Thomas A. Ban: Neuropsychopharmacology in Historical Perspective

Collated 31

Thomas A. Ban: Lithium

1. Discovery of its therapeutic effect in psychiatry

Johan Schioldann, William T. Hammond and Carl Lange

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Johan Schioldann's comment on William T. Hammond

In the early 1980s Arvid Carlsson drew the attention of Amid Amdisen (1985, 1987a,b) and Steven Tyrer to that of Yeragani and Gershon (1986, 1987) that William Hammond of Bellevue Hospital, New York, was possibly the first to have reported, in 1871 (not in the 1880s as writes Barry Blackwell), on the exclusive use of lithium in the treatment of acute mania in his: *Treatise On Diseases of the Nervous System* (Schioldann 2009). Hammond considered acute mania to be "the more common species of mental aberration" manifested as 1) *acute mania with exaltation* and 2) *acute mania with depression.*

Based on Hammond's view that *cerebral congestion* was the underlying cause, he wrote:

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

He emphasized that

> "the doses should be large, as high as sixty grains or even more – and should be repeated every two or three hours till sleep be produced, or at least till half a dozen doses be taken. After the patient has once come under its influence, the remedy should be continued in smaller doses, taken three or four times in the day, [whereas] in cases of cerebral congestion attended with illusions and hallucinations, but without mania the other bromides will answer the purpose – preferably the bromide of sodium. They may also be given in the more violent forms if the bromide of lithium cannot be obtained."

Thus, Hammond targeted mania without secondary features, illusions and hallucinations, but when caused by ***cerebral congestion***. He did not comment on any possible etiological causes, nor did he specify whether both type 1 and type 2 were treated, nor did he mention any inspirational sources. Most intriguingly, however, he did not mention use of lithium in his later works (1882, 1883 and 1890). In 1882 he wrote:

> "First among [internal remedies] must be placed the bromide of potassium. […] Latterly I have used the bromide of sodium […] instead of bromide of potassium. […] The bromide of calcium is also well adapted to the treatment of cerebral congestion and has the advantage over the other bromides of acting more promptly. […] Latterly I have made much use of arsenious acid in cerebral congestion, especially in cases which have been the result of mental exertion or anxiety."

Thus, he was not forthcoming with any comments on his having abandoned lithium therapy.

It must be speculated whether Hammond had ceased using lithium (the bromide!) due to lithium and/or bromide toxicity, in view of the "tremendously high doses" he had administered

(Yeragani and Gershon 1986, 1987; Amdisen 1987a,b; Schioldann 2009). However, as we learn from his 1882 work, undeterred he continued to use salts of bromide. Although, as was established by Gowers, that weight for weight there is "much more bromine in the lithium salt than in any other salt of bromine, the percentage of bromine in the molecule being 92 per cent," it cannot be ascertained whether Hammond opined that lithium *per se* had specific anti-manic properties (Gowers 1881; Tuke 1892). He eliminated lithium from his treatment regime but not bromide, and he did not substitute carbonate or citrate for bromide.

As can be established from Carl Lange's 1886 depression treatise (Schioldann 2009), it was around 1874 that he had commenced prescribing lithium (carbonate), the year he opened his private neurology clinic in Copenhagen. He, as well as his brother, Fritz, discouraged the use of bromides.

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Carl Lange: On Periodical Depressions and their pathogenesis

Speech delivered to the Medical Society of Copenhagen, January 19, 1886

Translated from the Original Danish into English by Johan Schioldann*

Gentlemen,

Introducing the statements that I have the honor of making tonight with an apology for their shortcomings and weaknesses, I must ask you not to consider this as a token of customary modesty, but as a genuine expression of my all-too-full awareness that the investigations and observations, the results of which I am about to present to you, are lacking in no small degree the scientific exactitude and precision that nowadays are mandatory even within the clinical field. Perhaps I dare even hope that at the end of this presentation you might agree that the shortcomings do not entirely stem from my own deficiencies, nor from the conditions under which the observations have been collected, i.e., in private practice, but that, in essence, they stem from the nature of the subject, so that it has been beyond me to remedy them. Thus, the importance of these shortcomings has not diminished, and I should probably have delayed the matter still further than I have done before daring to bring up the subject in a scientific forum, had it not been for two reasons.

One reason is the great importance of the matter, as it is about an extremely frequent, often most serious form of illness which strangely enough has almost completely escaped any notice in the literature. 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 which by far occurs as frequently. Even the most common *neuroses,* such as epilepsy, hysteria, all the various forms of neuralgia

taken together, are nowhere nearly so frequent. It is therefore that over the approximately 12 years during which I have particularly focused my attention on this disease, the material of my observations has grown to at least 7-800 cases. I suppose that I must be wary of drawing from my personal experiences definite conclusions regarding the relative frequency of the disease claiming that it really occurs more often than for instance epilepsy - although I am convinced that it does - for there are many ways in which a selection can easily happen concerning the cases that present to, or are referred to, a specialist. At any rate, my experience shows beyond doubt that the condition, at least in this country, is extremely common (Note 1). Moreover, that it is generally very serious will emerge in the following description which will illustrate to us a condition extremely painful both for the patient himself and for those surrounding him and which, despite remissions for major periods of life, often destroys or drastically reduces the happiness or capacity for work of its victim, causing him to waste his life, although rarely exposing him directly to danger.

