

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 8. Resurrection of Carl Lange's concept of periodical depressions

With the demise of the 'die-hard' uric acid concept,⁴⁰³ it is understandable that the Lange brothers' 'ingenious' observations,⁴⁰⁴ based as they were on a fallacious premise, were dismissed, eventually to fall into oblivion. Further investigations into the subject as recommended, for instance, by Carl Lange, Viggo Christiansen, and even Kraepelin, were not heeded.

In 1927 Carl Lange's periodical depression concept re-emerged in Danish medicine, coincidentally the same year that Kraepelin had delivered it its coup de grace.

The prelude to this resurrection was possibly the fact that at the celebration of the Centenaire de Charcot, held in Paris in May 1925, Viggo Christiansen, now an internationally acknowledged neurologist (and later the first professor of neurology in Denmark), was one of the inaugural speakers. In his Eloge he praised Carl Lange⁴⁰⁵ for his 'epoch-making' book on the pathology of the spinal cord,⁴⁰⁶ and in another speech, on migraine, he saw fit, though parenthetically, to mention 'Carl and Fritz Lange' and 'la dépression périodique'.⁴⁰⁷ Six months later, Christiansen delivered yet another centenary speech on Charcot, this time to the Medical Society of Copenhagen.⁴⁰⁸ He reiterated his praise for Lange's book on the spinal cord, and his theory of emotions, i.e. the James-Lange theory of emotions, but he did not mention his depression treatise. Instead, possibly in a bitter-sweet vein, he went on to state that 'it was an unexpected surprise to me that some months ago, at the University of Copenhagen, a candidate for the doctorate [probably Paul Reiter]⁴⁰⁹ could postulate—unopposed—that Fritz Lange had been of no importance to Danish psychiatry'. Christiansen then boldly conceded though that '[Fritz Lange] in his later works more poeticized over rather than studied psychiatry [emphasis added]', undeniably a strange contrast when at the same time he saw fit to eulogise his doctoral thesis on heredity in mental illnesses (1883),⁴¹⁰ comparing it with Morel's famous book on mental degeneracy.⁴¹¹

In all fairness to him it must be added that in a publication from 1906, Christiansen⁴¹² had deplored the fact that Lange's viewpoints and experiences, as laid down in his doctoral thesis, were not to have any impact worth mentioning on the development and direction of international psychiatry, simply because it was published in Danish.

It must not be forgotten that Christiansen, some years later seconded by Erik Faber, had as good as accused the Lange brothers of quackery in relation to periodical depression and its medicinal treatment, apparently an anathema to him. He had not mentioned them in his own recent work on depression, published in 1919.⁴¹³ Thus it must be speculated that he harbored professional jealousy towards them.

H. I. Schou

Christiansen's sixtieth anniversary in 1927 was celebrated with a Festschrift. In this publication the eminent psychiatrist, Hans Jakob Schou, a pupil of Christiansen, courageously contributed with the article: *La dépression psychique. Quelques remarques historiques et pathogéniques*.⁴¹⁴ It was the highest acclaim of Carl Lange's depression treatise and his importance to Danish psychiatry:

'In a [Festschrift to] Professor Viggo Christiansen', Schou wrote, 'there is a very special reason to speak about mental depression, and that even for a double reason'. One was that Christiansen himself had often dealt with this subject and shown 'a special interest' in this 'widespread' illness. Another was that 'our guest of honour', in his works 'more than once' emphasizes the name of Carl Lange.

Now, Schou wished to 'speak about' Lange, who 'has become famous for dealing with this question'. He queried whether what Lange had done for psychiatry had been realised, making reference to his depression treatise with which he

for the first time in Denmark and without any doubt also for the first time in the European literature has described the periodical psychic depression as an independent illness, in its nature typical and well-defined, and which has as its cause organic changes.

