Johan Schioldann: History of the Introduction of Lithium into

Medicine and Psychiatry

Birth of Modern Psychopharmacology 1949

Part I

Birth of lithium therapy 1859

Chapter 5. Lithium's entry into materia medica

Lipowitz, Ure, Binswanger

In 1841 Lipowitz[127] made the important observation that a lithium urate solution was formed when lithium was added to uric acid in water. Lithium carbonate was a better solvent for uric acid—about four times better—than sodium carbonate. Therefore, according to Sollmann,[128] he suggested its therapeutic use.

Two years later, Ure[129] demonstrated the solubility of a sample of human urinary calculus in vitro in a solution of lithium carbonate, and he therefore proposed the use of this 'substance of which no therapeutic application has been heretofore made [emphasis added]' as a solvent for calculi in the bladder. Ure also associated uric acid with gout.[130] Finally, in 1844, he took the 'remarkable affinity of uric acid to lithium' into the materia medica.[131] However, the difficulty of procuring sufficient amounts of lithium prevented him from further exploration until 1859 when he instilled a solution of lithium carbonate into the bladder of a patient with urinary calculus. However, the calcus 'refused', and the patient died.[132]

In 1847 Binswanger also,[133] according to Sollmann, used lithium therapeutically.

The epoch-making work of Garrod: lithium becomes a psychiatric drug

Based on his own in vitro experiments (and those of Lipowitz and Ure) Garrod concluded, though erroneously, that lithium carbonate could dissolve uric acid in vivo.[134] In his opinion, therefore, 'the salts of lithia offer to the physician most valuable agents in these cases, as their alkalising property is of the highest order, on account of the smallness of their atomic weight; and their solvent power for uric acid or urates, far greater than that of any other agent […] and their use does not appear to be attended with any injurious consequences'.[135] Garrod not only stated that 'the use of lithia in medicine is novel', he also emphasised that 'the lithia salts can scarcely be said to have been employed therapeutically until recently [in 1858] by myself,' paying tribute though to Lipowitz and Ure, 'in the treatment of uric acid gravel, and chronic gouty conditions of the habit'. Such was Garrod's satisfaction with the effect that he felt that 'these salts may probably one day become important additions to the list of our materia medica'.[136]

In the history of lithium treatment it is of particular importance that, like many medical authorities before him, Garrod linked affective disorders to uric acid diathesis, as for instance in the 1859 edition of his book:[137]

> When retrocedent gout attacks the head, apoplexy is commonly induced, but occasionally maniacal symptoms [emphasis added] arise, which I have myself witnessed […] During the progress of regular gout, especially in its chronic varieties, and sometimes without the development of the articular disorder, the nervous and muscular systems occasionally manifest symptoms clearly referable to the presence of the gouty diathesis. These manifestations are generally functional […] Neuralgia is not an uncommon manifestation of gout […] Sometimes the development of hysterical symptoms is caused by a gouty state of system and becomes relieved by the occurrence of articular gout […] More serious affections of the nervous system occasionally arise, depending on the central portions of the nervous system being involved. Sometimes epilepsy appears to be connected with a gouty habit […] Gouty mania [emphasis added] is occasionally seen [and, as he 'alluded', can] supervene after the cessation of the joint affection.

As Johnson[138] put it, when Garrod included gouty mania or gout retroceding to the head, 'at a stroke, lithium was extended from being a treatment for a physical condition to being a treatment for mental problems'.

It was due to 'the initial apparent success' of lithium treatment that this new agent, both the carbonate and citrate of lithium, was introduced into the first edition of the British Pharmacopoea in 1864.[139]

Many lithium compounds were listed in Merck's Index, from its first edition in 1889 until its fifth edition in 1940, containing the information that various lithium salts had been used in uric acid diathesis.[140] It was not until the following year that The Extra Pharmacopoiea denounced them, stating that 'their introduction into medicine was due to a misconception […] there is no rational foundation for the use of these salts'.[141]

Dissemination of Garrod's work

Garrod's treatise, which became a 'landmark' in its field,[142] appeared in several editions. It was also translated into German in 1861,[143] and French in 1867.[144]

From the second and third English editions, in 1863[145] and 1876,[146] we learn that 'extensive use […] has been made of [the salts of lithia] in medicine', thanks also to 'the recent discoveries of Kirchhoff and Bunsen'. Before the latter, Garrod said, it had been a matter 'of considerable difficulty' to detect the presence of small amounts of lithia, whereas, by means of the spectrum analysis, Bunsen had shown that 'even the most minute traces of the metal can be accomplished':

> 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 not mentioned above ['Carlsbad, Aix-la-Chapelle, Marienbad, Kissengen, Ems, Teplitz, Bilin, Kreuznach, Vichy &c.'

