Letter writers discuss whether on-site inspections in biological weapons control are necessary and, if so, how they should be conducted. The concept of treating Alzheimer patients as regressed toward infancy is questioned: "Each Alzheimer patient has a lifetime of experiences that determines their unique set of human qualities..." The use of chimpanzees in AIDS vaccine trials is debated. And the production of hydrogen in basalt aquifers is explored.

Biological Weapons Control

The current negotiations in Geneva to develop a legally binding instrument to strengthen the 1972 Biological and Toxin Weapons Convention (BTWC) are likely to result in an international declaration and inspection regime. This regime could have implications for both academic and industrial research, development, and production sites.

Army soldiers in a biowarfare training exercise.

In a recent Policy Forum (*Science*'s Compass, 20 Nov., p. 1423), Thomas P. Monath and Lance K. Gordon express their concerns about on-site inspections in biological weapons control, concluding with support of the concept and leaning toward on-site inspections with sampling at the site triggered by national "intelligence-gathering activities."

At an international symposium held at the Institute for Applied Microbiology, Vienna, Austria, in May 1998, the value of on-site inspections and sampling in a possible future biological weapons control regime was also addressed. The participants came from varied backgrounds: regulatory affairs and biosafety managers from industry and academia, diplomats, weapons inspectors, and representatives of various international and national authorities. They concluded that triggering inspections through suspicion could very likely stigmatize any of the inspected institutions.

In principal, a biological weapons control regime includes auditing, which presents the possibility of certifying that the site is compliant with the agreements on production, stockpiling, and use of biological weapons. If sites that possess dual use capabilities are inspected at random intervals, the inspection itself would leave no stigma; on the contrary, the outcome of the inspection could increase the level of confidence that the institution is complying with international agreements. This could reduce the need for restrictions in the international exchange of dual-use material, equipment, and know-how, a fear expressed at the symposium.

The delegates suggested that, to minimize the extra workload, a future protocol should take into account existing control regimes. For biopharmaceutical industries, in particular, consideration should be given to how the new protocol could be implemented nationally through use of existing infrastructures, such as those established under health and safety legislation.

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Response

As Rath, Jank, and Doblhoff-Dier correctly point out, there is considerable debate about the pros and cons of an inspection regime as a means of enforcing the ban on biological weapons. We would like to correct one apparent misinterpretation of our position, with respect to triggers for visits. We do not suggest that the selection of facilities for inspection would be based principally on "intelligence-gathering activities." Rather, it is anticipated that the content of declarations submitted by states or parties containing information about activities at research and production sites, specific biological agents, biological weapons defensive research, aerosol studies, containment level, and so forth will be the basis for visits. A system for right of entry to declared sites is needed to increase transparency and reduce suspicions. The declaration process has revealed, and will continue to reveal questions that can be clarified most effectively by on-site visits. Serious concerns about potential violations can be resolved only by challenge inspections, which would be conducted at very short notice and would be based on information sufficient to pass stringent criteria. Without challenge inspections and the possibility of on-site analysis, the treaty would remain a "dog without teeth." It is likely that those states engaged in offensive biological research and development will continue to deceive the international community and that illegal activities will be carried out at undeclared facilities. Ultimately, intelligence gathering may be useful in revealing such facilities and bringing them under the scrutiny of the inspectorate. It is our expectation, however, that some states or parties may decide that it is not worth the political and economic risk to initiate (or continue) offensive programs. The threat of enforcement of the Chemical Weapons Treaty resulted in the declaration and abandonment of previously denied programs.

We do not share the same apprehension expressed by participants at the Vienna conference with respect to the stigma attached to visits and inspections. Intrusive visits by various regulators are already frequent occurrences, and once biological weapons visits become regular events, they will hardly be "news." We also do not share the view that the fox should guard the henhouse; self-enforcement through national legislation does not provide a reasonable safeguard against state-sponsored biological weapons programs

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Managing Alzheimer's Patients

Behavioral interventions are important in the management of patients with Alzheimer's disease, as reviewed by Marcia Barinaga in her News Focus of 6 November (p. 1030). We do not agree, however, with her emphasis on the conceptual model of "regression toward infancy...backward march through development."