The other factor that has contributed to my overcoming my reluctance to present to you 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. I am 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. 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.

That sufferings of such common occurrence and importance as those conditions of depression being dealt with here can be so little known that they have left but few sporadic traces in the literature, consequently leaving most doctors in the dark and unclear about them, might appear strange at first sight, but on closer scrutiny this is easily explained. Psychiatrists under whose field the illness really belongs, according to its nature, only seldom get to see it because the patients rarely seek the asylum. To the other doctors who, as a matter of fact, do not readily accumulate large numbers of definite cases for comparison, the illness does not commonly manifest in a particular form and for obvious reasons these patients are not among those with

whom doctors in general practice prefer to occupy themselves. Generally, they are considered odd, difficult and uncooperative rather than insane, which in fact they are, even in a distinct and very characteristic form.

It also happens often enough, of course, that the doctor when faced with these patients has to "make a diagnosis" or, in other words, give the illness a label, place it somewhere in the nosological system. It is then usually placed under one or another of the common illness concepts, many of which are sufficiently vague to allow for the inclusion of quite a number of heterogeneous features. Very often these patients have been referred to me as *hypochondriacs*, although hypochondriasis, *sensu strictiori*, the morbid worry over and theorizing about imagined illnesses, from a symptomatic viewpoint, has but a very superficial similarity with the periodical depression and concerning course and other nosological features, none at all. Others are labeled as *melancholiacs* and undoubtedly this is a defensible approach as the somewhat vague descriptions of melancholy other than the typical forms also include descriptions which to an acceptable degree are applicable to our patients. I dare say that it is important to consider whether this may be caused by a not entirely fortunate delineation of the concept of melancholy and if this concept would not gain in clarity and obtain a more homogenous content if it clearly excluded the cases that we are about to deal with here. I shall allude later to the relationship between melancholy and periodical depression. It is of some pathological interest to us, as will later become clear to you, that previously some number of these cases were undoubtedly subsumed under the concept of *oxaluria* (*Golding Bird*) with which the younger generation is hardly familiar but which was very popular 30-40 years ago, from a symptomatic viewpoint a poorly defined nosological entity which was identified only by means of the presence of oxalic acid in the patient's urine and which, therefore, had to be abandoned when it was shown that the presence of oxalic acid in the urine did not necessarily predict the presence of oxalic acid in the blood. Finally, I shall again briefly touch upon the fact that a number of cases of periodical depression nowadays are undoubtedly included in the modern "box room" for ill-defined and hitherto unclassified nervous sufferings, the so-called *neurasthenia*.

That a group of pathological phenomena of individual cases only late and with difficulty take the form of a pathological concept *sui generis*, is usually due to the fact that they occur either too rarely to allow the individual observer easily to obtain a large enough number of cases so that

the characteristic common features leap to the eye, or because it is difficult to extract a typical pathological picture from the individual observations taken together because there is too much diversity amongst them. Regarding periodical depression, neither applies. I have already touched upon its frequency, at any rate, in a specialist practice and what constitutes the typical pathological picture is exceedingly easy to delineate. But it is not this common picture with which we are often faced, an abstract pathological picture, a kind of Galton photography that contains parts of all the components but without rendering any one of them clearly. Individual cases of periodical depression can, of course, vary according to the patients' mental inherent characteristics, their intellectual development, the degree of the illness, etc. Most of them are as like as two peas and one can often astonish patients by describing to them in detail all their sufferings once one has arrived at the main diagnosis.

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. However, the picture of the illness is in essence the same not only within the same period of depression but also in different periods.

The designation of the patient's condition as melancholy, depression, will at once bring forth in your mind a picture to which a verbal account cannot do justice but a picture which is certainly in need of a closer analysis in order not to be misinterpreted regarding its psychological conditions and significance. The pathognomonic characteristics of the illness, the patient’s most constant complaints, the feeling of heaviness, weariness, weakness, of a burden, which is mentally and physically exhausting and of apathy towards the ambience of his surroundings, these are symptoms which, from a psychological viewpoint, could have been caused in many different ways. This is also the reason that it will not do to attach the very same pathological weight and significance to all the various clinical pictures one encounters.

Our patients, who under the influence of the “mental pressure” that weighs them down, have a tendency to abandon all their work and duties to live absorbed only by their thoughts or rather - for of *thoughts* there are hardly any - by the experience of their own misery, in real terms have not suffered an absolute break in their work capacity. They rather feel it as a great strain, thus as a great unpleasantness, to have to do something, to throw themselves body and soul into things and, therefore, they understandably try to shirk it, particularly when they must show initiative or make decisions. If they succeed in pulling themselves together to get started with work or are

forced to do so, then it seems, as a rule, that it is carried out without deficiencies concerning quantity or quality. Indeed, it seems as if the initiative to stop again once they have got going with rather monotonous and routine work can prove just as difficult as the decision to start. For instance, I can recall patients who have indicated to me that once they had overcome their reluctance to go for a walk, then found it was "as if they had to walk to the end of the world."

