Bioterrorism: A New Challenge for the Medical Discipline

Whether the attack is a hoax, a small food–borne outbreak, a lethal aerosol cloud moving silently through a city at night, or the introduction of a contagious disease, the possibility of biological warfare is rapidly materializing into a daunting reality we will be forced to deal with.

History
Non-conventional weapons have been with us from time immemorial, altering the fate of history. The Greeks used biological warfare as long ago as 300BC when they intentionally polluted enemy wells with animal corpses. In 600BC, the Athenian army poisoned the water supply to the city of Kirrho using a toxin derived from the hellebore plant. Throughout the middle ages, catapults were used to hurl diseased animal & human corpses into besieged cities. Smallpox was used widely against Native Americans ironically, by French, British & Americans. The advent of World War I & II saw the introduction of mustard gas & the use of anthrax, cholera & glanders. During the 1980-88 Iran –Iraq war, mustard gas in addition to other chemical weapons were used. In 1995 the Aum Shinrikyo cult released Sarin nerve gas into 5 Tokyo subway cabs. In 2001 we saw the release of Anthrax into the American postage system. The question now arises: What was the agent used by Russian police in the recent Moscow hostage drama?? Was it fentanyl?? OR was it a newly developed, genetically modified chemical agent??

Introduction
A terrorist is one who favours or uses terror inspiring methods of governing or of coercing government or community. Hence the word terrorism. Terrorist organizations operate outside the law, therefore they are not restricted by their choice of weapons or their targets. Weapons are grouped as conventional or non-conventional.

Conventional weapon systems are primarily kinetic energy delivery systems such as firearms & explosive or thermal devices. Non-conventional weapon systems are those that include nuclear, biological & chemical elements. However, they may rely on delivery systems similar to those for conventional weapons.

Two terms are particularly useful when comparing the effectiveness of weapons. Lethality: is the fraction of the total number who die. Casualty generation: number of individuals in the target population who are injured by the single use of the weapon. Chemical & biological weapons are attractive because they have a high casualty generation & high lethality.

100kg of sarin gas released from an airplane would kill 8000 people. 100kg of the anthrax bacillus would kill 3 million people if optimally dispersed.

Methods of chemical and biological weapon dispersal
1. release into water supplies
2. release into food chains
3. airborne release
   a. bomb / missile explosion
   b. crop – duster / other aircraft which sprays the agent
   c. car / truck drives through a city spraying a fine mist along streets
   d. small bombs or aerosol containers

Principles of initial management
This includes triage, decontamination of patients & staff protection

Triage
Primary triage takes place at the sight of exposure whilst secondary triage takes place when the patient arrives at the hospital. During secondary triage, patients are classified according to their severity of injury & their need for medical intervention as expectant (death inevitable), immediate (life saving treatment required immediately), delayed (treatment can be delayed without interim harm), minor (walking wounded). Patent status may however change between primary & secondary triage.

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Decontamination
Decontamination refers to the removal or neutralization of chemical or biological weapons to limit human exposure. It protects patients from further damage & health care workers from injury. Preferably, decontamination should be conducted in the ambulance reception area & by patients themselves. It may be in the form of dilution eg. Showering, wound & eye irrigation, or require chemical agents eg. Hypochlorite solution. Priority is however given to life saving treatment. Provision must be made for barrier nursing & the appropriate disposal of fluids used for decontamination & patient clothes.

Staff protection
All staff must make use of universal precautions in the form of gowns, gloves, masks & face shields. Patients must be isolated & basic hygiene must be maintained. The gold standard is the use of Level C personal protective equipment. This comprises a full or half face mask, air purifying respirator, hooded chemical resistant clothing (splash suit), chemical resistant gloves & boots. Staff should be trained in advance as to the wearing & function of this protective clothing. Problems with this equipment include claustrophobia, difficulty with breathing apparatus, overheating, dehydration, failure to recognize danger and anxiety. Other methods of staff protection are vaccination against certain infections & post – exposure prophylaxis.

Agents that are used in bioterrorism can be classified as chemical agents or biological agents. This presentation looks at chemical agents only.

