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Review

Neuroleptic Malignant Syndrome: Mechanisms, Interactions, and Causality

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Abstract: This review focuses on new data from recent publications concerning how compounding interactions between different thermoregulatory pathways influence the development of hyperthermia and/or neuroleptic malignant syndrome (NMS), and the fundamental issue of the presumed causal role of antipsychotic drugs. The formal criteria for substantiating cause-effect relationships in medical science, established by Hill, are applied to NMS and, for comparison, also to malignant hyperthermia and serotonin toxicity. The risk of morbidities related to hyperthermia is reviewed from human and experimental data: temperatures in excess of 39.5°C cause physiological and cellular dysfunction and high mortality. The most temperature-sensitive elements of neural cells are mitochondrial and plasma membranes, in which irreversible changes occur around 40°C. Temperatures of up to 39°C are "normal" in mammals, so, the term hyperthermia should be reserved for temperatures of 39.5°C or greater. The implicitly accepted presumption that NMS is a hypermetabolic and hyperthermic syndrome is questionable and does not explain the extensive morbidity in the majority of cases, where the temperature is less than 39°C. The thermoregulatory effects of dopamine and acetylcholine are outlined, especially because they are probably the main pathways by which neuroleptic drugs might affect thermoregulation. It is notable that even potent antagonism of these mechanisms rarely causes temperature elevation and that multiple mechanisms, including the acute phase response, stress-induced hyperthermia, drugs effects, etc., involving compounding interactions, are required to precipitate hyperthermia. The application of the Hill criteria clearly supports causality for drugs inducing both MH and ST but do not support causality for NMS. © 2010 Movement Disorder Society

Key words: neuroleptic malignant syndrome; neuroleptics; hyperthermia; morbidity; causality

This article considers advances in the understanding of thermoregulatory mechanisms that might be relevant to neuroleptic malignant syndrome (NMS) and, especially, of how compounding interactions between different thermoregulatory control mechanisms play a role in precipitating hyperthermia. Evidence is reviewed suggesting the causal relationship with neuroleptics and the hyperthermic nature of NMS are not as securely founded as is usually assumed. These ideas are explored by applying the Hill criteria of causality and criteria for "hyperthermia" are suggested. It is not a general review of NMS. NMS has a 50-year history, Delay et al.[1] called it akinetic hypertonic syndrome, earlier reports of probable NMS exist in English,[2] and *Syndrome Neuroleptique Malin* is the French origin of the term NMS, which was not much used in English until the early 1980s. There have been many reviews; recent articles of note include Refs. 3 to 11. Most reviewers, and criteria and descriptions, recognize fever and muscle rigidity as the core features of the syndrome.[12–16] They also state or imply that it is a hypermetabolic syndrome, often with parallels drawn to malignant hyperthermia (MH).[17–21]

There is no established animal model of NMS, as there is for both MH and serotonin toxicity (ST). Several models have been proposed, e.g. Refs. 22–24, but have not been heuristically productive or adopted. Also, it may be noted that the human thermal eccrine

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system, and ability to control heat loss through the skin, is unique,[25] which would make extrapolations from animal models problematic.

MEASUREMENT AND DEFINITION OF HYPERTHERMIA

The term hyperthermia is often used imprecisely, and the extent to which NMS involves fever and/or hyperthermia is uncertain. This article will use the term hyperthermia, but a substantial and uncertain proportion of cases exhibit features of an acute phase response (APR), preceding symptoms. If hyperthermia is thought to be the main mechanism mediating morbidity in NMS (which is by no means certain), then the degree of temperature elevation required to produce morbidity is a key issue, and accurate measurement of relevant temperatures (muscle, core, brain, and skin) is vital. Fever (fever is synonymous with pyrexia) is different from hyperthermia, because it is mediated by pyrogenic cytokines triggering the APR. The APR involves a change in the thermal set point to a higher level (with engagement of physiological thermoregulation mechanisms) and a variety of other subsequent systemic responses, including somnolence, anorexia, changes in plasma protein and hormone synthesis, gluconeogenesis, and erythropoiesis (e.g., increased leucocyte count and altered iron distribution). The finding of low serum iron[26] is now understood as a consequence of APR-caused changes in serum iron,[27,28] as recently highlighted by Rosebush et al.[29] There is still no single reliable marker for the APR,[27,30] so, it is relevant to note that significant underestimation of the frequency with which an APR is associated with NMS may be occurring.