Finally, Schou emphasised that this work 'is still being cited today in foreign works, for few Danish works have had similar success, apart from [Lange's] previous work on the physiology of emotions'.⁴¹⁵

Schou proceeded to characterise the depression treatise as 'one of the most beautiful descriptions, absolutely classical, which can still enrich and instruct the readers of our time';⁴¹⁶ but he wished to point out that Lange had made three fundamental mistakes in his reasoning concerning his depression concept:

The *first mistake*, Schou said, was that Lange described mental periodical depression as an independent malady without any relation to melancholy and periodical mania. Schou went on to point out that the mental and physical symptoms of depression 'are completely analogous to those of melancholy, differing by degree only'. Furthermore, he argued that 'the two forms of the malady occur in manic-depressive families'. He conceded, however, that at the time of Lange, the concept of manic-depressive psychosis 'had not yet been launched by Kraepelin'.⁴¹⁷ Finally, Schou argued that the course of 'the two maladies' is the same, in that they commence and cease suddenly, and that between the phases of depression, in both instances, there are 'periods of manic exaltation'. In Schou's opinion, Lange had not observed the latter, though it was 'a very specific feature of the illness', for the reason that his patients were exclusively

non-hospitalised patients, and they would consult him when depressed but not in their exalted periods.

Lange's second mistake, 'chose assez curieuse', Schou went on, was that concerning the very treatment of the illness: he recommended work and exercise as the best cure for the depressed patients.

Lange's final mistake flowed from his theory of the pathogenesis of the illness: that mental depressions were caused by uric acid diathesis ('la goutte et la lithiase rénale'). Unfortunately, Schou noted, subsequent investigations (his own) had not been able to confirm 'cette simple et géniale théorie sur la pathogénie de la dépression psychique'.

Schou, who did not elaborate further on the important third mistake Lange made, proceeded to point out that what psychiatry owes to Carl Lange, apart from the classical description of the symptoms of periodical depression, 'is the emphatic declaration that endogenous depression has a physical cause and an entirely material pathogenesis', and he saw it as 'our task today, in the spirit of Carl Lange, to apply all biological investigation methods in the study of manic-depressive psychosis'!

Schou stated that this illness, especially due to its transitory nature, would lend itself well to laboratory investigations, and he was surprised that few researchers had undertaken this task hitherto. He thought that melancholic illnesses would be much more tempting to investigate than schizophrenia.

In order to contribute 'dans une modeste part à l'étude de la pathogénie de la mélancholie' and, if possible in this way to find an 'effective treatment', H. I. Schou and his collaborators had undertaken a series of basic metabolism studies in depressed patients. In some cases thyroid insufficiency was diagnosed, where improvement of the depression was observed after the administration of a thyroid gland extract.

Schou did not refer to the medicinal suggestions, at least not directly, made by Lange. He mentioned no investigations of his own using lithium.

Knud Faber: a close associate of Carl Lange

Also in 1927, Christiansen, now President of the Medical Society of Copenhagen,⁴¹⁸ invited Knud Faber, the leading physician in Denmark and former Chancellor of the University of Copenhagen, to deliver a commemorative speech on Carl Lange to this Society. Faber accepted this honourable task, but not without trepidation.

In his speech, Faber highlighted that Lange's depression treatise, 'an excellent clinical description', had been 'the starting point for considerable sensation and polemics', as Lange 'saw this illness as a manifestation of uric acid diathesis and instituted his treatment accordingly' (emphasis added). Faber praised Lange's 'ingenious' physiological interpretations and explanations of various kinds of pathology, although he had at times, in Faber's opinion, 'somewhat uncritically' deduced a therapy from physiological arguments.⁴¹⁹

Whether Faber was referring to Lange's recommendation for lithium, which he did not mention explicitly, cannot be established based on the available sources - but there

can be no doubt that he would have been fully acquainted with the Lange brothers' use of lithium.

