including immunosuppression and an immune response against the therapeutic agent itself. Indeed, in a study of hu1124 for the treatment of psoriasis, the ability to mount a T-cell–dependent immune response against a new antigen was examined by immunizing subjects with a bacteriophage and assessing the primary immunoglobulin response and the IgG response after rechallenge.<sup>9</sup> Treatment with hu1124 appeared to decrease the primary immunoglobulin response and the switch from an IgM to an IgG isotype in a dose-dependent manner. Also, there may be an increased risk of infections, including tuberculosis, in patients treated with agents directed against TNF- $\alpha$ .<sup>14</sup>

None of the new treatments I have discussed are currently approved by the FDA for the treatment of psoriasis, but one or more could be approved in the next few years. The development of agents that interfere with specific steps in the immune pathogenesis of diseases such as psoriasis represents a rational approach to the search for safer and more effective therapies. If its early promise is fulfilled, alefacept may prove to be an example of the success of this approach.

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## READY OR NOT — PREPAREDNESS FOR BIOTERRORISM

GLANDERS is a zoonotic disease of horses and related equids that was eliminated from the United States in 1934. The etiologic agent, *Burkholderia mallei*, has occasionally caused severe infection in humans after the transmission of small aerosolized particles from infected animals, and *B. mallei* was used for biologic warfare, directed against the horses of the Allied armed forces, during World War I. Before the case reported by Srinivasan et al. in this issue of the *Journal*,<sup>1</sup> the last infections in humans in the United States occurred in 1945 among laboratory personnel working on a biologic-weapons program at Camp Detrick, Maryland.<sup>2</sup> Srinivasan et al. suggest that this most recent laboratory-acquired infection with *B. mallei* may be a harbinger of the possible release of other long-forgotten infectious agents, such as the smallpox virus and anthrax bacillus, which reflects a concern about the national program of preparedness for bioterrorism and biologic warfare under whose auspices the recent infection with *B. mallei* occurred. However, this concern must be tempered by an acknowledgment that breaches in safety pro-

cedures led to both the current infection and those in the 1940s. Fortunately, the recent episode did not involve a readily communicable disease, and continued adherence to the otherwise successful procedures for personal and environmental protection against laboratory-acquired infections should prevent similar cases.

Nevertheless, the potential use of biologic agents to inflict disease is a pernicious consequence of advances in medical, laboratory, and engineering sciences. This threat cannot be dismissed, given the extensive biologic-weapons programs in Iraq and the former Soviet Union, and the terrorism targeted at Americans abroad, as well as acts of domestic terrorism perpetrated by Americans. The *Journal* has tacitly acknowledged these causes for concern in publishing articles about smallpox and anthrax.<sup>3-5</sup>

Containment of the threat of bioterrorism requires a strategy that includes the strengthening of international treaties and preparation for the potential use of biologic agents by rogue states and organizations. From the perspective of public health and health care delivery, the main obstacles to adequate domestic preparedness come from an inadequate public-service infrastructure. This was a major lesson learned from the \$3 million drill that tested the readiness of top government officials for a terrorist attack, which included a three-day exercise involving the release of plague in Denver.<sup>6</sup> Intelligence sources assert that biologic terrorism is inevitable in the United States. Regardless of the basis for this assertion, we are clearly vulnerable to new, emerging, and reemerging infectious diseases that can have a major effect on our communities. We should make the investment necessary to ensure optimal local, state, and national preparedness in the context of a defined set of standards for today's recognized diseases and bioterrorist activities, as well as for the unknown threats of tomorrow.<sup>7</sup>

Despite centuries of experience with zoonotic diseases such as yellow fever and plague and a decade of activities designed to enable us to recognize and control emerging diseases, we remain inadequately prepared for public health emergencies. For example, in the summer of 1999, an outbreak of West Nile virus<sup>7-9</sup> left New York and the surrounding states scrambling to handle a deluge of inquiries and to explain a rational policy for risk reduction. Agencies in these states struggled with issues that federal public health authorities must resolve, including an initial misdiagnosis and a delay in making a connection between the clinical data and reports of dead crows; the establishment of effective surveillance of humans and animals to monitor the disease; the integration of clinical, surveillance, and laboratory data from a variety of agencies across jurisdictional boundaries; the timely receipt of test results from the essential laboratories; and the coordination of all the public communication.<sup>9,10</sup> Problems arose despite the improvements that

had occurred thanks to the previous infusion of federal public health funding for preparing a response to bioterrorism and more effective liaisons with the Federal Bureau of Investigation and its New York City Office of Emergency Management. Conversely, the limited scope of the outbreak — 62 people infected and 7 deaths — is a testament to the extraordinary effort by the local public health officials and also attests to the dual benefits that result from activities designed to improve preparedness.