Chemical agents
Chemical agents are defined as chemical substances, either gaseous, liquid or solid which may be used because of their direct toxic effects on man, animals & plants. Any chemical may be used, but some in particular are more attractive because they are easy to produce, simple to assemble into a weapon, produce large numbers of casualties, are difficult to destroy, are easy manufactured and their chemical stability. They produce death by a variety of biochemical methods. Toxins used to date include saxitoxin, ricin, botulinum toxin, aflatoxin, clostridium perfringens toxin, trichothecane mycotoxin, staphylococcal enterotoxin B, diphtheria, tetanus and shigatoxin.

Botulinum toxin
This a neurotoxin produced by clostridium botulinum. Seven distinct strains exist (A–G). By weight they are the most toxic chemical known to man. It is five thousand times more toxic than sarin nerve gas. The toxin permanently inhibits acetylcholine in presynaptic nerve terminals. Functional recovery occurs by genesis of new terminal boutons. Neurotransmission is blocked at peripheral cholinergic synapses including the neuromuscular junction, postganglionic parasympathetic synapses and peripheral ganglia.

One to four days after exposure, patients present with a bulbar palsy and ocular symptoms followed by progressive, symmetrical, descending weakness that leads to respiratory failure.

Standard decontamination procedures are sufficient. Diagnosis is confirmed by single fibre electromyography. The toxin is inactivated within 12 hours. With early ventilatory support it results in a fatality rate of less than 5%. An antitoxin exists for all serotypes but efficacy in humans is not known. An antitoxin is available for serotypes A, B and E and appears to be useful against oral ingestion of toxin.

Ricin
This is a protein derived from the castor bean plant, Ricinus Communis. Waste from the commercial production of castor oil contains 5% ricin, therefore it is easily and cheaply obtained and fairly stable. It is less toxic than botulinum toxin and staphylococcal enterotoxin B. It also requires larger doses to produce its effects. Effects are due to interruption of protein synthesis.

Ingestion of ricin causes abdominal pain and diarrhoea. It is a rare cause of gastrointestinal haemorrhage. In severe cases it may result in hepatic, splenic and renal necrosis. Four to eight hours after inhalation patients develop fever, chest pain, dyspnoea and cough. With high dose exposure it is associated with drowsiness, confusion, coma and respiratory failure which rapidly progresses onto multi-organ failure and death within 36 – 72 hours

Management is supportive eg. Ventilation, fluids, GI decontamination. An avian ricin antitoxin has been developed for use in animals.

Saxitoxin
A toxin produced by dinoflagellate sea organisms viz. Alexandrium Tamarense, Gymnodinium catenatum, Pyrodinium bahamense. It is responsible for the red tide and is concentrated in shellfish. It causes paralytic shellfish poisoning. It is twenty times more lethal than sarin nerve gas. Effects are due to selective inhibition of sodium ion channels.

After ingestion, the toxin manifests with a prodrome of GIT
upset, cramping and diarrhoea. It is rapidly fatal after inhalation resulting in bulbar palsy, respiratory failure and cardiovascular failure.

There is no available treatment and management is organ supportive. An antitoxin has been developed in guinea pigs but it does not reverse the central neurological effects of the agent.

**Trichothecane Mycotoxin**

This is also known as T2 / yellow rain and is produced by filamentous fungi of the Fusarium, Trichoderma, and Stachybotris genera. It acts by inhibiting protein and nucleic acid synthesis. Onset of illness occurs minutes to hours after exposure. Skin exposure presents with pruritis, redness and vesicle formation followed by necrosis and sloughing. Ingestion causes nausea, vomiting and diarrhoea. Inhalation results in dyspnoea, wheezing, chest pain and haemoptysis. In severe cases it can lead to cardiovascular collapse and death. Gas – liquid chromatography and high–pressure liquid chromatography with mass spectrometry can be used to detect the presence of toxin in urine and blood. Management is supportive.

**Staphylococcal Enterotoxin B**

This toxin activates T lymphocytes and induces the production of TNF, IL-1, IL-2 and interferon gamma resulting a systemic inflammatory response syndrome. Clinical symptoms start 3-12 hours after exposure with a sudden onset of fever, chills, headache, myalgia and cough, followed by retrosternal chest pain and dyspnoea. Toxin ingestion causes nausea, vomiting and diarrhoea, resulting in dehydration and hypovolaemia. The toxin can be detected in the urine. Management is supportive.

