Meeting of Working Groups of the US National Academy of Sciences and the Academy of Sciences of the USSR on Biological Weapons Prevention

London, April 1-3, 1989

A meeting of working groups on biological weapons prevention of the U.S. National Academy of Sciences (Committee on International Security and Arms Control working group on BW) and the Academy of Sciences of the U.S.S.R. took place on April 1-3, 1989, in London.

The members of the NAS delegation were: Joshua Lederberg, chairman; Robert Chanock; Thomas Monath; Alexis Shelokov; John Steinbruner; Victor Robinowitch; and Lynn Rusten (see attachment #1).

The members of the Soviet Academy delegation were: Academician Vadim Ivanov, chairman; Evgeniy Sverdlov; Academician Sergei Prozorovskiy; Academician Dmitry Lvov; K. Rayevskiy; V. Abarenkov; A. Tutkevitch and Max Tyutikov (see attachment #2).

The agenda contained the following items (see attachment #3):

1) Delineation of permitted from unpermitted research under the Biological Weapons Convention
2) What can be learned from an on-site visit, possible groundrules for the conduct of site visits
3) BWC definitional issues: toxins
4) Issues related to Smallpox: a) examination of the continued vaccination of troops for smallpox in light of the cessation of vaccination of civilian populations; and b) examination of the continued retention of stocks of the smallpox virus.
5) Possible further measures for exchanges of epidemiological information in the event of human, animal and plant outbreaks
6) Non-proliferation
7) Progress of Scientific Exchange Programs
Lederberg began the meeting by reviewing the agreed groundrules for meetings of these Soviet and American Academy of Sciences delegations. It is understood that neither delegation represents its government, nor on the other hand does it try to be at cross-purposes with its government. The unofficial character of this dialogue promotes openness; in order to assure this, both sides agree not to make public announcements about the content of the meeting, nor to try to reach formal conclusions or come to agreed upon positions. Any presentations or papers reflect only the views of the individual presenter and not of his delegation, Academy or government. Lederberg said it was a good idea to keep minutes, but these are assumed to be private documents. Lederberg said both sides shared the conviction that they wish to prevent the catastrophe of the use of BW agents for military purposes. He said BW does not play a major role in the US-Soviet rivalry, but the possibility of BW use by third world countries is a concern, as evidenced by recent uses of chemical weapons.

Delineation of Permitted from Unpermitted Research under the Biological Weapons Convention (BWC)

The primary American contribution on this item was a paper by John Steinbruner (see attachment #4) discussing the possibility of strengthening the BWC by defining quantitative limits on allowed materials. Noting that the BWC does not define the amount of agents permitted for prophylactic and peaceful purposes, Steinbruner explained that his paper represented an effort to think out loud and stimulate discussion on how to approach the problem.

Steinbruner presented a scheme involving two types of thresholds whereby the first threshold would define a quantity of material which, if exceeded, would require full disclosure and explanation. As long as it is reported, quantities of material above this lower threshold would be permitted. However, a significantly higher second threshold would define a quantity of material that is prohibited except by specifically agreed exemptions.
The two thresholds would be set differently for three categories of agents classified by the level of threat they pose. Steinbruner suggested categorization as follows:

**Category E (Extreme):** Agents that rapidly produce fatal effects in a high proportion of infected hosts and that transmit from host to contact efficiently.

**Category S (Serious):** Agents capable of producing fatal effects or severe disability in a substantial proportion of infected individuals but do not spread efficiently from host to contact.

**Category N (Not Regulated):** Agents that cause a health hazard to exposed individuals but do not have sufficient virulence to be the basis for significant military operations.

Any agent or toxin not specifically assigned to the lesser categories would be subject by default to the more exacting standards of the high-threat category until otherwise categorized. Steinbruner noted that category E was currently empty as far as he knew and the hope was to keep it that way. Category S would cover all agents assigned to biosafety level 3 and 4, and some assigned to biosafety level 2. It is understood that E is not necessarily a desideratum for military use; but the collateral effects of developing, accumulating or disseminating E agents are the greatest threat to public health.

Steinbruner suggested that an arrangement to consolidate and strengthen the BWC might include the following five basic provisions: 1) an agreement that no military organization would develop, possess or operate missiles or aircraft equipped for aerosol spraying and that all such equipment operated by non-military organizations would be registered. (This would require that some existing capability be eliminated and probably would intersect with controls on chemical weapons.); 2) an agreement that all known biological agents and toxins be listed and assigned to one of the three categories of control and that all previously unlisted or experimentally created agents be subjected to the strictest controls (category E) until reclassified by a mutually agreed procedure; 3) a determination of disclosure and
prohibition thresholds in terms of infectious doses (ID 50) provisionally as follows:

**Category E**: disclosure at any amount; prohibition of amounts of live material exceeding $10^9$ ID 50's averaged over a 90-day period.

**Category S**: disclosure of amounts of live material exceeding $10^{12}$ ID 50's averaged over a 90-day period; prohibition of amounts of live material exceeding $10^{15}$ ID 50's averaged over a 90-day period.

**Category N**: all infectious agents to be listed but not subjected to disclosure or prohibition requirements on amounts of live material.

4) an extension of current reporting requirements under the BWC to include a listing of any inventories above the disclosure thresholds and a description of actual infectious outbreaks by agent categories as follows: Category E, every individual case; Category S, every laboratory outbreak and every unusual incidence of cases in the general population. 5) the development of inspection arrangements for all listed facilities to verify inventories of material.

Steinbruner suggested that in order to assure that the prohibitions in this arrangement do not interfere with desirable vaccine development, a general exemption should be made for live agents produced and stored in association with inventories containing ten times the amount of that live agent in killed or attenuated form. This 10% rule would protect properly balanced, legitimate vaccine development, as well as scientific investigation, while making the production of agents for BW purposes prohibitively expensive if the constraint was met. The rule would still require that full disclosure requirements be met.

Steinbruner emphasized that he advanced this paper only as a set of ideas for discussion, noting that it raised many issues and questions which the NAS delegation had been discussing and debating among itself. He acknowledged that it would have to evolve considerably before such a scheme could ever be implemented.

As an example of the controversy engendered by some of the ideas in Steinbruner's paper, Monath remarked that the proposed
prohibition on military aircraft equipped for aerosol spraying would undoubtedly face much opposition. He pointed out that such aircraft do exist for vector control, and that there was a division of opinion among the American delegation about the feasibility of prohibiting such aircraft. Lederberg said registration of such aircraft might open up a useful discussion of functionally related observable differences (FRODs) or signatures that could allay anxieties about their intended functions.

The Soviets had many questions about Steinbruner's paper, mainly probing the logic behind the threshold numbers and the scheme of categorization of agents. It was explained that the logic of the actual numbers was to permit most routine scientific lab work to proceed unencumbered, while mandating disclosure of larger-scale research with dangerous agents. The Soviets listened with interest, indicating they would study the paper, discuss it with experts in the USSR and have a more thorough response at the next meeting.

Lederberg noted that implicit in Steinbruner's scheme was the idea that there should be an international advisory group which would agree on the classification of agents and to which appeals would be made to exceed the prohibition thresholds in special circumstances. Rayevskiy, from the Institute of Military Medicine, said this was similar to ideas being considered by the Soviets, whom he said were in favor of setting up an international agency to deal with issues such as these, with infectious disease outbreaks, and to serve as an information bank on the state of knowledge of infectious agents. He noted the agency would have to confront how to protect commercial secrets.

A subset of both delegations met the following day to further discuss the categorization of agents. The group agreed on the need for such a listing, and agreed on the categorization of agents (see attachment #5) culled from a list of BL 2, BL 3 and BL 4 agents in the CDC-NIH handbook Biosecurity in Microbiological and Biomedical Laboratories. The Soviets suggested the addition of two agents to the list: Legionella to category S and Issyk Kyl fever to category N. The group identified the need to: 1) establish a repository of viruses to serve as a resource for molecular studies. Such a
collection would contain strains of virus isolated under conditions as close to nature as possible; and 2) establish a bilateral program to discuss and present research on these agents, perhaps modeled on the successful US-Japan program.

A second American presentation under agenda item #1 was made by Robert Chanock (see attachment #6) on the problems of distinguishing defensive from offensive R&D. He suggested that if research (particularly on attenuated mutants or recombinants), is to be defensive in intent, it must not be coupled to the production and storage of large amounts of virulent organisms and the development of weapons delivery systems. Furthermore, he suggested that the development of recombinants that express an unmodified bacterial, plant or animal toxin can be viewed as a threat especially if coupled to an efficient vector and that therefore such development should be declared and justified by the county where the work is performed, as well as be subject to inspection and surveillance. He suggested that the production and long term storage of large volumes of virulent organisms be strictly prohibited.

