Incapacitating Biochemical Weapons

Princeton Biosecurity Seminar

March 31, 2006
Nord-Ost Hostage Crisis

Dubrovka Theater Center – Moscow

26 October 2002
- Early-Middle Cold War programs
- Technical challenges
- S&T advances
- Current interest and efforts
- International Law
- Conclusions
Incapacitating Biochemical Agents

Biochemicals that temporarily incapacitate, but generally do not kill

Bioregulators and natural toxins, their derivatives and synthetic analogs

Alter or disrupt specific biochemical mechanisms and physiological systems, particularly the higher regulatory functions of the CNS

Generally active in minute quantities, unlike traditional chemical weapons agents

Examples
- neurotransmitters and other neuro-regulators
- anesthetics
- sedatives

“An incapacitating agent is an agent that produces temporary physiological or mental effects, or both, which render individuals incapable of concerted effort in the performance of their duties.” U.S. Army Field Manual 3-11.9, 2005

Incapacitation persists for hours or days after exposure

U.S. Army Field Manual 8-285
Early-Middle Cold War Programs

US

Started in 1951

Requirements (1955)

- onset of action <1 hr
- no permanent effect (not essential)
- as potent as nerve gases
- low toxicity in handling
- stable in storage
- capable of aircraft dissemination

100s of psychoactive agents explored
(stimulants, depressants (anesthetics, sedatives, opiates), psychedelics, deliriants)

UK

Smaller program

Lead agent was TL2636

3-quinuclidinyl benzilate (BZ) (1958)
Early-Middle Cold War Programs

Key characteristics

- Existed within offensive B and C programs
- Actively sought to develop a broad range of capabilities - lethal and non-lethal
- Stimulated by advances in psychopharmacology
- Developed critical relationship with pharmaceutical industry
Early-Middle Cold War Programs

Ultimately unsuccessful, discontinued by mid 1970s

BZ is “unlikely to be employed due to its wide range of variability of effects, long onset time, and inefficiency of existing munitions. … The U.S. currently does not have an effective operational incapacitating chemical capability.”

1969 Interdepartmental Political-Military Working Group

“On general grounds I think it unlikely that … a pure incapacitator agent will emerge. Any chemical agent, a small dose of which is capable of profound disturbance of bodily or mental function, is certain to be able to cause death in large dose … and no attack with a chemical warfare agent is likely to be designed with the primary objective of avoiding overhitting.”

R.B. Fisher, Chair, Chemical Defence Advisory Board - 1968
The Safety Margin Problem
A problem of science, application, and politics

Example
Two-receptor, equilibrium model

\[ TI = \frac{f_I(1-f_L)}{f_L(1-f_I)} \]

For \( TI = 1000 \) and \( f_I = 99\% \)

\( f_L = 9\% \)

For \( f_I = 99\% \), \( f_L = 0.5\% \)

\( TI = 19701 \)

Effects of slope, variable distribution, speed of onset, duration of exposure, specificity

Mixed population (age, size, gender, health, sensitivity)
The Safety Margin Problem
A problem of science, application, and politics

“Therapists of every type have long recognized and acknowledged that individual patients show wide variability in response to the same drug or treatment method.”

Goodman and Gilman’s Pharmacological Basis of Therapeutics, 2001

“The use of a drug cannot be predicted on the basis of a therapeutic index derived from the ED50’s and LD50’s alone.”

Veterinary Pharmacology and Therapeutics, 2001

“It’s hard enough to use them in the operating room without compounding the problem with larger groups.”

C Parker Ferguson, 2002
Technical Challenges

Dissemination rapid, often covert, in defined, controlled amounts
Highly potent and effective
Rapid onset, defined duration, reversible
Predictability – consistent effect at given dose (or dose range)
High safety margin

Wheelis/Dando: understanding of neurobiology and receptors insufficient in 1960s to enable development of agents with adequate specificity (all 5 muscarinic acetylcholine receptor subtypes bind BZ)
Scientific and Technological Advance

Is our understanding of neurobiology and receptors now (or will it soon be) sufficient to enable the development of agents with enough specificity to elicit very specific responses?

