sleepless nights, and the evidence indicates that these drugs would therefore help the restoration of the tissues during sleep.[21]

At the United States Army Institute for Surgical Research Wilmore and his colleagues, having reviewed the mechanisms and effects of surgical stress, concluded that adequate rest periods for uninterrupted sleep should be provided and the duration of sleep always recorded.[22] It remains an obligation on all who work in hospitals to reduce noise, to relieve patients' anxieties, and help them to sleep.

KIRSTINE ADAM
Research fellow

IAN OSWALD
Professor of psychiatry

University Department of Psychiatry,
Royal Edinburgh Hospital,
Edinburgh EH10 5HF

1 Minerva. Views. *Br Med J* 1984;**288**:1012.
2 Brandt R, Fernandes A, Mordhorst R, Kehlet H. Epidural analgesia improves postoperative nitrogen balance. *Br Med J* 1978;i:1106-8.
3 Elia M, Carter A, Bacon S, Winearls CG, Smith R. Clinical usefulness of urinary 3-methylhistidine excretion in indicating muscle protein breakdown. *Br Med J* 1981;**282**:351-4.
4 Long CL, Birkhahn RH, Geiger JW, Betts JE, Schiller WR, Blakemore W. Urinary excretion of 3-methylhistidine: an assessment of muscle protein catabolism in adult normal subjects and during malnutrition, sepsis and skeletal trauma. *Metabolism* 1981;**30**:765-76.
5 Weitzman ED, Zimmerman JC, Czeisler CA, Ronda J. Cortisol secretion is inhibited during sleep in normal man. *J Clin Endocrinol Metab* 1983;**56**:352-8.
6 Townshend MM, Smith AJ. Factors influencing the urinary excretion of free catecholamines in man. *Clin Sci* 1973;**44**:253-65.
7 Åkerstedt T, Fröberg JE. Sleep and stressor exposure in relation to circadian rhythms in catecholamine excretion. *Biol Psychol* 1979;**8**:69-80.
8 Sassin JF, Parker DC, Mace JW, Gotlin RW, Johnson LC, Rossman LG. Human growth hormone release: relation to slow-wave sleep and sleep-waking cycles. *Science* 1969;**165**:513-5.
9 Isaksson OGP, Jansson J-O, Gause IAM. Growth hormone stimulates longitudinal bone growth directly. *Science* 1982;**216**:1237-9.
10 Golde DW, Bersch N, Li CH. Growth hormone: species-specific stimulation of erythropoiesis in vitro. *Science* 1976;**196**:1112-3.
11 Wilmore DW, Moylan JA, Bristow BF, Mason AD, Pruitt BA. Anabolic effects of human growth hormone and high calorie feedings following thermal injury. *Surg Gynecol Obstet* 1974;**138**:875-84.
12 Adam K, Oswald I. Protein synthesis, bodily renewal and the sleep-wake cycle. *Clin Sci* 1983;**65**:561-7.
13 Gololobova MT. 24-hour rhythm of cell multiplication in rat epidermis during healing of skin wounds. *Biull Eksp Biol Med* 1960;**50**:118-22.
14 Saetren H. Diurnal variation of the first mitotic wave released among rat kidney tubule cells by partial nephrectomy. *Acta Pathol Microbiol Scand* [*A*] 1972;**80**:737-42.
15 Simmons DJ, Cohen M. Postfracture linear bone growth in rats: a diurnal rhythm. *Clin Orthop* 1980;**149**:240-8.
16 Bullough WS, Laurence EB. Accelerating and decelerating actions of adrenalin in epidermal mitotic activity. *Nature* 1966;**210**:715-6.
17 Fisker AV, Østergaard E, Karring T. The effect of environmental stress stimuli on cell division in rat palatal epithelium. *Cell Tissue Kinetics* 1982;**15**:661-6.
18 Scrimshaw NS, Habicht JP, Pellet P, Piche ML, Cholakos B. Effects of sleep deprivation and reversal of diurnal activity on protein metabolism of young men. *Am J Clin Nutr* 1966;**19**:313-9.
19 Kant GJ, Genser SG, Thorne DR, Pfalser JL, Mougey EH. Effects of 72 hour sleep deprivation on urinary cortisol and indices of metabolism. *Sleep* 1984;**7**:142-6.
20 Rechtschaffen A, Gilliland MA, Bergmann BM, Winter JB. Physiological correlates of prolonged sleep deprivation in rats. *Science* 1982;**221**:182-4.
21 Adam K. Do drugs alter the restorative value of sleep? In: Passouant P, Oswald I, eds. *Pharmacology of the states of alertness*. Oxford: Pergamon Press, 1979:105-11.
22 Wilmore DW, Long JM, Mason AD, Pruitt BA. Stress in surgical patients as a neurophysiological reflex response. *Surg Gynecol Obstet* 1976;**142**:257-69.

# MPTP parkinsonism

Our understanding of Parkinson's disease has progressed very substantially since its first description in 1817. The latest advance is the discovery that low doses of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) selectively destroy pigmented dopaminergic neurones in both man and monkeys and so may mimic the physical and biochemical signs of Parkinson's disease, including its response to levodopa.

