

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 7. Uric acid diathesis and lithium treatment in Great Britain, the USA, France and Germany - concurrent with, and after, the Lange brothers

British views: Maudsley, Haig, Roose, Bridger, Luff, Woods-Hutchinson

MAUDSLEY

In his depression treatise Carl Lange quoted Maudsley's 'renowned book' on mental illnesses, *The Physiology and Pathology of Mind*, but he does not appear to have been influenced by Maudsley, at least not directly:³³¹

It is true that one often finds the statement that the arthritic diathesis may cause mental illness, but then it is emphasized that it is the sudden suppression of an attack of gout that is succeeded by an outbreak of insanity. Whether this can be cited in support of what has been claimed in my point of view is obviously doubtful. It gains more support from a statement by Maudsley who in his renowned book on mental illnesses concerning their aetiology, after having emphasized in general the great importance of the presence of excretory substances in the urine, reports that a couple of times he has observed 'melancholia' in people with an arthritic diathesis and that he has seen the melancholia get cured by an efficient treatment of the gout.

Maudsley wrote on gout and its psychiatric manifestations in several editions of his famous book. In the 1868 edition, for example, he stated:³³²

In like manner the presence of some urinary product in the blood of a gouty patient gives rise to an irritability which no amount of mental control can remove, though it may succeed sometimes in repressing its manifestations [...] All writers on gout are agreed that a suppressed gout may produce severe mental disorder, and that the sudden disappearance of a gouty swelling is sometimes followed by an outbreak of insanity [...] I have recently seen two cases of severe melancholia in elderly persons of the gouty diathesis, in which

the best results followed the treatment suitable to gout; and in one old lady, who was deeply melancholic, rheumatism seemed finally to take the place of the mental unsoundness. It can admit of no question that every degree of mental disorder, from the mildest feeling of melancholic depression to the extremist fury of delirium, may be due to the non-evacuation from the blood of the waste matters of the tissues; but as we know very little at present of the nature of those waste products of the retrograde metamorphosis, and of the different transformations which they undergo before they are eliminated, we must rest content with the general statement, and set ourselves in practice to prosecute rigorous inquiries into the particular instances.

As mentioned before, Maudsley also made reference to Arnold's work stating that this author 'had known cases of people subject to frequent fits of gout who have had none while suffering from an outbreak of insanity'.

In the 1879 edition of his book Maudsley³³³ amended the text, stating that

After the cessation of the inflammation of the joint's gouty mania [emphasis added] sometimes occurs, characterized by acutely maniacal symptoms [emphasis added], with heat of head and fever; ending favorably in the slighter cases, but in severer cases passing into inflammation of the membranes, serous effusion, and coma.

Finally, in the last edition of his work, in 1895,³³⁴ Maudsley stated that various disturbances of metabolism could be causative factors in mental disorders. Reflecting the views of many other authors, he pointed out that

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, Maudsley added,

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 subtle changes in the intimate metabolic processes.

Not mentioning lithium salts for its treatment, he simply stated: 'Is the patient gouty? If so, treat the gout'.³³⁵ He made no reference to Carl Lange.

HAIG - A LEADING AUTHORITY ON URIC ACID

After Garrod, one of the leading British authorities on uric acid was Alexander Haig. He was mentioned by Lange in the postscript to the 1895 reprint of his depression pamphlet.³³⁶

In 1888 Haig published an article in the *Practitioner*, entitled: *Mental depression and the excretion of uric acid*.³³⁷ Here he expressed the view that mental depression and

‘its opposite condition’, mental exaltation, were closely related to the excretion of uric acid. This article caught the attention of Lange, who subsequently contacted Haig. In turn, the latter wrote in the periodical *Brain*, three years later:³³⁸

Since I first wrote on uric acid and mental depression I have heard from Professor C. Lange, of Copenhagen, that he has for a long time observed, and has written a monograph concerning certain conditions of periodical depression which he connects with uric acid diathesis, and treats successfully by a diminution of meat food, and certain rules as to exercise, &c.

Haig³³⁹ also referred to this contact in his well-known book, *Uric Acid as a Factor in the Causation of Disease*:

Soon after I wrote my first paper on mental depression, Professor Lange, of Copenhagen, kindly wrote to me and sent me a monograph, which he published in 1886 on periodical depression and its connection with the uric acid diathesis.

His clinical observations and his treatment of the trouble ran parallel to my own, but he knew at that time nothing about the relation of the disturbance of function to collaemia [uricacidaemia], and merely treated in a general sort of way the uric acid diathesis, which he had found by clinical observation to be related to this periodical depression. His observations and clinical experience are of great interest as confirming my own.

Carl Lange, for his part, in the postscript to the second edition of his depression treatise, made reference to this correspondence stating that ‘the tireless uric acid researcher Haig³⁴⁰ in England has accepted my understanding of the periodical depressions as one of the manifestations of the diathesis (Uric acid Diathesis and other works)’.³⁴¹

Initially, at the time of the Lange-Haig correspondence, Haig had been undecided about the efficacy of lithium. In a paper from 1888 on drugs and uric acid he related³⁴² that with regard to lithium he had

very little to say—it was at one time much used, then fell into disuse, and has finally been brought forward again, in the treatment of uric acid disease, but there is by no means a unanimous opinion as to its value at the present day.

Haig also made reference to some authors who had expressed doubt about the efficacy of lithium; Epstein, for example, to whom Levison also referred.³⁴³

Had Haig initially expressed some reservation or doubt regarding lithium, by 1892 he appeared convinced of its effect for the reason that ‘it relaxes the arterioles and quickens the pulse, causes well-being and a free flow of urine’, but, importantly, ‘not as was supposed by eliminating uric acid from the body’.³⁴⁴

However, in Haig's opinion, expressed in 1900, Lange 'had got but a small way into the real pathology of the trouble'.³⁴⁵ It is possible that Lange did not live to learn about this rather unkind, exacting opinion, as he died in the month of May, the same year.