(Garrod 1859, p.436)], in the ashes of sea-weed, and of many inland plants, as the vine, tobacco, and in the seeds of the gramineæ; also in the milk, blood, and the muscles of the human subject, and of many animals.

Lithia must therefore 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.

The quantities of Lithia existing in the above-named substances is small, but it is asserted that in some of the Baden-Baden springs, the Fettquelle and Murquelle, the amount is such as to render these waters not only powerful therapeutic agents, but useful as sources from which to procure the lithia salts […]

and Garrod took the opportunity to reiterate that

the proper administration of lithia has a considerable power in preventing the recurrence of gouty paroxysms, [and] we shall have no difficulty in believing that the salts of this alkali may prove most powerful in the treatment of gout, and likewise in other affections, the pathology of which is closely connected with an excess of uric acid in the system.

Garrod recommended dose ranges of carbonate of lithia from 'one to four grains dissolved in water, and repeated two or three times a day' (3–12 grains lithium carbonate per day, i.e. 9–18 millimoles of Li+) (1859 edition), in the 1863 and 1876 editions broadened to 1 to 5 grains, 2–3 times a day (3.5 to 26 millimoles of lithium daily).[147] One gram equals approximately 15 grains.

Charcot's contribution

In the history of lithium treatment too little attention has been paid to Charcot, himself a considerable authority on gout. In his Leçons sur les Maladies des Vieillards et les Maladies Chroniques,[148] held in 1866 and printed in 1867 and 1874, rendered in English for the New Sydenham Society in 1881, Charcot adopted Garrod's recommendation of lithium treatment of the constitutional state of gout:[149]

The action of potash in dissolving uric acid is much more energetic than that of soda. You know that urate of potassium is much more soluble than urate of sodium […] But there exists a still little-known substance, lithia, which seems to surpass potash and soda in all respects […] This new agent answers all the indications I have spoken of. [Thus, its] diuretic action is very decided; it makes the urine very alkaline, and speedily dissolves uric acid. In this respect it is very superior to potash, for lithic urate is the most soluble of all the urates […] The alkalis, especially potash and lithia, administered in small doses and much diluted […] and especially administered for a long period of time, have a remarkable action on gout. They defer its paroxysms, they sometimes dissolve and remove the deposits already formed […]

Charcot recommended lithium carbonate be administered in doses ranging from four to five grains (25 to 50 centigrammes according to the original version) in the twenty-

four hours. However, he had himself prescribed up to '6 grains' ('jusqu'à la dose de 40 centigrammes') without producing any unpleasant (fâcheux) effect on the stomach.

Charcot annotated the French edition of Garrod's work, in 1867, translated from the German edition of 1861, including the following important annotation regarding the dose of lithium:[150]

> In many attempts I have progressively pushed lithium carbonate up to the relatively considerable dose of 2 grammes, and even up to 3 grammes in the twenty-four hours without the production of any severe adverse side-effects. But when such high doses are maintained over several days, one soon enough observes symptoms of 'dyspepsie cardialgique', which soon make it necessary to suspend the use of this medicament.

In a footnote to Garrod's gouty mania, Charcot, using the term folie goutteuse, added that it was interesting to note that all forms of 'rhumatisme cérébral, la céphalée, le délire aigu, la folie enfin, se trouvent à peu près exactement reproduites dans la goutte'.[151]

Climent in his Traitement de la gravelle urique, published in 1874, made reference to Charcot, stating that he had tried to administer doses of two grammes, though it resulted in dyspepsia after four days.[152]

Importantly, Garrod had taken Charcot into authority regarding the dose of lithium in the third edition of his book (thoroughly revised and enlarged), in 1876: 'Dr. Charcot states, in his annotations to the French edition of this work, 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'.[153]

It is noteworthy that the latter dose is up to ten times larger than what Charcot had recommended in his 1866 lecture.

