# Blasted with ennui

## *Dangers in another drug fashion*

Ecstasy has been much in the news in Britain during recent months. Such a statement does not imply an epidemic outbreak of transcendental joy among a phlegmatic people but rather the arrival of yet another drug of misuse—ecstasy. The pharmacological name for this substance is 3,4-methylenedioxyamphetamine (or MDMA). It is a "designer drug" with both psychomimetic and stimulant properties.[1]

As so often happens with British drug fashions, MDMA achieved earlier notoriety in America: in perhaps 1985 it was beginning to be encountered as a recreational drug on that side of the Atlantic, and in 1987 a survey suggested that two fifths of 369 Stanford undergraduates had used it at least once.[2] There was the usual phase of therapeutic enthusiasm for the drug,[3,4] and it was advocated as adjunct to psychotherapy—providing echoes of lysergide (LSD). Allegedly it helped people to get in touch with their feelings and form close relationships. It was then shown that the drug could induce dependence,[5] which was not surprising given the chemical kinship to methylamphetamine. Next came the news that a man aged 22 had taken the drug, climbed a pylon, and died from electrocution[6]—an incident that might be expected with a psychomimetic substance. Possibly MDMA may also cause cardiac arrhythmias, at least in susceptible people.[6]

There is a sense of tired sameness as yet another drug fashion emerges with the familiar cycle of complacency followed by alarm and probable exaggeration. It was Ophelia who used the phrase "blasted with ecstasy" in relation to Hamlet's sad overthrow of mind; with current drug fashions we are perhaps in danger of being blasted with ennui. But what is new about MDMA and its congeners is the evidence that they cause damage to nerve endings concerned with serotonergic transmission in a few animal species.[7-11] There is an almost biblical vengeance about this finding: the price of ecstasy shall be damage to the capacity to feel pleasure. We seem to be dealing with a subtle and nasty neurotoxin, and whether such changes are reversible in all circumstances is still open. There must be the usual provision about extrapolating from animals to man, and the dosage equivalence also deserves scrutiny—but the comforting deception that this is just an innocent Californian fun drug no longer carries conviction.

Drugs often acquire euphemistic labels: "crack" for cocaine base, "speed" for amphetamine, "angel dust" for the highly dangerous phencylidine hydrochloride, and whisky, usquebaugh, or the spirit of life for ethanol. We should resist complicity and refer to this particular drug only as MDMA rather than giving it the benefit of the further advertising that goes so perniciously with the popular soubriquet.

GRIFFITH EDWARDS

Professor of Addiction Behaviour,
Addiction Research Unit, Institute of Psychiatry,
London SE5 8AF

1 Glennon RA, Young R. A psychoactive agent with dual stimulus effects. *Life Sci* 1984;**34**:379-83.
2 Peroutra SJ. Incidence of recreational use of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") on an undergraduate campus. *N Engl J Med* 1987;**317**:1542-3.
3 Greer G, Strassman RJ. Information on "Ecstasy." *Am J Psychiatry* 1985;**142**:1391.
4 Greer G, Tolbert R. Subjective reports of the effects of MDMA in a clinical setting. *J Psychoactive Drugs* 1986;**18**:319-27.
5 Lamb RJ, Griffiths RR. Self-injection of d,l-3,4-methylenedioxymethamphetamine (MDMA) in the baboon. *Psychopharmacology* 1987;**91**:268-72.
6 Dowling GP, McDonough EG, Bost RO. "Eve" and "Ecstasy": a report of five deaths associated with the use of MDEA and MDMA. *JAMA* 1987;**257**:1615-7.
7 Ricaurte G, Bryan G, Strauss L, Seiden L, Schuster C. Hallucinogenic amphetamine selectively destroys brain nerve terminals. *Science* 1985;**229**:986-8.
8 Schmidt CJ, Wu L, Lovenberg W. Methylenedioxymethamphetamine: a potentially neurotoxic amphetamine analog. *Eur J Pharmacol* 1986;**124**:175-8.
9 Commins DL, Vosmer G, Virus RM, Woolverton WC, Schuster CR. Biochemical and histological evidence that methylenedioxymethamphetamine (MDMA) is toxic to neurons in the rat brain. *J Pharmacol Exp Ther* 1987;**241**:338-45.
10 Finnegan KT, Ricaurte GA, Ritchie LD. Orally administered MDMA causes a long-term depletion of serotonin in rat brain. *Brain Res* 1988;**447**:141-4.
11 Battaglia G, Yeh SY, De Souza B. MDMA-induced neurotoxicity: parameters of degeneration and recovery of brain serotonin neurons. *Pharmacol Biochem Behav* 1988;**29**:269-74.