The Danish physician, Strandgaard, in his doctoral thesis *Gout and Uric Acid Diathesis*,³⁴⁶ commented that Haig had given a different description of periodical depression than Lange. He quoted Haig's statement that mental depression is 'a concomitant symptom of uric acid diathesis' and when the uric acid is removed from the blood 'the mental condition alters as if by magic, ideas flush through the brain, everything is remembered, nothing is forgotten, exercise of mind and body is a pleasure, the struggle for existence a glory'.³⁴⁷ Moreover, Strandgaard emphasized, Lange never saw any switch to exaltation, adding that Haig in contradistinction to Lange did not draw a sharp limit between periodical depression and melancholia.³⁴⁸ He reiterated that the Lange theory of depression was 'strongly doubted' by Steenberg and Pontoppidan, and 'partly' doubted by Levison.³⁴⁹ In response to the fact that 'some authors believe that mental illnesses proper, particularly melancholia and mania can be of a 'gouty nature', specially English clinicians often describe a "gouty insanity" [...]'. Strandgaard himself 'had not encountered unequivocal cases of this kind'.³⁵⁰ He did not enter into the issue of treatment with lithium,³⁵¹ although he had seen noticeable improvement with Vichy water in one case of periodical depression (prescribed as two bottles daily for eight weeks).³⁵²

In this connection it is worthy of note that the master himself, Carl Lange, was opponents ex officio at Strandgaard's defense of his thesis. Another official opponent was Knud Faber; Levison was opponents ex auditoria.³⁵³

ROOSE

Roose in his *Gout, and its relations to diseases of the liver and kidneys*,³⁵⁴ published in 1888, among the 'manifestations of nervous disorder in gouty subjects' counted 'hysteria, hypochondriasis and maniacal attacks'. In cases where 'the urine contains much free uric acid' and with 'a marked acid reaction', he found alkalies to be 'generally indicated', and 'some preparation of potash or lithia is to be preferred [emphasis added]'; these being 'the alkalies which form the most soluble salts with uric acid'. He even recommended that they should be given for lengthened periods '(four to eight weeks) in small doses, in very dilute solutions.

BRIDGER

In 1889, Bridger gave the following fascinating account in his work *Man and his Maladies*:³⁵⁵

Most of my readers know, either by experience or by repute, that periods marked by neuralgia, by great depression and irritability, by sleeplessness, and sometimes by slight mental hallucination, frequently precede, and are completely cured by, an attack of acute gout or acute biliousness [...] [The patients] imagining themselves hopelessly ill and feeling life a burden too great to bear, not unfrequently end their days by their own hand, when, if they

had but known that at the bottom of the whole trouble there lay but gout poison, bile acids, or imperfect products of digestion, which, never absent from the bloodstream, worried and fretted their nervous mechanism, they might have possessed courage to face the enemy. Certainly, more than 90 per cent of all cases of depression seem in people under fifty years of age, and who may be therefore assumed to possess nerve tissue not as yet degenerated, admit of a very simple explanation of the above order, and are but functional nerve derangements due to impurities in the food supply of the system.

‘The subject of latent gout or biliousness’, Bridger³⁵⁶ recommended in a book, published the year before, ‘should visit some mineral spa such as Vichy, Carlsbad, Wiesbaden, Contrexville, etc.’ Lithium, however, was not mentioned explicitly. In 1892 he published the work³⁵⁷ *Depression: What it is and how to cure it*, in which ‘A severe case of gouty depression’ was included. Intriguingly, Bridger stated that ‘even the nerve specialists unwillingly concede’ that ‘the presence of this gout-poison [uric acid] in minute quantities in the blood may be traced in a number of instances of very profound Depression’. Again, lithium was not mentioned.

Review of Carl Lange’s depression treatise in Journal of Mental Science in 1897

Regrettably, Carl Lange’s depression treatise was not translated into English until 2001 (by the present author). However, his views would have become known to Anglo-Saxon readers via a review of Kurella’s German edition of this treatise in the *Journal of Mental Science* in 1897,³⁵⁸ and to be extensively cited later.

It should be mentioned here though that the reviewer, with respect to ‘oxaluria’—Lange having implied the concept of ‘oxaluria insanity’ and having mentioned ‘nervous phosphaturia’³⁵⁹ - referred the readership to Clouston’s *Clinical Lectures on Mental Diseases*, a widely read and authoritative textbook of psychiatry. This book appeared in several editions, the last in 1904. The reviewer stated: ‘Lange refers with more favour to the researches of Haig on the uric acid dyscrasia’.

Like Maudsley, Clouston expressed the view that ‘mental phenomena due to gout are common enough, and have been described by all authors on the subject’. For instance, he found that ‘deep melancholia is a common accompaniment of the gouty diathesis’. He also made reference to Garrod’s description of gouty mania. However, he did not mention Carl Lange’s views.

Luff, Woods–Hutchinson

At the turn of the nineteenth century and during the first decade of the twentieth century, an important British authority on gout was A. P. Luff. In his 1898 treatise: *Gout. Its pathology and treatment*,³⁶⁰ he made reference to Levison but not to Carl Lange.

Like other authors on this topic, Luff mentioned mental depression and maniacal attacks caused by gout. Moreover, he referred to the various experimental studies quoted

in the literature in which animals, when fed with uric acid or given intravenous injections of urates, showed no signs of uric acid poisoning. Luff himself had undertaken experiments in which lithium carbonate 'would not in the slightest degree increase the solvent power of the blood for gouty deposits, even when present in larger proportions than could be introduced into the blood by medicinal administration'. Further details of Luff's work and views shall be discussed later.

Eventually, Woods-Hutchinson took this further, arguing in the *Lancet* in 1903 that 'the use of lithia or other "solvent" agents is irrational, and any benefits resulting are to be explained on other grounds.'³⁶¹

Notwithstanding, a London newspaper or some magazine at about this time advertised 'Backache Kidney Pills' with which to cure the 'Rheumatic London',³⁶² assumed to be caused by 'uric acid poison, which the kidneys are too weak to filter out', and resulting in symptoms such as 'bladder disorders', 'gravel', 'nervous headaches', 'irregular heart', and 'depression'. Thus, the dogma of uric acid poison prevailed.

American views: Whitehead, Hibbard, Leffmann

The Lithia Springs Sanatorium, Georgia, and various patented lithia waters

In 1890 Cloud, Garrett and Whitehead established the Lithia Springs Sanatorium in Georgia.³⁶³ Natural lithium water was used in a range of illnesses. As Whitehead³⁶⁴ wrote

A brief examination of the analysis of Lithia Water is sufficient to satisfy the inquirer that it is highly anti-acid and diuretic, and explains at once its wide curative range. What we consider the long list of maladies that have their source or origin in Uric Acid Diathesis, it is readily seen how wide the field and how great is the remedial power of this water.