Intelligent patients who strive to find appropriate expression for their subjective sensations often describe their condition as "a mental stiffness or paralysis" and thereby they probably give an apt expression of their feeling of exhaustion at, and thus displeasure with, any operation of thought, every decision, this loathing for all activity that is so characteristic of their condition. While one does not wish to read more into this expression than it actually yields, namely a picture, then I feel like saying that 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* that are their constant complaint. In the opinion of those surrounding them they cannot be bothered with anything, but according to themselves they are capable of nothing, are unfit for everything, their "lives are wasted." It is for the same reason that they usually shun human society. It is not the melancholiac's fear of or suspicion towards his fellow man, fear of persecution or the like that make him prefer solitude. The reason is simply that social intercourse demands more than he can cope with. When in the company of others, he has to talk, follow their train of thought, follow the rules of etiquette, etc., which cost him such a great effort and strain, it can seem only natural to us that he would rather evade it.

Therefore, when the depressed prefers to spend his days in solitude and idleness, then it is due neither to ruined working capacity nor to his being controlled by false ideas that inhibit his activities, nor fear of or abhorrence of his fellow man, but simply because he, like the tired or sorrow-stricken, feels most at ease where neither activity nor effort is demanded of him.

Yet, it is only relative well-being that he can procure by thus evading the painful effort that any demand on his activity causes him, for his suffering also spans other mental functions which are not within his power to suspend, as to some extent he can with regard to his "volitional" and reasoning power. This state of the nervous system, the "stiffening," if you like, which manifests

itself as slowness, strain, fatigue at any operation of thought or decision-making, in the area of emotions manifests itself in analogous ways with a more or less marked indifference towards everything, an often total lack of interest and concern even about those persons who are closest and dearest to him and towards everything that happens around him. In intelligent patients, particularly in cultivated circles, this profound indifference towards the surroundings is often disguised by their ability to comply fairly well with usual conventional forms of mutual interest and sympathy, their lack of depth becoming evident only in more intimate relationships or in the unreserved confessions of the patients. In many cases it is this feeling of "mental emptiness," where neither other people nor events nor natural surroundings, are able to arouse any warmth in them, which is the most bitter complaint of these patients.

The very essence of the patient's mental difficulties and his sufferings is often characterized by himself as a feeling of sorrow or disaster. The picture he presents to the observer is certainly that of the mourning, the more so because he is inclined to burst into tears at the slightest provocation. At any rate, even the relatively few patients who do not have fits of crying feel a strong urge to cry, and they themselves have a feeling that tears would do them good, that it would unburden their souls - being something which is certainly not usual for them. In reality there is no other difference between the condition described here and what is usually described as sorrow other than that the latter has a psychological basis which, as we shall learn later, the depression lacks, or at least does not have to a degree adequate fully to account for it. Moreover, the patients are always, in contrast to the melancholiacs, fully aware that this feeling of misery is completely unrelated to, or at any rate insufficiently caused by, the trivial and passing worries that perhaps might have been the final straw in its development.

With regard to its physiological characteristics, sorrow is so closely related to anxiety that we are not surprised often to find in these patients' morbid mental state a more or less pronounced admixture of anxiety. This is not the rule, however, as anxiety is completely lacking in a great number of cases, while in other cases it can be so strongly pronounced that the depression, at any rate periodically, for instance during the night, is almost overshadowed by it. No more than sorrow and misery, does anxiety stem from any delusion not to mention hallucinations. The patient is terrified neither by imaginary persecutions nor threatening voices. He is as fully aware of the groundlessness of his anxiety as that of his sorrow; nor that it has any particular object. He is not

afraid of this or that, but he has only an indescribable feeling of apprehension. As it is not rare to hear patients from the more unsophisticated social classes characterize this feeling as “agony,” they are certainly not describing a fear of dying but rather giving an expression of the intensity of their feeling.

There are, of course, nuances in the illness picture, depending on whether inertia or apathy predominates and on whether the feeling of misery or of anxiety is especially pronounced. Generally speaking, the state of male patients is to a high degree marked by lack of initiative, strain and difficulty in deciding to work, whereas in the case of women it is often the obtuseness of their emotions that comes to the fore. This fact is probably more due to the difference between the normal and the morbid state than to any difference between the two sexes and is not marked to such a degree that the illness picture should generally manifest any particularly different character in men or in women.

The physical symptoms are generally less significant and less constant than the mental symptoms and they do not keep pace with them in such a way that one can generally say that they are most pronounced in those patients who suffer the most mentally. The depressed mental state is particularly evident, of course, in both physical appearance and facial expression so that the patients look “despondent” or unhappy. This is not, however, a constant feature and one cannot in any way flatter oneself by always being able to diagnose the condition going solely by the patient’s appearance. This is partly due to the fact, which shall later be dealt with, that within the morbid period there often occur significant changes in well-being such that one can often encounter even a severely affected patient in a momentary state in which he does not appear to be unhappy. But this is also partly because many people, in particular those who are the most mentally developed, make great efforts to control themselves to such a degree that their appearance does not betray their mental state. Whereas it is often easy to read the illness from the facial expression of a patient of the peasantry - which yields a significant proportion of depressed people - it is the exception that in a patient from the “cultivated classes” one diagnoses the illness as he enters through one’s door.