**Nerve Agents**

These agents were first mass produced in Germany in April 1942 (tabun gas). They are toxic, colourless, odourless, tasteless substances. The four most commonly used agents are sarin, soman, VX – gas and tabun. Other agents currently produced are genetically modified to penetrate gas protection units and persist after deployment.

Nerve agents are structurally related to organophosphate insecticides and exert their effects by permanently inactivating acetylcholinesterase. This prevents the hydrolysis of acetylcholine resulting in its accumulation at muscarinic receptors, nicotinic receptors, adrenal medulla and central nervous system. They also work at cardiac muscarinic and glutamate NMDA receptors, causing effects as yet, undescribed. They also antagonize GABA neurotransmission, causing seizures, and other CNS symptoms.

Significant exposure incapacitates within 1-10 minutes and kills within 1-15minutes. This is slightly longer for VX-gas which is fatal within 4-24 hours. Generalised effects and death occur after rapid absorption of nerve agent vapour via the respiratory tract. The effects of cutaneous exposure depend on: the anatomical site, ambient temperature, and dose of the nerve agent. Percutaneous absorption results in localized sweating, muscle fasciculations and weakness. A triphasic clinical syndrome develops after exposure viz. a cholinergic phase, intermediate phase, third phase.

The cholinergic phase is due to acetylcholine accumulation which may manifest with bronchoconstriction, vocal cord paralysis, bradycardia, convulsions and paralytic respiratory failure. It is characterised by a depolarising neuromuscular blockade. The phase lasts 24-48 hours and warrants intensive care treatment. In the event that suxamethonium is used, its action is prolonged. Nondepolarising muscle relaxants may also cause a prolonged paralysis but they are thought to prevent acetylcholine –mediated damage of receptors. Ketamine may be beneficial for intubation but it does increase oropharyngeal secretions. It has also been shown to protect acetylcholine-esterase in vitro.

The second or intermediate syndrome begins after the cholinergic phase and lasts 4-18 days. It depends on the de-novo resynthesis rate of acetylcholine. It is characterised by muscle weakness (especially of the diaphragm), respiratory failure and cranial nerve palsies. The phase is associated with non-depolarising neuromuscular blockade which is due to acetylcholine receptor down-regulation.

The third phase is seen after instances of industrial organophosphate poisoning and is associated with a delayed polyneuropathy. It occurs 7-14 days after exposure and is characterised by symmetrical, peripheral muscle weakness and disturbances of sensation. The cause is thought to be due to the inactivation of the enzyme, neuropathy target esterase. Minimal data is available to suggest the presence of this phase with nerve agents, however postural imbalance, shoulder stiffness and blurred vision have been reported in years after exposure.

Pyridostigmine is a reversible, competitive antagonist of acetylcholinesterase. When administered, it has similar effects to nerve agents but the rationale for its use is that it produces a reservoir of temporarily inactivated acetylcholinesterase. Therefore after exposure, the nerve agents are unable to bind to the enzyme. With later dissociation of pyridostigmine, reactivation of acetylcholinesterase occurs. Pyridostigmine bromide is thus used for pre-treatment in the event of exposure to nerve agents. Soldiers carry around a NAPP pack (nerve agent pyridostigmine pre-treatment) which contains 21 tablets. The problem with its use is that it alters the pharmacokinetics of muscle relaxants because it causes accumulation of acetylcholine at the post synaptic receptor. Therefore less suxamethonium is required to produce a phase one block but a larger dose of non-depolarising muscle relaxant is required to maintain paralysis. Smaller doses of neostigmine are required to reverse neuromuscular blockade.

Atropine is an effective antidote if given early. It antagonizes the muscarinic side effects of nerve agents and is more beneficial than glycopyrrolate because of its longer duration of action and it crosses the blood brain barrier. Oximes (pyridostigmine, obidoxime) reverse nicotinic receptor dysfunction and decrease paralysis. They have 3 major beneficial effects in the management of nerve agent poisoning viz. reactivation of acetylcholinesterase, detoxification of unbonded nerve agent and an endogenous anticholinergic effect. It is recommended that pralidoxime and atropine are co-administered. Avoid the concurrent use of barbiturates and morphine because they potentiate side effects and worsen respiratory function and confusion.