Locock, Gibb, Lévy

Some clinicians used lithium in the salt of bromide. Bromides had first been recommended in the treatment for epilepsy by Locock in 1857.[154]

Lithium bromide was advocated as a mild tonic by Gibb[155] in 1864, and as a sedative by Lévy[156] in 1874:

> Le bromure de lithium […] a une action sédative bien marquée sur l'axe cérébro-spinal. Il a modifié favorablement diverses névroses, l'épilepsie spécialement. Il est même plus actif, sous ce rapport, que le bromure de potassium. Il a encore, sur ce sel, l'avantage de ne pas agir sur le coeur et, dans un certain nombre de cas, cette propriété négative est d'un haut intérêt. On peut donc, sans crainte, prometttre au bromure de lithium une place honorable dans la thérapeutique [emphasis added].

Weir Mitchell

Mitchell had spent a year in Paris specialising in, among others, neurology. Subsequently, he introduced lithium into the USA.

In 1870 Mitchell reported on the efficacy of lithium bromide in epilepsy.[157] Later, according to his 1877 Clinical lecture on nervousness in the male,[158] his 'assistants' had called his attention

> to the large number set down as general nervousness […] but in each year's report still appears a group in which either general nervousness is the dominant condition, or which at all events I find myself unable to classify under any other heading. We rarely see this condition delineated in the books.

In such 'nervousness' cases Mitchell found the bromides to be of the 'utmost utility', stating that

> among them I prefer the lithium bromide, which I introduced into medical use some years ago [emphasis added], and which has now stood the test of my own longer experience, as well as that of many French and German therapeutists, who have come to regard it as the most valuable of the bromides.

Mitchell emphasised that lithium bromide should be given 'in some simple bitter for many months, and in doses of not more than five or ten grains, thrice a day'. Later, in 1903, he supported Lévy's opinion that lithium bromide was as efficient as sodium or potassium bromide, and that its effect on insomnia was even greater.[159]

Hammond's use of lithium in acute mania

In the early 1980s Tyrer and Carlsson, respectively, drew attention to the fact that Hammond[160] of Bellevue Hospital, New York, was possibly the first to have reported, in 1871, the exclusive use of lithium in the treatment of acute mania. According to his Treatise on Diseases of the Nervous System,[161] Hammond considered acute mania to be 'the more common species of mental aberration', manifesting as acute mania with exaltation or acute mania with depression.

Based on his view that 'cerebral congestion' was the underlying cause, he recounted that

> latterly I have used the bromide of lithium in cases of acute mania, and have more reason to be satisfied with it than any other medicine calculated to diminish the amount of blood in the cerebral vessels, and to calm any nervous excitement that may be present. The rapidity with which its effects are produced renders it specially applicable in such cases.

He emphasised that 'the doses should be large', namely

> as high as sixty grains [45 mmol of lithium][162] 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, [whereas] in cases of cerebral congestion attended with illusions and hallucinations, but without mania the other bromides will answer the purpose

- preferably the bromide of sodium. They may also be given in the more violent forms if the bromide of lithium cannot be obtained.

As Hammond did not mention the use of lithium in his later works (1882, 1883, and 1890),[163] it must be speculated as to whether he had ceased using lithium (bromide), possibly due to lithium and/or bromide toxicity in view of the 'tremendously high doses' that he administered.[164]

Although it had been established with Gowers[165] that weight for weight there was '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', Hammond may well have observed lithium per se to have specific anti-manic properties.

Leale

Hammond appears to have made no mention of gouty insanity in his 1871 book, but by no means was this concept unknown to American medicine of the time. At the London Congress in 1881 Leale,[166] of New York, had raised the issue of 'functional symptoms [of gout], or those arising from disturbances of different organs or systems of the body, but not accompanied with any known or visible alterations in the implicated parts'. He proceeded to support the view that Rayner had expressed regarding the association between 'suppressed gout' and insanity—'a combination of symptoms that we, in the large cities of America, are becoming more familiar with as we increase in material wealth, and are surrounded by so many luxuries'. 'From closely observing these cases of suppressed gout, with functional disturbance […]', Leale was inclined 'to place these functional symptoms among the most important, as Dr. Garrod [who was present] has so ably done'. Leale expressed concern that

> when these gouty functional disturbances are ridiculed or neglected by the physician, and the sufferer is permitted to long continue in this irritable nervous condition, under the pleas that he is a hypochondriac, and permanent changes are allowed to occur in the cerebral meninges […] then we may have acute mania, ending in incurable insanity, with the remainder of a life spent in a lunatic asylum […] Illustrations of all these phases I have personally observed in the city of New York.

