Johan Schioldann: History of the Introduction of Lithium into Medicine and Psychiatry
Birth of modern psychopharmacology 1949

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

Chapter 22. Cade's professional biography, publications and (possible) scope of inspirational sources

In the attempt to establish the historical and epistemological roots, traditions and sources that Cade might have been acquainted with, inspired by and have drawn on when he generated his hypothesis of manic-depressive illness (and 'primary dementia' or 'dementia praecox'), and in the attempt to shed light on his possible or probable *prior* knowledge of affective disorders and their assumed association with the uric acid diathesis and the resultant use of lithium salts, now follows an outline of his professional biography.[705]

This includes his publications, as well as other sources deemed relevant, be it in a general and/or more specific sense. Moreover, sources pertaining to his interest in nutritional matters, 'protective foods', auto-intoxication, metabolism, electrolytes and vitamins will be included. Finally, consideration will be given to how he determined the doses of lithium salts he prescribed in his original clinical trial.

Cade was born in Victoria, Australia, in 1912. He studied medicine at Melbourne University, graduating in 1934 with honours in all subjects. In his final year he won the forensic medicine prize. The next two years he was a Resident Medical Officer, first at St Vincent's Hospital, Melbourne (under the physician and gastro-enterologist John Horan) and then at the Royal Children's Hospital, Melbourne. During this time, according to his biographer Ann Westmore,[706] he kept 'detailed lists and classifications'. In 1936, he eventually commenced training in psychiatry at Royal Park Psychiatric Hospital, Melbourne. He showed an early interest in research, which, according to Westmore, was influenced by Horan. He subsequently completed, in 1938, a postgraduate degree of MD (without thesis), at the University of Melbourne.[707]

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[705]cf. 'Timeline of John Cade's life'. Aust. NZ. J. Psychiatr. 1999;33, Suppl. S15–16. Cade JF.: 'John Frederick Joseph Cade: family memories on the occasion of the 50th anniversary of his discovery of the use of lithium in mania'. ibid. 1999;33:615-618. Chiu E, Hegarty RM.: 'John Cade: the man'. ibid. 1999; Suppl S24-26. Westmore A.: 'The many faces of John Cade'. (Appendix II).

[706] Westmore A.: op. cit.

[707]'The Melbourne University Calendar 1938'. Melbourne, 1937. pp.410-411, 1022-1023. cf. The requirements in the course of Diploma of Psychological Medicine. ibid., pp.432-434, 1044-1047. Other than references to psychological literature, not relevant in the current context, a list of courses in neuropathology and psychiatry were included. The former included among others 'intoxications and deficiency diseases', the pathology of epilepsy and dementia praecox'. The latter contained 'The causes, signs and symptoms, prognosis and treatment of all Psychoses, Psycho-neuroses and allied conditions'.

The subjects covered physiology, pathology, immunology and medicine. Knowledge of neurology, psychiatry, and pediatrics was also expected. In addition, an examination in the history of medicine was a requirement, as well as a familiarity with microscopical, chemical and bacteriological methods. Other than relevant books attached in the reading lists,[708] candidates were recommended to be acquainted with 'the more important articles' in the respective areas 'in the current British periodicals'. It can be concluded therefore that Cade was equipped with a solid, broad knowledge of the whole field of medicine and psychiatry, theoretical and practical.

It is little known that Cade became one of the Australian pioneers of insulin coma treatment of schizophrenia.[709] According to a paper he published in 1973 on Farran-Ridge to commemorate his contribution to this epoch-making treatment modality,[710] after having read Larkin's paper in 1937 on Sakel's insulin method from 1933[711] he, Cade, 'with youthful enthusiasm […] drew it to the attention of his chief ', Adey, at Royal Park in Melbourne. Then, 'a day in early June, 1937', Cade started using this treatment modality, only some months after Farran-Ridge and Reynolds had introduced it at Mont Park Hospital. Cade did not refer to Farran-Ridge's and Reynolds's own paper about their treatment initiative, published in the Medical Journal of Australia the following year.[712] In this paper the authors adopted as a working hypothesis the view that schizophrenia was, in essence, a deficiency disease, comparable with, but not so simple as, myxoedema.

Further details of Cade's involvement with insulin coma therapy are contained in the report of a meeting of the Section of Neurology and Psychiatry of the Victorian

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[708] ibid., pp.1022–1023 ('Details of subjects for examination for degrees of Doctor of Medicine'). In physiology the following books were recommended reading: Samson Wright: 'Applied Physiology' [1926]; Lovatt Evans: 'Recent Advances in Physiology'; John Pryde: 'Recent advances in Biochemistry' [1931]; Maxwell I.: 'Clinical Biochemistry' [1930]. In medicine 'including the History of Medicine', the recommended books were: Price FW: 'A Text-book of the practice of medicine' [1937] [incl. a chapter 'Psychological Medicine' by Mapother and Aubrey Lewis, referred to later; Lewis: 'Diseases of the Heart'; Foster Moore: 'Medical Ophthalmology'; the 'Recent Advances Series' (relevant volumes); Craig and Beaton: 'Psychological Medicine'; Ross: 'The Common Neuroses'; Still: 'Common Disorders of Childhood'; Singer: 'Short History of Medicine'. Finally, 'for reference' was recommended: Garrison FH.: 'An introduction to the history of medicine'. [Fourth edition, 1929]. Generally, in the medical curriculum at the University of Melbourne, not contained in the above, mention was also made of Dawson WS.: 'Aids to Psychiatry', [fourth edition 1940, cf. p.122]; Hart B.: 'The Psychology of Insanity' (Sixth Year) [1936] (ibid., p1018). Regarding Materia Medica and Pharmacy was recommended: Bruce and Dilling: 'Materia Medica and Therapeutics' (Fourth Year). [1926] (ibid., p.1018).

[709] Cade, 1979, op. cit., pp.55–57 ('Highly controversial—FCI and leucotomy'). 'It took four years [from 1933] before [full coma insulin treatment] arrived in Australia', Cade wrote. However, he did not mention his own involvement.

[710] Cade JF.: 'Clive Farran-Ridge, a man who missed fame by a whisker. A biographical annotation'. Med. J. Aust. 1973;1:1057–1060; Cade, 1979, op. cit. p.17.

[711] Larkin J.: 'Insulin Shock treatment of schizophrenia'. Br. Med. J. 1937;1:745–746.

[712] Farran-Ridge C, Reynolds GP.: 'The insulin treatment of schizophrenia'. Med. J. Aust. 1938;1:100–107.

Branch of the British Medical Association in 1937, recorded in the Medical Journal of Australia the following year.[713] Cade presented brief reports of seven patients whom he and Prendergast had treated with insulin shock. The patients were young people diagnosed with either primary dementia or schizophrenia. It is noteworthy that a distinction was made between the Kraepelian concept of 'dementia praecox', and the Bleulerian wider group 'schizophrenia'.

Cade also espoused the view that 'insulin shock was as valuable a method of study of schizophrenia as it was of treatment', and he thought that 'it was often possible to obtain some idea of the genesis of the psychosis in a particular case'. Further, he had gained the impression that 'the duration of the psychosis before treatment was commenced was less important than the reaction type of the individual'.[714]

In his Farran-Ridge article Cade made reference to Devine's textbook of psychiatry, Recent Advances in Psychiatry.[715] He mentioned it again in Mending the Mind (1979). However, he is also likely to have been acquainted with Devine's well-known book at the time he prepared for his MD, as the Recent Advances Series of which this book formed part, was recommended reading for MD candidates.

On the subject of shock treatment, according to Devine,[716] so-called leucogenic shock in psychoses—via fixation abscesses for the stimulation of leucocytosis—had been in use, for instance by Bruce,[717] whose 1906 book he quoted.

Cade resumed this topic in his 1979 book,[718] stating that 'a fixation abscess is a collection of pus produced by the injection of turpentine, a powerful tissue irritant, into the muscles of the lower back', and 'One writer [i.e. Bruce] claimed that he had found the treatment beneficial particularly in post-puerperal conditions!'

According to Devine, 'the fixation abscess is a collection of pus artificially produced by the injection of turpentine […] under the skin of the flank […] Bruce […]

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[713] Meeting Report: 'The insulin treatment of schizophrenia'. Med. J. Aust. 1938;1:133–135 (cf. ibid., p276 (Corrigendum)).

[714] cf. Kraepelin E.: 'Dementia Praecox and Paraphrenia', 1919. pp.235–240 ('Personal idiosyncrasy'), German Edn. op. cit.. III/II. Teil, 1913. pp.921-927. Kraepelin: 'Manic-depressive insanity and paranoia', 1919. p.177 ('personal idiosyncrasy'), German edition, op. cit., III/II.Teil, 1913. pp.1372–1373, 1365 ('Die persönliche Eigenart'). cf. 8th Edn., I. Band, 1909, pp.206–209.

[715] Devine H.: 'Recent advances in psychiatry'. London: Churchill, 1929.

[716] op. cit. pp.152–153.

[717] Bruce LC.: 'Studies in clinical psychiatry'. London: Macmillan, 1906 (p.231).

[718] op. cit. pp.26–27.

states that he has found this treatment beneficial, particularly in post-puerperal conditions'. Thus, Devine must be Cade's source.

Other things being equal, it is curious that in his book, in mentioning 'fixation abscesses', Cade did not draw attention to the fact that Devine wrote that '*nucleinate of sodium or lithium* have been used in the treatment of the psychoses for their powerful leucogenic action'. Bruce used terebene injections, but he did not mention lithium.

Bruce[719] described the (hyper) leucocytosis theory in 1901, published in the Journal of Mental Science, at the time 'when the toxic theory of the causation of insanity was attracting attention in this country [Great Britain]'. Therefore, to induce such a state he administered a subcutaneous injection of turpentine in manic patients. Having observed an agglutinative action of the blood of these patients upon streptococci—not found in healthy people—he believed that bacterial infections were the causative factor. In Bruce's opinion, in the treatment of acute mania 'the induction of a high polymorphonuclear leucocytosis is a most important point to be attended to'.

Kraepelin[720] mentioned 'treatment by leucocytosis', referring to Itten[721] who 'from this point of view has tried in nine patients injections of sodium nucleinate'. Nothing was obtained, Krapelin commented, and 'the same is true of some similar attempts, which I made myself '. He made no mention of lithium in the current context.

Other than by Horan, Cade would undoubtedly have been inspired to undertake research by Farran-Ridge, who, according to Cade's 1973 paper, had studied 'the constant occurrence of hypo-bromaemia in patients suffering from manic-depressive insanity', and 'the conditions of occurrence of oxaluria, injecting rabbits with the urine and serum of epileptic patients'.[722]

In this context it is relevant to draw to attention that Sullivan, in the Journal of Mental Science in 1901, reviewed a work by Roncoroni[723] in which the author discussed

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[719] Bruce LC.: 'Bacteriological and clinical observations on the blood of cases suffering from acute continuous mania'. J. Ment. Sci. 1903;49:219–231. Bruce LC.: 'Further clinical observations in cases of acute mania, particularly adolescent mania'. ibid. pp.441–447. Bruce LC.: 'On the experimental use of antiserums in acute insanity'. ibid. 1904;50:259–262. Bruce LC.: 'Clinical notes on a case of acute mania; bearing upon the effect of acute intercurrent disease as it affects the mental state'. ibid. 1904;50:283–285. Bruce LC, Peebles AS.: 'Quantitative and qualitative leucocyte counts in various forms of mental disease'. J. Ment. Sci. 1904;50:409–417. Shaw CJ.: 'Observations on the opsonic index to various organisms in control and insane cases'. ibid. 1908;54:57–68 (Bruce p.59). McDowall CF.: 'Leucocytosis: its relation to, and significance in, acute mental disorders'. ibid. 1908;54;669–690. Leeper RR.: 'Some suggestions as regards the origin of modern psychiatric ideas, together with a note of some cases of mania apparently due to microbic infection'. ibid. 1909;55:509–516; McDowall C.: 'The leucocyte and the acute insanities'. ibid. 1909;55:726–744.

[720] Kraepelin E.: 'Dementia Praecox and Paraphrenia'. Translated by R. M. Barclay. From the eighth German edition of 'Text-book of Psychiatry' [1913], vol. iii., part ii, section on the 'Endogenous Dementias'. Edited by G. M. Robertson. Edinburgh: Livingstone, 1919 (pp.281–282).

[721] Not identified.

[722] Cade, 1973, op. cit.

[723] Sullivan WC.: 'Review of Roncoroni L.: 'Relation between epileptic fits and auto-intoxication' [Rapporto tra accessi epilettici ed auto-intossicazione]. (Arch. di Psichiat., vol. xxi, fasc.vi)', J. Ment. Sci.

the published researches by many investigators, and including his personal observations, regarding the toxicity of fresh urine of epileptic patients compared with urine from normal subjects injected intraperitoneally into rabbits. The amount of reaction varied from 'slight depression to death', not only in the different cases, but also in experiments with the same urine, 'suggesting that the gravity of the phenomena depended more on the individual disposition of the animal than on the degree of toxicity of the urine […] Fall of temperature, lassitude, tremors, and paresis were the symptoms chiefly noted; convulsions did not occur'.

In fact, 'nothing distinctive in character or degree was observed in the action of the urine passed immediately after a fit'. In one instance, death ensued after injection of urine from a normal subject. Roncoroni concluded, therefore, that the means of investigation then available were inadequate to determine whether the urine of epileptic patients contained 'special toxic properties'.[724] Finally, his view was that, at most, auto-intoxication could only be considered to be one of the many exciting causes of epileptic fits in predisposed individuals.

It should be added that the 1902 and 1907 abstracted and adapted English editions of Kraepelin's textbook (the sixth and the seventh editions—both by Diefendorf[725] mention, here cited from the latter (1907 edition), that

> if the researches of Krainsky,[726] Cabitto,[727] Agostini,[728] and others can be corroborated, it would seem probable that idiopathic epilepsy is due to a toxic condition arising from faulty metabolism, and that the immediate cause of the convulsions is the accumulation of deleterious substances in the blood or a faulty chemotaxis of the cortical cells.

Krainsky saw some connection between fluctuations in uric acid levels in the blood and epileptic attacks, but he was critical of Haig's work in this field. Kraepelin added that

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1901;47:380-381. cf. Pearce FS.: 'Further laboratory studies on uric acid in neurasthenia, and on autointoxication in nervous disease'. Am. J. Insan. 1900;57:103–115 (Krainsky, vide infra).

[724] cf. Macpherson J.: 'Mental affections: an introduction to the study of insanity'. London: MacMillan, 1899. p.331. Bruce LC.: 'Studies in clinical psychiatry'. London: MacMillan, 1906. p.169.

[725] Kraepelin E.: 'Clinical psychiatry. A text-book for students and physicians. Abstracted and adpated from the seventh German edition of Kraeplin's Lehrbuch der Psychiatrie'. By A. Ross Diefendorf. New edition, revised and augmented. New York: Macmillan, 1907 ('Epileptic insanity', pp.434–456) (437); very similarly described in Diefendorf 's rendition of the sixth edition of Kraepelin's textbook, New York: Macmillan 1902 (pp.329–352).

[726] Krainsky N.: 'Zur Pathologie der Epilepsie'. Allg. Ztschr. Psychiatr. 1897;54:612–665. This work is briefly mentioned in Am. J. Psychol. 1898;9:244: 'The general results of the extended experiments of Dr. Krainsky of Charkow seem to indicate that the blood is the carrier of the epileptic poison. The author made special investigations of the chemical nature of the reactions obtained'.

[727] Cabitto.: 'Rivista sperimentale di freniatria' 23:36ff.

[728] Agostini: 'Rivista sperimentale di freniatria' 1896;22:267ff.

> It is now believed that the blood, sweat, urine, and gastric contents are hypertoxic for some time before, during, and after the seizure, and hypotoxic in the intervallary periods, but no definite conclusion as to the sources of this alteration in toxicity has been reached. [And] even if we should base the known cerebral changes upon a chronic intoxication, we would still need to explain the periodicity of the attacks, the accumulation of toxins, and also the hereditary relationship of epilepsy to other mental and nervous diseases.

What is not included in these English editions is the fact that Krainsky used lithium carbonate in the treatment of epilepsy, ascribing its effect to the lithium ion, via its interaction with carbaminic acid, a precursor of uric acid.[729]

In the Farran-Ridge paper Cade also made reference to a report from 1940, according to which, thanks to Farran-Ridge, 'the diet of the patients has been greatly improved'.

These efforts were 'of particular interest to the present writer [Cade] who, whilst a junior medical officer at Beechworth two years earlier [in 1938], had shown that severe ascorbic deficiency was almost universal in the patient population'.

At that time Australia was in the forefront of scientific nutrition, then an increasingly important topic in medicine. In 1938 the Commonwealth Advisory Council On Nutrition delivered its final report. It was characterised as the largest single statistical and medico-social study undertaken in Australia.[730]

In his 1979 book Cade gave an enthusiastic account of his own nutrition studies, according to which 'dietary deficiencies were manifold' among the patients in psychiatric hospitals in Victoria.[731]

Without naming himself, Cade had undertaken some nutritional surveys in two Victorian hospitals, one being of the Beechworth Mental Hospital in early 1938. 'A new young medical officer' was alerted by the many cases of 'extensive bruising' that he saw. Discarding 'unnecessary force' inflicted by staff or 'assaults' caused by other patients, he decided to seek other explanations and 'quickly came up with the answer'. In testing the

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[729] Krainsky, op. cit., 1897, pp.618, 656–657 ('Es erscheint also von diesem Standpunkte aus betrachtet nicht das Brom an und für sich als das wirksame Hauptagent, sondern eher das Alkalimetall, welches in Verbindung mit Brom am leichtesten in die oben geschilderte Reaction tritt […] [Es] lässt sich […] erklären […] dass mittlere Dosen von Lithiumcarbonat eine günstige Wirkung auf die Epilepsie erzeugen, während grosse Dosen scharfe Intoxicationserscheinungen und Verstärkung der Anfälle hervorrufen. Indem das kohlensaure Lithium in Wechselwirkung mit dem carbaminsauren NH3 tritt, erzeugt es carbaminsaures Lithium und kohlensaures Ammonium […]' Finally, Krainsky stated that 'die therapeutische Dosis des Lithiumcarbonats sehr schwer zu controlieren ist'. cf. Pearce FS.: 'Further laboratory studies on uric acid in neurasthenia, and on autointoxication in nervous disease'. Am. J. Insan. 1900;57:103–115 ('Krainsky demonstrated by a series of experiments that epilepsy is an intoxication and that the poison is in the blood. By injecting blood drawn from a patient in the status epilepticus into a rabbit, he produced violent epileptic seizures two or three minutes later. Blood drawn from the same patient after the seizure, when injected into the rabbit, produced no effect. He concludes that the irritant to the cerebral cortex in these cases, is a substance closely related to uric acid, i.e., carbamate of ammonia […]'). cf. Kraepelin: 'Psychiatrie. Ein Lehrbuch', 7th Edn., 1904, pp.678–679. Kraepelin, 1913, pp.1082–1083, 1130–1131, 1172–1173. Marr HC.: 'Review of Guidi G.: [The pathogenesis of epilepsy: an experimental research]. Riv. Speriment. Di Freniat. Vol. 34, fasc. i-ii. J. Ment. Sci. 1909;55:378–379.

[730] Anon.: 'Constructive medicine and nutrition'. Med. J. Aust. 1938;2:609–610. 'Final report of the Commonwealth Advisory Council on nutrition'. ibid., 1938;2:614–615. Anon.: 'Nutrition among the nations'. ibid., 1939;1:624–625; Anon.: 'The scientific basis of nutrition'. ibid., 1939;2:938.

patients for vitamin C levels, he established that these were 'grossly deficient'.[732] His alarming report'[733] resulted in the appointment of a departmental dietitian 'and the virtual disappearance of vitamin deficiencies within Victorian mental hospitals ever after'.[734]

Besides his interests in scientific nutrition, Cade had a strong research interest in the aetiology and nosology of schizophrenia and manic-depressive illness.

In 1940 he published: A statistical study of the onset of primary dementia.[735] Here he highlighted that 'present teaching, following the work of Kraepelin, is that there are all gradations in the schizophrenic states, from hebephrenic primary dementia at one end of the scale to true paranoia at the other'.

Cade commented that it was a well-known clinical fact 'that there is no sharp dividing line between paranoidal primary dementia and paranoia, that often enough it is impossible to make a differential diagnosis'. Therefore, it appeared to him 'quite unnecessary to attempt to distinguish between these states, as they are not closely related psychoses, not sub-species of the genus schizophrenia, but actually clinical variants of one and the same psychosis'.

Notwithstanding his own reservation about this diagnostic, Cade did not suggest that the terms primary dementia and paraphrenia be discarded 'in favour of the wider concept of schizophrenia', as he found them useful from a clinical point of view.

This interesting paper contains no formal references, but it must be assumed that Cade was well acquainted with Kraepelin's seminal work. This assumption is corroborated by his characterisation of Kraepelin in: Mending the Mind (1979), as 'the great German psychiatrist', a 'supreme' systematist, who belonged with 'the great thinkers' in psychiatry. 'Probably his greatest contribution', Cade thought, was that he 'sharply' separated 'the two major constitutional illnesses, manic-depressive or affective disorders, and what he called "dementia praecox" and its sub-types'. How important this was, Cade added, 'only became apparent many years later when it was shown that what was specific treatment in one was quite ineffective in the other'.[736] In other words, Cade is here referring to lithium.

If Cade had not consulted Kraepelin's work in its original language, German, he would have had ready access to important parts of it in English; for example, Dementia

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[731] Cade, 1979, op. cit. pp.18–19.

[732] cf. Anon.: 'Vitamin C and haemorrhagic conditions'. Med. J. Aust. 1936;1:475–476. Anon.: 'Vitamin C'. ibid. 1936;2:90–291.

[733] This item was not retrievable.

[734] op. cit. pp.18–19.

[735] Med. J. Aust. 1940;2:285–287. The same year, he co-authored (with F.M. Burnet and D. Lush): 'The serological response to influenza virus infection during an epidemic, with particular reference to subclinical infection'. ibid., 1940;1:397–401, containing an account of 'an acute epidemic in a ward of a mental hospital' in 1939.

[736] op. cit. pp.88–89 (cf. ibid. pp.72–73).

praecox and paraphrenia, from 1919—translated from Kraepelin's textbook, the eighth edition, of 1913.[737]

Kraepelin wrote here that 'the obscurity that hangs over the causes of dementia praecox' had often led to examination of the blood-picture and of metabolism; however, thus far the findings had not been 'very satisfactory'. Berger,[738] whom Kraepelin referred to, had attempted to prove the presence of toxic material in the blood of catatonics. Kraepelin also made reference to Pighini,[739] who in acute cases had observed increased excretion of nitrogen, phosphorus, sulphur, urea, uric acid, and xanthin bases—which he thought was connected with the increased breakdown of nucleoproteins containing phophorus and sulphur. In this connection, according to Kraepelin, Allers[740] had drawn attention to the possibility of insufficient nourishment playing 'an essential part in the states of excitement', whereas, during the chronic course, a retention of phosphorus and nitrogen, and a loss of lime and sulphur, were assumed. Kraepelin himself had observed 'diffuse enlargements of the thyroid gland, occasionally the disappearance of such enlargements immediately before the first appearance of morbid phenomena', as well as 'repeated rapid change in the size of the gland during the development of the malady'. Kraepelin went on to state, though with some reservation,

> that a series of facts in dementia praecox up to a certain degree makes probable the existence of an auto-intoxication in consequence of a disorder of metabolism, [but] about the source and kind of the toxin circulating in the body, we can certainly at present give […] little account as in the metasyphilitic or metalcoholic diseases […][741]

In 1921 followed the translation into English of the relevant chapters on *manic-depressive insanity* and *paranoia*, also from the eighth edition of Kraepelin's classic textbook (1913).[742] It contained a detailed account of the aetiology of 'manic-depressive

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[737] Kraepelin E.: 'Dementia Praecox and Paraphrenia'. Translated by R. M. Barclay. From the eighth German edition of 'Text-book of Psychiatry' [1913], vol. iii., part ii, section on the 'Endogenous Dementias'. Edited by G. M. Robertson. Edinburgh: Livingstone, 1919 (pp.85–87, 244–245) (In the German edition described under 'Die endogenen Verblödungen' A. Dementia praecox pp.668–972).