Alzheimer's patients are not children, despite superficial similarities. The physiological processes of learning in childhood and of skill loss with Alzheimer's disease are not the same. Learning in childhood is related, in part, to myelination of white matter tracts, but the dementia of Alzheimer's disease is not caused by demyelination, but by amyloid β protein deposition and loss of neurons and synapses. Moreover, the psy-

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chological processes underlying behavior in children are not the same as in Alzheimer's disease (for example, children often fail to cooperate because of inattention, Alzheimer's patients may not cooperate because of inability).

Each Alzheimer's patient has a lifetime of experiences that determines their unique set of human qualities, qualities that are not lost, even as the memories of these experiences are lost. To see Alzheimer's patients as recipients of "developmental age appropriate activities" is to see them defined by their incapacities and not by their distinctive human qualities. To view Alzheimer's patients as children is to deny their individuality (*1*).

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AIDS Vaccine Trials in Chimpanzees

In his excellent and comprehensive review article "Progress in the development of an HIV-1 vaccine" (19 June, p. 1875), Norman L. Letvin refers to the development of a highly virulent strain of human immunodeficiency virus type 1 (HIV-1) that rapidly causes $CD4^+$ lymphocyte loss, AIDS, and death in chimpanzees (*1*). Letvin suggests that a virus stock derived from this virulent isolate would "provide an important new tool for testing vaccine approaches."

To many of us who work with chimpanzees, the prospect of causing a rapidly progressive and fatal disease in this near-human species is abhorrent. Until now, HIV vaccine development experiments in chimpanzees have produced valuable information, but no disease. This has provided a justification for doing these experiments in this species.

The purpose of an AIDS vaccine is to prevent infection with HIV and, most important, to prevent chronic infection. Thus, new candidate vaccines should be evaluated for their ability to prevent acute and chronic infection after challenge with a strain of HIV that produces detectable viremia in chimpanzees. Prevention of disease is not relevant. If this occurred in the face of chronic viremia, it would not be considered a satisfactory outcome after challenge of an immununized chimpanzee in a vaccine trial. On the other hand, if chronic viremia is prevented, disease would automatically not occur.

In justification of his position, Letvin cites the fact that many primary HIV-1 isolates replicate poorly in chimpanzees, producing little or no plasma viremia. Protection experiments with such strains could be misleading and difficult to interpret. However, as shown in the table below, there are many HIV strains that have been titrated in chimpanzees and that regularly produce viremia, without producing disease (*2–6*). These include primary, or near primary, isolates (*3–6*).

We believe that HIV vaccine research should continue to use carefully chosen avirulent HIV strains for challenge. There is no substitute for such experiments in the evaluation of new vaccine strategies. The use of virulent strains is not required and is ethically unacceptable.

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Response

Vaccine protection against infection with AIDS virus isolates in a number of nonhuman primate species has correlated with the intensity of viral replication during primary infection. Thus, protection against infection with poorly replicating viruses

HIV STRAINS THAT CAN BE USED AS CHALLENGE STOCKS IN VACCINE EXPERIMENTS

Strain	Clade	Author	Reference	Primary isolate
IIIB/Lai	B	Berman *et al.* (1990)	*2*	No
SF-2	B	Berman *et al.* (1996)	*3*	Yes
90CR402	E	Girard *et al.* (1996)	*4*	Yes
DH12	E	Shibata *et al.* (1996)	*5*	Yes
5016	B	Conley *et al.* (1996)	*6*	Yes

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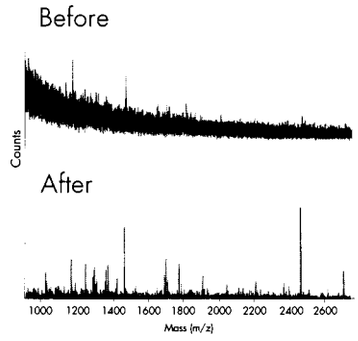

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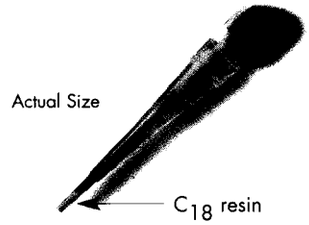

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