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Turned to Stone: A History of the Neuroleptic Malignant Syndrome

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Psychopharmacology changed (some prefer to say "revolutionized") the field of psychiatry. Over many decades, managing psychotic breaks involved trial-and-error prescribing of various drugs (e.g., morphine, potassium bromide, choral hydrate, barbiturates, insulin, amphetamines, chlorpromazine, lithium, and several others). This haphazard approach continued until the first neuroleptics—chlorpromazine, Thorazine, and fluphenazine—appeared in the early 1950s [1].

The Belgian physician Paul Janssen, one of the four children of the founder of Janssen Laboratories, undertook the synthesis of haloperidol. He was a prolific drug inventor—fentanyl was another (certainly, he would have been dismayed to learn that his invention is used as an illicit drug and now kills more Americans annually than any drug in history). As with so many other synthesized psychopharmacological breakthroughs, his discoveries were happenstance although not unfounded guesses. However, his rationale for creating these new drugs was to identify alternatives to morphine. While working on the analgesic pethidine (meperidine), he found out it could calm wild, possibly dangerous psychotic patients. He made no pretense of fully understanding the theoretical biochemical basis underlying the discovery. In fact, psychopharmacology was not in line with the classification of psychiatric disease, although there was a strong tendency to erase psychoanalysis from the clinical picture and to move to neuropsychiatry. The *Diagnostic and Statistical Manual of Mental Disorders* has always struggled with achieving consensus among psychiatrists and has profoundly revised each new version. The discovery of each new drug raised the obvious question of for whom it was really intended [2].

Undoubtedly, haloperidol fundamentally changed the treatment of major psychoses. The compound was a hundred times more potent than chlorpromazine and was thought to produce fewer side effects. When injected into mice, it produced profound relaxation in addition to the analgesic effect, and further manipulation of the carbons deleted its analgesic morphine effect (Fig. 1).

The first communication on its effect on patients (R 1625 or haloperidol) was found in the proceedings of the International Symposium on Haloperidol held in Beerse, Belgium, where Janssen Pharmaceuticals had its headquarters, on September 1959 [3]. Comprehensive pharmacokinetic studies appeared more than a decade later in 1976 [4]. Haloperidol became a novel treatment for manic states and schizophrenia with paranoid ideation. Many other analogues followed (e.g., droperidol). However, haloperidol's introduction to US practice was delayed by a negative trial in patients with chronic schizophrenic using increasing doses of haloperidol (up to 90 mg/day) and with worsening of behavior disorders [4]; it was ultimately approved for use in the United States by a court order [5, 6].

Haloperidol soon made its way into the intensive care unit (ICU), leading one psychiatrist to remark the following:

> *It is clear that psychiatric symptoms in this [ICU] setting, regardless of their cause, can be a serious problem. The confused, agitated patient can pull out infusion sets, catheters, and gastrointestinal drains and thus seriously interfere with his treatment. The anxiety or agitation which accompanies these symptoms can affect the patient's cardiovascular status and, in some situations, pose a serious threat*

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Un neuroleptique majeur non phénothiazinique et non réserpinique, l'halopéridol, dans le traitement des psychoses, par MM. J. Delay, P. Pichot, Mlle T. Lempérière, MM. B. Elissalde et F. Peigne.

Le « R. 1625 », ou Halopéridol, est un neuroleptique nouveau, dont l'introduction en thérapeutique psychiatrique marque une étape très importante dans la chimiothérapie des psychoses. L'halopéridol est le premier corps chimique connu, non phénothiazinique et non réserpinique, possédant les caractéristiques que l'un de nous a proposées pour définir le terme de neuroleptique. La rapidité de son action et son efficacité permettent déjà de le considérer comme un neuroleptique majeur.