Faber graduated from Copenhagen University in 1885, and had worked under Lange for a period of three years, 1891–94. From 1892 to 1898, he was co-editor of *Hospitals-Tidende*, of which Lange had been Editor-in-Chief. It was in this journal that Fritz Lange's important posthumous thirty-page rejoinder to Christiansen was published in 1908. Furthermore, as noted before, Faber had been opponens ex officio at Strandgaard's doctoral thesis in 1899. In 1896, Faber was appointed Professor of Medicine at Copenhagen University—he was its Chancellor 1915–17. It is also important to reiterate that he had been among the discussants, with Carl Lange and Levison, at a meeting at the Medical Society of Copenhagen in 1894 concerning issues related to uric acid diathesis and uratic arthritis.⁴²⁰

Faber had been closely associated with Lange professionally as well as personally. In fact, he characterized him as a fine, unselfish and warm person - 'this peculiar sympathetic demi-god'; 'the greatest scientific mind' of Danish medicine in the nineteenth century.⁴²¹ Another contemporary, the famous literary critic, Georg Brandes,⁴²² who was close to the Langes, related that 'better brains than [Carl Lange's] I have not known'.

Finally, Faber would also have been fully acquainted with the opposing, exacting views of Erik Faber, who happened to be his younger brother.

Before delivering his commemorative speech, with respect to Lange's depression treatise Faber had corresponded with the eminent Swedish psychiatrist, V. Wigert, who answered him⁴²³ that *Periodical Depressions* has its strength in 'the finely observed intimate description of the symptomatology of mild depressions'. Further, in Wigert's opinion, Lange with this description 'was ahead of his time [...] It is unambiguously the manic-depressive depressions that are described. Lange has here had a clear view of the connection between the depressive mood swings which fall within normal, now grouped under cyclothymia, and his views of the [depressions] to have a constitutional and hereditary basis are fully consistent with modern views'. However, 'the draw-backs' of the treatise, Wigert emphasized, were that Lange had not seen the identity between mild and more severe cases of depression, and that 'the exalted and manic phases had completely escaped his attention, or rather whose occurrence was categorically denied'.⁴²⁴ Wigert did not touch on medicinal aspects.

Over the years Faber would undoubtedly have discussed the Lange brothers with Christiansen, H. I. Schou and other prominent Danish psychiatrists, for example, Wimmer, Helweg, Thune Jacobsen and Geill.

H. I. Schou again

Schou's interest in Carl Lange's work was sustained. In 1938 he published a paper in which he argued that 'it was a misunderstanding when Lange earlier exercised these patients to remove the "uric acid diathesis", which does not exist'.⁴²⁵ Also in this publication, and in a paper from 1940, he did not mention treatment with lithium, or for that matter other alkaline remedies, but he revisited his views regarding periodical depression as a possible independent nosological entity. Schou did not feel convinced that

it could be grouped with manic-depressive psychosis,⁴²⁶ the physiology of which he studied in a later treatise.⁴²⁷

Schou and his associates devoted an article to this issue in 1947.⁴²⁸ They redefined Lange's concept of periodical depression, whose description 'holds good today'. Further, they emphasised that '*periodical depression has no manic phases and differs from manic-depressive psychosis with regard to heredity as well as distribution of somatic types and prognosis*'. In their opinion, it 'must thus be considered to be an independent nosological entity'. The authors also stressed that the likelihood of finding descriptions in the foreign literature of periodical depression as a nosological entity would be 'very poor'. In doing so they made explicit reference to Kraepelin and their countryman, Sophus Thalbitzer,⁴²⁹ who both maintained that in depression 'a subsequent slight mania will always occur'.⁴³⁰

Schou and his co-authors found it 'characteristic' that periodical depression 'was first described in Denmark by a professor of pathological anatomy who, in addition, practiced as a neurologist'.⁴³¹

Finally, considering why periodical depression had not been thought of as a nosological entity, independent of manic-depressive psychosis, the authors even debated whether it was possibly more frequent in Denmark than in other countries, or whether it was 'a common but hitherto oft-neglected nosological entity, as has been the opinion of one of the authors for about twenty years'⁴³² - this author probably being H. I. Schou himself. In fact, none of the authors themselves, they stated, had attempted 'to separate depression from the manic-depressive notion, so that it really looks as if the ingenious physician, Carl Lange, has displayed his ingenu[m] here as in other domains'.

Interestingly, in his monumental psychiatric textbook Wimmer had cited Lange's 'periodical depressions' in support of a similar view.⁴³³ However, it was not until the 1960s with Angst, Perris and Winokur that the distinction between unipolar and bipolar manic-depressive illness gained momentum.