In hyperthermia, the thermoregulatory control mechanisms are impaired, disabled, or overwhelmed, whereas in fever, they are intact.[31] The term hyperthermia is generally used for any elevation of temperature, even within the established physiological range. The normal physiological range of brain temperature is illustrated by rat hypothalamus measurements: 36°C during sleep, 37.3°C at rest, and peaking at ~39°C during physiological arousal and stress-induced states.[32–34] Indeed, "normal" human body core temperature spans the temperature range for other mammals, i.e., 36°C to 40°C (Ref. 35, from Table 1, p.111). The fact that stress and emotion-induced temperature increase are also applicable to humans is indicated by various observations,[36,37] most recently, by the reliably verified capabilities of a cold water swimmer, who is able to raise his core temperature to 38.4°C in his pre-swim mental preparation, without exercise, probably by increased thermogenesis.[38]

TABLE 1. *The Hill criteria of causality, applied to MH, NMS, and ST*

Hill criterion	MH	NMS	ST
Strength	Strong	Weak	Strong
Consistency	Strong	Equivocal	Strong
Specificity	Strong	Absent	Strong
Temporality	Strong	Weak	Strong
Biological gradient	Strong	Equivocal	Strong
Plausibility	Strong	Equivocal	Strong
Coherence	Strong	Weak	Strong
Experiment	Strong	Absent	Strong
Analogy	Strong	Absent	Strong

The evidence for criteria is rated as: strong, equivocal, weak, or absent.

MH, malignant hyperthermia; NMS, neuroleptic malignant syndrome; ST, serotonin toxicity.

In the NMS literature, hyperthermia is generally used to indicate any temperature elevation above 37°C, which is not the same as current ideas about what constitutes fever (a single measurement of 38.5°C or 38°C for 1 hour[39]). Since temperatures of up to 39°C are normal, in certain contexts, and heat damage to tissues occurs at around and above 39.5°C to 40°C, this seems unhelpful. It is notable that temperature, as a key physical variable and a criterion for NMS, has been unscientifically measured: the method and site of measurement and the accuracy of the instruments employed receives inadequate consideration: meticulous attention to serial measurements of skin, muscle, and brain and core temperatures would be expected to lead to advances. Until 2008, there were no guidelines for method and site of temperature measurement, and such as now exist are not widely disseminated or practiced.[40,41] Recent reviews of noninvasive methods have found that the widely used newer generation of infrared aural thermometers (they do not measure tympanic membrane temperature) are inadequate for routine clinical use and not of a sufficient standard for research, operative, or critical care uses.[42,43] Therefore, the issue of possible morbidity from temperature changes in different tissues (e.g., muscle, brain, and core) is hard to assess as there is no accurate data.

Morbidity Related to Hyperthermia

Various data give an indication of the risk of morbidities in hyperthermic states. A (rectal) temperature of 40.6°C is often used to define heat stroke, although more recent reviews use 40°C.[44] In the Dematte et al.[45] series, the acute mortality rate was 21%, and 33% had moderate to severe impairment on discharge. A core temperature of 40°C is associated with a disturbed level of consciousness, brain edema, and

increased mortality.[44,46–48] Experimental studies indicate that even small elevations in temperature worsen histopathological and behavioral outcome in central nervous system (CNS) injuries.[49,50] *In vitro* experiments show that the most temperature-sensitive elements of neural cells are mitochondrial and plasma (cell) membranes, in which irreversible changes in proteins occur around and above 40°C.[51–54] These observations clearly indicate that a temperature of 39°C to 40°C is the logical point to define "clinical hyperthermia," because, in both humans and other mammals, temperatures of up to 39°C occur during normal activities and above 40°C is associated with cellular injury and physiological and clinical impairment and substantial mortality. Furthermore, brain temperature may be higher than core temperature.[55,56] A true core temperature of 40°C, thus, demands immediate action, in minutes rather than hours, and an urgency of transfer to a (more) suitable medical facility comparable with an acute cardiac case. Therefore, when the temperature reaches 39°C, it is appropriate to have an action and treatment plan in place to prevent vulnerable cerebral tissues from being subjected to injurious hyperthermia.

