

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 6. Carl and Fritz Lange. The theory of periodical depressions  
& ‘the old Danish lithium treatment’**

According to Erik Faber, in Denmark ‘periodical depression’ was the most frequently diagnosed manifestation of uric acid diathesis, more so than in other countries.<sup>183</sup>

The proponents of this intriguing conceptualisation were the neuropathologist Carl Lange (1834–1900), famous for his contribution to the so-called James–Lange theory of emotions,<sup>184</sup> and his brother, the psychiatrist Frederik (Fritz) Lange (1842–1907).<sup>185</sup> Consecutively, from c. 1874 to 1907, they systematically treated periodical depression with lithium (carbonate), the former in private neurology practice in Copenhagen, the latter at Middelfart Lunatic Asylum, Fuenen.

In 1886 Carl Lange delivered to the Danish Medical Society the speech: On periodical depressions and their pathogenesis, published the same year.<sup>186</sup> A reprint, with a postscript by himself, was published in 1895.<sup>187</sup> A German edition of this work, translated by Hans Kurella,<sup>188</sup> was issued the following year. It was not until 1982 that Amdisen edited a reprint of the (Danish) 1886 edition.<sup>189</sup>

As Johnson and Amdisen pointed out:<sup>190</sup> ‘The 1886 document is clearly an important one, containing as it does the first unequivocal account of prophylactic drug treatment for an exclusively psychiatric—as distinct from physical—condition, and establishing Lange as one of the most significant forerunners of the modern era of lithium therapy’. Haenel, in 1986, also praised Lange’s contribution.<sup>191</sup>

The following year, Felber published a paper aptly entitled: Lithium prophylaxis of depression 100 years ago—an ingenious misconception, highlighting Lange’s ‘ingenious’ observations.<sup>192</sup> In 1996 followed Felber’s centenary reprint of Kurella’s edition with a foreword by Mogens Schou and himself.<sup>193</sup> It was in this work that Felber characterised Lange as ‘the first ever biological psychiatrist’.<sup>194</sup>

Considering Lange’s now classic depression treatise to be not only a masterly, unsurpassed nosography of endogenous depression, especially its milder forms, but also

a landmark in the history of lithium therapy, Schioldann rendered an English translation of the work in 2001, accompanied by an account of the early history of lithium therapy.<sup>195</sup>

### **Excerpts from Carl Lange's depression treatise**

According to Lange '[...] It is about an extremely frequent, often most serious form of illness which strangely enough has almost completely escaped any notice in the literature'. In fact, he went on,

The disease that in my announcement of this speech I have described as periodical depression is of such common occurrence that in my private practice, with which I have been occupied for a number of years, there is no other form of illness that by far occurs as frequently. Even the most common neuroses, such as epilepsy, hysteria, all the various forms of neuralgia taken together, are by no means nearly as frequent. It is therefore that over the approximately twelve years during which I have particularly focused my attention on this disease, the material of my observations has grown to at least seven to eight hundred cases [...] My experience shows beyond any doubt that the condition, at least in this country, is extremely common.

'As is suggested by the name that I have chosen for it, the illness manifests itself in distinct periods, of very varying duration and intensity'. 'In reality, there is no other difference between the condition described here and what is usually described as sorrow other than the latter has a psychological basis which [...] the depression lacks, or at least does not to a degree adequate to fully account for it'. 'One cannot help getting the impression from these patients that the protoplasm in their brain cells has really congealed so that their molecular transformations, which are basic to mental activity, require an unaccustomed, at times impossible, impulse to occur. This feeling that 'all has stiffened' in them results, of course, in the lack of spirits and joie de vivre which is their constant complaint'. 'Sleep is often disturbed, broken by anxious dreams, and at times insomnia becomes a very tormenting symptom [...] Awakening is then all the more painful as the early morning hours in the predominant number of cases are the most tormenting part of the day. The feeling of misery and anxiety [...] at these hours reach their highest degree, gradually abating during the day, in particular towards evening to the extent that the condition can be almost completely normalized later in the evening. This morning exacerbation and evening remission are extremely characteristic and very pronounced in well over the half of the cases [...] Appetite is in many cases only moderate [...] I shall later return to question of the urine to which I attach crucial importance in the understanding of the pathogenesis of the illnesses'.

Lange considered periodical depression to be a clinical entity sui generis, first described by himself, and being unrelated to melancholy:

I have followed many of my patients over a considerable number of years and know of accounts of life-long pathological histories involving an even greater number of patients. Yet not a single one of the hundreds of

patients I have had the opportunity to monitor is any closer to melancholia now than when his illness first afflicted him, perhaps thirty or forty years before, and not a single one has developed either delusions or hallucinations [...] <sup>196</sup>

In Lange's view,

There exists no other nervous illness, and very few illnesses at all, and then only such, as we shall learn later, which have a certain pathological affinity to periodical depression, where inheritability has such a decisive significance as for the illness with which we are concerned here [...] Depression is inherited, it seems, equally from the father or the mother.

As to the pathogenesis of periodical depression, Lange stated:

From the first, when experience taught me in periodical depression to recognize a peculiar form of mental illness and I thus started to separate out patients with this picture as a particular group I became struck by how often I received from these patients the unsolicited message that they were suffering or had suffered from 'gravel', an expression which among lay people usually means nothing else but the well-known 'sedimentum lateritium' [brick-dust] in the urine. When, as a result of these indications I systematically started investigating the patients' urine [...] I soon found that this was really the case, and that there was generally a strong tendency in them to pass urine containing an abundant, often colossal, sediment of urates and uric acid proper.

Comparing these patients' urine with that of other patients, Lange found 'the difference has been extremely striking'. On the other hand, 'I dare say with the greatest certainty that

depressed patients generally, both in their sick periods and outside them, have a tendency to pass a strongly sedimentous urine even when at random common causes for the production of uric acid deposits are not present.

But still, Lange emphasized, 'no matter how certain and decisive this fact is, I need not mention that in itself it teaches us absolutely nothing as such about the pathogenesis of periodical depression'. Expanding on this view, he added that

although the constant tendency of the urine to deposit uric acid sediment can be considered proof that there is an ample production of it in the organism or its metabolism insufficient—and there is hardly any reason to doubt this—in no way is it certain that uric acid diathesis is the cause of periodical depression, and although there is no doubt that there is in one way or other a relationship between the two phenomena, a priori, this can be assumed to have been of a very different nature.

One possibility Lange saw was that 'the abnormally high blood uric acid content - "the uric acid diathesis"—directly affects the central nervous system structures and causes a modification of their function'.

It was within this presumed association, if not causation, that Lange saw prospects of treatment.

Therefore, if we dare rely on the assumption that states of depression, when they occur in the form and with the course, that I have described here, bear testimony to the presence of uric acid diathesis, and that they must be understood as effects of this diathesis, to which the predisposition, as a rule, is inborn, this provides the basis for a rational treatment of the depression, a treatment which extends somewhat further than the exclusively symptomatic treatment or expectant or restrictive regime with which the mental illnesses usually have to make do. It is certainly true, however, that the rules for the rational treatment so far can only be given in the crudest outline. It is not yet possible to get closer to the matter than to the establishment of this general direction: to counteract the underlying diathesis. This is what we are limited to as long as we do not know anything about the way in which the diathesis affects or harms the nervous system.

However, Lange was inclined to believe that ‘the blood pathology’ causes ‘intoxication of the brain cells’ or ‘vasomotor disturbances’ as he had suggested in his famous treatise on emotions (1885),<sup>197</sup> resulting in ‘a spastic lack of blood, a certain degree of collapse which is the basic somatic problem in the patients’.

Although not knowing the exact underlying cause of periodical depression, ‘the treatment that I have already been using for a considerable number of years in cases of periodical depression’, Lange added, ‘has primarily consisted in the battle against uric acid diatheses. He did not make explicit mention of lithium, but the alkaline treatment method, which at that time generally included lithium salts, was implied.

It would be needless to give a special account of the remedies that I have applied in this regard, for I would not be able to communicate anything to you that is not well known to all of you. Indeed, you know as well as I do that the task is not only with medicaments to facilitate and accelerate the excretion of the uric acid but to an even larger extent it must be the task to prevent its abundant production by dietary measures, and, finally, where there exists such a tendency to overproduction, by means of those remedies that we generally have at our disposal to accelerate the oxidation processes of the body, in order to increase its metabolism.

Importantly, the treatment should be administered not only during acute phases of the depression but, Lange stressed, also long-term as a prophylactic measure:

There is one thing that I never neglect strongly to impress upon the patients as well as those around them, namely that the matter in question is neither a temporary measure nor a short-lasting treatment, but that the patients for the rest of their lives or, in all events, for a number of years must adjust their whole lifestyle to counteract the morbid predisposition that they carry. When the uric acid diathesis is inherited it is based on peculiarities in the structure of the organism about which we have but very incomplete knowledge, but about which we do know that we are unable to remove them,

and that we must simply be satisfied when we are successful in neutralizing their effects. Of course, in far too many cases it is impossible to engender in the patient and those who are associated with him, the admittedly not insignificant amount of energy and perseverance that is necessary for the carrying out of such permanent measures.

Or, as Lange expressed in another work,<sup>198</sup> ‘in accordance with my pathological theory, I always seek to make it clear to the patients that the treatment ought not be limited to the sick periods, but that also as prophylaxis it is just as important in the healthy periods’ (emphasis added).

As regards his treatment principles, Lange eloquently countered future criticism:<sup>199</sup>

Gentlemen, if you were now to ask me what results I have had with this therapy, whose fundamental features I have described here, you would put me into a very difficult situation, for it is in the nature of the matter that the therapeutic results, in all events, in no way are so striking or conclusive that they could not be disputed. As I have already stated, the issue cannot be to eliminate or to cure the inborn predisposition, which is fundamental to the illness, but only to counteract its effects. If treatment is ceased, be it dietetic or medicinal, these effects recur, even if for some time one has been successful in removing them. However, as regards the therapy, how can one decide whether one has achieved any influence on the course of the illness, whose changing pattern in itself is so irregular and unpredictable? After an usually unpredictable duration of morbid periods they improve spontaneously, independently of any therapy. Also the free intervals are of indefinite duration such that it is not easy to determine whether the treatment contributes in extending them. As for the course, variation occurs with respect to the intensity of the illness [...] Therefore, apparent effects of treatment in this regard also become disputable. Along with this, as it is obvious that it is usually impossible in the course of time—often years—accurately to control the patient in terms of his compliance with the imposed measures, one can easily understand that it is not possible to draw up anything that has the merest resemblance to statistics concerning the effects of the treatment, and that one must make do with a subjective estimate [emphasis added]. Therefore, I shall confine myself to a few brief remarks. Over the course of years I have arrived at the conviction, which has its best support that it is shared by a great number of patients, that it is possible, at any rate in younger persons, and in not too severe cases, to shorten and alleviate significantly the sick periods and to prolong the free intervals by means of a therapy that has had its indications pointed out earlier, whereas it is not possible to completely cure the illness.

At the time of writing his depression treatise, Lange would without any doubt have been current with what had been written in the international literature on uric acid diathesis<sup>200</sup> and the applied treatment methods, including lithium salts. His erudition was legendary. Moreover, he was a highly experienced editor, who from 1880 to 1885 introduced each annual volume of the Danish medical journal *Hospitals-Tidende*, with a yearly synopsis, *annus medicus*, of current events in medicine—national and

international, topics of the day etc. From a footnote he added to the postscript of his depression treatise in 1895, one must also conclude that he was also au fait with American medical journals.<sup>201</sup>

The direct incentive for Lange to publish his observations on periodical depressions and their treatment might have been the discussions at the London Congress in 1881, and perhaps, ultimately, in response to Müller's paper<sup>202</sup> presented at the Copenhagen Congress three years later.

Lange was eager to point out that his pathogenetic interpretation of periodical depression had probably not been advanced previously, as it 'has not [...] been put forward as a nosological entity, [and if so] only as a tentative hypothesis'. He conceded that he had not attached great importance 'to tracing every statement concerning this matter that might have been dropped in passing from some author's pen'. However, he would not exclude the notion that he had 'overlooked something, although hardly anything of significance, as for a number of years [...] I have paid attention to other observers' statements which might support my point of view. [But] unfortunately, my endeavours have yielded very little indeed'.

Despite this statement, Lange was 'convinced that significantly more than half of the uratic patients, at times, are more or less depressed'.<sup>203</sup>

Attention should also be drawn to the fact that Lange did not endorse the view that 'the arthritic diathesis may cause mental illness'—'it is emphasised that it is the sudden suppression of an attack of gout that is succeeded by an outbreak of insanity', but 'whether this can be cited in support of what has been claimed in my point of view is obviously doubtful', Lange stressing that

It gains more support from a statement by Maudsley who in his renowned book on mental illnesses [to be discussed later] concerning their aetiology, after having emphasised 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 melancholy get cured with an efficient treatment of gout.

To this Lange added that Huchard had stated in 1882 that among cases of neurasthenia, in Lange's words, one would certainly find many cases of periodical depression that, as a rule, developed on an arthritic soil.<sup>204</sup> Huchard did not mention lithium treatment.

Lange also mentioned Arndt<sup>205</sup> who, in his treatise on neurasthenia, expressed 'a kinship' between this condition and arthritis, and even rheumatism.

Lange (and his brother) did not mention Garrod's famous work as an inspirational source, nor his introduction of lithium into the treatment of afflictions such as gouty mania.

Importantly, mentioning mania, in Lange's experience, between the episodes of periodical depression there never developed states of mania—'the slightest sign of elevated periods'- which 'could place the whole illness within the sphere of the cyclical forms of insanity'.<sup>206</sup>

With respect to this issue it must be emphasized that Lange was more than well acquainted with the symptomatology of mania.<sup>207</sup> One of his patients (1897), for instance, manifested ‘stuporous depression’ alternating with ‘maniacal exaltation’, concurrently with ‘a considerable amount of uratic sediment’. This patient responded to a course of alkaline treatment such that it made Lange wonder whether he should draw ‘uratic periodical mania, the non-circular forms’, to the attention of the psychiatrists; not that he wanted ‘to intrude on them’, but because he himself had ‘too little psychiatric experience’!<sup>208</sup>

Similarly, Lange made reference to a colleague, Kragelund, who the year before had published a paper on atypical forms of uric acid diathesis.<sup>209</sup> It contained a case vignette of a lady who had manifested

unmotivated exaltation with incessant talking and laughter, jumping from one theme to the other [...] At one moment she is incessantly talking, the next lamenting and tearful, unreasonable [...] to the highest degree [...] Such a state can last weeks and months and is replaced by an apparently completely normal period.

