

are that renal disease also activates the renin-angiotensin system, sympathetic drive is high, and the glomeruli overgrow and fibrose, resembling the terminally failing heart. Thus the next round of renal trials may need, besides an ACE inhibitor or ARB and very large numbers, new modifications to lessen mortality. Speculations could include spironolactone to further decrease proteinuria¹⁹ and to lessen fibrosis, with β -blockers to dampen excess sympathetic stimulation. But instead of mounting giant and expensive trials to achieve the elusive reduction in mortality, the practical ideal in diabetic nephropathy could become early intervention, even before there is overt hypertension⁵ or proteinuria.¹²

I have given talks for Servier and for Aventis, which market an ACE inhibitor, and acted on an advisory board of Merck, which markets losartan. I am on the steering committee of the Val-Heft trial, which is testing valsartan in heart failure.

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Assessing long-term effects of MDMA (Ecstasy)

See page 1864

The synthetic psychostimulant 3,4-methylenedioxy-methamphetamine (MDMA, "Ecstasy") has a structural resemblance not only to amphetamine, but also to the hallucinogen, mescaline. These similarities, at least in part, probably account for its unique blend of psychomotor stimulation and mild psychedelic action.¹ Despite the rapidly increasing recreational use of MDMA, both in the USA² and western Europe,³ little is known about its pharmacology, although most experts suspect that, like other amphetamine derivatives, MDMA acts indirectly, primarily by stimulating the release of monoamines, such as dopamine and serotonin.⁴ The intriguing possibility that MDMA may have a novel mechanism of action, however, should not be overlooked.

Although much remains to be learned about the pharmacology of MDMA, a great deal is now known about its toxicology, largely because detailed studies in animals have shown that MDMA is a potent serotonin neurotoxin.^{4,5} There are also reports that MDMA produces serotonin neurotoxic effects in human beings.^{6–10} The report by Liesbeth Reneman and colleagues in this issue of *The Lancet* raises the interesting possibility that there may be differences between men and women in the long-term effects of MDMA on serotonin neurons, an issue that has not been explored in animals. In particular, on the basis of findings obtained with single-photon-emission computed tomographic (SPECT) imaging and the radioligand ¹²³Iodine-2 β -carbomethoxy-3 β -(4-iodophenyl)tropane ([¹²³I] β -CIT), which binds to serotonin and dopamine transporters, the researchers conclude that women may be more susceptible than men to MDMA-induced serotonin neural injury. This conclusion is intriguing but must be viewed with caution because if people who meet criteria for major depression are excluded from their analyses (a reasonable approach given the role of serotonin in depression) then there are only four women in two of the MDMA groups and only six women in the control group.

Reneman and colleagues also infer that MDMA-induced neurotoxicity is partly reversible in most regions of the brain. If true, these findings are important for understanding the neurotoxicology of MDMA and for public health. However, some technical issues need to be considered. First, whether SPECT imaging with [¹²³I] β -CIT is sensitive enough to measure the density of serotonin transporters in areas of the cerebral cortex is controversial.^{12,13} Second, the low signal-to-noise ratio (less than 1.5 to 1) with SPECT and [¹²³I] β -CIT, even in

regions with high density of serotonin transporters, compounds the difficulty of ascertaining the sensitivity of this method. Third, the cerebellum was used as a reference region, but it contains serotonin-transporter-bearing axons¹⁴ that are sensitive to MDMA neurotoxicity. Therefore, estimates of regional brain densities of serotonin transporters based on the cerebellum as a reference could be highly unstable. Given these methodological uncertainties, it would be premature to conclude that the long-term effects of MDMA in human beings are “reversible”.

The researchers based their conclusion on reversibility on the finding on the finding that ex-MDMA users have higher densities of serotonin transporters than do heavy users. Studies in non-human primates have shown that, over time, there is regrowth of ascending serotonin axonal projections after MDMA-induced injury but that a normal innervation pattern is not restored.¹⁴ In some regions of the basal forebrain, such as the lateral hypothalamus, density of serotonin axons becomes greater than normal,¹⁴ yet in other regions, such as the dorsal neocortex, density of serotonin axons remains significantly reduced for up to 7 years after MDMA exposure.¹⁵ Thus, use of the term “reversibility” could easily be misinterpreted since serotonin innervation in the brain may have been changed irreversibly.

Although the study is timely and potentially important, the small sample size and methodological questions limit confidence in the conclusions about differences between sexes or possibility of reversibility of the effects of MDMA in human beings. Studies in larger cohorts of both sexes, free of psychiatric illnesses in which serotonin is implicated, are needed.

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Use of food-challenge tests in children

See page 1871

Food allergies are an increasing problem in westernised countries. About 7% of children less than 3 years of age will have experienced an allergic reaction to a particular food and 2-2.5% of the general population are thought to have an allergy to at least one food.¹ Surveys suggest that up to a third of households have altered their eating habits in the belief that at least one family member is allergic to a food.² In the past, the diagnosis of food allergy was based on the patient's history and the finding of a positive skin-prick test or specific IgE measured by radioallergosorbent test (RAST). Although Loveless noted the poor diagnostic predictability of this approach over 50 years ago,³ use of a blinded food-challenge procedure, the double-blind placebo-controlled food challenge (DBPCFC), was not introduced until the mid-1970s.⁴ In his initial study of DBPCFCs, May emphasised the poor correlation between results of skin tests, which simply indicate the presence of food-specific IgE antibodies on cutaneous mast cells, and the development of symptoms after the ingestion of a food. Subsequent studies have confirmed the poor correlation between the history from the patient, results from skin-prick tests or standard RAST, and the outcome of DBPCFCs, with concordance rates in the range of only 30-40%.⁵ Recently, a threshold value of serum IgE antibodies for certain foods was shown to identify children at high risk of immediate hypersensitivity reactions.⁶ However, for the past 15 years the DBPCFC has been the "gold standard" for diagnosing allergic reactions to a food.^{7,8}

Although many conferences have been held to establish a standardised format for a DBPCFC, no universally accepted standardised protocol has been agreed upon. In a DBPCFC a person is given increasing quantities of the suspected food allergen or placebo, either in opaque capsules or camouflaged in a liquid or semisolid vehicle, over 1.5-2 h. Several steps have been suggested to optimise the outcome of the challenge:⁹ elimination of the suspected food from the patient's diet for at least 7-14 days, withdrawal of potentially interfering medications (eg, antihistamines), control of symptoms of chronic allergic disease, such as atopic dermatitis or asthma, administration of the challenge in a fasting state, use of fresh or dehydrated foods, and use of challenge vehicles that do not contain fat, which can interfere with protein absorption.¹⁰ The absence of an allergic reaction after ingesting up to an equivalent of 10 g of the dehydrated food essentially rules out a food allergy in that such a result has a high negative-predictive value. Nevertheless, May and others have stressed the need to follow a negative challenge with open feeding of the suspected food prepared in a standard fashion and served in normal meal-size quantities under medical supervision to exclude a false-negative result.^{4,7,10,11} As with any diagnostic test in