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PROTEINES À LA >UNE<

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# Ricin, a biological weapon. The intoxicating truth.

**Castor oil. Any childhood memories? Remember that disgusting spoonful of oil you had to swallow down at bedtime? Worse than poison, wasn't it? Actually, it is not so far from the truth since ricin – a by-product in the preparation of castor oil used as a laxative – is a toxic protein and one of the world's deadliest poisons. Indeed, castor oil is not only a childhood nightmare but could also become ours in the future since its toxin could be used as a weapon of mass destruction. Spotlight on a fearful protein.**

In January 2003, Scotland Yard announced that their anti-terrorist squad had arrested seven North Africans after discovering "traces" of a poison in a North London flat. The poison was ricin. Several castor oil plants (*Ricin communis*) were found along with the requisite equipment for extracting the deadly toxin, which suggested that a sizeable quantity had been processed before removing it elsewhere. This discovery arouses new fears of terrorist attacks in Great Britain and it is not the first of its kind. In November 2001, for instance, "Times" magazine reported that notes on how to produce the toxin had been found in a house in Kabul belonging to an Al-Quaida group. What are we to believe? Should we or should we not be scared of ricin?

### *From laxative to biological weapon*

*Ricinus communis* is a plant that comes from North-East Africa and the Middle East, and spread to India then China and finally to America in the l6th century. Its seeds are extremely viable and germinate easily in any soil so that the plant has adapted to tropical as well as sub-tropical regions all over the world. *Ricinus communis* is a shrub with long palmate leaves; its bean-like seeds are enclosed in spiky pods or capsules gathered in clusters. When ground, the seeds yield one of the finest oils in the world… but also a drastic laxative! Indeed, this was its main use for a very long time, although it was and still is being cultivated for many other reasons too. In Ancient Egypt, the oil was used in lamps – castor beans were found in tombs dating back to 4000 B.C. In the United States, in pioneering days and long after, castor oil became a universal cure for ailments such as constipation, heartburn and child labor. In the First and Second World Wars it was even used in the aircraft industry.



**Fig.1** *Ricinus communis*

Today, *Ricinus communis* is still largely cultivated for commercial purposes, essentially in the Southern States of America, although more gentle drugs are now used as a laxative. Not only is the plant ornamental, but castor oil and its derivatives are used in a number of ways: in industrial lubricants, soap, varnish, paint, nylon, moisturizing creams, in treatments against dermatitis, sunburn and open wounds, as hair tonics, ointments, cosmetics and even contraceptive gels…to mention but a few. So, in terms of production on an industrial scale, castor oil is one of the most important plant oils in the world.

With the permission of the Trustees of the Royal Botanic Gardens, Kew

**Fig.2** *Ricinus communis Seed*

In the Caribbeans, the colorful seeds are very popular in jewelry. Unfortunately, they are also very tempting for young children who have been poisoned by sucking or swallowing the beads made from the seeds. *Ricinus* contains a lethal toxin – ricin – the toxic properties of which have long attracted attention. Towards the end of World War I, the US were already contemplating the possibility of using ricin as a weapon under the code W. And, in collaboration with Britain, they developed a W bomb during World War II. The bomb, however, was never used. And when ricin is mentioned nowadays, it is for far more serious reasons than a passing bout of constipation…

***The Bulgarian Umbrella***

The most famous case of ricin-poisoning was that of a Bulgarian dissident's death in 1978. The murder of Georgi Markov's is worth the best of spy fiction. Markov was a journalist for the BBC and a fervent opponent to the Communist government in his country. As he stood in a queue one day, awaiting the bus which would take him to his office, he felt the end of an umbrella being pushed into the side of his leg. A seemingly harmless event. However, the owner of the umbrella was actually firing a ricin-loaded platinum pellet into Markov's thigh via the pointed end of the umbrella, though it was only understood some time later. He died within three days. Although ricin is very difficult to detect in the bloodstream, the murder was brought to light by the fact that the pellet containing the poison had not completely dissolved as intended. Both the Bulgarian secret services and the KGB were suspected of being behind this assassination. The affair has remained famous within the London police and is known as "The Bulgarian Umbrella".


**Fig.3** *The Bulgarian Umbrella*

Although most parts of *Ricinus communis* are more or less toxic, the seeds are by far the most dangerous, both for humans and animals. The toxic factor is mainly due to a protein discovered in l888 by a German chemist, Herman Stillmark, who named it ricin. Of course, pure castor oil does not contain ricin. However the residual mash – which remains once the seeds have been ground and the oil extracted – does and it can then easily be isolated. And if the oil is insufficiently refined, it can contain large amounts of ricin.

Though ricin is a thousand times less toxic than botulinum toxin, it still remains one of the most lethal natural poisons in the world. It is said that one or two seeds chewed by a child, or eight by an adult, can be fatal. Ricin is not volatile yet it is toxic if inhaled in spray form, but it is at its most dangerous when injected. What are the symptoms of ricin-poisoning? They vary according to the amount of poison used and how it penetrates the body. Inhalation of the poison, for instance, causes respiratory distress and lesions in the lungs; swallowing it causes gastro-intestinal hemorrhages and necrosis of the liver, spleen and kidneys. Either way causes general fatigue, fever, breathlessness and coughing, nausea and vomiting, violent abdominal pains and severe diarrhea. In both cases, these symptoms could be those of a natural illness - which makes ricin-poisoning very difficult to diagnose.

Since ricin-poisoning was relatively rare, no particular efforts had been made to find an ad hoc treatment or take preventive measures until the 90's, when ricin was recognized as a possible threat in biological warfare. Currently, research for a vaccine has been unsuccessful and since there is no antidote, only the symptoms can be treated…so there is little chance for a person to recover.

