Letters to the Editor

Levodopa withdrawal and the neuroleptic malignant syndrome

Sir,

In the paper: 'Levodopa withdrawal syndrome identical to neuroleptic-malignant syndrome' (Gibb & Griffith, 1986) the authors suggested that sudden withdrawal of dopaminergic drugs precipitated the development of neuroleptic-malignant syndrome (NMS) in their patient. However, it is difficult to reconcile the wide range of this patient's symptomatology with derangements of striatal and hypothalamic dopaminergic activity alone. We suggest that the factor operating in the patho-physiology of the NMS is based on hypothalamic endorphinergic dysregulation (Sandyk & Iacono, 1986).

In that the hypothalamus: (1) controls autonomic functions, level of consciousness and motor activity (Clar, 1985; Ranson, 1939) and (2) is known to show early, selective degeneration in Parkinson's disease (Langston & Forno, 1978) and (3) cerebrospinal fluid beta-endorphin levels are reported to be reduced in both aging and Parkinson's disease (PD) (Nappi *et al.*, 1985), and (4) L-dopa administration also reduced hypothalamic beta-endorphin content (Locatelli *et al.*, 1983) and (5) the activity of the hypothalamus is partially under endorphinergic control (Gambert *et al.*, 1980), then withdrawal of Sinemet in this patient would conceivably result in excessive opioid activity in an already compromised hypothalamus. In addition, increase in the activity of the intrinsic opioids would lead to inhibition of the locus coeruleus (LC) noradrenergic activity, possibly resulting in alterations of cerebral blood flow (CBF) and level of consciousness (Strahlendorf *et al.*, 1980; Demenet, 1976). Furthermore, intracerebro-ventricular administration of beta-endorphins has been reported to produce rigidity and catalepsy in rats (Sandyk, 1985), and a similar mechanism could have operated in the patient reported by Gibb and Griffith. Thus, a sudden excess of endorphinergic activity within the hypothalamus, analogous to that which is seen in septic shock rather than primary derangements of the dopaminergic system, may have been the central factor in the precipitation of NMS described in the patient reported. Given that this patient succumbed and mortality in NMS approaches 25% (Friedman *et al.*, 1985) then in the future a therapeutic trial of naloxone based on our explanation may be warranted.

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This letter has been shown to Dr Gibb who replies:-

Sir,

The possibility that derangement of beta-endorphin levels in the hypothalamus may be responsible for the neuroleptic-malignant syndrome (NMS) is interesting, if improbable. But the suggestions made are constructive. I am not aware however that hypothalamic beta-endorphins have been shown to mediate hyperthermia. As suggested by the authors a trial of naloxone is warranted, but the success of naloxone would not confirm their hypothesis that endorphins play a *primary* role in the genesis of NMS. The problem about NMS is that an hypothesis implicating the hypothalamus is entirely speculative. Contrary to the

view expressed by the authors I believe it is possible to explain clinical features of NMS without implicating the hypothalamus. The hypothalamus was originally suggested as a contributory cause of the hyperthermia, peripheral heat production being important too. This argument was supported by suggesting that other signs such as sweating, tachycardia, hypotension and altered consciousness (signs of 'disturbed autonomic function') were also of hypothalamic origin. However the severity of illness in these cases is sufficient to explain most features described in the literature, other than the muscular rigidity, akinesia and hyperthermia. The hypothesis suggested here depends on the assumption that hypothalamic disturbance plays a primary role in NMS. If endorphins are involved it may not be correct to assume that the hypothalamus is affected.

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Spontaneous rupture of the bladder in a patient with cor pulmonale presenting as acute abdominal emergency

Sir,

Spontaneous rupture of the bladder is usually associated with malignant disease, schistosomiasis (Jenkinson 1981; Powell *et al.*, 1983) and anatomical abnormalities (Cumes & Kessler, 1979). Acute spontaneous rupture of the bladder in the absence of these abnormalities and urinary retention has not been reported previously. The following case report describes its occurrence in a very common medical condition.

A 60 year old Chinese male with cor pulmonale on salbutamol, theophylline, frusemide, slow-K and low dose prednisone regularly was admitted in respiratory failure. He also complained of frequency and nocturia for 4 years. He was given intravenous aminophylline, antibiotics and chest physiotherapy. Rectal examination showed a moderately enlarged prostate. The daily

urine output varied between 2 to 3 litres, as did the intake.

He complained of sudden severe lower abdominal pain on the seventh day of admission, accompanied by signs of peritonitis. Bladder catheterization yielded 1.5 litres of blood-stained urine. At laparotomy 2 litres of urine was present in the peritoneal cavity, and a 3.5 cm tear was seen at the dome of the bladder. An intravenous urogram was normal. Cystoscopy showed a moderately enlarged prostate, with trabeculated bladder mucosa. A biopsy of the latter showed nonspecific chronic cystitis, and a biopsy of the prostate showed benign nodular hyperplasia.

Spontaneous rupture of the bladder in this patient was totally unexpected in the absence of any obvious urinary retention. Perhaps the combination of aminophylline in relaxing the bladder smooth muscle, a reduced elasticity due to nonspecific chronic cystitis, and raised intra-abdominal pressure in chronic obstructive airways disease all contributed to rupture of a bladder which would normally cope with the diuresis even in the presence of moderate prostatic hypertrophy.

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