Now that I am describing the patient’s behavior as presented to the doctor, it permits me to touch on another matter that is perhaps in itself quite inessential, but at the same time, quite characteristic of these patients and which can contribute to the difficulty of diagnosis. It is

exceptional, at any rate in my practice, that a patient of the kind described here who when asked to indicate what his suffering is, when he presents for the first time, immediately admits to and complains of his low spirits, mental state or the like. Almost constantly one is confronted with complaints of some type of physical feeling: headache, dizziness, backache, abdominal discomfort, etc., etc., complaints which, as a rule, appear to have very little objective basis as it is very rare for further mention of them to occur once one has established the real nature of the illness with the patient. In this matter there undoubtedly exists a conscious reluctance in the patients to admit to or rather to accuse themselves of suffering from a mental illness. On the other hand, however, they usually clearly feel relieved when they feel they have been seen through and are asked directly if it is not rather a mental condition from which they are suffering of which they have always been fully cognizant and which they never try to deny.

It is fairly common that patients lose some weight during their morbid periods, but whether it is a matter of loss of actual substance or often rather the diminished turgor, this collapse, which in many patients manifests itself concomitantly with the onset of the illness, that is the real cause of this apparent diminution of flesh, is not always easy to determine. It is impossible, of course, to carry out really convincing weight studies in ambulatory patients in whom there occur only insidious weight variations. The *collapse* that is being referred to is often clearly pronounced. Thus, the patients become more pale than usual and they are frequently very sensitive to cold, and in particular they complain of cold hands and feet, though in many patients this condition is often interrupted by sudden paroxysms of heat, sometimes throughout the body, at times only in the head. There are also many patients in whom *diaphoresis* is a prominent symptom, partly as a general tendency to perspire, partly as sudden apparently inexplicable paroxysms of perspiration - especially with frequent nightly occurrence. The *pulse* shows nothing remarkably abnormal. Some self-observant patients claim that in their bad periods it throbs somewhat slower than when they are well.

Sleep is often disturbed, broken by anxious dreams and at times insomnia becomes a very tormenting symptom. One must not become misled by the answer that one generally gets to one's questions about sleep: "Well, it seems to me that I could sleep forever." This is but an expression of the mental and physical feeling of fatigue and weakness of these patients who, as closer examination shows, is not at all indicative of sound and unbroken sleep. Yet, on the other hand, it

is not rare that patients, even in cases where the depression has become very pronounced, sleep well and calmly so that they long for the night as a refreshing intermission to their sufferings. 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, often accompanied by the well-known oppressive epigastric feeling, at these hours reach their highest degree gradually abating during the day, in particular towards the 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 half of the cases, although they appear to be lacking in a number of patients and a small number even state that the opposite occurs in them, but this never appears to reach such a pronounced degree as the contrast between the gloomy mornings and free easy-to-tolerate evenings.

Appetite is in many cases only moderate. *Digestion* appears to be somewhat sluggish in the majority of patients. There is often some constipation. *Menstruation* is undisturbed, also during the morbid periods and does not, as a rule, appear to have any influence as such on the patients' condition. Yet, a few women claim that they feel worse when they menstruate, whereas others claim quite the opposite, that they feel best during this time. These statements are, however, too vague and too sporadic to be given much significance. A small number of patients have vehemently claimed to have observed a pronounced periodicity in their illness, related to their menstruations, to a degree that they feel almost quite well during the days in between their periods of menstruation, yet increasingly unwell the closer they get to a period of menstruation or *vice versa*, but I have not had the opportunity to investigate the validity of these suggestions.

I shall later return to the matter of *the urine* to which I attach crucial importance in the understanding of the pathogenesis of the illness.

Gentlemen, there are perhaps among you those who would say that the illness picture which I have outlined to you here does not present anything peculiar as, at least concerning its main features, it gives us the picture of a melancholiac as he appears during the mildest degree of his illness and what I have called *periodical depression* is nothing but what some authors, at least in recent times, have described as the first stage of melancholia, the stage of depression. As I have already suggested, this is true in that in recent times the picture of melancholy has certainly been obscured and interfered with because psychiatrists who, as it has often been emphasized, "as a rule

do not get to see this first stage," have undoubtedly placed depression under melancholia and regarded the former as the first phase of the latter due to a certain superficial similarity. But depression, as I have described it, has nothing to do with melancholia; the depressed never become melancholiacs and it is therefore quite inadmissible to categorize them as being in the first phase of melancholia simply because their illness, from a superficial viewpoint, shows a certain similarity with mild cases of melancholia. 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 30 or 40 years before, and not a single one has developed either delusions or hallucinations (Note 2). Thus, if it is unjustifiable to place it under melancholia, using its course as a criterion, then it is, if possible, even more inadmissible to do so for psychological reasons - and certainly the psychiatric system is here psychologically based and, therefore, psychology must be the guiding principle in the delineation of these illness concepts. The distinctive feature of the melancholiac is that his feeling of misery, his anxiety stems from delusions, such as imaginary persecutions or tormenting and frightening hallucinations, and therefore he deems his sorrow and misery well-founded. In the depressed person, on the other hand, no matter how long his illness goes back and no matter how strongly it might have overwhelmed him, there is not the slightest suggestion of delusions or hallucinations. Their illness is purely and simply an anomaly of mood and these persons are always fully aware that it has no external basis. This is, I suppose, a radical and decisive psychological difference. To this should be added the whole course of the illness which, as a rule, makes the course of the lives of the afflicted so very different in the two types of patients. In melancholiacs the periodicity is, if not unknown, always an exception to the rule and would possibly become even less common than is the case were the depressed that are assumed to be melancholic meticulously separated out from them. As opposed to this, in the depressed the periodicity is constant and is such a prominent feature that it certainly provides the basis to choose the name of the illness accordingly. This periodical course I shall now go on to describe.