- Increased knowledge about the nervous system and neurological disorders (pain, depression, sleep, other)
  
  “The past decade has delivered more advances than all previous years of neuroscience research combined.”
  Society of Neuroscience, 1999

- Increased demand for pharmaceutical treatments following initial post-WW II demonstrations

- Continued discovery of new, more effective and safer neuropharmaceuticals having fewer side effects
Muscarinic Acetylcholine receptors (GPCR)

1980s - Five sub-types M1 – M5

Moderately (10-fold) sub-type selective ligands exist

1990s - MT7 snake toxin highly selective for M1 sub-type

2004 - Schering-Plough team reported highly selective M2 antagonist

1990s Knockout mice for each sub-type exist

- show distinct phenotypes (distinct physiological, pharmacological, behavioral, biochemical, or neurochemical deficits)

- agonist-induced analgesic responses mediated predominantly by M2 (hippocampus, cortex) and somewhat by M4 (striatum)

“The novel insights gained from these [knock-out] studies should prove instrumental for the development of novel classes of muscarinic drugs.”
α–adrenergic receptors (GPCR)

α1, α2, β sub-types
mid 1980s - 3 α1, 3 α2 sub-sub-types

Sub-type, but not sub-sub-type specific ligands exist

1960s - clonidine – α1D selective, all α2
1980s – dexmedetomidine – all α2 (5x selectivity of clonidine)

1990s - α2 sub-sub-type knockout mice

Show distinct phenotypes
Agonist-induced analgesic, anxiolytic, sedative (hypnotic), anesthetic
sparing and hypotensive effects mediated exclusively by α2A
S&T advances have generated continued military interest in, and provided a source for, potential incapacitating biochemical agents.

“Since the mid 1960s … the premier status of the US pharmaceutical industry … combined with the exponential developments in the fields of pharmacology, neuroscience, anesthesia, and biotechnology fields … has brought forth a diverse array of compounds that produce sedation and/or a calm state as either a primary or secondary effect.”

National Research Council, Naval Studies Board, 2003

“Advances in discovery of novel bioregulators, especially bioregulators for incapacitation, understanding of their mode of operation and synthetic routes for manufacture have been very rapid in recent time. Some of these compounds may be potent enough to be many hundreds of times more effective than the traditional chemical warfare agents.”

Bokan, et al  Croatian Military Academy, 2002
Late Cold War Programs

Soviet Union clearly continued efforts (including B agents)

US Army re-started program by mid 1980s (ARCAD)

- Serotonin antagonists – calmative
  (ketanserin late 1970s, R51703? Early 1980s)

- $\alpha_2$-adrenergic receptor agonists – sedative, immobilizer
  (dexmedetomidine 1980s)

- Synthetic opioids – analgesic/anesthetic, immobilizer
## Synthetic Opioids

Analgesia and sedation – “most advanced technology exists for the fentanyls than for any other chemical immobilizer candidates”

1994 ERDEC proposal

<table>
<thead>
<tr>
<th></th>
<th>Morphine</th>
<th>Fentanyl</th>
<th>Sufentanil</th>
<th>Carfentanil</th>
<th>Remifentanil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discovered</td>
<td>1803</td>
<td>1960</td>
<td>Mid 1970s</td>
<td>Late 1970s</td>
<td>1990s</td>
</tr>
<tr>
<td>Rel. Potency</td>
<td>1</td>
<td>100</td>
<td>500 – 1000</td>
<td>10,000</td>
<td>250</td>
</tr>
<tr>
<td>Onset time (min)</td>
<td>15-30</td>
<td>1-2</td>
<td>1-3</td>
<td>0.5</td>
<td>0.1-0.2</td>
</tr>
<tr>
<td>Duration (hr)</td>
<td>3-5</td>
<td>0.5-1</td>
<td>0.5-1</td>
<td>10,600</td>
<td>33,000</td>
</tr>
<tr>
<td>TI*</td>
<td>70</td>
<td>277</td>
<td>25,000**</td>
<td>10,600</td>
<td></td>
</tr>
<tr>
<td>ED50*</td>
<td></td>
<td></td>
<td>7.1 μg/kg</td>
<td>0.32 μg/kg</td>
<td></td>
</tr>
</tbody>
</table>