[738] Not identified.

[739] Pighini G.: 'Il ricambio organico nella demenza precoce'. Rivst. Sper. Freniatria 1906' Vol. 32, I-II. Pighini G, Statuti G.: 'Metabolism in dementia præcox'. Am. J. Insan. 1910;67:299–316 (Kraepelin refers to Rivist. Sper. Freniatria xxxiii, 566). In the 1910 paper Pighini compared 'the azotic balance' in four cases of dementia praecox with one of manic-depressive psychosis. The latter 'gave results that may be considered relatively normal'.

[740] Not identified.

[741] cf. Noll R.: 'Historical review: autointoxication and focal infection. Theories of dementia praecox'. Wld. J. Biol. Psychiatr. 2004;5:66–72.

[742] Kraepelin E.: 'Manic-depressive insanity and paranoia'. Translated by R. M. Barclay. From the eighth German edition of 'Text-book of Psychiatry', [1913] vols. iii. and iv. Edited by G. M. Robertson. Edinburgh: Livingstone, 1921. pp.48–49, 182–183; German edition: pp.1232–1233, 1371–1373.

insanity' from a wide variety of sources. Importantly, this English edition was reviewed the same year in both the Journal of Mental Science[743] and the Medical Journal of Australia.[744] Therefore, this particular work could not have escaped Cade's attention, for instance during his MD thesis preparations.

According to this book, Kraepelin placed an emphasis on the various reversible bodily changes in manic-depressive illness, stating 'that in [this illness] marked *disorders of metabolism* must take place'. However, he found it unfortunate that 'the results of investigations carried out in regard to this have been up till now still rather unsatisfactory'. He went on to refer to Mendel,[745] who in the urine of manic patients found a decrease of phosphorus, whereas Guérin[746] and Aimé[747] found the excretion of lime and magnesia to be increased. Seige[748] had been unable to show any abnormality in the metabolism of minerals. However, in melancholia he had observed a strong tendency to the storage of nitrogen, which 'then is suddenly excreted in increased quantity'. Importantly Seige opined that the endogenous excretion of uric acid 'remains in depressive patients at the lower limits of the normal, whereas in manics it is reduced'. Here, according to Kraepelin, 'it appeared to be a case of abnormally rapid breaking down of the purin bodies to still lower stages of disintegration', as he referred both to Carl Lange and Stegmann.[749]

Raimann[750] had established that in depression 'alimentary glycosuria' could be produced. Schultze and Knauer[751] had demonstrated the same phenomenon in manic-depressive insanity as in other forms of psychic disease. Pini[752] found that 'the reducing power of the urine' in general was raised, 'especially in mania', but 'lowered in long-continuing states of excitement'.

Futher, Kraepelin noted that Alberti[753] had investigated the toxicity of urine and blood serum, but 'without obtaining any useful results'. Pilcz[754] had fairly frequently been able to establish 'the appearance of all kinds of abnormal substances in the urine, acetone, diacetic acid, indican, albumose, which re-appeared in the attacks of the same patients, but without any definite relation to the colouring of the mood being recognized'.

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[743] Lord JR.: 'Book review: Kraepelin on manic-depressive insanity and paranoia'. J. Ment. Sci. 1921;67: 342–346.

[744] Anon.: 'Book review of: Kraepelin on manic-depressive insanity and paranoia'. Med. J. Aust. 1921;1:442.

[745] Possibly E. Mendel's 'Phosphorsäure im Urin von Geisteskranken'. Arch. Psychiatr. III (quoted from Stransky, op. cit. 1911). Mendel had also authored: 'Die Manie'. Wien-Leipzig, 1881 (from Stransky), reviewed by Chatelain in Ann. Méd-Psychol. 1881;2:159.

[746] ?Guérin: Rôle de l'auto-intoxication. Ann. Méd.-Psychol. 1881;2:159. (Stransky quotes a work by Guérin-Aimé [Revue neurol. 1901, p.690—metabolism]).

[747] idem.

[748] ?Seige: 'Stoffwechseluntersuchungen bei Melancholie und zirkulärem Irresein'. Neur. Zentralbl. 1909:550ff. (Monatsschr. Psych. Neur., 1908), quoted from Stransky.

[749] Not identified

[750] ?Raimann: 'Über Glykosurie und alimentäre Glykosurie bei Geisteskranken'. Zeitschr. Heilkd. 1902, quoted from Stransky.

[751] ?Schultze, Knauer: 'Störungen des Kohlenhydratstoffwechsels bei Geisteskranken'. Allgem. Zeitschr. Psych, vol 66, quoted from Stransky.

Taubert[755] found indicanuria in mania, often 'one or two days before the outbreak of incitement', whereas Seige[756] observed 'indican disappear almost completely from the urine in excitement'. Townsend[757] (also quoted by Devine) had been able to demonstrate an increased indoxyl excretion, especially 'strongly marked' in states of depression, disappearing 'shortly before the appearance of psychic improvement'.

Apparently, Kraepelin added, 'it is here everywhere a case of the consequences of intestinal disorders which are so frequent in manic-depressive insanity'. Pardo,[758] who had undertaken comprehensive investigations into the 'coprology' of the disease, was inclined to regard as its essential foundation 'the *intoxication* of the body by the metabolic products of *intestinal* bacteria', or that it was 'started by dietetic errors'. Hannard and Sergeant[759] had found 'frequent cholæmia' in states of depression. Parhon[760] and Marbe[761] had suggested an '*insufficiency of thyroid gland activity'*. Stransky,[762] who also searched for an explanation for manic-depressive disorder from the viewpoint of metabolic disorders, according to Kraepelin, 'conjectures *auto-intoxication by*

[752] Pini O.: 'Pouvoir réducteur des urines dans la folie maniaco-dépressive'. Ann. Méd.-Psychol. 1912;1:360ff.

[753] Not identified.

[754] Pilcz A.: 'Die periodischen Geistesstörungen'. Jena, 1901.

[755] Taubert: 'Über Indikanurie beim manisch-depressivem Irresein.' Neurol. Zentralbl. 1909, p.846 (from Stransky).

[756] Seige M.: 'Periodische Indicanurie bei zirkulärer Psychose. Vorläufige Mitteilung'. Monatsschr. Psychiatr. Neurol. 1908:178–180. In depression stages an enormous increase of indican excretion was observed. Stransky also quotes Seige's work: 'Stoffwechseluntersuchungen bei Melancholie und zirkulärem Irresein'. Neur. Zentralbl. 1909, p.550ff.

[757] Townsend AD.: 'Mental depression and melancholia considered in regard to auto-intoxication, with special reference to the presence of indoxyl in the urine and its clinical significance'. J. Ment. Sci. 1905;51:51–62. His work was inspired by the fact that 'the more modern and advanced opinion of the present day, not of necessity the most correct, regards toxic action as the most important factor in the pathogenesis of insanity […] It is necessary for those who advance the theory of toxaemia as the essential factor in the production of insanity to marshal facts supporting their contention'. He went on to state that 'by the term "auto-intoxication" we indicate toxins evoked within the body as a result of disordered metabolism, first, such as takes place in chronic Bright's disease, myxoedema, diabetes, etc.; and secondly, in the contents of the gastro-intestinal tract'. Townsend investigated patients suffering from 'acute melancholia' and 'acute mania', finding that in depressed states indoxyl 'is always present in excess, and that in maniacal states it is usually only in minute or normal amount', derived from the intestinal tract (this paper was quoted in Devine's book, p.70, ref. 8). cf. Bruce C.: 'The clinical significance of indoxyl in the urine'. ibid., 1906;52:501ff.. Easterbrook CC.: 'Insanity and indicanuria (indoxyluria): a note of criticism'. ibid. 1906;52:766–776.

[758] Pardo S.: 'Coprologie dans la folie périodique'. Ann. Méd-Psychol. 1912;2:259. He also authored: 'L'indoxylurie dans les maladies mentales'. ibid., 1910;1:151, 268, 309.

[759] Hannard P, Sergeant J.: 'Cholémie et états mentaux dépressifs'. Ann. Méd-Psychol. 1911;1:448.

[760] Stransky cites C. Parhon's 'Un cas de mélancholie, avec hypertrophie thyroid. succédant à la ménopause'. Revue neurol. 1906. In this connection Stransky mentions the 'Thyreoideatheorie'. Another work by Parhon was his 'Glandes endocrines et psychopathologie mentale'. Ann. Méd-Psychol. 1913;2:346. Stransky also made reference to Parhon and Marbe: Contribution à l'étude des troubles mentaux de la maladie de Basedow (cited from Antheaume).

[761] idem.

glandular products', (Stransky) mentioning the possible links between Basedow's disease and the occurrence of manic-depressive illness.[763]

It should be added that Stransky discussed the striking similarities between the so-called 'formes frustes' of Basedow's disease and manic-depressive illness, especially mania. Importantly, he also mentioned that Carl Lange, in states of 'periodical depression', had often found increased uric acid levels ('uratic diathesis'),[764] in which context he, Stransky, referred to Kowalewsky's work from 1901 on gout and neuroses,[765] expressing great amazement that he could recommend antigout ('antipodagrische') treatment in such cases resembling Lange's cases of cyclothymia. Among others, Kowalewsky discussed Lange's work and treatment with lithium water.

Kraepelin himself was of the opinion that the aetiology of manic-depressive illness was that of metabolic disturbance, and its pathogenesis that of auto-intoxication,[766] and he found some support for 'the thought of *internal poisons*'.[767] However, he also found it worthy of note that in 'manic-depressive insanity the special form of the picture appears to be in greater measure dependent on the psychic personality than we are accustomed to seeing it in pure effects of intoxication'.[768]

Kraepelin's work bears testimony to the fact that *auto-intoxication* as a causative factor in mental illness had gained considerable momentum.

However, as we learnt before, Kraepelin dismissed the Lange theory of periodical depressions in his book, now cited from the English edition:

> [Carl] Lange[769] [with full reference to his depression treatise] has arrived at the opinion that increased formation of uric acid may be regarded as the essential cause of states of depression […] Lange has assumed as the foundation of periodic depressive states with psychic inhibition, which indubitably belong to the domain of the malady here described [manic-depressive psychosis], a *gouty* mode of development [*uratic* not *gouty*!], a view which, however, till now cannot be regarded as proved or even as probable'.

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[762] Stransky E.: 'Das manisch-Depressive Irresein'. Leipzig: Deuticke, 1911 (Aschaffenburg's 'Handbuch der Psychiatrie'. Spezieller Teil. 6. Abteilung, 1911).

[763] ibid., pp.98–99, 131, 142–143.

[764] ibid., p.96. cf. ibid. p.99, p.142.

[765] Kowalevsky: 'Podagra und Neurosen'. Zentralbl. Nervenheilk. Psych. 1901;24:595–608. Stransky, 1911, p.142. cf. J. Ment. Sci. 1903;49:165 ('Gout and neuroses').

[766] Kraepelin E.: 'Psychiatrie'. VI. Auflage. 1899. II. p.408. cf. Thalbitzer, op. cit. 1902. p.31.

[767] Kraepelin 1921, op. cit. p.183 (from 8th Edn).

[768] loc. cit. cf. ibid., p.177 ('personal idiosyncrasy'), German edition, 8th Edn., III/II.Teil, 1913. pp.1372–1373, 1365 ('Die persönliche Eigenart'). cf. 8th Edn., I. Band, 1909, pp.206–209. Kraepelin: 'Dementia Praecox and Paraphrenia', 1919. pp.235–240 ('Personal idiosyncrasy'), German Edn. III/II. Teil, 1913. pp.921–927.

[769] ibid., pp.48, 182 (note 1).

In this context Kraepelin added that Stegmann[770] 'found in "periodic neurasthenia", which certainly belongs to manic-depressive insanity, diminution of uric acid excretion at the time of moodiness'.

In the opinion of the present author, at least the two English renditions (1919, 1921) of important sections of Kraepelin's classic textbook, the eighth edition of 1913, the latter (1921) having been reviewed in both the Journal of Mental Science and the Medical Journal of Australia, in 1921, can very well have been important inspirational sources for Cade when he generated his hypothesis of the aetiology of dementia praecox and manic-depressive illness.

Importantly, if Cade had read these works he would also have become acquainted with the *Lange theory of periodical depressions* and their presumed causative association with *uric acid diathesis*, thus establishing a link to treatment with lithium salts.

Among other 'great thinkers' in psychiatry, Cade mentioned Eugen Bleuler.[771] His textbook of psychiatry, also epoch-making, was translated into English in 1924 (the fourth edition by Brill).[772] However, this work contains nothing of relevance for the current topic.

Other than learning about Lange's work via Kraepelin, Cade could have become acquainted with it via a review of Kurella's German edition of Lange's treatise in the Journal of Mental Science in 1897:[773]

> Dr. Lange gives a graphic description of a form of mental depression which he has found frequent in Copenhagen. Since his attention has been expressly turned to this condition, the Professor has studied it in from 700 to 800 cases [in fact, at that time, more than 2000 cases].

Paraphrasing Lange, the reviewer described how the patient is weighed down, and how

> he dislikes to commence anything, and takes an interest in nothing. The state of the male patient is more often characterised by a want of initiative; that of the female by apathy [Lange wrote: it is often the obtuseness of their emotions that comes to the fore'; the German translation reads: 'Abstumpfung des

[770] . Not identified. cf. Wilcox RW.: 'A phase of the treatment of goutiness'. Medical News 1897;Nov.:684–687. The purpose of this paper was to point out that 'a very considerable number of so-called neurasthenics are really patients who are suffering from goutiness of the particular variety known as neurotic lithemia. The clearing of the mental atmosphere of depression as soon as the stored uric acid is set in motion toward excretion is remarkable […] Uric acid, as a causative factor in neurotic lithemia, a form of goutiness, should not be overlooked'. Further, in Wilcox's opinion, Piperazin in vitro has proven to be an efficient and harmless solvent for uric acid. When augmented with phenocol 'better results are obtained'. cf. Pearce FS.: 'Further laboratory studies on uric acid in neurasthenia, and on autointoxication in nervous disease'. Am. J. Insan. 1900;57:103–115.

[771] Cade, 1979, op. cit. p.89.

[772] Bleuler E.: 'Textbook of psychiatry' [from 'Lehrbuch der Psychiatrie']. New York: Macmillan, 1924.

[773] Lange, 1896, op. cit. Anon.: 'Periodische Depressionszustände und ihre Pathogenesis auf dem Bodem der harnsauren Diathese. Von Professor C. Lange. Hamburg'. J. Ment. Sci. 1897;43:344–346.

> Gefühls'; *added by the present author*]. The lowness of spirits is seldom so intense as to bring the subject into a lunatic asylum. The affection is distinct from both hypochondria and neurasthenia. With the latter condition it is often confounded. Though the general health is enfeebled, Dr. Lange considers that in this dyscrasia the mental symptoms are of more consequence than the bodily ones. The mental depression is not readily guessed from the faces of the patients. The sleep is unquiet […] the feeling of distress is worse in the morning and passes away in the evening. The melancholy is not progressive, and there are neither fixed ideas nor hallucinations.

Concerning the pathogenesis, the reviewer wrote:

> Dr. Lange considers that the most constant and important bodily symptom in this dyscrasia is the tendency to the deposit of a large sediment in the urine. This occurs independently of the occasional causes which favour the deposit of uric acid. An inquiry into the composition of the blood in this disorder is much to be desired [also referring to Boucheron].[774]

The reviewer drew to attention that 'the Danish physician' regards 'oxaluria', as described by Golding Bird 'thirty or forty years ago' to be an 'incomplete and ill-defined generalisation'.[775] Regarding this issue, the reader was referred to Clouston's Clinical Lectures on Mental Diseases,[776] containing 'a description of it, along with phosphaturic insanity'. However, 'Lange refers with more favour to the researches of Haig on the uric acid dyscrasia'.

The reviewer also quoted Lange's recommendation that the treatment of the depression 'should be directed to combat the uric acid diathesis'. Finally, he praised Lange for his pamphlet, which 'is written in an engaging style, and is clearly the result of ripe experience'.

In Lange's depression treatise *oxaluric insanity* was implied, and *nervous phosphaturia* was mentioned. This is suggestive of the fact that Lange could have been acquainted with Skae's classification from 1863 of mental illnesses,[777] which was adopted by Clouston. One group in the classification, 'group 8', was 'gouty (podagrous) insanity',

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[774] Lange wrote in a note to his depression treatise, 1886 (English edition 2001), Appendix I: 'A direct proof that a uric dyscrasia exists, the presence of uric acid in the blood of the depressed patients, would, of course, be very desirable, but this is just as difficult to provide in these cases as in other forms of this dyscrasia. Boucheron found that saliva gave a positive murexide reaction in a number of patients in whom he felt that he could assume the presence of uric acid diathesis (cf. l'Union Médicale 1881;121). The same appears to have been the case in several of my patients whose saliva I have tested according to Boucheron's method. But lacking sufficient comparative investigations, I do not thus far attach any importance to these results'. cf. 'Weidel's test' (Dorland's 'Illustrated Medical Dictionary', 25th Edn. 1975. pp.988, 1587).

[775] Lange 1886, 1895, 1896, op. cit.

[776] Clouston TS.: 'Clinical lectures on mental diseases'. 2nd Edn. London: Churchill, 1887. pp.463–465. idem, 6th Edn. 1904. pp.506–507.

[777] Skae D.: 'The classification of the various forms of insanity on a rational and practical basis'. 1863. cf. Tuke's 'Dictionary of Psychological Medicine'. 1892. Vol. 1, pp.231–232.

and ‘some rare varieties’ were added, among them ‘the insanity of oxaluria and phosphaturia’.[778]

It is also relevant to draw attention to Régis and Chevalier-Lavaure, who at the la Rochelle conference in 1893 on the subject of ‘Auto-intoxication in mental disease’,[779] reported the same year in Medical Week,[780] stated that ‘it has been shown by chemical analysis [‘and experimental evidence’] that the composition of the various fluids of the body (blood, urine, gastric juice, bile etc.) undergoes certain modifications in the insane’. Moreover, they stated, ‘during the last few years several investigators have succeeded in demonstrating by actual experiment that the physiological toxicity of these fluids was frequently below normal in mental diseases’. Régis and Chevalier-Lavaure went on to state that

> Most of these investigators agree that the urine is much less toxic than normal in cases of mania, while the lethal action of this fluid is increased in melancholia […] It is also stated that the urine of the maniacal and melancholic possesses different properties as shown by the effects produced on animals […] Maniacal urine is said to give rise to excitement and convulsions when injected into an animal; while the injection of the urine from a case of melancholia is followed by depression of spirits, restlessness and stupor, an irrefutable proof that auto-intoxication is the cause and not the effect of the mental condition.

To this the authors added that

> As in certain affections directly due to auto-intoxication, such as eclampsia for example, so in mental diseases the toxicity of the blood varies inversely with that of the urine. Thus in mania the blood is the more toxic, the less toxic the urine.

From the clinical point of view, they emphasised that

> the evidence afforded by the facts of clinical observations is still somewhat incomplete, but it is based on certain results which tend to show that auto-intoxication plays an important part in the aetiology of mental diseases.

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[778] In the opinion of Lemoine, neurasthenics generally suffered from phosphaturia that he treated with subcutaneous injection with phosphate solutions every two days. In his experience, ‘patients have, under its influence, come from a state of profound depression into a condition of excitement so marked that he was obliged to diminish or suspend the injections’ (quoted from Practical Notes, Practitioner 1901;13:716–717—the original source being ‘Nord Médical’, quoted in Medical Record, no year given).

[779] Chevalier-Lavaure FA.: ‘Des autointoxications dans les maladies mentales’. Thesis. Bordeaux, 1890.

[780] ‘Medical Week’ 1893. August 11:373–375 (a discussion by these authors and others at the ‘French Congress of Psychological Medecine’ [Congrès des Médecins Aliénistes des Pays de Langue Française]. La Rochelle, 1893:13). cf. Chevalier-Lavaure F.: ‘Des Auto-intoxications dans les maladies mentales’. Bordeaux, 1890.

These results, the authors stressed, ‘have lately been confirmed by recent researchers on the varieties of insanity associated with acute infectious diseases, and with visceral and diathetic affections’.

Among others, the authors also made reference to how in the febrile stage of infectious diseases ‘the mental symptoms frequently take the form of more or less violent delirium, so much like that produced by intoxicating substances that it is not always easy to distinguish it from the delirium of alcoholism’. Moreover, they related that from a clinical point of view, ‘disease of the internal organs does not give rise to such characteristic mental troubles as are observed as a consequence of infectious diseases’. However, they wished to mention that in cases of acute auto-intoxication, ‘the effect on the cerebral centres is manifested in the form of acute toxic delirium closely allied to that produced by alcohol […]’. Although they considered it probable that the insanity that is associated with disease of the internal organs, or ‘visceral insanity’, was due to auto-intoxication—‘indeed we are inclined to regard it as the most typical illustration of the influence of auto-intoxication on the mental faculties’—there ‘is not as yet sufficient experimental evidence […] in favour of this assumption […]’ This view, they emphasised, related especially to the mental disturbances that ‘are dependent on digestive troubles’ of which ‘we know next to nothing about the concomitant changes in the chemistry of gastric digestion and toxicity of the intestinal contents’.

The views of Régis and Chevalier-Lavaure on auto-intoxication were referred to by Oliver,[781] the following year, to underscore that ‘the part played by auto-intoxication in mental illness is attracting attention’.

Ballet, also at the la Rochelle conference, described a series of experiments performed with the assistance of Bordas and Roubinovitch on the toxicity and chemical composition of urine in the insane. The experiments were performed on rabbits with the urine from patients suffering from, for example, melancholia, mania and mental confusion. Urine from melancholics was ‘always more toxic than normal’, this being consistent with what other investigators had observed. Moreover, in most cases the increased *urotoxicity* coincided with the presence of digestive disorders. It was noted that in three cases of mania the urine was ‘apparently less toxic than normal’.

Ballet and Roubinovitch[782] expressed the view that the urine of melancholiacs was ‘hypertoxic’, and that of maniacs less so, whilst from *mental degenerates* ‘very variable results were obtained’. Chevalier-Lavaure[783] compared ‘the toxicity of serum with the urine’, and in two cases of mental confusion found that both were distinctly ‘hypertoxic’.

