

Angry puppet – a neurological syndrome in crime fiction

ESSAY

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***The Angry Puppet Syndrome* is a crime novel about a clandestine liaison between the pharmaceutical industry, academia, the criminal justice system and government agencies. The story is based on a rare side effect from medication, intermittent explosive disorder, which is an organic behavioural disorder.**



Figure 1 The fictional Dulcian pill. Illustration: Mariken Lie

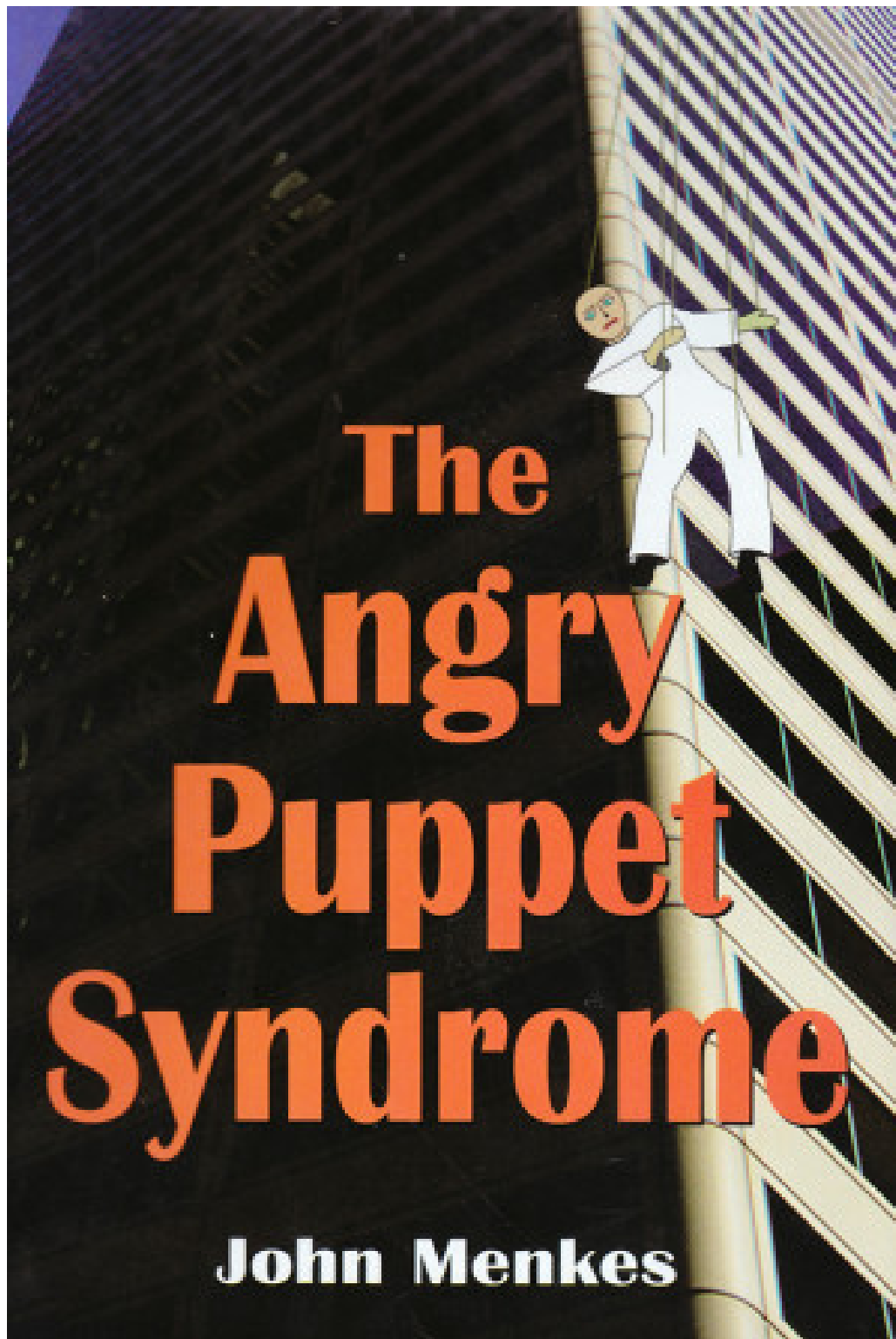
John H. Menkes (1928–2008) was born into a Jewish family in Austria and emigrated to the United States from Ireland after World War II. He graduated in organic chemistry before he trained as a doctor at Johns Hopkins University in Baltimore, Maryland. His areas of special interest were psychology, psychiatry and neurology. Gradually, he became the leading light in paediatric neurology.

