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THE POISON PEN

The Nature of Hyperthermia in Neuroleptic Malignant Syndrome and the Use of Bromocriptine

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The interesting and valuable case report of Morris et al. [1] invites further observations and speculations about this still mysterious syndrome: we do not know if NMS involves an abnormal degree of heat generation (and if so from where), or if there is a failure of heat dissipation. It is not even clear that NMS is a primarily hyperthermic/hypermetabolic syndrome, although psychiatrists certainly seem to think it is. Many reviews assume that, without discussion, or the presentation of direct evidence. This report supports the idea it may not be.

The term hyperthermia is not usually precisely defined: elevated temperature is not injurious until it reaches ~39.5–40°C, and the physiological range extends up to 39°C during normal activities [2]. Most patients with diagnosed 'NMS' do not develop a temperature exceeding 39°C even with only conservative treatment [3, 4]. Therefore, NMS is a misleading term: it is hardly justified to call the syndrome malignant (and it is clearly much less malignant than MH by an order of magnitude), it occurs frequently without dopamine antagonist drugs of any sort [5], and it is often not, by any meaningful definition, hyperthermic.

This report is especially interesting because it documents the deterioration of the mental and neurological state in the absence of significant hyperthermia (maximum 39°C), and it shows how changes unrelated to hyperthermia become life-threatening early in the development of the syndrome. If only we knew if this particular patient's brain temperature was 39°C, or more, or less?

The usefulness of bromocriptine is unclear, and in this case seemingly of no benefit, despite early initiation. Bromocriptine is not only a dopamine agonist but also a serotonin 5-HT2A agonist [6]. This property promotes hyperthermia because 5-HT2A receptor activation mediates hyperthermia in serotonin toxicity and worsens the outcome in other models of hyperthermia like MH and heatstroke [7]: conversely, 2A antagonism improves such states. A DA agonist that is also a 5-HT2A *antagonist*, like apomorphine [8], may be preferable, the theoretical rationale being that D2 agonism promotes heat loss [9], and this has been reported as an efficacious strategy in the NMS-like condition Parkinsonism–hyperpyrexia syndrome [10].

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