No mention was made of, for instance, Weir Mitchell, Da Costa, or Hammond.

Fascinatingly, we learn that the Sweetwater Park Hotel, Lithia Springs, Georgia,³⁶⁵ 'afforded the power brokers and the "rich and famous" a peaceful atmosphere for health renewal, as well as decision making and communications'.

Among those who 'took the waters and reveled in the Hot System of Baths' were the 'Presidents McKinley, Cleveland, Taft, Theodore Roosevelt'. Indeed, such was the enthusiasm of President Cleveland that on 21 November, 1895 he wrote to the Lithia Spring Water Company: 'Please send me a case of Lithia Water as soon as possible'.

Praise had also poured in from various doctors, here exemplified by the opinion of Douglass, Editor, *Second Opinion Monthly Newsletter*, Atlanta, to the effect that Lithia Springs Mineral Water

contains all of the right elements and none of the wrong ones. It is a very useful adjunct in the treatment of nervousness and insomnia. I have

enthusiastically recommended only one mineral water to my patients for years, the Lithia Springs Natural Alkaline Waters.

Lithia waters, 'nature's own remedy' were also sold under the label of 'Bear Lithia Water' with which to cure 'kidney and bladder troubles, uric acid, gout and rheumatism'. Other brands were 'Basic Lithia Water', 'Buffalo Lithia Water', 'Manadnock Lithia Spring Water', and '7-Up Anti-Acid Lithiated Lemon Soda'. Finally, lithium was also added to a beer, 'Lithia Beer', brewed by West Bend Lithia Co., Wisconsin.³⁶⁶

Hibbard, Leffmann

At the latest in 1898, Lange's theory of depression was mentioned in the American medical press by Hibbard³⁶⁷ in his paper: A study of the excretion of urea and uric acid in melancholia and in a case presenting recurrent periods of confusion and depression. With reference to Haig, he wrote that Lange 'connects mental depression and the uric acid diathesis'.

Leffmann,³⁶⁸ not unlike Woods-Hutchinson, expressed the view in 1911 that 'the time is now to overthrow the "lithia water" fetish, the only use of which is to extract annually many thousands of dollars from the pockets of real and imaginary sufferers'.

In this context it should be added that Sollmann³⁶⁹ noted that the popular 'Lithia waters have been shown to be practically devoid of lithium'. The best, according to him, contain 'only 0.01 to 0.02 per cent. "Buffalo Lithia Water" contains only a fifth as much lithium as Potomac River water'. Sollmann concluded that '200,000 gallons would be needed to supply the ordinary therapeutic dose of lithium'!³⁷⁰

French views: Mabile, Lallemand, Magnan, Kahn

The topic under discussion had been a darling of French medicine, as exemplified before, by authorities such as Pinel, Esquirol, Gilbrin, Trousseau, Berthier, Legrand du Saule, Delasiauve, and Charcot.

MABILLE AND LALLEMANT

According to Hibbard's work,³⁷¹ Mabile and Lallemand claimed in 1891 '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'. During remissions they would 'seem well'. Variation in the nitrogen content was also found.

MAGNAN

Magnan³⁷² expressed the view in 1907 that in periodical psychoses one witnesses intermittence in its full, or in other words full diathesis. He made reference to the

intermittent madman, who, similar to the sufferer of rheumatism, after a manifestation of his diathetic condition, returns to his normal without revealing his morbid predisposition. This, he said, is often due to just minor factors, in some manifested in the form of arthritis or torticollis, and in others by manic or melancholic attacks, at times accompanied by more or less systematic paranoid ideation.

KAHN

Kahn in his thesis *La Cyclothymie*,³⁷³ praised Carl Lange for having provided ‘le tableau le plus exact de cyclothymie légère, sous le nom de dépression intermittente’. However, Kahn was not right in stating that ‘malgré le titre, [Lange] note l’hyperthymie, l’excitation, entre les périodes de dépression. Il met en relief l’absence du retour à l’équilibre dans les soi-disant intervalles libres’, in that Lange did not mention this in his treatise.

In Kahn’s opinion, the relationship between cyclothymia and ‘biliary and gouty diatheses’ could not be doubted. He mentioned ‘Vichy traitement: cure alcaline, mécano-thérapie, régime végétarien’, but not lithium—at least not explicitly.

German views: Kurella, Hecker, Ziehen, Kraepelin, Binswanger

KURELLA

Kurella’s authorized translation of Lange’s depression treatise, *Periodische Depressionszustände und ihre Pathogenese auf dem Boden der harnsauren Diathese*,³⁷⁴ received wide attention, but probably made little impact. According to Kurella’s preface accompanying the translation: ‘My own experiences in a small private practice can only confirm Lange’s understanding [of this matter], being one of the reasons that I decided to make his work accessible to the German public’. He made no explicit mention of lithium; however, according to Felber—the 1996 reprint—he prescribed Lange’s treatment and was convinced of its effect.³⁷⁵ Kurella also took the opportunity to mention Lange’s emotion treatise, of which he had rendered a German edition in 1887, as ‘supplementary’ reading.

Kurella had already reviewed Fritz Lange’s psychiatric textbook from 1894, drawing attention to uric acid and periodical depressions.³⁷⁶ In this context it is worthy of note that Kurella had worked with Kaulbaum,³⁷⁷ who in 1884 coined the term cyclothymia, with which to denote the mildest form of circular insanity³⁷⁸ (twenty years before he introduced the term dysthymia, to denote chronic forms of melancholia).³⁷⁹

HECKER

Hecker, mostly known for his concept of hebephrenia, in his: *Die Cyclothymie, eine circulaire Gemüths-erkrankung*,³⁸⁰ pointed out that Carl Lange’s description of periodical depression was convincingly consistent with Kahlbaum’s concept of cyclothymia (‘Die völlige, bis ins Kleinste gehende Uebereinstimmung der Symptome

des von Lange geschilderten Zustandes mit denen des Depressionsstadiums der Cyclothymie [“Dysthymia”] erhebt meine Vermuthung nahezu zur Gewissheit’), but that the symptoms of exaltation (‘hyperthymia’) had probably escaped Lange’s attention. Hecker could not quite ‘as yet’ determine whether to agree with Lange regarding its pathogenesis ‘as my own observations thus far have not been concerned with this. However, from a couple of my own cases I do know that they were complicated by (hereditary) gout and renal colic’. But ‘Of course, I shall be particularly aware of this factor in the future’.