Schou and his co-authors had not only been unable to corroborate the theory of 'auto-intoxication' with their 'subsequent examinations', which they did not specify, but they had not seen improvement in these depressions 'when the forms of diets used in arthritis urica' by Lange had been applied.⁴³⁴ In a footnote they added that 'Lange apparently made a wrong estimate of the sediment that is deposited in normal urine allowed to stand overnight'.⁴³⁵ But again, his medicinal remedies, including lithium, were not mentioned.

In 1946 Schou authored a book chapter:⁴³⁶ Periodical depressions, written for the general reader. Here he again praised Lange highly for this contribution, but as Schou's text reads:⁴³⁷

what the cause of this illness is, is not known for certain, Lange writes, but as it occurs along with certain forms of gout ("uric acid diathesis"), and as an excess of uric acid in the patients' urine is observed, it can possibly be a kind of auto-intoxication. The treatment does certainly not help a lot; but diet, exercise and certain medicaments [not specified!] appear to shorten the duration of the illness. [emphasis added]

This was followed by Schou's own comments that 'the peculiar thing had happened' that Lange's classical description, 'which still stands today', had not gained recognition among Danish 'nerve specialists'.⁴³⁸ However, probably out of loyalty towards Christiansen, his 'old teacher',⁴³⁹ Schou added, obviously incorrectly, that 'one of the most important', Viggo Christiansen, 'took it to heart and spoke and wrote about it in vivid pictures', which the present author has not been able to confirm.⁴⁴⁰

Schou speculated that the reason why this illness, periodical depression, had not been 'officially recognised until late' was that Kraepelin had 'described another mental illness', manic-depressive psychosis [in 1899], and that there were some similarities between the two. More specifically, Schou pointed out, the melancholic phase of manic-depressive psychosis resembles 'the periodical depressions', although the latter 'as a rule are milder than the former'. Furthermore, referring to Lange's observations of '2000 patients', he stressed that in patients with periodical depressions, 'manic phases are lacking'.⁴⁴¹ Schou felt rather confident that over the course of 'approximately 30 years' he himself had been able to diagnose 'periodical depressions' in 'approximately 3000 cases' (emphasis added).⁴⁴² However, he again dismissed Lange's assumption of an underlying uric acid intoxication, for 'later assays of the blood uric acid level have not shown any deviations from the normal', and he concluded that Lange's observations of 'the red sedimentation in the patients' urinals' were due to the fact 'that the urine was more concentrated than normally'.⁴⁴³

Schou emphasised that the treatment of periodical depressions 'no longer follows the guidelines, which had been set out by Lange' (emphasis added).⁴⁴⁴ As before, he did not mention any of the medicaments used by Lange, at least not explicitly.

Schou and his associates had not seen improvement in the depressions, 'when the forms of diets used in arthritis urica' were applied.⁴⁴⁵ They could have given alkaline remedies when they tested Lange's observations. But, as shown, Schou held the opinion that uric acid diathesis did not exist,⁴⁴⁶ and furthermore, it had not proved possible to detect an excess of uric acid in the blood of their depressed patients.

Schou also referred to Christiansen several times in the 1946 book chapter concerning current treatment methods of periodical depression. Schou himself in milder cases used psychotherapy, sedative medication, namely opium and barbiturates, and in protracted and very severe cases 'the modern shock treatment'.

It must be reiterated that Lange's depression treatise provided only broad guidelines regarding the treatment of depression. Lithium was not mentioned explicitly. But from the previously cited anonymous letter from 'an old medical practitioner'⁴⁴⁷ to *Ugeskrift for Laeger* in 1901, one can only conclude that it was common knowledge that it was lithium that Lange made implicit reference to in 1886, when he first presented his views.⁴⁴⁸

In the present author's opinion, Schou, like for instance Christiansen, Knud Faber, Wimmer and Helweg ('a good friend' of Schou),⁴⁴⁹ would have been fully acquainted with the Lange brothers' use of lithium. However, as its use had been linked to uric acid diathesis, which did not exist, Schou, like the rest of his colleagues, may not have paid any attention to this medication. Unfortunately, the author has not had the opportunity to

sight any of H. I. Schou's personal papers, or case files held at 'Kolonien Filadelfia', a mental hospital, and 'Dianalund Nerve-sanatorium'—of which institutions he was Superintendent.