In two of his patients presenting the same symptoms, Sèglas found that urine, when injected into rabbits, was ‘less toxic than normal in one and more toxic in the other, while

[781] Oliver T.: ‘Preface’, in Bouchard C[J].: ‘Lectures on auto-intoxication in disease or self-poisoning of the individual’. Philadelphia: Davis, 1894. pp.v-xii. cf. Noll R.: ‘Historical review: autointoxication and focal infection. Theories of dementia praecox’. Wld. J. Biol. Psychiatr. 2004;5:66–72.

[782] According to A. Prunier (cf. Clarke S. in J. Ment. Sci. 1908;54:603), also at the Congrès des Médecins Aliénistes des Pays de Langue Française. La Rochelle, 1893.

[783] idem.

no change was observed in the toxicity of the blood-serum in either case'. Moreover, although he found auto-intoxication to be the cause, 'the fact cannot as yet be demonstrated with certainty by the chemical and experimental methods at our disposal'.

Voisin had investigated the toxicity of urine in epilepsy, observing, in accordance with investigations he had undertaken before, that the urine was less toxic than normal.

Michau had examined the urine of 'some fifty gouty patients'. In all of them the urine contained a large quantity of uric acid and traces of albumen; Mabille agreed that albuminuria was 'a very frequent complication of the gouty diathesis'. The patients, it was added, 'fall into a state of profound depression, worse in the morning', and they 'exhibit various disturbances of nutrition with the excretion of large quantities of uric acid at periodical intervals'. In most cases, it was reiterated, the urine contained 'a small percentage of albumen'. Indican was also frequently found in the examination of the patients' urine, and it was supposed to be associated with nutritive and digestive disturbances.

An important work in the field of *auto-intoxication* by Bouchard[784] appeared in an English edition in 1894.[785] He carried out one experiment with respect to the toxicity of uric acid in urine, injected intravenously into a rabbit,[786] and observed that the uric acid was dissolved into soda lye and distilled water. The animal died slowly after 'very strong convulsions'. Bouchard then undertook a control experiment with the same quantity of soda lye, but without uric acid. This time the animal died. He concluded therefore that the death ought to be attributed to 'the excess of the vehicle', i.e. the amount of distilled water injected.

Bouchard's work was not generally concerned with mental disorders; this was subsequently taken up by Viggo Christiansen in his doctoral thesis (1898).[787] As mentioned before, he had undertaken more than five hundred urotoxicity experiments, injecting rabbits with urine from normal and psychotic probands. The work was reviewed by Friis[788] in the Journal of Mental Science the following year.

According to Friis, 'unfortunately' the results of this work were 'not proportionate' to Christiansen's 'labours'.

> The book is difficult to read and hard to get a comprehensible view of, owing to the many numerical tables and tabulated statements of experiments which are introduced into the text. [Christiansen] has imitated the methods of

[784] Bouchard CJ.: 'Leçons sur les autointoxications dans les maladies'. Paris: Sauy, 1887.

[785] Bouchard C[J].: 'Lectures on auto-intoxication in disease or self-poisoning of the individual'. Philadelphia: Davis, 1894 (with a preface by T. Oliver).

[786] op. cit. pp.51–52.

[787] Christiansen V.: 'Om Urinens Giftighed, specielt hos Sindssyge. En experimentel Studie'. Copenhagen, 1898.

[788] Friis A.: 'On the toxicity of urine, especially in insane patients: an experimental study. By V. Christiansen'. J. Ment. Sci. 1899;45:389–390.

> Bouchard and his pupils, who have written on the toxicity of the urine under different conditions. He criticises the results of these authors, pointing out their weak points and deficiencies, but, as hinted above, his own results do not seem more valuable or more assured.

Friis then proceeded to inform the readers that Christiansen's

> researches were made at the St. Hans Mental Asylum at Roskilde [near Copenhagen], and involved more than 500 experiments on rabbits, injected with urine from patients in mental conditions which varied exceedingly, both aetiologically and symptomatologically [general paralysis and typical paranoia were excluded]. The principal result the author believes he has attained is to show that in all psychopathic conditions, notwithstanding their various clinical appearances and aetiology, the quantity of toxines secreted in the urine in twenty-four hours is less than in the normal conditions (the 'urotoxic co-efficient' ['the convulsant coefficient'] of normal urine being 0.32 to 0.49, of the urine of the insane about 0.2). No conclusion can be drawn from the intoxication of animals by urine as to the psychical condition of the patients. The author more especially remarks the oncome of convulsions in no way depends on a greater or lesser degree of exaltation, but they may set in even very violently in connection with cases resembling stupor. The symptoms of urinary intoxication depend, within rather wide limits, on the individual of the animal experimented on.

Uric acid was mentioned, reference being made to Bouchard's trial. However, Christiansen's thesis was not concerned with this matter.

Christiansen[789] took up the issue of uric acid in 1906 in connection with his strong criticism, two years before, of the Lange brothers' theory of periodical depression and its assumed causation by uric acid. For this purpose he had analysed the blood and urine in three patients suffering from 'typical periodical depression', but observed no uric acid abnormality.

Bruce,[790] in his well-known psychiatric textbook (1906), strongly supported the view, referred to above, that the causation of 'the vast majority of acute insanities', which was 'steadily gaining ground both in this country [Great Britain] and abroad', was 'the toxic theory of origin'. Inspired by Macpherson,[791] he described auto-intoxication resulting from: i) physiological instability; ii) defective metabolism; iii) defective gland secretion; iv) auto-intoxication from the alimentary tract; v) auto-intoxication from the liver and kidneys.

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[789] Christiansen V.: 'Kliniske Forelæsninger og Foredrag over Sindssygdomme'. Copenhagen: Lund, 1906. p.168.

[790] Bruce LC.: 'Studies in clinical psychiatry'. London: Macmillan, 1906. (pp.35–36, 47, 64, 71, 102, 112, 220, 223). Bruce LC.: 'The Symptoms and Etiology of Mania . The Morison Lectures 1908'. J. Ment. Sci. 1908;54:207–264.

[791] Macpherson J.: 'Mental affections: an introduction to the study of insanity'. London: MacMillan, 1899.

With respect to the second group, Bruce described insanities resulting from toxins of metabolic origin. He was emphatic, though, that 'metabolic toxaemia' was not a scientific term, because 'the toxines themselves are unknown'.

In Bruce's opinion, the most important metabolic toxins were 'probably the pre-urea bodies', and he presumed that 'the mental symptoms and the diminished or increased excretion of urine and urea have some definite relationship to one another'. However, he did not mention, as did Macpherson, that 'among the mental disorders which follow gout, or which may replace it, a condition of melancholia or great depression of spirits, with hallucinations, may be mentioned [and] occasionally maniacal attacks supervene'.

Although Bruce found evidence of metabolic disorder in all acute forms of insanity, the 'outstanding' example was that of acute melancholia, during whose acute stage there was a presumed accumulation of 'waste products' in the body, e.g. urea. In the early stages of acute mania, he wrote, 'the urine is scanty and high coloured at the onset of the attack, and there is an excessive output of the nitrogenous waste products of the body', whereas later in the disease 'the secretion of urine is abundant'.

Bruce[792] gave the 1908 Morison Lectures, I–III, for which he had chosen the subject of The Symptoms and Etiology of Mania, published in the Journal of Mental Science, the same year. He related that it was 'a commonly accepted belief that maniacal states are conditions of brain toxaemia or brain poisoning', the responsible toxines being bacterial toxines, resulting in the formation of some specific agglutinative factors and opsonins. In the blood serum of more than ninety percent of manic patients, he could demonstrate an agglutinin which would agglutinate the red blood-corpuscles of healthy persons. He observed an apparently similar agglutinin to be present in the blood serum of many sane and apparently healthy persons. When rabbits were infected with streptococcal and staphylococcal bacteria, a similar agglutinin was produced. As both the sane and the insane persons could show bacterial toxaemia, Bruce thought that 'there must be some further factor in the production of states of mania', this factor being 'probably, an inherited or acquired unstable nervous system'. In other words, he added, 'the sane and the insane may suffer from similar toxaemias, but whereas the brain of the sane man is stable, and the toxines produce no mental symptoms, the brain of the insane man is unstable and readily becomes disordered by toxic action'.

Whereas the blood serum in health contains 'protective agglutinins to certain strains of the staphylococcus and streptococcal organisms', Bruce found that these 'protective' factors could be demonstrated in over sixty per cent of manic patients. In these patients there was often a greatly increased leucocytosis, largely due to 'an actual and relative increase in the polymorphonuclear leucocytes'. Moreover, he found that there was a prevalence of disorders of the alimentary tract in manic patients, the bacteriological flora being altered in at least half of them.

Due to a lowering of the 'bacterial defences' in the intestinal tract, Bruce thought, 'certain strains of cocci become unduly increased', resulting in the formation of toxines that become absorbed by the blood vessels and lymphatics, and are thus passed into the general circulation, causing states of mania. He speculated that an apparent recovery

[792] op. cit., 1908;54:207–264.

would ensue the moment ‘antitoxine molecules’ had neutralised the ‘toxine molecules’, and that this pattern would repeat itself with the occurrence of a lowering of the general bodily health, or in the case of a failure of the body to form sufficient antitoxine molecules. Generally, he had formed the opinion that ‘manic-depressive cases suffer from recurrent attacks of toxaemia’.

Stransky[793] was one researcher who expressed scepticism of Bruce’s hypothesis.

Based on an examination of the urine in twenty cases of mania, Bruce observed that maniacal states were very similar to febrile conditions ‘in that the nitrogenous waste products [‘urea-nitrogen’] of the body are greatly in excess of the nitrogen ingested in the food […]’

However, he added that this would reverse to a state of balance, as the patients returned to normal.

As we learnt before, Bruce described so-called fixation abscesses (‘artificial leucocyte production’),[794] cited by Devine and later by Cade in his 1979 book on the history of psychiatry. Therefore, Cade might also have been acquainted with Bruce’s textbook, although he did not make any explicit reference to it. From the Beattie-Smith Lecture that Cade[795] delivered in 1951 we learn that he then was at least acquainted with Bruce’s work on thyroid treatment of schizophrenia.

Cade might well have read a paper by Anderson,[796] published in the Australasian Medical Gazette, 1913. Here Bruce is mentioned as ‘one of the leaders’ of Kraepelin’s view of mania and melancholia ‘as phases of the one psychological cycle, namely, Folie circulaire’.[797] To this the author added that

> it is now becoming more and more recognised that the disease called mania in all its form is the direct result of a toxaemia either of metabolic or of bacterial origin, and the most common focus of this toxaemia is some part of the alimentary canal.

After having emphasised that the attention of ‘all workers on the etiology of mental diseases has of recent years been directed towards the examination of the blood’, Anderson related that ‘very great progress has been made towards elucidating many of

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[793] Stransky, 1911, p.130, note 1.

[794] op. cit., p.231. cf. Devine, op. cit., pp.152–153.

[795] Cade JF.: ‘The problem of schizophrenia’. Med. J. Aust. 1951;2:245–251.

[796] Anderson JT.: ‘Some remarks on acute mania and its treatment’. Australasian Med. Gaz. 1913;34:285–289. This paper had been read before the Western Australian Branch of the British Medical Association.

[797] ‘Folie circulaire’ was coined by Falret in 1854, and it is defined as being a disease made up of a succession of maniacal and melancholic attacks, succeeded by a lucid interval of varying duration. At the same time, Baillarger described the disease ‘folie à double forme’ which corresponded exactly with Falret’s concept excepting the fact that Baillarger omitted the so-called ‘lucid interval’. It was in 1899 that Kraepelin introduced a new classification of mental diseases, and under the term maniacal-depressive insanity included the psychoses formerly termed intermittent, periodical, circular, etc. (cf. C. McDowall, J. Ment. Sci. 1908;54:587–588).

the mysteries obscuring our knowledge of insanity', and that 'Perhaps in no other form has such progress been made as in mania'. In the opinion of Anderson, who generally 'quoted freely from the leading authorities in psychiatry', 'one of the leaders of this ever-increasing army of research workers is Dr. Lewis C. Bruce'. Bruce's hyperleucocytosis method was also given mention: 'Dr. Bruce endeavoured to reproduce this condition by injecting turpentine subcutaneously into the flank'. However, no mention was made of lithium.

Craig in his textbook Psychological medicine (1917)[798] expressed the view that among the stress factors that could lead to insanity were 'poisons circulating in the blood', be they autotoxins or toxins derived from 'external agents'.

Referring to Bruce, Craig stated that convincing evidence of the importance of recognising 'that auto-toxins derived from the alimentary tract play no small rôle in the production of insanity' was increasing 'every year'. In his opinion, therefore, 'a careful study of the blood in cases of mental disorder cannot be overestimated'.

Still according to Craig, 'the quantity of urea excreted varies, being diminished in depressed states and increased to a small extent in mania', and 'in some cases of maniacal excitement—absorption of deleterious matter from the alimentary canal may give rise to mental disorder'.

Finally, what many previous authors had written was reiterated; namely, that 'gout and insanity may alternate', the blood being 'vitiated'. The most common mental symptoms, Craig found, were those of melancholia, but 'at times an outbreak of acute excitement may occur'.

The next edition of Craig's psychiatric textbook, its fourth, appeared in 1926, (with Beaton)[799]—recommended reading for MD candidates at Melbourne University in 1938—included a brief section on 'gout and insanity', to the effect that 'mental changes of some kind nearly always accompany or precede an attack of gout', with the usual symptoms being 'morning depression, great irritability, failure of attention and application, and at times sensory and motor disturbances'.

'Gout and insanity sometimes alternate', the authors added; this 'metastasis' (of gout) being 'a form of toxic insanity', unrelated to any measures of treatment applied for the gouty attack. Suicidal tendencies and hallucinations were also mentioned, and 'there is acute insomnia, and the patient may be very restless and at times acutely excited'. The usually 'easy' diagnosis of the condition was based on the anamnesis, the possible presence of gouty tophi, and affections of the joints, if still present. Therefore, an examination of the blood 'may assist'. Other than prophylactic treatment, curative treatment 'directed towards improving the state of the blood' was recommended. Lithium treatment was not mentioned.

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[798] Craig M.: 'Psychological medicine'. London: Churchill, 1917. (pp.28, 87, 110, 328–329).

[799] Craig M, Beaton T.: 'Psychological medicine. A manual on mental diseases for practitioners and students'. London: Churchill, 1926.

Via Devine's textbook, Cade could also have become acquainted with a 1923 paper by Gibbs and Lemcke,[800] Study in basal metabolism in dementia praecox and manic-depressive psychoses. 'The idea has long been current', the authors wrote, 'that disturbances of metabolism occur in certain mental disorders.' 'Theories of an intoxication, probably endogenous, have often been advanced'. They noted, however, that 'chemical methods' had not previously been available with which to obtain 'sufficient evidence to indicate the extent or nature of such disturbances', not to mention that there had been 'little to indicate what structures or functions might be involved'. However, the authors pointed out,

> more improved methods of clinical chemistry and the increasing evidence that the ductless glands are involved in many disturbances of growth and metabolism have recently caused a greatly increased interest and activity in the study of such disturbances in patients with mental disease. [Finally,] there is now some evidence and considerable opinion that disorders of the ductless glands and changes in metabolism may occur in certain psychopathic conditions and psychotic reactions.[801]

Among other works, the authors made note of a pioneering work in this field, by the Harvard professor Otto Folin (assisted by Shaffer and Hill): Some metabolism studies with special reference to mental disorders,[802] published in 1904–05. This work will be discussed at some considerable length later.

In Mending the mind (1979) Cade referred to Maudsley as 'a famous psychiatrist'.[803] Had he read or been acquainted with his work, e.g. the 1895 edition, he might well have become familiar with the fact that Maudsley espoused views and ideas more or less similar to those described above; namely, that various disturbances of metabolism could be causative factors in mental disorders.

According to Maudsley,[804] there was no certainty as to 'the morbid actions of the poisons bred in the body', 'because we know neither what they are, nor where they are bred, nor how they act'. But he did not doubt their existence or their 'action' of producing mental disorders, which, he said, 'are determined respectively by some minute and subtile organic compound which has been either insufficiently or sufficiently manipulated before its discharge into the blood-stream'.

Reflecting the views of many other authors, Maudsley pointed out that

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[800] Arch. Int. Med. 1923;31:102–115 (113), quoted by Devine p.186. This article commented on Folin's 1904 paper on metabolism in mental disorders.

[801] cf. Hamilton AM.: 'Insanity in connection with disease of the ductless glands'. Med. Rec. 1899;55:593–596.

[802] Am. J. Insan. 60:699–732 & ibid. 61:299–364.

[803] Cade, 1979, op. cit., p.22.

[804] Maudsley H.: 'The pathology of mind. A study of its distempers, deformities, and disorders'. London: Macmillan, 1895. pp.112–115.

> in like manner the presence of some malformed nutrient product in the blood of gouty patients, or of some waste-product which has been incompletely broken up or incompletely removed, is sometimes the cause of a genuine melancholia, during which they are perhaps free from their regular attacks of gout, getting them back again when they lose their mental disorder.

But according to Maudsley, 'the excess of uric acid which is found in the blood and urine of these gouty persons is only the ultimate product and gross token of latent and subtile changes in the intimate metabolic processes'.

This also applied, he thought, to

> the states of disordered urine which are known as *oxaluria*, *phosphuria*, and *glycosuria*; states which are frequently accompanied with symptoms of much mental discomfort or distress and sometimes with severe depression, anxious apprehension, and extreme irritability.

Maudsley emphasised not only the many dangers 'which everybody runs everyday moment of his life in the building-up of his tissues', but also the dangers associated with

> the waste or decompositions of them; for although their proteids are changed eventually into such comparatively harmless crystalline bodies as urea, uric acid, kreatin, and the like, yet the intermediate decompositions before they arrive at these gross and stable products may be fraught with perils.

Maudsley found the 'insanity' which 'almost invariably occurs in *myxoedema*' to be 'of especial interest'. This condition, he said, 'is caused by something lacking in the blood by reason of the atrophy of the thyroid, and it is cured by the artificial supply of the lacking element'. Likewise, he thought that 'it is probable that some toxic product of metabolism is the cause of the acute gouty mania which, breaking out after the cessation of the inflammation of the joints, is characterised by fierce frenzy, heat of head, and fever'. However, as pointed out before, he did not mention lithium salts for its treatment, but simply added: 'Is the patient gouty? If so, treat the gout'.[805]

Finally, it must be emphasised that according to Maudsley, 'it is only now, for the first time that inquiry has entered on the track of the minute chemical changes which are the conditions and accompaniments of disease'.

Therefore, Maudsley might well have been or probably was acquainted with the fact that, from 1891 to 1895 at the McLean Hospital for the Insane, at Boston Massachusetts, studies of urea and uric acid excretion in melancholia were undertaken in a more systematic way by Hibbard and his associates. The results of these studies were published in the American Journal of Insanity.[806]

Hibbard pointed out that 'one of the articles which called attention to the possible connection of uric acid and some forms of mental disease', and which led to the carrying

[805] Maudsley, 1895, op. cit., p.546.

[806] Hibbard CM.: 'A study of the excretion of urea and uric acid in melancholia and in a case presenting recurrent periods of confusion and depression'. Am. J. Insan. 1898;April:503–531.

out of these observations ‘as tests of such relationship’, was a paper by Haig, Uric acid in diseases of the nervous system, published in Brain.[807] The topic in Haig’s work that especially caught Hibbard’s attention was ‘mental depression’.

Hibbard accompanied his important article with a ‘historical review’, in the hope that this would give some idea of the work done by others. Some of these works were mentioned earlier, but are repeated here in an the attempt to establish the scope of literature with which Cade was, or could have been, acquainted.

According to Hibbard, as early as 1845 Sutherland and Rigby[808] were ‘among the first, if not the earliest’ to make observations on urea and uric acid in the insane. In forty cases of melancholia they found urea and uric acid were increased in nineteen cases, whereas Voppel,[809] some years later, found ‘urea diminished in the insane’. Next, Hibbard mentioned Selin, who according to an abstract in 1863,[810] observed that in melancholia urea and uric acid were diminished ‘in the period of an aggravation of the symptoms’. Due to the lack of a ‘volumetric test’ for uric acid, Addison[811] had been unable ‘to subject this element for examination’, whereas he found that ‘the excretion of urea was diminished during the maniacal paroxysm in all the cases’. He also found decreased urea quantities in melancholia. Further, he found that there was an increased excretion of the phosphates, being a ‘pathognomonic phenomenon of maniacal excitement’. Rabow[812] observed that the quantity of urine and urea was diminished, and he included the results in two cases of ‘circular insanity’, comparing ‘depression’ with ‘exhilaration’, to illustrate this. A comparative study had also been undertaken by Schäfer.[813] Lombroso[814] had observed urea to be diminished.

Hibbard was also acquainted with Carl Lange’s work, at least via Haig’s article in Brain. He noted that

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[807] Brain 1891;14:63–98 (74, 91).

[808] Hibbard did not quote their work but made reference to a review in Allg. Ztschr. Psychiatr. 1846;3:56. Morel in his ‘Traité des maladies mentales’. Paris, 1860, p.447, refers to Sutherland’s and Rigby’s observations and according to Morel published in Analyses of the Urine of Insane Patients in St. Luke’s Hospital, 1844.

[809] Hibbard referred to a review by Reissner of Voppel’s work in Allg. Ztschr. Psychiatr. 1862;19:500. Reissner was critical of the results obtained by both Sutherland and Voppel.

[810] Allg. Ztschr. Psychiatr. 1863;20:600.

[811] Addison A.: ‘On the urine of the insane: a contribution to urology’. s.a, s.l. Abstract in J. Ment. Sci. 1865;11:262–268. The author drew to attention that most of our knowledge of the chemistry of the urine in insanity was derived from a work by Sutherland in the Med. Chir. Transact. 1855 (not sighted). Addison hoped that his observations would assist in pointing out ‘the foundation upon which an exact pathology of the urine of the insane must be built’.

[812] Rabow: ‘Beitrag zur Kenntniss der Beschaffenheit des Harns bei Geisteskranken’. Arch. Psychiatr. 1877;7:62.

[813] Schäfer: ‘Ein Fall von circulärer Geistesstörung’. Neurol. Centralbl. 1:201

[814] Quoted in Krafft-Ebing’s ‘Lehrbuch der Psychiatrie’. 5th Edn. 1893:137.

> Lange,[815] of Copenhagen, connects mental depression and the uric acid diathesis, and on that basis he claims to treat this depression successfully by a diminution of meat diet and certain rules as to exercise.

Hibbard went on to mention a work by Smyth, An Inquiry into the Blood and Urine of the Insane, published in the Journal of Mental Science.[816] He compared the amount of 'azotised products' such as urea, uric acid and creatinine in healthy men and insane patients, and found that 'healthy men do not excrete more urea than insane patients', whereas 'uric acid is increased in the excretions of the insane'. Mabille and Lallemant claimed, Hibbard noted[817]

> that in those cases of insanity in which the ascendants suffer from gout, arthritis, and diabetes, or in which the patient is subject to a diathesis himself, they find an increase of uric acid over urea. These cases are sometimes mania, but mostly melancholia. They have periods of remission, in which they seem well. Their urine is dense, the nitrogen is diminished, and the uric acid is sometimes normal and sometimes greatly diminished.