Kragelund prescribed Vichy water, but made no mention of lithium.

## **The introduction of lithium into Danish medical literature**

The first mention that the present author has been able to retrieve from the Danish medical literature of lithium’s entry into *materia medica*, was from 1863. This occurred in *Hospitals-Tidende* (Copenhagen),<sup>210</sup> to the effect that Garrod had given lithium the leading place in the treatment of uric acid diathesis.

As medical students the Lange brothers would have been taught therapeutics by O.L. Bang, who in 1852 authored the first Danish textbook of internal medicine, reprinted in 1869.<sup>211</sup> In this work, consistent with old tradition, dietary measures, mineral water and alkaline remedies were recommended for gouty conditions, such as *dyschaemia arthritica* and *dyschaemia lithica*. These conditions, according to Bang, could cause *hyperdynamia nervosa*.

More generally, the solubility of kidney stones with lithium salts were discussed ten years later in papers by Budde and Madsen.<sup>212</sup>

## **Carl Lange’s lithium prescription**

From Lange’s comprehensive epilogue to the 1895 reprint of his depression treatise we learn that nothing had changed in his views regarding periodical depressions.

Although my observation material has grown very considerably during the almost ten years, which have lapsed since the first edition of my treatise [‘now approximately two thousand patients’], I have virtually nothing to change in my description of [periodical depression] or in my view of its pathogenesis [...] As far as I am concerned I can only state that the very considerable amount of new experiences made since the appearance of my treatise have fully confirmed the correctness of my theory on the relation between periodical depression and uric acid diathesis [...] Haig in England has accepted my view of the periodical depressions as one of the manifestations of the uric acid diathesis.’<sup>213</sup>

But, as before, Lange did not mention lithium explicitly.

Firm evidence that Lange prescribed lithium can be found in an article he published in 1891 on idiopathic pruritus,<sup>214</sup> which he assumed was caused by uric acid diathesis: Bicarb. Natr. c. Carb. Lith was prescribed. In a work from 1897, Contribution to the clinic of the uric acid diathesis,<sup>215</sup> which contains twenty-five case vignettes with a variety of symptoms - including a couple of cases with periodical depression - assumed caused by uric acid diathesis, Lange included the following prescription noted in figure 1.

A similar formula, *Mixtura Gentianae Lithica*, was also included in the Copenhagen Hospital Formulary of 1913.<sup>216</sup>

This formula would yield a daily dose of 11.86 mmol of lithium (equalling 81.83 mg; 460 mg of lithium carbonate), estimating one tablespoon at 15 ml, in accordance with the Danish Pharmacopoea.<sup>217</sup> Felber, on the basis of Garrod, whose lithium doses ranged from 1 to 5 grains, 2 to 3 times daily (5 to 25 mmol of lithium daily), and contemporaneous German pharmacopoeas, estimated that Lange's lithium regime ranged from 8 to 40 mmol daily.<sup>218</sup> In the estimate of Amdisen, it ranged from 5 to 25 mmol daily.<sup>219</sup>

Bicarb. natrici		20 Gram.
Carb. Lithii		
Extr. Gentianae	aa	2 Gram.
Aq. destill.		250 Gram.
d[etur] s[ignetur]	1 tablespoon	q. i. d.

**Figure 1.** Lange's lithium prescription, as it appeared in 1897.

Johnson commented that 'if Lange followed Garrod's prescription, as seems likely, he will have used doses similar to those employed in the early days of lithium treatment for affective disorders'.<sup>220</sup> In his foreword to Felber's 1996 reprint of the German translation of Lange's depression treatise, Mogens Schou wrote that the Lange brothers used lithium carbonate in high enough doses to achieve serum concentrations comparable to those of today.<sup>221</sup>

At times Lange added alkaline spring waters, e.g. Salzbrunner Kronenquelle and Vichy water, to his regime.<sup>222</sup> One litre of mineral water contained approximately 1 mEq of lithium.<sup>223</sup>

Final proof that Lange made implicit reference to lithium in his 1886 treatise is found in an anonymous letter from 'an old medical practitioner'<sup>224</sup> to Ugeskrift for Læger (Copenhagen) in 1901:

Perhaps Dr. L. [Levison] will be surprised to hear that there really are a number of rather sensible doctors who are not certain what to believe concerning this ['mystical' uric acid] diathesis, and Dr. L. will probably recall that when Prof. Lange presented his view of the matter as an explanation of his treatment of many people with lithion etc., one had the feeling that his documentation was extremely insufficient, and that his usual sharp critical sense appeared to have become blunted. The illness described was well known to us under other names, and our insight into the nature of the illness and its treatment probably did not advance significantly by the new name [periodical depression]. [emphasis added]

### **Fritz Lange's inclusion of lithium therapy in his psychiatric textbook, 1894**

Fritz Lange's textbook of psychiatry, *The most important group of insanity* (1894), possibly contains the first explicit mention of systematic lithium treatment of periodical depression. His case material consisted of patients who had required admission to a psychiatric hospital: Middelfart Mental Asylum at Middelfart.<sup>225</sup> It has also been mentioned by Amdisen and Johnson.<sup>226</sup>

Making reference to his brother's depression treatise, Fritz Lange included a case vignette with which to illustrate 'the strikingly prompt and unequivocal effect that a treatment, ['carbonas lithicus'], which is directed against the uric acid diathesis, has had on the psychosis': 'a kind of auto-intoxication'.

A farmer, forty-nine years of age with no known predisposition to insanity. His health had always been good. At the age of twenty-three, he experienced a period of melancholy, lasting six months. After some psychological stress, in 1888, he started experiencing a melancholic mood. He was able to continue working until one day he suddenly developed agonizing lumbar pains, followed by regular occurrence of gravel in the urine. He recovered spontaneously, but at Christmas tide melancholic features recurred. For no apparent reason he became irritable, agitated and suspicious, and violent toward his wife, whom he allegedly threatened to kill. He had attempted to hang himself, but his wife managed to 'cut him down' in time. He found his own behavior to be 'unreasonable and meaningless', and felt that he was possibly 'possessed'. Throughout his illness period he complained of headaches.

On 20 March 1889 he was admitted to the 'Middelfart Asylum'. On admission he was correctly oriented and calm. He showed features of agonizing melancholy, and he complained of pain and sensations in the head, which, he said, had made him quarrelsome towards his wife. Delusions were not elicited, but slight auditory hallucinations, 'like a whistle tone or bird song'. He had insomnia and lack of appetite.

A rather copious amount of urinary calculi was observed. Therefore, on 24 March 'treatment with Carbonas lithicus was instituted [emphasis added], and already on 28 March he expressed that he felt better'. On 30 March, his mood

was again more depressed; but from the first days in April, his condition improved evenly and rapidly. He ‘felt so light’, his sleep, appetite and mood gradually normalised, ‘and he could not quite understand how he could have been so depressed before’. ‘Concurrently, calculi vanished from his urine. Three weeks after admission he could be considered cured, but he remained admitted for some time to continue with his treatment, and during this time he showed himself to be a good and energetic worker, whose depression had seemingly blown away’.

Approximately one year after discharge, however, admission to the hospital was applied for again, ‘and his condition then was reported to be of essentially the same kind as described above. Therefore, the Asylum recommended he be prescribed a similar treatment as before, and shortly after he was reported to have recovered. He has not contacted [the Asylum] since’.

This patient most likely suffered from a severe agitated suicidal depression with psychotic features, for which treatment with lithium carbonate was instituted.

Fritz Lange placed emphasis on the presence of various physical symptoms that were considered to be consistent with uric acid diathesis. Concurrent occurrence of ‘copious amounts’ of uric acid sediments was the final diagnostic criterion. His mention of auto-intoxication must be noted.

Other, similar, cases treated by Lange, some of which will be described later, made him wonder whether there were ‘interconnecting threads between three factors such as inheritability, periodicity and uric acid diathesis’. Against the difficulties and complaints that the mechanical accumulation of concrements so often causes, he wrote, ‘lithion, in the form of powder [...] has a good effect’.

Lange’s textbook (written in Danish) was reviewed by Hans Kurella, a well-known German psychiatrist,<sup>227</sup> in *Centralblatt für Nervenheilkunde und Psychiatrie*,<sup>228</sup> the following year (1895). He expressed the opinion that Lange’s thorough description of ‘the psychoses in uric acid diathesis, especially the periodical depressions that occur due to this, would be of special interest to the German reader’. Unfortunately, he ‘could not go into further details in the recension about these very interesting accounts’.

Claes Flach, a former psychiatrist superintendent at the Middelfart Psychiatric Hospital, searched the hospital’s medical records in the early 1980s and retrieved the files of thirty-five depressed patients whom Lange had treated with lithium.<sup>229</sup> It was established that he used ‘dose powders’, the lithium content of which, according to communications from the pharmacist Jørgensen of Middelfart to Flach,<sup>230</sup> it had not been possible to determine. Some guidance may be found in the Danish Pharmacopoea of 1907, which included carbonas lithicus, to be dispensed in doses of ‘50–300 mg several times daily’, either as ‘powder or mixture’.<sup>231</sup> As we shall learn later, in some cases Fritz Lange applied ‘rather vigorous lithium treatment’.

## **Carl Lange’s call for further research into periodical depressions Criticism from his colleagues**

In his 1886 speech on periodical depressions and their pathogenesis, Lange expressed to his colleagues that what had assisted him in overcoming his 'reluctance' to present to them

such an insufficient account is my long and often rather urgent-felt need to make a report to those of my colleagues who have referred their patients of this kind to me, although I have not yet had the opportunity to contact them concerning my view on the nature of the cases and on the indications for their treatment.

Moreover, he stated that he was 'convinced and can fully understand that the advice with which their patients have been returning from me must usually have appeared enigmatic to them, at times even worse than that'. Notwithstandingly, 'I have often longed not only to make clear to these colleagues, who are not few, that I did have a definite opinion and plan concerning my prescriptions, but even, if possible, to win them over to my views'.

As he had 'virtually nothing to rely on from previous observers', the more he hoped that his 'understanding of this matter is going to be tested by future investigators'. For, in all events, he dared expect that

the remarks that I have had the honour of presenting here [the Medical Society of Copenhagen] tonight, no matter how imperfect they may be in more than one regard, may contribute to drawing the attention of my colleagues to a very serious, very frequent and very neglected form of illness[!]<sup>232</sup>

Steenberg<sup>233</sup> and Pontoppidan,<sup>234</sup> both leading contemporary Danish psychiatrists, were critical and skeptical in their respective reviews of Lange's depression treatise. They especially queried his separation of depression from melancholia, emphasising that what he described were but mild cases of melancholia: melancholia simplex, melancholia sine delirio, melancholia in optima forma.<sup>235</sup>

Steenberg asserted that 'Prof. Lange's theory has attracted great attention among Danish doctors, and I am certain that it will attract no less attention among doctors abroad once it becomes known to them'. He did not mention medicinal aspects, but emphasised that he agreed with Lange with regard to psychological treatment aspects 'with which we until further have to make do'.

Pontoppidan, for his part, strongly disagreed with Lange concerning psychological treatment but, like Steenberg, he did not mention medicinal aspects. Importantly, he criticized Lange for his relying only on 'uroscopic' rather than proper quantitative investigations, 'without which the Lange hypothesis lacks its necessary foundation'. Pontoppidan found it 'deplorable', though, that none of the 'younger doctors' had become inspired by Lange's hypothesis. But he felt that Lange himself was to blame for this, as he had 'generalized too strongly, and that he has wanted to lay down as facts what hitherto is only an attractive hypothesis.'

An outspoken critic against Carl Lange - in whose criticism some professional jealousy cannot be excluded - was another countryman, the physician Ferdinand Levison,

an expert on uric acid diathesis. His main work on the topic, published in 1893, appeared in English translation the following year.<sup>236</sup>

In this work Levison related that ‘the Danish author Lange has also contributed valuable information on the symptomatology of the uric acid diathesis.’ He went on to describe cases of children in whom ‘A symptom almost as constant as pain is the sudden onset of unaccountable indisposition, tiredness, and depression, which may advance to a state of complete melancholia [...] A similar great depression has been shown by Lange to occur in adults’, Levison making reference to his 1886 depression pamphlet. He then expanded on his views as follows:

Lange has, moreover, collected a number of observations, which show that the uric acid diathesis is able to occasion a peculiar mental affection, showing itself by periodic states of depression, without hallucination tendencies. [The patients] do not lose the ability of comprehending their condition as purely morbid, but they are completely unable to shake off the disinclination and dislike for all things and all people, which makes their existence so unbearable. Along with the depression of spirits there is usually tiredness, some sleepiness, and loss of flesh.

However, Levison was not convinced by Lange’s observations.

Among my adult patients I have seen only in one case a morbid condition accurately corresponding to Lange’s description and this occurred in a patient with mild arthritic symptoms, but with no signs of gravel. I have seen, in three cases of uratic precipitation in the kidney, slight symptoms of periodic depression [...]

Despite Levison’s view, Lange<sup>237</sup> in his postscript to the reprinted edition of his treatise, mentioned Levison as being among the few who supported his views.

Alkalies, Levison<sup>238</sup> went on (also in the English edition), ‘have been recommended as the special medicinal treatment from time immemorial’, and of which he found

The compounds of lithia, the carbonate, the citrate, acetate, benzoate, and salicylate have the greatest therapeutic properties [...] The lithia salts have been recommended, because the urate of lithia is more soluble in water than the other compounds of uric acid.