Did H. I. Schou 'uncompromisingly' deny 'the old Danish lithium treatment'? a generational disagreement between father and son?

Johnson concluded⁴⁵⁰ that although Carl Lange's ideas became 'quite widely disseminated', and 'despite the clear connections between Carl Lange, Alexander Haig and Sir Alfred Garrod, nothing much appears to have been said in the psychiatric literature about Lange's work - Fritz Lange's work did not come to the attention of international psychiatry. However, as has been documented in the present work, contemporary German psychiatry considered it; especially Kraepelin, who dismissed it. As Johnson wrote, Lange's use of lithium 'in particular, seems to have been totally ignored'.

'The final dismissal', Johnson stated, 'came in 1938 in an article in the Danish Ugeskrift for Læger, and here there occurs a strange historical coincidence'. He expanded on this to say that 'this article, whilst giving Carl Lange full and glowing credit for the detailed description of endogenous depression which he had presented in the 1886 paper [his depression treatise], nevertheless did not mention the claims which had been made for the success of the lithium treatment and its success was uncompromisingly denied [emphasis added]', Johnson adding that the author of this 1938 paper was Dr H. I. Schou⁴⁵¹, 'father of Professor Mogens Schou, the foremost exponent of modern-day lithium therapy'.

Johnson⁴⁵² based this view on a translation by Amdisen into English of pertinent parts of H.I. Schou's paper: 'The treatment of depression consists of isolation and confinement to bed. It was a misunderstanding when Carl Lange earlier exercised [...] these patients to remove the "uric acid diathesis" which does not exist' (being a reiteration of points 2 and 3 in Schou's 1927 paper). Finally, Johnson added Amdisen's analysis: 'And, of course, if the uric acid diathesis did not exist, nor did the justification for using lithium as a treatment for depression'.

Amdisen expressed the same opinion in other works of his on the historical aspects of lithium therapy.⁴⁵³ In his preface to the 1982 reprint of Lange's depression treatise, the Danish edition, he wrote that H. I. Schou had 'totally refuted Carl Lange's pathogenetic theories, and thereby also his three methods of treatment ['preventive diets, daily exercise and first of all daily prophylactic intake of alkaline salts'] are being negated'. Thus, in Amdisen's opinion, Schou 'brought about the abandonment of long-term prophylactic therapy of recurrent masked, unipolar depression with lithium (a particular irony in view of the later emergence of his son, Mogens Schou, as a major proponent of lithium therapy)'.⁴⁵⁴ However, in the opinion of the present author, Amdisen's interpretation must be dismissed as fallacious.

It is no wonder that the staunch critic of modern prophylactic lithium therapy, Barry Blackwell, took the opportunity to state in his review of Johnson's book⁴⁵⁵ that Carl Lange was credited for his description of depression but that his claims for lithium were denied: 'foremost among these critics was the father of Mogens Schou' and, he added, 'The dramatic irony of this generational disagreement seems strangely appropriate to

Hamlet's homeland'. Years later, Mogens Schou—to the present writer⁴⁵⁶ and to David Healy,⁴⁵⁷ respectively - refuted Amdisen's claim, to Healy characterising it as a 'ludicrous' idea: 'my father never even mentioned lithium'. Amdisen died in 1990.

H.I. Schou died in May 1952 after some years of failing health, though he remained active with research.⁴⁵⁸ It was in 1951 that Mogens Schou had first heard about the rediscovery in 1949 of lithium's antimanic effects.⁴⁵⁹ However, he maintained that he never discussed lithium with his father. Moreover, he was strangely dismissive of the importance of the Lange brothers' work.

