Part II
Renaissance of lithium therapy. Birth of modern psychopharmacology 1949

Chapter 21. Reines's analysis of Cade's discovery

Whilst Johnson went some way towards an epistemological historical contextualisation of Cade's revolutionary discovery, in 1990 and 1991 Reines[696] took it a step further, based on Cade's 1949 paper and the views that Johnson expressed in his book.

Reines's starting point was that 'among the better known tales of serendipitous laboratory discovery in pharmacology is the identification of the antimanic action of lithium by John Cade'.

With reference to Hartigan's 1959 account as to the calming effect of lithium in guinea pigs and Cade's direct transition from animals to 'excited psychotics', Reines noted that Cade's discovery 'is generally attributed to "accidental" observations which occurred during the experiments on his pet guinea pigs'.

Reines credited Johnson for having attempted 'to put Cade's experimental findings in a more realistic historical context'. He pointed out that Johnson 'too has contended that Cade's discovery of the antimanic action of lithium was a result of the celebrated laboratory accident'. In making this statement he referred to a view that Johnson had espoused in his speech in 1983[697] that

> Instead of killing the guinea pigs, both lithium urate and lithium carbonate made the animals less timid, calmer, and less responsive to stimulation. Cade had discovered the calming effect of the lithium ion. He wondered whether it might have the same effect on patients that it had in guinea pigs.

[696]Reines BP.: 'Psychopharmacologic discovery: the relative contributions of clinical and laboratory studies'.AFMA/EFMA/JFMA.Online[URL:http://www.curedisease.com/Perspectives/vol_2_1990/PsycholDisc.tml]. Reines BP.: 'On the locus of medical discovery'. J. Med. Phil. 1991;16:183–209 ('Discovery of anti-manic action of lithium', ibid. pp.197–201).

[697] Johnson FN.: 'The early history of lithium therapy', in Bach RO. (ed.): 'Lithium: current applications in science, medicine, and technology'. New York: Wiley, 1985. pp.337–344.

However, in Reines's opinion, in order to appreciate the nature of Cade's discovery, it would be necessary to understand 'the received view of psychopharmacology' with which Cade had to contend.

Reines pointed out that the nineteenth century literature contains 'abundant clinical evidence' that 'chemotherapy' could affect the mood of human beings; evidence, he contended, not to have been given consideration throughout the first half of the twentieth century. According to him, Cade's discovery 'grew out of his awareness of the 19th century clinical literature'.

Guided by Johnson's book, which, Reines stated, 'traced Cade's rationale for lithium therapy' to Garrod's work - the 1859 edition - on the then ubiquitous 'uric acid diathesis' theory of disease, he went on to give some account of Garrod having postulated that many diseases including gout and rheumatism were caused by an excess of uric acid in the bloodstream, and that the consequent symptomatology was explainable on the basis of uric acid deposition in the joints/or internal organs.

Reines then turned his attention to Garrod's 'simple experiments' in which he demonstrated the solubility of uric acid concretions with lithium salts *in vitro*, observations which made Garrod argue that lithium might have therapeutic properties in diseases that were assumedly associated with uric acid diathesis, for instance, in Reines's words, 'a wide variety of ill-defined disorders of mood': 'gout retrocedent to the head'; 'when retrocedent gout attacks the head, apoplexy is commonly induced, but maniacal symptoms occasionally arise'. Adding that Garrod also referred to 'gouty mania' and 'complete mental derangement', Reines emphasised that Garrod found that 'treatment with lithium cured many of the symptoms' of the mentioned conditions including, in his words, 'their psychic manifestations, leading to increased feelings of well being'.

In the opinion of Reines therefore, Johnson 'hypothesizes that Cade attempted to explain manic psychoses in terms of the uric acid diathesis framework'.

It must be added that Johnson had mooted that this could have been the case, although he expressed it with greater circumspection than Reines leads one to believe.