Other than being sceptical of Haig's work, Hibbard levelled criticism at Marzocchi,[818] who found that in some forms of melancholia 'there occurs an increase, absolute and relative, of the uric acid in the blood'. Hibbard even found this author's method to be 'notoriously unreliable'.

Babcock[819] showed there to be an excess of urates, using the murexide test. However, in Hibbard's opinion no conclusions could be drawn on this test.[820] Moreover, according to Hibbard, Régis[821] observed that 'urea is sometimes below the normal in melancholia'; Dagonet[822] similarly found that urea is diminished in depression, especially in melancholia.

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[815] Hibbard wrote that this work was quoted by Haig in Brain 1891;14:74.

[816] op. cit., vol. 36, pp.504–518.

[817] According to Hibbard quoted by Régis and Chevalier-Levaure in 'Des Auto-intoxications dans les maladies mentales'. Congrès des Médecins Aliénistes des Pays de Langue Française. La Rochelle, 1893:13. cf. Medical Week 1893:373–375 (a discussion by these authors and others at the 'French Congress of Psychological Medecine', La Rochelle, 1893). cf. Chevalier-Lavaure F.: 'Des Auto-intoxications dans les Maladies mentales'. Bordeaux, 1890.

[818] Marzocchi: 'L'acido urico nelle forme di Depressione Mentale'. Rev. Speri. Freniatr. Med. Leg. 1892;18(2):330.

[819] Babcock: 'A study of the urinalyses [*sic*] of 110 cases of insanity'. Med. & Surg. Rep. (Phil.) 1894;80:126.

[820] cf. Boucheron's method, also referred to by Carl Lange. cf. Dorland's 'Illustrated Medical Dictionary', 25th Edn. 1975. pp.988, 1587.

[821] Régis: 'Practical manual of mental medicine', translated by H. M. Bannister. Utica, New York, 1894.

[822] Dagonet J. Duhamel G.: 'Traité des maladies mentales'. Paris, 1894. p.101.

Finally Hibbard made mention of Stefani,[823] who had analysed sixty cases. This work only referred to the specific gravity of the urine in 'acute psychoses'. However, from an abstract in the section 'The progress of psychiatry in 1896' in the Journal of Mental Science,[824] it can be seen that Stefani performed experiments on rabbits, administering intravenous injections of the urine from twenty insane persons who suffered 'from the acute forms of the malady, and exacerbations'. He also used 'the urine of three healthy individuals'. He observed that 'the toxicity of urine of the insane varies in different individuals, and even in the same person there are rapid variations'. His conclusion was that 'the physiological action of the urine of the insane does not differ from that of normal urine, except by greater intensity', but 'convulsive and myotic effects' were frequently augmented.

Hibbard and his associates themselves made observations, which were consistent with those they cited showing that urea and uric acid, as a rule, were diminished in melancholia.

In 1900, Otto Folin, a pioneering metabolicist,[825] and an authority on the constituents of urine, was called to the McLean Hospital 'to study insanity from a chemical standpoint, and more particularly to make investigations into the nutrition of the patients of this hospital'. The results of his investigations were published in American Journal of Insanity in 1904–05, entitled: Some metabolism studies with special reference to mental disorders.[826]

Folin held the opinion that 'abnormal metabolic processes must unquestionably play a more or less important part among the pathological conditions that produce various forms of insanity', but that 'it may well be that the chemical methods at present available are entirely too crude for the detection or study of these deviations from the normal'. Moreover, he noted that the incompleteness of all metabolism experiments of the past, as judged by the comprehensiveness of the accompanying urine analyses, was 'particularly pronounced in the metabolism records of the mental diseases'. He made reference to a work by Schaefer,[827] a review of the literature in this field, to the effect that by 1897 there existed nine papers on toxines in the urine, fifteen on uric acid, eight on creatinine, and seven on oxalic acid. He also found that the state of affairs concerning the papers published subsequently were no less open to question than the aforementioned.

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[823] Stefani N.: 'Sul peso specifico dell orina nelle malattie mentale'. Rev. Speri. Freniatr. Med. Leg. 1894; 20(1):1.

[824] Stefani N.: 'On the physiological action of the urine of the insane. Italian Congress of Psychiatry, 5th–9th October, 1896'. J. Ment. Sci. 1897;43:399–400.

[825] cf. Hawk PB.: 'General consideration of metabolism', in Osler W, McCrae T. (eds.). 'Modern medicine. Its theory and practice'. Philadelphia: Lea & Fibiger, 1914 (Folin's theory, pp.594–596).

[826] Am. J. Insan. 60:699–732 & ibid. 61:299–364; also referred to by Pighini & Statuti (1910, op. cit.) and in Gibbs CE, Lemcke D.: 'Study in basal metabolism in dementia praecox and manic-depressive psychoses'. Arch. Int. Med. 1923;31:102–115 (113) (quoted by Devine p.186).

[827] Monatsschr. Psychiatr. Neurol. 1897, Nos. 2, 3, 5, 6 (quoted from Folin).

It should be added here that Bruce and Alexander[828] reported in 1900 that the excretion of urea in melancholia was deficient. To remedy this they used ammonium carbonate.

Folin highlighted the difficulties involved regarding the analytical techniques, especially the methods for determining the more important nitrogenous constituents of urine.

From experiments with normal persons, Folin proceeded to experiments with patients. He was emphatic that these investigations 'have so far failed to show any characteristic metabolism peculiarities corresponding to the different psychiatrical groups of cases', including patients suffering from dementia praecox, manic-depressive insanity or melancholia.

According to Folin, from

> a destructive, negative or critical point of view it is believed that the data given [Folin's] prove the untrustworthiness of all those metabolism experiments, old and new, which report a 'characteristic' 'increase' or 'diminution' of any of the urinary constituents included in this research (i.e., volume of urine, total nitrogen, urea, ammonia, uric acid, kreatinin, organic bases, total sulphates, ethereal sulphates, 'neutral sulphur', phosphates, chlorides, organic or mineral acids, indican)[829] as associated with any particular one of the ordinary mental disorders […]

Folin did not claim that 'such characteristic abnormal metabolism may not exist', but that the experiments available were 'insufficient to demonstrate' this.

Neither Hibbard nor Folin touched on the subject of lithium, nor the assumption made by many of the old authors of its therapeutic effect in uric acid diathesis. This is perhaps an indication of the fact that this concept was now recognised by most investigators as erroneous.

Be that as it may, Clarence Good[830] was well aware of this association when he undertook his important 'experimental study of lithium' in its own right, published in the American Journal of Mental Science in 1903.

Good included an overview of the history of lithium, referring to Garrod (the second edition of his book, 1863)[831] and, for instance, Lipowitz, Ure, Lévy, Haig, Bence Jones, and Cash and Brunton. A number of lithium experiments on animals were also mentioned.

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[828] Bruce LC, de Maine Alexander H.: 'Some observations on the various physical changes occurring during the acute and subacute stages of melancholia'. J. Ment. Sci. 1900;46:725–731.

[829] cf. Pearce FS.: 'Further laboratory studies on uric acid in neurasthenia, and on autointoxication in nervous disease'. Am. J. Insan. 1900;57:103–115. Stanford RV.: 'The production of indigo in the human organism'. J. Ment. Sci. 1911;57:291–311.

[830] op. cit., 1903;125:273–284.

The first, or one of the first, of the animal experiments was that of Rabuteau in 1868.[832] In 1873 Blake[833] experimented with lithium (and sodium, rubidium, tellurium, and cæsium) on rabbits. Two years later, Hesse[834] experimented with lithium on frogs, rabbits, and doves, and he found that in 'warm-blooded' animals lithium salts decreased the excitability of the nerve centres, decreased the temperature, and sometimes caused diuresis.

In 1884 Krumhoff[835] published 'a careful experimental investigation of the effects of lithium on animals, and reviewed the literature thoroughly'. He found that 'when a lithium salt was injected into the blood it depressed the heart's action and caused a fall of blood pressure, and if the dose was large enough stopped the heart in diastole'. He also found that 'vomiting and diarrhoea were caused by its subcutaneous use, and the prolonged ingestion of small doses killed the animal sooner or later by causing a fatal gastro-enteritis'.

The same year, Cash and Lauder Brunton[836] in Philosophical Transactions of the Royal Society described their experiments on frogs. They found that lithium, rubidium, and cæsium had a tendency

> to affect either the upper part of the spinal cord or the higher motor centres connected with the forelimbs, the reflexes disappearing sooner from the arms than from the legs, and that stiffness was noticed in the arms.

The authors also found 'the motor nerves [were] paralysed to a greater or lesser extent by lithium and potassium'.

It shall be discussed in greater detail later whether Cade had in fact read Good's paper and whether he was thus acquainted with Cash's and Brunton's work. In two papers, Cade[837] quoted from Brunton's A Text-book of Pharmacology, Therapeutics, and Materia,[838] a work that was not cited by Good.

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[831] Garrod AB.: 'The nature and treatment of gout and rheumatic gout'. 2nd Edn. London: Walton and Maberly, 1863. (p.425).

[832] Rabuteau P.: 'Études expérimentales sur les effets physiologiques des fluorures et des composés métalliques en générale'. Paris: Baillère, 1868.

[833] California Academy of Science, 1873 (from Good).

[834] Hesse: 'Lithion. Inaugural dissertation'. Göttingen, 1876 (from Good).

[835] Krumhoff: 'Wirkung des Lithium. Inaugural Dissertation'. Göttingen, 1884 (from Good).

[836] Brunton TL, Cash JT.: 'Contributions to our knowledge of the connexion between chemical constitution, physiological action, and antagonism'. Phil. Trans. Roy. Soc. 1884;175:197–244 (from Good).

Returning to Good, we learn that

> to carefully study the effects of lithium salts on animals and determine where it was excreted, I made thirty-odd experiments on cats and dogs, administering [lithium chloride] subcutaneously and by mouth.

Good used lithium citrate because of its easy solubility and because the carbonate was, to some extent, changed to the chloride in the stomach. His experiments showed that

> shortly after the administration of the lithium salt the animal is taken with nausea, vomiting, and diarrhoea, and dies sooner or later with all the characteristic signs and symptoms of gastro-enteritis, the progressive emaciation and weakness being wholly the result of the gastro-enteritis […] The stiffness and inability to use the hindparts is also due to the weakness caused by the gastro-enteritis.

Moreover, there was 'practically a total absence of nervous symptoms, although in a few cases slight tremors were noticed'. Good found this to be 'of importance, as tremors have been noted in a few cases of poisoning in man'. When lithium salts were administered orally he observed 'essentially the same symptoms and changes as when given hypodermically'.

Good then turned his attention to the 'very few cases mentioned in the literature of poisoning from the [therapeutic] use of lithium', as he pointed out that lithium was 'not generally considered as inducing any deleterious symptoms'. He mentioned various reports of such by Wood,[839] Hare,[840] Charcot (the aforementioned note to the French edition of Garrod's book on gout), Rabuteau,[841] Climent[842] (who had administered lithium to himself), Althaus,[843] and Kolipinski.[844]

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[837] Cade JF.: 'Lithium in medicine', in Burrows GD, Chiu E.: 'Research in affective disorders. Proceedings of the Scientific Meeting in Honour of Dr. John F. J. Cade. February 4, 1977'. pp.7–9. Cade JF.: 'Lithium—past, present and future', in Johnson FN, Johnson S.: 'Lithium in medical practice. Proceedings of the First British Lithium Congress, University of Lancaster, England. 15–19 July 1977'. Lancaster: MTP Press, 1978. pp.5–16.

[838] London: MacMillan, 1891. pp.556, 630–633.

[839] cf. Wood HC.: 'Therapeutics: its principles and practice etc'. 7th Edn. London: Smith, Elder, 1888. pp.296 (bromide of lithium), 727–728 (lithii carbonas: 'In twenty-grain doses I have seen it apparently produce severe general prostration, amounting almost to general paralysis, in a feeble adult female, but I have given it very largely to other patients without inducing any constitutional symptoms', 'and the drug [Lithia salts] was strongly recommended by Dr. Garrod in uric acid diathesis and in chronic gout, given in doses of three or four grains three times a day. The drug was extensively employed, but fell into disrepute until recently, when its claims have been revived, especially by Professor Ditterich (Schmidt's Jahrbücher, Bd. cli. p.270). As stated by the latter observer, it is very generally given in too large dose').

[840] cf. Hare HA.: 'A text-book of practical therapeutics etc'. 9th Edn. London: Kimpton, 1902. pp.121 (bromide of lithium), 291–292 (lithium), 498 (mineral springs and climate), 642–644 (gout).

Emphasising that the salt of lithium used in medicine was the carbonate, Good mentioned— without reference—that 'bromide of lithium has been used in the treatment of gout, epilepsy and other nervous diseases'. He went on that

> since the atomic weight of lithium is so small, there is, of course, more of the bromide ion in lithium than in an equal weight of potassium bromide, and the actions of the bromide ion completely overshadows the action of the lithium ion.

In 1913, Folin[845] (assisted by Denis) supplemented his aforementioned work on urine analyses with investigations of blood and tissue, undertaken at Boston Psychopathic Hospital. He found normal uric acid findings in the bloods of 38 cases. These findings were corroborated the following year by Adler and Ragle,[846] who examined the blood of 156 cases at the same hospital. In 1920 Weston[847] reported that the blood of 30 epileptic, dementia praecox and manic-depressive patients showed normal levels of uric acid, urea, creatinine and creatin, among other agents. Four years later, Bowman[848] published a sample of 229 psychiatric patients at Bloomingdale Hospital in New York, among them 70 with depression and 30 with mania, concluding that uric acid was normal for all types of mental illness.

In 1924, Folin and his associates[849] published the important work: The Uric Acid Problem. An experimental study on animals and man, including gouty subjects. It highlighted 'the apparent inapplicability of animal experimentation, and second, the lack of suitable analytical technique'. The investigators were convinced that uric acid in blood could be determined with a precision which had been 'quite unattainable in earlier work',

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[841] op. cit.

[842] Climent E.: 'Traitement de la gravelle urique'. Thèse. Paris, 1874. p.33, quoted from Johnson, 1984, op. cit., p.158.

[843] [?] Boston Med. Surg. J. 1896;135:644 (from Good, cf. Johnson, 1984, op. cit., p.158, note 42: 'the accuracy and appropriateness of the references given by Good are of generally low standard').

[844] Kolipinski L: 'Notes on some toxic effects from the use of citrate of lithium tablets'. Maryland Med. J. 1898;40:4–5 (from Good, cf. Johnson, 1984, op. cit., p.158, notes 42 & 47).

[845] Folin O, Denis W.: 'Protein metabolism from the standpoint of blood and tissue analysis. Sixth paper. On uric acid, urea and total non-protein nitrogen in human blood'. J. Biol. Chem. 1913;14:29–42.

[846] Adler HM, Ragle BH.: 'A note on the increase of total nitrogen and urea nitrogen in the cerebrospinal fluid in certain cases of insanity, with remarks on the uric acid content of the blood'. Boston Med. Surg. J. 1914;171:769.

[847] Weston PG.: 'Analyses of blood of insane patients'. Arch. Neurol. Psychiatr. 1920;3:147–150.

[848] Bowman KM.: 'Blood chemistry in mental diseases'. Am. J. Insan. 1922-23;79:379-408. cf. Looney JM.: 'A biochemical study of the blood in mental disorder'. Am. J. Psychiatr. 1924;4:2–39.

[849] J. Biol. Chem. 1924;60:361–471.

and one of their aims was to find out the 'behaviour of administered uric acid' in man and in animals. As a solvent agent for uric acid they used lithium carbonate. An extensive historical review of uric acid was included.

It can be established that Cade was fully acquainted with the work of Clouston. Incidentally, it transpires from the editorial preface to the English edition of Kraepelin's work, Dementia praecox and paraphrenia, that Kraepelin cited Clouston's views on dementia praecox and manic-depressive illness.[850] Cade's acquaintance with Clouston's work is corroborated by a speech Cade delivered to the Australian and New Zealand College of Psychiatrists in 1972, entitled Masturbational Madness: an historical annotation.[851] In this presentation, remarkable in several ways, he informed the audience that he had drawn heavily upon the views of 'that eminent physician, T. S. Clouston, as expressed in his Clinical Lectures on Mental Diseases (1904)'.[852] Clouston's work was 'a well-known and widely read textbook of mental diseases', Cade added in his 1979 book on the history of psychiatry.[853] In his speech he expressed regret that the time allotted to him did not allow him to submit to the audience Clouston's observations on Insanity of oxaluria and phosphaturia (and 'Postconnubial insanity'), for, in Cade's opinion, 'they are clearly fascinating themes for future study'.

As we learnt before, Clouston's authoritative textbook, which went through many editions, incorporated Skae's classification of 1863.[854] For instance, 'Group 8' of this classification was 'gouty (podagrous) insanity'. 'Some rare varieties' were added, among them 'the insanity of oxaluria and phosphaturia'.[855]

In a chapter on 'gouty and podagrous insanity' (Lecture XIII),[856] Clouston, like Maudsley, emphasised that 'mental phenomena due to gout are common enough, and have been described by all authors on the subject [emphasis added]', and he found that 'deep melancholia is a common accompaniment of the gouty diathesis [emphasis added]'. He also made reference to Garrod's description of gouty mania, whereas the Lange theory

[850] Robertson GM.: 'Editor's preface' (July 1919): 'Professor Kraepelin informs us that he got the starting point which led to dementia præcox being regarded by him as a distinct disease, in the year 1896. He admits "that Clouston also, who spoke of an 'adolescent insanity', had evidently before everything dementia præecox in view, though he did not yet separate it from manic-depressive cases, which likewise often begin about this time". The identity of Clouston's "secondary dementia of adolescence" with the chief forms of dementia præcox—is quite apparent to anyone reading the remarkable address on dementia which he delivered in 1888 when President of the Medico-Psychological Association' (Robertson, pp. 3, 224; Kraepelin 1913, pp. 669, 909. Quoted from the English edition, p.225 (original edition, 1913, p.909)).

[851] On the occasion of the 9th Annual Congress, published in Aust. NZ. J. Psychiatr. 1973;7:23–26.

[852] cf. Clouston TS.: 'Clinical lectures on mental diseases'. 6th Edn. London: Churchill, 1904.

[853] Cade, 1979, op. cit., pp.20–23.

[854] Skae D.: 'The classification of the various forms of insanity on a rational and practical basis'. 1863. cf. Tuke's 'Dictionary of Psychological Medicine'. 1892. Vol. 1, pp.231–232.

[855] cf. 'Practical Notes', Practitioner 1901;13:716–717, the original source being 'Nord Médical', quoted in Medical Record, no year given).

[856] Clouston, 1904. op. cit. pp.506–507.

of depression was not mentioned. ‘Insanity of oxaluria and phosphaturia’ was described in the chapter on ‘Rarer and less important clinical varieties of mental disturbances’ (Lecture XVIII).[857]

It was in a General Meeting of the Medico-Psychological Association in London in 1900, reported in the Journal of Mental Science, that Duckworth,[858] on the topic of mental disorders, toxaemia, and gout, asserted that ‘no clearer evidence of the influence of auto-intoxication is afforded than that which results in aberrant cerebration in some cases of gout’. He added that

> the patient generates his own toxin in his tissues, and the effects are recognised in the form of stupor, delirium with delusions, and excitement, sometimes as melancholia, such symptoms lasting occasionally for days or for many weeks, and yielding to some overt metastatic gouty development, generally articular, or to an anti-gouty development, with complete recovery.

Duckworth also made reference to some Turner for saying that ‘all forms of acute mania are probably of toxic origin’.[859] Further, Duckworth related that ‘the condition of myxoedema sometimes leads to brain symptoms, such as instability, delusions, mania, and melancholia, the result […] of altered metabolism from deficient thyroidal influences’.

Savage took the opportunity to espouse the intriguing view that ‘one feels sure that some observer will yet discover what is the auto-toxin which gives rise to [‘acute delirious mania’].

Mercier stated that ‘toxaemia is the only agent which we certainly know will produce insanity, and it is not unlikely, I think, that eventually we shall find toxaemia at the bottom of every form of insanity’. He went on to draw some analogy to alcohol intoxication in that ‘When we administer alcohol in sufficient quantity we render the person insane, and we find the degree of insanity is in proportion to the amount of alcohol administered’.

Clouston’s views on the topic were discussed and reviewed two years later in the Scottish Division of the Medico-Psychological Association.[860] In brief, Clouston was

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[857] ibid., pp.656–674.

[858] Duckworth D.: ‘Mental disorders dependent on toxæmia’. J. Ment. Sci. 1901;47:226–236. ‘Discussion’ 233–236 (Gowers, Mott, Savage, Goodsall, Mercier, Briscoe, Duckworth). cf. his article: ‘The pathogeny of gout’ in Lancet 1900;ii:571–573. Duckworth expressed the view that this issue was ‘one of the most obscure problems in medicine […] No careful clinical student of gout can fail to recognise the nervous element in the disorder. The onset of a paroxysm is often due to such influence. The condition of urichaemia grows up, as it were to saturation. A nerve storm is aroused by mental influences or arises either out of shock, depression, or excitement, and forthwith the crisis occurs and the attack is localised’.

[859] Source not retrieved.

[860] Lord JR.: ‘Aetiology of insanity’. J. Ment. Sci. 1902;48:352–353 (a review of Clouston: ‘Melancholia and the toxæmic theory: a clinical sketch’. Scot. Med. Surg. J. Febr. 1902). cf. ‘Toxæmia in the etiology of mental disease’. A discussion opened by Clouston, at the Spring Meeting of the Scottish Division of the Medico-Psychological Association, Glasgow, March 28th, 1902. J. Ment. Sci. 1902;48:434–450.

‘unable to accept the absolute toxaemic origin of insanity […] which has of late assumed a position of great importance’. Bruce was mentioned, for teaching that melancholia is ‘a disease of disordered metabolism’, as was Mott for his theory of ‘auto-poisoning’ by choline and other products of nerve-degeneration.

In the Journal of Mental Science for 1903, Kowalewsky[861] published a brief notice of the Russian Literature of Nervous and Mental Diseases. He quoted Popoff ’s work on auto- intoxication as a cause of mental disease.[862] According to the reviewer, this was a very detailed work ‘which advocates that the strongest aetiological factor in psychoses is auto-intoxication’: ‘A healthy man can deal effectually with his normal toxines. When from some cause or other he can no longer do so the organism is poisoned and mental disease is a result’.

As has been comprehensively illustrated in the present work, theories as to toxaemia and auto-intoxication being important causative factors in psychoses were widely disseminated in the late 1800s and early 1900s. ‘Rheumatic and gouty insanities’ were often included. Some of this rich literature, very relevant in the context of the history of lithium in medicine and psychiatry, cannot have escaped Cade’s attention.

Cade might also have been acquainted with the important work, Early Mental Disease, in the Lancet Extra Numbers, No. 2 (1912)—Devine referred to it. The topic of toxaemia was taken up again.

Mapother, very influential in British psychiatry, with respect to dementia praecox, related that ‘that toxaemia and infection in some cases play a part is suggested by certain writers’. Conceding that the general metabolic disturbances of dementia praecox ‘are sometimes extreme, and certainly they are not always explicable as resulting directly from conduct’, he saw fit to add that all attempts thus far had failed to demonstrate that external toxic agencies, ‘whether specific or not’, ‘are constantly or even very frequently responsible for dementia praecox’. Finally, he emphasised that efforts had been made ‘to trace this and other “functional” psychoses to bacterial toxins absorbed from the alimentary canal, tonsils, the gums, the nasal accessory sinuses’, but to no apparent avail.[863]

Pierce[864] contributed to the same publication with a paper on manic-depressive psychosis. Discussing physical causative factors, he expressed the view that ‘a hidden focus of infection or even reflex irritation, may be the exciting cause’. Intriguingly, he found the resemblance between hypomania and mild degrees of alcoholic intoxication to be ‘so striking’ that

[861] op. cit., 1903;49:163–164.