Chanock also expressed the view that recombinant techniques do not present unlimited opportunities for the design and implementation of novel agents against which vaccines could not work. Only a few intraspecies recombinants have proved to be more virulent than either parent, and in these instances the result was anticipated, implying that the most dangerous constructs could be identified a priori and prohibited.

In response to Chanock's presentation, Sverdlov and Rayevskiy both addressed the issue of exaggerated public fears about genetic engineering research, but also stressed the importance of recognizing its potential hazards and ensuring that genetic material is not released into the environment. Rayevskiy said greater confidence about each other's research was necessary and could be achieved through greater openness and more scientific cooperation, joint research, exchanges and symposiums and the establishment of an international scientific information bank. In response to a question from Lvov, Rayevskiy said the basic
direction of genetic engineering research and even the vector used should be declared.

Prozorovskiy expressed a less optimistic point of view, noting that while these working groups had made progress in discussing how to deal with research on natural strains that could be used as BW agents, there needed to be much more thought given to the problem of the possibilities of genetically engineering potentially dangerous pathogens. He said large problems were posed by this potential.

What Can Be Learned from an On-Site Visit, Possible Groundrules for the Conduct of Site Visits

The American presentation on this agenda item was made by Alexis Shelokov, who addressed the issue of how an inspection of a relevant research center or laboratory might be carried out and what sorts of advance information should be exchanged to make the visit more meaningful. He did not address the issue of under what auspices or legal regime such an inspection might be conducted.

This presentation was a natural outgrowth of the two delegations' visit one year ago to USAMRIID. That visit led the American side to reflect more systematically upon how a site visit should be conducted to ensure that it is meaningful.

Shelokov suggested that a meaningful site visit would permit the inspecting team to inspect the facility and site, checking its findings against information supplied in advance. The team should be permitted to interview employees at all levels. The issue of safety for the inspecting team would have to be addressed and arrangements agreed upon concerning immunization of the inspectors, access to protective clothing and respirators, possible decontamination of parts of the lab, etc.

Shelokov suggested that the process of selection of one or more sites to be inspected might begin with a review of the data already submitted to the U.N. Department of Disarmament Affairs on Form #1. for exchange of data on research centers and laboratories. The host country could further assist by providing on request additional information such as lists of those facilities that require prior immunization of laboratory personnel; have had
accidental laboratory infections or intoxications during the preceding five years (specify causal agent and number of cases); are engaged in scale-up production of experimental vaccines or have produced them in large quantities; or are equipped with large walk-in low temperature freezers designed to store biologics, fermentation tanks, or aerosolizing devices and aerosol chambers.

Shelokov said it would also be valuable for the inspection team to review a list of national and regional regulatory agencies that are responsible for monitoring the safety of such centers and laboratories—environmental impact, procedures for shipment and transportation of infectious and toxic agents, regulations controlling development and production of new immunobiologics, and clinical testing of experimental vaccines in volunteers.

Shelokov suggested that once one or more sites to be inspected have been selected, additional advance information could be requested regarding each facility to be visited—its activities, its personnel, and its physical features—and the name, address, and telephone numbers of a responsible representative (and alternate) to be contacted for further information.

Information about activities could include: copies of latest annual reports; reprints of recent publications by staff and by other authors whose work utilized the products of the laboratory under review; a list of recent presentations by staff at scientific meetings; a list of ongoing and recently completed projects, specifying live microbial agents employed; and a list of accomplishments, including products and recent technological advances.

Information about personnel could include a table of organization with titles of key personnel and their educational background; numbers of personnel by occupational categories and by assignment to identifiable buildings; a list of outside "visiting scientists" who are or were working on temporary assignments (give titles of projects and dates); and a list of laboratory infections or intoxications occurring during the past five years (give numbers of cases).

Shelokov said information about physical features could include: a map of the area showing location of the site in
relation to nearby population centers and means of communication; overall site plan and general topography of immediate area, showing railroads, highways, and other roads to and from the site; a detailed site plan; and detailed floor plans of main buildings.

In the ensuing discussion, protecting proprietary information was recognized to be a legitimate concern when talking about inspections, but neither side had concrete suggestions for how to deal with this other than to examine how this problem is finally addressed in the chemical weapons treaty negotiations.

The Soviets focused largely on the broader issues which Shelokov's paper intentionally had not addressed: the legal framework under which inspections would be triggered and carried out. Abarenkov, who said he had been a junior member of the Soviet BWC negotiating team, asked specifically when inspections would be required. The Americans reiterated that they had chosen not to address the broader issues of treaty regime and mechanism, but only to look at how an inspection might be carried out from a technical point of view. However, Lederberg said that since there are declared facilities for biological research, the hope would be that they would voluntarily open themselves to inspection as a confidence-building measure. He added that the intention was not to focus on alleged treaty violations, but to provide information about legal activities to enhance confidence.

Rayevskiy referred to a proposal from the United Nations General Secretary for an International Biological Monitoring Agency which would have the authority to conduct inspections and collect samples. He said the USSR had agreed to cooperate with such an agency, and so the conceptual framework was in place.

Prozorovskiy and Abarenkov proposed that a bilateral SCC-like commission be established which would have the responsibility of jointly reviewing both side's BW defense programs. The members might be Members of the US Congress and the Supreme Soviet plus high level representatives from both side's Ministries of Defense, Health, Foreign Affairs, etc., and outside scientists expert in infectious diseases and molecular biology. They said such a system would both improve confidence about each side's activities and also help each side's Congress or Supreme Soviet monitor their own government's activities. Abarenkov noted that this could not be
practically implemented until their Supreme Soviet has organized itself to establish committees with the authority to act as US Congressional committees do.

The Americans thought this was an interesting idea which could promote self-monitoring and verification and which might also provide a mechanism for discussion according to the Steinbruner conception of special circumstances when an agreed threshold might need to be exceeded.

Sverdlov expressed the view that US-Soviet confidence in the BW area was improving. He said verification of industrial production related to means of delivery seemed relatively easy, but that the terrorist threat and control of research on biological materials is very complicated. He said one could consider a range of mandatory and voluntary inspections including 1) permanent on-site surveillance; 2) challenge inspections; 3) inspections according to schedule; or 4) stationing of technical means (sensors in place) which would trap biological material. Sverdlov said the matter of which measures countries would be willing to accept was a political question. The technical side is what experts could do when they arrive to carry out an inspection. He said Shelokov's ideas seemed reasonable and that they would study them further and make their own suggestions at the next meeting.

Rayevskiy suggested that research on highly dispersible agents should be a matter of strict verification, and that research in the field of aerosol was always a matter of concern. He advised: 1) having an international body register all R&D technologies and enterprises which can potentially produce BW and list all scientific R&D in epidemiology, microbiology and infectious diseases. Labs would register information about their research tasks, purposes, expected results and volume of financing. The information should be computerized and available to all participating countries; 2) drawing up a list of biotechnology which should be subject to strict control and of specific products the production of which should be banned. Such a list would include aerosol technology, delivery means, R&D methods and technologies, and materials and agents used in research that should be subject to control, prohibition or verification; 3) clearly listing
technologies and products that would not contravene the convention and therefore are permitted.

Sverdlov disagreed with Rayevskiy's third suggestion, saying one should only register on an agreed list agents to be monitored under the BWC. Registering all permitted agents and activities is impractical and could inhibit research. Other Soviets and Americans thought Rayevskiy's second and third suggestions abstract and perhaps impractical. He agreed to elaborate his ideas in more detail and in writing for the next meeting.

There was, however, support for the concept of an international data bank on research on infectious diseases. Lederberg suggested that retrospective reporting from the commercial sector was more practical than advance reporting. Lederberg also agreed that all aerosol research should ideally be fully disclosed. There was also a discussion about PCR (polymerase chain reaction) technology and its use for diagnostics. There was agreement that critical probes for infectious agents should be made widely available.

**BWC Definitional Issues: Toxins**

For this agenda item, Lederberg made a brief presentation (see attachment #7) identifying the problem that while the BWC prohibits toxins whatever their origin, there is no precise definition of toxins in the convention. The problem will become moot once a chemical weapons treaty is concluded, but for the time being there is a zone of ambiguity about which chemical substances are toxins under the BWC. The ambiguity arises from the existence of toxic chemicals which resemble, in structure or in pathological effect, the toxins of biological origin which are clearly forbidden.