Da Costa's recommendation of lithium continuation therapy in 'American gout'

Da Costa[167] in 1881, and Dana[168] in 1886 reported in the American medical press that people who were predisposed to lithiasis or arthritis, with an excess of uric acid in the urine, would show symptoms from the nervous system remarkably often. Da Costa coined the term American gout, whereas Dana used that of metabolic neuroses.[169]

Da Costa found that 'able research' had done much 'to direct the attention of the medical mind' to lithiasis or lithaemia. The outcome, he said,[170]

> is that it is now distinctly known that a state exists which is closely allied to gout, a half-gout [emphasis added] that does not bring with it the inflammation, pain, and obvious swellings of the gouty paroxysm, but which

works more silently, is characterised by the abundance of lithic acid or lithates in the urine.

It is no wonder that he wished to confine himself particularly 'to the less obvious, less known results which show themselves in the nervous system':

> A certain nervousness which may pass into hysteria is also among the symptoms of lithaemia; and I am certain that the hysterical symptoms of women no longer in their youth, and which are attributed to nervous break downs, to menstrual disorders, to approaching change of life and the like, are often really of lithaemic origin, and curable by the treatment which removes the constitutional cause.[171]

There cannot be much doubt that the symptomatology Da Costa went on to outline, is clearly recognisable today as features of mood disorders:

> There are spells of languor and lassitude which befall the man whose blood I charged with lithic acid, in which all exertion is painful, and which strangely contrast with his usual energy. Then there is depression of spirits and gloom that may amount to melancholy. But above all is irritability of temper; odours annoy, sounds infuriate, nothing pleases, and it requires more than ordinary self-control to prevent explosions of temper. The man is on edge, and the acid blood literally makes an acid temper. Indeed, many a man who has the reputation of being a curmudgeon, is simply a lithaemic who finds it impossible to control his engendered irritability […] Lithaemia is much more common in men than in women. Its chief sufferers are men in the prime of life […] My list of lithaemic patients, embraces many a name distinguished at the bar, in medicine, in the pulpit, in literature, and in the world of finance. And it is not only brain-work, and all the habits this implies, but strain and worry, which induce it. Our present civilization is very rife with its causes. It is a growing disease in this country, especially in our cities.[172]

Da Costa was confident that the symptoms of

> nervous derangement in lithaemia are interchangeable. Sometimes one or several exist for a time; the lithaemic condition gets better, they disappear; the lithaemic condition returns, but with it comes a fresh set of nervous symptoms; and so on, until the state is permanently remedied, they may appear for years.
>
> Indeed, recurrence of lithaemia is one of its characteristics, and the nervous symptoms may be so persistent that it is difficult to set aside the thought that they are not due to an organic cause.[173]

The symptoms of nervous affection, Da Costa firmly believed,[174] 'were the result of the waste-laden blood [the 'impure lithaemic blood'[175]]; but whether the lithic acid, or the compounds generating it, get into the blood in consequence only of deficient glandular action, as of liver, is not clear'.

No details about the regime that he generally prescribed were provided, but he included an illustrative case history (‘case 8’) where he had prescribed a course of lithium citrate.[176]

The patient was a man, thirty-five years of age, of ‘extremely nervous temperament’. His father had also suffered with lithaemic symptoms. The patient himself presented with ‘mental depression and almost hysterical outbreaks of nervousness. Sleeplessness and irritability of the heart were also among the symptoms’. (In this context it is interesting to note that one of the synonyms of Da Costa’s Syndrome is ‘neuro-circulatory asthenia’).[177]

Studying the case, Da Costa found ‘no organic disease of any organ’, but

> ascertained that he passed habitually three pints of urine, of specific gravity of 1022, very acid, free from albumen and sugar, but loaded with lithates […] It often shows a considerable deposit of red sand, and when this happens to a marked degree his nervous symptoms previously very bad are strikingly relieved […] This patient was placed on a diet of fish, green vegetables, a little oatmeal, milk, the white meats; he was directed to drink Apollinaris freely, to exercise, and to give himself as much relaxation as was compatible with his pursuits […] A little calomel and sodium bicarbonate’ [were occasionally prescribed, and] […] while the uric acid deposits were so marked, a course of citrate of lithium [emphasis added]. He is very much better; but he is not as yet quite well; fresh anxieties and worries bring about relapses.