Thermoregulatory Mechanisms and Control

Core temperature at rest varies by about 1°C as a result of the circadian rhythm, the influence of the menstrual cycle, and body heat distribution[57] and varies by about 3°C with various normal activities, from 36 to 39°C.[32] Although recognition that all hyperthermic states are substantially influenced by ambient conditions should be a *sine qua non* in all considerations of hyperthermia, it is sometimes forgotten, and ambient conditions are rarely reported, except in heat stroke studies. This makes it impossible to do even crude *post hoc* reassessment of ambient conditions in most published material on NMS.

The most important CNS control center for thermoregulation is the preoptic anterior hypothalamic area,[41,58] but thermoregulation is hierarchical at successive levels of the nervous system with substantial overlapping redundancy: some mechanisms operate at the spinal, some at brainstem, and some at hypothalamic level (Gurrera et al.[19] discuss the role of the sympathetic nervous system and other detailed considerations in depth). Recent evidence demonstrates two aspects on which this article focuses: first, thermoregulatory redundancy, and second, potentiation by compounding interactions, e.g., of drug-induced antimuscarinic effects and the APR and exercise. Carter et al.[59] have demonstrated an interaction between the processes of thermal set point alteration *via* the APR and exercise hyperthermia, which alters the threshold at which thermoregulatory mechanisms are triggered, thus leading to increased rate of heat accumulation on exercise and a greater than usual degree of hyperthermia. That seems consequential in humans because heat stroke patients have had frequently (>50%) recent infection,[45,60,61] suggesting that an APR compounds increased heat accumulation. Stress-induced hyperthermia (SIH) and the APR may also interact, they are induced by different neurotransmitter pathways,[33] and also SIH and antimuscarinic drugs (see Ref. 62).

Knowledge of basic human heat physiology highlights how various other factors may affect heat stress in nonathletic individuals and can rapidly reveal compromised heat coping ability due to reduced skin blood flow (e.g., impaired cardiac output). Vascular volume is critical to optimum cardiovascular system function and, hence, thermoregulation, therefore, fluid and sodium loss must be balanced by supplementation.[63] Reductions in cardiac output progressively impair heat dissipation capacity,[64] and hypovolemia precipitates peripheral vasoconstriction, with a consequent reduction of skin blood flow, which diminishes heat dissipation by as much as eightfold.[65–67] Cutaneous vasodilation, for maximal heat loss, requires an increase in skin blood flow of 8 L/min.[68–70] Aged and ill individuals may have maximum attainable cardiac outputs of approximately 10 L/min (e.g., in heart failure, of moderate severity, maximum cardiac output during exercise is <10 L/min[71]). There is little leeway for added insults before heat accumulation becomes inevitable, as a result of cardiovascular system inability to maintain the high skin blood flows needed for higher rates of heat dissipation.

In summary, various different pathways, e.g., those producing SIH, the APR, and acetyl-cholinergic input, definitely do interact and produce compounding effects on temperature dysregulation.[33,62]

Thermoregulation: Acetylcholine and Dopamine

The known effects of antipsychotic drugs likely to be relevant to thermoregulatory pathways are those on acetylcholine (Ach) and dopamine (DA), which are both potently antagonistic and tend to increase body temperature. However, the striking initial observation is that these effects do not commonly give rise to significant temperature elevation, nor is that a feature of supratherapeutic doses or overdoses of such drugs[72,73] (and Page personal communication, March 16, 2009). This is true both of selective antagonists of Ach and DA, and of drugs that combine both effects, i.e., antipsychotics. DA

agonism in the preoptic area triggers increased heat loss, which is blocked by DA antagonists and which reduces the ability of rats to accommodate to a heat load,[74] probably D2 mediated.[75] DA transporter knockout mice (DAT−/−) display functional hyperdopaminergia and hyperactivity; their body temperature is significantly lower than normal mice during inactive periods.[76]

DA agonists, especially bromocriptine, have been used as treatment; they are mostly also 5-HT2A receptor agonists.[77] Since activation of 5-HT2A receptors worsens, and antagonism reduces, the consequences of most forms of hyperthermia,[78–80] 5-HT2A agonism is a undesirable property. There is disagreement concerning bromocriptine's efficacy, and some evidence supports the notion that it could worsen NMS.[81–83] Apomorphine is the only clinically available DA agonist that is also a 5-HT2A antagonist and, therefore, may be preferable to bromocriptine.[84,85] Central cholinergic M2 receptor agonism mediates increased heat dissipation[86] promoting reduction of temperature, whereas antagonists like atropine reduce heat loss.[87] Mice genetically engineered to lack the M2 receptor showed reduced hypothermic response to M receptor agonism, whereas in normal mice, agonism produces pronounced hypothermic effects.[88]

