Biodefense: Scenarios, Science, and Security

by Steven E. Koonin

On November 7, Caltech sponsored a forum on biodefense, free and open to the public in Beckman Auditorium. Moderated by veteran Southern California news broadcaster Jess Marlow (now with KCET's "Life and Times"), the panel included Dr. Alan P. Zelicoff, chief scientist of Sandia National Laboratories' National Security and Policy Planning Division, who developed the Rapid Syndromic Validation Project (RSVP), a medical database designed to report and contain outbreaks of disease; Dr. Jonathan E. Fielding, director of public health of Los Angeles County and professor of health services and pediatrics at UCLA; and Steven E. Koonin, professor of theoretical physics and Caltech provost. Koonin has advised the government for more than a decade on the technical aspects of national security and in 1998–99 led a large study on civilian biodefense for the Department of Defense. His remarks at the forum are adapted here. The entire forum can be viewed on line at http://atcaltech.caltech.edu/theater/.

My involvement in the biodefense business started about two and a half years ago, when I led a study by some 20 academics looking at the defense of the civilian population against biological terrorism. We submitted our report in the fall of 1999. Over the past few weeks, it has been an eerie feeling for me to go back and read that report in the context of recent events.

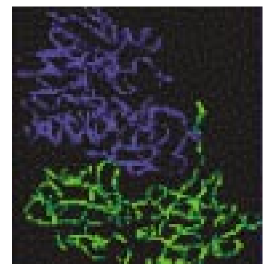
I'd like to share with you some of the contents of that report. First I'll describe some of the "what if . . . ?" situations that we used to get our minds around the problem. No one expected events to play out exactly as described, but they give a good idea of what the general aspects are. Then I'll go through some of the technical recommendations that we made, to give you some sense that there *are* things that we can be doing to better defend ourselves against bioterrorism. And finally, I'll make a few remarks about organization.

We came up with four scenarios. The first involves anthrax, which we are all too familiar with these days. What we hypothesized two and a half years ago was the spreading of anthrax spores from the platforms of the New York City subway. It turns out that the trains in tunnels are very effective at spreading the spores around. In our scenario, this is done without any prior notice, no tipoff that it's going to happen. But then on the following Saturday comes a tip that a terrorist group has attempted to carry out such an attack.

What would happen if this were to take place today? First, we don't have validated dispersal models; it would be very difficult for us to say, a priori, where the spores would go and, hence, who would be affected. Second, about 4 million people ride the New York subways every day, and even if only one percent of them contracted the disease, that's still 40,000 people.

If an attack is overt—that is, if we have warning ahead of time—then we can try to reduce casualties by distributing the appropriate antibiotics. The names are familiar these days: Cipro, doxycycline, penicillin, and so on. But if the event is covert—that is, if we don't know about it—then there is no "event." There are no first responders to distribute medication. A few days later, people start checking into hospital emergency rooms with severe distress, and by that time, most of the people who exhibit symptoms will be lost. Or at least that's the rule from previous experience; I think the rule is being updated as we deal with the cases of inhalation anthrax that have taken place recently. In any case, there will be a panic rush on medical facilities as soon as it becomes known that there has been a wide-scale dispersal of spores.

Scenario number two involves smallpox: a terrorist cell plants smallpox in the air ducts of a flight from Europe to the United States with 265 people aboard. The first sign of a problem is when the whole air crew reports in sick two weeks later (the smallpox incubation time is about 12 days). At the same time, some group takes credit for "infecting the Great Satan" with smallpox. This disease, as we have all heard lately, is highly contagious. To give you a sense of how serious it can be, let me offer a historical digression: on March 1, 1947, a man arrived in New York City by bus from Mexico. Four days later he was hospitalized with a fever and died five days after that. Because he had a variant of the disease called hemorrhagic smallpox, which is not as obvious to identify, it took about a month before this was diagnosed correctly. He induced three secondary and twelve tertiary infections, mostly among the health-care workers who were caring for him. Three of them died. Among unvaccinated populations, the fatality rate is about 30 percent for smallpox, so this number is consistent. As a result of that one case and those secondary and tertiary infections, New York City immunized more than 6 million people, essentially depleting the whole U.S. vaccine supply on just one case.