Hecker prescribed opium, galvanising treatment of the sympathetic nerve system, balneotherapy, and, in milder cases, hypnosis. However, he made no comments on the alkaline method, and thus not lithium.

ZIEHEN

Ziehen in his psychiatric textbook,³⁸¹ in the section on ‘constitutional illnesses of doubtful aetiology’, mentioned gout (‘Gicht’) with reference to Lange’s depression treatise. Moreover, he emphasised how English and French psychiatry still attached considerable aetiological importance to gout in the occurrence of psychoses [‘Während man in England and Frankreich der Gicht noch meistens eine grosse ätiologische Bedeutung für die Entstehung von Psychosen beimisst’]. German psychiatry, he said, was clearly more sceptical [‘erheblich skeptischer’]. Ziehen did not rule out, however, that now and then in cases of gout recurrent depressions could occur at irregular intervals as well as cases of severe neurasthenia (‘in unregelmässigen Intervallen recidivirende Depressionszustände und auch schwere Neurasthenien vorkommen’).

KRAEPELIN

If Ziehen’s views could be seen as a concession to the Lange theory of depression, eventually in 1904 no less an authority than Kraepelin in the seventh edition of his epoch-making psychiatric textbook³⁸² strongly questioned Lange’s theory of depressions:

Lange [with reference to the Kurella edition, 1896] has described peculiar periodical states of depression with psychic inhibition, whose cause he presumes to be of a gouty nature. Going by his description, I cannot, like Hecker, doubt that he had milder forms of manic-depressive insanity on his mind, whose manic stages he missed. That gout really plays an essential role has been neither demonstrated nor is probable, at this time; yet metabolic investigations might someday bring some clarification of this matter.

Kraepelin also related that Stegmann³⁸³ in ‘periodical neurasthenia’, ‘which undoubtedly belongs with manic-depressive insanity, had found a decrease in the excretion of uric acid at the time of the depression’.

With respect to medication in manic-depressive insanity, in this seventh edition Kraepelin mentioned bromides (Kohn), atropine (Hitzig), and paraldehyde, Trional, Sulfonal, coffein and Digitalis.³⁸⁴ Interestingly, in Kraepelin’s description of the treatment of epilepsy, he made reference to Krainsky for using lithium.³⁸⁵

Kraepelin reiterated his dismissal of the Lange depression theory in the eighth edition of his textbook, in 1909.³⁸⁶

French and English researchers especially, Kraepelin stated (likewise, Ziehen), found gout ('Gicht') to play a significant causative role in mental illnesses. He then turned his attention, firstly to the assumption made by some that both neurasthenia and anxiety could be caused by an accumulation of uric acid in the blood; and secondly to Carl Lange, pointing out that he, Lange, had also linked periodical depressions with fluctuations in the excretion of uric acid. Going by Lange's description, Kraepelin added, such cases might well belong with manic-depressive insanity. Further investigation, he thought, would need to demonstrate whether such a causative link existed or whether it could be ascribed to secondary features. However, he emphasised, concerning 'the manic-depressive forms' the first assumption 'to me [appears] extremely unlikely for many reasons'.³⁸⁷ He elaborated no further on this 'investigation'.

Kraepelin's description of manic-depression insanity followed in the third volume of the eighth edition, published in 1913.³⁸⁸ His opinion about Lange's depression theory was virtually unchanged.

Lange ist zur der Ansicht gelangt, dass vermehrte Harnsäureausscheidung als die wesentliche Ursache der Depressionszustände anzusehen sei [...] Lange [this time with explicit reference to the German edition of his depression treatise] hat als die Grundlage periodischer Depressionszustände mit psychischer Hemmung, die zweifellos in das Gebiet des hier beschriebenen Leidens ['das manisch-depressive Irresein] fallen, eine gichtische Entstehungsweise angenommen, eine Ansicht, die jedoch bis jetzt weder als erwiesen noch auch als wahrscheinlich betrachtet werden kann.

This time no investigation was mentioned.

In earlier years, Kraepelin had assumed that the pathogenesis of manic-depressive psychosis was auto-intoxication ('Selbstvergiftung').³⁸⁹ But in later years (around 1913) he favoured metabolic disturbances ('Stoffwechselstörungen').³⁹⁰ His treatment recommendations were unchanged,³⁹¹ and he also repeated Kraepelin's use of lithium in epilepsy.³⁹²

BINSWANGER'S VIEWS

Binswanger, in his psychiatric textbook (1911), expressed the opinion that 'pronounced mental disturbances' due to uric acid diathesis occur only rarely, 'at least according to the experiences of German psychiatrists'. However, 'in the foreign literature, "Kopfgicht", as presumed by older doctors, plays a greater role'. Binswanger finally mentioned the Lange theory of depression: 'So sollen verhältnismässig oft periodische gemüthliche Depressionszustände durch Retention von [uric acid] im Blute verursacht sein (Lange)'.³⁹³

Kraepelin's final verdict on Lange's theory of periodical depressions

Kraepelin returned to the Lange theory of depression in the 1927 edition of his textbook, under the section on metabolic disturbances.³⁹⁴ He now commented that 'mental disturbances ["Geistesstörungen"] have often been explained on the basis of gouty predisposition', especially by Carl Lange, who, he said, related 'a major part of the periodical depressions ["einen grossen Teil der periodischen Verstimmungen"]', which we link with manic-depressive psychosis, to an increased production and excretion of uric acid'. After again dismissing this view ['keine Stütze gefunden hat'], he stressed that Lange's assumptions had not been confirmed by clinical observations. Among his own patients Kraepelin had encountered only a few attacks of gout ('spärliche Gichtanfalle') which he interpreted to be only secondary features associated with otherwise caused mental disturbances. He mentioned, though, that Bonhoeffer thought that there was possibly a more frequent connection between uric acid diathesis and certain forms of psychopathic predisposition ('psychopathische Veranlagung').