As uniform as the illness picture generally must be considered to be within the limits of the periods of depression, just as varying it is concerning the periodicity itself, not only in such a way that it differs from patient to patient but also such that it is usually quite irregular within the individual patient. This irregularity occurs not only due to the fact that at times the morbid periods

- as I shall later show - are hastened or precipitated by unfavorable external conditions and probably delayable or also preventable by more beneficial conditions, but to a significant degree appears to be inherent in the nature of the illness, as it is only exceptional that its course is influenced by external circumstances - or, at any rate, that such an influence can be established.

Accordingly, if one inquiries about the duration of the periods of depression and of the free intervals, then there exists no rule, no common picture. To be able to talk of what is common then, at any rate, one must allow considerable scope. One can probably say that the morbid period most often lasts three to six months, the good interval perhaps a little longer. However, it is not at all unusual that the period of depression lasts much longer: a year, even perhaps two years, and the free periods can spread over yet longer periods, three or four years, possibly more. On the other hand, one can also see cases in which the periods are very short lived. The depression may last for about one month, even for only a couple of weeks with similarly short intervals. On the whole, one can probably say that long periods of depression belong with long free periods and *vice versa*, but the individual cases show many exceptions to this rule.

Although it is impossible to establish any rule for most of the patients, either regarding the type of changeability or the duration of the individual periods, on the other hand, there exists a fair number in whom the illness in the above regards can occur with a certain regularity, at any rate for longer periods of their lives. As a rule, one can say that the shorter the periods of illness are, the greater is their tendency to occur in a regularly intermittent manner. Not a few patients for instance, over a number of years, have periods of depression lasting one to two months every six months, spring and fall or summer and winter. Others have only a single bad period each year. If this happens to occur during winter, of course they then assume that it is the cold that adversely affects them, whereas, in the opposite case, they think that it is the heat that is causing their troubles. However, I do not believe that temperature has any noticeable influence. Depression occurs during summer and winter alike. On the other hand, during summer, under more favorable conditions the patients generally feel more able to resist the morbid state and, therefore, perhaps manage it better at this time of the year than in winter. In the rare cases of the type with short periods, at least according to the claim of some patients, these can be so regular that they can predict on which day the depression will occur and on which day it will end. Here we are only dealing with periods of

depression that last approximately one week with free intervals of a couple of weeks, although this is extremely rare, and as the disease persists this appears to be replaced by the usual irregularity.

The morbid period itself, at any rate when it is of longer duration, never passes evenly and uniformly, even disregarding the aforementioned common evening remissions. Much more common is a constant fluctuation in the patient's state such that weeks or months of profound illness alternate with similar periods of relative well-being and within these greater or longer swings one can, on the other hand, again observe numerous regularly small swings with a duration of days or just hours.

When one observes this continual rise and fall within the morbid periods, which certainly can vary to an extreme degree in different patients but which is hardly ever completely lacking, then one will necessarily have to ask the question if not all the changes during the course of the illness are due to similar swings and if these patients, once their illness has started, will ever again return completely to a normal level; in other words, whether these periods that I have described as the free intervals are really full intermissions or possibly just an expression of strong remissions with relative well-being which in contrast to the periods of suffering are described by the patient himself and those surrounding him as good health. Concerning the answer to this question one is, true enough, to a significant degree dependent on an estimation by the patient himself and the circle within which he moves daily and in most cases, therefore, one has to leave the matter undecided. However, often enough one learns that never since the start of the illness or even never, as far as the patient can remember, has he felt completely free of a certain mental oppression, never has he had a confident or cheerful nature, yet without in his everyday life in any way having felt that he was abnormal or in a proper sense suffering. On the other hand, however, there are also many patients, and at times amongst them those who suffer the most in their bad times, who are described as, or who themselves testify that they are, “by nature” good-spirited and that before the manifestation of their illness they felt, and in the free intervals still feel, as easy and happy as anyone, although, and this should be emphasized, as far as my experience goes, between the periods of depression there never develop states of morbid “elevation” that could place the whole illness under the sphere of the cyclical forms of insanity. Even in cases where there are initially complete intermissions, particularly in persistent and protracted cases and on the whole in elderly people, these intermissions gradually appear to become less clear cut and I have experienced

several elderly patients in whom the hope of obtaining an even tolerable remission of their sufferings appears to be very slim.

Under such constant swings between suffering and well-being, in absolute or relative terms, these miserable people drag on often for a large part of their lives and their deplorable condition becomes all the more burdensome, as it is only rarely considered to be morbid by those surrounding them, but rather much more frequently as evidence of oddity, uncooperativeness, moroseness, indifference or the like. They themselves often share this opinion to a degree and from this it follows that probably, on the whole, only a fraction of the patients think of seeking medical assistance for their sufferings. The one who has sharpened his eye to the manifestations of depression will have no difficulty in recognizing its milder forms in a great number of people who are accustomed to bearing their periods of "bad moods," "indisposition," as something which belongs with the vicissitudes of any human life. Indeed, perhaps one dares say that there are probably only few people who completely escape any taint of the illness described here.