The lethal ricin protein (right) is derived from castor beans (center), the seed of the castor oil plant (*Ricinus communis*, left).

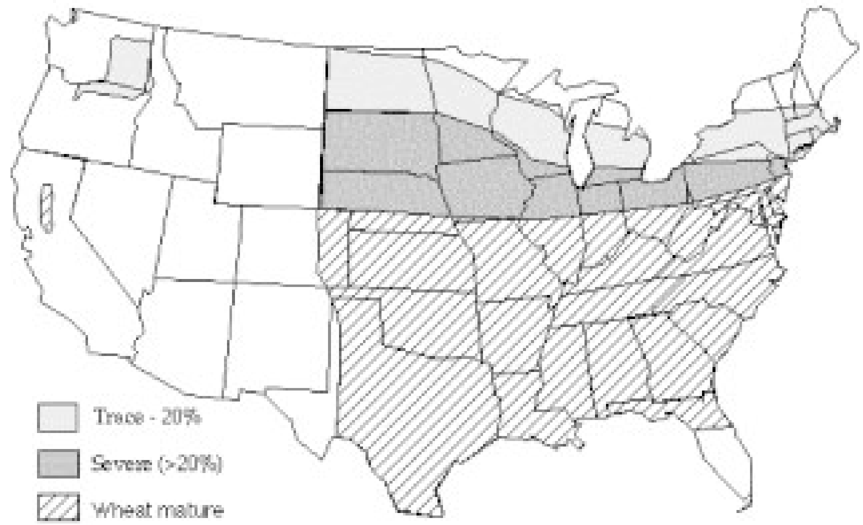
So, what would happen today if this event were to occur? Again, there's no actual "event" and no responders. Nothing happens for two weeks. Eventually we would realize what's going on and would quarantine and vaccinate. Right now we have 15 million full-strength doses on hand. Medical experts think that this can be diluted to about 75 million, and, as you've probably read in the newspapers recently, drug companies have already started cranking up vaccine production.

Returning to our smallpox scenario, the effects spread continentwide, because all of these passengers would be catching their connecting flights and dispersing across North America before anything was noticed. There's certainly the possibility of an epidemic, and, as I mentioned, 30 percent of unvaccinated people typically die. While vaccinations stopped in 1975, some of us may still have some immunity from the vaccinations we received as children, but it is thought that the efficacy of the vaccine decays on a five- to 10-year timescale. As in the previous scenario, as soon as the cases start showing up, a panic rush on medical facilities will ensue. The fact that smallpox is communicable and so virulent make this probably the most devastating possibility, and you can understand why the public health officials are so worried about it.

Scenario number three is not quite a biological attack, but it's an attack using a chemical agent derived from a biological system. The agent in this case is ricin. You can imagine this scenario in terms of the Oklahoma City bombing attack, but with the bomb wrapped with ricin.

Ricin is a chemical produced from castor beans, which contain this biologically very interesting protein. This protein manages to get into cells and gum up the ribosomes, which are the little machines that make proteins in your body, and so are essential for you to keep on living. A lethal dose of ricin is as small as 10 micrograms when inhaled; that's a very small droplet. The symptoms occur within a few hours: fever, cough, nausea, and death within three days at most. There is no known treatment; once you've been exposed to ricin, you die.

Wheat rust exists naturally in the United States, as shown in this map tracing its occurrance in the first week of July 1999. But deliberate infection would still have economic and psychological effects.



What would happen today? The local first responders, the people who show up to deal with the explosion, would be unlikely to consider a biological agent. Eventually it would be recognized as a hazardous-material incident, but because the effects would be very rapid, the likely casualty figures would be in the thousands rather than the hundreds you would have expected from the explosion by itself.

The last scenario is an agricultural one: a wheat-rust attack in the Great Plains by an enemy state. Remember, this was two and a half years ago, and at the time it was President Milosevic whom we were concerned about. In our scenario, Milosevic announces that if NATO doesn't stop bombing, he's going to infect the American wheat crop with wheat rust in several counties in the Great Plains.