Lederberg suggested three possible ways of addressing the issues: 1) Within the negotiating framework of the CW disarmament discussion, interim declarations that disavow any novel chemical agents other than those now in admitted stockpiles or closely related to them. This would leave mustards and organophosphates as a class under the same heading as existing chemical weapons, but would label all novelties (including synthetic peptides) as already forbidden by the BWC. Such entities would be encumbered with the same verification problems, no better, no worse, as biological
agents and toxins; 2) As a specific and emphatic subset of the
class of novelties, defining as subsumed by toxins, under the BWC,
any chemical substances targeted against specific cellular
receptors other than those (cholinesterase) associated with nerve
gas; or 3) more specific designations of oligopeptides and other
chemical categories. This would not be foolproof, but would
promptly cover the most likely, immediate prospects.
Non-polypeptide myco- and zoo-toxins generally offer no dramatic
advantage in lethality compared to nerve gas; hence there is less
motivation to invest in synthetic chemicals that mimic their
activity.

Lederberg said he personally was coming to believe that the
first option is probably the best, and that it might be useful to
initiate bilateral discussions on the possibility of making interim
declarations to clarify the ambiguities in the period before the
chemical weapons treaty is concluded. He suggested that since
these are still, to his knowledge, hypothetical innovations, there
should not be great reluctance to accept these restrictions. He
concluded that broadening the toxin provisions of the BWC would not
solve the verification dilemmas, but would be a confidence-building
measure especially if associated with free scientific discussion of
permitted R&D on toxic activities and their receptors.

In the very short discussion of the issue, the Soviets,
particularly Ivanov and Rayevskiy, took the position that it is the
source which determines whether an agent is chemical or
biological: everything toxic that is produced by a biologic
organism is subject to the BWC; everything produced chemically
should be subject to the Chemical Weapons Treaty when concluded.
Abarenkov reminded them that the BWC also prohibits toxins "however
produced." The Soviets said they hoped a CW Treaty would be
concluded soon so that these questions would be resolved. There
was no great enthusiasm on the Soviet side for interim measures or
declarations. Lederberg said he too hoped the CW Treaty would be
concluded and would automatically embrace all toxins. He said he
hoped in the meantime both sides would be very careful; it would be
alarming if there were large-scale chemical production of toxins
without justification for peaceful use. He averred that he knew of
no activities, on the US side, of concern in this regard.
Issues Related to Smallpox

Under this item, Monath on the American side made a presentation (see attachment #8) examining the continuation of vaccination of US and Soviet troops against smallpox and the continued retention of stocks of the smallpox virus (variola). Monath said it was anomalous that both the United States and the Soviet Union still vaccinate their military forces despite the global eradication of smallpox virus and the discontinued use of vaccine in most, if not all, civilian populations. One rationale for continued vaccination of military forces is the threat that smallpox virus would be used as an offensive biological weapon or in retaliation for another form of biological warfare.

Monath said that since there is no consensus on the issue of military vaccination, it might be useful to examine and discuss both sides of the polemic and thereby search for common ground. He listed as premises in support of the present policy: 1) smallpox virus itself is still retained by both the United States and the Soviet Union; 2) there is no mechanism in place to assure and verify that smallpox virus is not being or could not be developed as a biological weapon; 3) although smallpox is not an "ideal" biological weapon, it is not inconceivable that it could be so used; 4) implementation of an effective defensive posture by both sides assures that smallpox will not be developed as an offensive weapon; 5) there is considerable interest and intensive research on the use of vaccinia as a gene vector expressing immunogenic antigens against a variety of other agents. This research may improve the production methods and safety of vaccinia itself.

Monath listed as premises against the present policy: 1) unlike other BW agents, smallpox virus does not constitute a natural disease threat to operational military forces; 2) smallpox is not a particularly effective biological weapon; the incubation period is relatively long; the disease is easily recognized and diagnosed; prophylactic measures to contain further spread are readily available, etc.; 3) since the sole proprietors of variola are the U.S. and USSR, there is little or no concern about development of smallpox as a BW agent by third-world or terrorist groups; 4) vaccinia vaccines are produced by antiquated techniques,
 unacceptable by modern standards. Vaccines are not innocuous and their use in military populations is associated with a significant risk of complications, such as generalized vaccinia. In addition to the unnecessary economic burden imposed by production of vaccine and implementation of a vaccination policy, further resources are diverted towards treatment of vaccine complications and manufacture of vaccinia immune globulin; 5) the policy of vaccination is viewed as evidence of bilateral mistrust and is a hindrance to disarmament efforts.

Monath noted that in one respect, smallpox is absolutely unique among potential biological weapons: The agent itself exists only in laboratory repositories in two nations. If these repositories were eliminated the threat itself would vanish. Use of vaccinia for protection against smallpox would become unnecessary. However, he said although this seems a reasonable objective, with obvious medical and political benefits, two problems must be resolved: 1) There must be absolute assurances and verification that all remaining stocks of variola virus are eliminated; 2) Consideration must be given to the scientific and academic objections to the final and irrevocable destruction of the variola genome (which has not been mapped). Monath said that solution of the first problem will be difficult; it relies on measures to be worked out in relation to similar disarmament issues. Solution of the second problem is scientifically achievable, since it is now possible to define the genetic structure of variola virus. Full elucidation of the gene sequence of variola would secure the essential knowledge base, provide for future needs to study or compare the variola genome and allow destruction of infectious stocks. Monath said the investment required to accomplish this task is considerable because of the size of the variola genome and the probable need to measure genetic variability between variola strains, e.g. alastrim. Moreover, although variola DNA is not itself infectious, the possibility remains that functional viral genome could be rescued by recombination with a heterologous pox virus (Sam, CK and Dumbell, KR, Ann. Virol. (Inst. Pasteur) 132E:135-150, 1981).

Monath suggested that in light of this discussion, the group might discuss the desirability and feasibility of a bilateral,
cooperative research effort to clone and sequence variola virus. Monath said his personal view was to research the virus with the ultimate goal of destroying the virus, suggesting that it was a good area for collaborative research.

In the ensuing discussion, Lvov and Prozorovskiy both expressed their concern that smallpox or something very similar could recur in the human population, despite the WHO's formal certification that smallpox has been eradicated. Lvov confirmed that the USSR had abandoned vaccination of the civilian population, but he expressed his personal reservations about this cessation. Prozorovskiy said the first priority should be to constitute a safer strain on the basis of which a vaccine should be made and preserved for humanity. Only then would it become unnecessary to vaccinate military forces.

Rayevskiy explained at length the Soviet military's rationale for continued troop vaccination. He said their military commanders did not think it possible to stop vaccinating because their military contingents face a high risk of spread of infection due to the housing conditions of the armed forces, troop location, etc. He said they believe there is a possibility of natural recurrence, and that the military could be at risk because in their country the military is the first to respond to disasters such as Chernobyl, the Armenian earthquake, etc.

Rayevskiy said smallpox can exist for 100 years in a corpse, and that the existence of monkey pox is a serious warning. (In response to a question from the American side, Rayevskiy promised to provide data at the next meeting on the 100 year survival in corpses statement.) He said all of these concerns are grounds for medical personnel and commanders to insist on continued vaccination of military contingents. Rayevskiy added that smallpox vaccination in the Soviet Army should not be associated with BW because if used, smallpox would spread indiscriminately among the unvaccinated civilian population which would remain vulnerable; therefore it is not a practical agent for BW.

Monath responded that there is a prevalent suspicion that Soviet practice responds to the threat of smallpox as a BW agent. He said most scientists believe that if the disease is to recur, it
would have done so by now. Moreover, since the vaccinia vaccine still exists, it could be produced if necessary. He said the central question remained whether we might ease tensions over BW by eliminating variola or vaccination of troops.

Lederberg expressed sympathy with the Soviets' medical skepticism about the elimination of smallpox. He agreed that the premise deserved re-examination and said thought should be given to a strategy to deal with potential reemergence. He also said that more open Soviet discussion of their rationale for troop vaccination could dispel some of the concerns it causes.

There was then a discussion of the costs and benefits of continued civilian vaccination as a precaution against future reemergence. Chanock raised the possibility of sequencing the variola genome and storing only the genome, not the virus. Lederberg expressed caution that the reconstitution of variola from genetic information be experimentally corroborated before variola is destroyed. It may be crucial for scientific purposes to revive historic variola if new smallpox-like diseases should emerge.

There was consensus that an international conference should re-examine the possibility of a reemergence of smallpox in nature, and this might be done in connection with this year's 10th anniversary of the WHO declaration of eradication of smallpox.

Possible Further Measures for Exchanges of Epidemiological Information in the Event of Human, Animal and Plant Outbreaks

As it turns out, neither side came prepared to discuss this topic very thoroughly. However, Prozorovskiy did deliver a very interesting talk on the status of Soviet epidemiology of human disease outbreaks.