Heat stroke cases show a greatly increased likelihood over controls to have been taking antimuscarinic and antipsychotic drugs.[44,89] The role of antimuscarinic mechanisms is underestimated, because there are many commonly used drugs that have unrecognized antimuscarinic properties.[90,91]

It is important to emphasize that overdoses of antimuscarinic drugs that are sufficiently severe to cause delirium are not generally associated with elevated temperature: e.g., in a series of 200 cases of promethazine overdoses, only one case had a temperature of >38.5°C, and the average was not elevated[73] (and Page personal communication and Ref. 72). Reports of hyperthermia subsequent to atropine or hyoscine are very rare[62]; but physostigmine is an effective treatment, not only for delirium but also for the hyperthermia.[62,92] A number of authors have suggested that antimuscarinic drugs may be harmful in patients with NMS and that they should be ceased if NMS with hyperthermia is developing.[7,93–98]

Neuroleptic Malignant Syndrome

NMS, as it is usually defined, has the major features: mental state changes, bradykinesia and rigidity, autonomic dysfunction, and hyperthermia. The DSM criteria include "elevated temperature," which is not defined[13]; the DSM features include 37.2°C to 37.8°C (expressed as 99 to 100°F). As mentioned above, there is usually an implicit or explicit acceptance that it is also a "hypermetabolic" syndrome.

NMS is acknowledged to respond frequently to conservative management, after cessation of drugs, and mortality is estimated at about 10%[9]: Caroff et al.[18] states "NMS is a self-limited disorder in most cases, regardless of specific therapy" and that the complications that may lead to fatalities are "Cardio-respiratory arrest, acute renal failure, rhabdomyolysis, pulmonary emboli, aspiration pneumonia…." These usually occur at temperatures lower than 39°C. The central dopamine hypoactivity hypothesis is widely accepted as a key element of the pathogenesis of NMS,[8] and Mann and Caroff[99,100] have proposed the spectrum of Catatonia—NMS—Parkinson's disease. An essential role for defective heat dissipation was proposed in 1988.[101]

However, it is not meaningful to regard a substantial proportion of patients (who meet formal diagnostic criteria for NMS) as hyperthermic, since their temperatures do not exceed 38.5°C: in Lee's[5] recent series only 1 of 13 cases of NMS had a temperature of 39°C or greater. The effect of early recognition and treatment on those temperatures may not be great, since 7 of 13 were less than 38°C with only conservative treatment (antipsychotics ceased, supportive measures, and benzodiazepines). In Spivak et al.'s large prospective series[102] surveying 79,000 patients over 10 years, a total 19 cases of NMS (0.02%), only 5 of 19 developed temperature of >38.5°C (2 were fatal, both had recorded temperatures of a maximum of 39°C). If these temperatures represent true core temperatures, then they are most unlikely to be sufficiently great to account for the morbidities or mortality.

Muscle rigidity in NMS is abolished by neuromuscular blockade.[103–105] This was verified using somatosensory-evoked potentials, before and after an atracurium besilate bolus of 0.05 mg/kg, in a single recording session, in patients with NMS (N = 7) and also Parkinson's disease.[85] In MH, rigidity is not abolished by neuromuscular blockade, because the pathology is within the muscle.[106] The observation that neurogenic muscle contraction (rigidity) associated with Parkinson's disease (and other conditions), does not cause hyperthermia, argues against a great degree of primary muscle heat generation in NMS; indeed, if thermoregulatory mechanisms are intact, it is doubtful that muscle contraction alone is able to generate sufficient heat to induce hyperthermia. For comparison, current data indicate the maximum heat output in top athletes is approximately 20 j/s/kg,[107] which generates an oxygen demand of approximately 70 mL/kg/min.[108] In MH-susceptible

swine, experiencing MH model hyperthermia, excess oxygen demand only reaches 20 mL/kg/min.[109,110] Thus, the heat generation in MH (approximated from oxygen consumption) appears to be approximately 3 times less than the total that the normally functioning system is able to dissipate. The slower rate of increase and lower body temperatures in NMS (vs. MH) suggest that excess heat production is less in NMS than it is in MH. This would seem to indicate NMS does not involve a degree of increased metabolism any greater that the normally functioning system generates; so, it may not be helpful to characterize that as hypermetabolic. The term hypermetabolic suggests increased heat production sufficient to overwhelm a competent thermoregulatory system. Also, the occurrence of acidosis and rhabdomyolysis, etc., *per se*, is not evidence of a hypermetabolic condition. However, experimental measurements are required to clarify these issues.