The duration of the illness is very variable in individual patients and significantly dependent on the time of the manifestation of the first period of depression. For once a person has fallen victim to this illness, he is rarely rid of it until sometime into his advanced years. I believe, however, that I can say that the earlier in life the periods of depressions occur, the earlier they show a tendency to diminish. But I must admit that even with a good many years of experience it is difficult to be completely certain regarding this matter which, in all events, is in no way constant. The first pronounced period of depression in more than half of the cases probably manifests itself during the period from the ages of 25 to the age of 35, yet very frequently between the age of 20 and 25 as well, and even between puberty and the age of 20. I have never myself encountered children with typical and marked depression. But the accounts of quite a number of patients of their childhood make it obvious to me that children as well, albeit probably only rarely, can be afflicted by this illness. After the age of 35 the number of sufferers rapidly diminishes year by year so that it can be said that it is a rarity for people to develop the illness if they have not shown signs of it before the age of 50. Yet it can happen. I have even encountered patients who were adamant that they had never had the slightest trace of depression until they were 60-years-old and in these cases the illness has appeared to me to be particularly tormenting, the remissions short and incomplete, the treatment without result.

If the illness is left to itself then the regular course appears to be this: that for a number of years, commonly to about the 50th year, it worsens as the periods of depression gradually become longer, the depression deeper, the intermissions less clear cut. At a more advanced age, approximately after the 60th year, there appears to be, at any rate in many cases, a tendency towards spontaneous improvement. In earlier periods of life such a "spontaneous" improvement or recovery is extremely rare; yet, every now and then I learn from parents that in their children's illness they recognize conditions which they themselves experienced but had recovered from at a young age.

Here I shall mention that pregnancy does not appear to be compatible with depression (a view he corrected in his preface to the second edition of this treatise: *translator's note*). As far as my experience goes, it is an established rule that depression, if it is present, is interrupted with the commencement of pregnancy and it does not recur until after the period of gestation - and probably also that of lactation.

Regarding the *causes* of the illness as we first consider the predisposing factors, next to age, the significance of which I have already touched upon, it is only inheritability that is of importance, but this is certainly of decisive importance indeed. Gender is without significance except that women are perhaps afflicted at a slightly younger age than men. It appears that one need attribute little influence to profession, job and level of education. The significance in the development of nervous and mental illnesses that one so often ascribes to the hectic, restless life in big cities does not apply to periodical depression. It thrives as well among the rural population, even in the most remote regions as in the capital, and with the same frequency afflicts those individuals whose intellectual life is the least developed, the most monotonous and apathetic and those who live the most intensive business or intellectual life. Although all walks of life, both gender and practically all age groups, are equally exposed to the ravages of this illness, then in another way it is extremely limited in terms of the persons it afflicts. Regarding those who do not have an *inhereditary predisposition* it is powerless. 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. It is only a rather small minority among my patients in whom it has not been possible to establish inheritability with certainty and only a few cases in

whom it has been possible to exclude inheritability with certainty, and even in those cases where the parents of the depressed have been known not to have been victim of depression themselves, there has often been an inheritable predisposition present in another form as I shall demonstrate to you shortly.

Depression is inherited, it seems, equally from the father or the mother. At times it has been possible to recognize the heritable predisposition only because several siblings have fallen victim to the illness. This is something that is particularly often the case, although it has not been possible to establish with certainty that any of the parents have been afflicted. It is not easy to say if the children ever completely avoid the illness when one of their parents and particularly if both of them are suffering, as it is rare that it falls to one's lot to be able to keep an exact account of the pathological history of a whole generation for a sufficient length of time. It is certain, however, that it is not rare to come across families who down through several generations, in a tragic manner, have been burdened by this illness.

Yet, although it is firmly established that the great majority of patients from birth are predisposed towards this illness that manifests itself sooner or later in their lives, this does not mean that randomly occurring causes or the manner in which their lives take shape, their internal and external mode of living, can be considered to be without significance for the development of the illness or for the time when the depression first manifests itself and the subsequent morbid periods erupt. In a short while when I address the pathogenesis of the illness, it will occur to you that an appropriate diet in the widest sense of the word is of extreme importance in the fight against the inborn predisposition and it will become easily understandable that this can be kept under control for a long time, perhaps even throughout life, where the conditions of life are such that they constantly work against the morbid predisposition and where occasional triggering events are avoided. As mentioned before, the latter are certainly not necessary either for the development or for the manifestation of the individual periods of depression. In a significant number of cases, all searches for occasional factors have been entirely futile and the patients themselves remain adamant that their morbid periods occur “quite spontaneously.” Yet there are quite a few exceptions to this rule. It is not rare at all that patients blame some kind of effort or another for the eruption of a period of depression, in particular when it has been connected with mental unrest or tension - as for instance vigil over very ill relatives - or a mental “shock” or finally, and frequently,

a sorrow which to us would appear quite natural, as the effect of so-called sad experiences, as mentioned before, has an impact which appears to be consistent with the patient's state of mind during their morbid periods. Such periods of depression, which have been provoked by occasional events, often develop acutely so that the morbid state of mind very quickly, at times virtually immediately, reaches a pronounced degree, as opposed to the usual pattern of a slow and gradual development.