Prozorovskiy explained that for years, epidemiologic information in the USSR was considered classified. As a result, it was difficult to conduct comparative analyses internally and with scientists from other countries. However, he said the fundamental changes brought about by glasnost and perestroika have now made it possible for Soviet scientists to look differently at epidemiology.

As an example, he pointed to Burgasov's recently published tables on Soviet morbidity from 1950-1985, and to a recent news
article reporting on a meeting of the All-Union Epidemiological Commission which examined the recent case where 32 children in one hospital contracted AIDS from blood transfusion. He said this commission holds special sessions to deal with emergencies and to talk about Soviet deficiencies in dealing with epidemics. He also referred to a March 24, 1989, news article criticizing the occurrence of parasitic diseases in the USSR. Prozorovskiy said epidemiologic data on outbreaks of malaria, plague, typhoid and cholera are no longer classified and are now being published. He cited a recent article in one of their journals on the present situation with hepatitis.

Prozorovskiy said he hoped for work toward establishing in the future an open system of quick publication of events as they occur, with systematic coverage including information on indicators and periodicity, and fundamental conformity of information published by all contracting parties. He said the CDC Morbidity and Mortality Weekly Report (MMWR), which Alex Langmuir discussed at our last meeting, was an excellent model which they would eventually like to replicate. For now, Prozorovskiy hopes to establish a semi-annual and later a monthly report on communicable diseases. He said information on animal and plant diseases should eventually be treated along parallel lines.

The Americans expressed gratitude for this forthright evaluation of the state of Soviet epidemiology. In the ensuing discussion they explained how surveillance and reporting is conducted in the US and discussed possibilities of exchange and collaboration aimed at helping the Soviets set in place a workable system of epidemiologic surveillance and publication. A number of state health departments in the U.S., including California and New York, have expressed willingness to receive visiting Soviet epidemiologists for training. Prozorovskiy noted that the conclusion of an official agreement obligating the USSR to provide such information would provide an impetus to them to have a publication such as the MMWR.

Non-Proliferation

Both sides recognized that BW proliferation was a serious concern and posed a very difficult challenge. Steinbruner
expressed the view that control of the basic technology is not feasible because it is too related to basic medical technology. Therefore it becomes a matter of controlling policy, for instance ensuring that there are not dedicated military units trained and prepared for BW operations. He suggested that well developed US-USSR cooperation on establishing and verifying controls on such operations in other countries could be effective in discouraging proliferation and in dealing with ad hoc cases as they arise. A formal regime would involve global monitoring and detection of development of large quantities of BW materials. With timely warning, ad hoc sanctions could be brought to bear by the superpowers and their allies.

Steinbruner said monitoring and verifying procedures and organizations would help to deal with the more probable threat, which is the terrorist threat. These threats will require extensive cooperation between the US and the USSR, and a likely prerequisite would be greater control over their own activities in this area. Steinbruner suggested that strengthening the BWC and more bilateral cooperation could provide an important base for ad hoc cooperation against third party BW development.

Abarenkov agreed that proliferation was largely a political problem. He suggested something along the lines of the London Suppliers Group be established to control the export of BW-related materials. He emphasized that the Paris Conference demonstrated that third world countries resent the approach of the superpowers to nuclear and chemical weapons proliferation, and therefore the superpowers must live up to the commitments they have made about reducing their own nuclear arsenals in order to get third world support on CBW issues. Steinbruner agreed, but suggested that it was still possible to make BW activity be perceived globally as illegitimate in a way which is already impossible with CW.

Ivanov read aloud some proposals he said were made by the Soviet BWCRC negotiator Antonov, but Ivanov said he did not know where these proposals were made. Antonov's proposals were: 1) to prohibit all agreements between countries for joint development of BW and CW; 2) condemn all contradictions of the spirit of the BWC; 3) the US Army should "cease instructing how to transport and
deliver BW", and such activities should be considered a contradiction of the spirit of the treaty; 4) some patents should be declared inconsistent with the BWC; 5) accusations of violations which used false arguments should cease and never be made again (Ivanov said he thought this referred to Yellow Rain). Ivanov said Antonov's paper concluded that scientists should give their authoritative opinion about how to distinguish between allowed and forbidden activities. Ivanov was asked to clarify point #3; he said he was merely quoting Antonov and agreed that allusions like that should be made concrete.

Prozorovskiy said one could envision three tiers of actors: 1) the US and USSR; 2) third party countries which could set the goal of creating a BW potential; and 3) terrorist groups which create clandestine BW capability. He suggested the US and USSR could set up a system of diagnostics and protection against BW agents. Together, they would have some knowledge or suspicions about whether third countries were working on BW offensive and defensive ability, and hopefully they would be able to detect terrorist development of an offensive threat.

Rayevskiy noted that preventing small-scale BW agent use by terrorists is the most difficult task. He said it would be easier to control delivery systems and national efforts for preparing for biological war; the acts of individuals would be much more difficult to control.

Monath said limits on dissemination of strains might be an area worth discussing. Many strains are present only in a few labs around the world, and controls on the ease of distribution of these strains, without hindering scientific research, could be advantageous. He noted that the WHO plays a role in regulating access to biologicals, but it is not a tight, well-controlled system.

Scientific Exchanges
Lederberg briefly summarized the status of inter-Academy scientific exchanges in biomedicine. He informed Ivanov that the opportunities for post-docs in Ivanov's lab were being advertised in the US in the NAS USSR newsletter. There was a brief discussion
of sensitivities (technology export control) about cooperation on biotechnology; it was recognized that cooperation in medical research is less sensitive.

**General Observations**

This was the third meeting of these working groups. The atmosphere was good. The substantive content was more concrete and directly aimed at thinking about how to strengthen the BWC regime than it has been in prior meetings. The Soviets were more engaged in the subject matter than they have been previously. Ivanov made a point of saying that their group had been asked by their government to provide recommendations as scientists on these matters. The addition of Rayevskiy from the Institute of Military Medicine was notable. The Soviet scientists had only met him once before, and there were often interesting exchanges between them and Rayevskiy, primarily asking him to clarify the Ministry of Defense position on certain matters. The scientists occasionally expressed their disagreement with Rayevskiy on particular issues, and were sometimes impatient with his "Army" vs. a scientific perspective.

Abarenkov, who said he had been a junior member of the original BWC negotiating team, and who had participated in the NPT and other negotiations, was polished and well-informed about current and past Soviet arms control policies. In a discussion of exchange of information under the BWC, he registered the Soviet complaint that the US declarations have not been very forthcoming. Americans pointed out the existence of a very large volume of open publications from the U.S. and suggested that similar publications from the Soviet labs would be very welcome.

Lvov made a point of criticizing an American para-scientific publication which made the accusation that AIDS was created as a result of experiments conducted by Zhdanov, who was Lvov's predecessor as Director of the Institute of Virology. The Americans had not heard of this article, but nevertheless agreed that any such attribution was an outrage. They asked for more particulars; Lvov later sent the article to Lederberg. The Americans recalled earlier articles in Soviet-connected media charging that AIDS was a US Army creation. Lvov also expressed
concern about future funding from the US side of the US-Soviet agreement on cooperation on viral infections.

While most of the inputs to this meeting came from the Americans, the Soviets made it clear that they would study the American ideas carefully, discuss them with other experts, and be prepared to respond concretely at the next meeting. In fact, very specific homework writing assignments were taken on by individuals on both sides to be completed for the next meeting, tentatively scheduled for October 6-8, 1989, in Moscow.