Da Costa’s account is the first that the present author has been able to retrieve in the medical literature where a lithium salt other than lithium bromide was used to relieve or ‘remove’ exclusively nervous symptoms. Intriguingly, it would appear that Da Costa thought that the remedies should be taken on a more or less permanent basis, for ‘until the state is permanently remedied’, the nervous symptoms ‘may appear for years’.[178]

Gray

In 1886 Gray[179] published a paper in the New York Medical Journal, entitled The Nervous Symptoms of so-called Lithaemia. Among the ‘manifold’ symptoms he counted ‘insomnia’ and ‘nervousness’, which ‘may be accompanied by irritability of temper’, ‘a delusional mental disorder’, ‘hysteria’, ‘neurasthenia’, and even ‘epilepsy’. He prescribed various medications and referred to the fact that Da Costa ‘recommends citrate of lithium’.

Aulde’s recommendations of systematic lithium therapy

Non-compliance and recurrence risk

According to an article John Aulde of Philadelphia published in 1887,[180] he had ‘successfully’ used lithium bromide over a period of three years in twenty patients with symptoms ranging from rheumatism, dyspepsia, insomnia, to constitutional tiredness and melancholia. The lithium bromide was given in up to fifteen grains three times daily. One

patient suffered from ‘a marked depression of the vital powers’ and another was ‘irritable and out of sorts with everybody’. The cases were ‘generally classed as lithaemia, lithiasis, or uric acid diathesis’. However, Aulde was greatly frustrated by the ‘unwillingness’ of some of his patients ‘to pursue a systematic course of treatment’, who were only ‘to seek the doctor when trouble overtakes them’. Failure to comply with the regime of lithium bromide would result in ‘the old trouble coming back’. Hence the need ‘to be more docile in the future’.

Aulde acknowledged that he had drawn largely upon ‘the current literature rather than from textbooks’. Among his referent authors were Garrod,[181] and the Danish physician Johannes Mygge, who in 1886 had published a paper on ‘the clinical value of uric acid sediment in the urine’.[182] In his review he mentioned an important treatise on uric acid diathesis, and its assumed association with periodical depression, by his countryman the neuropathologist, Carl Lange. However, in the abstract that Aulde was referring to, Lange was not mentioned.

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[127] Lipowitz A.: ‘Versuche und Resultate über die Löslichkeit der Harnsäure’. Annalen der Chemie und Pharmakologie 1841;38:348–355, quoted here from Johnson, 1984, op. cit. pp.5, 20, 139. Johnson, 1999, op. cit., p.199.

[128] Sollmann T.: ‘A manual of pharmacology and its applications to therapeutics and toxicology’. 6th Edn. Philadelphia: Saunders, 1942. pp.906–907 (‘Lithium salts’).

[129] Ure A.: ‘Observations and researches upon a new solvent for stone in the bladder’. Pharmaceutical Journal Transactions 1843–1844;3:71–74. Buchner JA.: ‘Einführung des Lithions in die Materia medica durch Dr. Andrew Ure’. Repertorium für die Pharmazie 1844;84:259–263. Ure A.: ‘Researches on gout’. Medical Times 1844–45;11:145. cf. Johnson, 1984, op. cit., pp.5–7, 20, 27, 32–33, 51, 139, 148. Johnson, 1999, op. cit., pp.199–200. Copeman, 1964, op. cit.

[130] Ure, op. cit., 1844–45.

[131] Ure A.: ‘Einführung des Lithions in die Materia medica’. Repert. Pharm. 1844;84:259–263 (cited here from Schäfer U.: ‘Past and present conceptions concerning the use of lithium in medicine’. J. Trace Microprobe Techn. 1998;16:535–556 (536)).

