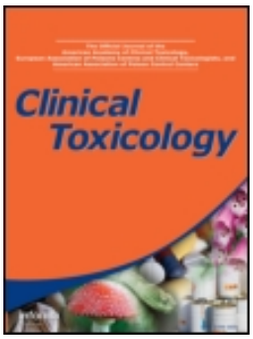

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The conference organisers omitted to include the abstract below in the EAPCCT Abstracts. Please also notice the updates to the Keyword and Author index as listed below.

353. The Many Faces of Botulinum Toxin

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Objective: To review the pathophysiology and diversity of clinical effects induced by botulinum toxin and how these effects cause disease, make it an attractive biowarfare agent, and can be used therapeutically for a large number of medical conditions. *Discussion:* The term botulism refers to a disease caused by the toxin liberated primarily from the gram positive obligate anaerobic spore forming rod *Clostridium botulinum*. That toxin, which is secreted in the form of a 750 kD complex, contains an approximately 150 kD protein neurotoxin and other proteins and glycoproteins, the latter referred to as hemagglutinins because they were discovered as a result of their erythrocyte agglutinating properties. It is theorized that the associated proteins stabilize the neurotoxin, particularly against the acidic and proteolytic milieu of the gastrointestinal tract and enhance its absorption in the small intestine - the latter possibly accomplished by endocytosis mediated by carbohydrate moieties on neurotoxin-associated glycoproteins. The precise composition of neurotoxin-protein complexes differs among *C. botulinum* serotypes. Botulinum toxin is the most potent chemical substance known, with animal LD50s in the 1–3 nanogram/kilogram range. The neurotoxin is synthesized as a single chain pro-toxin with an internal disulfide linkage. Post-translationally a segment of the neurotoxin is removed giving rise to a protein with 100 and 50 kD chains held together by the disulfide bond. The heavy chain contains sites that bind to the nerve terminal and translocate the neurotoxin into the cell. Once internalized into the nerve terminal the light chain, which has protease activity, degrades one of the family of SNARE proteins which are required for fusion of acetylcholine-containing vesicles with the cell membrane and hence prevents the endocytosis of the vesicle contents. The final result is a state of peripheral acetylcholine deficiency, manifested primarily at the neuromuscular junction. The consequent syndromes, therefore, are primarily those of motor weakness with some degree of autonomic instability. For unknown reasons the motor weakness occurs in a descending pattern, with cranial nerve abnormalities, particularly ptosis and bulbar dysfunction, as initial manifestations. Human botulism, which occurs in several forms, is almost always the result of the neurotoxin derived from *C. botulinum* serotypes A, B, E or, less commonly, F. The best known form is the foodborne disease, resulting from of the ingestion of pre-formed botulinum toxin in foods that have been stored in anaerobic conditions, thus allowing spores to germinate. The most common form, however, is infant botulism, caused by the ingestion of spores which then germinate in the small bowel. The gastrointestinal environment conducive to intestinal germination is generally present up to approximately 6 months of age. Rarely, individuals of any age may develop botulism from intra-intestinal sporulation if they have gastrointestinal pathology creating a conducive environment. Wound botulism, which may be recurrent, tends to occur in intravenous drug abusers as a result of sporulation in the anaerobic environment of skin abscesses. Iatrogenic botulism may occur if botulinum toxin, meant to be used for cosmetic or therapeutic purposes, is incorrectly administered and given at excessive doses. Inhalational botulism may occur from the inhalation of the toxin. This form of the disease does not occur naturally but could occur as a result of the intentional generation of a toxin-containing aerosol.[1] Botulinum toxin has uses both in medicine and as a potential biowarfare agent. In 1973 Scott and colleagues demonstrated the therapeutic utility of botulinum toxin injections into extraocular muscles[2] leading to its use in the treatment of strabismus. Following that observation the use of botulinum toxin to treat conditions that would benefit from muscle relaxation has, and continues to, proliferate. Examples of contemporary medical uses of botulinum toxin are the treatment of spasticity, such as that which occurs in cerebral palsy or post-stroke, dystonias, and the relaxation of facial muscles to reduce wrinkling. Adverse effects of botulinum toxin used therapeutically are mostly restricted to the occasional spread to, and consequent weakness of, muscles adjacent to those injected. Incorrect administration of excessive doses can lead

to systemic dissemination toxin leading to a botulism-like syndrome.[3] There are a number of botulinum toxin preparations available for therapeutic use derived from *C. botulinum* serotypes A or B. Some examples are: onabotulinumtoxin A, abobotulinum toxin A, incobotulinumtoxin A, and rimabotulinumtoxin B.[4] Currently, in addition to supportive care, there are two treatment options for botulism in the US: Trivalent (A, B, E) Antitoxin and Botulism Immune Globulin Intravenous–Human (BabyBIG). The former is an equine-derived whole antibody preparation. BabyBig is human derived, very expensive, and used primarily for the treatment of infant botulism. Because of its potency and potential lethality botulinum toxin has been developed as a potential bioweapon. It was thought to have been produced by the Germans during WWI and Saddam Hussein is known to have developed large stockpiles. As a bioweapon it could be used to contaminate the food supply or can be aerosolized. *Conclusion:* Despite having a single mechanism of action botulinum toxin has diverse biological roles: it causes the various botulinum disease syndromes, can be a biowarfare agent, and is a powerful and highly effective medication. *References:* 1. Bleck TP, Reddy. Toxin-mediated syndromes of the nervous system. In: Ross KL, Tunkel AR, eds. Handbook of Clinical Neurology. Vol 96. Bacterial Infections. Amsterdam, The Netherlands: Elesevier, 2010:257–72. 2. Scott AB, Rosenbaum A, Collins CC. Pharmacologic Weakening of extraocular muscles. Invest Ophthalmol 1973; 12:924–7. 3. Chertow DS, Tan, ET, Maslanka SE, et al. Botulism in 4 adults following cosmetic injections with an unlicensed, highly concentrated botulinum preparation. JAMA 2006; 296:2476–9. 4. Albanese A. Terminology for preparations of botulinum neurotoxins: what a difference a name makes. JAMA 2011; 305:89–90.

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