Lynn Rusten
April 1989
Meeting of Working Groups of the US National Academy of Sciences and the Academy of Sciences of the USSR on Biological Weapons Prevention

London, April 1-3, 1989

American Delegation

Joshua Lederberg, chairman
President
Rockefeller University

Robert Chanock
Laboratory of Infectious Diseases
National Institute of Allergy and Infectious Diseases
National Institutes of Health

Thomas Monath
Director, Virology Division
U.S. Army Medical Research Institute of Infectious Diseases

Alexis Shelokov
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The Salk Institute

John D. Steinbruner
Director
Foreign Policy Studies Program
The Brookings Institution

Victor Rabinowitch
Executive Director
Office of International Affairs
National Research Council

Lynn Rusten
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Committee on International Security and Arms Control
National Academy of Sciences

La'Faye Lewis
Senior Secretary
Committee on International Security and Arms Control
National Academy of Sciences
Meeting of Working Groups of the US National Academy of Sciences and the Academy of Sciences of the USSR on Biological Weapons Prevention

London, April 1-3, 1989

Soviet Delegation

Academician Vadim Ivanov
Head of Delegation
Director
Shemyakin Institute of Bioorganic Chemistry

Evgeniy Sverdlov
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Director
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Academician Sergei Prozorovskiy
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Ministry of Health

Academician Dmitry K. Lvov
Director
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Dr. K. Rayevskiy
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Research Institute for Military Medicine
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Dr. V. Abarenkov
Senior Fellow
Institute for USA and Canada Studies

Mr. A. Tutkevitch
Interpreter
Head of Department
Institute for USA and Canada Studies

Mr. M. Tyutikov
Foreign Relations Department
Academy of Sciences of USSR
Meeting of Working Groups of the US National Academy of Sciences and the Academy of Sciences of the USSR on Biological Weapons Prevention

London, April 1-3, 1989

Agenda

1) Delineation of permitted from unpermitted research under the Biological Weapons Convention

2) What can be learned from an on-site visit, possible groundrules for the conduct of site visits

3) BWC definitional issues: toxins

4) Issues related to Smallpox: a) examination of the continued vaccination of troops for smallpox in light of the cessation of vaccination of civilian populations; and b) examination of the continued retention of stocks of the smallpox virus.

5) Possible further measures for exchanges of epidemiological information in the event of human, animal and plant outbreaks

6) Non-proliferation

7) Progress of Scientific Exchange Programs
The Possibility for Strengthening the Biological Weapons Convention by Defining Quantitative Limits on Allowed Materials

By John Steinbruner
The Brookings Institution
March 20, 1989

1. Article I of the 1972 Biological Weapons Convention prohibits the development, production, or storage of harmful agents and also delivery systems designed for using such agents in warfare. With regard to the agents themselves, the prohibition refers to quantities of material that cannot be justified in terms of "prophylactic, protective, or peaceful purposes" and thus implicitly exempts material that can be justified in these terms.

In commenting on the treaty in an official statement issued on September 28, 1971, the U.S. representative to the CCD, James Leonard, noted that the term "prophylactic" was intended to refer to medical procedures such as immunization and therapy and that "protective" referred to direct personal protection such as masks and clothing, filtration and detection systems, and decontamination equipment. Leonard acknowledged that research for both of these purposes "might well require laboratory quantities" of harmful agents and that such quantities were to be permitted. He explicitly rejected, however, the legitimacy of quantities justified for deterrent purposes. A statement by the Soviet representative Roshchin issued on the same day confirmed this interpretation.

This analysis expresses solely the views of the author and not those of any organization.
2. Since that time, there appears to have been no official discussion between U.S. and Soviet representatives attempting to determine specifically what quantities of biological agents or toxins would be considered permissible. Both governments have affirmed, however, that a strengthening of the Convention is desirable. As a possible means of accomplishing that, it is logical to consider how the distinction might be made between permissible and prohibited quantities of material and how it might be enforced. Professional discussions of this issue in the United States have recognized the difficulty of defining reasonable limits for the many agents that would have to be considered and the associated difficulty of determining with appropriate confidence that the limitations were being honored. With the progress made in recent years on acceptable methods of verification and control, in particular with the inspection arrangements incorporated into the INF treaty, there has been renewed interest in the possibility of defining useful limits in a way that would promote cooperation and limit contentiousness.

3. There are technical facts and conceptual distinctions that might be used to constrain the problem within practical boundaries and in combination they offer some possibility for meaningful although undoubtedly incomplete control arrangements.

First, the convention prohibits weapons delivery technology without exception, and that provision provides in fact a very promising means of preventing the development of military units trained and equipped for conducting biological warfare.

Second, the fact that a reasonable determination of justifiable and unjustifiable quantities of biological agents might differ substantially
for different types of agents can be mitigated somewhat by devising controls involving two types of thresholds and a limited number of agent/toxin classes. The first threshold would define a quantity of material in excess of which full and reasonably detailed disclosure of its purposes would be required. Possession of material above the disclosure threshold would be allowed as long as it is reported. The second, significantly higher threshold would define a quantity of material that is prohibited except by specifically agreed exemptions. These thresholds might then be differently defined for three categories of agents representing combinations of virulence, rate of action, and efficiency of transmission that create different levels of threat. For example:

Category E (Extreme)

Agents that rapidly produce fatal effects in a high proportion of infected hosts and that transmit from host to contact efficiently.

Category S (Serious)

Agents capable of producing fatal effects or severe disability in a substantial proportion of infected individuals but do not spread efficiently from host to contact.

Category N (Not Regulated)

Agents that cause a health hazard to exposed individuals but do not have sufficient virulence to be the basis for significant military operations.

Any agent or toxin not specifically assigned to the lesser categories would be subject by default to the more exacting standards of the high-threat category. That scheme does not appear to be infeasibly complex.
Third, for currently known agents there is a fortunate trade-off between virulence and efficiency of transmission. Anthrax and several toxins are fatally virulent once a person or animal is exposed but to a close approximation are not transmitted at all from one infected individual to another. The influenza virus, the most efficient known transmitter between individuals, can spread worldwide with up to 80% infection rates in the course of a year but is not normally as virulent and has so far resisted genetic manipulation to change its virulence. Small pox, which spreads much less efficiently than influenza, has been eradicated in the natural environment. Eradication of strains in storage is feasible and probably desirable. Cholera, typhus, and the hemorrhagic fevers are intermediate in virulence and transmission efficiency. Vaccinia, the most effective vehicle for manipulated genetic material, is highly attenuated and an inefficient transmitter.

These facts suggest that the category of highest threat (category E) is so far empty and might be kept so by careful monitoring of research activity. The conditions associated with category S would be met by all of the agents assigned to biosafety level 4 and level 3, and some selected number of those assigned to biosafety level 2 (cf. Biosafety in Microbiological and Biomedical Laboratories. HHS publication no. (CDC)84-8395, March 1984). Some of these agents, such as anthrax, are virulent enough to have potential military applications but only in combination with delivery system techniques capable of covering relatively large areas. In that sense, they are functionally equivalent to chemical weapons, though probably less efficient for military purposes. Other agents in this category, such as cholera, typhus, and the hemorrhagic fevers pose naturally occurring health problems that might have a
potentially serious strategic effect if deliberately manipulated but could not compete with conventional munitions for use in immediate tactical engagements. Category N agents would probably be of concern only if introduced in very large quantities and can reasonably be excluded from control.

Fourth, there is an important distinction regarding the type of hostile use of biological agents that the control arrangements are designed to prevent. Applications that could affect the outcome of major military engagements are in principle easier to restrict successfully than lesser-scale terrorist-type applications designed to disrupt the usual peacetime functioning of society or to create sensational events. Though the latter is an exceedingly important problem and is undoubtedly the most probable threat, a control scheme that reliably limits only military applications would nonetheless be very valuable, in part because it would establish a base for cooperation in dealing with the more troublesome threats of lesser scale.

4. As in many other areas of arms control, any effort to specify and to verify the biological weapons convention inevitably encounters trade-offs among the degree of control, the degree of confidence, and the direct and indirect costs. A scheme designed to detect with nearly perfect confidence even the smallest and most elaborately clandestine violation would be infeasibly expensive and intrusive. In this area, in particular, impractical demands are a serious threat to feasible objectives. If that tendency can be mastered, however, there do appear to be important objectives that can be achieved. Fortunately neither the United States nor the Soviet Union appears to have incorporated a biological weapons mission
in its military doctrine or to have developed military units dedicated to an operational mission of this sort. The BWC appears in fact to have prevented these developments and a consolidation and protection of that accomplishment is one obvious objective to be pursued. We do not, in other words, have to reverse a well-established pattern of military activity, and that is an advantage. Prevention is much easier to accomplish than eradication.

5. Following these many considerations, an arrangement to consolidate and strengthen the BWC might be suggested having the following provisions:

a) an agreement that no military organization would develop, possess or operate missiles or aircraft equipped for aerosol spraying and that all such equipment operated by non-military organizations would be registered. (This would require that some existing capability be eliminated and probably would intersect with controls on chemical weapons.)

b) an agreement that all known biological agents and toxins be listed and assigned to one of the three categories of control and that all previously unlisted or experimentally created agents be subjected to the strictest controls (category E) until reclassified by mutual agreement.

c) a determination of disclosure and prohibition thresholds in terms of infectious doses (Id 50) provisionally as follows:
Category E

. disclosure at any amount.

. prohibition of amounts of live material exceeding $10^9$
  Id 50's averaged over a 90-day period.

Category S

. disclosure of amounts of live material exceeding $10^{12}$
  Id 50's averaged over a 90-day period.

. prohibition of amounts of live material exceeding $10^{15}$
  Id 50's averaged over a 90-day period.