In turn, Lange<sup>239</sup> was very critical in his review of Levison’s work. Levison<sup>240</sup> reciprocated, strongly criticizing Lange’s treatise. Levison not only recommended the ‘indeed so undefined and vague concept of uric acid diathesis’ be abandoned,<sup>241</sup> he also rejected Lange’s intoxication theory and the diagnosis applied by him: Depression due to Uric Acid Auto-intoxication.<sup>242</sup> Finally, he reminded the reader that Steenberg and Pontoppidan disagreed with Lange’s nosological views of the periodical depressions.<sup>243</sup>

Regarding the aetiology of depression, Levison stressed the view that it was caused by mechanical irritation of the kidneys by uric acid concernments, a ‘reflex neurosis’.<sup>244</sup> Emphasising this theory to be the underlying mechanism in depression, he again dismissed Lange’s work.<sup>245</sup>

Prof. Lange's treatise on the periodical depressions gives a general description of the illness picture as he has perceived it, but the treatise is not accompanied by case histories or case files that would enable the reader to check whether these conditions, which he believes necessarily indicate intoxication, if one looked at such cases from another viewpoint, could be fitted in with the reflex neuroses.

On the other hand, Levison,<sup>246</sup> polemically it would seem, referred to Fritz Lange, not only praising him for having provided a concise delimitation of the forms of insanity—by the latter assumed to be caused by uric acid diathesis—but also for having provided 'a thorough typical case vignette' (his textbook, 1894):

The main proof of the connection between this abnormality [uric acid diathesis] and the psychosis, Fr. Lange rightly seeks in the fact that a treatment [not mentioned explicitly by Levison], which results in the uric acid being excreted in dissolved form, has a remarkably prompt curative effect on the psychosis.

In Levison's opinion, the prompt effect of the alkaline remedies was strongly indicative of an underlying reflex neurosis. Yet he stressed that those of his patients who presented with depression due to abnormal uric acid excretion 'were much more similar to what Fritz Lange had described than the form of depression described by Carl Lange'. He stated that

patients with a tendency to sadness, with periods of depression alternating with well-being, not infrequently with lifted mood and mild exaltation, are known by every medical practitioner, and I have also often observed such cases. However, I have never managed to become convinced that there was a causal connection with uric acid abnormality of any kind concerning the illness of these patients.<sup>247</sup>

What had determined this matter for Levison was the fact that 'a treatment, which eliminated the uric acid crystals from the urine, had been without any influence on the mental state of the patients, even if the treatment was continued for a very long time'.<sup>248</sup> He would label such patients 'neurasthenics if I did not fear to be hit by the anathema that Prof. Lange has enounced over this term'.<sup>249</sup> But 'in contradistinction to this', Levison intriguingly asserted that

there is another group of patients [with] mental depression, usually associated with other symptoms of lithiasis, such as neuralgia of various kinds, frequent urge to urinate and constipation etc., and in whom the urine turns out to contain copious sedimentation of large and sharp-edged conglomerates of uric acid crystals [...] When the depression in these patients is quickly cured simultaneously with all the other symptoms with alkaline treatment, and as long as it does not recur, as long as the patient makes certain that he keeps his urine clear, slightly acid and without concretions, I feel justified in drawing the conclusion that the depression has had the same origin as the other reflex neuroses and being caused by the kidney irritation.<sup>250</sup>

Referring to a couple of his own cases, Levison proceeded to defend his theory of

reflex neurosis or psychosis:

The theory that mental depression is caused by uric acid intoxication cannot be accepted, because it has not been proved that the blood of patients suffering from this depression actually contains more uric acid than in normal individuals. This is supported by the fact that the illness, which according to the theory is the basis for the depression, namely arthritis urica, is not caused by an overproduction of uric acid, and, finally, because results from experimental pathology clearly speak against the view that uric acid has any toxic effect in human or animal blood. This is confirmed by clinical observations [emphasis added].<sup>251</sup>

Levison had found support for this view in experimental works of Roberts, Ebstein and Nicolaier,<sup>252</sup> who had fed rabbits and dogs, or injected them, with large amounts of uric acid intravenously or intraperitoneally with no poisonous effects, either locally or universally. As solvent agents they used piperazine or sodium phosphate. Lithium was not mentioned in this context. According to Clarence Good,<sup>253</sup> who in 1902 carried out experimental animal studies with lithium, the effect of lithium salts in animals had been studied as early as 1867, by Rabuteau.<sup>254</sup>

In Levison's opinion:<sup>255</sup>

the clinical experiences and particularly the result of the treatment strongly indicate that the mental symptoms that occur together with the reflex neuralgias and vanish as promptly and definitely as those [in uric acid intoxication] treated with alkaline remedies have the same origin, and must be considered as reflex neuroses triggered by kidney-irritation due to uric acid concretions. A real periodicity of this form of psychosis has only been observed and described by C. Lange. How the periodicity must be explained, and what role uric acid has in this regard, must probably wait until a larger and more closely described material is at hand to shed light on this question [emphasis added].

Eventually, as Levison put it in a meeting at the Medical Society of Copenhagen in 1894, he had not yet given up hope of winning Carl Lange over to his views.<sup>256</sup>

### **Fritz Lange's aetiological theories: uric acid diathesis – auto-intoxication**

In 1904 Fritz Lange expanded on his aetiological theories in his book *Degeneration in Families: Observations in a lunatic asylum*. Its general subject was mental degeneration (also the topic of his doctoral thesis, twenty years before),<sup>257</sup> of which he was heavily influenced by the teachings of Morel. An English edition followed in 1907.<sup>258</sup>

Lange operated with four different forms of mental degeneracy: the insane, the potatory, the epileptic, and uratic degeneracy. The latter, he assumed, was caused by uric acid diathesis. In recent years, he wrote, 'I have attempted to pursue this phenomenon [uratic degeneration] in all directions across the realm of insanity, where, for a long time, in the form of periodical depressions (C. Lange), it has had a recognized and indisputable place'.

It was on the basis of the doctrine of degeneration that Lange explained mental decline in a number of great or famous families he had encountered, some of whom ending up as patient aristocracies in mental asylums. Some of these patients, he added, had a family history of milder forms of mental illness, e.g. ‘melancholia’, ‘exaltation’, and ‘eccentric behavior’. Suicide had been a rather frequent occurrence. Many of their relatives had held high, academic positions, and they enjoyed high social status—Lange had close contact with many artists and intellectuals in Denmark, and of whom some, when ‘in nervous crises’, would seek his treatment.<sup>259</sup>

Among twenty-eight great families he found twenty-four cases - uratic degenerates - where with certainty he had ‘been able to demonstrate the phenomenon’ of uric acid diathesis causing auto-intoxication. In this instance, he made no mention of treatment aspects, alkaline or otherwise.

### **Viggo Christiansen’s scathing attack on Fritz Lange’s (and thus Carl Lange’s) views**

Still in 1904, Lange’s book received a scathing review by Viggo Christiansen,<sup>260</sup> who was then becoming influential in Danish medicine. Having completed his thesis on the toxicity of urine, especially in insane patients: an experimental study,<sup>261</sup> some years before, he would have been considered an authority in this field. His thesis was inspired, among others, by Bouchard’s work on *les autointoxications dans les maladies et la toxicité des urines*<sup>262</sup> (also in an English edition),<sup>263</sup> topics that, as mentioned, had been presented at the Copenhagen Congress in 1884.

Christiansen conducted more than five hundred experiments, injecting rabbits with urine from psychotic patients. He observed that the urotoxicity, i.e. the convulsant coefficient of urine, was independent of both the patients’ mental state (exaltation, depression, confusion) and their physical state, and that it was due rather to the individuality of the test animals. Not only did he find it to be independent of aetiological factors, but also that ‘the amount of toxins, which are excreted in the urine, is less than under normal conditions’: approximately fifty per cent less. Thus Christiansen felt it justified to dismiss the Lange theory of depression.

Undoubtedly, this critique must be taken into account when one today tries to analyse why Danish psychiatry failed to heed the Lange brothers’ observations and their recommendation as to the use of lithium. As Christiansen stated:

The author [Fritz Lange] has adapted Carl Lange’s postulate of a supposed causal relation between periodical depression and uric acid diathesis, a phenomenon, he claims, ‘for a long time has had a recognised and indisputable place’. However, the real situation is that, apart from a couple of authors, the majority both at home and abroad, who have been studying this question, either deny the connection outright or, although they admit to the possibility of such, state that this is quite unproven.<sup>264</sup>

Further, Lange was strongly criticised, if not derided, for not having provided any information about his investigation method, for

has it, as all points towards, been restricted to his purely macroscopic finding of uric acid crystals or tile-coloured sediment in the urine, then it is quite an unscientific method which means nothing at all. It must really, to put it mildly, be characterised as a much too primitive investigation method, this walking around, peering into the patients' chamber pots, for in this manner to draw conclusions about what harmful substances are circulating in their blood. And this is, in reality, what the author has done. The excretion of uric acid in the urine in no way is proof of the presence of uric acid diathesis. This can be caused by an excess of quite particular salts, it can be caused by the degree of concentration of the urine, its temperature, the patient's diet, and at times it happens that all the uric acid there is in the urine is excreted spontaneously.<sup>265</sup>

Christiansen advised that 'the only way any reliable results concerning the solution of this question can be obtained is to conduct combined systematic blood and urine analyses.' He stated that this is

the only way one can learn whether uric acid is circulating to excess in the body, in other words, whether there really is an intoxication of the body with uric acid. It is deplorable that the author has not followed this path, even more so for the reason that a mental asylum, where the patients' lifestyle and diet can be arranged more regularly than in any other place, and where their stay is long-term, must be well suited for investigations of this kind.<sup>266</sup>

Generally, from 'the medical scientific point of view' Christiansen found the book 'remarkable', for

it is very strange indeed when a doctor thinks he has found the cause of an illness, and this is but one of the forms of manifestation of a whole range of other illnesses for which there exists a rational treatment, that the author not with one word touches on this for the patients so extremely important point. [...] Also here, a lunatic asylum would be one of the places where a dietary and medicinal treatment could be carried out as consequently as in few other places. It would have been of extremely great interest to learn something about how the results of such a treatment would have turned out [emphasis added].<sup>267</sup>

Like Crichton-Browne had argued before that 'many thousands of gouty people never manifested mental disorder',<sup>268</sup> Christiansen 'had no doubt' that Lange

would have been less categorical in his emphasis on the significance of uric acid diathesis for the form of mental degeneration that interests him in particular, had he seen the many cases of gout or podagra which are admitted to a general hospital, without it being possible to detect a single one of the mental peculiarities that distinguishes 'the great families'.<sup>269</sup>

Concerning these great families, Christiansen could not accept the view 'that giftedness of whatever kind, high culture and rare intelligence, or for that matter any high spiritual achievement could be caused by chronic auto-intoxication'.<sup>270</sup> Therefore, he

could not help comparing Lange's book with 'a similar more comprehensive book by the renowned psychiatrist Havelock Ellis', entitled *A Study of British Genius*, published in 1904. 'Also this author', Christiansen wrote, 'has been struck by the relative frequency [...] with which gout occurs in outstanding people'.<sup>271</sup>

Ellis in this 'rather curious book'<sup>272</sup> had taken it further to state that 'these gouty men of genius have frequently been eccentric, often very irascible [...] and occasionally insane'. 'The poison', he said, 'is sometimes in the blood, and sometimes in the joints'.<sup>273</sup>

It should be inserted here that an equally scathing, anonymous review of Lange's book, which appeared in the *Journal of Mental Science* in 1908,<sup>274</sup> not only questioned whether 'the clinical work and the laboratory records referring to toxines have been overlooked', but also placed an emphasis, though ironic, on 'the "aristocracy of mental diseases - the great families" - which would seem to be the dreary remainder [among Lange's four categories]', being 'marked' by uratic degeneration.

Carl Lange, who was of the opinion that some of his patients were among 'our most competent and most outstanding men', did not agree that they could be characterised as degenerates.<sup>275</sup>

It should be added that the Lange brothers were not to know that it was manic-depressive predisposition with which many of the great or famous families were 'tainted', according to Ib Ostenfeld.<sup>276</sup>

With barely veiled caustic Christiansen finished his review of Lange's book, thanking him for his eye-opener:<sup>277</sup>

No matter how much one disagrees with [Lange] on many points, one will always be owing thanks to him for the ability he has to stimulate one's thoughts and for the intrepidity with which he opens up the view to new viewpoints and new paths.

Christiansen reiterated his dismissal of the Lange theory of depression in his *Clinical Lectures on Insanity*, two years later, in 1906.<sup>278</sup> He had now analysed the blood and urine of three patients suffering from 'typical periodical depression', but without finding any uric acid abnormality. However, consistent with Kraepelin's epoch-making psychiatric classification, in 1899, he had regrouped 'periodical depression' with manic-depressive psychosis, thus, in a way, removing the Lange-diagnostic criterion of uric acid diathesis.

### **Fritz Lange's 'rejoinder' to Christiansen: His lithium therapy casuistry**

Lange eventually answered Christiansen's stinging review with a thirty-page article, *Uratic Insanity*, published (in Danish only) in 1908;<sup>279</sup> He, Lange, had died three weeks before, in December 1907. He refrained from making any mention of Christiansen's name, but the address was clear. He also took the opportunity to respond to the criticism that had been more generally levelled at his brother, who had died seven years before, in 1900.

Lange illustrated his own views with ten case vignettes, of which seven provided details about the treatment with lithium he prescribed - the dose range excepted.

Furthermore, we learn that this was the ‘general’ treatment for periodical depression (‘uratic depression’) at Middelfart Mental Asylum.

This article was probably ignored by Lange’s contemporaries, only to fall into oblivion. It was first retrieved in connection with Schioldann’s earlier studies in the history of lithium.<sup>280</sup> It sheds crucial light on ‘the old Danish lithium treatment’ and must be considered a key document in the history of lithium treatment alongside Carl Lange’s depression treatise.

Fritz Lange opened the article by announcing that it was very rare that new disease entities were included in the Annual Reports from the Danish Mental Asylums,<sup>281</sup> but

over the last decade, the Middelfart Asylum in the aetiological section of its Annual Report has included uratic insanity as a constant number, although it is not particularly great. However, it has not escaped my attention that the same doubt that in so many ways is being raised concerning this illness, is also being raised towards our specifications, and I have, therefore, found it proper with a small casuistic material to substantiate the Asylum’s information and explain its diagnosis.<sup>282</sup>

Lange also pointed out that his view of the matter ‘essentially confirms the previously by the late Carl Lange presented teachings of the periodical depressions’.<sup>283</sup> He was possibly also referring to the statements made by Levison,<sup>284</sup> stating that

If there here and there, concerning details, is some divergence between his [Carl Lange’s] and my view and presentation, then this is probably caused by the difference between our areas of work. He based his teachings on a very rich material of a more outpatient character, generally milder cases such as they occur in life in general, whereas I have worked with a much more limited material which virtually consisted of patients whose sufferings were of a more intense character. They understandably sought the Mental Asylum because it was overwhelming for them to carry their sufferings on their own shoulders. It is only a matter of difference in degree, therefore, but not in essence that there exists between Carl Lange’s and my material.