NMS-Like Syndromes

Many terms have been used for NMS-like syndromes, and these have generally been considered very similar or the same as NMS, both in presentation and etiology.[7,8,11,111] The terms used include parkinsonism-hyperpyrexia syndrome,[7,112] neuroleptic malignant-like syndrome,[113,114] levodopa-withdrawal hyperthermia, lethal hyperthermia,[115] dopaminergic malignant syndrome,[116] acute dopamine depletion syndrome,[117] akinetic crisis,[118] and acute akinesia,[111] which leads back to Delay et al.'s original akinetic hypertonic syndrome. There is strong clinical evidence that multiple thermoregulatory control mechanisms are relevant in a large proportion of these cases, *viz*, the thermoregulatory effects of antipsychotic and antimuscarinic drugs (decreased heat dissipation), the APR (surgery and infection), and the dehydration/reduced cardiac output. The influence of the APR may have been underestimated, because measures for establishing its presence are imperfect.[30]

A prospective 12-year study described a cohort of 675 Parkinson's disease patients, of which 26 patients (3% per year) developed Parkinson's disease hyperthermia.[111,119] In 17 of 26 instances, it presented after the onset of infectious diseases or surgery (both of which trigger the APR); and it occurred independently of treatment withdrawal, as it did in earlier descriptions of neuroleptic malignant-like syndrome.[114,120,121] In Takubo et al.'s[121] large series, the most frequent precipitant was dose change and then intercurrent infection, hot weather, and dehydration. Seventy-five (of 99) patients developed fever above 38°C, and mean maximum temperature was 38.5°C.

Long-term treatment with tetrabenazine, with or without the tyrosine hydroxylase inhibitor alpha-methyl-*p*-tyrosine, induces profound DA depletion: in ~600 patients,[122–125] this did not precipitate any cases of NMS or hyperthermia in patients observed for many months (but did precipitate anxiety/depression in 15–20%). Nevertheless, cases of NMS with tetrabenazine have been reported,[126–129] but it is clearly rare in this situation also. Ceasing treatment for Parkinson's disease also causes relative DA depletion but leads to NMS or hyperthermia infrequently.

This well-documented occurrence of a syndrome indistinguishable from NMS, without antipsychotic drugs, demonstrates clearly that they are not the exclusive implicated agent. This has major implications for the notion of causality (see "Hill" criteria below).

Malignant Hyperthermia

MH was once considered similar to NMS,[130] but key differences were evident early on. Among these were (1) a clear familial tendency, (2) triggering by specific drugs (usually within 1 or 2 hours), (3) definite treatment response to dantrolene, (4) an identifiable abnormality on muscle biopsy testing, and (5) a robust animal model.[131] These features have major implications for considerations of cause-effect relationships, as particularized in the Table 1 below that compares NMS, ST, and MH using the Hill criteria for causality. MH is a pharmacogenetic disorder of skeletal muscle precipitated by volatile anesthetic gases such as halothane and the depolarizing muscle relaxant succinylcholine. The estimates of incidence of MH reactions range from 1:5,000 to 1:50,000 anesthesias, and the typical signs of MH are hyperthermia (>39°C), tachycardia, tachypnea, increased carbon dioxide and oxygen consumption, acidosis, muscle rigidity, and rhabdomyolysis.[132] Advances in genetics have now unraveled much of the story and clarified the relationship between the genotypes of this autosomal dominant disorder and the phenotypic presentations, and the relationships to other similar conditions. It is characterized by abnormal calcium ion control in skeletal muscle, due (largely) to the various ryanodine receptor mutations that have now been elucidated in considerable detail in recent reviews.[133–135]