Concerning *the pathogenesis of periodical depression*, I must admit that I would probably have acquiesced with the same negative attitude which one usually assumes regarding mental illnesses, were it not for the reason that during my preoccupation with this illness reasons for a more positive viewpoint have gradually been forced upon me.

From the first, when experience taught me in periodical depression to recognize a peculiar form of mental disease 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' (from *later* brick, brick-red, *added by this writer*) in the urine. When, as a result of these indications I systematically started investigating the patient's urine in this regard, 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. Other than having investigated virtually all my depressed patients' urine regarding its content of uric acid, I have, for reason of comparison, made a similar investigation of an even far greater number of other patients' urine, and the difference has been extremely striking to the effect that when not one of the well-known factors - fever, profuse perspiration, considerable cooling down of the urine, rich meals and other factors - which in everybody could cause urine sediments, are present, then it is very exceptional for the average man's urine to be sedimentous, whereas the urine of the patients concerned here usually is. Of course, it can be free of sediment, partly for the reason that there is undoubtedly some periodicity regarding the content of uric acid in the urine, not to mention its metabolism in the body, and partly for the reason that a coincidental consumption of alkali, plenty of liquids or the like can momentarily make it disappear. Its presence, however, has been so common, and in those cases where I have only been able to do a few investigations in which it has been lacking, information

from the patient or those surrounding him about the condition of the urine has usually been so confirmative that I dare assert 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* (Note 3).

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. 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 organisms or its metabolism insufficient - and there is hardly any reason to doubt this - then it is in no way certain that *uric acid diathesis* is the cause of periodical depression and although there is no doubt that there is, in one way or another, a relationship between the two phenomena then, *a priori*, this can be assumed to have been of a very different nature. The following possibilities, in particular, appear to me: 1) the uric acid in the individuals here concerned can have an analogous significance to phosphoric acid in so many other "nervous" patients; a significance, which is probably very disputable and which can never be considered such that the presence of phosphoric acid in the organism should be considered the cause of the nervous symptoms, but rather that the nervous disturbances in one way or another causes the phosphaturia; 2) the presence of a surplus of uric acid, particularly by precipitation, gives rise to uric acid infarcts and, consequently, an irritation in the kidneys that, one can imagine, can have a "reflex effect" on brain functions just as it is thought possible that these can be influenced by irritative conditions in the digestive tract and in other places; 3) 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.

Of these three theories concerning the significance of the uric acid surplus in depressed patients, the former two, however, at closer scrutiny, soon turn out to be unsustainable. As proof of this I will particularly stress the fact, which I have already touched upon above, that the increased secretion of uric acid is not limited to the depressed periods, but occurs continuously, although always with interruptions - during normal periods as well, even if they last for several years. This has no analogy at all with "nervous phosphaturia" nor would it fit in with any "reflex theory." That the abnormal condition of the urine could in no way be considered as a secondary phenomenon to the nervous dysfunction is also demonstrated by another circumstance which, on

the whole, regarding the pathogenesis, is very striking. When I spoke about the significant inheritability, I remarked that, at times, the condition is manifested other than for the reason that depressed persons were descendants of depressed parents. With this I wanted to point out that generally, where parents have not been depressed, it can be shown that they were carriers of a "uric acid diathesis" as they had suffered from either urine sediments or arthritis urica. Thus, the inheritable factor *per se* turns out to be the diathesis - the surplus of uric acid in the organism - and should be considered to be the primary, the basic illness, of which the depression is a function, similar to what uric acid arthritis or the production of sediments could be. This is a manifestation that at first glance could appear to be somewhat peculiar in an area where one is used to seeing stones and tophi as the products of the illness, but which, on the other hand, shows several very striking similarities with the other clinical forms of the diathesis. If one juxtaposes the pictures of the arthritic patient, the lithiasis sufferer and the one suffering from periodical depression, then on closer scrutiny the immediately obvious differences might carry but little weight in comparison with the similarities, such as the particularly significant inheritability and the spontaneous periodical occurrence. The dissimilarities are easily and simply explicable by the various localizations of the dyscratic manifestations, whereas periodicity and inheritability - and in addition inheritability between the various illness forms - in the sense and in the form in which we experience them in the conditions dealt with here - are hardly known in any other area of pathology (Note 4).

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 a uric acid diathesis, and that they must be understood as effects of this diathesis, to which the predisposition, as a rule, is inborn, then this provides the basis for a rational treatment of the depression, a treatment that extends somewhat further than the exclusively symptomatic treatment or expectative 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. In this regard there exist different possibilities, but I shall not enter into a discussion of them as I do not believe that it is possible for me to judge between them with certainty.

The *treatment* that I have already been using for a considerable number of years in cases of periodical depression has primarily consisted in the battle against the uric acid diathesis. 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.