[862] Russian Medical Messenger, 1902.

[863] op. cit., p.74.

[864] op. cit., p.94.

> it suggests that the disorder may be caused by some unknown toxic agent, the varying reactions of different persons to alcohol corresponding to the varying phases of the manic-depressive psychosis.

This is not dissimilar to what Cade was to espouse.

In his history of psychiatry book, in referring to his first years in psychiatry, Cade touched on the theories of auto-intoxication. He mentioned the work of Metchnikoff on 'the product of the flora of the colon'.[865] He also mentioned that 'the archpriest' of focal sepsis was Cotton,[866] who, according to Cade, believed that 'the most important cause of the functional psychoses, manic-depressive illness and schizophrenia, was toxaemia coming from chronic foci of infection, situated anywhere in the body'. More generally, Cotton expressed the view that the 'so-called functional psychoses' were due to a combination of many factors: 'the most constant one [being] the intra-cerebral, biochemical and cellular disturbance arising from circulatory toxins originating in chronic foci of infection situated anywhere throughout the body, and probably secondary disturbances of the endocrine system' (quoted by Watson). Cotton speculated that 'dementia praecox and manic-depressive insanity may not be distinct entities'.[867]

One of Cotton's papers was published in the Journal of Mental Science in 1923. This volume contained a number of other articles on auto-intoxication, for instance one by Watson,[868] quoted in Devine's textbook, on the role of auto-intoxication or auto-infection in mental disorders. This article contained a survey of the literature on the subject in this journal 'for the past twenty years' in order to 'adequately reveal the general outlook and the practice of alienists in regard to the relationship of physical disorders to mental disease'.[869]

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[865] Cade, 1979, p.12.

[866] ibid. pp.25–27. cf. Cotton HA.: 'The etiology and treatment of the so-called functional psychoses. Summary of results based upon the experience of four years'. Am. J. Psychiatr. 1922;2:157–210. Cotton HA.: 'The relation of chronic sepsis to the so-called functional mental disorders'. J. Ment. Sci. 1923;69:434–465 (also quoted by Devine, p.135). Kopeloff, N., Kirby, GH.: 'Focal infection and mental disease'. Am. J. Psychiatr. 1923;3:149–197, (also quoted by Devine, p.136). cf. Watson DC.: 'Further reflections on the role of auto-infection in the aetiology of acute and chronic mental disorders'. J. Ment. Sci. 1924;70:537–541 (Devine p.136). Hobbs AT.: 'A survey of American and Canadian psychiatric opinion as to focal infections (or chronic sepsis) as causative factors in functional psychoses'. ibid. 1924;70:542–553 (Devine p.136). cf. Valenstein ES.: 'Great and desperate cures. The rise and decline of psychosurgery and other radical treatments for mental illness'. New York: Basic Books, 1986. pp.37–43.

[867] According to P. Clark: 'Manic-depressive psychoses: a symposium' (J. Nerv. Ment. Dis., not retrieved), quoted from J. Ment. Sci. 1923;69:379–380.

[868] Watson C.: 'The rôle of auto-intoxication or auto-infection in mental disorders'. J. Ment. Sci. 1923;69: 52–77.

[869] Dawson WS.: 'A study of the endocrine-autonomic disorders of dementia præcox'. J. Ment. Sci. 1923;69:182–199. Walker J.: 'The significance of urea in dementia præcox'. J. Ment. Sci. 1923;69:322–327 (he found a lowering of the urea-nitrogen ammonia-nitrogen ratio which he ascribed to 'a general slowing of metabolic processes' as part of a 'diminished arterial tone'). Walker J.: 'The reaction of the urine in 120 cases of mental disorder'. J. Ment. Sci. 1923;69:327–330 (he concluded that the reaction of the urine in the cases of mental disorder examined varied within physiological limits). Parfitt DN.: 'The

Apart from the works of Clouston, Bruce and others, Watson cited a paper by a French physician, Prunier,[870] (reviewed in Journal of Mental Science, 1908) who carried out experiments in guinea pigs by injecting them with urine selected from patients who were suffering from mental confusion and concomitant various gastro-intestinal disturbances. He found the urine to be 'hypertoxic' in each case, and concluded that this hypertoxicity exceeded the amount of toxins absorbed from the intestinal canal, 'so that an autotoxication of the body is produced', resulting in 'various physical signs' and 'mental confusion'. All the animals died in convulsions, never in coma, and he attributed this to the presence of a 'ptomaine' in the injected urine.[871]

The reviewer, Clarke, thought that Prunier jumped 'too readily to the conclusion that the hypertoxic urine indicates the body is poisoned with toxines'. He found, though, that the question of auto-intoxication was 'most interesting and fascinating, and about which much has been written, but the exact observations there are but very few'.

According to a review by Dawson,[872] also in the 1923 volume of the Journal of Mental Science, Frigerio had undertaken research on the theory that auto-intoxication, via nitrogen residue in the blood, from disturbance of the protein metabolism, caused by lesions of the liver or kidney, might cause mental symptoms. He found 'a low figure' in manic-depressive illness, dementia praecox and epilepsy. In the same volume of this Journal, Walker[873] had a paper on The significance of urea in dementia praecox. He estimated the percentage urea concentration using Maclean's modification of the hypobromite method, and he found that an abnormal urea-nitrogen, ammonia-nitrogen ratio to be 'in all probability the consequences of diminished metabolic processes'. In the 1933 issue of the Journal, Parfitt[874] had a paper on blood-urea in psychotics, partly inspired by Walker's work. Parfitt found that 'although the blood-urea level is not uniformly distinctive of any type of psychosis or phase of psychosis, yet its estimation in general psychiatric practice is probably as useful as any other test or reaction in use to-day'.

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blood urea in psychotics'. J. Ment. Sci. 1933;79:501–510. Anon.: 'Chronic sepsis and mental disease'. J. Ment. Sci. 1923;69:502–504.

[870] Clarke S.: 'Review of A. Prunier: Contribution to the study of auto-intoxication in mental confusion (thesis)'. J. Ment. Sci. 1908;54:603–604. cf. Watson, J. Ment. Sci. 1923;69:(57–58). According to Prunier, the subject of toxicity of the urine has been of interest for many years, 'for Maron in 1868 first injected some subcutaneously, but obtained negative results and declared that it was inoffensive'.

[871] The term 'ptomaine' (gr. ptoma=corpse), was coined by the Italian toxicologist, Selmi, to denote chemical compounds basic in character, and formed by the action of bacteria upon organic matter (cf. Oliver T.: 'Preface', in Bouchard C[J]. (ed.): 'Lectures on auto-intoxication in disease or self-poisoning of the individual'. Philadelphia: Davis, 1894).

[872] Dawson WS.: 'Review of some facts concerning the nitrogen residue of the blood in cases of mental disorder [Alcuni dati su l'azoto residuo del sangue negli alienati]. Friegerio, A. in (Riv. Pat. Nerv. Ment. October, 1922)'. J. Ment. Sci. 1923;69:387–388 (Dawson added that this work confirmed the results of Weston).

[873] J. Ment. Sci. 1923;69:322–327. Walker referred to Maclean H, Russell AE.: 'Some observations on the investigation and treatment of nephritis'. Lancet 1920;1:1305–1309.

[874] Parfitt DN.: 'The blood-urea in psychotics'. J. Ment. Sci. 1933;79:501–510.

Cade in prisoner-of-war camp 1942-45

Cade enrolled in the Australian Army Medical Corps in 1935, and was appointed Captain in July 1940. The next year he became engaged in active service, assigned to an overseas Field Ambulance, stationed at Singapore from February 1941. Seven months later he was promoted to the rank of major. From February 1942 until the end of the war, in September 1945, he was prisoner of war of the Japanese, incarcerated in the Changi camp at Singapore.[875]

According to Chiu,[876] Cade 'set up a 270-bed hospital for the reception of sick and wounded who were marched in'. And 'because of his interest and background in psychiatry', he added, Cade 'was often referred to as "the mad major" (John's own words)'.

An idea of the medical services at Changi can be gained from a paper by Harvey that was published in the Medical Journal of Australia in 1946.[877] Two large hospitals, British and Australian, were established by March 1942 'in a small area of seven blocks, and became Roberts Hospital with 2.500 patients'. The following year, the hospital was moved from Changi to the adjacent Selarang barracks.

According to Harvey, many combinations of deficiency diseases, e.g. beri beri, encephalopathies and pellagra, 'eclipsed all other medical problems'. From his reports in 1944, he cited the following extract: 'The mental ward has been kept busy, with a steady deterioration in the condition of most of the patients, and an average number of patients greater than at any previous time'.

Despite the hardship being endured, academic pursuits were possible.

> Post-graduate work; ward rounds and lectures were carried out for many months until they were prevented by circumstances, while an august body called the Changi Medical Society held monthly meetings for over two years, at which many important topical and other papers were read, and which commanded an audience that often topped the century.

And, Harvey emphasised, 'if this body ever publishes its archives, they will make interesting reading, as the standard was high'.

Harvey also described how various entertainment theatres 'rose almost mushroom-like'—'all putting on rattling good shows' thus giving 'a great fillip to the morale'. However, 'pride of place as morale builder', he said, 'must go, of course, to the daily news bulletin, to obtain which men literally took their lives in their hands'. 'The "canary", as it was euphemistically called, practically never failed us in the whole three and a half

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[875] Ironside W.: 'John Cade' in Australian Dictionary of Biography, 1983:330–331.

[876] Chiu E, Hegarty RM.: 'John Cade: the man'. Aust. NZ. J. Psychiatr. 1999;33. Suppl. pp.S24–S26.

[877] Harvey C.: 'Medical aspects of the Singapore captivity'. op. cit. 1946;1:769–772. This paper was read at a meeting of the New South Wales Branch of the British Medical Association on March 15, 1946.

years. The men who collected the news deserve full marks for cool courage and devotion to duty'.

Cade was one of these men risking their lives as a 'canary'. As Jack Cade wrote,[878] his father

> had a remarkable memory. His task was to listen to the nightly BBC broadcast on the hidden radio in Changi, and when it was too dangerous to carry written reports he committed the entire news to memory and repeated it verbatim to his audience of fellow POWs.

However, according to his son,[879] Cade left no notes regarding his medical experiences during this time. But, as cited previously, on 26 September 1945, on his way home from captivity, he wrote to his wife, Jean,[880] that

> the old brain box is simmering with ideas. I believe this long period of waiting has allowed many of my notions in psychiatry to crystallise, and I'm just bursting to put them to the test. If they work out, they would represent a great advance in the knowledge of 'manic-depressive' insanity and primary dementia—sounds like my usual over-optimism, doesn't it? Well, there is only one way to find out—test it and see.[881]

Very similarly, as also cited previously, three months before his death in 1980, Cade wrote to Johnson that during his time in the prison camp

> I could see that so many of the psychiatric patients suffering from the so-called functional psychoses appeared to be sick people in the medical sense.[882] This fired my ambition to discover their etiology […] I returned from three and a half years as a POW of the Japanese mourning the wasted years and determined to pursue the ideas that had germinated in that interminable time.[883]

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[878] Cade JF.: 'John Frederick Joseph Cade: family memories on the occasion of the 50th anniversary of his discovery of the use of lithium in mania'. Aust. NZ. J. Psychiatr. 1999;33:615–618.

[879] Cade, personal communication.

[880] Quoted from Westmore A.: 'The many faces of John Cade'. (Appendix II). Westmore A.: 'John Cade and biological research; possible motivations'. Abstract. '50 Years of Treatments for bipolar disorder. A celebration of John Cade's discovery. Final Program, 1999'. Paper presented at : Fifty years of treatments for bipolar disorder. A celebration of John Cade's discovery, Sydney, 4–5 December 1999.

[881] cf. Cade's mention of 'the famous Hunterian dictum: Don't think. Try', in his: 'Mending the Mind. A short history of twentieth century psychiatry'. Melbourne: Sun Books, 1979. pp.5, 41.

[882] cf. Mitchell PB, Hadzi-Pavlovic D.: 'Lithium treatment for bipolar disorder'. Bull. Wld. Hlth. Org. 2000;78:515–517. Westmore A.: 'John Cade and biological research: possible motivations' (Abstract). op. cit. 1999.

[883] Johnson FN.: 'John F. Cade, 1912-1980: a reminiscence'. Pharmacopsychiatr. 1981;14:148–149. Johnson, 1984, op. cit., p.34.

This raises the question of whether Cade discussed his ideas with other doctors in the camp. There are no extant sources, however, with which to answer this question. Moreover, it seems that Cade left no notes about the origin of the (his) hypothesis or 'notions' of manic-depressive illness and 'primary dementia', and which formed the basis of his experimental work upon his return from captivity.

Intriguingly, at the semi-centennial celebration of Cade's discovery of lithium in Sydney in 1999, according to Gordon Johnson,[884] it was suggested that Cade's experience with vitamin deficiency, both within the psychiatric hospitals in Victoria and during his war years in a concentration camp, Changi 'may well have influenced his search for a chemical cause for manic-depressive illness'.

Cade's publications after 1949

On 7 and 14 May, 1951, Cade[885] delivered two parts of a prestigious Beattie-Smith Lecture at the University of Melbourne; Lecture I: Research in Psychiatry, and Lecture II: The Problem of Schizophrenia.

In these contributions, one looks in vain for any direct revelations regarding Cade's path(s) to lithium and its anti-manic effect. In print, it appears, Cade remained silent about this until at least 1962.

However, in the first lecture, when it is read in the context of some of his later papers, it becomes apparent that Cade did, in fact, refer to his lithium research. He pointed out that 'there is nothing peculiar about psychiatric research except perhaps the material upon which it works'.

> My qualifications for discussing medical research in general or even psychiatric research in particular are best left unstated. I might most kindly describe myself as an enthusiastic amateur, full of curiosity, with fair determination, golden opportunities, inadequate knowledge and woeful technique. But even the small boy, fishing after school in a muddy pond with string and bent pin, occasionally hauls forth a handsome fish.

As Cade went on, 'One of the major criticisms that may be levelled at much of the work published in psychiatry is the tendency to uncontrolled observation', and 'from my own reading the impression left by much of the literature is one of ingenious and airy hypotheses, superficially plausible at times, but too often couched in an incomprehensible jargon, and quite lacking in a foundation of solid fact'.

Cade emphasised that 'The method or tactics or technique to be adopted in approaching a problem depend so largely on the situation that I doubt if any useful rules can be laid down; the results depend so much on ingenuity and perseverance'. But one can say that 'an essential for successful research is thorough training in the established

[884] Johnson G.: 'A celebration of John Cade's discovery: 50 Years of Treatment for Bipolar Disorder'. ISBD Global Vol. 1, September 2000.

[885] Med. J. Aust. 1951;38:213–219. ibid., 1951;38:243–251.

techniques and a systematic gathering of all known facts relevant to the investigation. Even more important, perhaps is the determination to use any and every means to the end, no matter how humble, how unorthodox or how tedious'.

Cade then turned his attention to the question, 'how can clinical research best be organized in the mental health services of this state [Victoria]?'

> The first thing we must decide is this: does it need organizing at all?
>
> How have the biggest advances in medical knowledge been made in the past? We must agree that many of the most spectacular have been made by individuals working largely by themselves, with a minimum of help from others and a paucity of equipment.

Cade did not dismiss 'team endeavour', but emphasised that 'sometimes a particular problem is tackled and solved by one person working alone'. In fact, 'Some workers are naturally "lone wolves" and give of their best when left to themselves […]'.

Cade did not miss the opportunity to deliver some remarkable anti-Freud tirades—as both before and after.[886]

Further, he touched on the issue of whether schizophrenia and manic-depressive insanity might be due to 'subtle organic and biochemical changes'. Notably, he did not mention the hypothesis of these conditions that he had set out to test in 1945, at his release from captivity.

Cade did not mention lithium therapy in his first Beattie-Smith Lecture. Interestingly, immediately after the printed version of this lecture, in the Medical Journal of Australia, followed the also now-classic paper: The Lithium Treatment of Maniacal Psychosis by Noack and Trautner,[887] the opening statements of which had that

> Cade (1949) claimed great benefit from lithium medication in states of psychotic excitement, but its use has been discredited since several fatal cases of poisoning were reported in the United States as well as in Australia […]

In Part II of his Beattie-Smith Lecture, Cade provided a wealth of various theories, by as many authors, to illustrate that 'the real cause of schizophrenia at present eludes us'. Manic-depressive illness was also mentioned, but there was no trace of 'his own' hypotheses of the two conditions, which he had recently tested, nor of lithium treatment. Attesting to a considerable erudition Cade mentioned Kraepelin, Mott, Alzheimer, Kretschmer, Gjessing, Bruce, Lingjaerde, Selye, Ashby, Rosen, Bleuler, Henderson and Aubrey Lewis, among others.

After having referred to Kraepelin's 'important differentiation between manic-depressive psychosis and dementia praecox', Cade pointed out how 'it soon becomes evident to anyone treating psychotic patients that a proportion of them have so-called

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[886] cf. Cade JF.: 'The biochemistry of schizophrenic and affective psychoses'. Med. J. Aust 1964;1:878–881 ('Freudian psychopathology'). Cade's history of psychiatry book (1979), p.90. Haigh G.: 'Matter over Mind'. The Bulletin (Australia) December 21, 2004–January 11, 2005:91–95.

[887] Med. J. Aust. 1951;2:219–222.

"mixed psychosis" with symptoms of both groups'. Accordingly, he emphasised, it could be impossible to determine 'whether a restless and excited young person is suffering from true mania or catatonic excitement, or whether a depressed and delusional patient should be regarded as suffering from paraphrenia or melancholia'. In addition, he drew attention to the fact that a small percentage of patients with undoubtedly schizophrenic illness 'exhibit a cyclical course of regular remissions and relapses, just as manic-depressives do so much more commonly'—characterising them as cases of 'periodic catatonia'.

On the other hand, Cade went on, it is evident that the validity of classification of the major psychoses, manic-depressive psychosis and dementia praecox, 'rests on a most insecure basis'. As he had stated before, and more or less reflecting Kraepelin's views,[888] he said that 'it is quite possible that [these psychoses] are merely different reactions of various personality types to the one underlying disturbance'. As far as Cade was concerned, 'it is easy to see how one person will react with depression to adverse circumstance, another will sink into indifference, whilst yet another will become fearful or irrationally excited'. Therefore, he queried whether

> we [are] dealing with a nicely clear-cut disorder with a single cause, or with a syndrome analogous to the symptoms of anaemia with many possible causes, or have we merely a number of different personality reactions to a constantly present adverse factor?

Pursuing an organic pathology of schizophrenia, Cade then turned to Mott's work on gonadal degeneration,[889] his paper in the Proceedings of the Royal Society of Medicine possibly having been the source; he followed this with an equally brief, non-referenced mention of Alzheimer and Kretschmer.

In the context of the present investigation of the possible sources that were inspirational as to Cade's hypothesis of manic-depressive illness and schizophrenia, it is important to consider his view of Gjessing's work on periodic catatonia, also given attention, non-referenced, in his Beattie-Smith Lecture.

After having concluded that 'there have of course been innumerable physiological and biochemical studies which […] have been largely inconclusive', Cade said that one of the most important biochemical investigations on the metabolic changes in patients with periodic catatonia was 'the painstaking work of Gjessing'.

He went on to explain that Gjessing 'held that the total nitrogen excretion was increased in the "bad" phases, whether of excitement or stupor, and that there was

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[888] cf. 'Meeting Report: The insulin treatment of schizophrenia'. Med. J. Aust. 1938;1:133–135 (Cade). Kraepelin E.: 'Dementia Praecox and Paraphrenia', 1919. pp.235–240 ('Personal idiosyncrasy'), German Edn. III/II. Teil, 1913. pp.921–927. Kraepelin: 'Manic-depressive insanity and paranoia', 1921, p.177 ('personal idiosyncrasy'), German edition, 8. Edn., III/II.Teil, 1913. pp.1372–1373, 1365 ('Die persönliche Eigenart'). cf. 8th Edn., I. Band, 1909, pp.206–209.

[889] Mott FW.: 'Studies in the pathology of dementia praecox'. Proc. Roy. Soc. Med. 1920;13:25–63. cf. Mott FW.: 'Normal and morbid conditions of the testes from birth to old age in one hundred asylum and hospital cases'. Br. Med. J. 1919;2:pp.655, 698, 737. Mott's work is given some consideration by Henderson DK, Gillespie RD.: 'A text-book of psychiatry for students and practitioners'. Oxford University Press, 1944. pp.289–291, Cade quoted this work in his 1949 paper.

nitrogen retention during “good” phases’. ‘This anabolic phase’, still in Cade’s words, ‘continued until just before the “bad” phase commenced, when breaking down exceeded anabolism once more’. But as Cade put it, things are not so simple as all that, for

> Gjessing himself describes cases in which the very reverse metabolic picture occurs—that is, nitrogen retention in the “bad” phases and excessive excretion in “good” phases—and also other cases in which there is no relationship whatever between mental state and nitrogen excretion.

Cade then mentioned that Gjessing observed ‘a favourable therapeutic action of thyroxine’ in periodic catatonia. Thus, after depletion of the nitrogren store of the body by thyroid treatment, Cade went on, there was no recurrence of the active, stuporose or excited phases, nor were there further alternating swings of positive or negative nitrogen balance.

With respect to thyroid treatment, Cade stated, this method had been introduced by ‘the Scottish psychiatrist Lewis Bruce’, referred to previously.

Cade’s Beattie-Smith Lecture contains no bibliographical reference to Gjessing’s work; Cade limited himself to mention and provide reference to a work by Hardwick and Stokes[890] to the effect that these authors were able to confirm ‘some of Gjessing’s findings’. In this work Cade noted that the authors ‘observed that the swings in nitrogen balance were related to the state of general nutrition and could be avoided by improved nutrition without interference with the rhythm of the mental illness’. Generally, Hardwick and Stokes noted, Gjessing had had to consider whether the activity of the thyroid gland was ‘specific’ in producing the phasic disorder so characteristic of periodic catatonia. Finally, they concluded that an investigation of quickly swinging manic-depressive cases, and of women with phasic mental disturbances was required, the authors querying whether there were endocrine disturbances more fundamental than the periodic nitrogen swings.

It is not unlikely that Cade had read ‘a short review’ by Gjessing himself of his remarkable work, published in the Journal of Mental Science in 1938.[891] Of special interest in this publication is that Gjessing expressed the opinion that the essential metabolic change in periodical catatonia is periodical variation in nitrogen balance, with a phase of maximum retention and maximum excretion of nitrogen, respectively. He assumed that at the time of change from one to the other, ‘one or more toxic substances are formed which act, through the blood-stream, on the vegetative and myostatic centres of the diencephalon’. Moreover, he stated that

> such a hypothetical substance occurring at both these times might reasonably be connected with [protein disturbances], and may possibly be a biogenic amine or a protein breakdown product of unknown or atypical kind.