Au point de vue clinique, les premiers essais thérapeutiques de l'halopéridol en psychiatrie ont été rapportés en 1958 par Divry, Bobon et Collard. Employé par voie veineuse, chez des sujets pour la plupart psychotiques, en état de grande agitation, l'halopéridol apparut comme un sédatif très puissant, non hypnotique, agissant à dose minime, entraînant chez tous les malades un retour très rapide au calme psychomoteur. Poursuivant l'expérimentation de l'halopéridol par voie orale comme traitement de fond chez des malades psychotiques, ces mêmes auteurs mirent en évidence les propriétés neuroleptiques très puissantes de ce produit. Ces résultats furent confirmés par les travaux de nombreux auteurs, parmi lesquels il faut citer ceux de Jacobs, de Paquay, Arnould et Burton dans la schizophrénie, ces derniers mettant en outre l'accent sur l'efficacité des doses modérées.

Etude pharmacologique

Au point de vue pharmacologique, l'halopéridol est une amine tertiaire nouvelle ; il s'agit de la 4'-fluoro-4-1-(4-hydroxy-4-(4'-chloro)-phényl-pipéridine)-butyrophénone.

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Fig. 1 Title page of the article by Delay et al. [9]

to life. Immediate treatment is therefore essential. Phenothiazines are the most effective symptomatic treatment. [7]

This alarming assessment and psychopharmacy endorsement was driven by the assertion that 38% of all adult open-heart surgery patients experienced some manifestations of a psychotic-like syndrome while in the recovery room or even after a 3- to 5-day postsurgical, clinically lucid interval [8].

The drug haloperidol was given not only in single repeated doses but also in a continuous infusion. Side

effects were noted in 50% of this small series of patients and included intermittent tremors, an increased QTc interval, and other potentially serious major cardiac arrythmias but not commonly torsades de pointes or cardiac arrest. The authors concluded with recommendations to start infusions if more than eight boluses of 10 mg of haloperidol were required in a 24-h time period [8]. One wonders how rigid these patients were.

An Emerging Major Side Effect

Dosing of drugs and, in particular, finding a ceiling were other challenges. In the early days of haloperidol, the neuroleptic threshold was defined as the appearance of micrographia, but such symptomatology must indicate that the patient has been already "over the edge." Jean Delay proposed the word "neuroleptic" (from the Greek for taking control of the nerve) and also coined the word "psychopharmacology." Delay, a neuropsychiatrist in La Salpétrière Hospital in Paris, joined the Sainte Anne Hospital in Paris as one of its few professors of psychiatry. Some regarded him as "one of the greatest psychiatrists France ever produced" [1]. He became a major target of the antipsychiatry movement, which violently protested the use of these very potent drugs.

Ironically, Delay published one of the first articles warning about a major side effect—neuroleptic malignant syndrome (NMS) [9]. Indeed, Delay's article jump-started recognition of NMS. It described 62 patients with "melancholies" or "manies" treated with haloperidol (Fig, 1); many of these also received intramuscular injections to treat paranoid behavior. In two cases, they observed what they called "*dereglements vegetatifs*." These patients developed hyperthermia with excessive drooling, rapid dehydration, extreme (stone-like) rigidity, stupor lasting for several days, and diffuse maculopapular erythema. Symptoms resolved spontaneously, but the presentation resembled an apparently malignant, deteriorating clinical syndrome. Delay and associates called it "*syndrome malin des neuroleptiques*" (the term "neuroleptic malignant syndrome" is therefore a literal translation from French). After this initial description, several more cases were described. It was recognized as an "idiosyncratic, life-threatening complication" because of its associated rhabdomyolysis with the potential for acute renal failure.

The incidence of NMS over several decades has shown considerable variation. Prospective studies of NMS are rare, considering the frequency of neuroleptic use and the low incidence (0.07–0.15%). Retrospective chart reviews led to expanded diagnostic criteria, including partial forms of NMS, which led to higher reported incidence rates.

The concept of an NMS spectrum has been criticized and, indeed, may have contributed to the neuroleptic-associated mismanagement of extrapyramidal disorders. The incidence has now been placed at 0.01% in patients treated with antipsychotics, and in larger series, recovery time has lasted approximately 2 weeks. Mortality is low and a result of systemic complications, such as aspiration pneumonitis, and other complications associated with prolonged ICU care.