*Analgesia in rats
**800 in dogs
Synthetic Opioids

Wide variation in blood levels after aerosolized fentanyl

Respiratory Depression

- Therapeutic index is for analgesia (not sedation) in rats
- Sedation/anesthesia TIs often 10% or less of analgesia TIs
  - “Earlier materials showed high safety ratios in rodents, but much lower ratios in primates because of respiratory depression.”
    1994 ERDEC proposal

Outcomes

- “The principal effect was still unconsciousness, which is unacceptable under most interpretations of the CWC.”
  2002 NRC Report
- Nord-Ost
“Recent pharmaceutical developments suggest that new approaches to safer chemical immobilizers with improved performance characteristics may be available.”

CBD 00-108 Army SBIR Solicitation, 1999

“Technologies of interest:” “chemical technologies [that] could act on the central nervous system by calmatives, dissociative agents, equilibrium agents.”

NATO Research and Technology Organization Technical Report, 2004

“Non-Lethal Technology: Taxonomy”

Col George Fenton
Director JNLWD, 2000

Center for Arms Control and Non-Proliferation
Current Activities – U.S.

Project Objective:
- Identify advances in the pharmaceutical industry and elsewhere for potential non-lethal applications
- Conduct military user workshops to identify range of desired operational effects
- Create a searchable database of potential candidates
- Provide a list of promising candidates to Judge Advocate General's office for preliminary legal review

Potential Applications:
- Improved Riot Control Agents for crowd, area denial and clearing facilities

“Workshops and analyses culminating in a database of all potential riot control agents, calmatives, etc. with an emphasis on technology advances in the past 10 years”
Experienced sedative-hypnotics, anesthetics, muscle relaxants, opioid analgesics, anxiolytics, antipsychotics, antidepressants, selected drugs of abuse.

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>Diazepam (Valium), midazolam</td>
</tr>
<tr>
<td>$\alpha_2$ adrenergic rec agonists</td>
<td>Desmedetomidine</td>
</tr>
<tr>
<td>Dopamine D3 rec agonists</td>
<td>Pramipexole, Cl-1007</td>
</tr>
<tr>
<td>SSRI</td>
<td>Fluoxetine (Prozac), WO-09500194</td>
</tr>
<tr>
<td>5-HT1A rec agonists</td>
<td>Buspirone (Buspar), WAY-100,636</td>
</tr>
<tr>
<td>Opioid receptor mu agonists</td>
<td>Carfentanil</td>
</tr>
<tr>
<td>Neurollept anesthetics</td>
<td>Propofol, droperidol/fentanyl (Innovar), phencyclidines</td>
</tr>
<tr>
<td>Corticotropin-releasing factor</td>
<td>CP 154,526 (antagonist)</td>
</tr>
<tr>
<td>CCK B rec antagonists</td>
<td>CCK-4, Cl-988</td>
</tr>
</tbody>
</table>
“New classes of pharmaceutical agents and new compounds are poised to meet the unique requirements of the non-lethal warfare arena.”

Develop “partnerships with the pharmaceutical industry” to examine compounds shelved or discarded during the search for marketable drugs and “to better incorporate their knowledge and expertise.”

Pursue synergies

agent combinations – to increase safety by reducing dose requirements or counteracting negative effects

with other NLW modalities – “the interesting phenomenon of potentiating acupuncture [with dexmedetomidine] opens the possibility [of] use … in conjunction with existing (sticky shocker) and proposed (electro-magnetic waves) non-lethal techniques.”

PSU Calmatives Study, 2000
Current Activities – U.S.
Current Activities – U.S.

Bullet Trap Rifle Grenade
Cargo Projectile
Current Activities – U.S.