Menkes' particular area of study was metabolic disorders. He described two such disorders in great detail: *maple syrup urine disease* (OMIM# 248600) – defective amino acid metabolism – and Menkes disease, a rare disease in children (OMIM# 309400) which is caused by a defect in the copper metabolism and which is considered a prototype of rare genetic disease in children (1). In 1974, Menkes published his *Textbook of Child Neurology* (2) which he later revised and re-published in a total of six additional editions (3). Menkes took an interest in vaccination side-effect issues and often appeared as an expert witness for patients who felt they had suffered adverse effects after immunisation (4, 5). When he died, he was honoured with an obituary by the World Federation of Neurology (6).

Angry puppet syndrome

Menkes was interested in art and literature and he published a number of novels and plays. *The Angry Puppet Syndrome* from 1999 is a crime novel set in the university and hospital circles of Los Angeles and branching out to pharmaceutical and legal circles on the US east coast (7). The questions raised by Menkes in this fictional story are still topical, and the neurobiological explanation of the syndrome in the book's title remains a topic of scientific discussion. A synopsis of the plot and some excerpts from the story may be helpful for readers to understand what this is all about:

The story starts with a patient consultation in the surgery of neurologist Dan Lerner at Southwestern University, Los Angeles. The patient has recently been referred to him by a colleague in private practice. On telephoning this colleague, Dr Lerner learns that the patient's wife compares her husband's changed personality to an angry puppet (7, p. (8). Cerebral CT, MRI and EEG have been normal. They agree that the clinical findings do not fit with epilepsy, multiple sclerosis or AIDS. Dr Lerner says he expects there is little he can do, but promises to follow up the patient.



Topical novel: John H. Menkes, *The Angry Puppet Syndrome*. New York: Demos Medical Publishing, 1999.

Angry puppet syndrome is an expression that conjures up associations with the developmental disorder known as *puppet syndrome*, later referred to as *happy puppet* or Angelman syndrome (OMIM# 105830) based on Harry Angelman's description of three patients who presented with puppet-like behaviour (8). One symptom of Angelman syndrome is emotional outbursts, particularly in the form of laughter, which like the *angry puppet syndrome* has a neurobiological foundation in the limbic system.

As expected, Dan Lerner's clinical neurological examination of his new patient, Arnold Barton, is normal. But paradoxically, this provokes Barton, who responds with rage ((7), pp. 17–18). He starts by accusing his wife of 'controlling' him before he throws his shoe, and then the chair, onto the floor while his eyes became drunken and unfocused and his movements appear to be controlled by invisible wires. He tears an overhead coat hanger which has been screwed to the back of the office door, and is about to hit his wife, but suddenly becomes fixed and throws the hanger on the floor with jerky movements. Frothing at the mouth, pale and sweating, he hurls abuse at his wife and Dan in a mechanical voice. He proceeds to put his shoe back on and straightens up the chair before he apologises to his wife. He is bleeding from a finger that was hurt when he tore the coat hanger off the door, but he is oblivious to his own injury. Dan later speculates whether what he has witnessed may have been an epileptic seizure, or perhaps the personality disorder referred to as episodic dyscontrol. He settles on the latter diagnosis as the most probable ((7), p. 19).