[890] Hardwick SW, Stokes AB.: ‘Metabolic investigations in periodic catatonia’. Proc. Roy. Soc. Med. 1940-41;34:733–755.

[891] Gjessing R.: ‘Disturbances of somatic functions in catatonia with a periodic course, and their compensation’. J. Ment. Sci. 1938;84:608–621.

Cade returned to Gjessing again in 1964, to be discussed later, and in 1979.[892]

Cade now turned to the question of possible disturbance of liver function in schizophrenia. Among others, he referred to a work, written *in German*, by Lingjaerde.[893]

As Cade wrote, this author, who was inspired partly by Gjessing's work,[894] reported disturbances of liver function evidenced by increased urobilin excretion, ketonuria and various positive turbidity test results. According to Cade, other authors had not been able to confirm the theory of liver damage being a causative factor in catatonia or in other symptoms of schizophrenia.

According to Lingjaerde's work—this information not mentioned by Cade—the author wondered whether the aforementioned factors occurred as a result of hepatic impairment due to inanition (lack of carbohydrate intake, and thus glycogen deficiency, being a pathogenic factor, and possibly also in cases of vitamin deficiency). However, he also discussed the theory of enterogenic (i.e. intestinal) intoxication as a possibility. It should be added that Lingjaerde also included patients with manic-depressive illness, senile dementia and epilepsy in his investigations.

As far as Cade was concerned, 'during the last twelve months or so I have studied the urinary urobilin excretion of various schizophrenics by a rough quantitative method', (a 'small and very preliminary investigation'). In both 'chronic' and 'non-schizophrenic' patients he found normal urobilin excretion, whereas in 'a small group of schizophrenics' with spontaneous fluctuations of symptoms, or resulting from electroconvulsive treatment, he observed 'a similar fluctuation in urobilin excretion', that is, significantly increased excretion when in a state of deterioration; reduced excretion usually to within normal limits when improved. Cade, pointing out that this outcome did not necessarily spell liver damage, found this to be 'a promising line of investigation, as in some cases at least there appears to be a correlation between mental state and urinary urobilin excretion'.

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[892] Cade, 1979, op. cit., p.40: 'One popular treatment was dosing patients with huge amounts of thyroid. It was based on Gjessing's work in the mid-twenties on the protein metabolism of schizophrenics: he observed that in a small group suffering from a form of the illness known as periodic catatonia, there were fluctuations in protein metabolism paralleling changes in their mental stage' (as before, Cade provided no explicit references).

[893] Lingjaerde O.: 'Leberuntersuchungen bei Geisteskranken unter besonderer Berücksichtigung des Verhältnisses von Krankheitsverlauf, Leberfunktion und Nahrungszufuhr bei Schizophrenen'. Acta Psychiatr. Neurol. 1934. Suppl. V. The issue of urobilin excretion and ketonuria and nutrition is discussed pp.189–295.

[894] Gjessing R.: 'Beiträge zur Kenntnis der Pathophysiologie des katatonen Stupors'. Arch. Psychiatr. Nervenkrankh. 1932;96:319–392; 393–473.

In 1956 Cade published a paper on the aetiology of schizophrenia, based on its distribution pattern in metropolitan and rural areas.[895] To throw some light on this matter he had undertaken a survey in Victoria. It led him to generate a hypothesis based on the possibility of *protective foods* that 'would certainly explain the known facts' of the uneven distribution of schizophrenia 'better than any other postulated cause'. He concluded that 'when consumption of protective foods falls below a certain minimum level those with a constitutional predisposition develop frank schizophrenia'. He also thought that it was reasonable to consider 'the possibility of a relationship to *trace elements*'.

Cade resumed the subject of trace elements in his next paper in 1958, entitled Manganese and Mongolism,[896] to the effect that manganese had been shown to be 'an essential trace element' in certain animal species.[897] He drew attention to the fact that chondrodystrophy in chick embryos is a result of 'manganese deficiency' in the diet of the hen, characterised by 'greatly shortened, thickened legs and thickened wings, shortening of lower mandible, globular head, protruding abdomen and retarded down and body growth'. He was, however, cognisant of the fact that 'it is always a dangerous exercise of the imagination to draw parallels between animal and human structure, function or behaviour, but although fallacious', he proceeded to express the view that 'it is not difficult to detect similarities between this condition [chondrodystrophy] of chick embryos and mongolism in man'.

With reference to the 'manganese deficient' diet of the hen, Cade now thought that it was 'precisely this sort of dietary imbalance that is so common amongst pregnant women', thus increasing the risk of mongolism in their offspring. Therefore, as 'no other ordinary item of diet approaches tea in manganese content', he suggested that a 'prospective experiment' be undertaken jointly with obstetricians and general practitioners 'of urging all pregnant women to continue or commence to drink tea generously', especially in the first trimester, and to 'compare the subsequent incidence of mongolism amongst the children of this group of mothers as compared with that amongst women consuming little or no tea'. Cade realised, though, that 'it would be much easier and quicker to refute the proposition', if experienced colleagues could ascertain that 'mothers of mongol babies' had consumed 'considerable quantities of tea' during the pregnancy, and thus it would not be worthwhile 'pursuing the suggestion further'.

However, as Cade noted in his book on the history of psychiatry, it was the following year, in 1959, that three French cytologists discovered Down syndrome to be a chromosomal aberration.[898]

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[895] Cade JF.: 'The aetiology of schizophrenia'. Med. J. Aust. 1956;2:135–139.

[896] Med. J. Austr. 1958;2:848–849 (retrieved by Sam Gershon). cf. Cade JF.: 'Research in psychiatry'. Med. J. Aust. 1951;2:213–219. Cade also mentioned mongolism in his Beattie-Smith Lecture.

[897] Cade referred to E. J. Underwood: 'Trace elements in human and animal nutrition'. New York: Academic Press, 1956.

[898] Lejeune J, Gautier M, Turpin R.: 'Étude des chromosomes somatiques de neuf enfants mongoliens'. C. R. Acad. Sci. (Paris) 1959;248:1721–1722. Cade, 1979, op. cit., p.85.

Cade published a paper in 1962 on sodium, potassium and chloride levels in manic, depressive and schizophrenic states.[899] He expressed the view that there was a specific hypokalaemia in mania. Next, he reiterated that 'whether a disorder is labelled schizophrenic or affective is largely a matter of observer bias in many cases'. Finally, he briefly commented that lithium possibly acted on 'neuron excitability', the mechanism possibly being the alteration of intracellular and extracellular cation concentrations. Importantly, this appears to be the first mention of lithium in print by Cade after his 1949 paper.

Cade[900] followed up his electrolyte studies with a work published in 1964 that dealt with the question of whether manic, depressive and schizophrenic states were associated with 'other identifiable and statistically significant alterations in plasma electrolyte levels'. For the reason that 'hypomagnesaemia is associated with states of hyperexcitability, whereas raised levels have a sedative, depressant and, even in sufficient concentration, anaesthetic and respiratory paralysant effect', he chose to investigate plasma magnesium levels. He found these were significantly raised in both severely affected depressive and schizophrenic patients. However, none of his patients had shown a drop in their plasma magnesium levels after remission. From the viewpoint of hypomagnesaemia, possibly predisposing to fits and hypermagnesiaemia in schizophrenia, he finally queried whether Meduna 'was at least partly right when he postulated some biological antagonism between epilepsy and schizophrenia—the theoretical basis for his introduction of convulsive therapy'.[901]

In another publication in 1964, Cade[902] discussed, among others, 'Freudian psychopathology',[903] and Kraepelin's belief 'that manic-depressive and schizophrenic states were organically produced'. In the latter instance, he felt that that it would be 'profitless' to engage in a detailed historical survey of 'a vast number' of inconclusive works, and thus limited himself to mention the work on gonadal degeneration by Mott,[904]

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[899] Cade JF.: 'The relation between recovery and plasma potassium levels in manic states'. Med. J. Aust. 1962;2:911–913.

[900] Cade JF.: 'A significant elevation of plasma magnesium levels in schizophrenia and depressive states'. Med. J. Aust. 1964;1:195–196. cf. Watson D.: 'A significant elevation of plasma magnesium levels in schizophrenia and depressive states'. Med. J. Aust. 1964;1:461–462, in which Watson criticised Cade's paper on two counts, the first being 'the brevity of an article making an important biochemical discovery', the second being that the possibility existed that the 'significant elevation' of plasma magnesium levels 'may be entirely unrelated to the state of primary or secondary depression in the patients studied by Cade'.

[901] cf. Cade, 1979, pp.41–45 ('Convulsive therapy').

[902] Cade JF.: 'The biochemistry of schizophrenic and affective psychoses'. Med. J. Aust. 1964;1:878–881.

[903] Cade referred to Bernhard Hart's synopsis of this subject. According to 'The Melbourne University Calendar 1938'. Melbourne, 1937, p.1018. Hart's book: 'The Psychology of Insanity', 1936, was included in the Sixth Year reading list. cf. Cade's history of psychiatry book (1979), p.90. Haigh G.: 'Matter over mind'. The Bulletin (Australia) December 21, 2004–January 11, 2005:91–95.

[904] Cade provided no reference. cf. Mott FW.: 'Normal and morbid conditions of the testes from birth to old age in one hundred asylum and hospital cases'. Br. Med. J. 1919;2:pp.655, 698, 737. Mott, F.W.: 'Studies in the pathology of dementia praecox'. Proc. Roy. Soc. Med. 1920;13:25–63. Mott's work was

and the changes that Vogt[905] claimed existed in certain neurons of schizophrenics. He also mentioned 'Gjessing's biochemical studies in periodic or cyclical states', though he again provided no references for them.[906] Cade himself hypothesised biochemical disturbances to be the causative factors.

With respect to the specific anti-manic effect of lithium salts, Cade stated that this 'is almost certainly related to the fact that lithium replaces potassium within the cell and affects potassium-mediated metabolism'. On the basis of 'the presence of a significantly raised plasma magnesium level in both schizophrenia and psychotic depression and a greatly increased variability of plasma magnesium level in these two conditions as well as in mania', he then formulated 'a tentative hypothesis' as to an increased variability of plasma magnesium levels in all of the three mentioned psychotic states. He postulated that 'the primary failure is in the mechanisms responsible for magnesium homoeostasis': in cases of uncompensated 'primary failure' schizophrenia results; if 'the compensatory path' is via the sodium ion, psychotic depression is the result; if via the potassium ion, mania is the result.

Cade paid special attention to the effect of dietetic factors in magnesium absorption. He found it 'reasonable', therefore, to look for the possibility of 'a nutritional cause' and reiterated the suggestion that proper diet contains a *protective factor*, and conversely, that poor diet is either toxic or that it interferes with the absorption of 'other factors necessary'.

Cade felt that his hypothesis, other than explaining 'the epidemiological phenomena which have hitherto been so puzzling, throws light on the following clinical observations, which have for long been a source of bewilderment and argument':

'1. Why so many patients react successively in different ways'. Faults of diagnosis or differing diagnostic criteria were suggested, and also 'the employment of differing psychological defence mechanisms by the patient'.

'2. The frequent mixed or schizo-affective reactions'.

'3. The irregular alternations of manic and depressive states', Cade wondering if these could be explained 'simply by whether the sodium or potassium compensatory mechanism is operative'.

'4. The fact that long-standing psychotic states, originally diagnosed as affective, can end up as a condition indistinguishable from regressed schizophrenia'.

'5. A long-discredited hypothesis', for 'if hypomagesaemia does predispose to fits, and if schizophrenics are hypermagnesaemic, perhaps Meduna was at least partly right when he postulated some biological antagonism between epilepsy and schizophrenia—the theoretical basis for his introduction of convulsive disorder'.

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given consideration by Henderson DK, Gillespie RD.: 'A text-book of psychiatry for students and practitioners'. Oxford University Press, 1944. pp.289–291; Cade quoted this work in his 1949 paper.

[905] Oskar Vogt was a pioneer in schizophrenia research. The work Cade referred to has not been retrieved.

[906] e.g. Gjessing R.: 'Disturbances of somatic functions in catatonia with a periodic course and their compensation'. J. Ment. Sci. 1938;84:608–625. cf. Cade, 1979, op. cit., p.40.

In Cade's further studies on 'internal ionic environment' ('ionic profile-neuronal excitability') in mania, melancholia and schizophrenia, published in 1967,[907] he investigated the response of melancholic and schizophrenic patients to 'a loading dose of magnesium salt and the marked difference of response compared with normal subjects'. He found 'hypermagnesaemia' in melancholia and 'a lesser but still significant rise of plasma magnesium in schizophrenia'. He thought that 'Another highly significant biochemical correlate of melancholia has been identified'.

Finally, Cade wondered 'how many of our depressive patients are chronic ingesters of ant-acid preparations containing magnesium or purge themselves with Epsom salts?' Accordingly, he asked whether these salts were 'merely exchanging dyspepsia and constipation for depression?'

Cade's sources in his 1947 and 1949 papers

THE 1947 PAPER

In this paper, without providing references, Cade related that his urea estimations were carried out with the hypobromite method. In the assaying of creatinine he used Folin's colorimetric method with alkaline picrate solution.

An early mention of the hypobromite method was that of Hibbard in 1898.[908] Folin's test was described in Beard's book,[909] to which Cade made reference, but not in this connection. Whether he knew that Folin was an authority on the uric acid problem,[910] and that he had used injections of lithium urate in his experiments, cannot be established with certainty.

In 1922, Folin[911] published his Manual of Biological Chemistry. He gave a description of his own colorimetric method for creatinine. However, he did not provide any specific information regarding the hypobromite method other than to state that it had been used for the quantitative determination of urea, 'but as ordinarily used for this

[907] Cade JF.: 'The metabolism of melancholia'. Aust. NZ. J. Psychiatr. 1967;1:23–29.

[908] Hibbard CM.: 'A study of the excretion of urea and uric acid in melancholia and in a case presenting recurrent periods of confusion and depression'. Am. J. Insan. 1898;April:503–531.

[909] Beard HH.: 'Creatine and creatinine metabolism'. Brooklyn, NY: Chemical Publishing Co, 1943. pp.7–10, 323 (Folin). cf. Hunter A.: 'Creatine and Creatinine'. New York: Longmans, 1928 (with many references to Folin, incl. his 1904 study on metabolism in mental disorders).

[910] Several works, e.g.: Folin O, Berglund H, Derick C.: 'The uric acid problem. An experimental study on animals and man, including gouty subjects'. J. Biol. Chem. 1924;60:361–471.

[911] New York: Appleton, 1922.

purpose the method has very little use'. The next year, Walker[912] made reference to Maclean's modification of the hypobromite method, described in the Lancet in 1920.[913]

Cade provided no particulars with respect to the uric acid solutions he used, other than to thank the pharmacist at Mont Park Hospital for having been 'untiring in his preparation of the varied solutions required'.

As discussed several times before, 'the great difficulty' Cade had encountered in his animal experiments, was 'the insolubility of uric acid in water', and it was therefore that 'the most soluble urate was chosen'.

According to Folin's Manual, as uric acid 'is almost completely insoluble in form […] it has been a matter of no little difficulty to find a suitable solvent for the preparation of stable standard uric acid solutions'. He directed, however, that lithium carbonate could completely dissolve the uric acid, and he described the method.[914] The methodological problems surrounding uric acid determination in blood and urine, including Folin's contribution in this field, was given thorough investigation by Brøchner-Mortensen[915] in 1937, who made reference to the aforementioned work of Strandgaard,[916] but not to that of the Lange brothers.

Cade also made reference to a work by Merritt[917] and Putnam in 1938 on the testing of anticonvulsant drugs, including bromides, using electrical stimulation on animals. 'Both the bromides and phenobarbital were first introduced as soporifics and their employment in the treatment of epilepsy was based on clinical trial only', the authors stated. In the ensuing discussion, Spiegel made reference to his own investigations with bromide salts, injected into rabbits. He mentioned various bromides, but not that of lithium. In another paper on the same subject, also by Merritt[918] and Putnam, from the year before, they related that 'the introduction of bromides and later of phenobarbital may well be considered the two greatest steps forward ever made in the practical treatment of

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[912] Walker J.: 'The significance of urea in dementia præcox'. J. Ment. Sci. 1923;69:322–327

[913] Maclean H, Russell AE.: 'Some observations on the investigation and treatment of nephritis'. Lancet 1920;1:1305–1309.

[914] cf. Folin O, Macallum AB.: 'A new method for the (colorimetric) determination of uric acid in urine'. J. Biol. Chem. 1912–13;13:363–369. Folin O, Denis W.: 'A new (colorimetric) method for the determination of uric acid in blood'. ibid. 1912–1913;13:469–475. Folin O.: 'Laboratory manual of biological chemistry'. New York: Appleton, 1922. Folin O.: 'Unlaked blood as a basis for blood analysis'. J. Biol. Chem. 1930;86:173–178. Folin O.: 'An improved method for the determination of uric acid in blood'. ibid. 1930;86:179–187.

[915] Brøchner-Mortensen K.: 'Uric acid in blood and urine'. Acta Med. Scand. 1937; Suppl. 84:1–269.

[916] Strandgaard NJ.: 'Gigt og urinsur Diatese, kritisk belyst'. Copenhagen: Lund, 1899.

[917] Merritt HH, Putnam TJ.: 'A new series of anticonvulsant drugs tested by experiments on animals'. Arch. Neurol. Psychiatr. 1938;34:1003–1015.

[918] Putnam TJ, Merritt HH.: 'Experimental determinations of the anticonvulsant properties of some phenyl derivatives'. Science 1937;85:525–526.

the convulsive state'. However, Cade did not mention this work, but another of their works, not retrieved by the present author.

As Cade's own investigation also concerned 'the anticonvulsant properties of creatinine', being the title of his 1947 paper, it would appear likely that in his reading within the field of anticonvulsants, he gained familiarity with the use of bromides, and thus with lithium bromide.

THE 1949 PAPER

The relevant sources Cade referred to in this paper were:

i. Garrod, A. (1859) Gout and Rheumatic Gout, page 438.
ii. The Practitioner (1907) Volume I, page 166, quoted in Squire's The Companion to British Pharmacopoeia.
iii. The Practitioner (1909) Volume II, page 130, quoted by Squire, loco citato.
iv. Culbreth, D. M. R. (1927) Materia Medica and Pharmacology. Seventh Edition. page 743.
v. Henderson D. K., and Gillespie, R. D. (1944) Textbook of Psychiatry. Sixth Edition. page 3.

SOURCE I: GARROD, 1859

Cade opened his paper with a reference to Garrod's important work—the 1859 edition—to the effect that

> Lithium salts enjoyed their hey-day in the latter half of [the 19th] century when, commencing with their introduction by Garrod, they were vaunted as curative in gout, and so doubtless in a multitude of other so-called gouty manifestations. This followed the demonstration that lithium urate was the most soluble of the urates.

Garrod wrote (op. cit. p.438f) that the 'solvent power for uric acid or urates [is] far greater than that of any other agent'.

It must be pointed out that Cade did not mention that Garrod (op. cit. pp.506, 517, 520–522) linked excess of uric acid in the body (uric acid diathesis) to the assumed occurrence of 'maniacal symptoms'—in retrocedent gout—which, Garrod added, 'I have myself witnessed'. Other than reiterating that 'gouty mania is occasionally seen', Garrod also noted that 'sometimes epilepsy appears to be connected with a gouty habit'.

Cade thought that 'there is no doubt that in mania patients' improvement has closely paralleled treatment and that this criterion has been fulfilled in the chronic and subacute cases just as closely as in the cases of more recent onset'. Furthermore, 'the quietening

effect on restless non-manic psychotics is additional strong evidence of the efficacy of lithium salts, especially as such restlessness returned on cessation of treatment'.

Cade went on to point out that 'lithium salts have no apparent hypnotic effect; the result is purely sedative. The effect on patients with pure psychotic excitement—that is, true manic attacks—is so specific that it inevitably leads to speculation as to the possible aetiological significance of a deficiency in the body of lithium ions in the genesis of this disorder'.[919] He thought, in consequence, that '*lithium may well be an essential trace element. It is widely distributed, has been detected in sea-water and in many spring and river waters, in the ash of many plants, and in animal ash*' (emphasis added).

It will be remembered that it was Bunsen and Kirchhoff who in the 1850s could demonstrate, with the first flame spectrophotoscope, that lithium occurs ubiquitously, but mainly as a trace element.[920]

However, it must been drawn to the reader's attention that Garrod had expressed a very similar opinion, not in the 1859 edition but in both the *1863 and the 1876 editions* of this famous book (and not quoted by Cade): 'Lithia must […] now be regarded, *not* as a drug foreign to the economy, but as a normal constituent of the body, and essential to its well-being'.

> *It has been shown that lithia, instead of being , as its name implies, a constituent of minerals only, is extensively diffused throughout the vegetable and animal kingdoms, and it has already been detected in the water of the ocean, in many mineral springs […] in the ashes of sea-weed, and of many inland plants […] also in the milk, blood, and the muscles of the human subject, and of many animals'.* (emphasis added).

It must also be pointed out that Clarence Good,[921] in his aforementioned 1903 experimental study of lithium related that since Lithia was discovered in 1817 it had been shown

> *to be widely distributed in nature, but occurring only in small quantities. It occurs in various minerals, in mineral water, in sea water, in ash of plants, and in some vegetables used as food. It has also been found in the ashes of blood and milk'* (emphasis added).

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[919] cf. Johnson G, Gershon S, Hekimian LJ.: 'Controlled evaluation of lithium and chlorpromazine in the treatment of manic states: an interim report'. Compr. Psychiatr. 1968;9:563–572. Gattozzi AA.: 'Lithium in the treatment of mood disorders'. [NIMH]. Waskington DC.: National Clearinghouse for Mental Health Information Publication No. 5033, 1970. p.8.

[920] Kirchhoff G, Bunsen R.: 'Chemische Analyse durch Spectralbeobachtungen', in Poggendorff JC. (ed.): 'Annalen der Physik und Chemie'. Vierte Reihe, zwanzigster Band. Leipzig: Barth, 1860 (quoted from Amdisen A.: 'Lithium as a pharmacological agent. Historical aspects. Topical aspects in monitoring of psychiatric lithium therapy'. Thesis. Aarhus, 1985. Amdisen A.: 'Lithium treatment of mania and depression over one hundred years', in Corsini GU. (ed.): 'Current trends in lithium and rubidium therapy'. Lancaster: MTP Press, 1984:11–26.

[921] Good CA.: 'An experimental study of lithium'. Am. J. Med. Sci. 1903;125:273–284.

Good more generally referred to the second edition of Garrod's work.

However, it cannot be ascertained which of the two sources might have been Cade's primary source, Garrod or Good; he might have adapted both.

Similarly, Strömgren and Schou wrote—without reference—that 'small amounts of lithium are found in several minerals, in sea water, and in many spring waters, and traces of lithium also can be detected in plant and animal tissues'.[922]

Also Gershon,[923] with reference to Bunsen, wrote—no source provided—that lithium had been 'detected in trace amounts in plants, marine life, in milk from several animals, and in various animal and human tissues but not in human bone', adding that it was not known whether these traces of lithium 'naturally present in the organism play any physiological role'.