Lange deemed it necessary by means of ‘short excerpts’ to ‘present my casuistic material in the way that it has appeared to me over time, and which I have thought I could not disregard’.<sup>285</sup>

This material is likely to be describing the first systematic use of lithium, the carbonate salt, in the acute treatment of mood disorders; the patients being at times very disturbed and suicidal, thus requiring admission to a secure ward in a mental asylum, Middelfart Mental Asylum. It is important to note that the Lange brothers advised against the use of bromides.<sup>286</sup>

Unfortunately, I have not had the opportunity to sight the thirty-five Lange case files retrieved by Flach,<sup>287</sup> nor have I had the opportunity to sight the case files of a number of Lange’s patients, subsequently indexed by Laigaard.<sup>288</sup> Therefore, I have not been able to establish whether Lange’s case vignettes (quoted later) form part of them.

Together with the case vignette that Lange included in his textbook, these case vignettes can be considered an essential supplement to his brother's depression treatise, which does, as correctly pointed out by Levison, lack case material.<sup>289</sup> However, it must be emphasised that Carl Lange was mainly focusing on the nosography, nosology and pathogenesis of periodical depressions, rather than the specifics of their medicinal treatment.

The description Lange provided was mainly based on his observations of patients admitted to Middelfart Mental Asylum, 'where, as a rule, only people with a certain social position and importance come',<sup>290</sup> in accordance with what he had written in his 1894 textbook regarding 'uratic degeneracy'. They were often members of families in which there generally was a 'rather significant' prevalence of 'melancholic and irritable natures', and suicide among them was not rare.<sup>291</sup> The patients, Lange stated, are prone to mood swings: melancholy, exaltation, and phases of normal equilibrium, but with a predominance of melancholy, 'attacks of depression'. The patients themselves and their relatives, he emphasised, neither understand nor can explain 'the occurrence of constantly recurring mood swings'.

When not depressed, the patients would often be sanguine and optimistic; when depressed, some of them would be seized by doubt and lose their self-confidence. 'The same kind of thoughts, doubts, keep occurring during the constantly recurrent periods of depression', at times accompanied by suicidal thoughts.<sup>292</sup>

The readership was also reminded that Lange was referring to severe cases with a prolonged course 'as they occur in the Middelfart Asylum'. It was a 'striking' experience for Lange to see the feeling of 'relief and liberation' in some of these patients when their depression remitted. To illustrate this he recounted the case of a young woman from his private practice, who 'shortly after the treatment [not specified by Lange] had been established', exclaimed: 'Oh, it is like coming from a dark cellar back into daylight again'.<sup>293</sup> In another patient he observed that an 'abrupt transition' had affected the man's brain function particularly strongly and thrown him 'into a transitory switch to exaltation being much more noticeable than the euphoric lift of mood one usually encounters when the depression remits'.<sup>294</sup>

Lange frequently observed that his depressed patients were also suffering from physical symptoms,<sup>295</sup> although these were 'often of an extremely vague and varying nature'. He wrote that 'it is always the depression, the psychic torment that the patients remember'. The physical symptoms mentioned were 'pressing sensations' in the head, cardiac palpitation, autonomic instability (that is, sensations of hot and cold) and finally, pain from the kidneys caused by the excretion of urinary uric acid concernments.

'As criterion for periodical depression, I shall limit myself exclusively to the excretion of unquestionable uric acid crystals in the urine', Lange stated.<sup>296</sup> This was what Da Costa apparently did. Lange wished to refrain from further theoretical considerations of the matter. As he had stated in his 1894 textbook,<sup>297</sup>

in a small number of cases of this kind it has been possible to demonstrate the presence of uric acid diathesis, and a contra-verification of

the connection between (melancholy and periodical depression) is not unlikely to have been observed in the remarkable prompt and unequivocal effect of (lithium) aimed at the uric acid diathesis.

Retrospectively, Lange's description of his patients' psychopathology can leave no doubt that they were suffering from manic-depressive illness. As Ostenfeld pointed out many years later,<sup>298</sup> Lange was on the right track from the viewpoint of heredity, that in these patients, uratic degenerates, there was a confluence of manic-depressive predisposition.

Lange included ten case vignettes (i-x) in his article, in seven of which (1-7) lithium carbonate was prescribed.

**Case Vignette No. 1 (ii)** concerned an agriculturalist, forty-three years of age.<sup>299</sup> Lange noted the recurrent nature of his psychopathology and the apparent prompt response to lithium carbonate:

He had always been very mood swinging and sensitive. At the age of twenty, he had a brief but more pronounced attack of depression, and again eleven years later. Between these episodes he had 'numerous fluctuating depressions' with a seasonal tendency. The patient himself had noted concurrent presence of dark-coloured urine. In all, he was admitted to Middelfart Asylum three times. During his first admission, treatment with 'mixt. carbonatis lithici' [emphasis added] was instituted, as his urine contained uric acid crystals. His condition 'improved quickly' such that he could be transferred to an open ward, and finally, six weeks later, discharged as cured. During the following years, he constantly experienced 'the same mood swings as before, interspersed with regular periods of depression'.

Five years later, he experienced a relapse of depression, similar to his first attack, and was readmitted. 'Mixt. carbonatis lithici [emphasis added] was prescribed at once, and ten days after, the condition started to ease, as it had done during his previous admission' with the result that two months later he was discharged as cured. However, he had 'to toil under his usual mood swings'.

One year later, he again required admission as he had become 'idle, insomniac, filled with the old hypochondriacal ideation and was very preoccupied with suicidal thoughts'. 'His urine was very acid with sharp and very red sediments'. After a couple of days, 'Mixt. carbonatis lithici [emphasis added] and distilled water' were prescribed as before and 'the condition improved quickly'. After a stay of two to three months, 'he could again be discharged as cured'.

**Case Vignette No. 2 (iv)** was that of a lady in her fifties,<sup>300</sup> who was given 'rather intensive treatment':

Her father was extremely hypochondriac, and her mother 'always very nervous, in her older years insane'.

‘Nervousness, insanity, and degeneracy [had been] pronounced in her family for generations’. Since youth, she had been a hypochondriac, strongly given to many and varying sensations which often influenced her mood, whereas, at other times, she could be ‘merry and happy with life’. By and large, she had very fluctuating and ‘jumpy’ moods.

During a prolonged menopause her condition worsened. Particularly during the last year before admission to hospital she had felt very agonized, experiencing a range of accompanying somatic sensations, and later, mental unrest, failing memory, a feeling of vertigo and sensations of cold in the head, leading her to believe that it was a stroke.

On admission she was correctly oriented but had great difficulty in collecting herself in conversation. She was extremely preoccupied with her many hypochondriacal complaints and misinterpretations. Her mood was ‘strongly excited and anxious’.

Three days after admission her urine was blurred by urates, and on the tenth day she excreted a copious amount of dark-colored crystals. ‘Mixt. carbonatis Lithici’ [emphasis added] was prescribed, which, the patient thought, at once brought about good improvement. She was discharged as ‘very significantly improved’.

This case, ‘with constantly recurring mood swings of which both herself and those around her had lacked any understanding and explanation, and with menopausal exacerbation’, had not been diagnosed with certainty, Lange said, until the occurrence of the copious excretion of uric acid crystals. ‘Under a rather intensive treatment [emphasis added], the excretions repeated themselves copiously and during a longer period of time; it was first then that the real and lasting improvement occurred’.

**Case Vignette No. 3 (v)** concerned a farmer, forty-nine years of age:<sup>301</sup>

No family history had been provided. In his younger years, he had been ‘weakly and ailing’, but in his adult years, his health improved. He was sensitive and had some problems with alcohol. Under some occupational stress he had become depressed and apprehensive, felt that he had mismanaged his property and that he had been unable to care for his family. Eventually, he was admitted to the asylum due to suicidal thoughts.

On admission he did not appear to be particularly depressed, and showed no delusions or hallucinations. His urine was clear and acid and without concrements. But a few days after admission, his condition changed completely. He became anxious, complaining, full of worries about his health and insomnia. He was rather preoccupied by sensations such as a ‘feeling of cold’ in the skin of the abdomen, and of ‘burning sensations’ in the internal organs; agonizing insomnia persisted. Already a couple of days after the admission, some red-coloured uric acid crystals had been observed in the urine, but no improvement in his condition occurred, and shortly after, these concrements vanished again. Over the next two months or so, he expressed similar complaints, ‘cold or heat’ in the body. This was followed by an

aggravation of his physical complaints, and his mood became ‘extremely’ anxious and preoccupied. Over the following days, ‘copious amounts’ of uric acid crystals were observed in his urine, concurrently with the same complaints of feeling too cold or too warm. ‘Now, Mixt. Carbonat. Lithici [emphasis added] and distilled water were prescribed’ — ‘his mood improved quickly and noticeably’; he became more active and wrote ‘good and hopeful’ letters to his family, and enjoyed their ‘visit’. His sleep and bowel motions improved. Eventually, he could be transferred to an ‘open and free’ ward, and one month after the last excretion of uric acid concrements ‘all the old worries and the hypochondriacal sensations were forgotten’. However, as ‘the same somewhat sensitive and easily roused mood, which was habitual for him, was manifested at times, he was not unwilling to prolong his stay for a while’. On a subsequent visit, his family had found him deteriorating, whereas in the presence of his doctors, he ‘kept calm and natural’. Subsequently, he took his own life by hanging, leaving an incomplete farewell letter, saying that he was either ‘too cold or too warm’, ‘could not get his natural sleep back, and that he would become a burden to his family’.

The patient’s sensations of being ‘too cold or too warm’ and other physical complaints, were consistent with what Lange had observed in some of his other ‘uratic’ patients.

**Case Vignette No. 4 (vi)** concerned a businessman in his late thirties.<sup>302</sup>

He was heavily predisposed to kidney stones and gravel. There was also a strong family history of eccentricity, insanity and one case of suicide.

Since early youth he had been prone to melancholic periods associated with obsessional thoughts, at times very tormenting. Currently, under some professional stress his obsessional symptoms had reached ‘a previously unknown height’, such that he found life ‘unbearable’. His thoughts increasingly revolved around homicide, especially towards his own children, but also towards others. On admission, he was calm, cooperative and collected, but melancholic and very tearful. He had insight into the morbidity of his obsessional thoughts, but he was fearful of becoming insane and losing control over himself. There were no signs of delusions or hallucinations. His urine was clear and acid, no abnormalities being detected. His mental state remained virtually unchanged over the following months. A course of bromide was administered but with little and transitory effect only. After five months, at times his urine became dark-coloured and unclear, due to urates. Therefore, ‘Mixt. Carbonatis Lithici [emphasis added] and distilled water’ were prescribed. Three days after he commenced the mixture, he spontaneously stated that ‘it had been the most tolerable day he had had here’. Subsequently, his condition was somewhat more fluctuating than before. Approximately five weeks after the commencement of the treatment, ‘a very copious excretion of uric acid crystals occurred’, and during this time he was less depressed, ‘but very irritable and unreasonable, oppositional towards situations which he had put up with before, and very contrary to his habitual

pattern he even instigated trouble among the other patients'. However, he settled quickly and gradually assumed a pleasant somewhat sensitive and easily moved mental state which appeared habitual for him in his good periods. Finally, he was discharged and could return to his business.

Lange regarded this case as typical of uratic insanity: agonising obsessions with associated anxiety, and deep depression. Furthermore, he again wished to draw attention to the attempt at treating obsessive disorder with potassium bromide

which in other circumstances, from the olden times, has claimed its significance; [however] in this case its effects were absolutely transient only, almost like a sort of doping, but quickly showed to be without any effect at all, whereas the lithion treatment, which was not instituted until there was a firm basis for the diagnosis, very soon showed to be of the most beneficial effect.

Lange also emphasised how the occurrence of depression 'with its obsession features and anxiety', was generally followed by a 'transitional phase' during the evacuation of uric acid, and eventually a somewhat irritable mood at times, and finally 'relief and liberation', which could result in 'brief exaltation'.

**Case Vignette No. 5 (vii)** was that of a lady, aged forty-nine.<sup>303</sup> She had been non-compliant with 'lithion' treatment:

Her mother suffered from 'periodical attacks of depression, a sister very nervous'. Twenty-five years before, she had been diagnosed with gravel. Subsequent to giving birth to one of her five children, thirteen years before, she had required admission to the asylum for six months due to 'a very pronounced depressive confusion', but since then she had been well. Currently, she was 'menopausal', and she had developed psychotic depression in the form of melancholy with strong self-reproaches of a religious nature. Over the years, it was revealed, she experienced 'periodical nervous attacks' and, at other times, she was 'difficult and irritable'.

Her own doctors had treated her with 'lithion [emphasis added], boiled water, mineral water, Fachinger water, and so on, but she admits that she never used it except at the very time of her attacks; as soon as they were over, she forgot about it'.

According to her husband, she regularly had arthritis and unclear dark-coloured urine, at other times her urine was clear with brick stone-red gravel, and her depressions were becoming stronger than before.

'During the initial time of her stay here in the asylum, her depression was of a strongly marked, active nature'. She was 'lamenting and complaining and could not at all control her dark religious self-reproaching thoughts'. Furthermore, she could not accept that she was ill, 'it was all sin and disaster'. She was so disturbed that she could hardly be with other calmer patients. Three weeks after admission her urine started to become acid, clouded by urates, concurrently, at times, brighter moments occurred, and she could now

admit that she was ill. Two weeks later her mood was noted to be ‘very dark, it gets worse and worse’. Within a week this was followed by ‘strong daily evacuations’ of large red uric acid crystals, and subsequently, her symptoms gradually remitted, and she could be transferred to an open ward. Finally, after a period of recreation she was discharged home as cured.