Menkes allows his protagonist Dan Lerner to set a diagnosis of episodic dyscontrol, which refers to uncontrollable outbursts of anger after minimal provocation (9). Episodic dyscontrol syndrome is a concept that was first used by Menninger & Mayman in 1956 (10) but which has later become synonymous with intermittent explosive disorder. This is classified as a separate diagnosis in the DSM code table (11) and in the ICD-10 (F63.8). The psychiatrist Kenneth Nunn maintains that the disorder differs from other forms of aggressive behaviour (12). Intermittent explosive disorder can sometimes be confused with temporal lobe epilepsy (13). Already in Menkes' first edition of his textbook, he describes aggressiveness as a manifestation of psychomotor epilepsy (2). He lets Dan Lerner consider this as a differential diagnosis in the novel's fictional case of angry puppet syndrome.

Other important characters include Dan Lerner's girlfriend Maureen Durrell who works for the Cosgrove & Costello law firm, Dr Jack Brennan who is a director of Southwestern University, and the 'wunderkind' that is the promising Dr Marty DiChiro (Table 1). Brennan has hired DiChiro on extremely lucrative terms to build a PET department for behavioural and hypothalamus research. Brennan has received the required funding from the Wallace Foundation. However, it is a condition of this funding that the department accepts a commission from Mr Wallace to conduct research on 'episodic dyscontrol syndrome', a congenital incurable personality disorder which Wallace's son suffers from.

Table 1

Characters and institutions in *The Angry Puppet Syndrome* (7).

Character	Role
Dr Dan Lerner	Neurologist, Southwestern University, Los Angeles
Arnold Barton	Dan Lerner's first patient with angry puppet syndrome
Maureen Durrell	Lawyer and Dan Lerner's girlfriend
Dr Jack Brennan	Neurologist and Director of Southwestern University
Dr Marty DiChiro	Neurologist employed by Southwestern University to conduct research on hypothalamus-related behavioural disorders

Character	Role
Wallace Foundation	Sponsor for Marty DiChiro's research
Marat International	Major pharmaceutical company, producer of the Dulcian antidepressant

In this way, Menkes describes two different causes of intermittent explosive disorder, one congenital, the other acquired. The syndrome can be caused by either psychogenic or organic factors and it affects children as well as adults (14).

Dan Lerner speculates on how a well-adapted individual in his fifties, like his patient Arnold Barton, may have developed episodic dyscontrol and started behaving like 'an angry puppet'. Could the cause be related to a recent infection ((7), p. 19), or perhaps it is linked to the medication he started taking a few months ago, prescribed for a mild depression ((7), pp. 44–5)?

The medication that Barton has been taking, Dulcian, has only recently been introduced on the market (figure 1). Because the indication is mild depression, it can be prescribed by general practitioners without referral to a specialist. The number of users is therefore substantial. The manufacturer, Marat International, considers Dulcian to be a potentially major source of income, but one important obstacle remains: monitoring for possible side effects as part of phase 3 of the clinical trial. With Jack Brennan's approval, the manufacturer hires Dr. Marty DiChiro as their expert on side effects. Unfortunately, DiChiro is drowning in work and finds himself in a financial dilemma, so he ignores reports of worrisome mental responses to the new medication. Dan Lerner gradually comes into contact with another three new patients who suffer from the same syndrome and who have also been taking Dulcian. Although they stop taking the drug, it turns out that the behavioural disorder is irreversible, and the outcome is fatal for all four of them, either because they take their own life, for example by jumping out of a window (see the book cover), or they are killed in retribution for their violent actions.

In the fictional story, patients show pronounced signs of self-harming. In a real-life study undertaken in 2008 of 376 patients with intermittent explosive disorder, the incidence of self-inflicted injuries and attempted suicide was 16 and 12.5 % respectively (15). Treatment is difficult, but haloperidol, lithium and propranolol have been reported to be effective (16, 17). Cognitive behavioural therapy, individually as well as in groups, has also proved to be helpful (18). Neurosurgical treatment has occasionally been mentioned but has not been the subject of scientific studies.