SOURCE II: AN ARTICLE FROM THE PRACTITIONER, 1907

With reference to The Practitioner, 1907, Vol. I, p.166, according to Cade as quoted in Squire's The Companion to British Pharmacopoeia, 'about fifty years later [after Garrod's 1859 book] cases are reported

> of cardiac depression and even dilatation, as a result of excessive and continued consumption of Lithia tablets' […] 'Cardiac depression and even dilatation' was perhaps very vague physiology, but the note of warning was clear […]

According to the source, Squire,[924] lithium carbonate 'has been given in cases of gout with the view of increasing the alkalinity of the blood, and acting as a solvent of the Sodium Biurate deposits'. In turn, Squire referred to Luff (he had the largest 'rheumatic' practice in London),[925] who wrote that 'lithium salts do not exercise any special solvent effect on Sodium Biurate, and […] their administration to gouty subjects with the object of removing uratic deposits in the joints and tissues appears to be useless' (Squire refers the reader to Lancet 1898;1:1609)—'In the treatment of gout Potassium salts were the most useful, and the Lithium salts ranked next' (here Squire refers to Lancet 1900;1:931 (Luff) & British Medical Journal 1900;1:836 (Luff)).[926] Finally, Luff was quoted for

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[922] Strömgren E, Schou M.: 'Lithium treatment of manic states'. Postgrad. Med. 1964;35:83–86.

[923] Gershon S.: 'Lithium in mania'. Clin. Pharmac. Ther. 1970;11:168–187. cf. Georgotas A, Gershon S.: 'Historical perspectives and current highlights on lithium treatment in manic-depressive illness'. J. Clin. Psychopharmacol. 1981;1:27–31. cf. Strobusch AD, Jefferson JW.: 'The checkered history of lithium in medicine'. Pharm. Hist. 1980;22:72–76.

[924] Squire PW.: 'Squire's companion to the latest edition of The British Pharmacopoeia etc'. 18th Edn. London: Churchill, 1908. pp.733–739.

[925] According to the Heberden Library Catalogue No. 86.

[926] In the latter: The gelatinous form of sodium biurate and its bearing on the treatment of gout, Luff, with reference to the former wrote that according to his experimental evidence, potassium, sodium, and lithium

constantly having encountered ‘cases of cardiac depression and even dilatation, as the result of the excessive and continued consumption of Lithia tablets, which are so persistently vaunted as curative in gout’ (here Squire refers to The Practitioner 1907;1:166).[927]

In 1897, before the Royal College of Physicians of London, Luff delivered the ‘Goulstonian Lectures’ on The chemistry and pathology of gout, published in Lancet,[928] the same year. The next year, followed his book: Gout. Its pathology and treatment,[929] ‘originally founded’ on these lectures.

According to Luff, gout was ‘associated with the presence of an excess of uric acid in the blood’, and he discussed whether ‘the soluble uric acid compound which is circulating in the fluids of the body acts as a poison, the toxic effects of which are responsible for a number of the symptoms associated with the gouty state’. Among them he counted ‘insomnia’, and ‘mental depression’ (op. cit. p.120). In retrocedent gout of the brain ‘congestion of the brain or meninges may occur, and may be followed by headache, stupor, convulsions, delirium, and occasionally by maniacal attacks’, he added (op. cit. p.125).

Luff also described experiments he had undertaken on ‘artificial blood serum’, for instance using lithium citrate and lithium carbonate, gaining the impression that these salts ‘would not in the slightest degree increase the solvent power of the blood for gouty deposits’. Lithium was generally given ‘in doses of one to five grains three times a day’ (op. cit. p.184).

A third and considerably extended edition of Luff ’s book was published in 1907.[930] Here he reiterated that in irregular gout both ‘mental depression’ (op. cit. p.140) and ‘congestion of the brain or meninges may occur, and may be followed by headache, stupor, convulsions, delirium, and occasionally by maniacal attacks’ (op. cit. p.146).

In Luff ’s opinion, lithium salts in the treatment of gout ‘are not so useful as the potassium and sodium salts’, ‘the principal objection to their use [being] their greater toxicity, and depressing action on the heart, as compared with the potassium salts’, whereas, when given in small doses, he was doubtful whether ‘in such doses, they possess any remedial effect at all.’ However,

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salts and piperazine and lysidine exercised no appreciable solvent action on gouty deposits. He emphasised, though, that he did not question—‘still less deny’—the utility of many of these drugs in the therapeutics of gout, ‘for I am constantly employing many of them in the treatment of various phases of that disease’. But Luff wished to point out that ‘the oft-repeated statement that most of these drugs are useful for their great solvent action on gouty deposits is a loose and erroneous statement which it would be wiser in future to avoid’.

[927] Also quoted in: ‘Treatment of subacute and chronic gout’. Ther. Gaz. 1909:798.

[928] op. cit., March 27, 1897, pp.857–863; April 3, 1897, pp.942–949.

[929] London & Melbourne, 1898. pp.120, 125, 183–184.

[930] Luff AP.: ‘Gout. Its pathology, forms, diagnosis and treatment’. New York: William Wood, 1907. Also printed at Oxford, the same year.

> on the other hand, I constantly meet with patients suffering from cardiac depression, and even dilatation, as the result of the excessive and continued consumption of Lithia tablets, which are so persistently, so speciously, and so wrongly vaunted as curative in gout [op. cit. p.222].

Luff also made reference to Levison,[931] but not to Carl Lange, stating that 'the administration of the alkalies of lithium salts […] with the object of either dissolving sodium biurate or of preventing its deposition is decidedly useless' (op. cit. p.208).

In his 1907 paper[932] Luff espoused the view that gout

> is due to faulty metabolism, probably both intestinal and hepatic, as the result of which some toxin or toxins are produced and lead to an auto-intoxication, which is an early factor in the development of the gouty condition

'With increasing intensity' he had formed the view that 'the intestinal tract is a very powerful factor, if not the primary factor, in the development of gout ['abnormal intestinal fermentation', 'excessive numbers of intestinal bacteria', 'abnormal intestinal toxins'], the deposition of urate in certain joints or tissues constituting but the climax of the gouty attack'.

Importantly, Luff thought that

> not only in the medical world has an unmerited importance been attached to uric acid as a factor in the causation of disease, but unfortunately, among a considerable section of the public, there has arisen a fetichism of uric acid, which has been pandered to, and fostered by, the proprietors of the various quack remedies that are so persistently advertised as being able of dissolving or removing uric acid from the system. The time has come to recognise that uric acid possesses no toxic properties worth speaking of.

In support of his belief that uric acid 'is practically devoid of toxic properties', Luff made reference to studies on animals which, when fed with large amounts of uric acid or injected intravenously with urates, elicited no signs of uric acid poisoning. He also referred to experiments on frogs' muscles, showing that muscle rigidity and tetanus were produced by hypoxanthin, whereas uric acid was inert.

Among possible symptoms, Luff mentioned 'insomnia', which as a rule 'is not complete, but consists of restlessness, interspersed with varying intervals of light or broken slumber'. However, in this 1907 paper he mentioned neither mental depression nor mania.

Finally, with respect to the use of lithium salts in the treatment of gout Luff expressed the opinion, as before, that

> they are not so useful as the potassium- and sodium-salts. The principal objection to their use is their greater toxicity, and depressing action on the

[931] op. cit., 1894.

[932] Luff AP.: 'The treatment of some of the forms of gout'. Practitioner 1907;1:161–175.

> heart, as compared with the potassium-salts. They consequently have to be given in such small doses that I am very doubtful as to whether, in such doses, they possess any remedial effect at all

whereas

> I constantly meet with patients suffering from cardiac depression, and even dilatation, as the result of the excessive and continued consumption of lithia-tablets, which are so persistently, so speciously, and so wrongly vaunted as curative in gout. [op. cit. pp.166–167]

As Johnson pointed out, Cade often quoted The Practitioner, 1907 but that he 'never managed to get the reference quite right'.[933] In fact, Cade never made explicit reference to the title of Luff 's paper or, for that matter, his name. But 'it is, perhaps, worth pointing out', Johnson added, 'that if Cade actually ever read Luff 's paper he would have been aware of the use of lithium in treating what was referred to as the "irregular" forms of gout, including insomnia—a condition often associated with mood disturbance'.

Had Cade also been acquainted with the other of Luff 's works described above, he would have been *fully* aware that 'mood disturbance' in the nineteenth century psychiatry often included gouty depression and gouty mania, and that these conditions were often, and by many, treated with lithium salts.

SOURCE III: AN ARTICLE FROM THE PRACTITIONER, 1909

From this source: 'The Practitioner (1909) Volume II, page 130, quoted by Squire [1916], *loco citato*' [Companion to the British Pharmacopoeia], Cade quoted Squire to the effect that: ' "Lithia salts upset the stomach very easily" '.

According to Squire (1916)[934] 'cases of cardiac depression and even dilatation [were seen] as the result of the excessive and continued consumption of Lithia tablets, which are so persistently vaunted as curative in gout' (Squire refers to The Practitioner 1907; 1:166), and 'lithia salts upset the stomach very easily' (Squire refers to The Practitioner 1909; 2:130).

It is worthy of note that this page 130 forms part of a *revised* 136-page Special Gout Number of The Practitioner, of July 1903.[935]

Attention should first be given to the 1903 issue of the journal, containing contributions by Haig[936] and Luff, among others.[937]

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[933] Johnson, 1984, op. cit., p.158 (note 50).

[934] Squire PW.: 'Squire's companion to the latest edition of The British Pharmacopoeia etc'. 19th Edn. (Reprinted 1918). London: Churchill, 1916. pp.838–847.

[935] Anon.: 'Notes by the way'. The Practitioner 1907;2:132.

In his article, and consistent with his other works, Luff wrote that ‘as regards the use of lithium-salts in the treatment of gout, my opinion is that they are not so useful as the potassium- and sodium-salts’, as he emphasised that ‘the great objections, however, to the use of the lithium-salts is their greater toxicity and depressing action on the heart as compared with the potassium salts’.—‘Consequently [they] have to be given in such small doses that I am very doubtful as to whether in such doses they possess any remedial effect at all.’—‘On the other hand, I constantly meet with patients suffering from cardiac depression as the result of the excessive and continued consumption of lithia-tablets, which are so persistently, so speciously, and so wrongly vaunted as curative of gout’.

It is also relevant to add that in the August 1903 issue of this journal, London[938] reiterated the view—also held by numerous other authors—on the relationship between various nervous and mental disorders, and uric acid in excess in the blood, that ‘according to the published observations of Charcot, Dyce,[939] Duckworth, Lecorché,[940] Olivier and other careful clinicians, it would appear that the nervous system may be affected by the specific gouty changes’. Therefore, ‘neurasthenia with its protean manifestations, is often met with, particularly mental depression and hypochondriasis’, and moreover, ‘many authors assert a relationship between an excess of uric acid in the blood and epilepsy [and] Bayle,[941] Garrod, Lorry,[942] Lynch[943] and others have observed psychoses, particularly maniacal manifestations appearing after the sudden subsidence of articular gout [retrocedent gout], which are looked upon as relapses, or the phenomena of masked gout, and which vanish with the onset of a regular attack of gout’.

Finally, London added: ‘It must be mentioned that psychoses, which are ascribed to the influence of gout, are sometimes (especially the maniacal forms of toxaemic psychoses) referable to encephalopathia alcoholica or saturnina and to chronic uraemia’.

> London had tried
> to facilitate the solubility of uric acid in the body by giving basic salts, such as lithium, which, in a laboratory experiment, will form easily-soluble salts with uric acid [for] it was thought that the same experiment would succeed in the organism.

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[936] Haig A.: ‘The causation, prevention, and treatment of gout’. Practitioner 1903;July:40–60.

[937] Luff AP.: ‘The treatment of gout in its various forms’. ibid. pp.91–110.

[938] London B.: ‘The treatment of gout in Carlsbad’. ibid. August:161–180, 320–337.

[939] Not identified.

[940] Not identified.

[941] Not identified.

[942] Not identified.

[943] Not identified.

His comment was that ‘This has, however, not been verified’.

To this important article London appended an invaluable comprehensive international bibliography: Literature On Gout,[944] current up until 1902.

The 1909 revised edition of the Special Gout Number 1903 contained contributions by Duckworth,[945] Goodhart,[946] Luff,[947] West,[948] Kidd,[949] Taylor,[950] Galloway,[951] Bannatyne,[952] Gore,[953] Rendall,[954] Watson,[955] Hall,[956] McCracken,[957] and Sikes,[958] followed by ‘Notes from foreign Journals’ and some editorial notes.[959]

Goodhart wrote (op. cit. p.20f) that in a large number of cases the formation of uric acid might be ‘first of all a nervous aberration’, ‘it is often associated with considerable nervous depression’.

Luff reiterated the view (op. cit., p.31f) that

> as regards the use of lithium salts in the treatment of gout, my opinion is that they are not so useful as the potassium and sodium salts. The principal objection to their use is their greater toxicity, and depressing action on the

[944] ibid. pp.337–353. cf. ‘Bibliography and references’ in Copland J.: ‘A Dictionary of Practical Medicine’. London: Longman, 1844. Vol. II. pp.59–61.

[945] Duckwoth D.: ‘Notes respecting the dietary for goutily-disposed persons’. Practitioner 1909;2:1–9.

[946] Goodhart JF.: ‘The treatment of uric acid’. ibid., pp.10–25.

[947] Luff AP.: ‘The treatment of gout in its various forms’. ibid., pp.26–49.

[948] West S.: ‘On the relation of gout to granular kidney and to lead poisoning’. ibid., pp.50–55.

[949] Kidd P.: ‘The cardio-vascular manifestations of gout’. ibid., pp.56–58.

[950] Taylor J.: ‘Gout in relation to disease of the nervous system’. ibid., pp.59–62.

[951] Galloway J.: ‘The cutaneous manifestations of gout and their treatment’. ibid., pp.63–69.

[952] Bannatyne GA.: ‘Balneological treatment of gout, with special reference to Bath’. ibid., pp.70–86.

[953] Gore WR.: ‘The balneological treatment of gout’. ibid., pp.87–90.

[954] Rendall S.: ‘The balneological treatment of gout at the Continental spas’. ibid., pp.91–102.

[955] Watson CG.: ‘Changes in the joints in gout’. ibid., pp.103–107.

[956] Hall IW.: ‘The metabolism of nucleins in gout’. ibid., pp.108–112.

[957] McCracken JE.: ‘Clinical notes on gouty throat’. ibid., pp.113–116.

[958] Sikes AW.: ‘Some remarks on the recent literature of gout’. ibid., pp.117–124.

[959] ibid., pp.125–136.

> heart, as compared with the lithium salts. They consequently have to be given in such small doses that I am very doubtful whether, in such doses, they possess any remedial effect at all. On the other hand, I constantly meet with patients suffering from cardiac depression, and even dilatation, as the result of the excessive and continued consumption of Lithia tablets, which are so persistently, so speciously, and so wrongly vaunted as curative in gout.

Taylor, for his part, asserted the view (op. cit., pp.59, 61f) that 'an acute attack of gout may be ushered in or accompanied or succeeded by grave nervous disturbance—even acute maniacal disorder—but this is not common'—'it cannot be denied that manifestations of nervous disorder, frequently of considerable importance, tend to occur in gouty persons, and many such diseases are directly or indirectly the result of the gouty state'—'the psychical condition sometimes attending gout may also be briefly alluded to. Depression is common, irritability the rule. Symptoms of excitement, even maniacal symptoms, may come on before, during, or after an attack of gout'.

Bannatyne emphasised (op. cit. p.72) that 'gout presents itself in many and various guises, e.g. as regular or irregular gout'. These irregular forms, he said, frequently 'have no relationship to the more regular attacks, and patients suffering from them may never have a regular gouty paroxysm', and the principal systems affected 'may be the circulatory, nervous, urinary, and respiratory'.

Finally, page 130—Cade's explicit reference—forms part of 'Notes from foreign journals' on 'the treatment of gout', and in this instance from the Journal des Practiciens. Its message was that 'Lithia salts not only do not dissolve uratic concretions, but they upset the stomach very easily'.

Cade, at least indirectly, referred to the articles in The Practitioner, but it cannot be established with absolute certainty whether or not he had read them.

Cade's formulation that 'Lithia salts […] were vaunted as curative in gout' and 'cases are reported "of cardiac depression and even dilatation, as a result of excessive and continued consumption of lithia tablets" […]', are obviously taken from either Squire (quoting Luff) and/or directly from Luff, who, as shown, reiterated this in several of his publications.

It is relevant to draw to attention that uric acid and gout were a frequent topic in the Medical Journal of Australia in the 1930s and 1940s.[960] An article by Lambie[961] in 1940 included an extensive list of the literature concerned with this. Among the many works referred to were that of Garrod, the 1876 edition, and those of Folin, including his 1923 work.

The terms gouty mania and gouty depression have not been found in these publications, nor for that matter has any mention of experimentation with lithium salts.

Of special relevance to Cade would have been an article by Bollinger of Sydney, on 29 March 1947, thus coinciding with his own uric acid studies. The paper, Recent Observations on Uric Acid, concerned 'the fundamental question' of the fate of administered uric acid.

Importantly, Bollinger also quoted Folin's 1923 work, The Uric Acid Problem. An experimental study on animals and man, including gouty subjects. As we learnt before, Folin used injections of lithium urate in his experiments. If no other source, this work could have led Cade to Folin's work, Some Metabolism Studies With Special Reference to Mental Disorders, from 1904–05.[962]

It is also relevant to mention that Cade would probably have been acquainted with Price's A Textbook of the Practice of Medicine,[963] as it was recommended reading for the degree of MD at the University of Melbourne. A general account of gout—with reference to Garrod and Folin—was given, but no mention of lithium salts. In the chapter on psychological medicine by Mapother and Aubrey Lewis the view was expressed that 'Gout may occur in people predisposed to affective disorder; often a depressive phase precedes an attack'.—'Chronic toxaemia […] can be responsible for the illness', i.e. affective disorder.

Mapother and Lewis also took the opportunity to espouse the view that 'it is in some cases proven and in others highly probable that less obvious metabolic disturbances are either among the primary symptoms of "functional" mental illness, or are its pathological basis'.

Finally, more or less reflecting the teaching of others, these authors pointed out that

> the acid-base equilibrium and the electrolytes of the blood, the metabolism of carbohydrate, fat and protein, and the chemical regulation of the vegetative activities are all, in such forms of mental illness as schizophrenia and mania, subject to changes which have not as yet been used in the pathology or treatment of these conditions, because the findings are not sufficiently constant or specific; it is also likely that our methods of investigations are not delicate enough.

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[960] Anon.: 'Diathesis: Gout, tuberculosis, cancer'. Med. J. Aust. 1931;1:22–23. Anon.: 'Gout'. ibid., 1936;2:861. Derrick EH.: 'Gout in Australia'. ibid., 1937;1:384–385. Anon.: 'Extensive gout'. ibid., 1937;2:326. Anon.: 'Chronic gout with acute exacerbations'. ibid., 1937;2:1135–1136. Rose T.: 'Blood uric acid estimation in eclampsia'. ibid., 1938;2:87–89 (cites Folin). Anon.: 'Allergy gout. ibid., 1939;2:479. Anon.: 'Arthritis, fibrositis and gout'. ibid., 1940;1:271–272. Dane PG.: 'Ménière's disease and gout'. ibid., 1940;2:108. McKay WJ.: 'Ménière's syndrome and gout'. ibid., 1940;2:250–251. Anon.: 'Gout, the forgotten disease'. ibid., 1941;1:554–555. Anon.: 'Gout: still a forgotten disease'. ibid., 1946;2:278–279. Bollinger, A.: 'Recent observations on uric acid'. ibid., 1947;1:394–395. Anon.: 'The nature of gout'. ibid. 1948;2:19. Attention should also be drawn to a curious pamphlet by a Melbourne medical practitioner, Louis L. Smith: 'Discoveries in the nature and treatment of gout, with original notes and observations after twenty-six years' constant treatment of that disease'. Melbourne: Cordell, 1878.

[961] Lambie CG.: 'A study of juvenile gout in a patient suffering from chronic erythronoclastic anaemia of obscure origin, together with observations upon the physical state of uric acid in the blood and the effects of splenectomy'. Med. J. Aust. 1940;1:535–558 (extensive list of references).

[962] Am. J. Insan. 1904;60. ibid. 1904;61:364.

[963] Price FW. (ed.): 'A textbook of the practice of medicine by various authors including sections on diseases of the skin & psychological medicine by various authors'. Oxford University Press, 1937. (pp.436–444, 1298, 1836, 1846).

SOURCE IV: CULBRETH, 1927

Referring to Culbreth (1927),[964] Cade wrote that this author 'says of lithium bromide that it is the most hypnotic of all bromides'.

For comparison, Culbreth's original text has: 'Lithium Bromide […] Most hypnotic of all bromides; epilepsy, gout, etc.'

In this context Cade wrote that 'Squire, too, states that "in epilepsy it is the best of all bromides" […]'

Squire himself wrote in the aforementioned 1916 work[965] that

> owing to the low atomic weight of Lithium, this salt contains more Bromide than either Potassium or Sodium Bromide, and consequently has been recommended as a hypnotic for gouty patients, in epilepsy, and in the insomnia of neurasthenia (30 grains three times a day).—In epilepsy, for rapid action and for soothing purposes, it is the best of the Bromides [with reference to Therapeutic Gazette. 1912:153].[966]

According to Cade, 'it was worth noting that the hypnotic action of lithium bromide was thought to be due to the fact that, the atomic weight of lithium being so small, weight for weight, lithium bromide must contain more bromide ion than any other bromide'.[967] 'There is no evidence', he went on, 'that the lithium ion was recognised as having a marked sedative action superior in some respects to that of the bromide'.

It was in 1970 that Cade added that 'there is no evidence that the lithium ion was recognised as having any psychotropic action itself ';[968] but as he wrote in 1978,[969] 'And so lithium, after its dubious beginning in medicine and its disastrous apparent finale, was launched again—precariously, it is true—as a powerful psychotropic drug in affective illness'.

Culbreth also wrote that lithium was found sparingly as silicate in a few rare minerals and 'as chloride in soils and spring water, and as carbonate in plant ashes'. Lithium carbonate he described as a 'diuretic; to remove uric acid calculi, gout, gouty diathesis—best solvent for uric acid, renders urine alkaline, slight depressant'. With respect to lithium citrate, he said, its diuretic property was similar to the carbonate, but that it 'has more pleasant taste, is more soluble and less irritating to the stomach'.

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[964] 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. He mentioned five anti-rheumatic and diuretic lithium preparations: the carbonate, bromide, benzoate, citrate and salicylate.

[965] op. cit., 1916, p.844.

[966] Weir Mitchell S.: 'The treatment of epilepsy'. Ther. Gaz. 1912;36:153–157. Mitchell wrote: 'For rapid action and for soothing purposes, I am of the opinion that the lithium bromide is the best. I state this with the doubt of self-criticism, because I myself introduced it into medicine'.

It is noteworthy that Squire wrote that the lithium ion was considered to be 'useful' in uric acid diathesis,[970] which term Cade, surprisingly, did not use in his writings, excepting the 1975 Johnson–Cade paper,[971] where the authors made reference to 'four papers by [Carl] Lange, published in 1897, in which the use of lithium salts in the treatment of "uric acid diathesis" was described: this condition apparently involved both gout and mental depression and some improvement was noted in the latter'.