Other agents that have been used in the management include diazepam, clonidine, inotropes and magnesium.
Blistering Agents

They are also known as vesicants. Two main classes exist viz. arsenicals eg. Lewisite and mustards eg. Nitrogen mustard, mustard gas. Arsenicals are more volatile, have a sharp irritating odour. Conjunctival exposure causes immediate eye pain. Mustards are poorly volatile, almost odourless with no initial eye pain. They have more debilitating and lethal complications and therefore are more likely to be used by terrorists.

Mustard Gas

Mustard gas was first used in World War I and its most recent use was during the 1980-1988 Iran-Iraq war. It is a colourless or pale yellow liquid that smells faintly of mustard or garlic. The threshold for odour sensation is low and therefore allows a few minutes for detection before lethal, incapacitating doses are reached. Because of its low volatility, it results in greater clinical effects in hotter climates but tends to persist in more temperate climates. Its persistence places medical responders at greater risk of intoxication. Initially a leucocytosis and reactive airways dysfunction syndrome. With severe exposure, pulmonary haemorrhage, oedema and respiratory failure occurs within 24 hours. In the long term it has led to chronic pulmonary obstructive disease, bronchiectasis and causes the release of destructive proteases. There is a latent period between exposure and development of symptoms, therefore patients who are thought to have been exposed must be carefully observed and reviewed.

Mustard gas forms highly reactive sulphonium ions in the body. These ions alkylate sulphhydryl and amino groups on macromolecular proteins such as DNA and enzymes, resulting in carcinogenesis especially of the pharynx, skin and respiratory tract in the long term. Clinical manifestations of exposure result from NAD+ depletion which disrupts glycolysis and causes the release of destructive proteases. There is a latent period between exposure and development of symptoms, therefore patients who are thought to have been exposed must be carefully observed and reviewed.

Cutaneous manifestations are universal. The first symptom is usually stinging of the skin, followed 4-12 hours later by diffuse erythema, oedema and first degree burns on exposed areas. Severe oedema and vesication are seen in the axillae, groin and antecubital fossa after high dose exposure. Particular attention must be paid to pain relief and fluid therapy in these individuals. Anaesthetists may encounter them for wound debridements and skin grafts.

Ocular symptoms are seen in 85% of patients. After several hours after exposure, patients may present with eye pain, blurred vision and lacrimation. Vision returns after a few weeks. 0.5% develop an ulcerative keratitis which causes blindness.

Respiratory complications are seen in about 70% of victims. Its causes a severe tracheobronchitis resulting in cough and hoarseness. Bronchospasm is common. Tracheobronchitis is characterised by ulceration, purulent discharge and fibrinous pseudomembrane formation. This may present as acute airway obstruction or collapse of distal lung segments. With severe exposure, pulmonary haemorrhage, oedema and respiratory failure occurs within 24 hours. In the long term it has lead to chronic pulmonary obstructive disease, bronchiectasis and reactive airways dysfunction syndrome.

Haematological manifestations are seen after high dose exposure and herald a poorer prognosisInitially a leucocytosis is seen followed by a leucopenia by the 10th day. Anaemia and thrombocytopenia occur but less commonly. The gastrointestinal system is affected in about 69% of cases. Nausea and vomiting are commonly seen. Rarely it may cause upper GIT bleeding.

Sodium thiosulphate, Vitamin E and dexamethasone in combination have been shown to be effective. No topical or systemic antidote exists. Fatality rates range between 2-3% and death usually ensues after respiratory complications and bone marrow suppression.

Choking Agents

These comprise chlorine, phosgene, chloropicrin and diphosgene. They were the classical agents of chemical warfare. Chlorine and phosgene were first used in 1915. Because their acrid smell and respiratory irritancy gave early warning of their presence, their use was superseded by blistering agents in 1917. Chlorine and phosgene are still widely used in industrial manufacturing processes and therefore may now be encountered during industrial accidents.