In 1976 a 23 year old American addict manufacturing his own pethidine analogue took a synthetic shortcut and injected himself daily with what was later with his help proved to be two closely related byproducts; one was MPTP.[1] On the third day he developed a pure and severe parkinsonian syndrome which responded dramatically to levodopa but persisted (with some spontaneous improvement) until his suicide 18 months later. Results of biochemical studies on his cerebrospinal fluid were consistent with severe disruption of dopamine metabolism, and his brain showed destruction solely within the substantia nigra.

Last year a cluster of identical cases was reported from California of patients who had injected the same substance sold to them as "synthetic heroin."[2] These patients, also young and severely affected, showed no spontaneous improvement. Their symptoms responded well to levodopa, but some soon developed a fluctuating response and hallucinations. That these complications developed so early supports the view that when seen in idiopathic disease they are due to the severity of the disease rather than to any long term toxicity of levodopa.[3] About 100 other persons exposed at around the same dosage were clinically unaffected, perhaps indicating some individual susceptibility factor. Their follow up may answer the question whether Parkinson's disease is caused by a persistently active agent or whether a fixed insult may become clinically manifest later by superimposed aging.[4] The drug abusing community was informed with commendable speed, bringing this epidemic to an end. Subsequently one further probable case has occurred in a 37 year old chemist exposed while doing laboratory work—a warning to others handling this compound.[5]

As soon as the episode became known attempts were made to reproduce the syndrome in animals. This proved easy: low doses of MPTP given to primates produced striking clinical, pathological, and biochemical changes.[6,7] Other species seem resistant, however—though with much higher doses—biochemical evidence of dopaminergic dysfunction occurs in mice.[8] Pathological studies in primates show fewer abnormalities outside the substantia nigra than is usual in Parkinson's disease and Lewy inclusion bodies, long held to be fundamental to idiopathic parkinsonism, are absent. These abnormalities, however, may yet prove to develop in animals kept alive longer. The only human brain examined showed one possible inclusion body.[1] Dopamine cells elsewhere in the brain are not affected.

Analysis of the mechanism of action of the toxin should provide further insights. Already, selegiline, a monoamine oxidase inhibitor concerned with dopamine breakdown, has been found to prevent toxicity, possibly indicating that an oxidation metabolite produces the damage.[8,8a] Another interesting question is whether nicotine reduces toxicity, for smoking is suspected of reducing the incidence of Parkinson's disease. The reason pigmented dopamine cells are susceptible may be linked with the high affinity of MPTP for melanin.[9] Also their high concentration of metal ion might stimulate free radical production during the oxidation of MPTP and dopamine[10,11]; and relatively poor inherent or acquired antioxidant capabilities—for instance, the amount of available glutathione peroxidase—then exaggerate these effects. An inability to cope with unpleasant oxygen species has been advanced as a factor in parkinsonism[12] and in the action of other dopamine cell toxins such as manganese and 6-hydroxydopamine.[13,14] This hypothesis is worth pursuing, as the generation of these products is potentially containable by antioxidants.

The strong evidence against any important genetic element in the aetiology of parkinsonism argues an environmental cause. Postencephalitic Parkinson's disease is so different from the idiopathic form that a toxin is at least as attractive a proposition as another virus. Such a toxin would be ubiquitous, given the lack of any known geographical or occupational factor, and might be modern. Other culprits

might emerge; but MPTP is a simple molecule consisting of a benzene and a piperidine ring, both of which exist separately in many compounds in plants, animals, and man. For example, some tryptamine metabolites look remarkably close to MPTP. Conceivably, therefore, an environmental source may exist for MPTP or an acquired metabolic defect may produce it or its toxic metabolite in vivo.

The phenomenon of MPTP toxicity has opened up many new testable approaches likely to help us understand parkinsonism and given pharmacologists a superior animal model for searching for better dopaminergic agents and—more important—novel approaches to prevent or slow progression of the disease. Lessons are also apparent for other diseases in which neuronal systems selectively disintegrate.