[132] Garrod, op. cit. 1859. Anon.: ‘Calculus in the bladder, treated by litholysis, or solution of the stone by injections of the carbonate of lithia, conjoined with lithotrity (Under the care of Mr. Ure)’. Lancet 1860;2:185–186. cf. Amdisen, 1983, op. cit. Johnson, 1984, 1999, op. cit.

[133] Sollmann, 1942, op. cit., no reference given.

[134] cf. Redmann B, Jefferson JW.: ‘Lithium and Wisconsin—A medicinal trip through history’. Wisconsin Med. J. 1985;84:23–26, quoted here from Johnson, 1984, op. cit.

[135] Garrod, op. cit. 1859, p.439. 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.

[136] Garrod, 1859, op. cit., pp.435, 437–438. Garrod, 1873, op. cit.

[137] Garrod, 1859, op. cit., pp.506, 517, 520–522 (‘Irregular Gout’, ‘Gout affecting the Nervous and Muscular Systems’). cf. 1876 edition, pp.441, 455, 458, 459–460.

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

[139] Copeman, 1964, op. cit., p.115

[140] Johnson, 1984, op. cit., p.31

[141] ibid., p.30

[142] Copeman, op. cit., p.115

[143] Garrod AB.: 'Die Natur und Behandlung der Gicht und der rheumatischen Gicht. Uebersetzt von Dr. Eisenmann'. Würzburg: J. M. Richter, 1861. (Lithiumsalze gegen die Gicht, pp.288–297).

[144] 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).

[145] Garrod AB.: 'The nature and treatment of gout and rheumatic gout'. London: Walton and Maberly, 1863. p.425.

[146] Garrod AB.: 'A treatise on gout and rheumatic gout (rheumatoid arthritis)'. 3rd Edn, thoroughly revised and enlarged. London: Longmans, Green, & Co., 1876 (pp.369–370).

[147] Strobusch AD, Jefferson JW.: 'The checkered history of lithium in medicine'. Pharm. Hist. 1980;22(2):72–76. Amdisen A.: 'Lithium as a pharmacological agent. Historical aspects. Topical aspects in monitoring of psychiatric lithium therapy' (Danish text). Psykiatrisk Hospital i Aarhus [Risskov], 1985. p.26. Johnson, op. cit, 1984. Yeragani VK, Gershon S.: 'Hammond and lithium: historical update.' Biol. Psychiatr. 1986;21:1101–1102. Amdisen A.: 'The history of lithium'. Biol. Psychiatr. 1987;22:522–523.

[148] Charcot JM.: 'Traitement de la goutte et du rhumatisme articulaire chronique', in his Leçons sur les maladies des vieillards et les maladies chroniques. Paris: Asselin, 1866 (incomplete). 2. Edn. Paris: Delahaye, 1867. 3. Edn. Paris: Delahaye 1868. 4. Edn. Paris: Delahaye 1874 (pp.233–248) (H. Ferreira-Lopes, Conservateur, Service d'historie de la médecine, Bibliothèque interuniversitaire de médecine, Paris, personal communication, 13.10.2000). Charcot's inaugural thesis, defended before the Faculty of Medicine of Paris in 1853, was entitled: 'Étude pour servir à l'histoire de l'affection décrite sous le nom de goutte asthénique primitive, nodisités des jointures, rhumatisme articulaire chronique (forme primitive)'.

[149] Charcot JM.: 'Clinical lectures on senile and chronic diseases'. Translated by William S. Tuke. London: New Sydenham Society, 1881 (pp.215–219). cf. Charcot JM.: 'Clinical lectures on the diseases of old age'. Translated by Leigh H. Hunt. With additional lectures by Alfred L. Loomis. London: Sampson Low, 1882 (pp.160–163).

[150] Garrod, 1867, loc. cit., p.486 (footnote): 'J'ai eu maintes fois l'occasion de constater la réalité de ce fait; j'ai, dans plusieurs essais, porté progressivement le carbonate de lithine jusqu'à la dose relativement considérable de 2 grammes et même 3 grammes dans les vingt-quatre heures, sans qu'il se soit produit aucun effet fâcheux. Mais lorsque ces doses élevées sont soutenues pendant plusieurs jours, on ne tarde pas à voir survenir des symptômes de dyspepsie cardialgique qui obligent bientôt à suspendre l'emploi du médicament. (J. C.)'. Garrod, 1876, p.372.