How would that play out now? Wheat rust is an ongoing problem in the United States, even without somebody releasing it deliberately. You can see on the map of wheat rust, above, for the first week of July 1999 when we did our study, that it ranges from "trace" through "severe" in a band across the country. So there would be only a modest economic impact. In fact, in some years, 10 to 12 percent of the California wheat crop is lost to this fungus. But there would be an unknown psychological impact, because we would see the ability of a foreign country to reach into our homeland. Wheat rust does come in a variety of strains local to a given area, and so you might be able to distinguish a deliberate introduction of a strain by its difference from the naturally occurring local ones.

But you just need to remember what happened with foot and mouth disease in Great Britain this past year to get some sense of how disruptive an agricultural attack could be to the economy.

You don't hear much about agriculture as a bioterrorist target. But agriculture accounts for 13 percent of the U.S. gross domestic product and 17 percent of employment, most of it in the food-processing and distribution chain. A number of agents, such as foot and mouth disease, African swine fever, wheat rust, and rinderpest, don't harm humans but can severely disrupt the economy, which is the purpose of attacks like this. It's not about the food supply; the food supply is much more robust than could be taken out with a single agent. But you just need to remember what happened with foot and mouth disease in Great Britain this past year to get some sense of how disruptive an agricultural attack could be to the economy.

What lessons can we draw from these four scenarios? There are several. The first is that good intelligence is the best defense. Knowing our opponents' goals, capabilities, and intentions and trying to stop a release before it happens is obviously the best way to go about things, *if* we can manage to do that.

The second lesson is that there is often no "event." The revelation of an attack can be either delayed because of incubation times or hidden in the natural background. The third is that people are currently the "canaries" for biodefense. We wait until people show up sick in the emergency room before realizing that an event has occurred.

Fourth, I believe that the public health system is ill prepared to deal with bioevents. Reporting is haphazard, and the signal is not being sought. (Actually, I should say "was" not being sought; these days the public health system is much more vigilant for attacks involving the sorts of agents I've mentioned.) Our stockpiles of vaccines and antibiotics to combat some of these agents are inadequate, and we have no surge capability in our health-care system. Our hospitals are designed to

When all the Kaopectate disappears off pharmacy shelves, you know something has happened!

Some 3,000 physicians report daily on the incidence of flu to the National Flu Surveillance Network, which puts maps of flu incidence on line (http://www.fluwatch.com/ above). European physicians also keep track of flu in their countries, as illustrated below for three successive weeks in the spring of 1999. Such surveillance systems already form the backbone of the sort of disease tracking essential to defense against a biological attack.

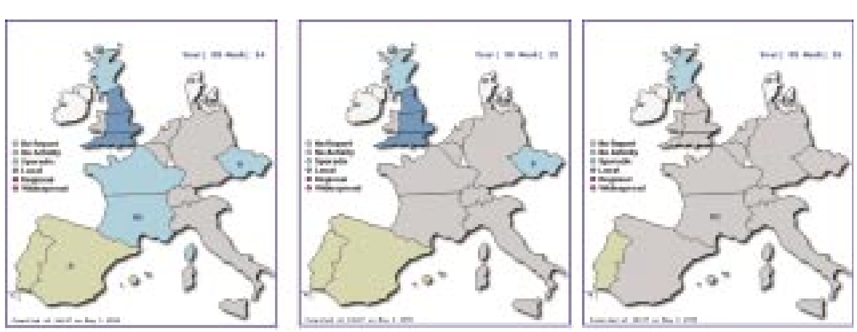
run at capacity for economic reasons; we try to keep the beds filled, just as we try to keep airline seats filled, so any surge associated with a biological attack would severely tax the system. But the United States is a leader in biomedical technology; can't we harness some of that technology to do a better job on biodefense?