RADIAL EXPULSION DEVICE

Static Test for for frangible case (OLDS contract DAAE30-99-C-1072)
Current Activities – Other Nations

Russia

“If the level of 95% efficiency is absolutely required to neutralize terrorists and to prevent mass destruction, there is no chance to eliminate hard consequences and fatalities. This is the cost of releasing if no other solution is left.”

Kolochikin et al, 2005

Czech Republic

Combinations of dissociative anesthetics, benzodiazepines, $\alpha_2$ agonists, opioids

Experiments in monkey and in humans (nurses, pre-operative patients)

“The transdermal technique … could possibly be used to induce long-term sedation with alpha2 agonists, benzodiazepines, and a combination of them … using the paint-ball bun principle” and dimethyl sulphoxide (DMSO) to facilitate absorption through the skin.

Hess, et al 2005
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Hess, et al. 2005
Science and Technology Continues its Advance

5-HT$_{4(a)}$ Receptors Avert Opioid-Induced Breathing Depression Without Loss of Analgesia

Till Manzke,$^1$ Ulf Guenther,$^2$ Evgeni G. Ponimaskin,$^1$
Miriam Haller,$^1$ Mathias Dutschmann,$^1$ Stephan Schwarzacher,$^3$
Diether W. Richter$^1$

Opiates are widely used analgesics in anesthesiology, but they have serious adverse effects such as depression of breathing. This is caused by direct inhibition of rhythm-generating respiratory neurons in the Pre-Bötzinger complex (PBC) of the brainstem. We report that serotonin 4(a) [5-HT$_{4(a)}$] receptors are strongly expressed in respiratory PBC neurons and that their selective activation protects spontaneous respiratory activity. Treatment of rats with a 5-HT$_{4}$ receptor-specific agonist overcame fentanyl-induced respiratory depression and re-established stable respiratory rhythm without loss of fentanyl’s analgesic effect.

These findings imply the prospect of a fine-tuned recovery from opioid-induced respiratory depression, through adjustment of intracellular adenosine 3’,5’-monophosphate levels through the convergent signaling pathways in neurons.

11 JULY 2003 VOL 301 SCIENCE www.sciencemag.org
CBW Spectrum

Adapted from scheme of G. Pearson

Biochemical ("mid-spectrum") agents
Center for Arms Control and Non-Proliferation

Biological Weapons Convention (1975)

Article I

Each State Party to this Convention undertakes never in any circumstances to develop, produce, stockpile or otherwise acquire or retain:

(1) Microbial or other biological agents, or toxins whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes;

Fourth Review Conference (1996) Final Declaration

The Convention unequivocally covers all microbial or other biological agents or toxins, naturally or artificially created or altered, as well as their components, whatever their origin or method of production.
Chemical Weapons Convention (1997)

Article I

Each State Party to this Convention undertakes never under any circumstances:

(a) To develop, produce, otherwise acquire, stockpile or retain chemical weapons, or transfer, directly or indirectly, chemical weapons to anyone;

(b) To use chemical weapons;

(c) To engage in any military preparations to use chemical weapons;

(d) To assist, encourage or induce, in any way, anyone to engage in any activity prohibited to a State Party under this Convention.
Chemical Weapons Convention (1997)

Article II

1. "Chemical Weapons" means the following, together or separately:

   (a) Toxic chemicals and their precursors, except where intended for purposes not prohibited under this Convention, as long as the types and quantities are consistent with such purposes;

2. "Toxic Chemical" means:

   Any chemical which through its chemical action on life processes can cause death, temporary incapacitation or permanent harm to humans or animals.
Chemical Weapons Convention (1997)

Article II

9. "Purposes Not Prohibited Under this Convention" means:

(a) Industrial, agricultural, research, medical, pharmaceutical or other peaceful purposes;

(b) Protective purposes, namely those purposes directly related to protection against toxic chemicals and to protection against chemical weapons;

(c) Military purposes not connected with the use of chemical weapons and not dependent on the use of the toxic properties of chemicals as a method of warfare;

(d) Law enforcement including domestic riot control purposes.
"What is ‘law enforcement?’ Nowhere in the Convention is it defined. Whose law? What law? Enforcement where? By whom?"