Attention should here be drawn to a paper published in the *Lancet* in 1968 by Aumoye and associates.³⁹⁵ With reference to Kraepelin³⁹⁶ and Jaspers,³⁹⁷ for having suggested 'an association between manic-depressive illness, gout, uric acid excretion, and hyperuricaemia', the authors wrote about their own investigations on uric-acid metabolism in manic-depressive illness and during lithium therapy. They found that cyclic changes in manic-depressive were followed closely by changes in daily urinary uric-acid excretion, and when treatment with lithium was instituted, it seemed to exert an uricosuric effect. They also found uric-acid-clearance studies indicated that uric-acid excretion during manic-depressive illness became 'substantially increased' in the early phase of remission—whether natural or lithium induced—being suggestive of an alteration in tubular reabsorption. Generally, they postulated that lithium may interfere with the active transport of organic acids both in the kidney and in the brain. From a historical perspective, they wrote, Carl Lange was 'the first of many workers' to claim beneficial results from the use of lithium in 'both gout and mental depression'.

Kraepelin would have been well aware that in the early years of the 1900s it was a proven fact that the uric acid diathesis was a mistaken, erroneous concept.³⁹⁸ Fittingly, Fitcher had written in 1903 that³⁹⁹ 'The uric-acid diathesis [...] is a scrap-basket for all improperly diagnosed cases'. Furthermore, lithium was discarded as a uric acid solvent, because it had been established that even the intake of toxic amounts of lithium salts, as for example emphasised by Luff,⁴⁰⁰ had no appreciable dissolvent action.⁴⁰¹ As Daniels⁴⁰² pointed out in 1914, it became established that the reaction which took place 'so readily in the test-tube', when lithium and uric acid were the only reacting substances, did not occur when salts of phosphoric acid, in similar concentration to those in the blood, were present. Instead, he noted, lithium formed an insoluble compound with the sodium phosphate. He concluded therefore that 'lithium as a remedy for gout fell into disrepute', whereas 'formerly [...] lithium salts constituted one of the most used remedies for gout and rheumatism'. Finally, he recommended from 1 to 2 gm. daily of lithium citrate for gouty patients. He made reference to the works of Ure, Garrod, Luff, and the uric acid authority, Folin.

³³¹ Appendix I.

³³² Maudsley H.: 'The physiology and pathology of mind'. 2nd Edn. London: Macmillan, 1868. pp.264–265.

³³³ Maudsley H.: 'The pathology of mind. Being the 3rd Edn. of the second part of the Physiology & pathology of mind', recast, enlarged, and rewritten. London: Macmillan, 1879. pp.111, 120, 196–198.

³³⁴ Maudsley H.: 'The pathology of mind. A study of its distempers, deformities, and disorders'. London: Macmillan, 1895. pp.112–115.

³³⁵ Maudsley, 1895, p.546.

³³⁶ Lange, 1895, 1896. Felber 1996, *op. cit.*, p.52.

³³⁷ Haig A.: 'Mental depression and the excretion of uric acid'. *Practitioner* 1888;41:342–354.

³³⁸ Haig A.: 'Uric acid in diseases of the nervous system'. *Brain* 1891;14:63-98 (74, 91).

³³⁹ Haig A.: 'Uric acid as a factor in the causation of disease. A contribution to the pathology of high arterial tension, headache, epilepsy, mental depression, gout, rheumatism, diabetes, Bright's, and other disorders'. Editions 1–6. London: Churchill 1892–1907; quoted here from the 5th Edn., 1900.

³⁴⁰ According to the proceedings of a meeting in the British Medical Association, on August 1, 1900 (*Lancet* 1900;2:147) Haig 'had examined his urine on nearly 3000 days' regarding the contents of uric acid and urea!

³⁴¹ Lange, 1895, 1896, Felber (p.52), *op. cit.* Levison wrote (1896, *op. cit.*, p.375) that Haig 'regardless of his "tirelessness", as praised by Lange, could not be considered a valuable supporter [...] One cannot have much confidence in his [Haig's] arguments' regarding uric acid in the body. cf. Rasch, 1896, *op. cit.*, p.1154. Rasch, 1899, *op. cit.*, p.1030.

³⁴² Haig A.: 'Effects in health and disease of some drugs which cause retention of uric acid, in contrast with the action of salicylates, as shown in a previous paper'. *Med. Chir. Transact.* 1888;71:283–295 (referring to Yeo: *Br. Med. J.* 1888;1:68). cf. Amdisen A.: 'Lithiumbehandling af mani og depression i forrige århundrede'. *Med. For. (Cph.)* 1983;110–119.

³⁴³ Levison, 1896, *op. cit.*, pp.356–361. Levison, 1897, *op. cit.*, pp.338–339, 342.

³⁴⁴ Haig, 1892, *op. cit.* (1st Edn.)

³⁴⁵ Haig, 1900, *op. cit.*, p.287 (5th Edn.)

³⁴⁶ Strandgaard NJ.: 'Gigt og urinsur Diatese, kritisk belyst'. Copenhagen: Lund, 1899. cf. Johnson, 1984, *op. cit.*, p.25. Johnson, 1999, *op. cit.*, p.210.

³⁴⁷ Haig, 1894, *op. cit.*, p.146 (Strandgaard, *op. cit.*, p.64).

³⁴⁸ *ibid.*, p.150 (Strandgaard, *op. cit.*, p.65).

³⁴⁹ Strandgaard, *op. cit.*, pp.64, 66. cf. Jacobæus, 1906, *op. cit.*, p.460.

³⁵⁰ Strandgaard, *op. cit.*, p.72.

³⁵¹ cf. Johnson, 1984, *op. cit.*, p.25. Johnson, 1999, *op. cit.*, p.210.

³⁵² Strandgaard, *op. cit.*, p.68 (case vignette no. 13).

³⁵³ ‘Aarvog for Kjøbenhavns Universitet, den polytekniske Læreanstalt og Kommunitet indeholdende Meddelelser for de akademiske Aar 1898-1901 med Sagregister udgivet efter Konsistoriums Foranstaltning af H. Matzen.’ Copenhagen 1902. p.542, communicated to the current author by Nina Flindt-Jensen, University of Copenhagen. It is interesting that Strandgaard did not mention Lange in his preface to this work. Strandgaard’s mother was Henriette Cathrine née Lange. However, I have not been able to establish whether she was related to the Lange brothers.

³⁵⁴ Fifth edition. London: Lewis, 1888. pp.100, 145, 159.

³⁵⁵ Bridger AE.: ‘Man and his Maladies; or, The way to health. A popular handbook of physiology and domestic medicine in accord with the advance in medical science’. London: Hogg, 1889, and New York: Harper, 1889 (quoted here from van Lieburg, op. cit., 1988, pp.19–20).