Reines also scrutinised Cade's experiments with the urine of manic patients. He found that these experiments 'lend credence to Johnson's suggestion'. In particular, he noted that in order to inject uric acid into the guinea pigs Cade 'had to add lithium salts to produce lithium urate, the most soluble of the urates'. He also noticed that Cade injected guinea pigs with lithium urate 'and then lithium alone'. However, in his opinion it was 'not clear' from Cade's technical report of his experiments why he had injected the animals 'with lithium alone'. Instead of such clarification, he added, Cade 'simply' reported that 'a noteworthy result' was that the animals 'although fully conscious, became extremely lethargic and unresponsive to stimuli for one to two hours before once again becoming normally active and timid'.

Reines then pointed out that most accounts of Cade's discovery begin with this 'accidental' observation of the behaviour of the animals, accounts which, he said, 'suggest that the guinea pig results were the crucial evidence that led Cade to try lithium on manic patients'. He also found that such accounts are suggestive of the fact that 'lithium's CNS

depressant effects in guinea pigs led Cade to hypothesize that lithium might also have CNS depressant effects in man'.

However, Reines thought, Cade 'testified against such a simplistic interpretation' of his original report in 1949; he wrote: 'It may seem a long distance from lethargy in guinea pigs to the excitement of psychotics, but as these investigations had commenced in an attempt to demonstrate some possibly excreted toxin in the urine of manic patients, the association of ideas is explicable'.

Therefore, in Reines's view, Cade 'seems to be saying that he had been looking for a treatment for mania and that the image of guinea pigs rendered inactive by lithium impressed him, but he leaves the connection between those two "ideas" to the imagination'. Reines pertinently pointed out that 'just which hypotheses Cade had in mind that connected lithium effects on guinea pig behaviour to potential effects on man is the primary enigma of Cade's work'.

Reines added some explanatory attempts as to what 'hypotheses' Cade 'had to have been guided by':

i) hypotheses relating guinea pig behaviour to human consciousness,

ii) hypotheses about the potential effects of lithium on human consciousness.

Reines decided to examine 'the second class' first, as he thought that this 'will likely shed light on the first class'.

Intriguingly, having consulted Webster's Third International Dictionary, Reines then applied a 'careful linguistic analysis' of Cade's statements regarding the guinea pig results.

The outcome of this search revealed to the author that Cade's statement that the animals became 'extremely lethargic' after injections of lithium was 'anthropomorphic'. Accordingly, basing his observations of the animals' 'unresponsiveness to stimuli' Cade was 'imputing the human feeling of lethargy to guinea pigs'.

Next, he considered Cade's use of the term "sedative effect" in relation to the animals to be their 'unresponsiveness', expressed in 'more-or-less behavioural terms'. Amazingly though, he found that Cade's usage of the term 'lethargy' to signify 'slow-moving guinea pigs', constituted 'projection' in the 'psychoanalytic' sense.

The fact that it is now known, Reines emphasised, that the guinea pigs were more likely 'in a state of acute lithium intoxication', referring to Nathan Kline,[698] than sedation, 'clarifies the extent to which Cade was projecting on the guinea pigs'.

According to Reines, Cade 'must have brought to the guinea pig experiment the expectation of "seeing" an alteration in the mentation of the guinea pigs'. This expection he thought no less amazingly 'may have been subconscious'.

[698] Kline NS.: Lithium: 'The history of its use in psychiatry'. Mod. Probl. Pharmacopychiatr. 1969;3:76–87.

However, it should be reiterated that Healy[699] in his interview with Schou in 1998, without resorting to psychoanalytical explanatory models, also seized on the 'huge contrast' he saw there to be between Cade's talking about lithium's 'seemingly non-specific sedative effect on the guinea pigs' and his subsequent statement that in people with mania it has 'a specific effect almost to the point where he gives the impression that mania must be a lithium-deficient disorder'.

In the view of Mitchell,[700] looking for 'the unexpected' and finding lithium (urate) to be 'protective' and that 'it also sedated the guinea pigs', perhaps Cade thought that it 'might be a good sedating agent' in manic patients. Furthermore, Mitchell thought that Cade was 'really quite surprised by the very specific effect' he then observed. It should be brought to attention again that Schou was of the opinion that Cade had interpreted his animal experiments 'wrongly'.

In Reines's opinion, Cade 'must have had a hunch that lithium had mood-altering properties prior to undertaking the experiment'. In other words, he said, 'he must have had at least a vague working hypothesis about the potential effect of lithium on human cognition prior to the experiment'. Or, some time later, he 'projected on the imagined scene of the guinea pigs'.