[151] ibid., p.586.

[152] Climent E.: 'Traitement de la gravelle urique'. Thèse. Paris, 1874. p.33, quoted here from Johnson, 1984, op. cit., p.158. cf. Good CA.: 'An experimental study of lithium'. Am. J. Med. Sci. 1903;125:273–284.

[153] Garrod, 1876, op. cit., p.372.

[154] Locock C.: 'Discussion of a paper by E. H. Sievking. Analysis of fifty two cases of epilepsy observed by the author'. Lancet 1857;1:527. It was believed in the mid-19th century that excessive sexual activity (and masturbation) contributed significantly to epilepsy. As bromides were known to cause impotence Charles Locock in 1857 proposed that suppression of sexual function and menstruation with bromides would result in suppression of seizure activity. He was right, but for the wrong reason (cf. Scott DF.: 'The discovery of anti-epileptic drugs'. J. Hist. Neurosci. 1992;1:111–118. Rolak LA. (ed.): 'Neurology secrets'. Philadelphia: Henley & Belfus, 1993, p.401).

[155] Gibb GD.: 'Note on the action of bromides of lithium, zinc, and lead'. Reports at the 34th meeting of the British Association of Advances in Science. September 1864. Transactions, p.123. London, 1865. cf. Wood HC.: 'Therapeutics: its principles and practice.' London: Smith, Elder, 1888. p.296. Johnson, op. cit., 1984, pp.17, 51–52, 145, 157.

[156] Lévy E.: 'Essai sur l'action physiologique et thérapeutique du bromure de lithium'. Thèse. Paris, 1874 (quoted from Johnson, op. cit., 1984, p.143).

[157] Mitchell SW.: 'On the use of bromide of lithium'. Am. J. Med. Sci. 1870;60:443–445. cf. Olfson M.: 'Weir Mitchell and lithium bromide'. Am. J. Psychiatr. 1987;144:1101–1102. Scott DF.: 'The first use of lithium?' Br. J. Psychiatr. 1992;160:709–710. Schou M.: 'The first psychiatric use of lithium'. Br. J. Psychiatr. 1992;161:279–280.

[158] 'Medical News and Library' 1877;35(420):177–184. cf. Olfson M.: 'Weir Mitchell and lithium bromide'. Am. J. Psychiatr. 1987;144:1101–1102. In this paper Olfson pointed out that 'the higher dose' which Mitchell mentioned is equivalent to 276 mg of lithium carbonate three times daily, and 'because such a dose might well result in lithium levels within the currently accepted therapeutic range, there is reason to believe that Dr. Mitchell's preference for the lithium salt was based on the now well-established mood-stabilizing properties of that ion'.

[159] Cited in Good CA.: 'An experimental study of lithium'. Am. J. Med. Sci. 1903;125:273–284. cf. Gershon S.: 'Use of lithium salts in psychiatric disorders'. Dis. Nerv. Syst. 1968;51–55.

[160] Yeragani VK, Gershon S.: 'Hammond and lithium: historical update'. Biol. Psychiatr. 1986;21:1101–1102. Steven Tyrer had brought Hammond's use of lithium, in 1871, to the attention of Yeragani and Gershon. Arvid Carlsson had alerted Amdisen to Hammond (Amdisen A.: 'Lithium as a pharmacological agent. Historical aspects. Topical aspects in monitoring of psychiatric lithium therapy (Danish text)'. [Risskov], 1985:26). Amdisen, 1987, op. cit. Yeragani VK., Gershon S.: 'Response [to Amdisen]'. Biol. Psychiatr. 1987;22:523. Johnson, 1999, op. cit., p.205.

[161] Hammond WA.: 'Treatise on diseases of the nervous system'. New York: Appleton, 1871. pp.358–366 'Mania', pp.380–381 'Treatment'.

[162] Yeragani and Gershon, 1986, 1987, op. cit. Amdisen, 1987, op. cit. ('The history of lithium'). Amdisen A.: 'The first lithium era', in Johnson FN. (ed.): 'Depression & mania. Modern lithium therapy'. Oxford: IRL Press, 1987. pp.24–28. Johnson, 1999, op. cit.