Chlorine is a greenish-yellow gas with a distinctive smell. It is denser than air and has a low odour threshold giving ample warning to potential victims. Reaction with water liberates hypochlorous acid, hydrochloric acid and oxygen free radicals which cause tissue damage. Initial exposure causes eye pain, blepharospasm and lacrimation.

Phosgene is a colourless gas which smells of newly mown hay. It is four times heavier than air and therefore remains close to the ground, concentrating in trenches and cellars. Clinical features manifest 12-24 hours after exposure, however high doses are fatal within an hour. The gas dissolves in water, undergoing hydrolysis to form carbon dioxide and hydrochloric acid. It enters the respiratory tract causing inflammation and necrosis. Resultant leaky capillaries cause pulmonary oedema and hypoxia.

Blood Agents

These are metabolic poisons which are fatal within 15 minutes after a lethal dose. They include arsenic, hydrogen cyanide (prussic acid, AC) and cyanogen chloride (CK).

Hydrogen cyanide is a colourless liquid that smells of almonds. It is disseminated as a vapour because of its high volatility. Most commonly it is encountered after industrial spills and house fires. Inhalation produces high fatality rates. It binds to the trivalent iron atom of cytochrome oxidase enzymes, interrupting cellular utilization of oxygen resulting in histotoxic hypoxia.

Clinically patients present with dizziness, confusion and tachypnoea which progresses onto seizures, coma and cardiorespiratory arrest. Arterial blood gas analysis shows a metabolic acidosis, increased lactate and a decreased arteriovenous oxygen difference.

Management is basically ICU based. Antidotes are sodium thiosulphate which converts cyanide to sodium thiocyanate, sodium nitrite which converts haemoglobin to methaemoglobin and hydroxycobalamin which converts cyanide to cyanocobalamin. Dicobalt edetate is reserved for second line therapy because of its side effects of nausea and hypertension.

Harassing Agents

These are commonly referred to as tear gas. A number of compounds such as CS gas (“-chlorobenzalmalononitrile), CN gas (chloroacetophenone) and capsacin spray are used alone or in combination. CN gas is the active ingredient found in MACE. Immediate effects result from intense irritation of the mucous membranes of the eye, respiratory tract, stomach and skin. Lacrimation and temporary blindness are common.
Cough, diarrhoea and vomiting subsequently ensue. Symptoms decrease within a few minutes.

CS gas is a more potent lacrimator but has less long term injury. These agents do have the potential to cause contact dermatitis, chemical pneumonitis, heart failure and hepato-cellular damage. Symptoms of asthma and COPD may also be worsened following exposure. In addition they are metabolised to cyanide in peripheral tissue but whether toxic levels are reached is controversial.

**Vomiting and Incapacitating Agents**

Vomiting agents are substances like adamsite and diphenylchloroarsine. Incapacitating agents include lysergic acid, mescaline and phencyclidine. Both types of agents are primarily used to incapacitate their victims and are unlikely to cause serious damage warranting ICU or immediate surgical intervention.

**Summary**

Until recently discussions regarding chemical, biological & nuclear warfare have been limited to the military & government intelligence communities. It was only when the realisation dawned that the use of such weapons would put a huge demand on national health care that the medical discipline was included.

Most chemical & biological weapons cause a large number of casualties in addition to deaths. Person to person transmission occurs through many ways, resulting in an exponential potentiation of their effects. These intangible, invisible threats leave us ill-equipped conceptually & practically to assess the nature & extent of the injury. This difficulty is worsened by the non-specific nature of associated symptoms.

It is only through a very high index of suspicion can these exotic agents be included as possible differentials. Only a sound knowledge of the nature & characteristics of these agents & the understanding of the pathophysiology of their effects will enable effective management. Anaesthetists will play a vital role because they have the necessary pharmacological & physiological background to understand the nature of injuries caused by these agents. They will be involved in both the initial resuscitation and the continued intensive care management of these patients.

Appropriate public healthcare strategies need to be put into place in order to manage such unusual catastrophes. The assumption that South Africa is unlikely to be affected is a naive & uninformed view! South Africa has also had its hand in such games, in our not so distant past. The release of such agents into an ignorant, unprepared, unprotected population will have disastrous outcomes!

**References**

8. www.howstuffworks.com