# Botulinum toxin: a new ally of an old adversary

## *Minute doses useful for some muscle disorders*

Although toxins of *Clostridium botulinum* are among the most lethal known,[1] minute doses can be used in treating ocular-facial disorders. The toxin blocks the release of acetylcholine from motor neurones, inducing paralysis lasting about four months.[2] The toxin was originally developed for treating concomitant squint, the rationale being that injecting it into the overacting muscle would cause transient paralysis; the position of the eye would be altered and hence the eye muscles would change their length. When the treated muscle recovered its function after four months the strabismic eye could be straightened and the normal sensory fusion mechanisms would maintain this position.

Unfortunately injections often have to be repeated for concomitant strabismus and the treatment has been more successful in preventing the contracture of the antagonist muscles during recovery from paralytic strabismus.[3] Limited benefits have also been reported in the treatment of dysthyroid ocular myopathy[4,5] and infantile esotropia.[6] Botulinum toxin has also transformed the miserable prognosis of patients with essential blepharospasm,[7] hemifacial spasm,[8] and to a lesser extent Meige syndrome.[9] Although patients often require injections ever four to six months, these are a welcome alternative to the uncertainty of surgery to the facial nerve or the orbicularis muscle or to the side effects of drugs.

Ptosis is sometimes a complication of toxin injections, but it may act as a natural "bandage" to the eye and hence be useful in protecting the cornea from exposure. Ptosis may be induced by a direct injection of toxin into the levator palpebrae,[10] and similar treatment may improve the unsightly upper lid retraction of dysthyroid eye disease or entropion—in this case by injecting the orbicularis of the lower lid.[11] Side effects of the injection of botulinum toxin include paresis of other extraocular muscles, but this may be prevented or reversed by injecting antitoxin.[12]

Though this treatment has been successful mostly for the extraocular and finer facial muscles, larger muscles (such as

the sternomastoid in spasmodic torticollis) can also be injected.[13 14] Nevertheless, large doses are required for treating bulky muscles and may cause systemic side effects besides stimulating antibody production.[15] A further benefit has been for spastic dysphonia,[16] but less satisfactory results have been obtained with other small muscle groups such as in the hand and detrusor-sphincter abnormalities.[17]

ROGER C HUMPHRY

Senior Registrar,
Bristol Eye Hospital,
Bristol BS1 2LX

1 Scott AB. Botulinum toxin injection of eye muscles to correct strabismus. *Trans Am Ophthalmol Soc* 1981;**79**:734-70.
2 Melling J, Hambleton P, Shone CC. Clostridium botulinum toxins: nature and preparation for clinical use. *Eye* 1988;**2**:16-23.
3 Scott AB, Kraft SP. Botulinum toxin in the management of lateral rectus paresis. *Ophthalmology* 1985;**92**:676-83.
4 Scott AB. Injection treatment of endocrine orbital myopathy. *Doc Ophthalmol* 1984;**58**:141-5.
5 Dunn WJ, Arnold AC, O'Connor PS. Botulinum toxin for the treatment of dysthyroid ocular myopathy. *Ophthalmology* 1986;**93**:470-5.
6 Magoon E, Scott AB. Botulinum toxin denervation in infants and children: an alternative to incisional strabismus surgery. *J Pediatr* 1987;**110**:719-22.
7 Elston JS, Russell RWR. Effect of treatment with botulinum toxin on neurogenic blepharospasm. *Br Med J* 1985;**290**:1857-9.
8 Elston J. Toxin treatment of hemifacial spasm. *J Neurol Neurosurg Psychiatry* 1986;**49**:827-9.
9 Mauriello JA. Blepharospasm, Meige syndrome and hemifacial spasm: treatment with botulinum toxin. *Neurology* 1985;**35**:1499-500.
10 Kirkness CM, Adams GGW, Dilly PN, Lee JP. Botulinum toxin A induced protective ptosis in corneal disease. *Ophthalmology* 1988;**95**:473-80.
11 Clarke JR, Spalton DJ. Treatment of senile entropian with botulinum toxin. *Br J Ophthalmol* 1988;**72**:361-2.
12 Scott AB. Antitoxin reverses botulinum side effects. *Eye* 1988;**2**:29-32.
13 Tsui JK, Eisen A, Sroessl AJ, Calne S, Calne DB. Double blind trial of botulinum toxin in spasmodic torticollis. *Lancet* 1986;ii:245-6.
14 Stell R, Thompson PD, Marsden CD. Botulinum toxin in spasmodic torticollis. *J Neurol Neurosurg Psychiatry* 1988;**51**:920-3.
15 Brin MF, Fahn S, Moskowitz CB, *et al*. Local injections of botulinum toxins for the treatment of focal dystonia. *Neurology* 1986;**36**:120.
16 Blitzer A, Brin MF, Fahn S, Lange D, Lovelace RE. Botulinum toxin for the treatment of "spastic dysphonia" as a part of a trial of toxin injections for the treatment of other cranial disorders. *Laryngoscope* 1986;**96**:1300-1.
17 Cohen RA, Hallett M, Geller B, *et al*. Treatment of focal dystonias of the hand with botulinum toxin injection. *Neurology* 1987;**37**:123-4.