In his impressive 1957 review of the lithium ion, Schou⁴⁶⁰ wrote that Carl Lange 'gave lithium salts to patients with gout and mental depression; he claimed beneficial results in both diseases, but he did not present any documentation'. Schou reiterated this view to Johnson⁴⁶¹ in 1984, namely that he attached virtually no significance to the reports of the Lange brothers - the reports in his opinion being 'speculative and without any evidence that the treatment worked'. To the present author he stated in 1996, 'I consider the Lange brothers' observations interesting, but in view of the lack of documentation of therapeutic or prophylactic effect it is understandable that the therapeutical suggestion died out together with the uric acid diathesis hypothesis'.⁴⁶² Schou reiterated this some months later at a meeting in Amsterdam.⁴⁶³ However, in his foreword to Felber's centenary reprint of the German edition of Carl Lange's depression treatise, in 1996, he conceded that the Lange brothers 'treated many hundreds of patients with doses large enough to lead to serum concentrations of the same order of magnitude as those used today'. But strangely enough he did not cease his criticism of them.⁴⁶⁴ In his interview with Healy in 1998 he now dismissed the work of the Lange brothers outright, emphasising that they

claimed to see substantial improvements in their patients. But [...] they did not publish convincing case histories, and statistics and double-blind trials were not known at that time. The Lange brothers cannot be said to have presented conclusive evidence of a lithium induced prevention of depressive recurrences.⁴⁶⁵

It must be added that from the references included in Schou's Amsterdam paper, it can be gleaned that he then had no knowledge of Fritz Lange's important 1908 work. In 2005 Schou⁴⁶⁶ communicated to the present author,

The Lange brothers can be said with certainty that they did not make me curious. Why should they? My father never mentioned lithium, and Carl Lange's work contained only clinical 'anecdotes', but no systematic documentation. I had no knowledge of the existence of Frederik Lange.

It is correct that Carl Lange did not publish case vignettes in support of his views. However, in view of his posthumous article from 1908, the same cannot be said for Fritz Lange. Therefore, it must be assumed that neither Mogens Schou nor Amdisen had read it.

Did H. I. Schou 'unwittingly' prescribe lithium-containing nerve-mixtures?

According to H.I. Schou's 1946 publication, 'periodical depressions still belong with the misunderstood illnesses', and he said intriguingly that 'the number of patients, who seek their doctor and get the right treatment, is small compared to those who stay at home, only to be nagged at - or perhaps consult their doctor and are being prescribed nerve mixture'.⁴⁶⁷ It was his impression, furthermore, that depression occurred more frequently among women, menstruation and menopause being aggravating factors.

Fascinatingly, at this time some of these 'nerve mixtures' contained lithium.⁴⁶⁸ For example, Carbonas lithicus and Citras lithicus were listed in the Danish Pharmacopoea in 1907, Mixtura Gentianae Lithica, similar to Carl Lange's prescription, in 1913.⁴⁶⁹ Uricedinum, containing lithium citrate, was recommended for arteriosclerosis and 'uric acid diathesis', as late as 1924. Urisalin, also containing lithium citrate, was available until 1984, in recommended daily doses of 12 to 17 mmol lithium. Lithacyl, containing lithium carbonate, was available without prescription until 1965, and on prescription until 1971, and was recommended for rheumatic pains, neuralgia, influenza and menstrual discomfort.

⁴⁰³ cf. Schäfer U.: 'Past and present conceptions concerning the use of lithium in medicine'. *J. Trace Microprobe Techn.* 1998;16:535–556. Schäfer U.: 'Highlights of lithium use in medicine. I. (1817-1970)'. *Mengen und Spurenelemente* 1999;19:791–796.

⁴⁰⁴ Felber, 1987, 1996, op. cit.

⁴⁰⁵ Christiansen V.: 'Quelques aphorismes à l'occasion du centenaire de Charcot'. In: 'Centenaire de Charcot'. *Revue neurologique* 1925;32:1116–1118. Lange was, Christiansen said: 'un élève et un admirateur ardent de Charcot' (ibid.). cf. Schioldann: Carl Lange, op. cit, 2001.