It is quite clear however, that along with these rational treatments there will generally be a need for remediation of symptoms. In this regard I believe, particularly concerning the somewhat unfortunate way in which these patients are often treated from a psychological viewpoint, I must emphasize that they must not be permitted to follow their own inclination to withdraw from the company of other people and from their usual occupation, only to live with their feeling of misery all by themselves. On the contrary, one must do all that is possible to provide them the mental stimulus of which the inertia of their nervous system is in need, so that to a reasonable degree it can assume its usual level of functioning. As far as it is possible the patients must be forced into being constantly active, doing something, and it does them good to be exposed to changing and strong stimuli. In endeavoring to accomplish this, one almost always faces considerable resistance from the patients for the reason that a concentrated effort is demanded from them and of which only a few have sufficient energy and perseverance to mount during the often-long period before improvement starts to show. Therefore, in this matter, it is rare that the doctor gets anywhere if he does not receive intelligent and unflagging support from those nearest and dearest to the patients.

There is one thing that I never neglect to strongly impress upon the patients as well as those around them, this being 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 which we do know that we are unable to remove 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, although these in no way upset the duties and activities of everyday life, for this often demands the abandonment of some habits and the acquisition of others - and, unfortunately, the habits which must be acquired are of a more active nature than those to be abandoned - a matter which makes them have little attraction for the patients to whom any demand of activity is so tormenting.

Gentlemen, if you would now ask me what results I have had with this therapy whose fundamental features I have described here, then 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, are in no way 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, then these effects recur, even if for some time one has been successful in removing them. Regarding the therapy, however, 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 a 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 regarding the intensity of the illness. From a very pronounced intensity in one period one cannot with certainty conclude that there will also be just as great an intensity of the illness in the next. 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, then 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 completely subjective estimate. Therefore, I shall confine myself to a few brief remarks. In 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 significantly alleviate 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.

Before I finish I must very briefly mention the question of whether the pathogenetic interpretation that is being advanced here has ever before been advanced if not as a fully formed theory - for such has not been possible of course - as periodical depression has not hitherto been put forward as a nosological entity, then at any rate only as a tentative hypothesis. At the same time, I must readily admit that I have not attached great importance to tracing every statement concerning this matter which might have been dropped in passing from some author's pen. Therefore, it is very possible that I have overlooked something, although hardly anything of significance, as for a number of years, as a matter of course, I have paid attention to other observers' statements which might support my point of view. Unfortunately, my endeavors have yielded very little indeed. It is true that one often finds the statement that the arthritic diathesis may cause mental illnesses, but then it is emphasized that it is the sudden suppression of an attack of gout that is succeeded by an outbreak of insanity. Whether this can be cited in support of what has been claimed in my point of view is obviously doubtful. It gains more support from a statement by *Maudsley* who, in his renowned book on mental illnesses concerning their etiology, after having emphasized in general the great importance of the presence of excretory substances in the urine, reports that a couple of times he has observed "melancholia" in people with an arthritic diathesis and that he has seen the melancholy get cured by an efficient treatment of the gout. In some remarks about "neurasthenia" *Huchard* in *l'Union médicale* (1882) states that this illness - 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. Also, *Arndt* in his thorough - almost too thorough - treatise on neurasthenia 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 (!).

As far as I know this is all that previous authors have stated or rather suggested concerning the pathogenetic factor which has been put forward here. Consequently, I have virtually nothing to rely on from previous observers; the more reason I have to hope that my understanding of this matter is going to be tested by future investigators, for in all events I dare expect that the remarks that I have had the honor of presenting here 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.

Notes:

1. Here I shall only talk about the more severe cases in which medical attention is being sought. As will be touched on later, there are surely very many people who suffer from milder forms of the illness which do not come to the attention of a doctor.

2. 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 melancholics. Moreover, it would not be particularly remarkable if the often 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 harboring the feeling that their illness will end with suicide, but this risk is small or non-existent.

3. **Not only would it be impossible to carry out exact quantitative assays of the uric acid amounts in outpatient, but also, even if they could be done, they would not be of any value. For the amount of uric acid in a single urine sample, or the daily excreted amount, or the amount excreted in a shorter period of time is, in the first place, under normal conditions so varying that one would have no norm with which to compare one's results. A normal person's daily excretion of uric acid is not known, partly because the amount is influenced by the varying conditions of daily life and partly because there undoubtedly exist individual differences concerning the quantitative factors of this substance to be excreted.**

4. Direct proof that a uric dyscrasia exists, the presence of uric acid in the blood of the depressed patients, would, of course, be very desirable, but this is just as difficult to provide in these cases as in other forms of this dyscrasia. *Boucheron* found that saliva gave a positive murexide reaction in a number of patients in which he felt that he could assume the presence of uric acid diathesis (*cf.* l'Union Médicale 1881;121). The same appears to have been the case in several of my patients, whose saliva I have tested according to *Boucheron's* method. But lacking sufficient comparative investigations, I do not thus far attach any importance to these results.

* Johan Schioldann's translation of Carl Lange's speech "On Periodical Depressions and Their Pathogenesis" was included in:

1. Johan Schioldann: *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: Adelaide Academic Press; 2001, pp. 23-49.
2. Johan Schioldann: *History of the Introduction of Lithium into Medicine and Psychiatry. Birth of Modern Psychopathology 1949.* Adelaide: Adelaide Academic Press; 2009, pp. 293-308.
3. Periodical Depressions and their Pathogenesis. *History of Psychiatry* 2011; 22:116-30.

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