Dan Lerner wants to write an article based on the four case histories and calls it 'The Angry Puppet Syndrome: An Unusual Adverse Response to Dulcian'. However, his boss Jack Brennan declares the manuscript to be unscientific. He bans its publication and threatens with sanctions that may jeopardise Dan's job ((7), pp. 69–71, 74). Dan sticks to his guns and after a cryptic rejection from the New England Journal of Medicine, the article is printed in the Journal of Clinical Neuropsychology. Following the publication, numerous new cases are identified and a national patients association is formed for the syndrome. The association demands compensation from Marat International and is offered an out-of-court settlement of USD 400,000 ((7), p. 181).

The offer is turned down and Maureen takes on the case against Marat. With Dan's assistance they discover that serious adverse effects from Dulcian were covered up during the first clinical trial and that the falsified report was written by none other than Dr Jack Brennan, who was working for Marat at the time. The company had known all along about the serious mental side effects and had estimated that it affected 1 in 5,000 Dulcian users ((7), p. 295).

Marat feels the pressure and raises their settlement offer to USD 85 million ((7), p. 295). This is accepted and the case is closed with a settlement out of court and no verdict passed. Dulcian is quietly withdrawn from the market while the value of Marat International's shares on the stock exchange drops from USD 6.17 to USD 6.10 ((7), p. 296). Under the circumstances, the company directors are happy with this market value adjustment. The company is running several other promising drug trials.

The story has a happy ending for most of the characters. Maureen becomes a partner in the law firm and she marries Dan Lerner. Marty DiChiro is hired by a Japanese pharmaceutical company to monitor the trial of a new antidepressant with even better qualities than Dulcian.

Based on reality?

Menkes was working for the Cedars-Sinai Medical Center in Los Angeles when he wrote *The Angry Puppet Syndrome*, so it is reasonable to think that Southwestern University was modelled on this institution. In the fictional story, everyone is bought off: doctors, researchers and the university, as well as the US Food and Drug Administration (FDA). Suspicion is also directed at medical journals like the New England Journal of Medicine, with their clandestine links to the FDA. According to Menkes, university hospitals allow commissioned research, exemplified by the Wallace Foundation, to be conducted at the cost of independent research, which depends on the vagaries of support from the National Institutes of Health. The university administration is authoritarian and corrupt and accepts money for projects they ought to stay clear of. It is also depressing that the 'heroes', as represented by Dan Lerner and Maureen Durrell, allow themselves to be silenced by money. The cheating of the promising Marty DiChiros is never discovered and he secures himself an even better paid job with a competing company.

«In the fictional story, patients show pronounced signs of self-harming»

In an interview, Menkes said that *The Angry Puppet Syndrome* is really about his experience of lawyers and the pharmaceutical industry in cases that concerned complications following pertussis vaccination (5). The analogy between vaccines and antidepressants is that rare side effects can be misinterpreted and considered a random occurrence, to the extent that the manufacturer does not accept liability. At the time however, the experts never came to a consensus about the causality of encephalopathy after pertussis immunisation (19). This vaccine has gradually improved and has not given rise to debate in recent years (20).

Like Menkes, and at the same time, the Danish economist, author and Parkinson's patient Hans-Erik Lystrup also criticised the pharmaceutical industry. In his crime novel *Parkinsonmysteriet* (The Parkinson's Mystery) we see how clinical trials are manipulated in the case of a drug that millions of Parkinson's patients all over the world may benefit from (21). But the trial results must be covered up, and in both novels a contract killer is hired to protect the company's market value – while the crimes go undetected.

More recent research

Menkes used intermittent explosive disorder as a model for a type of brain damage that patients may suffer. This was linked to a neurochemical disorder, which in the novel is exemplified by a drop in serotine levels in 25 % of test mice on intake of the Dulcian medication (7), p. 169). The role of serotonin in impulsive aggression has yet to be fully explained ((22). The anatomical localisation of intermittent explosive disorder has rarely been a matter of discussion in the literature. We must assume that in Menkes' opinion, the hypothalamus plays a key role ((7), p. 58), but there is little research to support this.