**Case Vignette No. 6 (viii)** concerned a sixty-nine-year-old lady with a significant family history.<sup>304</sup>

Her maternal grandfather was insane, her mother ‘always melancholic’, her brother had been insane, and one of her sisters, ‘repeatedly insane’, died from a stroke. Another sister suffered from chronic rheumatism. The patient herself had suffered from bleedings from the kidneys, and at times, she had observed ‘red gravel’ in her urine. Although she was usually of ‘a lively temperament’ with a taste for ‘seeing many people, arts and music’, throughout all her life she had suffered from ‘periodical attacks of depression’. In her younger years these attacks had been of milder, more transient nature, but in her early forties they became ‘more intense and long-lasting’. In one instance, she had to be removed from home, but eventually she recovered. It happened again some years later, and she required admission (to the Sixth Department, Copenhagen Municipal Hospital), and from there she was placed in a nursing home for nervous diseases. Eventually, she returned home and settled. At the age of sixty-five she again experienced a period of ‘very deep depression’. As before, no triggering events could be established. On admission to the ‘Middelfart Mental Asylum’ she presented a picture of pronounced debilitation with a rather senile stamp. She experienced tormenting thoughts and insomnia; her memory was failing. Her urine was clear and acid. On the fourth day, ‘a very copious evacuation’ of uric acid crystals occurred. This continued for a couple of weeks, and during ‘this process’ she was still melancholic and somewhat irritable, then followed signs of some improvement. Treatment with ‘Mixt. Carbonatis Lith. [emphasis added] plus distilled water’ was instituted. Three weeks after the evacuation of the crystals, she was ‘merry’ and could ‘joke’ about the fact that now her clothes needed to be let out, and her stamp of senility decreased. She became lively and easy to get on with, and although she showed somewhat impressionable features, which were said to be habitual for her, after a period of recreation she could be discharged home as cured. The following years she spent at home, during which time she reportedly suffered from periodical lumbar pain and one episode of severe haematuria, but evacuation of urinary concrements had not been observed. She also suffered from arthritis. Her mental state was characterised by a ‘milder degree of exaltation’. Approximately twenty-seven months after her last admission, she again experienced an attack of depression, her symptoms being rather similar to before. According to her own wish, she was promptly readmitted to the asylum. Her rheumatic condition had progressed, and she manifested the same senility-resembling features. The same treatment as before was instituted [emphasis added], resulting in ‘a gradual improvement of her condition, and the senility features vanished gradually’.

A comparative study of this patient's respective case files, the Middelfart case file and that of the Psychiatric Department, Copenhagen Municipal Hospital, should be considered.

**Case Vignette No. 7 (ix)** was that of a lady, sixty-nine years of age.<sup>305</sup> A rather vigorous lithium treatment was prescribed.

Her father suffered from gout; her mother and two of her brothers from periodical melancholy. Previously she had enjoyed good health. In youth, there was a tendency to melancholy. From her early fifties, depressions occurred again, now with a pronounced periodical course, particularly during spring and autumn. During these periods, the patient, who was otherwise of a lively and active nature, would become taciturn and withdrawn, and would also express a multitude of hypochondriacal complaints. She experienced an itching sensation in the upper extremities and had congestions to the head, lumbar pain, and, at times, she noticed a red sediment in the otherwise clear urine. Four years before, for about a year, she had suffered attacks of gout. During this time, and for the next couple of years, she was completely free of periods of depression, but then they started to recur, and during the two years prior to her admission they had been very pronounced. Reportedly, the current attack had lasted approximately three months, its course being similar to the previous ones, with melancholic mood. She had no drive for work, and there were many hypochondriacal concerns. She had also developed suicidal thoughts, not being customary for her.

On admission, she was somewhat depressed. She complained of a 'general feeling of cold', itching in the extremities and pains in the lumbar region. There were signs of gouty deformation of the finger joints. She became very irritable and unreasonable. Three days after admission 'many fine red uric acid crystals were found in the urine', but her morose mood persisted. 'Now a rather vigorous lithium treatment was prescribed' [emphasis added]. Signs of improvement were quickly noted, and one week after the commencement of treatment, she stated that 'now it begins to clear in my head'. However, within the following week she showed some deterioration and attempted suicide by slashing her wrist. 'The next day uric acid sediments recurred'.

At her own request, and that of her family, she was discharged. Later, she wrote a letter to Dr. Lange stating that upon discharge she had felt very unwell for about a month, followed by full remission.

### **Fritz Lange's exhortation to use systematic prophylactic lithium therapy**

Fritz Lange considered uric acid diathesis (uratic degeneration) to be the result of impaired metabolism or digestion, leading to uric acid (uratic) auto-intoxication manifested with a great variety of physical symptoms, including reflex neuralgia and cerebral pathology, but mainly mood disorder. In some contradistinction to his brother, from the casuistry presented here it can be gleaned that he apparently saw an (alternating) association between gout and affective symptoms. His treatment recommendations

consisted of dietary, physical and medicinal therapy.<sup>306</sup> Concerning the latter, ‘the use of alkali, since olden times, remains of primary importance’. He discouraged the use of bromides, as did his brother.

The message in Lange’s (posthumous) 1908 article, obviously ignored by contemporary psychiatry, was unequivocal: use lithium (carbonate) in the acute treatment and prophylaxis of ‘uratic’ periodical depression:<sup>307</sup>

Here in [the Middelfart Mental Asylum] lithium salts, in combination with copious amounts of distilled water, are very generally used. Also the recognised mineral waters: Fachinger, Wildung, Salzbrunner, Kronenquelle etc. are useful [...] In such patients [suffering from periodical depressions] it could perhaps be useful to send them out into the world with an explanation of their illness and a prescription for the medicament [lithium] which has shown fit and beneficial for them. In fact, I have attempted to do this several times and I am still trying, but the result has not matched the good intent. In their free and good intervals between the depressions, they never think of their past illness, and when it hits them again, they are quite constrained and helpless and are not at all able to reason over their own condition. Their faculties are inhibited and paralysed. For a long time they suffer in silence, and then they seek the help where they have found it before.

It is indeed intriguing that Christiansen, who was more than familiar with the medical literature in this field and the Lange theory of depression, and also with the claims of lithium’s antidepressant effect, would have been in a unique position to discover the later proven therapeutic effects of lithium in manic-depressive psychosis, had he conducted the systematic trial with this ‘medicinal treatment’ that he had previously identified as wanting.

The thirty-five case files, retrieved by Flach, and others retrieved subsequently, should be compared with those Middelfart Asylum case files, which during (and after) the Lange superintendency carried a diagnosis of melancholy and/or mania; these being diagnostic categories that, consistent with the teachings of his time, are described in his 1894 textbook under periodical and circular insanity.<sup>308</sup>

Such a study should also address the question of whether ‘uroscopic’ screenings were carried out in all patients admitted to the hospital, as it appears that lithium would have been used only in patients suffering from periodical depression when producing urinary concrements and gravel, and thus paradoxically withholding lithium therapy from some ‘manic-depressive’ patients admitted alongside uratic depression sufferers. The antimanic remedies Lange prescribed were opium, digitalis, sulphonal and hyoscine. In cases of melancholy, opium was generally used.

### **Carl and Fritz Lange: founding fathers of lithium therapy**

The Lange brothers (consecutively from approximately 1874 to 1907, when Fritz Lange died) not only used and recommended systematic lithium (carbonate) in the acute treatment of ‘periodical depressions’ (‘uratic depressions’),<sup>309</sup> but they were also possibly the first to raise the possibility that continuation treatment may prevent recurrence of a psychiatric condition.<sup>310</sup> In addition, Fritz Lange was possibly also the first who

systematically treated hospitalised excited patients—some of them undoubtedly in manic phases, with lithium (at times ‘a rather vigorous lithium treatment’)—and prophylactically as well, although, as we know today, the treatment was used for the wrong reason: the association with the die-hard uric acid diathesis.

### **The fate of the Lange method of lithium treatment in Denmark after Fritz Lange’s death**

As illustrated above, contemporary Danish doctors would have been fully acquainted with the Lange theory of depression. In 1901 Carl Lange’s pupil, Friedenreich,<sup>311</sup> made a brief mention in his psychiatric textbook of Lange’s depression theory, stating that these patients are ‘periodically depressed due to uric acid diathesis’; but he made no mention of alkaline remedies in its treatment.

In 1906 the physician Fløystrup contributed to the literature with an article on uric acid diathesis to *Salmonsens Konversationsleksikon*,<sup>312</sup> a major encyclopaedia in Scandinavia. He wrote that this diathesis, particularly in Denmark, had been expanded to include ‘the so-called periodical depressions (C. Lange) and certain forms of insanity proper (Fr. Lange)’. After a brief mention that the treatment method, which was generally being promoted for this diathesis, consisted of a vegetarian meat-free diet, but without any reference to medical remedies, the author concluded that the Lange theory was a ‘very doubtful’ concept, for which there hitherto had been no proof. The physician Bing,<sup>313</sup> in the second edition of this encyclopaedia, revised Fløystrup’s article to the effect that the uric acid diathesis now had only ‘historical interest’. He made no mention of lithium or other alkaline remedies.

Holger Iacobæus,<sup>314</sup> who had worked under Lange at the Middelfart Asylum, came out in defense of the Lange theory at a meeting at the Medical Society of Copenhagen in 1906, stating that ‘Over the last years I have observed at least a couple of hundred cases of this peculiar illness picture’. He used potassium bromide combined with valerian, but he did not mention lithium.

Eventually, in a meeting of the Medical Society of Copenhagen in 1911 the Lange theory of depression was dealt its death-blow.<sup>315</sup>

The rheumatologist Erik Faber saw fit not only to criticise the concept of uric acid diathesis in general, but with barely disguised irony, to make comments about the Lange theory, which, he said, ‘in this country is the diathesis manifestation, which is being diagnosed most frequently, whereas it has never gained any greater importance abroad’.<sup>316</sup> He also took the opportunity to remind the audience that periodical depression ‘has always caused great resistance from the nerve specialists’, referring to Steenberg, Pontoppidan and Christiansen.<sup>317</sup> Moreover, he asserted, ‘the late Prof. Levison, our most outstanding specialist in the field of gout, with respect to “the whole uric acid question” had a strongly differing opinion’,<sup>318</sup> to the effect that ‘in the edifice of uric acid diathesis the physiological pillars are hollow or decayed ages ago, the most important connections between the individual links are missing, and the steeple of the edifice, the therapy, is mostly all in the air’.

On this basis Faber strongly recommended the name of uric acid diathesis be abandoned:

the dilapidated ruins of uric acid diathesis should be removed, partly because it is a hindrance to newer and more correct understandings, partly because it also results in useless or even harmful therapy' [emphasis added].<sup>319</sup>

Faber stated,<sup>320</sup> intriguingly, that 'in various authors - among them also C. Lange - the diagnosis is made *e juvantibus*, as they, when the morbid symptoms vanish with alkaline therapy, see this to be a confirmation of the diagnosis: uric acid diathesis'.

To Lange's defence, the reader must be reminded that he himself had queried this mode of lithium's action.

Finally, Faber astoundingly expressed the opinion that 'in cases of mental illnesses, the theory of uric acid diathesis will often make the doctor abstain from really getting to the bottom of the patient's psyche and find the real causes of the illness, the only way in which one can be guided concerning the right treatment'.<sup>321</sup> Faber was obviously being influenced by the teachings of Freud.

Apart from Iacobæus, August Wimmer and Thune Jacobsen, both to become eminent psychiatrists, had also worked under Fritz Lange at the Middelfart Asylum.

It was during some time between 1897 and 1899 that Wimmer worked under Lange. He also wrote Lange's obituary,<sup>322</sup> mentioning the Lange 'uratic degeneration' concept 'with its somewhat vague considerations from the viewpoint of general psychopathology' - 'the nebulous and no less all-embracing concept of uric acid diathesis - applicable to everything'.<sup>323</sup> Furthermore, he made a brief mention of Carl Lange's depression treatise in his psychiatric textbook (1936).<sup>324</sup>

In 1955 Thune Jacobsen,<sup>325</sup> Superintendent Psychiatrist of Risskov Mental Asylum from 1921 to 1945, wrote to his successor, Erik Strömngren, about how 'in my younger days at Middelfart Lange used lithium mixture with plenty of water in the treatment of depression caused by uric acid diathesis'. 'As soon as macroscopic investigations revealed sedimentation of uric acid crystals, Lange said to the patient that now the cause of the depression had been found [...] and that now the patient would recover as long as he drank water and lithium mixture'. Jacobsen added that 'in fact, the patients recovered in many cases' (emphasis added). The young doctor had had to examine the crystals under the microscope. In many instances they turned out to be of another kind than uric acid crystals, or it was simply an 'amorphous sedimentation' that he saw. Intriguingly, he added, Lange had 'especially based his treatment method on self-observations. At times he could feel in a low mood without knowing why - and then suddenly he discovered uric acid crystals in his urine - "Hoho" - he told himself - now it was eliminated and then he was relieved and felt happy again, meaning that his hypothesis had proven correct'.

It should be added that from other sources it is known that a tendency to mood swings was 'not rare' in the Lange family.<sup>326</sup> Therefore, the intriguing but unanswerable question is whether the Lange brothers treated themselves with lithium carbonate.

Hjalmar Helweg, another eminent psychiatrist, had worked at the Middelfart Asylum at some time between 1911, when he graduated, and 1913, when he was

appointed to Sct. Hans Mental Asylum at Roskilde (and where he would have met Wimmer). He mentioned Fritz Lange in his work on the history of the provisions for the insane in Denmark.<sup>327</sup> More generally, reference was made to his psychiatric literary work and his ‘aesthetic studies’, but none to his (and his brother’s) work concerning the periodical depressions.

Irrespective of the fact that Wimmer and Helweg did not mention lithium, during their residencies at the Middelfart Asylum, *ceteris paribus*, they would both have encountered patients - or read their case files - whom Fritz Lange until 1907, when he died, had prescribed lithium, and had written about it in the Danish medical press, enthusiastically exhorting its use as a preventive therapy against uratic depression, not to reiterate that some of the lithium-treated patients, examined in retrospect, are not unlikely to have suffered from bipolar mood swings.

According to a letter from a general practitioner, Clausager-Madsen,<sup>328</sup> to Mogens Schou in 1956, the psychiatrist Christian Geill<sup>329</sup> of Viborg Mental Asylum used lithium - ‘not in manic patients’, but in the treatment of his private patients suffering from ‘nervousness’.