³⁵⁶ Bridger AE.: ‘The demon of dyspepsia, or digestion: perfect and imperfect’. London: Sonnenschein, 1888 (quoted here from van Lieburg, op. cit., 1988, p.21).

³⁵⁷ London: John Hogg, 1892. (pp.14–25: Ailments conducive to depression. Case 7: ‘A severe case of gouty depression’, *ibid.*, pp.66–67), quoted here from van Lieburg MJ.: An unknown monograph on depressions. Organon International bv, 1988.

³⁵⁸ Lange, 1896, op. cit. Anon.: ‘Periodische Depressionszustände und ihre Pathogenese auf dem Boden der harnsauren Diathese. Von Professor C. Lange’. Hamburg. *J. Ment. Sci.* 1897;43:344-346.

³⁵⁹ cf. Lemoine, ‘Practical Notes’, *Practitioner* 1901;13:716-717. *Nord Médical* (quoted in *Medical Record*, no year given).

³⁶⁰ Luff AP.: ‘Gout. Its pathology and treatment’. London, 1898.

³⁶¹ Woods-Hutchinson: ‘The meaning of uric acid and the urates’. *Lancet* 1903;1:288–294. cf. Buckley CW.: ‘Arthritis, fibrositis and gout. A handbook for the general practitioner’. London: Lewis, 1938, p.141: ‘Lithium salts and various proprietary preparations of piperazine, thymine acid, etc., have had a popular vogue for years for the prevention and treatment of gout and “rheumatism”. While much of their popularity is due to skilful advertising, it is hardly likely that they would have been used so extensively unless they had some apparently beneficial effect. It is improbable that they have any solvent effect on uric acid in the body, and the explanation of their effect must be sought in other directions’.

³⁶² ‘Rheumatic London’. Illustration of an advertisement for ‘Doan’s Backache Kidney Pills’, included in Schiötz EH. & Cyriax JH.: ‘Manipulation [of osteopathy] past and present, with an extensive bibliography’. London: Heinemann, 1975, p.175. The present writer’s source is ‘Garrison-Morton’s Medical Bibliography’. 5th Edn., 1993, where Schiötz’s work is included in the section on the ‘history of pharmacology and therapeutics’ (p.325, No. 2068,17) and indexed under ‘lithium therapy’ (*loc. cit.* p.1184). However, I have not been able to confirm that Doan’s Backache Kidney Pills contained lithium, based on a scrutiny of successive editions of Martindale’s ‘The Extra Pharmacopoeia’ (Linda Fellows of Graylands Hospital, Mt. Claremont, and Rod Hurley of Glenside Hospital, Eastwood), and ‘Secret Remedies’. London: British Medical Association 1909 (kindly retrieved by Sue Jacobs of the Pharmaceutical Council of Western Australia). According to the latter source (p.62), an analysis of Bishop’s Gout Varalettes showed the presence of lithium, lithium citrate, whereas an analysis of Doan’s Backache Kidney Pills (pp.67–69) showed them to contain none. Concerning the comparative pathology of gout in London and Paris, cf. Drysdale CR.: ‘Gout among hospital patients in London and Paris’. *Br. Med. J.* 1877;1:375. Drysdale found that ‘one of the most striking facts in the comparative pathology of London and Paris resides in the paucity of cases of gout seen among hospital patients in the latter city’, where he had discussed this matter with Dr. [P.-C.] Potain to the effect that in Paris, ‘where wine is plentifully consumed, gout is conspicuous by its absence’, as opposed to the drinking of ‘strong beer and ale’ among ‘working men in London’. cf. Willaim Gull’s inaugural address at the London Congress, op. cit., vol. 1:2–6: ‘The pathology and treatment of gout, rheumatoid arthritis, and rheumatism, to which, in one form or another, the English seem rather especially prone, will come up for discussion’.

³⁶³ ‘History of lithium’, online [URL: www.termpaperaccess.com/doc]. ‘Everything old is new again’, online [URL: www.lithiaspringswater.com/id18_m.htm].

³⁶⁴ Whitehead WH.: 'Lithia water in the treatment of disease'. Circa 1890, reprinted online [URL: www.lithiaspringswater.com/id18_m.htm].

³⁶⁵ Sweetwater Park Hotel—Lithia Springs, Georgia, online [URL: www.lithiaspringswater.com/id42]

³⁶⁶ Strobusch AD, Jefferson, JW.: 'The checkered history of lithium in medicine'. *Pharm. Hist.* 1980;22:72–76. Redmann B, Jefferson JW.: 'Lithium and Wisconsin—A medicinal trip through history'. *Wisc. Med. J.* 1985;84:23–26. Jefferson JW.: 'Lithium: A therapeutic magic wand'. *J. Clin. Psychiatr.* 1989;50:81–86. El-Mallakh RS, Jefferson JW.: 'Prethymoleptic use of lithium'. *Am. J. Psychiatr.* 1999;156:129. Friedrich MJ.: 'Lithium: Proving its mettle for 50 years'. *JAMA* 1999;281:2271-2273. Aita JA.: '7-Up Anti-Acid Lithiated Lemon Soda or early medicinal use of lithium'. *Nebr. Med. J.* 1927;Oct.:277–280.

³⁶⁷ In *Am. J. Insan.* 1898;April:503-531. cf. *Ann. Méd.-Psychol.* 1901:474. (Hibbard referred to Haig's reference to Lange's work in *Brain* 1891;14:74).

³⁶⁸ Leffmann H.: 'Lithia waters as therapeutic agents'. *Mth. Cyclop. Med. Bull.*, Philadelphia 1910;111:138–144, quoted here from Jefferson JW, Greist JH.: 'Lithium. Introduction and history', in Kaplan HI, Sadock BJ. (eds.): 'Comprehensive textbook of psychiatry'. Vol. 2. 6th Edn.. Baltimore: Williams & Wilkins, 1995:2022–2023, 2031. cf. Johnson, 1984, op. cit., pp.21, 148. Johnson, 1999, op. cit., p.209.

³⁶⁹ Sollmann T.: *Pharmacology*, op. cit., 1942:906–907. cf. Cogen PH, Whybrow PC.: 'Lithium: a fascinating element in neuropsychiatry', in Bauer M, Grof P, Müller-Oerlinghausen B. (eds.): 'Lithium in neuropsychiatry. The comprehensive guide'. Abingdon: Informa, 2006:3–7.