Reines felt led to conclude that 'the most likely source' of Cade's working hypothesis was 'the abundant clinical literature on the side-effects of lithium in the clinical literature from the 19th and early 20th centuries'. Underscoring this conclusion he drew to attention that the first page of Cade's classic 1949 paper 'reviews the long standing clinical evidence that lithium exerts powerful effects on the human CNS'. He noted, furthermore, that Cade had referred to Garrod's 1859 work but 'without explicitly citing its relevance, and then leaps to the 20th century, when lithium treatment was often attended by side-effects such as "mental depression, nausea, and giddiness […]" (Cade, 1949, p.349)', finally to refer to Culbreth.[701]

Reines also gave some weight to the fact that lithium had been used 'expressly as an antidepressant' by physicians before Cade's time, and he speculated whether Cade might have known some of them personally: an issue Johnson had brought up.

Reines's final intriguing conclusion was that Cade's discovery of the anti-manic action of lithium was 'based on the clinical evidence that lithium affects human mood, [and] coupled with his wish that it prove a useful treatment for human manic psychoses, Cade hypothesized that lithium would prove useful as a therapeutic agent for mania'. No less intriguing is his view that the discovery 'grew out of the recognition that the 19th

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[699] Healy D.: 'The psychopharmacologists II'. London: Altman, 1998.

[700] Radio National:6.12.1999: 'Manic-Depression'.Online[URL:http://www.abc.au/rn/talks/8.30/healthrpt/stories/s71353.htm].

[701] Culbreth DM.: 'A manual of materia medica and pharmacology, comprising the organic and inorganic drugs which are or have been recognized by the United States Pharmacopoeia and national formulary etc'. 7th Edn. (large edition). Philadelphia: Lea & Fibiger. pp.743–745.

century clinical literature on the mood-altering effects of lithium clearly refuted the early 20th century doctrine that chemotherapy does not induce therapeutically-exploitable side effects in man'. He found that Johnson in his 'seminal' account 'edges' toward such a notion, but 'stops short' of it.

Reines took the opportunity to express amazement that historians have 'regularly cited the guinea pigs results as the source of discovery—and not prior clinical evidence'. This to him was indicative of the fact 'that animal experiments are more memorable than are clinical hypotheses', even to such an extent that 'the former dramatize the latter'.

In this context Reines drew attention to 'a recent paean to animal studies', viz. an editorial by Pincus, Fine, Pardes and Goodwin in the American Journal of Psychiatry in 1986.[702] The authors expressed the view that 'it is essential to recognize the vital importance of research use of animals to progress in psychiatric practice and knowledge […] Lithium, a drug whose clinical potential was first suggested by animal experiments, has dramatically benefited hundreds of thousands of manic-depressive patients'. Similarly, in Reines's words, Goodwin[703] in 1989 'claimed that experiments on guinea pigs led to [the] discovery of lithium's antimanic action'. As before, Reines argued that lithium was used in the treatment of 'various mood disorders, such as depression and "gouty mania", in the 1880s and 1890s'. Moreover, he stressed the fact that Cade 'even reviewed lithium's CNS depressant side-effects in the introduction to his classic paper'.

Notwithstanding this, Reines wrote: 'many modern pharmacologists either are unaware of or choose to ignore the older clinical literature'. - 'Discovery of lithium's antimanic action fits the historical pattern: Lithium's mood-altering side-effects were first identified in humans'.

In 2005 Johnson[704] also commented on Reines's analysis to the present author, to the effect that he and Reines had probably arrived very much at the same opinion; namely, that

> Cade may well have been influenced, guided, predisposed etc., in his decision to try lithium in patients, by some awareness—even of the vaguest and most general kind—of the clinical implications of the uric acid diathesis and the fact that lithium had been used for very many years in a range of therapeutic contexts.

[702] Pincus HA, Fine T, Pardes H, Goodwin FK.: 'The Animal Rights Movement: a research perspective'. Am. J. Psychiatr. 1986;143:1585–1586.

[703] Goodwin FK.: 'We can't sacrifice people for the sake of animal life'. Newsday 1989; May 21:5.

[704] Johnson, personal communication, 25 May 2005.