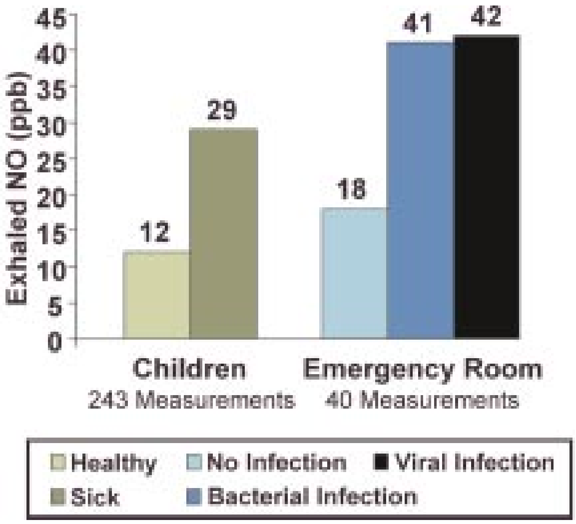
I like to compare the potential of our public health system to the situation in the 1950s, when the federal government decided to build the interstate highway system. Those roads were put in ostensibly for national security reasons: we were going to move tanks or missiles or troops over those roads. Of course, we never had to do that, but the roads turned out to be a tremendous benefit to us for civilian travel and commerce. In the same way now, addressing the public-health issues important to biodefense will have many salutary effects beyond defense.

Let me now take you through some of the things that, two and a half years ago, we thought the government should be doing to respond to those threats. One is to strengthen public-health information systems. It is extraordinarily important to detect an attack as quickly as we can. We can use that knowledge to contain contaminated areas, to prevent new exposures, and to stem epidemics of contagious agents. And we can start treating people who have been exposed before they start showing symptoms. The sooner we can pick up an attack, the better off we will be. The question is: how can we do that?

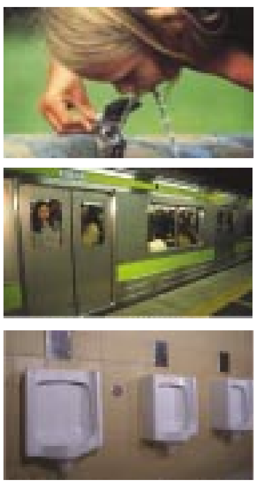
One way is to collect and mine existing data. The health system produces all kinds of information about the health state of the population. We have billing and insurance records (and certainly the billing records, in my experience, come in very promptly!). We also have admissions to emergency rooms—the symptoms that people show there, the lab results, and so on. And we have pharmacy sales. (When all the Kaopectate, for example, disappears off pharmacy shelves, you know something has happened!) What you want to do is collect and analyze this sort of data to look for the natural patterns, the natural variability, and then look for anomalies in the data.

In our report we pulled out a couple of examples to illustrate what could be done. The map of western Europe below shows the incidence of flu during three successive weeks in the spring of 1999. The colors of the countries are changing as the flu comes and goes, as reported by physicians in the European health system. In this country, we found a Web site hosted by a commercial drug company that produces a drug for flu. It has a reporting network of physicians across the country, and you can sign up for a weekly e-mail telling you the incidence of flu in your state in any given





Measuring exhaled nitric oxide (produced by the body's immune system to fight infections) could predict disease before its onset. In the clinical studies at left, presymptomatic sick children showed higher levels of nitric oxide, as did (presumably already sick) emergency room patients.



Facility sampling to monitor the health of the population could make use of all sorts of existing "facilities."

week. So, we already have the beginnings of surveillance systems, and steps have been taken toward more sophisticated reporting systems.

The next thing we suggested that might be done is facility sampling—anonymously monitoring the population with some specificity in terms of time and place. This could be a device like a smoke detector sitting somewhere in a room, analyzing what people are breathing in and out, or analyzing people's sweat, sputum, and so on. You can imagine numerous opportunities for this: drinking fountains, pay phones, and spaces where people are confined close together, such as subways, buses, and elevators. There are obvious public health spin-offs here. Although the data aren't very specific, you might be able to use them to track TB, flu, and so on.

Another way of monitoring the health state of the population is wearable instrumentation. Non-invasive means of measuring pulse, blood pressure, respiration, temperature, blood sugar, and so on have already been developed, and you can imagine packaging all of them in something that could be worn on the wrist. If you combine those data with some time-averaging, geolocation, and cellular telemetry, you could monitor the health state of the population in real time. You wouldn't have to do it for everybody; perhaps people with existing medical conditions might volunteer to wear such a thing. Or you could ask that first responders wear it. There are obvious privacy issues, but probably a lot of interesting science would result from it, in addition to the biodefense aspects.