³⁷⁰ cf. Pokorny AD, Sheehan D, Atkinson J.: 'Drinking water. Lithium and mental hospital admissions'. *Dis. Nerv. Syst.* 1972;33:649-652. cf. Kline N.: 'Lithium: the history of its use in psychiatry'. *Mod. Probl. Pharmacopsychiatr.* 1969;3:73-92. Johnson, 1984, op. cit., pp.67-68 (M. Schou).

³⁷¹ Hibbard, 1898, op. cit., quoted here from Régis and Chevalier-Levaure: 'Des Auto-intoxications dans les maladies mentales. Congrès des Médecins Aliénistes des Pays de Langue Française'. La Rochelle, 1893:13. Mabile H, Lallemand E.: 'Des folies diathésiques'. *Academie de médecine* 1891 (Camuset, *Ann. Méd-Psychol.* 1892;1:317). cf. *Medical Week* 1893:373–375 (a discussion by these authors and others at the 'French Congress of Psychological Medicine', La Rochelle, 1893). Régis E.: *Précis de psychiatrie*. 3rd Edn., p.590 (quoted here from Kahn, op. cit., p.203). Chevalier-Lavaure F.: 'Des Auto-intoxications dans les Maladies mentales'. Bordeaux, 1890.

³⁷² Magnan JJ. In his: 'Les psychoses périodiques'. *Congrès de Genève*, 1907, p.42: 'Dans ces formes mentales [periodical psychoses], nous sommes en pleine intermittence, on pourrait dire aussi en pleine diathèse, c'est-à-dire que le fou intermittent, comme le rhumatisant, après une première manifestation de son état diathésique revient à la santé sans que rien ne trahisse au dehors sa disposition malade qui, à la suite des causes les plus légères et parfois sans cause appréciable, se traduira chez l'un par une arthrite, un torticolis, chez l'autre par un accès maniaque ou mélancolique, accompagné parfois d'idées délirantes plus ou moins systématisées' (quoted from Kahn P.: 'La cyclothymie. De la constitution cyclothymique et de ses manifestations. (Dépression et excitation intermittentes)'. Thèse. Paris: Steinheil, 1909. pp.148–149. Kahn found it interesting that Magnan would use the notion of diathesis. cf. Mabile H, Lallemand, E.: 'Des folies diathésiques'. *Academie de médecine* 1891 (Camuset, *Ann. Méd-Psychol.* 1892;1:317). Régis, E.: 'Précis de psychiatrie'. 3rd Edn., p.590 (quoted here from Kahn, op. cit., p.203).

³⁷³ Kahn P.: 'La cyclothymie'. 1909, op. cit., 1909, pp.18, 130, 149, 197, 203, 207, 210–211, 216–217, 226.

³⁷⁴ Kurella, 1896, op. cit.

³⁷⁵ Felber W. op. cit., 'Vorwort 1'.

³⁷⁶ Kurella, 1895. op. cit.

³⁷⁷ Felber, 1987, 1996, op. cit.

³⁷⁸ Kahlbaum K.: 'Ueber cyclisches Irresein'. Breslauer ärzt. Ztschr. 1882;Oktober:217 (from Kahn P.: *La cyclothymie*. 1909, op. cit., pp.13, 247). Hecker E.: 'Die Cyclothymie, eine circuläre Gemüths-erkrankung'. Ztschr. Prakt. Aerzte 1898;1:6–15, also quoted by Kahn (p.14) and Amdisen). Hecker also refers to an article by Kahlbaum in *Irrenfreund*, 1882. Lewis AJ.: 'Melancholia: A historical review'. *J. Ment. Sci.* 1934;80:1–42.

³⁷⁹ Freeman HL.: 'Historical and nosological aspects of dysthymia', in Costa e Silva, J. A., Freeman, H. L. (eds): 'Dysthymia in clinical practice'. *Acta Psychiatr. Scand.* 1994;89 (Suppl. 383):7–11.

³⁸⁰ E. Hecker, 1898, op. cit. Johannes Lange reiterated Hecker's opinion in Oscar Bumke's authoritative *Handbuch der Geisteskrankheiten*. Band VI, Spezieller Teil II. Berlin: Springer, 1928. p.121: '[...] Hecker verdanken wir die erste gesonderte Bearbeitung des Themas [‘Die leichtesten Formen des zirkulären Irreseins’], in der besonders Langes Behauptungen über die angebliche gichtische Grundlage der periodischen Depressionszustände (1896 [Kurella's edition]) bekämpft wurden'. *ibid.* p.211: 'Demgegenüber [what suggested by others] leitet C. Langes durch keine chemische Untersuchung beschwerte Theorie von der gichtischen Grundlage der periodischen Depressionszustände zu den zahlreichen hier nicht im einzelnen auszuführenden Stoffwechsellypothesen hinüber'.

³⁸¹ Ziehen T.: 'Psychiatrie für Ärzte und Studierende bearbeitet. Zweite, vollständige umgearbeitete Auflage'. Leipzig: Hirzel, 1902. p.263.

³⁸² Kraepelin E.: 'Psychiatrie. Ein Lehrbuch für Studierende und Ärzte. Siebente, vielfach umgearbeitete Auflage. II. Band. Klinische Psychiatrie'. Leipzig: Barth, 1904. p.561: 'Lange hat eigentümliche periodische Depressionszustände mit psychischer Hemmung beschrieben, für die er eine gichtische Entstehungsweise annimmt. Nach seiner Schilderung kann ich, wie Hecker, nicht zweifeln, dass er leichte Formen des manisch-depressiven Irreseins im Auge gehabt hat, deren manische Abschnitte ihm entgangen sind. Dass wirklich die Gicht eine wesentliche Ursache bilden sollte, ist jedoch bis jetzt weder erwiesen noch auch wahrscheinlich; immerhin dürfte von Stoffwechseluntersuchungen vielleicht einmal Aufklärung in dieser Frage zu erwarten sein'. [cf. also 1899 edition, p. 408].

³⁸³ Not identified. Kraepelin, 1904:561: 'Stegmann fand bei der "periodischen Neurasthenie", die wohl zweifellos dem manisch-depressiven Irresein angehört, Verminderung der Harnsäureausscheidung in den Zeiten der Verstimmung.'