Category N

. all infectious agents to be listed but not subjected to
  disclosure or prohibition requirements on amounts of live
  material.

d) An extension of current reporting requirements under the BWC to
include a listing of any inventories above the disclosure thresholds
and a description of actual infectious outbreaks by agent categories
as follows:

  Category E

  . Every individual case.

  Category S

  . Every laboratory outbreak.

  . Every unusual incidence of cases in the general population.

e) The development of inspection arrangements for all listed
facilities to verify inventories of material.
In order to assure that the prohibitions in this arrangement do not interfere with desirable vaccine development, a general exemption should be made for live agents produced and stored in association with inventories containing ten times the amount of that live agent in killed or attenuated form. This 10% rule would protect properly balanced, legitimate vaccine development while making the production of agents for BW purposes prohibitively expensive if the constraint were met. The rule would still require that full disclosure requirements be met.
<table>
<thead>
<tr>
<th>Biosafety Classification</th>
<th>Agent</th>
<th>Stability</th>
<th>Route</th>
<th>Case Fatality</th>
<th>ID&lt;sub&gt;50&lt;/sub&gt; Morbidity</th>
<th>Transmission to Close Contacts</th>
<th>General Population</th>
<th>Treatment</th>
<th>Immunization</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td><em>Bacillus anthracis</em></td>
<td>Very High</td>
<td>Aerosol</td>
<td>100%</td>
<td>Estimated ID&lt;sub&gt;50&lt;/sub&gt;~10,000 spores</td>
<td>0</td>
<td>0</td>
<td>Not effective</td>
<td>Effectiveness not demonstrated for pulmonary disease</td>
</tr>
<tr>
<td>S</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td><em>Francisella tularensis</em></td>
<td>Moderate</td>
<td>Aerosol</td>
<td>High</td>
<td>Estimated ID&lt;sub&gt;50&lt;/sub&gt;~10-50 organisms</td>
<td>0?</td>
<td>0</td>
<td>Effective (Streptomycin) vaccine partially protective</td>
<td></td>
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<tr>
<td></td>
<td><em>Brucella</em></td>
<td>Moderate</td>
<td>Aerosol</td>
<td>Low (chronic sequelae)</td>
<td>Estimated ID&lt;sub&gt;50&lt;/sub&gt;~1000-2000 organisms</td>
<td>0</td>
<td>0</td>
<td>Effective (tetracycline + Streptomycin); 2% relapse rate</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td><em>Yersinia pestis</em></td>
<td>Moderate</td>
<td>Aerosol</td>
<td>High (40-100%)</td>
<td>Estimated ID&lt;sub&gt;50&lt;/sub&gt;~2000 organisms</td>
<td>+</td>
<td>+</td>
<td>Not effective in pulmonary form or disease. (75% mortality)</td>
<td>Formalin-inactivated vaccine. Must be given every 6 months.</td>
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<tr>
<td></td>
<td><em>Chlamydia psittaci</em></td>
<td>Moderate</td>
<td>Aerosol</td>
<td>Low</td>
<td>?</td>
<td>Reas</td>
<td>0</td>
<td>Tetracycline effective</td>
<td>Vaccine not available for humans</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>N</td>
<td><em>Coccidioides immitis</em></td>
<td>High</td>
<td>Aerosol</td>
<td>Low (chronic sequelae)</td>
<td>Estimated ID&lt;sub&gt;50&lt;/sub&gt;~1000-1500 spores</td>
<td>0</td>
<td>0</td>
<td>Amphotericin&lt;sup&gt;®&lt;/sup&gt; effective but relapse common in disseminated disease</td>
<td></td>
</tr>
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<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td><em>Histoplasma capsulatum</em></td>
<td>High</td>
<td>Aerosol</td>
<td>Low</td>
<td>?</td>
<td>0</td>
<td>0</td>
<td>Amphotericin&lt;sup&gt;®&lt;/sup&gt; effective in most severe illnesses</td>
<td>None available</td>
</tr>
<tr>
<td>S</td>
<td><em>Legionella</em></td>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>
### Potential Offensive Microbial Agents Which Are of Concern: High Biosafety Classification and Lack of Significant Immunity in the General Population

<table>
<thead>
<tr>
<th>Pathogen/Agent</th>
<th>Stability</th>
<th>Route</th>
<th>Case Fatality</th>
<th>Toxicity</th>
<th>Transmission to Close Contacts</th>
<th>General Population</th>
<th>Treatment</th>
<th>Immunization</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Botulinum Toxins</strong></td>
<td>Moderate</td>
<td>Aerosol</td>
<td>High</td>
<td>5-10 mg</td>
<td>0</td>
<td>0</td>
<td>Antitoxin A-E</td>
<td>Toxoids for types A-E</td>
</tr>
<tr>
<td><strong>Staphylococcal enterotoxins</strong></td>
<td>Moderate</td>
<td>Aerosol</td>
<td>High</td>
<td>5-10 µg</td>
<td>0</td>
<td>0</td>
<td>Supportive</td>
<td>None</td>
</tr>
<tr>
<td><strong>Coxiella burnetii</strong></td>
<td>High</td>
<td>Aerosol</td>
<td>Low</td>
<td>ID₅₀ ~ 10⁸ organisms</td>
<td>0</td>
<td>0</td>
<td>Effective (Doxycycline)</td>
<td>Investigational inactivated vaccine available</td>
</tr>
<tr>
<td><strong>Rickettsia prowazekii</strong></td>
<td>Low</td>
<td>Aerosol</td>
<td>High (up to cut)</td>
<td>?</td>
<td>0</td>
<td>0</td>
<td>Effective (Doxycycline)</td>
<td>None available</td>
</tr>
<tr>
<td><strong>Rickettsia mooseri</strong></td>
<td>Low</td>
<td>Aerosol</td>
<td>Low</td>
<td>?</td>
<td>0</td>
<td>0</td>
<td>Effective (Tetracycline)</td>
<td>None available</td>
</tr>
<tr>
<td><strong>Rickettsia rickettsii</strong></td>
<td>Low</td>
<td>Aerosol</td>
<td>High (20%)</td>
<td>?</td>
<td>0</td>
<td>0</td>
<td>Effective (Tetracycline)</td>
<td>None available</td>
</tr>
<tr>
<td><strong>Rickettsia mooseri</strong></td>
<td>Low</td>
<td>Aerosol</td>
<td>Variable (&lt;1 to 60%)</td>
<td>?</td>
<td>0</td>
<td>0</td>
<td>Effective (Tetracycline)</td>
<td>Vaccine not available; marked antigenic variability. However, chemoprophylaxis can be achieved using tetracycline.</td>
</tr>
</tbody>
</table>
### Potential Offensive Microbial Agents Which Are of Concern: High Biosafety Classification and Lack of Significant Immunity in the General Population

<table>
<thead>
<tr>
<th>Biosafety Classification</th>
<th>Agent</th>
<th>Stability</th>
<th>Route</th>
<th>Case Fatality</th>
<th>IDₜ Morbidity</th>
<th>Transmission to Close Contacts Population</th>
<th>Treatment</th>
<th>Immunization</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Rio Bravo (Flavivirus)</td>
<td>Moderate</td>
<td>Aerosol</td>
<td>0</td>
<td>?</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N</td>
<td>Wesselsebron (Flavivirus)</td>
<td>Moderate</td>
<td>Aerosol</td>
<td>0</td>
<td>?</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N</td>
<td>West Nile (Flavivirus)</td>
<td>Moderate</td>
<td>Aerosol</td>
<td>Rare (Infants, elderly)</td>
<td>?</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N</td>
<td>Yellow Fever (Flavivirus)</td>
<td>Moderate</td>
<td>Aerosol</td>
<td>High 20-50%</td>
<td>IDₜ,pipfu Infect. 1:5</td>
<td>Secondary spread by vectors</td>
<td>0</td>
<td>Live attenuated vaccine</td>
</tr>
<tr>
<td>S</td>
<td>Germiston (Bunyavirus)</td>
<td>Moderate</td>
<td>Aerosol</td>
<td>0</td>
<td>?</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N</td>
<td>Oropouche (Bunyavirus)</td>
<td>Moderate</td>
<td>Aerosol</td>
<td>0</td>
<td>Illness: Infect 1:1.5</td>
<td>Secondary spread by vectors</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N</td>
<td>Nairobi-Sheep disease (-Carnivorous Virus) (Bunyavirus)</td>
<td>Moderate</td>
<td>Aerosol</td>
<td>0</td>
<td>?</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N</td>
<td>LCN (Arenavirus)</td>
<td>Moderate</td>
<td>Aerosol</td>
<td>Low</td>
<td>?</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
### Potential Offensive Microbial Agents Which Are of Concern: High Biosafety Classification and Lack of Significant Immunity in the General Population