SOURCE V: HENDERSON AND GILLESPIE, 1944

In support of the efficacy that Cade observed lithium to have, he quoted Henderson's and Gillespie's 1944 textbook of psychiatry.[972] In Cade's words, 'the waters of certain wells were considered to have special virtue in the treatment of mental illness, and [Henderson and Gillespie] mention some of the more famous in the British Isles', Cade adding that 'it is very likely that their supposed efficacy was a real efficacy [*sic*] and directly proportional to the lithium content of the waters'.[973] Importantly, he did not refer to Garrod's 1859 book which more inclusively mentioned that lithia 'has been found in many medicinal springs, as those of Carlsbad, Aix-la-Chapelle, Marienbad, Kissengen, Ems, Teplitz, Bilin, Kreuznach, Vichy &c.' (op. cit. p.435). This appears to be contradicting certain of his later statements concerning the use of lithium by the old authors.

Cade's lithium prescription

A cardinal issue in the history of lithium therapy is on what basis Cade had determined the lithium dosage to administer in his clinical trial, and the possible sources he had drawn on.

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[967] cf. Gowers WR.: 'Epilepsy and other convulsive diseases etc'. London: Churchill, 1881:253. Aulde J.: 'The use of lithium bromide in combination with solution of potassium citrate'. Med. Bull. 1887;9:229. 'Lithium bromide', in Tuke, 1892, op. cit., p.1130. cf. Scott DF.: 'The first use of lithium?' Br. J. Psychiatr. 1992;160:709–710.

[968] Cade JF.: 'The story of lithium', in Ayd F, Blackwell B.: 'Discoveries in biological psychiatry.' Philadelphia: Lippincott, 1970. pp.218–229.

[969] Cade JF.: 'Lithium—past, present and future', in Johnson FN, Johnson S.: 'Lithium in medical practice. Proceedings of the First British Lithium Congress, University of Lancaster, England. 15–19 July 1977'. Lancaster: MTP Press, 1978. pp.5–16.

[970] op. cit.,1916, p.22.

[971] Johnson FN, Cade JF.: 'The historical background to lithium research and therapy', in Johnson FN. (ed.): Lithium research and therapy. London: Academic Press, 1975. pp.9–22. Schou M.: 'Biology and pharmacology of the lithium ion'. Pharmacol. Rev. 1957;9:17-58. Schou's reference was: Lange C.: 'Bidrag til Urinsyrediatesens Klinik'. Hospitalstid. (Cph.) 1897;5:1–15, 21–38, 45–63, 69–83.

[972] Henderson DK, Gillespie RD.: 'A text-book of psychiatry for students and practitioners'. 6th Edn. Oxford University Press, 1944. p.3.

As Georgotas and Gershon[974] pointed out, 'No reliable predictions based on preclinical pharmacological studies could have been made about the profile of clinical activity of lithium'.

Gershon[975] further questioned how it could be that Cade's 'choice of dosage of lithium in humans—i.e. the first clinical experience—was the correct therapeutic dose without any human work on dose response studies and without plasma lithium levels'. He stressed that 'there was no reliable way of extrapolating a dose from Cade's guinea pig studies to a correct therapeutic dose in manic patients'.[976] In other words,[977] Gershon put it, 'the lithium story does *not* fulfil the requirements of currently established animal screen for activity as a major tranquilizer'.

As Cade himself wrote in 1967:[978] 'The older pharmacopoeias did *not* prescribe any toxic effects of lithium salts, but was that good enough?' But 'there is always the number one experimental animal, oneself '.

Cade proceeded to self-administer 'single and repeated doses of lithium citrate and lithium carbonate in the doses contemplated for human use'. He observed no 'discernible ill-effects'.

As Jack Cade communicated to Johnson[979] regarding his father's original investigations:

> Our kitchen refrigerator usually had jars of manic patients' urine and racks of blood samples in it, always on the top shelf and much to my mother's consternation. Her greatest distress came when Dad started taking lithium carbonate himself for a few weeks before giving it to patients.

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[973] cf. Cade JF.: 'Lithium—past, present and future', in Johnson FN, Johnson S.: 'Lithium in medical practice. Proceedings of the First British Lithium Congress, University of Lancaster, England. 15–19 July 1977'. Lancaster: MTP Press, 1978. pp.5–16.

[974] Georgotas A, Gershon S.: 'Historical perspectives and current highlights on lithium treatment in manic-depressive illness'. J. Clin. Psychopharmacol. 1981;1:27–31.

[975] Gershon, personal communication, 13 March 2000.

[976] cf. Gershon S.: 'Methodology for drug evaluation in affective disorders: mania', in Levine J, Schiele BC, Bouthilet L.: 'Principles and problems in establishing the efficacy of psychotropic agents'. American College of Neuropsychopharmacology 1971. pp.123–135.

[977] Gershon S.: 'Lithium in mania'. Clin. Pharmacol. 1970;11:168–187.

[978] Cade JF.: 'Lithium in psychiatry: historical origins and present position'. Editorial. Aust. NZ. J. Psychiatr. 1967;1:61–62. cf. Cade, 1970, 1975. op. cit.

According to Chiu and Hegarty,[980] Cade took 'lithium carbonate for 2 weeks to test whether it was toxic or had unpleasant side-effects', and they recounted that his wife, Jean, recalled that 'I looked at him the next day, and the weeks that followed and wondered what I would do if he was changed by the lithium'. Eventually, according to Cade's 1970 paper:[981] 'The original therapeutic dose decided on fortuitously proved to be the optimum, that is 1.200 mg of the citrate thrice daily or 600 mg of the carbonate'.

In the original trial the patients were generally commenced on lithium citrate gr (grains) 20 t.i.d. (*the first recipient*, W.B., was commenced on lithium citrate gr 10 t.i.d. (29 March, 1948); after a few days increased to gr 20 t.i.d., then for a few days to gr 40 t.i.d. He subsequently 'commenced to vomit […] nocturnal enuresis'; dosage was reduced and later replaced with lithium carbonate gr 5 b.i.d.).[982] One grain equals approximately 60 mg.

Some sources as to lithium dosage mentioned by Cade in 1949

From Garrod's 1859 work[983] Cade cited as follows: "When given internally in doses of from one to four grains dissolved in water, two to three times a day, ['lithium carbonate'] produces no direct physiological symptom—their use does *not* appear to be attended with any injurious consequences", and 'certainly', he added, 'in that dosage, there should never be any toxic symptoms'.

Garrod, in turn, referred to Aschenbrenner to the effect that lithium carbonate 'might be given in doses of from five to ten grains daily'.[984]

According to the 1863 edition of Garrod's book,[985] *not* cited by Cade, lithium carbonate 'was given internally in doses of from one to five grains dissolved in water, and repeated two or three times a day'.

It should be added that Garrod in his The Essentials of Materia Medica and Therapeutic (1868),[986] *not* cited by Cade, recommended a dosage of lithium citrate, 5 to 10 grains and of lithium carbonate, 3 to 6 grains. Similar recommendations are found in the 1886 edition of Garrod's work.[987]

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[979] Cade J. Jr. to Johnson, 18 May, 1981 (Johnson, 1984. op. cit.).

[980] Chiu E, Hegarty RM.: 'John Cade: the man'. Aust. NZ. J. Psychiatr. 1999;33, Suppl.: S24–S26.

[981] Cade JF.: 'The story of lithium', in Ayd F, Blackwell B.: 'Discoveries in biological psychiatry'. Philadelphia: Lippincott, 1970. pp.218–229. Cade JF.: 'Lithium—past, present and future.' , op. cit.

[982] Case cards, Medical History Museum, University of Melbourne, MHM00985/MHM00986.

[983] op. cit., p.438.

Garrod, in another paper, from 1873, on the value of lithium salts in the treatment of gravel and gouty deposits,[988] also *not* cited by Cade, described a case treated with 'about 60 grains [of citrate of lithium] twice a-day […] afterwards […] 20 grains of citrate of lithium, [later] 15 grains of neutral citrate of lithium were given three times a day', but 'from an extensive experience in their administration' of these salts, he commonly gave 'about ten to fifteen grains of the carbonate and twenty to thirty grains of the citrate'.

Garrod took the opportunity to take stock of lithium therapy as 'thirteen years have now elapsed since the salts of lithium were introduced into medical practice as internal remedies'. Moreover, 'for a period of nine years both the carbonate and citrate of the metal have been made official by being placed in the British Pharmacopoeia; sufficient time has therefore elapsed for their value as medicinal agents to have been fairly established'. 'Having introduced lithium salts to the notice of the Profession, and having had considerable experience of their action upon the system and therapeutic value, I consider myself in a position to give some opinion upon their merits'.

As we learnt before, Garrod also drew to attention the notion that the distribution of lithium was

> much more extensive than was at first supposed, and it is now capable of being detected by the method of spectrum analysis, in the ashes of many vegetables, and in that of the blood itself, and likewise in many mineral waters.

In the third and thoroughly revised edition of Garrod's treatise, published in 1876, *not* cited by Cade, the lithium carbonate dosage remained unaltered; 'from one to five grains dissolved in water' daily (60 mg to 300 mg or 5–25 mmol).[989] This, according to Amdisen,[990] was more or less identical with the lithium dose in modern prophylactic therapy of recurrent manic-depressive illness, where daily doses range from 8 to 80 mmol lithium.

It was in this 1876 edition that Garrod took Charcot into authority:

> Dr. Charcot states, in his annotations to the French edition of this work,[991] that he has given carbonate of lithia to the extent of 30 and 45 grains in the 24 hours without the production of any unpleasant symptoms. In larger doses, continued for some days, dyspepsia ['dyspepsie cardialgique'] was often produced.[992]

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[984] loc. cit.

[985] op. cit., p.422.

[986] Third edition. London: Walton, 1868. pp.104–106.

[987] Twelfth edition. London: Longmans, 1886. pp.108–110.

[988] Garrod AB.: 'Renal calculus, gravel, and gouty deposits and the value of lithium salts in their treatment'. Medical Times and Gazette 1873;1:83–84, 246–247, 299–300.

[989] Garrod, op. cit., 1876, p.367.

The British Pharmacopoeia, Cade stated,

> gives the dose of lithium carbonate as two to five grains and that of lithium citrate as five to ten grains, but such figures convey little information of value in therapeutics in the absence of any information as to how often such a dose may be given in each twenty-four hours, or of the rate of elimination.

Furthermore, Cade referred to Culbreth, who, he said, 'is more liberal and gives the dose of lithium carbonate as five to 15 grains and of the citrate as 10 to 30 grains'.

> In his mention of Culbreth's use of lithium bromide Cade related that the dosage stated there is the relatively enormous one of 10 to 30 grains. [But] it is not stated how often this huge dose might be repeated each day, but one presumes the traditional two to three times.

In addition, he commented, 'Squire too, states that "in epilepsy [lithium bromide] is the best of all bromides" and gives the dose more conservatively as five to 15 grains'.

Other lithium sources

In his 1977 and 1978 papers Cade[993] also cited Brunton's A text-book of pharmacology, therapeutics, and materia medica,[994] which was adapted to the United States Pharmacopoeia.

Cade emphasised that 'at least [Brunton] gives a rationale for the use of lithium as follows':

> The urate of lithium being much more soluble than those of either potassium or sodium, lithia is often employed in preference to these others in gout. It is given internally in order to aid in the elimination of uric acid by the kidneys, to prevent gouty paroxysm, and to lessen the acidity of the urine […].

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[990] Amdisen A.: 'Lithiumbehandling af mani og depression i forrige århundrede'. Med. For. (Cph.), 1983:110–119. cf. Amdisen A.: 'Serum level monitoring and clinical pharmacokinetics of lithium'. Clin. Pharmacokinet. 1977;2:73–92. Amdisen A.: [Carl Lange's flying call to psychiatry]. Bibl. Læg. 1985:9–37. Prien RF.: 'Long-term pharmacological treatment of bipolar illness', in Psychiatry update. The American Psychiatric Association. Vol. II. Washington D.C.: American Psychiatric Press, 1983. U.S. Department of Health and Human Services: 'Mood disorders. Pharmacologic prevention of recurrences'. Consensus Development Conference, Consensus Statement. Vol. 5, No. 4, 1984. Amdisen A.: 'Lithium as a pharmacological agent. Historical aspects. Topical aspects in monitoring psychiatric lithium therapy'. Thesis (Dan.). Aarhus: Psykiatrisk Hospital i Aarhus, 1985. Løkkegaard H, Andersen NF. et al.: 'Renal function in 153 manic-depressive patients treated with lithium for more than five years'. Acta Psychiatr. Scand. 1985;71:347–355. Amdisen A.: 'Historical origins', in F. Neil Johnson (ed.): 'Depression & mania. Modern lithium therapy'. Oxford: IRL Press, 1987:24–28.

[991] Garrod AB.: 'La goutte. Sa nature, son traitement et le rhumatisme goutteux. Ouvrage traduit de l'anglais par Auguste Ollivier et annoté par J. M. Charcot'. Paris: Delahaye, 1867. ('Sels de lithine dans le traitement de la goutte', pp.482–491). (p.486 (note)).

[992] Garrod, 1867, op. cit., p.372.

As for lithium salicylate, Cade went on to cite, "It is used as a remedy in gout and rheumatism and is intended to unite the properties of salicylic acid and lithium", adding that 'the recommended dose was 20–40 grains (frequency of dosage not mentioned)'.

Lithium bromide, Cade finally quoted, "by some [is] said to have a stronger hypnotic action than the other bromides […]. It may be preferable to the potassium salt in the irritability of gouty subjects", Brunton recommending doses from 15 to 30 grains.

The recommended dosage of lithium carbonate was 3 to 6 grains, and lithium citrate 5 to 10 grains, similar to those recommended by Garrod in 1868 and 1886, and the British Pharmacopoeia, this *august publication* as Cade characterised the latter source.[995]

In Johnson's opinion, Cade's decision as to dosage was not fortuitous, but 'in fact […] rather more thoughtful and based upon a consideration of values given in the British Pharmacopoeia and a number of textbooks of materia medica'.[996] He also made reference to personal communications he had had with Cade,[997] which have not been preserved.[998]

Amdisen[999] for his part drew to attention 'that the ideas behind Cade's suggested dose regimen were astonishingly similar to that of Hammond'.

According to Hammond,

> the doses [of bromide of lithium] should be large—as high as sixty grains [= 45 mmol Li+] or even more—and should be repeated every two or three hours till sleep be produced, or at least till half a dozen doses be taken. After the patient has once come under its influence, the remedy should be continued in smaller doses, taken three or four times in the day.

Amdisen expanded on his opinion, stating that although 'Cade chose a dose schedule which was in some respects similar to that of Hammond', 'it is evident' that it 'differed critically' in some aspects in that Cade's 'rather high dosages were admittedly lower, but administered for a longer time'.

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[993] Cade JF.: 'Lithium in medicine', in Burrows GD, Chiu E.: 'Research in affective disorders. Proceedings of the Scientific Meeting in Honour of Dr. John F. J. Cade. February 4, 1977'. pp.7–9. Cade JF.: 'Lithium—past, present and future'. 1978, op. cit.

[994] London: MacMillan, 1891. pp.556, 630–633. cf. Biddle JB.: 'Materia medica and therapeutics for physicians and students'. 12th Edn. Philadelphia: Blakiston, 1892 (quoted from Talbott JH.: 'Use of lithium salts etc'. 1950, op. cit.) has 0.7 to 2.0 gm per day of lithium carbonate for gouty patients.

[995] Cade, 1977, 1978, op. cit.

[996] Johnson, 1984, op. cit., p.37

[997] ibid. pp.37, 154 (note 21).

[998] Johnson, personal communication, 2000.

[999] Hammond, 1871, op. cit. Amdisen A.: ['Carl Lange's flying call to psychiatry']. Bibl. Læg. 1985:9–37. Amdisen A.: 'The history of lithium'. Biol. Psychiatr. 1987;22:522–523 (letter with response from V. K.

Although Amdisen—with reference to Garrod's 1876 edition—also mentioned that Charcot (1867) would at times give 'lithium carbonate to the extent of 30–45 grains [1800 mg to 2700 mg, i.e. 50–75 mmol lithium] in the 24 hours without the production of any unpleasant symptoms', he did not make any comments as to the apparent similarity between this dosage regime and that of Cade.[1000]

Another source worth mentioning, and Cade might well have consulted it, is that of Futcher in Osler's famous textbook of medicine.[1001] He wrote that since Garrod in 1858 [1859] first recommended the use of lithium carbonate in the treatment of gout 'the various lithium salts have been in high favor'. Lithium carbonate and lithium citrate, he added, 'in an effervescing tablet of 5 grains, dissolved in […] water and administered 4 to 6 times daily, are still popular remedies'. He thought, however, that 'the good effects' of mineral waters were due more to the water than to the contained salts', quoting Osler for saying: 'Much of the humbuggery of the profession still lingers about mineral waters, more particularly about the so-called Lithia-water'.

A standard textbook of pharmacology in 1942 was Sollmann's.[1002] 'By a misinterpretation' of the chemical facts, he wrote, lithium salts were used 'as remedies against gout, rheumatic conditions, etc. (lithium carbonate, 0.12 to 0.3 Gm; citrate 0.3 to 0.6 Gm; both soluble in water)'. However, he emphasised that, due to the above, lithium salts 'have no rational foundation', adding that 'they may be considered inefficient, and in larger doses somewhat dangerous'.

It can be concluded that Cade was well acquainted with a number of sources regarding the dosage of lithium he deemed safe ('*primum non nocere*') to administer to his patients. Importantly, he was fully aware of lithium's potentially serious, at times fatal, side-effects. Thus, in the 1949 paper, after having mentioned 'the symptoms of over-dosage', alimentary and nervous, he emphasised that 'unless such symptoms are followed by immediate cessation of intake there is little doubt that they can progress to a fatal issue'.

The question was raised previously whether, during his pioneering investigations Cade was acquainted with Good's work[1003] regarding lithium's ubiquitous distribution in nature. The question is also whether Cade was implicitly referring to this work when he studied the toxic effects of lithium. Like Good, in the 1949 paper Cade remarked that

> it is worth noting that the hypnotic action of lithium bromide was thought to be due to the fact that, the atomic weight of lithium being so small weight for weight, lithium bromide must contain more bromide ion than any other bromide. There is no evidence that the lithium ion was recognised as having a marked sedative action superior in some respects to that of the bromide.

Yeragani and S. Gershon). Amdisen A.: 'Historical origins', in F. Neil Johnson (ed.): 'Depression & mania. Modern lithium therapy'. Oxford: IRL Press, 1987. pp.24–28. Amdisen A.: 'Lithium as a pharmacological agent. Historical aspects'. 1985, op. cit. Amdisen A.: 'The first lithium era', in F. Neil Johnson (ed.): 'Depression & mania. Modern lithium therapy'. Oxford: IRL Press, 1987:24–28.

[1000] Amdisen, 1985, op. cit., ('Lithium as a pharmacological agent' etc.).

[1001] Futcher TB.: 'Gout', in Osler W, McCrae T. (eds.): 'Modern medicine. Its theory and practice'. Philadelphia: Lea & Fibiger, 1914. pp.729–760 (756).

[1002] Sollmann, 1942, op. cit. pp.906–907.

However, it has not shown possible to establish what Cade's and Good's (common) source(s) might have been.

It should be reiterated that it was Weir Mitchell[1004] who introduced the use of lithium bromide in the treatment of epilepsy. It seemed to him that it acted more rapidly than the other bromides, and that this could be due 'to its easy solubility, which is ordinarily associated with a high osmotic equivalent'. Further, for the reason that lithium bromide contained 'nearly 92 per cent.' bromine compared with respectively 66 per cent and 78 per cent in bromide of potassium and bromide of sodium, he found that as an hypnotic bromide of lithium 'is superior to the potassium salt and to the other bromides'.

Gowers[1005] in his classic account of epilepsy and other chronic convulsive diseases, and referring to Weir Mitchell, wrote that 'were the influence of [bromide of lithium] proportional to the amount of bromine they contain, it might be expected to be of special use, since it contains no less than 92 per cent', and 'I have watched its effects in a considerable number of cases, but have not been able to trace any superiority in its action'.

Equally, an article by Ringer and Harrington[1006] in Tuke's famous A dictionary of psychological medicine should be drawn to attention, as according to these authors, 'weight for weight there is much more bromine in the lithium salt than in any other salt of bromine, the percentage of bromine in the molecule being 92 per cent.'

The first mention by Cade of Good's important work appears to be in the paper he wrote with Johnson in 1975,[1007] stating that Good, in 1903, 'demonstrated many of the toxic symptoms and side-effects with which later physicians have become all too familiar'. In fact, the authors claimed that the findings of Good 'and the early experimenters […] were in many ways instrumental in impairing the ready acceptance of lithium therapy'.

Notably, Johnson, in his book, expressed the view that Cade 'could hardly have failed to have known that lithium salts were associated with some toxic effects in view of the work of one or two earlier experimenters such as Good and Cleaveland'.

Cleaveland[1008] had provided an important report on self-administration of lithium in 1913. He duly referred to Good's work.

[1003] Good CA.: 'An experimental study of lithium'. Am. J. Med. Sci. 1903;125:273–84.

[1004] Mitchell SW.: 'On the use of bromide of lithium'. Am. J. Sci. 1870;60:443–445.

[1005] Gowers WR.: 'Epilepsy and other chronic convulsive diseases: their causes, symptoms, & treatment'. London: Churchill, 1881. p.253. cf. Wood HC.: 'Therapeutics: its principles and practice'. London: Smith, Elder, 1888. p.296. Hare HA.: 'A text-book of practical therapeutics etc'. London: Kimpton, 1902. p.121: 'Bromide of lithium "is much weaker than the other salts, and must be given in larger dose. Dr. S. Weir Mitchell states that it is of value in epilepsy after the potassium salt fails. The dose is 30 to 90 grains (2.0–6.0) a day".'

[1006] op. cit. 'Bromide of lithium', pp.1130–1131.

During the course of ‘twenty-eight hours’ Cleaveland self-administered a total of 8 gm, about 125 grains, of lithium chloride, resulting in increasing dizziness, fullness of the head, much blurring of vision, tinnitus, intense weakness,[1009] tremor, and insomnia, such that he had to take to bed. However, he experienced no gastro-intestinal symptoms. Several months later he repeated the experiment ‘to make certain that the effects were really due to lithium’. This time, he took 4 gm of lithium, enough to cause dizziness, tinnitus and blurring of vision, and the general symptoms ‘were much less marked than before’. However, again he experienced no gastro-intestinal effects, noting that this was in contrast to Good’s observation.

[1007] Johnson FN, Cade JF.: ‘The historical background to lithium research and therapy’, in Johnson FN. (ed.): Lithium research and therapy. London: Academic Press, 1975. pp.9–22.

[1008] Cleaveland SA.: ‘A case of poisoning by lithium, presenting some new features’. JAMA 1913;60:722

[1009] cf. Rockwood EW, van Epps C.: ‘The influence of some medicinal agents on the elimination of uric acid and creatinin’. Am. J. Physiol. 1907;19:97–107. The authors had administered to a male subject 2 gm. of lithium carbonate on three consecutive days: its depressant effects upon the general physical condition were ‘noticeable’. Thus, there was ‘some loss of muscular control, the muscles of the lower limbs being affected, and those of the eye so much so that the power of accommodation was nearly lost’. The authors found that ‘while nitrogenous metabolism appears to be unchanged, the uric acid steadily decreased during the lithium period’.

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