⁴⁰⁶ Carl Lange was not only the founder of Danish neurology, but also a founding father of neurology. cf. Snorrason E.: 'Carl Lange', in C. C. Gillespie (ed.): 'Dictionary of scientific biography'. New York, Charles Scribner, 1973. Vol. 8, pp.7–8. Lund M.: 'Carl Lange—Danmarks første neurolog [Denmark's first neurologist]'. *Bibl. Læg.* 1991;153:362–377. Schioldann J.: 'Carl Lange: a biographical portrait'. In his: 'In commemoration of the centenary of the death of Carl Lange. The Lange theory of 'periodical depressions' etc'. 2001, op. cit., pp.11–22. Lange's classical neurological works are: ['Comments on aphasia'] (1866), ['On acute bulbar paralysis'] (1868), a term that he coined; ['On conduction in the posterior spinal cords and some remarks on the pathology of tabes dorsalis'] (1872), Lange being the first to describe the pathogenesis of tabes dorsalis, the 'root theory'—an anticipation of the neuron doctrine; ['Contribution to the knowledge of chronic spinal myelitis'] (1873), and ['Lectures on the pathology of the spinal cord']. (1871-76): the work that Christiansen made reference to.

⁴⁰⁷ Christiansen V.: 'Rapport sur la migraine (Étude clinique)', in Centenaire de Charcot, op. cit. pp.854–880 (857).

⁴⁰⁸ Christiansen V.: 'Nogle Betragtninger i Anledning af Hundreårsdagen for Jean-Martin Charcots Fødsel'. *Hospitalstid.* 1925;68:1049–1067 (1066). The same work appeared in *Københavns Medicinsk Selskabs Forhandling* with the same title, 1925/26:27–41.

⁴⁰⁹ Reiter P.J.: 'Nogle Undersøgelser over Sukkerstofsiftet ved Psychoser'. [Some investigations on glucose metabolism in psychoses]. Copenhagen: Levin & Munksgaard, 1925.

⁴¹⁰ Lange F.: 'Om Arvelighedens Indflydelse i Sindssygdomme'. [On the influence of heredity on insanities]. Thesis. Copenhagen, 1883.

⁴¹¹ Morel BA.: 'Traité Des Dégénérescences Physiques, Intellectuelles Et Morales De L'Espèce Humaine Et Des Causes Qui Produisent Ces Variétés Maladives'. Paris: Baillière, 1857.

⁴¹² Christiansen V.: 'Kliniske Forelæsninger og Foredrag over Sindssygdomme'. Copenhagen, 1906. pp.114–116. With reference to the viewpoints of the Heidelberger School (Kraepelin) on dementia praecox, Christiansen praised Lange's 'sharp clinical acumen', stating that when reading his work again 'one is struck how in more than one direction he has been a pioneer and, moreover, on many points has anticipated the development that modern psychiatry has undergone'. While expressing some reservation towards Lange's close adherence to Morel's work, Christiansen found that the way in which Lange had delimited the subject, but also 'the wealth of clinical and symptomatological details he injected into this, renders his description the most significant I remember having read'. Christiansen was, of course, well versed with German and French psychiatric literature. From Lange's thesis he especially recommended the chapter on 'acquired idiotism' as the reader here, in Christiansen's words, 'both regarding the delimitation of the individual forms and their manner of manifestation, their symptoms and the description of the terminal stages will find defined the very core of the illness picture that now goes under the name of dementia praecox'. cf. Helweg H.: 1915, op. cit., 192–194. Strömngren E.: 'Dansk psykiatri i historisk lys'. 1988, op. cit. (Schmidt. 100 år. Middelfart. etc.).

⁴¹³ Christiansen V.: 'Den sjælelige Depression'. Bibl. Læg. 1919:233–253.

⁴¹⁴ Schou HI.: Acta Psychiatr. Neurol. 1927;2:345–353.

⁴¹⁵ 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. (2nd Edn. 1910). 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. pp.33–90.

⁴¹⁶ Appendix I.

⁴¹⁷ Kraepelin E.: 'Psychiatrie. Lehrbuch etc'. 6. Auflage. Leipzig: Barth, 1899. As mentioned before (note 207), 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 did.

⁴¹⁸ cf. Genner J.: 'The Medical Society of Copenhagen'. Odense University Press, 1972.