DISCUSSION

NMS is a rare condition. NMS where the temperature exceeds 39°C is even more rare. There is strong evidence that many of the estimates of incidence have methodological flaws that produce substantial overesti-

mates of incidence. A review of NMS studies concluded that, "study size accounts for 90% of the variance in published estimates of NMS incidence."[6] Large samples consistently indicate a lower incidence, the range was from 30 per 1000 in the smallest studies, to as low as 0.17 to 0.2 per 1000 in the largest studies[102,136]; all the larger studies indicate lower rates of less than 5 per 1000. The idea that, supported in this article, NMS is not a homogeneous and unitary entity is not new,[137–140] but has not received much attention, perhaps because substantive evidence has not been martialed to support it. Levinson and Simpson[139] commented "The cases of extrapyramidal symptoms with fever are too heterogeneous to justify the assumption of a unitary and malignant syndrome."

Two major issues, the definition and the etiology of the condition, are intricately related to the question of causality. This is especially so because there are multiple demonstrated and relevant mechanisms that are capable of influencing temperature elevation and because there is no clear mechanism linking antipsychotic drugs with either frequent pathological temperature disturbance or NMS itself. Nevertheless, it has been generally implicitly accepted that there is a cause-effect relationship linking antipsychotic drugs with NMS. The application of formal logical rules and criteria has not been undertaken to substantiate this notion, which, thus, cannot be assigned the formal status of a hypothesis. It is important to address this question of causality, because the answer has considerable influence on guiding research and possible active treatment strategies about which there is currently only a modest degree of consensus.

Criteria for establishing cause-effect relationships in medical science, established by Sir Austin Bradford Hill[141] have recently been applied in several situations similar to NMS[142,143] and refinements have been discussed.[144,145] These criteria or considerations are, as initially enumerated by Hill[141]: "1) Strength, 2) consistency, 3) specificity, 4) temporality, 5) biological gradient (dose-effect), 6) plausibility, 7) coherence, 8) experiment, and 9) analogy" (see references for more detailed expositions of these points).

Since NMS is often compared with both MH and ST, it is helpful to illustrate how they all rate for causality, using the Hill criteria (Table 1). From Table 1, it is immediately clear that there is a great difference between ST and MH on the one hand, and NMS on the other, and that the evidence on NMS falls short of a convincing case for causality. The most important criteria that are not fulfilled are as follows: criterion 1—strength, the very infrequent association of DA-blocking/depleting drugs with either NMS or hyperthermia (especially when coupled with the lack of evidence of genetic factors, compared with MH); criterion 2—consistency, is not satisfactorily met because of the lack of agreement about the definition of NMS, or "caseness," combined with large variations in the apparent observed rates of occurrence (a 100-fold difference[6]); criterion 3—specificity, is not satisfied, because NMS is not specific to antipsychotic drugs, and its association with DA depletion is also very infrequent[119]; criterion 4—temporality and criterion 5—biological gradient (i.e., a dose-effect relationship) are connected. The fact that there is an almost complete absence of any hyperthermia or NMS following supratherapeutic doses or overdoses argues strongly against any dose-effect relationship. The association between low DA, from either idiopathic or iatrogenic causes, and hyperthermia or NMS is very weak: in a great majority of cases, they do not occur. Also, the variation in interval to onset of NMS postdrug commencement, combined with the relatively low rates of subsequent recurrence on rechallenge (i.e., most patients can be safely reexposed to the drug after a relatively short interval[146]) does not fit the temporality criterion. Criterion 6—plausibility, is especially unconvincing when it is recognized that no other therapeutic dose single-drug ingestions predictably cause hyperthermia, that ODs do not lead to NMS or hyperthermia, and that there is no well-supported pathophysiological mechanism (as there is for both MH and ST). Similarly criteria 8—experiment, and 9—analogy offer no support, whereas for both MH and ST, they give strong support. This is especially pertinent when one appreciates that MH is genetic and rare, yet there is clear familial propensity and a good animal model, and there is an animal model for ST; but there is no familial propensity or useful animal model of NMS.

NMS is substantially less malignant than MH, either as assessed by the rate of onset of hyperthermia or the ultimate percentage of fatalities. MH is frequently fatal within hours, unless aggressive active treatment is instituted. In NMS (and parkinsonism-hyperpyrexia syndrome), a majority of cases do not ever develop the degree of hyperthermia usually associated with morbidity (i.e., 39.5°C or greater), even with only conservative treatment. Also, deterioration of clinical status and morbidity and mortality occur in the absence of a degree of hyperthermia that is injurious: deterioration of renal, mental, neurological, and respiratory function, despite a maximum temperature of less than 39°C, is documented in many reports.[5,83,102,121] To regard NMS as a primarily hyperthermic syndrome is an inadequate

explanatory model and may lead to underestimation of clinical severity or exclusion of NMS because the patient is not hyperthermic.