³⁸⁴ Kraepelin, 1904:587–588.

³⁸⁵ Kraepelin, 1904:678–679: 'Krainsky hat auf Grund seiner Auffassung von der Entstehung der Epilepsie nach einem Mittel gesucht, welches imstande wäre, das carbaminsaure Ammoniak im Blute zu zerstören. Er fand es im kohlen-sauren Lithion, das er in mittleren Gaben von 2 bis höchstens 5 oder 6 gr[am] in Anwendung brachte. Seine Erfolge waren nicht nur bei der Epilepsie, sondern auch bei der Eklampsie vorzügliche, doch traten bei höheren Gaben des Mittels Vergiftungserscheinungen, Benommenheit, Niedergeschlagenheit, Ataxie auf. Krainsky stellt sich vor, dass sich bei seiner Behandlung das kohlen-saure Lithion mit dem carbaminsauren Ammoniak in carbaminsaures Lithion und kohlen-saures Ammoniak umsetzt. Letzteres wird in kleineren Mengen vom Körper fortwährend ausgeschieden, sammelt sich aber bei reichlicher Bildung an und erzeugt dann die erwähnten Vergiftungserscheinungen. Es bleibt abzuwarten, ob sich diese verhältnismässig einfache Lösung der Frage als richtig erweist, und ob das kohlen-saure Lithion auch in anderen Händen ähnlich günstige Wirkungen entfaltet'.

³⁸⁶ Kraepelin E.: 'Psychiatrie. Ein Lehrbuch für Studierende und Ärzte. Achte, vollständig umgearbeitete Auflage. I. Band. Allgemeine Psychiatrie'. Leipzig: Johann Barth, 1909. ('Stoffwechselkrankheiten', pp.80–81).

³⁸⁷ Kraepelin: 'Lange hat auch periodische Depressionszustände mit Schwankungen der Harnsäureausscheidung in ursächliche Verbindung gebracht. Nach der Schilderung [Kurella's edition] hat es sich um Anfälle gehandelt, die dem manisch-depressiven Irresein angehören dürften. Ob wir es hier überall mit ursächlichen Beziehungen oder mit einfachen Begleiterscheinungen zu tun haben, muss weiterer Prüfung überlassen bleiben; für die manisch-depressiven Formen ist mir die erstere Annahme aus vielen Gründen äusserst unwahrscheinlich'.

³⁸⁸ Kraepelin E.: 'Psychiatrie. etc'. III. Band. Klinische Psychiatrie. II. Teil. 1913. p.1232 'Allgemeine Krankheitszeichen', p.1371 'Wesen der Krankheit'.

³⁸⁹ Kraepelin E.: 'Psychiatrie'. 1884. p.408 (quoted here from Thalbitzer, 1902. p.31). cf. Kraepelin E.: 'Psychiatrie. Ein Lehrbuch für Studierende und Ärzte'. 5th Edn. Leipzig: Barth, 1896. p.643. Kraepelin, 1904. p.561.

³⁹⁰ cf. Kraepelin, 1913, pp.74–83,1232–1233.

³⁹¹ Kraepelin, 1913. pp.1391–1393 (cf. Kraepelin, 1909. pp.560–574).

³⁹² Kraepelin, 1913, pp.1082–1083, 1130–1131, 1172–1173 (slightly modified compared with the seventh edition, with the addition that 'Ranninger konnte mit allerdings wesentlich kleineren Gaben [von Lithion] (1–1.5g) gar keine Wirkung erzielen—Látrány, der von ähnlichen Gedankengängen ausgeht und die Bildung der Harnsäure einschränken, ihre Ausscheidung befördern will, sucht das erstere durch eine Mischung von Colchicin und Chinasäure, das letztere durch Lithiumgaben zu erreichen; er erzielte mit diesem "Epuratin" genannten Gemisch sehr befriedigende Erfolge').

³⁹³ Binswanger O, Siemerling E.(eds.): 'Lehrbuch der Psychiatrie. Dritte vermehrte Auflage'. Jena: Fischer Verlag, 1911, p.66 (also in 1920 edition, p.68). cf. Binswanger O.: 'Die Hysterie'. Wien: Hœlder, 1904. pp.55–58.

³⁹⁴ Kraepelin E.: 'Klinische Psychiatrie'. Erster Teil. Neunte, vollständig umgearbeitete Auflage. Leipzig: Barth, 1927. p.308.

³⁹⁵ Anumonye A, Reading HW, Knight F, Ashcroft GW.: 'Uric-acid metabolism in manic-depressive illness and during lithium therapy'. *Lancet* 1968;1:1290-1293. cf. 'Uric acid and the psyche (Editorial)'. *JAMA* 1969;208:1180. Johnson, 1984, op. cit., p.33. Schäfer U.: 'The importance of lithium in medicine. A historical review and modern therapy conception'. Proceedings of Satellite Symposium on Lithium 12 October 2005, Athens, Greece. pp.42–52.

³⁹⁶ Kraepelin E.: 'Manic-depressive insanity and paranoia' (translated by R. M. Barclay). Edinburgh, 1921.

³⁹⁷ Jaspers K.: 'General Psychopathology' (translated by J. Hoenig and M. W. Hamilton). Manchester University Press, 1963 (1959, 7th Edn):p.521 (German edition (8th), 1965, p.437): Jaspers cited Luxenburger to the effect that siblings of schizophrenics succumb to tuberculosis four times as frequently as siblings of non-schizophrenics, whereas in manic-depressives there is no relation to tuberculosis but to gout, obesity, and rheumatism.

³⁹⁸ The presumed association between gout and (high, higher) social status and achievement in the 1960s led to comparative studies of uric acid levels, as related to achievement, occupation, and individual personality traits. The outcome of these investigations supported such an association (cf. 'Uric acid and the psyche (Editorial)'. *JAMA* 1969;208:1180).

³⁹⁹ Fitcher TB.: 'The occurrence of gout in the United States'. *Practitioner* 1903;July:6-16.

⁴⁰⁰ Luff, 1898, 1907, op. cit.

⁴⁰¹ Atsmon A, De Vries A, Frank M, 1963, op. cit.

⁴⁰² Daniels AL.: 'The influence of lithium and atophan on the uric acid excretion of a gouty patient'. *Arch. Int. Med.* 1914;3:480-484.

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