***An anti-protein protein!***

Ricin belongs to the family of A-B toxins which also includes anthrax toxins (cf Protéines à la "Une", Issue 3). It is a long chain of amino acids which is subsequently halved to form an A chain and a B chain. Despite this, the two chains remain connected. Not surprisingly really since separated they are quite harmless: A without B cannot penetrate a cell and B without A is non-toxic. All that is needed therefore is to break down the "bridge" linking these two chains (in green in the drawing) so as to neutralize the ricin's toxicity.

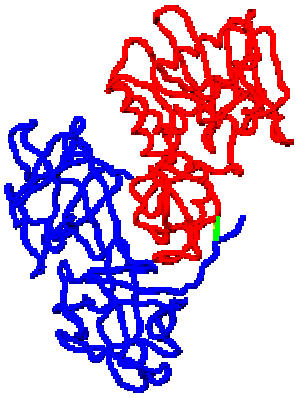

**Fig.4** *Ricin structure*

Chain B anchors the toxin to the cell surface by linking up with a sugar molecule, or galactose. Since the sugar itself is attached to a variety of proteins and lipids – also present in large numbers in the cell's membrane – there are thousands of "linking sites" for the ricin on the surface of an average-sized cell!

Chain A is the toxic one; once inside the cell, it blocks protein synthesis consequently causing cell death. To understand how this happens, let us take a quick look at how proteins are made. There are two requirements: a "recipe" and a "machine". The latter will read the instructions given in the recipe and then assemble the different parts of the protein. The recipe is brought by what is called an RNA messenger, i.e. a sort of "photocopy" of a fragment of DNA that contains the recipe for making a particular protein (the DNA fragment is also called a gene). The machine, called a ribosome, is itself made up of several proteins and every cell has millions of these ribosomes. Once a ribosome has assembled a new protein, according to the given recipe, the protein still has to submit to certain modifications – it is particularly important for it to be correctly folded so that it can fulfill its function, for instance. In order to go through these 'perfecting' stages, a protein is sent from one cell compartment to another.

Once the ricin toxin is anchored to the cell surface, a depression forms around it in the cell membrane. The toxin is subsequently trapped within a kind of pouch and engulfed into the cell cytoplasm. The pouch then detaches itself from the inner wall of the cell (cf. diagram). From this point, most of the ricin will then either be expelled once again from the cell or eliminated by it. Only a fraction of the toxins will follow the – reverse – route and end up where they were initially made, i.e. the ribosomes. Exactly how the toxins can follow the reverse route remains a mystery but it may be that they join the stream of ill-folded proteins that have been rejected and are sent back towards the ribosome to be eliminated.

Once it has reached a ribosome, the A chain - which is an enzyme - can modify the ribosome's chemical composition. As a result, the ribosome will neither function correctly nor produce new proteins. Consequently, a single A chain can inactivate 2000 ribosomes a minute! Which is faster than a cell can produce new proteins. So one single A chain is able to kill a cell!! Animal cells are the most sensitive to ricin, more so than plant cells. While bacteria are, on the whole, quite resistant.

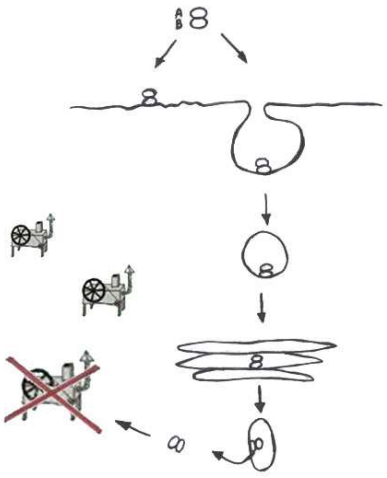

**Fig.5** *Ricin mechanism*

***From biological weapons to anti-cancer torpedoes***

Even though ricin is not the most deadly poison in the world, it has been tagged as a category B (average security risk) agent by the CDC (Center for Disease Control). It could be considered as a possible biological weapon since it is so easy to extract as a by-product in the preparation of castor oil and, what is more, it is extremely easy

to purchase. It follows that the two most likely methods of ricin-poisoning would be food-poisoning or sprays. However, in both cases, the number of victims would be relatively small unless substantial amounts were used. Given the relative difficulty in propagating ricin, it is not really suitable for use in massive destruction but it certainly remains a choice weapon for murder!

Another use for ricin has been developed in the past few years. Thanks to its toxicity, some of its properties can be used in the treatment of cancer. One of the most promising applications is the production of immunotoxins. Indeed ricin could be attached to tumor cell antibodies, which would enable the toxin to reach a patient's tumor directly and without interference. In this way, the ricin toxin would destroy the cancerous cells without damaging the patient's healthy cells. Such an immunotoxin would act as a true mini "torpedo" which could attack the metastasized cancerous cells or manage to penetrate inoperable solid tumors.

Once more, man has shown he is capable of the best and the worst. Only the future will tell whether ricin will owe its fame to biological warfare or treatment against cancer…

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***For further information***


- Olsnes S. et al., "Ricin", Toxicon. 39:1723-1728(2001) PMID: 11595634


**Internet:**

- Ricin Toxin (in English): http://www.nbc-med.org/SiteContent/HomePage /WhatsNew/MedAspects/Ch-32electrv699.pdf

***Illustrations:***

- Heading illustration, Source: Nova Scotia Museum (Canada): http://museum.gov.ns.ca/poison/fr/castor1.htm
- Fig.3, Source: Virtual Naval Hospital : http://www.vnh.org/MedAspChemBioWar/chapters/chapter_18.htm

***At UniProtKB/Swiss-Prot:***

- Ricin, Ricinus communis : P02879


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