Thermoregulatory redundancy is sufficiently great, so that a concatenation of circumstances and disruptions is required to precipitate significant hyperthermia. Even concurrent antagonism of Ach and DA does not usually cause hyperthermia. Hyperthermic states usually result from combinations of factors and mechanisms, as described and illustrated above. Various factors are associated with the temperature elevation in NMS and NMS-like syndromes, more frequently than generally recognized. Temperature elevation appears to show features of both hyperthermia and fever. Carter et al.'s[59] recent demonstration of the compounding effect of an APR (due to acute infection) and exertion is important, as is Noakes et al.'[38] with SIH and exercise. Particularly, the factors often seen that have been shown to have compounding interactive effects are high physical activity, high ambient temperatures, stress and agitation (i.e., SIH), an APR, impaired skin blood flow, and impaired sweat production (e.g., from antimuscarinic drug effects, dehydration, or cardiac failure). These interactions are important, sometimes fatal, and must be assumed to contain lessons for models of NMS. It is proposed that collectively the co-occurrence and interaction of these factors contribute to that small proportion (approximately one tenth) of NMS cases that do become seriously hyperthermic.

Both DA and Ach influence CNS temperature control in the same direction and stimulation of the relevant postsynaptic receptors (D2 and M2), in the preoptic area promotes heat loss. The DA agonist, apomorphine, has been used to treat NMS with apparent good results[117,119,147–151] and is also a 5-HT2A antagonist (unlike bromocriptine, which is a 5-HT2A agonist[152]). The acetylcholinesterase inhibitors, physostigmine and tacrine, are rapidly effective in the antimuscarinic toxidrome,[62,72,73,92] although they are very rarely required specifically for the treatment of hyperthermia. It is important to repeat that overdoses of antimuscarinic drugs (that are sufficiently severe to cause delirium) are not generally associated with hyperthermia, nor are overdoses of DA antagonists (antipsychotic drugs, most of which also posses significant antimuscarinic potency). The case reported by Torline[62] is remarkable for the interaction of SIH and scopolamine, co-occurrence of previous severe anxiety attacks (accompanied by well-documented temperature elevation, i.e., SIH) and then a temperature of 42°C soon after preoperative scopolamine administration, which rapidly normalized after physostigmine.

The method, site, and accuracy of temperature measurements require continuing critical attention. Research harnessing recent technologies to measure temperature changes in muscle, skin, core, and brain has become possible and is a high priority. Such measurements would put theorizing on a firm base: a fundamental unaddressed question is, does NMS involve excess generation, or failed dissipation, of heat: Is sufficient excess heat being generated in muscle (or other organs) to account for temperature increase and morbidity, or not? The high temperatures reached, in a small proportion of cases, accompanied by prolonged diaphoresis and evidence of muscle injury, suggests a possibility of excess muscle heat generation. But, evidence from heat production in athletes and oxygen consumption in MH compared with athletes does not support NMS being hypermetabolic to a degree sufficient to overwhelm normally functioning thermoregulatory mechanisms. Firm evidence is required and is obtainable. Temperature mapping of the brain, and other tissues, is now possible *via* magnetic resonance spectroscopy, which has been used to study the brains of piglets and humans. Proton resonance frequency provides absolute temperature measurements.[153–155] Also, ingestible temperature sensor capsules could be utilized. They are accurate and correlate well with rectal temperature.[42,156] Infrared aural/tympanic thermometers are neither adequate for research nor even for routine clinical use, because they are neither accurate nor do they measure tympanic membrane temperature.[41]

An ironic lesson of NMS research is the inadequate attention given, both to assessing causality and to the most fundamental (and accurately measurable) physical parameter, temperature. The importance of answering the question about causality and heat generation can hardly be overstated. The answers will indicate what kind of treatment approach is most logical. Reducing muscle rigidity with dantrolene, which remains controversial, will not be the optimal strategy if the problem is reduced heat dissipation, and focusing on temperature and cooling is insufficient if morbidity is, to some degree, independent of temperature.

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