Progress has been made in preparedness since Congress approved new emergency funding in 1999. We now have a national network of laboratories that can test for "critical agents" (the term used by the Centers for Disease Control and Prevention for agents that could cause major medical and public health disruption). We now have a national stockpile of drugs with which to combat these agents, a contract for 40 million additional doses of smallpox vaccine, new epidemiology and laboratory staff in state and local health departments, a national health-alert network to link and train local public health officials, and pilot programs in place at health care facilities that are implementing strategies for "real-time" surveillance.<sup>11</sup>

Despite these strides, deficiencies remain in the medical care delivery infrastructure that would be necessary to mount a response to bioterrorism or other, more predictable, public health emergencies. The challenges that would face the health care delivery system are already evident in routine emergency room diversions, and the problem is exacerbated by the shortage of nurses and the fiscal goal of hospitals to eliminate unused beds. In an oft-cited example of such inadequacy, the health care delivery system was unable to handle an increase in cases of influenza in northern California in 1998. This shortcoming bodes ill for our ability to respond to the predictable recurrence of pandemic influenza; the 1918–1919 outbreak killed 0.5 percent of the population of the United States, which would amount to about 1.4 million people if it happened today. It bodes worse for our ability to respond to the unpredictable occurrence of bioterrorism.

Local, county, and state medical societies can help facilitate community disaster planning with call-up systems for physicians, the coordination of care at standard and emergency health care sites, the designation of hospitals to receive certain types of patients, and plans for integrating state and federal medical assistance sent to the community (including health care workers as part of the national disaster medical system and stockpiles of antibiotics).<sup>12,13</sup> States should consider contracting with their local medical societies to perform these medical-coordination functions, should require continuing medical education on preparedness for epidemics, and should require that the disbursement of a portion of Medicaid funds be contingent on the implementation of training programs

for physicians that focus on disaster preparedness at the health care facility. Although no one would propose funding for staffed but vacant hospital beds, our effort to ensure national preparedness must include assisting emergency medical systems to develop a real-time electronic inventory of all the public, private, and federal hospital beds within a broad geographic area. Federal programs can focus on making investments in graduate medical education that can help improve our preparedness.

For a comprehensive preparedness effort to be truly effective, these proposed state and federal measures must be funded. Most of the federal funding for antiterrorist efforts is earmarked for law enforcement and public-safety institutions. Moreover, federal funds for public health are not reaching the health care community, even though we all recognize the central part that physicians, associated health care providers, and acute care hospitals would play during a bioterrorist attack. The case reported by Srinivasan et al. demonstrates some of these points; for instance, there was a delay in diagnosis and an inadequacy of the technology currently in use in hospital laboratories for identifying the causative agent of an unusual illness. Physicians must champion important changes and help secure the resources that will give them the tools to do their part.

Our goal should be enhanced collaboration, but public health officials and clinicians must move beyond relationships that too often are limited to the acquisition of surveillance data. This change can happen only if public health officials stake their claim as a vital resource for clinicians. We should establish 24-hour hot lines (preferably a single nationwide, toll-free number) that provide a directory service to link clinicians to the appropriate public health officials for consultation on an unusual illness or cluster of illnesses, to assist with laboratory diagnosis, and to advise on current public health recommendations. Public health programs, in turn, must have trained epidemiologists and clinicians ready to handle these calls.

Finally, we should prepare for bioterrorism by applying what we have learned from planning for an influenza pandemic, ensuring the safety of our food, controlling other infectious diseases, and responding

to the routine strains on our health care delivery system. Preparing for these needs can better prepare us for bioterrorism, and vice versa. The first question for physicians to ask themselves regarding preparedness should be "Can I identify and contact a public health official in my state about suspected bioterrorism or another public health emergency?" The second should be "Does my institution have a well-rehearsed plan if the next case or cluster represents an outbreak or bioterrorism?" The more emergency procedures are in place and rehearsed before the next complex public health emergency occurs, the better our nation will fare.

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