Deadly toxin calms excited muscles

BOTULINUM toxin is possibly the most poisonous substance known. But it has a kinder, gentler side: in tiny doses, it can relieve several serious disorders of movement. Last month, a panel of experts convened by the National Institutes of Health (NIH) in Bethesda, Maryland, recommended that the toxin be used more widely for a class of disorders known as the dystonias. In these conditions, involuntary muscle contractions cause twisting, repetitive, sometimes painful, movements; or abnormal postures.

Botulinum toxin, or "botox" as scientists know it, is usually associated with food poisoning, not medical treatment. But, ironically, the same qualities that make botox highly poisonous and sometimes fatal also make it an effective therapy.

Ten years ago, an American ophthalmologist in San Francisco hit on the idea that the muscle paralysis induced by the toxin might help in cases where patients suffered from excessive muscular activity. Alan Scott of the Smith-Kettlewell Eye Research Institute in San Francisco thought of using the toxin for strabismus, or misalignment of the eyes. In this condition, a person’s eyes do not look in the same direction, and they are cross-eyed.

In the past decade, scientists have accumulated enough evidence to persuade the US Food and Drug Administration to approve injection of botox for strabismus, blepharospasm (forcible closure of the eyelids) and hemifacial spasm (muscle contractions on one side of the face). The NIH panel recommends that these uses be expanded to include other dystonias, which involve the neck, jaw, limbs, and vocal cords, as well as stuttering and rare, but quite troublesome, spastic closure of the anal or urinary sphincter. At present, the toxin is available from two sources: Smith-Kettlewell and the Centre for Applied Microbiological Research, Porton Down.

Botulinum toxin is a composite of two toxins—"inhibitory" and "neurotoxin"—together with an auxiliary protein, which acts as a stabilizer. When botulinum neurotoxin is ingested in spoiled food, the neurotoxin travels to the junctions of skeletal muscles and nerves, where it eventually blocks the release of the neurotransmitter acetylcholine, causing muscle weakness and, sometimes, paralysis.

According to Lance Simpson at the Jefferson Medical College in Philadelphia, Pennsylvania, no one knows exactly how the toxin reaches the acetylcholine receptor. However, researchers know that the neurotoxin consists of two linked chains of polypeptides, and that one chain binds to the muscle cell's plasma membrane while the other blocks the acetylcholine receptor.

If the chains are separated, says Simpson, toxicity is lost. This could be important for future manipulation of the toxin, says Simpson. For example, it may be possible to decouple the chains and attach a different kind of toxin or other drug to the binding chain, or change the binding site of the receptor-blocking chain.

For the time being, however, clinicians and researchers are happy with the neurotoxin as it is. Virtually everyone who has used the toxin in clinical trials reported their results at the NIH meeting, and the consensus was that when properly administered, the toxin is safe, effective, and, in some cases, the treatment of choice for surgery and drug therapy—particularly for focal dystonias, which affect only one or a few muscles in the body.

The response to localized injections of botox is far more reliable than that of other drugs such as anticholinergics and other neurotransmitter inhibitors. If a person is going to respond to botox, he usually does at the beginning of treatment, and continues to respond through repeated injections. Furthermore, botox is less drastic, less disfiguring, and less expensive than surgery (hundreds of dollars per botox treatment).

Of course, botox is not entirely problem-free. The panel stressed that the toxin is not a cure—nerves that the toxin blocks eventually sprout new terminals—so the blocking must be maintained through repeated injections. Although given in much smaller amounts than would be needed to produce botulism, it can still cause side effects, such as difficulty in swallowing, which result from excessive weakening of the target and surrounding muscles. However, the panel stated that such effects are relatively uncommon, usually transient, and often avoidable if clinicians are properly trained and muscle activity is accurately measured before treatment.

Furthermore, there is so far no report of any patient or handler of the toxin developing botulism or of the toxin adversely affecting patients with compromised immune systems. Indeed, the main problem with patients’ response is that some form antibodies to the toxin. Scientists speculate that such a reaction could be the result of too much toxin in too short a period, or perhaps a genetic predisposition to immunity.

-NIH Consensus Development Conference on Clinical Use of Botulinum Toxin, 12-14 November, 1990, Bethesda, Maryland.

Can monkeys read each other’s minds?

WE OFTEN try to imagine another person’s state of mind, so that we can modify our behaviour in the light of it. For instance, we often consider what other people’s moods are likely to be, the desires they might have, and we guess the things that they might or might not know. But do other primates have this ability?

Dorothy Cheney and Robert Seyfarth of the University of Pennsylvania attempted to test this in the laboratory, with two species of macaque (Animal Behaviour, vol 40, p 742). There is some evidence that chimpanzees are able to attribute “mental states” to each other, but for all other primates, including the macaques, the evidence up until now is anecdotal.

Cheney and Seyfarth placed females in cages from which they could see a test arena. They put down a plate of appealing food, or sent in a threatening human “predator”, who subsequently hid behind a screen.

In half of these trials, the researchers allowed a female’s offspring to stay with her so that they could also see what was happening in the arena. But in the rest of the tests, the offspring saw nothing of what went on.

Cheney and Seyfarth then released the young of all these mothers into the arena. Half of the infants had prior knowledge of what they would find, and half of them had not.

If the females could attribute mental states to their young, reasoned the zoologists, then the mothers of the “ignorant” young ought to make more of a show of alerting their infants, for example, either to the food, with soft, hooting “food calls”, or to the hidden “predator”. But Cheney and Seyfarth found no difference in the behaviour of any of the mothers.

Perhaps the mothers did, indeed, recognise a difference between ignorant and knowledgeable young, but they just did not act on it. However, Cheney and Seyfarth believe it is more likely that macaques cannot put themselves in another’s place, unlike humans.

They seem unable to understand that individuals can differ from themselves, and from other monkeys, in the beliefs that they have.

Georgia Mason

Macaque mothers: fail to warn offspring of danger