*Regular Review*

# Calcium supplementation of the diet—I

## *Not justified by present evidence*

O, reason not the need: our basest beggars
Are in the poorest things superfluous:
Allow not nature more than nature needs,
Man's life's as cheap as beast's.—*King Lear*

It is commonly believed that the amount of calcium in our diet is critically important and that many people are deficient in calcium because of an inadequate dietary intake.[1-6] From this arises the view that supplements of calcium confer benefits to the community. In 1986 about $166m was spent in the United States on calcium supplements,[7] and the cost could rise to $1·7 billion.[8] In Britain a statutory obligation on millers to add calcium to the flour used for making bread ensures that the whole population has a daily supplement.

The "calcium lobby" has been countered by those who hold that even low dietary intakes of calcium are sufficient to maintain the skeleton.[9-12] The growing awareness of the clinical and economic impact of osteoporosis in countries with increasing numbers of elderly people has led to arguments on whether to supplement the dietary calcium intake of both patients with osteoporosis and those at risk from osteoporosis in later life.

The arguments have been intense, and in this article and next week's we examine the way in which these diverging views arose and re-examine the evidence. It shows how theoretical dogma may persist long after empirical observations have shown it to be unsound, a lesson taught to medical students by William Cullen 200 years ago.[13]

### History of calcium nutrition

Present concepts of the importance of calcium in the diet are a product of our heritage, and so it is instructive to examine the conclusions of the past and the manner in which they arose. Influential American textbooks of nutrition published at the beginning of this century encouraged the idea that calcium deficiency was common. Lusk's *The Science of Nutrition* stated that the ordinary American diet in respect of calcium presented "a sorry spectacle": its calcium content was only 700 mg/3000 kcal, one quarter of the amount consumed by Finns.[14] The Finnish figure came from a paper by Tigerstedt, a well known physiologist.[15] He had recorded diets in a rural area where the average daily milk consumption was 1570 ml among men and 913 ml among women. Lusk gave no evidence that the Americans were disadvantaged because they drank less milk. Biblical tradition would, however, have informed him and his readers that milk was a desirable food (Exodus iii.8).

In six editions published between 1920 and 1950 Sherman's *Chemistry of Food and Nutrition* contained the statement that "the ordinary mixed diet of Americans and Europeans, at least among dwellers in cities and towns, was often more deficient in calcium than in any other chemical element."[16] This conclusion was based on a review of 97 measurements of calcium balance in healthy adult men and women.[17] The apparent daily calcium requirement of young men was 450 mg and ranged from 270 mg to 829 mg (mean 450 mg/70 kg body weight). An analysis of the diets of 225 typical Americans showed that one in six contained less than the indicated requirements of calcium.

It is instructive to examine the major assumptions from which these figures were derived. Firstly, the requirement was calculated as the sum of the calcium balance and the dietary intake after abrupt changes (generally a decrease) in diet over three to eight day periods. It was assumed therefore that in subjects with a negative balance the addition of the apparent requirement of calcium to the diet would restore the balance. This implies that intestinal absorption of the extra calcium would have been 100%—a notion now known to be erroneous. This fallacy is illustrated in the apparent relation between dietary intake and "requirements" for calcium calculated in this way (fig 1)—the higher the calcium intake the greater the apparent requirement, a view that even the calcium protagonists might not consider reasonable.

Secondly, the balance technique used relied on analysis of food and faeces and overestimated retention.[20] Thirdly, it was assumed that a decrease in calcium balance resulting from a decrease in dietary intake would be perpetuated indefinitely,