“The language used to exempt other law-enforcement purposes has created an ambiguity in the heart of the Convention. If states parties come to act on differing interpretations of the ambiguity, even if they do so in good faith, the stability of the treaty regime will suffer, perhaps catastrophically. … What is at stake is the ability of the treaty regime to withstand technical change. For new chemical agents and technologies have begun to emerge whose attractions for weapons purposes may eventually drive them through the loophole which the ambiguity has created.”

Chemical Weapons Convention (1997)

“Convulsives and calmatives may rely on their toxic properties to have a physiological effect on humans. If that is the case, and these two NLWs are not considered RCAs, in order to avoid being classified as a prohibited chemical weapon, they would have to be used for the article II(9)(d) “purpose not prohibited,” the law enforcement purpose. … The limits of this “purpose not prohibited” are not clear and will be determined by the practice of states.”

Navy JAG, 1997

Conclusions

- Technology not yet mature
- S&T advances may yet lead to effective incapacitating biochemical weapons
- These weapons could be useful for a few specific scenarios (e.g. hostage rescue)
- Bigger picture mitigates strongly against their development and use, except perhaps in very limited and well defined cases
- Concerns raised by HSP in 1994 are even more salient today.
Conclusions

- Ongoing pursuit of incapacitating biochemical weapons may greatly weaken the protections afforded by the CWC and BWC
- Absent clarification and reinforcement, one breakthrough agent that works “well enough” may be all it takes for the prohibitions to crumble

Consequences
- Erosion of norms and goals: to exclude completely the possibility of the use of chemical and biological weapons, which would be repugnant to the conscience of mankind
- Widespread proliferation
- Increasing tolerance for negative effects, including lethality
- Retreat from chemical, and perhaps biological, disarmament
Conclusions

- **Consequences**
  - Development of lethal agents will be facilitated
  - Lethal agents may also become more attractive
  - Spur use of incapacitating biological weapons? (Q fever)
  - Potential use by terrorists

- Chance of achieving meaningful standards remote

- Military necessity may govern the use of incapacitating biochemical weapons
Non-lethal weapons “must be conceived … as augmenting the use or threat of use of lethal force and of providing commanders with wider options for delivering fighting power and achieving strategic, operational, and tactical objectives. Integration [of lethal and non-lethal capabilities] is critical; there must be a concerted effort to counter the perception of purely “non-lethal operations.”

“NLWs may be used in a variety of different missions. In some cases they may be employed to save innocent lives and property, while in others they may be used to enhance the effectiveness of lethal weapons.”

The Future Outlook

Leading edge of larger category of potential biochemical weapons agents that could specifically manipulate almost any physiological system

“A greater understanding of how small molecules and naturally-occurring bioregulatory peptides function in higher organisms will open up novel opportunities to design agents … that target particular physiological systems and processes, such as the brain and the immune system, in very precise ways.”

National Research Council  2006

“As our ability to modify fundamental life processes continues its rapid advance, we will be able not only to devise additional ways to destroy life, but also be able to manipulate it - including the processes of cognition, development and inheritance. Therein could lie unprecedented opportunities for violence, coercion, repression or subjugation. “

Matthew Meselson

Center for Arms Control and Non-Proliferation
Solutions

- New Convention prohibiting non-consensual manipulation of human physiology
- Strengthen existing arms control regime
  - Clarify meaning of “law enforcement” and “peaceful purposes”
  - Bring in considerations of IHL, HRL
  - Clarify scope of RCA prohibition
  - Circumscribe legal RCAs to those already in common use
  - Strictly prohibit any use of incapacitating biochemical weapons or RCAs in mixed combatant/non-combatant situations
Solutions

- Take steps outside of the treaties
  - Engage the human rights and humanitarian communities
  - Implement system of national and international regulation of life sciences research and military development, with strong oversight
  - Increase transparency of military biodefense programs
  - Raise awareness and concern among life scientists about the depth of the problem
“This paper is addicted to toxic chemicals that can be used for military or terrorist purposes only.”

Patoka, *et al* 2004