«In the fictional story, everyone is bought off: doctors, researchers and the university, as well as the US Food and Drug Administration»

A case from 2016, involving a woman with lifelong episodic dyscontrol, suggests that the uncinate fasciculus may play a key role (Figure 2). After a strong blow to the head, the woman's unfortunate personality trait disappeared (23). The post-traumatic clinical course was documented by a validated ratings scale of personality change (24), while detailed imaging of the brain over time showed atrophy of the uncinate fasciculus (particularly the right fasciculus). The uncinate fasciculus connects the prefrontal and temporal cortex via the limbic system. Myelination of this nerve bundle happens slowly and is not complete until the individual is in his or her thirties, and psychosocial factors may have an impact (25). The microstructure of the uncinate fasciculus and myelination are key to pathophysiological mechanisms associated with various forms of anxiety and emotional instability (26).

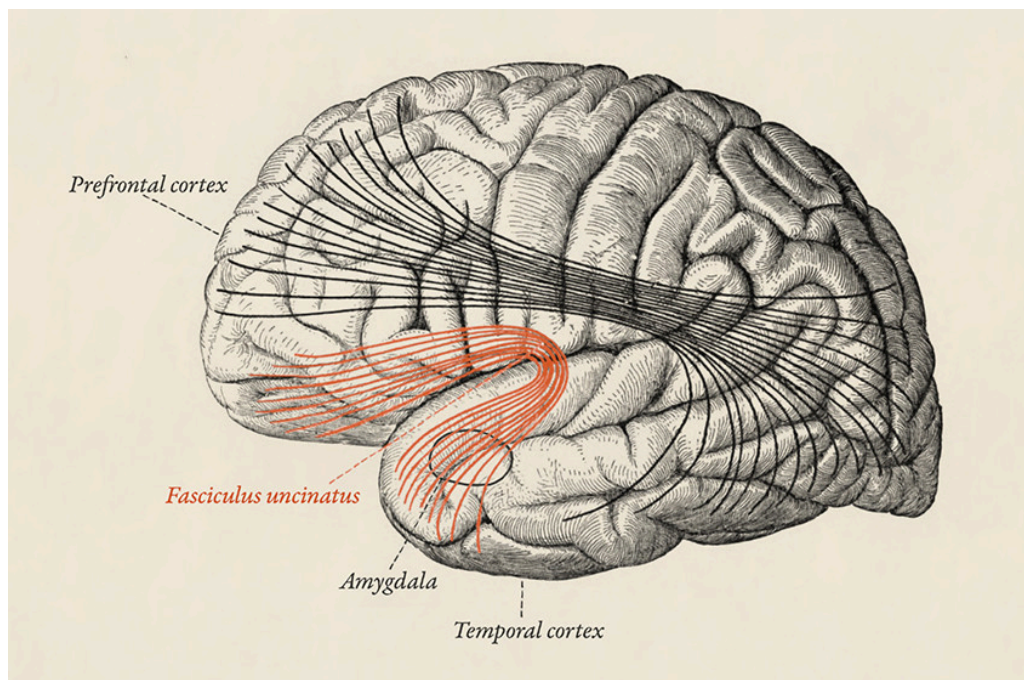


Figure 2 The uncinete fasciculus is the last neural pathway to be myelinated, a process which is not complete until the individual is in his or her mid-thirties. Illustration: Sobotta's Atlas and Textbook of Human Anatomy published in 1909, adjusted by the Norwegian Medical Journal.

Conclusion

The angry puppet syndrome exists only in a novel by Menkes, but the syndrome is associated with an actual neurological condition: intermittent explosive disorder. We must presume that Menkes knew this condition from his long career as a psychiatrist and paediatric neurologist. In recent years, research has indicated that this disorder has a neurobiological explanation, possibly located in the uncinete fasciculus which communicates with what is loosely referred to as the limbic system, much like in Menkes' hypothalamus hypothesis (27).

Menkes used his experience as a researcher, hospital administrator and expert medical witness to construct the fictional story about a rare but particularly serious side effect of medication, which the pharmaceutical industry tried to conceal for reasons of financial gain.

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