We should also be investing in presymptomatic triage—testing to determine who has been infected before they get sick. Knowing who has been infected can be used to stem an epidemic by contagious agents. You can use such tests to deploy medicines and quarantine or allocate hospital resources efficiently.

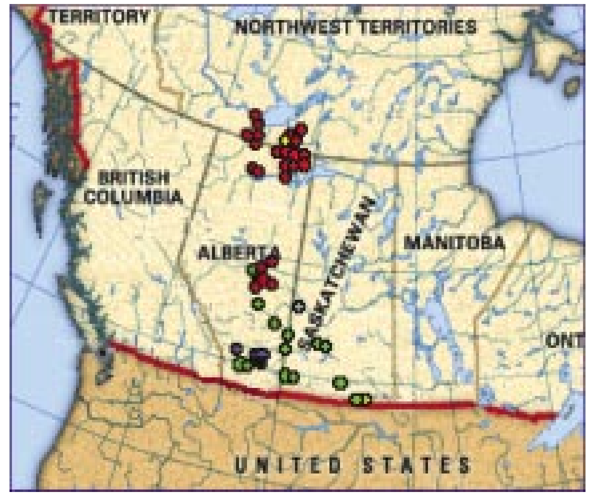
Such testing can exploit the increasingly sophisticated analysis of simple molecules—nitric oxide, for example, a gas the body's immune system produces to fight infections. Above are some measurements of the nitric oxide in children's exhaled breath. You can see that healthy children showed low amounts; sick children showed increased amounts—before they were actually exhibiting symptoms. They got sick a few days later. Similar results have come from emergency room visits, although I think these people were already sick when they checked in. Such technologies will have obviously useful clinical applications quite beyond biodefense.

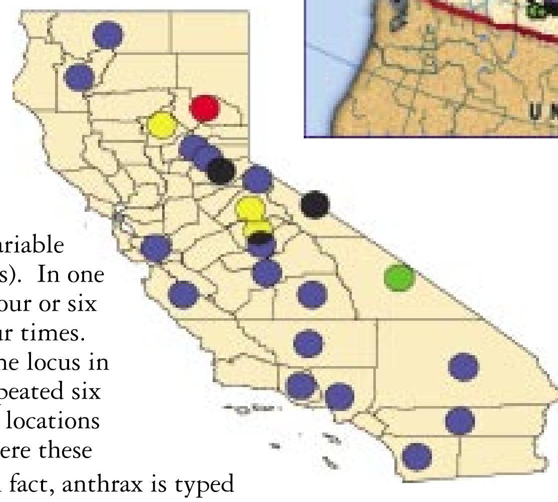
Besides monitoring people, we can also utilize sensors for the environment. One no-brainer is a better field detector for anthrax. We've seen so many false positives and some negatives reported in the news in recent weeks. We need something reliable and robust for the field. Another thing we can do is area surveillance for anthrax and other bioagents. A number of people have suggested putting biodetectors on every street lamp or at every intersection, but it turns out that this would cost a lot of money. You would need about 10,000 sensors to cover the Los Angeles basin. Just one of the 20 or so air-quality-monitoring systems that are currently deployed in the basin costs about $100,000 a year to run. So we'd be looking at a billion-dollar investment. Of course, there would be some economies of scale, but it's still an awful lot of money.

Instead, we might deploy sensors on municipal vehicles—police, fire, and postal vehicles, and subways and buses. These drive around the city; they are where the people are; they have power and communications. And every bus pulls into a depot at the end of its run, where the sensor could be removed and checked. You wouldn't even have to put them on every bus.

