Breach of Safety and Security in United States Government Institutions: How it Applies to Israel

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Scientific research and development, as well as diagnostic procedures, involving high biohazard class organisms is a responsible and complicated mission. It calls for strict laboratory procedures in addition to safety and security rules. Institutions that work with dangerous organisms must abide by rules and regulations published by local health and safety organizations, and if not existing, by acceptable international bodies. In the United States, a law termed “Possession, Use, and Transfer of Select Agents and Toxins” regulates all aspects of this issue [1]. All scientific and industrial institutions must follow these directives. The main purpose of this law is to prevent “leakage” of organisms capable of serving as bio-terror weapons into the wrong hands. Called “The Select Agent Rule,” it is a comprehensive law that also targets security of information. In 2008 Israel published a law for regulating research with infectious agents. The purpose and implementation of this law is similar to that in the U.S., and every institution in Israel – whether research, medical, diagnostic or industrial – must abide by its injunctions. A committee was appointed by the Minister of Health to lead and provide guidance for following the regulations, headed to date by Prof. Bracha Rager. It is crucial that all entities dealing with organisms on the “select agent” list be alert to breaches of safety and security in these regulations.

In recent months, the U.S. Centers for Disease Control and Prevention (CDC) announced the occurrence of three major incidents that raised concerns about the implementation of safety and security regulations within the CDC, the National Institutes of Health (NIH), and the Federal Drug Administration (FDA). These lapses of biosafety and biosecurity included the mishandling of Bacillus anthracis spores, the shipment of low pathogenic influenza virus unknowingly contaminated with a highly pathogenic avian strain, and an inventory lapse of hundreds of samples of biological agents including six vials of variola virus that were kept in a cold storage room for decades, unnoticed.

In this issue of IMAJ Weiss et al. [2] present the published data regarding these events, provide the CDC inquiry’s main findings and discuss the main lessons to be taken for safer scientific practice in biomedical and microbiological services and research laboratories. Actions were taken in both the anthrax and the influenza laboratories.

In the anthrax lab these included:
- a moratorium on the movement (i.e., transfer inside or outside the agency) of biological materials from biosafety level (BSL) 3 or 4 facilities. The moratorium will remain in place pending lab-by-lab review of policies and procedures for laboratory safety and security
- the creation and appointment of a CDC Director of Laboratory Safety to serve as the single point of accountability to improve all laboratory safety protocols, practices and procedures
- establishment of an internal biosafety working group under the leadership of the CDC Director of Laboratory Safety
- establishment of an external group on biosafety comprising leading scientists and biosecurity experts, which will advise the internal Biosafety Working Group
- in addition, the CDC provided the Animal and Plant Health Inspection Service with standard protocols for inactivation of anthrax as well as a plan outlining required refresher training of laboratory personnel with access to anthrax on the appropriate use of the inactivation protocol

In the influenza lab, the following steps were instituted:
- reviewing existing laboratory protocols and modifying them or developing new protocols to ensure consistency and that best laboratory protocols are used across Influenza Division laboratories
- developing better documentation processes that will improve record-keeping and compliance with protocols
- implementing standardized testing for cross-contamination of samples before they are transferred to other locations or to other laboratories within the CDC
- re-assessing current use of BSL-3 enhanced space to ensure that work done on select agents and non-select agents is separated by an appropriate amount of time to reduce the chances of cross-contamination
- identifying and closing gaps in existing skills and knowledge of laboratory staff and providing additional extensive training. This includes training to further clarify incidents that qualify as...
It is crucial that the medical and scientific community in Israel take home the messages learned from these incidents, namely, the need for a biosafety management program, and fully implementing a culture of safety in order to prevent the reoccurrence of biosafety incidents. Laboratories must define compatible methods relevant to the biological agents used in its facilities, and adopt strict inactivation protocols. Transportation and shipment of any biological agent is extremely accident prone and therefore requires special attention. Cross-contamination of samples is a high risk factor in laboratories that utilize the same instruments and biosafety cabinets for multiple microorganisms or species with different pathogenicity. Biosafety programs must involve all management levels within the organization, especially the head of the pyramid.

**References**

1. Department of Health and Human Services, Possession, Use, and Transfer of Select Agents and Toxins; Biennial Review; Final Rule. 61084 Federal Register / Vol. 77, No. 194/ Friday, October 5, 2012 / Rules and Regulations
2. Weiss S, Yitzhaki S, Shapira SC. Lessons to be learned from recent biosafety incidents in the United States. IMAJ 2015; 17: 269-73.

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**Capsule**

**Fatty acid carbon is essential for dNTP synthesis in endothelial cells**

The metabolism of endothelial cells during vessel sprouting remains poorly studied. Schoors et al. report that endothelial loss of CPT1A, a rate-limiting enzyme of fatty acid oxidation (FAO), causes vascular sprouting defects due to impaired proliferation, not migration, of human and murine endothelial cells. Reduction of FAO in endothelial cells did not cause energy depletion or disturb redox homeostasis, but impaired de novo nucleotide synthesis for DNA replication. Isotope labeling studies in control endothelial cells showed that fatty acid carbons substantially replenished the Krebs cycle, and were incorporated into aspartate (a nucleotide precursor), uridine monophosphate (a precursor of pyrimidine nucleoside triphosphates) and DNA. CPT1A silencing reduced these processes and depleted endothelial cell stores of aspartate and deoxyribonucleoside triphosphates. Acetate (metabolized to acetyl-CoA, thereby substituting for the depleted FAO-derived acetyl-CoA) or a nucleoside mix rescued the phenotype of CPT1A-silenced endothelial cells. Finally, CPT1 blockade inhibited pathological ocular angiogenesis in mice, suggesting a novel strategy for blocking angiogenesis.

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**Capsule**

**Distinct plasma immune signatures in ME/CFS are present early in the course of illness**

Myalgic encephalomyelitis/chronic fatigue syndrome is a disabling disorder that may affect up to 4 million people in the United States alone. Distinct features include fatigue, memory and concentration deficits, sleep disturbances, headache, joint and muscle pain, post-exertional malaise, and gastrointestinal and immune system dysfunction lasting for 6 months or more. Until now no validated laboratory marker to help confirm the diagnosis existed. Hornig et al. report distinct alterations in plasma immune signatures early in the course of ME/CFS (n=52) compared to healthy controls (n=348) that were not present in subjects with longer duration of illness (n=246). In early disease lasting less than 3 years they found prominent activation of pro-inflammatory (interleukin (IL)-1a, IL-8, IL-12p40, IL-17A, tumor necrosis factor-alpha (TNFa), TNF-related apoptosis-inducing ligand (TRAIL), chemokine ligand (CCL)-2, monocyte chemoattractant protein 1 (MCP1), stem cell factor (SCF), resistin and anti-inflammatory cytokines (IL-1RA, IL-4, IL-13) as well as dissociation of intercytokine regulatory networks (especially CD40 ligand). They found a stronger relationship of cytokine alterations with illness duration than with measures of illness severity. Their findings suggest that immunopathology of ME/CFS is not static.

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“I am so clever that sometimes I don’t understand a single word of what I am saying”

Oscar Wilde (1854-1900), Irish author, playwright and poet. One of London’s most popular playwrights in the early 1890s, today he is remembered for his epigrams, his novel *The Picture of Dorian Gray*, his plays, as well as the circumstances of his imprisonment and early death.