Geill, who graduated from Copenhagen University in 1885, had not worked with Fritz Lange, but he would have been fully familiar with the Lange theory of periodical depression and its treatment with lithium. Clausager-Madsen had prescribed *mixtura gentiana lithica* since 1936 as a vehicle for sedative medication (containing phenobarbital, antipyrine and bromide). He was under ‘the firm impression’ that especially the ‘mildly exalted patients’ were very fond of this ‘mixture’.

In passing it should also be mentioned that lithium treatment had spread to Iceland, but not via the Lange brothers. Thus in 1956 Tómasson<sup>330</sup> of Reykjavik wrote to Mogens Schou that he had used lithium carbonate since 1938 as a sedative in the treatment of ‘exalted alcoholics’ and ‘hypomanics’. During a visit to Laignel-Lavastine in Paris a couple of years before, he had been inspired by some French pharmacology, published some time in the nineteenth century, but he did not remember exactly when.

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<sup>183</sup> Faber E.: ‘Urinsyrediathesen’. *Ugeskr. Læg.* 1911;73:751–771.

<sup>184</sup> Lange C.: ‘Om Sindsbevægelser. Et Psyko-Fysiologisk Studie’. Copenhagen: Lunds Forlag, 1885. Lange C.: ‘Ueber Gemüthsbewegungen. Eine psychologisch-physiologische Studie’. H. Kurella trans. Leipzig, 1887. Lange C.: ‘Les émotions’. G. Dumas, trans. Paris, 1895. (2nd Edn. 1902). Lange C.: ‘The emotions. A psychophysiological study’. Translated by Istar A. Haupt from the authorised German translation of H. Kurella. (Dunlap, K. ed.). Baltimore: Williams & Wilkins, 1922. pp33–90. James W.: ‘What is an emotion’. *Mind* 1884;9:188–205. With this work Lange became one of the founders of psychophysiology. It also described conditioned reflexes, two decades before Pavlov (cf. Lange, 1885, *op. cit.*, pp75–84 (Dunlap, *op. cit.*, pp73–79). Bender Petersen P.: ‘La description de réflexes conditionnels par C. Lange comme base de sa théorie d’émotion vaso-motrice’. *Acta Psychiatr. Scand.* 1966;42(Suppl. 191):188–192. Lund M.: ‘Carl Lange—Danmarks første neurolog [Denmark’s first neurologist]’. *Bibl. Læg.* 1991;153:362–377 (366).

<sup>185</sup> Schioldann, 2001, *op. cit.*

<sup>186</sup> Lange C.: ‘Om Periodiske Depressionstilstande og deres Patogenese’. Copenhagen: Lunds Forlag, 1886.

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<sup>187</sup> Lange C.: 'Om Periodiske Depressionstilstande og deres Patogenese'. Andet Oplag. Med en Efterskrift. Copenhagen: Lunds Forlag, 1895.

<sup>188</sup> Lange C.: 'Periodische Depressionszustände und ihre Pathogenese auf dem Boden der harnsauren Diathese. Autorisierte deutsche Ausgabe nach der zweiten Auflage des Originals von Dr. Hans Kurella'. Hamburg und Leipzig: Verlag von Leopold Voss, 1896.

<sup>189</sup> Lange C.: 'Om Periodiske Depressionstilstande og deres Patogenese'. 1886. Reprint. Introduction by Amdisen. Copenhagen: Duo, 1982.

<sup>190</sup> Johnson FN, Amdisen A.: 'The first era of lithium in medicine. An historical note'. *Pharmacopsychiatr.* 1983;16:61–63. Johnson, 1984, op. cit., p.x (Preface), p.16. Johnson, 1999, op. cit., pp.205–206. 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.

<sup>191</sup> Haenel T.: 'Zur Geschichte der Depressionsbehandlung'. [Engl. Abstr.]. *Schweiz. Med. Wschr.* 1986; 1652–1659.

<sup>192</sup> Felber W.: 'Die Lithiumprophylaxe der Depression vor 100 Jahren—ein genialer Irrtum.' [English summary: Lithium Prophylaxis of depression 100 years ago—an ingenious misconception]. *Fortschr. Neurol. Psychiatr.* 1987;55:141–144. (Reprinted in 1996).

<sup>193</sup> Lange C.: 'Periodische Depressionszustände und ihre Pathogenese auf dem Boden der harnsauren Diathese'. 1896. Reprint, 'herausgegeben von Werner Felber zum 100-jährigen Erscheinen der deutschen Übersetzung von Alfred Kurella mit einem Vorwort von Mogens Schou und Werner Felber und einer Publikation zur historischen Würdigung und Richtigstellung: Die Lithiumprophylaxe der Depressionen vor 100-Jahren—ein genialer Irrtum'. Erschienen in: *Fortschr. Neurol. Psychiatr.* 55 (1987) 141–144. Regensburg: Roderer Verlag, 1996.

<sup>194</sup> Felber, 1996, op. cit. 'Vorwort 1'. F. based this opinion on (1) Lange's depression treatise being the first description of recurrent unipolar depression, 'die modernsten Ansprüchen genügt'; (2) Lange being the first to use mainly medicinal treatment in psychiatry 'mit dem Schwerpunkt Lithium-Langzeitprophylaxe der depression'—'[ein] Meilenstein in der anbrechenden psychopharmakologischen Ära in der Psychiatrie', irrespective of his erroneous understanding of the pathogenesis; (3) referring to footnote no. 2 in Lange's depression pamphlet concerning suicide, Felber found this to be the first mention of the possible suicide-protective effect of lithium—'die mögliche suizid-protective Wirkung einer Lithiumbehandlung'—which has been shown in recent years. Lange's footnote should also be compared with his previously mentioned statement in his emotion treatise to the effect that sorrow and despair 'often enough' result in suicide. cf. Amdisen, 1985, op. cit., p.37 ('C. Lange's flying call to psychiatry'): Lange 'never focused on lithium as a specific psychotropic drug. He simply regarded this affective mental illness ['the periodic depression'] as belonging to the gouty diathesis'. According to Lange (1897, op. cit., p.76) the pathogenesis of uratic depression 'is thus far obscure'.

<sup>195</sup> Schioldann J.: 'In Commemoration of the centenary of the death of Carl Lange. The Lange Theory of 'Periodical Depressions'. A landmark in the history of lithium therapy'. Adelaide Academic Press, 2001. pp.23–49; included in this work as Appendix I.

<sup>196</sup> Delusions and/or hallucinations were the main constituents in the classic concept of melancholia. However, consistent with the redefining of 'melancholia' since the 1820s, the condition was considered to be a primary disorder of emotions. To what extent, if any, Lange had been acquainted with this redefining and subsequent 'renaming' to 'depression' (Berrios, Jackson 1986. Knoff WF.: 'Depression: a historical overview'. *Am. J. Psychoanal.* 1975;35:41–46), cannot be established. Around the middle of the century, Griesinger had introduced the term psychic depression as a synonym for melancholy. By 1860 it appeared in medical dictionaries. Kraepelin, in the 1880s, used the term depressive insanity. Tuke's 'Dictionary of psychological medicine', 1892, listed mental depression as a synonym for melancholy. Lange later used the concept of masked depression as 'the uratic symptomatology can be distorted, can be difficult to recognise, as even its main features, the depression phenomena, can be masked' (Lange 1897).

<sup>197</sup> Lange C.: 'Om Sindsbevægelser. Et Psyko-Fysiologisk Studie'. Copenhagen: Jacob Lunds Forlag, 1885. Lange C.: 'Ueber Gemüthsbewegungen. Eine psychologisch-physiologische Studie'. H. Kurella trans. Leipzig, 1887. Lange C.: 'Les émotions'. G. Dumas, trans. Paris, 1895. (2nd. Edn. 1902).

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Lange C.: 'The emotions. A psychophysiological study'. Translated by Istar A. Haupt from the authorised German translation of H. Kurella. (Dunlap K. ed.) Baltimore: William & Wilkins, 1922. pp. 33-90.

<sup>198</sup> Lange versus Steenberg, 1886, op. cit., p.647.

<sup>199</sup> cf. Levison F.: 'Resultaterne af den urinsure Diateses Behandling ved Silkeborg Vandkuranstalt i Aarene 1896-1900 [F. E. Klee]'. Ugeskr. Læg. 1901;5R;8:450-451. Schou M.: 'Biology and pharmacology of the lithium ion'. Pharmacolog. Rev. 1957;9:17-58 (45). Schou M.: 'Phases in the development of lithium treatment in psychiatry', in Samson F, Adelman G. (eds.): 'The neurosciences: Paths of discovery II'. Boston. Basel. Berlin: Birkhäuser, 1992:149-166. Schou, 1992, op. cit., pp.279-280. Schou M.: 'Lithiumbehandling af manio-depressiv sygdom'. Copenhagen: Welner & Rygaard, 1991, p.16. Schou M.: 'Vorwort 2—Einführung', in Felber, 1996, op. cit., pp.ix-xi. Healy D.: 'The Psychopharmacologists II'. London: Altman, 1998, pp.282-283. Schou M.: 'Lithium treatment for half a century. How did it all start?' Nord. J. Psychiatr. 1999;53:383-384. Schou M.: 'Lithium treatment at 52'. J. Affect. Disord. 2001;67:21-32.

<sup>200</sup> cf. Amdisen, 1985, op. cit., p.35. Amdisen expresses a somewhat different opinion.

<sup>201</sup> Lange, 1895, 1896 (Felber 1996), 'Postscript', op. cit., p.54 (German editions): Ordonaux J.: 'Neurasthenia in its relations to melancholia'. Brooklyn Med. J. 1895; June. In 'Bidrag til Urinsyrediatesens Klinik' (Hospitaltid. 1897;4R;5(1):83), Lange cited from Dr. Frank's article 'On lithaemia', in N. Y. Med. J. 1896;27. June.

<sup>202</sup> op. cit.

<sup>203</sup> Lange C.: 'Bidrag til Urinsyrediatesens Klinik'. Hospitaltid. 1897;4R;5:1-15, 21-38, 45-63, 69-83 (2).

<sup>204</sup> According to Lange 'in some remarks about "neurasthenia" Huchard in l'Union médicale (1882) [cf. his 'Neurasthénie', Annales Médico-Psychologiques, 1884;1:494: 'nervosisme chronique'] states that this illness [gout]—amongst the variegated elements of which, as already noted, one will certainly also find many cases of periodical depression—as a rule develops on an arthritic soil. This statement, however, is so casual and unsupported that it is easily explained that it has remained unnoticed'.

<sup>205</sup> Lange wrote: 'Also Arndt in his thorough—almost too thorough—treatise on neurasthenia ['Die Neurasthenie (Nervenschwäche). Ihr Wesen, Ihre Bedeutung und Behandlung von anatomisch-physiologischen Standpunkte für Ärzte und Studierende. Wien u. Leipzig: Schwarzenburg, 1885] claims a kinship between this condition and not only arthritis, but also rheumatism, which he is even inclined to consider as one of the manifestations of neurasthenia (!)'. Berrios has perused this difficult-to-obtain work for the present author. According to Berrios, it contains no mention of the use of lithium salts.

<sup>206</sup> Lange, 1886ff., op. cit. 'Rejoinder from C. Lange to V. Steenberg'. Hosp. Tid. 1886;3R;4:647. In Lange's postscript to the second edition, 1895 (ibid. p.48) he emphasised that 'among my approximately two thousand depressed patients, of whom I have been able to follow the course of their illness reasonably well in most of the cases, I have never observed the slightest sign of elevated periods'; Kurella (1896) translated this sentence wrongly (op. cit., p.55): 'Ich habe bei meinen ca. 2000 an Depression leidenden Patienten, bei denen ich doch grösstenteils den Verlauf der Krankheit verfolgen konnte, niemals auch nur eine Spur von bestimmter Zeitdauer der Perioden beobachtet'.

<sup>207</sup> In his famous work on the theory of emotions, Lange came close to formulating alternating periods of mania and depression as a nosological entity, years before Kraepelin's concept: 'das manisch-depressive Irresein', in 1899 (cf. Kraepelin E.: 'Psychiatrie. Ein Lehrbuch etc'. Leipzig: Barth, 1899. Vol 2, p.359. Thalbitzer S.: 'Den Manio-Depressive Psykose—Stemningssindssygdom—Et Forsøg til Bestemmelse af dens Pathogenese og patologisk-anatomiske Grundlag med særligt Henblik paa de manio-depressive Blandingsformer'. Copenhagen: Gyldendal, 1902 (German edition: 'Die manio-depressive Psychose—das Stimmungsirresein'. Arch. Psychiatr. 1908;43:1071-1136). Thalbitzer S.: 'Emotion and insanity'. With a preface by Harald Høffding. London: Kegan Paul, 1926. pp.41-42,49-50. Berrios GE.: 'Mood disorders', in Berrios GE & Porter R. (eds.): 'A history of clinical psychiatry'. London: Athone, 1995. pp.384-408). After having stated that 'it is our vasomotor system that we can thank for all of the emotional side of our

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psychic life, our happy and unhappy hours' (Lange, 1885, op. cit., pp.86–87 (Dunlap, op. cit., p.80)), Lange proceeded to state (cf. Lange, 1885, op. cit., p.69. Dunlap, op. cit., p.70 —retranslated from the Danish original text by the current author): 'Every psychiatrist knows the strongly developed forms which occur as 'melancholia' or 'mania'. Every doctor, who occupies himself with nervous illnesses, has abundant opportunity to observe the even more instructive mild cases which lie on the border between the insanities proper and such 'indispositions' that could be subsumed under concepts such as oddity, morosity, despondency and so on and so forth. Most frequently sadness is encountered, the picture of sorrow, at times even despair, which often enough results in suicide in spite of the clear awareness that there is a complete lack of any psychic motive for the sorrow. Almost as common is the morbid anxiety, which is often linked with its close relative, sorrow, but often it also occurs alone. It is a more rare occurrence, of course, that joy is manifested in a morbid way as such; the mere fact that joy appears in an unmotivated way, without cause, as can be easily understood, will usually not be sufficient, not for the layman at any rate, to characterize it as something morbid, and even less to seek the condition changed by medical treatment; [for this] would usually require either the happy mood to vent itself in an absolutely careless and uncontrollable manner, in the form of a more or less pronounced mania, or that in a striking manner it alternates with periods of depression and thus leaps to the eye as something abnormal'. It was Wilmanns who in 1906, influenced by Kraepelin, re-grouped cyclothymia under manic-depressive illness (Wilmanns K.: 'Die leichten Fälle des manisch-depressiven Irrseins (Zyklothymie) und ihre Beziehungen zu Störungen der Verdauungsorgane'. Leipzig, 1906). In accordance with Carl Lange's views, it becomes understandable that he would also stress that 'the study of "the emotional illnesses" becomes particularly important from a psychological viewpoint, or at any rate, this will be the case once it [the study] has become more systematised than hitherto has been the case'.