[163] Hammond WA.: 'A treatise on the diseases of the nervous system'. London: Lewis, 1882. (pp.65–71: 'First among [internal remedies] must be placed the bromide of potassium […] Latterly I have used the bromide of sodium […] instead of the bromide of potassium […] The bromide of calcium is also well adapted to the treatment of cases of cerebral congestion, and has the advantage over the other bromides of acting more promptly […] Latterly I have made much use of arsenious acid in cerebral congestion, especially in cases which have been the result of mental exertion or anxiety'). Hammond WA.: 'A treatise of insanity'. New York: Appleton, 1883 (pp.744–745). Hammond WA.: 'A treatise on diseases of the nervous system'. New York: Appleton, 1890 (pp.66–67).

[164] Yeragani and Gershon, 1986, 1987, op. cit. Amdisen, 1987, op. cit. ('The history of lithium'). Amdisen A.: 'The first lithium era', in Johnson FN. (ed.): 'Depression & mania. Modern lithium therapy'. Oxford: IRL Press, 1987. pp.24–28. Johnson, 1999, op. cit. cf. Macleod N.: 'The bromide sleep: a new departure in the treatment of acute mania'. Br. Med. J. 1900;Jan.:134–136. Ragg P.: 'The bromide sleep in a case of mania'. ibid. 1900;Nov.:1309–1310. Wright WW.: 'Results obtained by the intensive use of bromides in

functional psychoses'. Am. J. Psychiatr. 1926;5:365–389. Lithium was not mentioned in any of these papers; that of Ragg refers to Clouston (Mental Diseases, 3rd Edn. 1892:171): 'I have used bromide alone in acute mania extensively and experimentally. In small doses it seems to have no effect'.

[165] 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. Ringer S, Sainsbury H.: 'Sedatives', in Tuke DH.: A dictionary of psychological medicine. London: Churchill, 1892:1128–1147 (1130-1131: 'Bromide of lithium'). cf. Scott DF.: 'The first use of lithium?' Br. J. Psychiatr. 1992;160:709–710.

[166] Leale CA.: 'Discussion', in Garrod AB.: 'Eczema and albuminuria in relation to gout', in Mac Cormac W. (ed.): 'Transactions of the International Medical Congress. Seventh Session'. Held in London, 2–9 August, 1881. Vol. 2. London: Kolckmann, 1881. pp.107–109. Hammond (1882, op. cit., p.69) wrote: 'If the urine is scanty and high-coloured, saline diuretics are useful'.

[167] Da Costa JM.: 'The nervous symptoms of lithæmia'. Am. J. Med. Sci. 1881;144 (Oct.):313-330. cf. Mygge J.: 'Den kliniske Betydning af krystallinsk Urinsyresediment i Urinen'. [Dan.]. Nord. Med. Ark. 1886;18(23):1–17 (cf. Levison F.: 'The uric acid diathesis. Gout, sand and gravel'. Cassell: London, Paris & Melbourne, 1894. pp.118–119, 135).

[168] Dana CL.: 'On the relation of lithæmia, oxaluria, and phosphaturia to nervous symptoms'. Med. Rec. 1886;29(3):57–64, quoted here from Mygge, op. cit., p.1. He also quoted Gray LC.: 'The nervous symptoms of so-called lithæmia'. N. Y. Med. J. 1886;3:57–60, 91–95.

[169] Da Costa, op. cit., pp.328–329. Mygge, op. cit., p.1.

[170] Da Costa, op. cit., 1881, p.313.

[171] ibid., p.324.

[172] ibid., pp.325–328.

[173] ibid., p.326.

[174] ibid., p.328.

[175] ibid., p.318.

[176] ibid., p.325.

[177] Durham RH.: 'Encyclopedia of medical syndromes'. New York, 1966.

[178] ibid., p.326.

[179] Gray LC.: 'The nervous symptoms of so-called lithaemia'. N. Y. Med J 1886;16. Jan.:57–60, 91–95.

[180] Aulde J.: 'The use of lithium bromide in combination with solution of potassium citrate'. Med. Bull. 1887;9:35–39. ibid. pp.69–72. ibid. 'The use of bromide of lithium in combination with solution of potassium citrate'. pp.228–233.

[181] op. cit.

[182] op. cit. 'The clinical value of uric acid sediment in the urine (Mygge)'. Am. J. Med. Sci. 1887; April:540.