<table>
<thead>
<tr>
<th>Biosafety classification</th>
<th>Agent</th>
<th>Stability Route</th>
<th>Case Fatality</th>
<th>ID, morbidity</th>
<th>Transmission to Close Contacts</th>
<th>General Population</th>
<th>Treatment</th>
<th>Immunization</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>VEE, Everglades, Mucambo, subtype 70 (Alphavirus)</td>
<td>Moderate Aerosol</td>
<td>Low (&lt;0.5%)</td>
<td>Illness: Infection 1:1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Investigational live attenuated vaccine; vaccine effective in humans and animals.</td>
</tr>
<tr>
<td></td>
<td>Chikungunya (Alphavirus)</td>
<td>Moderate Aerosol</td>
<td>Low</td>
<td>?</td>
<td>0</td>
<td>Secondary spread by vectors</td>
<td>0</td>
<td>Investigational live, attenuated vaccine available.</td>
</tr>
<tr>
<td></td>
<td>Rift Valley Fever (Bunyavirus)</td>
<td>Moderate Aerosol</td>
<td>High (3-14%)</td>
<td>?</td>
<td>0</td>
<td>0</td>
<td>Ribavirin effective in experimental animals</td>
<td>Investigational inactivated vaccine available; live attenuated vaccine under development.</td>
</tr>
<tr>
<td></td>
<td>Hantaan virus (Bunyavirus)</td>
<td>Moderate Aerosol</td>
<td>High (&lt;5 to 32%)</td>
<td>?</td>
<td>0</td>
<td>0</td>
<td>Ribavirin</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Lassa virus (Arenavirus)</td>
<td>Moderate Aerosol</td>
<td>High (&lt;16 to 30%)</td>
<td>?</td>
<td>+ (Requires close contact)</td>
<td>0</td>
<td>Ribavirin effective within 6 days of onset.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VEE</td>
<td>Moderate Aerosol</td>
<td>High (50-70%)</td>
<td>Illness: Infection 20:1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Investigational vaccine</td>
</tr>
<tr>
<td>Biosafety classification</td>
<td>Agent (virus family)</td>
<td>Stability</td>
<td>Route</td>
<td>Case Fatality</td>
<td>IDa Morbidity</td>
<td>Transmission to close contacts</td>
<td>General Population</td>
<td>Treatment</td>
</tr>
<tr>
<td>--------------------------</td>
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</tr>
<tr>
<td>IV</td>
<td>Machupo virus (Arenavirus)</td>
<td>Moderate</td>
<td>Aerosol</td>
<td>High (~45%)</td>
<td>?</td>
<td>+ (Requires close contact)</td>
<td>0</td>
<td>Ribavirin effective in experimental disease.</td>
</tr>
<tr>
<td>S</td>
<td>Junin virus (Arenavirus)</td>
<td>Moderate</td>
<td>Aerosol</td>
<td>High (~15%)</td>
<td>?</td>
<td>+ (Requires close contact)</td>
<td>0</td>
<td>Passive immunotherapy (i.e., antibody) effective within 8 days of onset</td>
</tr>
<tr>
<td>S</td>
<td>Marburg virus (Filovirus)</td>
<td>Moderate</td>
<td>Aerosol</td>
<td>High (10-15%)</td>
<td>?</td>
<td>+ (Requires close contact)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>S</td>
<td>Eboia virus (Filovirus)</td>
<td>Moderate</td>
<td>Aerosol?</td>
<td>High (~51 to 28%)</td>
<td>?</td>
<td>+ (Requires close contact)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>S+</td>
<td>Congo-Crimean hemorrhagic (Bunyavirus)</td>
<td>Moderate</td>
<td>Aerosol</td>
<td>High (~10 to 30%)</td>
<td>?</td>
<td>+ (Requires close contact)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>S</td>
<td>Variola virus (Orthomyxovirus)</td>
<td>High</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Tickborne Disease Agent</td>
<td>Route of Entry</td>
<td>Stability</td>
<td>Case Fatality</td>
<td>Immunity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kyasanur Forest Fever</td>
<td>Aerosol, Moderate</td>
<td>High</td>
<td>Low</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omsk Hemorrhagic Fever</td>
<td>Aerosol, Moderate</td>
<td>Moderate</td>
<td>Low</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tickborne Encephalitis</td>
<td>Arbovirus</td>
<td>High</td>
<td>Low</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tickborne Fever</td>
<td>Arbovirus</td>
<td>Moderate</td>
<td>Low</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Immunization:**

- Inactivated vaccine said to be protective.
- Clinical trial data for specific vaccines used in USSR.

**Treatment:**

- None noted for specific diseases.
Personal views of Robert M. Chanock, M.D.

**Defensive research and development (R&D) is distinguishable from offensive R&D.**

Research and development dedicated to the prevention or treatment of disease caused by biological weapons can be uncoupled from offensive R&D if: (i) the research is clearly identified as only prophylactic or therapeutic in nature and (ii) this is clearly stated during frequent public disclosures and is subject to verification by challenge inspection at any time.

Although organisms which are developed or constructed for the purpose of preventing disease may be novel attenuated mutants or recombinants they should not be viewed as an offensive threat. I find the argument that such attenuated mutants or recombinants will necessarily be used for offensive purposes to be specious. For example, an experimental vaccine consisting of an attenuated mutant or a recombinant vector which expresses the gene for a non-toxic, protective antigen of a human or animal pathogen would not be expected to pose a threat of disease because the mutant or recombinant could only be considered for use in immunoprophylaxis if it were completely or almost completely attenuated for both humans and animals. Viral and bacterial mutants or recombinant vectors now under study in experimental immunoprophylaxis are restricted in their replication in humans and as a consequence the mutants or the recombinants produced from the vectors are also attenuated and exhibit diminished transmissibility. Such
attenuated mutants or recombinant vaccine constructs are useful for prevention of disease, not its induction. Before a research program can be considered an offensive threat it must be linked to a weapons implementation effort and there must be large scale production and storage of virulent organisms. On the other hand, large scale production of attenuated vaccine mutants or recombinants intended for use solely in defense against an offensive threat would not be linked to weapons delivery systems or large scale production and storage of virulent organisms. However, in defensive research it is necessary to produce large volumes of attenuated vaccine organisms in order to perform safety tests and other types of characterization required by regulatory authorities (the FDA in the US) before the mutants or recombinants can be evaluated in humans for immunogenicity and attenuation.

There is no threat as long as development of attenuated mutants or recombinants that induce protective immunity is not coupled to the production and storage of large amounts of virulent organisms and the development of weapons delivery systems. In contrast, the development of recombinants that express an unmodified bacterial, plant or animal toxin can legitimately be viewed as a threat especially if coupled to the development and utilization of a vector that: (i) is highly infectious for humans, (ii) grows to high titer during infection, and (iii) is highly transmissible among humans. For this reason the development of such recombinants and/or efficient vectors
must be declared by the country in which the work is performed. In addition, adherence to the relevant guidelines for research involving such hazardous organisms (BSL-4), and scientific justification for their derivation and study must be clearly spelled out. The development of such recombinants from highly efficient vectors will undoubtedly elicit many requests for inspection, continuous surveillance and repeated assurance of peaceful intent. As a consequence it may be difficult to justify and perform such studies.

The production and long term storage of large volumes of viable, virulent organisms should be strictly prohibited. Of course, virulent organisms would be required for challenge of immunized animals in order to demonstrate protective efficacy, but the quantity of organisms needed for this purpose would be relatively small (~ 500ml to one liter). However, large amounts of virulent organisms would be required if an inactivated vaccine were being prepared, but the shelf life of these organisms could and should be relatively short. Lengthy storage of large volumes of virulent organisms destined for inactivation can legitimately be interpreted as an offensive threat. For this reason there is no justification for more than momentary storage of large volumes of live, virulent organisms. Long term storage constitutes a serious, implied threat that must be avoided at all costs.
Overreaction to the dangers inherent in the use of recombinant DNA technology for defensive purposes.

The view that recombinant techniques present unlimited opportunities for the design and implementation of novel agents against which vaccines could not work is probably an overreaction to the potential dangers inherent in this methodology. For example, most recombinant or reassortant viruses are less virulent than either parental organism. Only a few intraspecies recombinants or reassortants have proved to be more virulent than either parent. In these instances the result was anticipated based upon a consideration of the gene products of the two temperate parents which were brought together in the new organism. In other words, there have been no surprises. This means that it should be possible to identify and prohibit most potentially dangerous constructs a priori.