<sup>208</sup> Lange, 1897, op. cit., pp.72–73, 76 (case no. 23). 'Rejoinder from C. Lange to V. Steenberg', op. cit. p.648

<sup>209</sup> Lange, 1897, op. cit. Kragelund: 'Urinsyre-Diatesens atypiske Form'. *Bibl. Læg.* 1896;7R;7:389–409.

<sup>210</sup> 'Therapeutik. [Lithium salts]'. *Hospitalstid.* 1863;6(20):79–80 (from *Gazette des hôpitaux* 1863, No. 43).

<sup>211</sup> Bang OL.: 'Haandbog i Therapien'. Copenhagen: Gyldendal, 1852, pp.118–125: *dyschœmia arthritica*, *dyschœmia lithica*, p.35: *hyperdynamia nervosa*.

<sup>212</sup> Budde V.: 'Om Nyrestenenes medicinske Behandling'. *Ugeskr. Læg.* 1879;3R;28(28):433–441. *ibid.* (29):449–452. Attached: Madsen HP.: 'Nyrestens Opløselighed ved Behandling med benzoësurt Lithion og borcitronsur Magnesia udenfor Organismen'. *ibid.* pp.452–459.

<sup>213</sup> Lange, 1895, 1896, op. cit. Felber, op. cit., 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 arguments regarding uric acid in the body'. cf. Rasch, 1896, op. cit., p.1154. Rasch, 1899, op. cit., p.1030.

<sup>214</sup> Lange C.: 'Et Par praktiske neuropatologiske Notitser. 2. Bidrag til Behandlingen af Pruritus universalis idiopathica'. *Hosp. Tid.* 1891;3R;9(21):553–560.

<sup>215</sup> Lange, 1897, op. cit., pp.33, 34, 50, 60, 62.

<sup>216</sup> 'Formulae Nosocomiorum Civitatis Havniensis' [Copenhagen], 1913, op. cit.

<sup>217</sup> Haase H, personal communication, 11.9.1999. Amdisen, personal communication to Neil Johnson, 25.7.1981 (Johnson, 1984, op. cit., pp.16, 144 (note 90). Johnson, 1999, op. cit., p.206).

<sup>218</sup> Felber, 1987, 1996, op. cit. Felber referred to comments to the *Pharmacopœia Germanica* by H. E. Richter (1871), H. Hager (1884) and B. Hirsch and A. Schneider (1891), '[die] als Standard gelten dürfen'.

<sup>219</sup> Amdisen A.: 'The first lithium era', in Johnson FN. (ed.): 'Depression & mania. Modern lithium therapy'. Oxford: IRL Press, 1987. pp. 24–28.

<sup>220</sup> cf. Johnson, 1984, op. cit. p.144 (note 90).

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<sup>221</sup> Schou, Vorwort in Felber, 1996, op. cit.

<sup>222</sup> Lange C. 1897, op. cit.

<sup>223</sup> Waller E.: 'Determination of lithia in mineral waters'. *J. Am. Chem. Soc.* 1890;12:214–233. cf. Sollmann, 1942, op. cit., pp.906–907 ('The popular "Lithia waters" have been shown to be practically devoid of lithium. The best contain only 0.01 to 0.02 per cent'). Gershon S.: 'Lithium in mania'. *Clin. Pharmac. Ther.* 1970;11:168–87. Georgotas A, Gershon S.: 'Historical perspectives and current highlights on lithium treatment in manic-depressive illness'. *J. Clin. Psychopharmacol.* 1981;1:27–31. Johnson, FN: 1984. op. cit. pp.67–68 (M. Schou).

<sup>224</sup> Anon.: Letter from 'an old medical practitioner'. *Ugeskr. Læg.* 1901;5R;8:422–424. cf. Levison F.: 'Om Urinsyren som Sygdomsaarsag'. *Ugeskr. Læg.* 1897;5R;4:337–352 (p.337: 'Among all the obscure concepts in pathology, there hardly exists anything which is as undefined and vague as the concept of uric acid diathesis'). Levison F.: 'Resultaterne af den urinsure Diateses Behandling ved Silkeborg Vandkuranstalt i Aarene 1896-1900 [F. Klee]'. *Ugeskr. Læg.* 1901;5R;8:396–399, 450–451. Levison agreed with 'the old medical practitioner', and added that Lange's concept was so 'loose', 'vague' that it could not be subjected to 'statistical' analysis (p.450). cf. Amdisen A.: 'The standardized twelve-hour serum or plasma concentration (12h-stSLi) in lithium therapy and the use of lithium concentration in lithium intoxication', in Cooper TB, Gershon S, Kline NS, Schou M: 'Lithium. Controversies and unresolved issues'. *Proceedings of the International Lithium Conference, New York, June 5-9, 1978.* Amsterdam: Excerpta Medica, 1979. pp.304–332 (304). Vestergaard P.: 'Book review: Schioldann JA. In commemoration of the centenary of the death of Carl Lange. The Lange theory of 'Periodical depressions'. A landmark in the history of lithium therapy'. *Ugeskr. Læg.* 2001;163:7063.

<sup>225</sup> Lange, 1894, op. cit., pp.294–300, 359 ('Den urinsyre Diathesis' & case vignette).

<sup>226</sup> Amdisen A.: 'Lithium treatment of mania and depression over one hundred years', in G. U. Corsini (ed.): *Current trends in lithium and rubidium therapy.* Lancaster: MTP Press, 1984. pp.11–26 (17). Johnson, 1984, op. cit., p.17. Johnson, 1999, op. cit., pp.206–207. cf. Levison F, *Hospitalstid.* 1896;4R;4(16):375–377.

<sup>227</sup> cf. Felber W.: 'Die Lithiumprophylaxe der Depression vor 100 Jahren—ein genialer Irrtum'. [English summary: Lithium Prophylaxis of depression 100 years ago—an ingenious misconception]. *Fortschr. Neurol. Psychiatr.* 1987;55:141–144. (reprinted, 1996).

<sup>228</sup> Kurella H.: 'Fr. Lange: De vigtigste Sindssygdomsgrupper i kort Omrids. (Die wichtigsten Psychosengrupper in kurzem Umriss). (Kopenhagen, Gyldendal, 1893)'. *Centralbl. Nervenheilk. Psychiatr.* 1895;406–411: 'Für deutsche Leser wird die eingehende Behandlung der Psychosen bei harnsaurer Diathese, besonders die der dabei vorkommenden periodischen Depressionszustände, von besonderem Interesse sein. Leider muss ich mir ein näheres Eingehen auf diese sehr interessanten Ausführungen versagen'.

<sup>229</sup> Amdisen, 1985, op. cit., p.25.

<sup>230</sup> Flach C., personal communication, 1999.

<sup>231</sup> 'Pharmacopoea Danica' 1907. cf. Panum P.: 'Illustreret Lægebog Leksikon for Sunde og Syge'. 2. Udgave. Copenhagen: Hagerups, 1904 (Carbonas lithicus: 50 to 500 mg). Hansen A, Overbye L. (eds.): 'Farmaceutisk Lommehaandbog 1908'. Randers: C. Nielsen, 1907. 'Formulae Nosocomiorum Civitatis Havniensis' [Copenhagen] 1913, 1922. 'Danmarks Apotekerforening: DAK Præparater. Udarbejdet af Danmarks Apotekerforenings Kompositionsudvalg'. Copenhagen, 1924. Zeuthen HR.: 'Danske Farmakopeer indtil 1925'. Copenhagen: Munksgaard, 1927. Bie V, Jensen N.: 'Lægeforeningens Aarbog 1928'. Copenhagen, 1927, p.28. 'Pharmacopoea Danica' 1933 (lithii carbonas). 'Repertorium Pharmazeutischer Spezialpräparate'. Basel, 1946. p.549. Laursen J.: 'Danske farmakopéer 1923–1951'. Haase H., personal communications, 1999–2000. Marcher A., personal communication, 6.10.2000.

<sup>232</sup> Lange, 1886, op. cit. (Schioldann, 2001, op. cit., pp.47–48). Lange, 1893 (Levison), op. cit., p.629. Lange, 1897, op. cit. Appendix I.

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<sup>233</sup> Steenberg V.: 'I Anledning af Prof. Lange's Skrift om periodiske Depressionstilstande'. *Hosp. Tid.* 1886;3R;4:628–640; 'Rejoinder from C. Lange', *ibid.*, pp.640–648. cf. Johnson, 1984, *op. cit.*, pp.144–145, note 92. Johnson, 1999, *op. cit.*, p.206.

<sup>234</sup> Pontoppidan K.: 'To psykiatriske Afhandlinger'. *Hosp. Tid.* 1895;38:1204–1210. Rejoinder by C. Lange: 'Et Par Ord om "den periodiske Depression" '. *ibid.*, pp.1235–1238. cf. Johnson, 1984, *op. cit.*, p.145, note 92.

<sup>235</sup> cf. Lewis AJ.: 'Melancholia: A historical review'. *J. Ment. Sci.* 1934;80:1–42. Lewis AJ.: 'Melancholia: A clinical survey of depressive states'. *J. Ment. Sci.* 1934;80:277–378. Knoff WF. 'Depression: A historical overview'. *Am. J. Psychoanal.* 1975;35:41–46. Haenel, *op. cit.* Jackson SW.: 'Melancholia and depression. From Hippocratic times to modern times'. New Haven: Yale University Press, 1986. Berrios GE.: 'Melancholia and depression during the 19th century: A conceptual history'. *Br. J. Psychiatr.* 1988;153:298–304.

<sup>236</sup> Levison F.: 'Urinsyre-Diathesen. Gigt og Nyregrus'. Copenhagen: Philipsen, 1893 (reviewed by C. Lange in *Hospitalstid.* 1893;4R;1:629–642). German edition: 'Die Harnsäure-Diathese'. Berlin, 1893. English edition: 'The uric acid diathesis. Gout. Sand and Gravel'. London & Melbourne: Cassell. 1894. (pp.126, 131, 134–5, 145).

<sup>237</sup> Lange, 1895 (p.46), 1896 (p.52), *op. cit.* Felber, 1996, *op. cit.*, p.52. In fact, the supporters Lange mentioned were Levison (sic), Fr. Lange and A. Haig—'das ist alles'. cf. Rasch C.: 'Om Forholdet mellem Hudsygdomme og den arthritiske diatase'. *Hospitalstid.* 1896;4R;4(48):1154. Rasch praised Lange's depression pamphlet. He himself had encountered periodical depression in people who were strongly predisposed for arthritis but without uric acid gravel in the urine. In *Hospitalstid.* 1899;4R;7(43):1030 Rasch wrote that concerning treatment, the uric acid diathesis gives the only causal indication.

<sup>238</sup> Levison, 1894, *op. cit.*, pp.144–146. cf. Levison: 'Om Depressionstilstandes Forhold til Urinsyre'. *Hospitalstid.* 1896;4R;4:353–363, 373–384 (review of the second edition of C. Lange's depression pamphlet, 1895). cf. Levison: 'Om Behandling af Urinsyrekonkrementer'. *ibid.* 1895;4R;3:683–685. Levison: 'Om nogle Lægemidler, som i de senere Aar ere anbefalede ved Behandlingen af Urinsyrekonkrementer'. [On some medications which in recent years have been recommended in the treatment of uric acid concrements]. *Ugeskr. Læg.* 1896;5R;3:1–14.

<sup>239</sup> Lange, 1893 (Levison), *op. cit.*

<sup>240</sup> Levison, 1896, *op. cit.* Levison F.: 'Om Urinsyren som Sygdomsaarsag'. *Ugeskr. Læg.* 1897;5R;4:337–352.

<sup>241</sup> Levison, 1896, *op. cit.*, pp.353–363, 373–384. Levison, 1897, *op. cit.*, pp.337, 350. Levison, 1901, *op. cit.*, p.450.

<sup>242</sup> Levison, 1896, *op. cit.*, p.355.

<sup>243</sup> *ibid.*, p.353.

<sup>244</sup> Levison, 1896, 1897, *op. cit.* Lange, 1897, *op. cit.* Jacobæus, *op. cit.*, pp.462–463.

<sup>245</sup> Levison, 1896, *op. cit.*, p.374.

<sup>246</sup> Levison, 1896, *op. cit.*, pp.375–377. cf. Lange F, *Hospitalstid.* 1908;5R;1(4):73–74.

<sup>247</sup> *ibid.*, p.377.

<sup>248</sup> *loc. cit.*

<sup>249</sup> *ibid.*, pp.377–378.

<sup>250</sup> *loc. cit.*

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<sup>251</sup> *ibid.*, pp.378–383.

<sup>252</sup> Levison, 1896, *op. cit.* Levison F.: ‘Om Urinsyren som Sygdomsaarsag’. *Ugeskr. Læg.* 1897;5R:4:337–352. (Roberts W.: ‘Uric acid, gravel and gout’. London 1892. Weintraud W.: ‘Ueber Harnsäure im Blute und ihre Bedeutung für die Entstehung der Gicht’. *Wien klin. Rundschau* 1896, No. 1–2. & *Centralbl. Med.* 1896, p.752ff. Ebstein W, Nicolaier: ‘Ueber Ausscheidung der Harnsäure durch die Nieren’. *Virchows Arch.* 1896;143:337–368). *cf.* Strandgaard NJ. *op. cit.*, pp.139–147. Johnson, 1984, *op. cit.*, p.15 (W. Roberts).

<sup>253</sup> Good CA.: ‘An experimental study of lithium’. *Am. J. Med. Sci.* 1903;125:273–284.

<sup>254</sup> Rabuteau P.: ‘Études expérimentales sur les effets physiologiques des fluorures et des composés métalliques en générale’. Paris: Baillière, 1868.

<sup>255</sup> Levison, 1896, *op. cit.*, pp.338–384.