We need to learn more about the bioscience of biological pathogens. We've all heard a lot about the Ames strain of anthrax; how was that source determined? Bacterial genomes show repetitive

The geographical distribution of naturally occurring anthrax in the Canadian Rockies (right) shows that the same strains tend to show up clustered together. The same is true of plague outbreaks in California over the last few decades (below). An international database of bacterial strains would allow rapid determination of a foreign bioagent.





patterns, called VNTRs (Variable Number of Tandem Repeats). In one strain, a simple pattern of four or six bases might be repeated four times. In another strain, at the same locus in the genome, it might be repeated six times. There are numerous locations throughout the genome where these kinds of repeats happen. In fact, anthrax is typed by looking at the number of repeats at eight loci in the genome. (Humans, by the way, are typed by looking at 13 loci in the genome.) Many naturally occurring anthrax strains have been analyzed in this way, and maps (above) made of their geographical distribution. Sometimes you see a few outliers, which you can trace to, say, a cattle drive that has moved a particular strain from one place to another. In the map of plague in California over the last several decades, you can again see a spatial segregation of the strains. If we build a worldwide database of bacterial genomes, we will be better able to tell whether or not a bacterium is foreign, whether it is native or has been introduced in a particular locale, and perhaps where it came from.

Let me say a few words about protecting people in buildings. There are many existing systems in buildings that could do a better job of protecting us. Some of them, such as those used to combat "sick-building syndrome," already involve keeping small particulates out of buildings and could be put to dual use. Lots of very simple technologies work very well; for example, the so-called HEPA filters that you've heard about, which stop fine particles. We can install scrubbing systems in the building that clean the air as it circulates. We could put positive pressure in buildings to keep particulates outside. Simple estimates of what it would cost to do this in office buildings come up with about tens of dollars per person per year—not a bad investment.

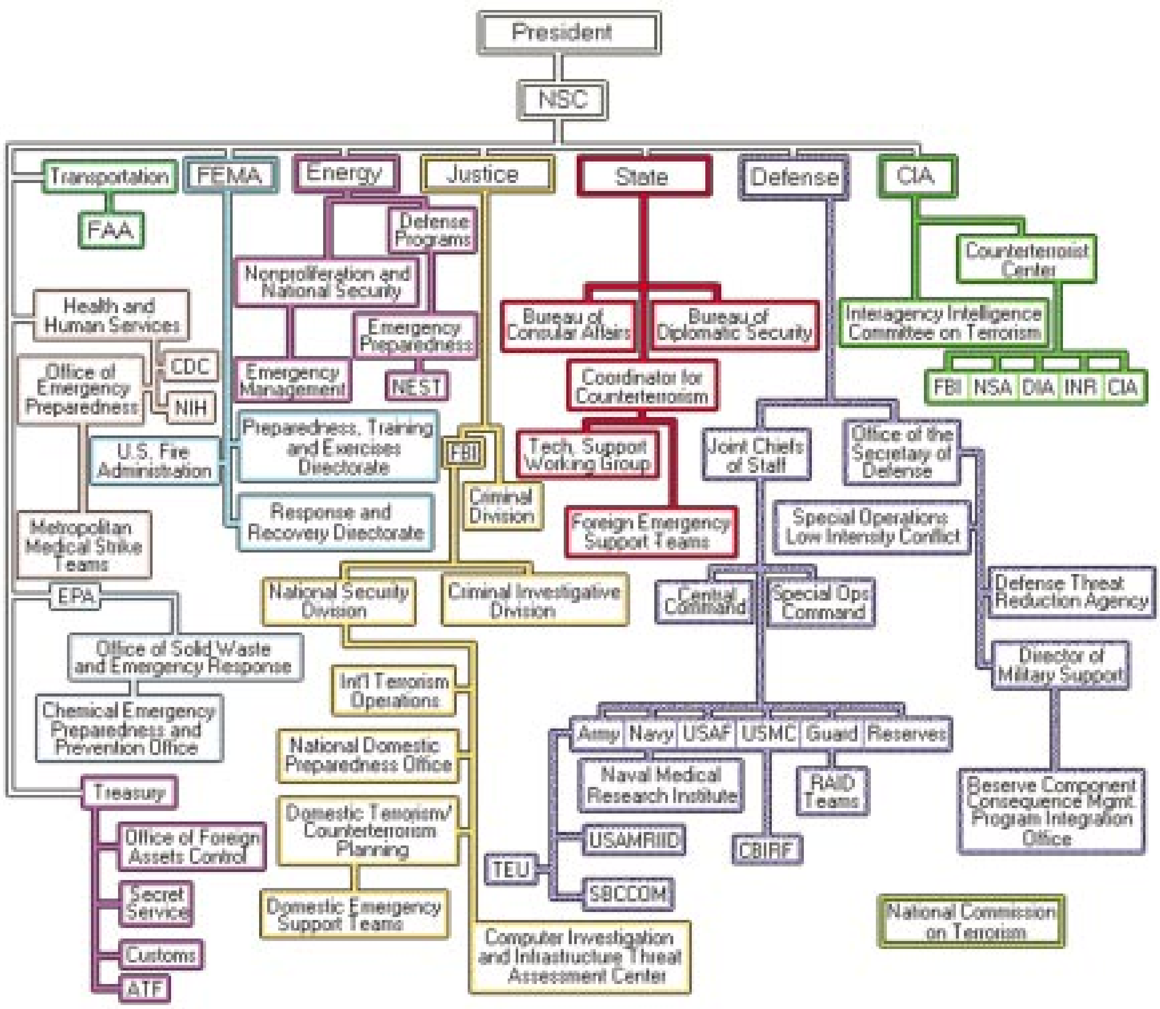
The first thing we should be doing from an organizational standpoint is erecting a scientific infrastructure for biodefense. We should be getting national labs, academia, and industry working on these things and arrange efficient mechanisms for transferring the technology out to the field.