Also, the bacterial or viral vectors which are now available for expression of foreign genes or gene segments are poorly transmissible. More transmissible vectors may be developed in the future but this does not appear to be imminent. For example, influenza A virus, the most highly transmissible human virus, cannot be used for this purpose at this time because it has not been possible to transfer alterations in influenza cDNA back into viral RNA in infectious virions. Similar constraints exist for other highly transmissible negative strand RNA viruses.

Furthermore, a large proportion of antigenic mutants of
viruses produced by molecular biological methods have been considerably less virulent than their parent. Tampering with the neutralization epitopes which are located in close proximity to a site of functional activity, such as a receptor pocket, an enzyme or a region involved in membrane fusion, most often down regulates virus replication and virulence. In addition, the mixing of genes from different viruses, even closely related viruses that differ in their host range, most often results in attenuation. This form of gene incompatibility is not surprising because multiple gene products commonly act cooperatively in structural or functional enzyme complexes. Such proteins which act cooperatively have been selected over a long time for their ability to work together efficiently. As a consequence, the creation of a mixed constellation of genes encoding such a functional complex, either by genetic recombination or reassortment, usually leads to restriction of replication with resultant attenuation.
The BWC prohibits "Microbial or other biological agents, or toxins whatever their origin or mode of production" [if for other than peaceful purposes.] There is no definition of toxins either in the treaty, nor so far as I am aware in the negotiating history of the Convention -- they were thrown in as an afterthought. The historical context does identify biological agents with those that proliferate in the course of doing harm. Review conference discussions have fairly certainly included infectious nucleic acids and recombinants among forbidden biological agents. "Toxins" are generally understood to be poisonous substances generated as byproducts of biological growth -- examples are botulinum toxin or mycotoxins (like trichothecenes). They generally have complex chemical structures, but not always. New methods of chemical synthesis leave open the possibility that any toxin could be produced by chemical methods as an alternative to biological but the "whatever mode of production clause" would prohibit such products as well.

Toxins (as well as microbial agents) are clearly also included under the provisions of the Geneva Protocol. Our discussion may be moot if a general Chemical Disarmament treaty is concluded. But until that eventuates, there is a zone of definitional ambiguity about just which chemical substances are "toxins" under the BWC. So far, this is purely hypothetical: we are not aware of any allegation about "development, production, stockpiling, acquisition or retention" of substances in the gray zone, nor has any country asserted that its possession of a toxin-related chemical was permissible under the treaty.

The difficulty arises from the existence of toxic chemicals which resemble, in structure or in pathological effect, the toxins of biological origin which are clearly forbidden. For example, a synthetic polypeptide may well be identified which comprises the active site of the botulinum toxin. Indeed, it is often discussed that such a substance, especially if built along with skin penetration aids, might be far more potent than nerve gas, and as such would be an attractive target for chemical weapons development (a dangerous vertical proliferation). Further developments in the understanding of molecular structure may allow non-polypeptide structures to be designed which bear no direct analogy to botulinum toxin, but which are conceptually derived from insights into how this toxin works. Mycotoxins and zootoxins likewise could have synthetic molecular variants that are conceptually but not structurally related to biological prototypes.

As the BWC is silent or vague, there has been a certain amount of discussion about more precise definitions to clarify the existing uncertainties. At the Quinquennial Review, it was agreed that synthetically produced analogues are covered; but this begs the question of what is an analogue. Three lines of further progress can be envisaged:

1) Within the negotiating framework of the CW disarmament discussion, interim declarations that disavow any novel chemical agents other than those now in admitted stockpiles or closely related to them. This would leave mustards and organophosphates as a class under the same heading as existing chemical weapons, but would label all novelties (including synthetic peptides) as already forbidden by the BWC. Such entities would be encumbered with the same verification problems, no better, no worse, as biological agents and toxins.
or, as a specific and emphatic subset of the class of novelties:

2) Defining as subsumed by toxins, under the BWC, any chemical substances targeted against specific cellular receptors other than those (cholinesterase) associated with nerve gas.

or

3) More specific designations of oligopeptides and other chemical categories. This would not be foolproof, but would promptly cover the most likely, immediate prospects. Non-polypeptide myco- and zoo-toxins generally offer no dramatic advantage in lethality compared to nerve gas; hence there is less motivation to invest in synthetic chemicals that mimic their activity.

While CW-disarmament must be concurred with multilaterally, the high technology associated with toxin extensions would lend great value to interim declarations initiated on a bilateral basis. These might be revocable in the unlikely event that third parties were found to be proceeding along these denied paths. Since we are dealing with still hypothetical innovations, there should be far less reluctance to accept these restrictions than would apply to well established chemical weapons.

The broadening of the toxin provisions lends nothing to the verification dilemmas, but would be a confidence building measure especially if it is associated with free scientific discussion of permitted R&D on toxic activities and their receptors.

Joshua Lederberg
3 March, 1989
SMALLPOX VACCINATION*

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The United States and the Soviet Union still vaccinate their military forces despite the global eradication of smallpox virus and the discontinued use of vaccine in most, if not all civilian populations. The sole rationale for continued vaccination of military forces is the threat that smallpox virus would be used as an offensive biological weapon or in retaliation for another form of biological warfare.

I. Pros and Cons of the Present Policy:

Since there is no consensus of opinion on the issue of military vaccination, it will be useful to examine and discuss both sides of the polemic and thereby to search for common ground.

A. Premises in Support of the Present Policy:

1. Smallpox virus itself is still retained by both the United States and the Soviet Union.

2. There is no mechanism in place to assure and verify that smallpox virus is not being or could not be developed as a biological weapon.

3. Although smallpox is not an "ideal" biological weapon, it is not inconceivable that it could be so used.

4. Implementation of an effective defensive posture by both sides assures that smallpox will not be developed as an offensive weapon.

5. There is considerable interest and intensive research on the use of vaccinia as a gene vector expressing immunogenic antigens against a variety of other agents. This research may improve the production methods and safety of vaccinia itself. Moreover, a continued policy of military vaccination may assist in the evaluation of genetically engineered, vaccinia-vectored vaccines.

*The views expressed in this paper are those of the author and do not represent those of the U.S. Government, any of its agencies, or the National Academy of Sciences.
B. Premises Against The Present Policy:

1. Unlike other BW agents, smallpox virus does not constitute a natural disease threat to operational military forces.

2. Smallpox is not a particularly effective biological weapon; the incubation period is relatively long; the disease is easily recognized and diagnosed; therapeutic and preventive measures are readily available, etc.

3. Since the sole proprietors of virus are the U.S. and USSR, there is little or no concern about development of smallpox as a BW agent by third-world or terrorist groups.

4. Vaccinia vaccines are produced by antiquated techniques, unacceptable by modern standards. Vaccines are not innocuous and their use in military populations is associated with a significant rate of complications, such as generalized vaccinia. In addition to the unnecessary economic burden imposed by production of vaccine and implementation of a vaccination policy, further resources are diverted towards treatment of vaccine complications and manufacture of vaccinia immune globulin.

5. The policy of vaccination is viewed as evidence of bilateral mistrust and is a hindrance to disarmament efforts.

II. Possible Solutions and Further Points for Discussion:

In one respect, smallpox is absolutely unique among potential biological weapons:

The agent itself exists only in laboratory repositories in two nations. If these repositories were eliminated the threat itself would vanish. Use of vaccinia for protection against smallpox would become unnecessary. Although this seems a reasonable objective, with obvious medical and political benefits, two problems must be resolved:

1. There must be absolute assurances and verification that all remaining stocks of variola virus are eliminated.

2. Consideration must be given to the scientific and academic objection that final and irrevocable destruction of the variola genome (which has not been mapped) is undesirable.

Solution of the first problem will be difficult; it relies on measures to be worked out in relation to similar disarmament issues.

Solution of the second problem is scientifically achievable, since it is now possible to define the genetic structure of
variola virus. Full elucidation of the gene sequence of variola would secure the essential knowledge base, provide for future needs to study or compare the variola genome and allow destruction of infectious stocks. The investment required to accomplish this task is considerable because of the size of the variola genome and the probable need to measure genetic variability between variola strains, e.g. alastrim. Moreover, although variola DNA is not itself infectious, the possibility remains that functional viral genome could be rescued by recombination with a heterologous pox virus (Sam, CK and Dumbell, KR, Ann. Virol. (Inst. Pasteur) 132E:135-150, 1981). Safeguards against this possibility could, however, be easily worked out.

In light of this discussion, the group may consider the desirability and feasibility of a bilateral, cooperative research effort to clone and sequence variola virus.