<sup>256</sup> Levison F.: ‘Om Nyrennes Forhold til Arthritis uratica’. *Hosp. Tid.* 1894;4R:2:269–274. Meeting in Copenhagen Medical Society, 9 January 1894. Discussion: pp.270–274 (among the discussants were Carl Lange, Knud Faber and F. Levison [272]).

<sup>257</sup> Lange F.: ‘Slægter. Iagttagelser fra en Sindssygeanstalt’. Copenhagen: Nordisk Forlag, 1904. Lange F.: ‘Om Arvelighedens Indflydelse i Sindssygdomme’. Copenhagen, 1883. Thesis. *cf.* Ostenfeld I.: ‘Herman Bang og århundredskiftets degenerationslære’, in his ‘Seks patografiske miniaturer’. Copenhagen: Novo Industri, 1966. pp.31–39.

<sup>258</sup> Lange F.: ‘Degeneration in families: Observations in a lunatic asylum’. Translated by C. C. Sonne. London: Kimpton, 1907.

<sup>259</sup> Ostenfeld I. (Schmidt, M.), ‘Dansk Biografisk Leksikon’, 1981, *op. cit.*, p.481. Starklint, *op. cit.*, p.346. One of Lange’s patients was the painter P. S. Krøyer (*cf.* Starklint JF.: ‘Kunstneren P. S. Krøyer’. *Med. For. (Cph.)* 1980;33:147–150. Søgaard I.: ‘P. S. Krøyers sygdom—dementia paralytica eller maniodepressive psykose?’ *Bibl. Læg.* 1997;337-371. Krøyer painted Lange’s portrait, included here as figure 6.)

<sup>260</sup> Christiansen V.: ‘Dr. Fr. Lange, Overlæge ved Middelfart Sindssygeanstalt: Slægter, Iagttagelser fra en Sindssygeanstalt. Copenhagen, 1904’. *Bibl. Læg.* 1904;96:459–472.

<sup>261</sup> Christiansen V.: ‘Om Urinens Giftighed, specielt hos Sindssyge. En experimentel Studie’. [On the toxicity of urine, especially in insane patients: an experimental study]. Copenhagen, 1898 (reviewed by A. Friis in *J. Ment. Sci.* 1899;45:389–390).

<sup>262</sup> Bouchard CJ.: ‘Leçons sur les auto-intoxications dans les maladies’. Paris: Sauy, 1887. Bouchard CJ.: ‘Sur les poisons qui existent normalement dans l’organisme et en particulier sur la toxicité urinaire’. *Compte-Rendu de la Société de Biologie.* 1886, quoted here from Christiansen, *op. cit.*—*cf.* Stephani [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. Roncoroni L.: ‘Relation between epileptic fits and auto-intoxication’. *Arch. Psychiatr.* vol. 21, fasc. 6 (reviewed by W. C. Sullivan in *J. Ment. Sci.* 1901;47:380–381). Frigerio A.: ‘Some facts concerning the nitrogen residue of the blood in cases of mental disorder’. *Riv. Pat. Nerv. Ment.* October, 1922. According to a review by W. S. Dawson (*J. Ment. Sci.* 1923;69:387–388), ‘research was undertaken on the theory that auto-intoxication from disturbance of the protein metabolism arising through lesions of the liver or kidney might be the cause of mental symptoms’. Goodall E.: ‘Considerations, bacteriological, toxicological and hæmatological, and others thereto akin, bearing upon the psychoses’. *J. Ment. Sci.* 1923;69:417–434. Cotton HA.: ‘The relation of chronic sepsis to the so-called functional mental disorders’. *J. Ment. Sci.* 1923;69:434–465. *cf. ibid.* pp.379–380. Graves TC.: ‘The relation of chronic sepsis to so-called functional mental disorder’. *ibid.* pp.465–471. Maudsley H.: ‘The physiology and pathology of mind’. London, 1867ff. Watson C.: ‘The rôle of auto-intoxication or auto-infection in mental disorders’. *J. Ment. Sci.* 1923;69:52–77 (cited by Devine). 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. Walker J.: ‘The reaction of the

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urine in 120 cases of mental disorder'. *J. Ment. Sci.* 1923;69:327–330. Anon.: 'Chronic sepsis and mental disease'. *J. Ment. Sci.* 1923;69:502–504.

<sup>263</sup> Bouchard C[J].: 'Lectures on auto-intoxication in disease or self-poisoning of the individual'. Philadelphia: Davis, 1894 (with a preface by T. Oliver).

<sup>264</sup> Christiansen V.: 'Dr. Fr. Lange' etc., 1904, *op. cit.*

<sup>265</sup> *ibid.*, p.469–470.

<sup>266</sup> *ibid.*, p.470.

<sup>267</sup> *ibid.*, p.471.

<sup>268</sup> 'Discussion'. *J. Ment. Sci.* 1881;119:471.

<sup>269</sup> Christiansen, 1904, *op. cit.*, p.471.

<sup>270</sup> *loc. cit.*

<sup>271</sup> *ibid.* p.471–472.

<sup>272</sup> Grosskurth P.: 'Havelock Ellis. A biography'. New York: Alfred Knopf, 1980. pp.217 (note), 226.

<sup>273</sup> Ellis, *op. cit.*, pp.180–187. Ellis H.: 'A study of British genius. VIII—Pathology'. *Pop. Sci. Mth.* 1901;July:266–272. cf. 'Editorial: Uric acid and the psyche'. *JAMA* 1969;208:1180.

<sup>274</sup> Anon. *J. Ment. Sci.* 1908;54:396–397.

<sup>275</sup> 'Lange versus Steenberg', 1886, *op. cit.*, pp.647–648.

<sup>276</sup> Ostenfeld I.: 'Herman Bang og århundredskiftets degenerationslære', in his *Seks patografiske miniaturer*. Copenhagen: Novo, 1966.

<sup>277</sup> Christiansen, *op. cit.* p.472.

<sup>278</sup> *op. cit.*, p.168.

<sup>279</sup> Lange F.: 'Den uratiske Sindssygdøm'. *Hospitalstid.* 1908;5R;1(4):73–81; *ibid.* 5R;1(5):97–107; *ibid.* 5R;1(6): 137–150.

<sup>280</sup> Schioldann, 2001, *op. cit.*

<sup>281</sup> cf. Friis A.: 'Danish Asylums'. *J. Ment. Sci.* 1898;44:426.

<sup>282</sup> Lange, 1908, *op. cit.* 1908, p.73.

<sup>283</sup> *ibid.*, pp.73–74.

<sup>284</sup> Levison, 1896, *op.cit.*, p.374–377.

<sup>285</sup> Lange, 1908, *op. cit.*, pp.73–74.

<sup>286</sup> Lange C., 1895, *op. cit.*, pp.45–46; Lange, 1896, *op. cit.*, pp.50–51; Felber's reprint, 1996, *op. cit.*, pp.50–51.

<sup>287</sup> Amdisen, 1985, *op. cit.* p.25; Flach, personal communication, 1999.

<sup>288</sup> Kindly placed at the author's disposal by the late Dr. Ole Laigaard, Middelfart Psychiatric Hospital.

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<sup>289</sup> Levison, 1896, op. cit., p.374.

<sup>290</sup> Lange, 1908, op. cit., pp.74, 76, 81, 100–102, 137–139.

<sup>291</sup> As it has been thought-provokingly drawn to attention by W. Felber (in his centenary reprint of the German edition of Carl Lange's depression treatise (1896)) Carl Lange in a foot note made remarks which retrospectively point towards the now established anti-suicidal effect of lithium, but not recognised by him: 'Three have committed suicide, but they were all patients whom I only knew very superficially. Perhaps, therefore, their diagnosis was wrong. It is possible that they were melancholiacs. Moreover, it would not be particularly remarkable, if the very profound sufferings of the depressed patients would sometimes drive them to suicide without paranoid ideas being involved. Nothing is more common than the [depressed patients] themselves to be harbouring the feeling that their illness will end with suicide, but the risk of this is small or non-existent'.

<sup>292</sup> *ibid.*, pp.137–138.

<sup>293</sup> *ibid.*, p.138.

<sup>294</sup> *ibid.*, pp.79–81.

<sup>295</sup> *ibid.*, pp.100–103.

<sup>296</sup> *ibid.*, p.74.

<sup>297</sup> Lange, 1894, op. cit., p.295.

<sup>298</sup> Ostenfeld: 'Herman Bang', 1966, op. cit., p.37.

<sup>299</sup> Lange, 1908, op. cit., pp.77–79.

<sup>300</sup> *ibid.*, pp.97–100.

<sup>301</sup> *ibid.*, pp.103–105.

<sup>302</sup> *ibid.*, pp.105–107.

<sup>303</sup> *ibid.*, pp.140–142.

<sup>304</sup> *ibid.*, pp.141–144.

<sup>305</sup> *ibid.*, pp.145–146.

<sup>306</sup> *ibid.*, pp.107, 149–150.

<sup>307</sup> *ibid.*, pp.79, 149.

<sup>308</sup> Lange, 1894, op. cit., pp.166–194.

<sup>309</sup> cf. Johnson, 1984, op. cit., p.16, plate VI. Johnson, 1999, op. cit., p.206.

<sup>310</sup> cf. Soares JC, Gershon S.: 'The psychopharmacologic specificity of the lithium ion: origins and trajectory'. *J. Clin. Psychiatr.* 2000;61 (Suppl. 9):16–22.

<sup>311</sup> Friedenreich A.: 'Kortfattet, speciel Psykiatri'. Copenhagen: Eibe - Schultz. 1901 (not sighted). cf. later editions, 1914 (p. 39) and 1921, with A. Wimmer (p. 33). - 1901 edition now sighted [2021] - F. cast doubt on any efficacy of alkaline remedies; lithium was not mentioned.

<sup>312</sup> Fløystrup A.: 'Urinsyreidatese', in 'Salmonsens store illustrerede Konversationsleksikon'. Copenhagen: Salmonsens, 1906. Vol. 17.

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- <sup>313</sup> Bing HI.: 'Urinsyrdiathese', in 'Salmonsens Konversationsleksikon'. 2nd Edn. Copenhagen: Schultz, 1928. Vol. 24.
- <sup>314</sup> Iacobæus, 1906, op. cit.
- <sup>315</sup> Faber E.: 'Urinsyrdiathesen'. Ugeskr. Læg. 1911;73:751–771. (Introductory speech, 7.3.1911). cf. Faber E., *ibid.*, 1912;74:853–855 (M. Hindhede).
- <sup>316</sup> Faber, 1911, op. cit., pp.752–753.
- <sup>317</sup> *ibid.*, p.755.
- <sup>318</sup> *loc. cit.*
- <sup>319</sup> op. cit., pp.755, 770.
- <sup>320</sup> *ibid.*, p.754.
- <sup>321</sup> *ibid.*, p.770.
- <sup>322</sup> Wimmer A.: 'Frederik Lange'. Hospitalstid. 1908:45–48 (reprinted in Schmidt J.: 'Hospitalets første overlæge Frederik Lange', in Jens Schmidt (ed): '100 år Middelfart Sygehus psykiatrisk afdeling 14. Juli 1988'. Middelfart: mv-tryk, 1988. pp.19–26. pp.20–25.
- <sup>323</sup> It is not unlikely that Wimmer in his 'Psychogenic Psychoses', 1916 (edited and translated with introduction by J. Schioldann. Adelaide Academic Press, 2003) pp.34, 169–170 referred to uric acid diathesis and Carl and Fritz Lange's concept of periodical depressions ('uratic degeneration', F. Lange)
- <sup>324</sup> Wimmer A.: 'Speciel klinisk Psykiatri for Studerende og Læger'. Copenhagen: Levin & Munksgaard, 1936. p.375.
- <sup>325</sup> Letter 2.3.1955 (in Schou's private papers and correspondence, kindly placed at the author's disposal by Mogens Schou). Jacobsen thanked Strömngren for having 'discovered a substance which in actual fact in many cases has kept what it had promised', being, of course, a reference to Schou M, Juel-Nielsen N, Strömngren E, Voldby H.: 'The treatment of manic psychoses by the administration of lithium salts'. J. Neurol. Neurosurg. 1954;17:250–260. He referred to neither Fritz Lange nor John Cade.
- <sup>326</sup> cf. Schioldann J.: 'Carl Lange: A biographical portrait', in his 'In commemoration of the centenary of the death of Carl Lange'. op. cit., 2001:11–22. Fritz Lange authored a psycho-biography of his maternal uncle, the famous poet Fr. Paludan-Müller (1808–1876) who suffered from mood swings (Frederik Paludan-Müller: 'Et Levnedsløb'. Copenhagen: Nordisk Forlag, 1899). Ostenfeld I.: 'Det besjælede Univers'. Copenhagen: Busck, 1948. Lund M.: 'C. Lange—Danmarks første neurolog'. Bibl. Læg. 1991;153:362–377. According to a letter from J. Nellemann to H. Deuntzer (1.9.1896), a son of Carl Lange suffered from a mental illness (Lange's Private Paper, NKS No. 2313, Royal Library, Copenhagen). A. Bertelsen, personal communication, 2007.
- <sup>327</sup> Helweg H.: 'Sindssygeværnsnets Udvikling i Danmark'. Copenhagen: Lund, 1915. pp.192-194. cf. Strömngren, E.: 'Dansk psykiatri i historisk lys', in: Jens Schmidt (ed): '100 år Middelfart Sygehus psykiatrisk afdeling 14. Juli 1988'. Middelfart: mv-tryk, 1988. pp.32–44 (38).
- <sup>328</sup> A. Clausager-Madsen to Mogens Schou, letter, 17.6.1956 (in Schou's private papers and correspondence, kindly placed at the author's disposal by Schou). C.-M. would have prescribed 10–30 centigrams of lithium carbonate daily. M S. commented in his reply of 20.6.1956 that the lithium doses used by him and his associates in manic patients generally varied from 100 to 200 centigrams daily, however, he would not exclude that 10–30 centigrams might have 'a certain sedative effect in suitable cases'.
- <sup>329</sup> Peter Christian Frederik Geill (1860–1938), 'Dansk Biografisk Leksikon'. 3rd Edn. vol. 5:135-136.
- <sup>330</sup> H. Tómasson to Mogens Schou, letter, 10.9.1955 (in Schou's private papers and correspondence, kindly placed at the author's disposal by Schou).