Finally, a lot of this is not about technology; it's about getting all parts of the system to play together well. The first thing we should be doing from an organizational standpoint is erecting a scientific infrastructure for biodefense. We should be getting national labs, academia, and industry working on these things and arrange efficient mechanisms for transferring the technology out to the field. This is not being done right now. We should also foster an operational infrastructure. There are lots of players involved here, and we need to clarify and adjust their roles and responsibilities. Who has the right to forcibly decontaminate an area? To impose quarantine? To determine the use of stockpiled medicines? We're starting slowly to address some of these questions as we run exercises with the various government agencies. And, of course, we need to train our frontline responders in how to deal with the various bioagents.

The organization chart on the opposite page, of federal agencies that deal with bioterrorism, is two years old. A more recent one that the Bush administration has been passing around Congress is even more complicated than this. The problem here is that there are many players who have complementary and overlapping capabilities and responsibilities. Just think about it for a minute: we're worried about intelligence matters; we're worried about law enforcement—catching the bad guys; we're worried about public health and medical care; we're worried about science and technology; and we're worried about agriculture as well. There are a host of other issues, and the various parts of the government that are associated with these functions are not used to working together. The big thing that Homeland Security Director Tom Ridge has got on his plate is to try to get everybody singing from the same page. It's not so easy to do.

I'll leave you with some take-home points. One is that the present preparation for biodefense doesn't meet the full spectrum of homeland threats that are plausible. What do I mean by this? We *are* able to deal with a fair number of threats that we can imagine. There are, however, some plausible threats that we can't yet deal with. Some of the scenarios highlight what they are (of course, reasonable people can differ on what the word "plausible" means). But there is cause for optimism because there *are* steps that can be taken to bolster our defenses, and in some cases these are, in fact, being taken now. □

*Steve Koonin graduated from Caltech in 1972, left Pasadena briefly to earn his PhD from MIT in 1975, and returned in the same year as assistant professor of theoretical physics. He has stayed at Caltech ever since, becoming associate professor in 1978 and full professor in 1981. Koonin served as chair of the faculty from 1989 to 1991 and was appointed provost in 1995. His research interests include theoretical nuclear and many-body physics, nuclear astrophysics, and computational physics, but he has also ventured broadly outside his field into current issues of public concern: refuting cold fusion (*E&S*, Summer 1989); global climate change as measured by "earthshine" reflected back from the moon (*E&S*, Winter 1994); as well as biodefense and national security.*



Vast numbers of federal agencies have their fingers on some aspect or other of bioterrorism. Coordinating these agencies and getting them to cooperate in the name of efficiency will be a major problem for homeland defense. This chart is from the 1999 report; the current one wouldn't fit on the page.