A variety of risk factors have been found, which include dehydration, physical exhaustion, exposure to heat, hyponatremia, iron deficiency, malnutrition, trauma, thyrotoxicosis, alcohol use, use of psychoactive substances, and presence of a structural brain disorder, such as encephalitis. Clinicians should suspect NMS if there is hyperthermia, rigidity, tachycardia, hypertension, diaphoresis, a high serum creatinine kinase level, and a history of prior psychotic episodes or schizophrenia. The symptoms usually begin within a day of administration, but the presentation may be insidious. The diagnosis has been (arguably) based on the development of severe rigidity and fever plus two or more of the following ten symptoms: diaphoresis, dysphagia, tremors, incontinence, changes in level of consciousness ranging from confusion to coma, mutism, tachycardia, elevated or labile blood pressure, leukocytosis, and an elevated CPK level, excluding other explanations. Patients may progress to coma, but the cause is unclear and could actually be due to hypertensive crises or acute uremia. The result of a computed tomography scan of the brain is usually normal, but magnetic resonance imaging has rarely been performed [10–12].

An Emerging Treatment

Dantrolene is an effective drug. It was originally synthesized by Snyder and associates in 1967 [13]. The name was derived from "dan" (hydantoin derivative), "tro" (nitrofurantoin), and "olene," a muscle-relaxant effect designated by the US Adopted Names Council.

Dantrolene was primarily used to treat spasticity. Its effect was first demonstrated in a pig model of malignant hyperthermia. Porcine stress syndrome, sometimes called malignant hyperthermia or transport myopathy, reduced meat quality by turning it into "gray, pale, soft, exudative" pork that turns hard with cooking. Once malignant hyperpyrexia was induced in susceptible pigs, administration of dantrolene caused rapid loss of muscle rigor within 20 min, as well as a precipitous decline in temperature. Similarly, the progressive, inexorable acidosis resolved [14]. The drug fed to rats and mice caused paralysis within 24 h, although breathing, pupillary reflexes, and blood pressure remained normal.

It is unclear if NMS is primarily a muscular problem. Keith Ellis, a research scientist with a strong background in skeletal

muscle physiology and pharmacology and expertise in single skeletal muscle cell recordings, was employed by Norwich Eaton in 1967 to elucidate it. Pollock recalls the following:

> *In about 1973, Keith Ellis received a general scientific bulletin across his desk containing a short article written by Lauren Christian. Ellis describes this in the following way, "The publication was in full colour, was really an advertisement with copies sent to anybody and everybody.... This communication—perhaps about a paragraph long—outlined a syndrome of muscle rigidity and sudden death in certain pigs, triggered by a variety of causes. The article noted the economic implications of the syndrome and indicated that abnormal calcium release was the likely cause. [15]*

The current hypothesis, based on studies in the early 1990s, is that the clinical symptoms of NMS are likely due to hyperactivity of the sympathoadrenergic system, which could lead to increased intracellular calcium ion concentrations and contribute to increased muscle tone. Dopamine D2 receptor antagonism of neuroleptic drugs may cause hyperthermia through blocking heat-loss pathways or producing heat from muscular rigidity. Genetic mutations may cause changes in calcium regulatory proteins. In the most severe cases, electroconvulsive therapy might be necessary to treat the severe vegetative symptoms, such as treatment-refractory hypertension, tachycardia, and rigidity.

Haloperidol is here to stay and is commonly used. Neurointensivists may occasionally observe that the pendulum may have swung too far back because severe rigidity requires urgent treatment. Though not approved by the US Food and Drug Administration, intravenous haloperidol remains widely used off-label to manage agitation and psychosis in patients with delirium in the ICU setting [16].

There has been concern that intravenous drug use increases the risk of NMS, although very few cases have been identified in a literature survey [16]. It is possible that akathisia or extrapyramidal symptoms were not commonly reported or recognized in critical illness.

This major side effect blurs the boundary of neurology and psychiatry, with many psychiatric patients potentially admitted to a neuro-ICU with NMS with variable severity. It may occur in any neurocritical care patient treated for agitated delirium with haloperidol. But the dose does not always make the poison, and complications are rare and unpredictable.

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