ADRIAN WILLIAMS

Consultant Neurologist,
Queen Elizabeth Hospital,
Birmingham B15 2TH

1 Davis GC, Williams AC, Markey SP, *et al.* Chronic parkinsonism secondary to intravenous injection of meperidine analogues. *Psychiatry Res* 1979;1:249-54.
2 Langston JW, Ballard P, Tetrud JW, Irwin I. Chronic parkinsonism in humans due to a product of meperidine-analog synthesis. *Science* 1983;**219**:970-80.
3 Langston JW, Ballard P. Parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP): implications for treatment and the pathogenesis of Parkinson's disease. *Can J Neurol Sci* 1984;**11**:160-5.
4 Calne DB, Langston JW. Aetiology of Parkinson's disease. *Lancet* 1983;ii:1457-9.
5 Langston JW, Ballard PA. Parkinson's disease in a chemist working with 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine. *N Engl J Med* 1983;**309**:310.
6 Burns RS, Chiueh CC, Markey SP, Ebert MH, Jacobowitz DM, Kopin IJ. A primate model of parkinsonism: selective destruction of dopaminergic neurons in the pars compacta of the substantia nigra by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *Proc Natl Acad Sci USA* 1983;**80**:4546-50.
7 Langston JW, Forno LS, Rebert CS, Irwin I. Selective nigral toxicity after systemic administration of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) in the squirrel monkey. *Brain Res* 1984;**292**:390-4.
8 Heikkila RE, Manzino L, Cabbat FS, Duvoisin RC. Protection against the dopaminergic neurotoxicity of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine by monoamine oxidase inhibitors. *Nature* 1984;**311**:467-9.
8a Markey SP, Johannessen JN, Chiueh CC, Burns RS, Herkenham MA. Intraneuronal generation of a pyridinium metabolite may cause drug-induced parkinsonism. *Nature* 1984;**311**:464-7.
9 Lyden A, Bondesson U, Larsson BS, Lindquist NG. Melanin affinity of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine, an inducer of chronic parkinsonism in humans. *Acta Pharmacol Toxicol (Copenh)* 1983;**534**:29-32.
10 Burns RS, Markey SP, Phillips JM, Chiueh CC. The neurotoxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in the monkey and man. *Can J Neurol Sci* 1984;**11**:166-8.
11 Bannon MJ, Goedet M, Williams B. The possible relation of glutathione melanin and 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (TP) to Parkinson's disease. *Biochem Pharmacol* 1984; **33**:2697-8.
12 Ambani LM, Van Woert MH, Murphy S. Brain peroxidase and catalase in Parkinson's disease. *Arch Neurol* 1975; **32**:114-8.
13 Donaldson J, McGregor D, La Bella F. Manganese neurotoxicity: a model for free radical mediated neurodegeneration. *Can J Physiol Pharmacol* 1982;**60**:1309-405.
14 Heikkila RE, Cohen G. Inhibition of biogenic amine uptake by hydrogen peroxide: a mechanism for toxic effect of 6-hydroxydopamine. *Science* 1971;**172**:1257-8.

# *Regular Review*

# Scandinavian model for eliminating measles, mumps, and rubella

ERIK RABO, JOHN TARANGER

Both the individual and society should be protected against measles, mumps, and rubella. Measles is often troublesome for the child and the family, but the main reason for vaccinating against it is the rare but sometimes severe encephalitis. Mumps often causes meningitis and encephalitis and sometimes orchitis and one sided deafness. Rubella is a mild disease but has teratogenic effects.

In a community in which no one has been vaccinated the number of individuals susceptible to a disease increases between outbreaks, and an epidemic starts when enough of them have accumulated. When the epidemic finishes some susceptible people will still remain.

In industrialised countries almost all adults have antibodies against measles, but at the end of an epidemic about one third of children aged under 15 are not immune. In the prevaccination community about a tenth of adults lack antibodies against mumps and about a seventh lack antibodies against rubella. Thus the number of people susceptible to these diseases will be much higher than the number susceptible to measles. For Sweden we have calculated (fig 1) that the number of children and adults without immunity to mumps will never be less than 10 year groups and against rubella 15 year groups—where a year group is the number of people born in one year.

If vaccination manages to reduce the number of susceptible individuals below the minimum number found in the prevaccination community no epidemic will occur and the circulation of the virus may stop. In the short term this is easily accomplished with a one dose programme and a high frequency of vaccination.

In the long term, however, even if one dose vaccination gives lifelong immunity such a programme will build up a susceptible population in older age groups. All individuals will not be vaccinated and all those vaccinated will not become immune. The accumulation of susceptible adults is undesirable—obviously in the case of rubella, since the only

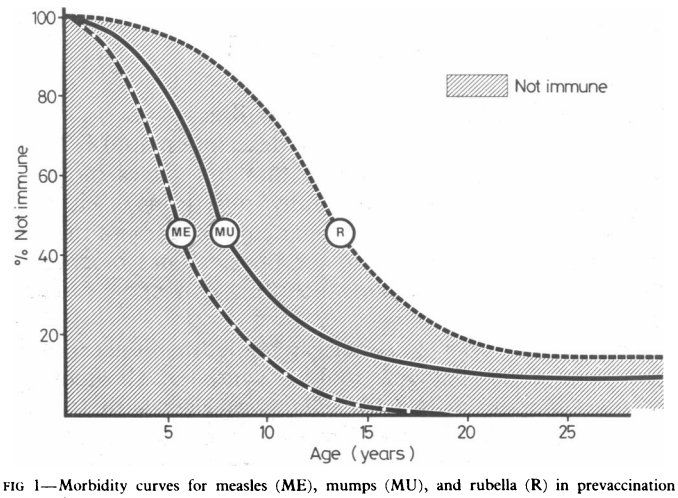


FIG 1—Morbidity curves for measles (ME), mumps (MU), and rubella (R) in prevaccination community.