⁴¹⁹ Faber KH.: 'Erindringer om C. Lange'. Copenhagen: Levin & Munksgaard, 1927 (pp.16, 26–28).

⁴²⁰ Levison, 1894, op. cit. Discussion: pp.270–274 (Kn. Faber, p.272).

⁴²¹ Faber KH.: 'Carl Lange', *4. December 1834, †29. May 1900. Hospitalstid. 1900;4R;8(23):573-578. Faber, 1927, op. cit., pp.48–50. Faber K.: 'Personlige Erindringer'. Copenhagen: Gyldendal, 1949. pp.29–31. Faber K.: 'Mit Universitetsliv. Fra Volontør til Emeritus'. Copenhagen: Gyldendal, 1933. pp.62–74.

⁴²² 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. 'When a young man,' Brandes wrote, '[Carl Lange] in full earnest would take a bet that he, extempore, could obtain a Masters Degree in any subject. He could not comprehend which questions one could not answer if given six weeks and the Royal Library [of Copenhagen] at one's disposal. (Therefore, [Lange] did not have much respect for Masters degrees) [...] better brains than his I have not known'.

⁴²³ 4.10.1927, in Lange's private papers, Ny kgl. Samling No. 2313, Royal Library, Copenhagen. Faber does not mention Wigert in his speech, but it is clearly Wigert's opinion that he conveyed.

⁴²⁴ cf. Kahn, 1909, op. cit.

⁴²⁵ Schou HI.: 'Lette og begyndende Sindssygdomme og deres Behandling i Hjemmet'. Ugeskr. Læg. 1938;100:215–220.

⁴²⁶ Schou HI.: 'De saakaldte neuroser og deres Behandling'. *Maanedsskr. Prakt. Lægegern. Soc. Med.* 1940;18:153–168.

⁴²⁷ Schou HI.: 'Studier over den manio-depressive Psykoses Fysiologi'. Copenhagen: Gad, 1945. This work included studies of residual nitrogen levels, but no mention was made of lithium.

⁴²⁸ Pedersen A, Poort R, Schou, HI.: 'Periodical depression as an independent nosological entity'. *Acta Psychiatr. Neurol.* 1947;22:285–327.

⁴²⁹ Thalbitzer, 1902, op. cit. He discussed Lange's famous treatise on emotions at length, but made no mention or reference to his depression treatise.

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⁴³¹ *ibid.*, p.293f.

⁴³² *ibid.*, p.294.

⁴³³ Wimmer A.: 'Speciel klinisk Psykiatri for Studerende og Læger. Copenhagen': Levin & Munksgaard, 1936. p.375.

⁴³⁴ Pedersen, Poort and Schou, 1947, op. cit., p.285.

⁴³⁵ *loc. cit.*

⁴³⁶ Schou HI.: 'Periodiske Depressioner', in Jørgensen C (ed.): 'Sjælens Lægebog'. Copenhagen: Jespersen og Pios Forlag, 1946. pp.162–169.

⁴³⁷ *ibid.*, p.163.

⁴³⁸ *loc. cit.*

⁴³⁹ Schou, 1946, op. cit., p.167.

⁴⁴⁰ *loc. cit.* cf. Christiansen, 1919, op. cit.

⁴⁴¹ Schou, 1946, op. cit., p.163f.

⁴⁴² *ibid.*, p.164.

⁴⁴³ *ibid.*, p.166.

⁴⁴⁴ *ibid.*, p.167.

⁴⁴⁵ Pedersen, Poort and Schou, 1947, op. cit., p.285.

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- ⁴⁵⁷ Healy D.: 'The psychopharmacologists II'. London: Altman, 1998, pp.282–283. cf. Schou M.: 'Lithium: personal reminiscences'. *Psychiatr. J. Univ. Ottawa* 1989;14(1):261. Cogen PH, Whybrow PC.: 'Lithium: a fascinating element in neuropsychiatry', in Bauer M, Grof P, Müller-Oerlinghausen B. (eds.): 'Lithium in neuropsychiatry. The comprehensive guide'. Abingdon: Informa, 2006:3–7.
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