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Clinical and Neuropathological Aspects of Long-Term Damage to the Central Nervous System After Lithium Medication

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Summary. A female patient, who died at the age of 61 and had suffered from several manic-depressive psychoses for more than 30 years, developed three phases of intoxication under lithium therapy. There was a 15-year history of electro- and Pentetrazol-induced convulsive therapy prior to lithium medication; neuroleptics were still administered during lithium therapy. The last lithium intoxication, 3 years prior to death was during a low-dosage therapy with normal lithium levels followed by severe lasting impairment: akinesia, rigidity, dysarthria, ataxia, and an organic alteration in character. For the first time, neuropathological findings could be established in such a case: extensive damage to granule and Purkinje cells in the cerebellum; gliosis in the dentate nucleus, the inferior olives, and the nucleus ruber; cytoplasmic inclusions in various nerve cells of the cranial nerve nuclei; cytoplasmic vacuoles, especially in the cells of the supra-optic nucleus.

Surprisingly little damage could be found in the substantia nigra and in the neostriatium. The clinical course as well as the pattern and intensity of the brain damage oppose an interpretation as a consequence of preceding convulsive shock therapy.

Key words: Lithium therapy – Manic depressive psychoses – Long-term lithium damage – Lithium intoxication – Cerebellar degeneration

Zusammenfassung. Eine mit 61 Jahren verstorbene Patientin hatte während einer sich über dreißig Jahre hinziehenden manisch-depressiven Psychose dreimal unter der Lithium-Therapie eindeutige Intoxikationsphasen durchgemacht, nachdem eine Krampf-Therapie (Pentetrazol, Elektroschock, Insulin-Subcoma) Jahre zuvor durchgeführt worden war. Die letzte, drei Jahre vor dem Tod erfolgte Intoxikation bei niedriger Dosierung und normalem Lithium-Serumspiegel war von schweren Dauerschädigungen gefolgt (Akinese, Rigor, Dysarthrien, ataktische Störungen, Wesensänderung). Die neuro-

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pathologische Untersuchung — die Erstbeschreibung einer derartigen Schädigung — ergab ausgedehnte Schädigungen der Kleinhirnkörnerschicht und der Purkinjezellen, eine Gliose im Dentatum, den unteren Oliven und dem Nucleus ruber, Cytoplasmaeinschlüsse in verschiedene Nervenzellen der Hirnnervenkerngebiete und intracytoplasmatische Vacuolen, vor allem in Nervenzellen des Nucleus supraopticus. Überraschenderweise ergaben sich nur geringgradige pathologische Veränderungen in der Substantia nigra und im Neostriatum. Klinischer Verlauf sowie Verteilungsmuster und Intensität der Gewebsschäden sprechen gegen eine eventuelle Deutung als Folge einer vorausgegangenen Cardiazol- und Elektrokrampfbehandlung.

Schlüsselwörter: Lithium-Therapie – Manisch-depressive Erkrankung – Lithium-Vergiftung – Lithium-Dauerschäden – Kleinhirnatrophie

Introduction

Lithium chloride has been used for decades in biological research, at first for inducing malformations (Lehmann 1938) and later to provoke behavioural disorders associated with food aversion (Balagura and Smith 1970; Johnson et al. 1975; Gaston 1977). As a component of mineral waters, lithium salts have been used therapeutically since antiquity. For some time they were used as a substitute for normal cooking salt until cases with negative side effects were reported. In such cases, the symptoms corresponded to the signs of intoxication that became apparent soon after lithium was used in the therapy of endogenous psychoses (Hanlon et al. 1949). After a self-experiment, Cleaveland had already in 1913 drawn attention to the negative side effects. Lithium therapy for endogenous depression and mania subsequently showed that the therapeutic range of lithium-containing medications is very small (Cade 1949; reviews by Schou et al. 1954 or Fieve 1978).

Minor *side effects* include nausea, fine tremor of the hands (differing from that of parkinsonism), and polyuria. Signs of a threatening *intoxication* are vomiting and diarrhea, coarse tremor, drowsiness, dizziness, and dysarthria (Gershon and Yuwiller 1960; Schou 1974; Degkwitz et al. 1976; Fieve 1978; Reisberg and Gershon 1979; Vestergaard et al. 1980), and, less frequently, coma and convulsions (McCawley et al. 1975). Nephrotic syndromes were reported by Häfner et al. (1978), Jenner (1979), and Singer et al. (1978, 1979). The latter authors, however, expressed some restraints concerning these symptoms.

Schou (1968) has already pointed out the necessity for prophylactic measurements: patients with heart or kidney disease should not be submitted to such therapy (Corcoran et al. 1949). The lithium dosage should be carefully controlled, especially when administered in combination with other drugs to avoid drug incompatibility. Throughout the course of the therapy, regular checks on the lithium serum level must be carried out. As a maximum value for the therapeutic serum concentration, suggested Schou (1968) 2 mEq/l.

Above this level signs of intoxication are possible. Schou, however, pointed out that doses even up to 3 mEq/l could be tolerated in some cases, whilst in other

cases, minor signs of intoxication could appear even at 1.5 mEq/l. Strayhorn and Nash (1977) and also van der Velde (1971), Herrero (1973), and König et al. (1978) had noted similar signs of intoxication at therapeutic doses (0.5–1.2 mEq/l). In view of the individual reactions to lithium medication, pharmacogenetic influences have to be taken into consideration. During the treatment of our case, Benkert and Hippius (1974) recommended a dose giving lithium serum levels between 0.8 and 1.2 mEq/l for prophylaxis and between 1.0 and 1.4 mEq/l for treatment.

Clinical long-term damage was first noticed by Hartitzsch et al. (1972) in three cases where the lithium serum concentration had risen to a level of 3.0–5.0 mEq/l. Ataxia, choreiform kinetic disorders, tremor, nystagmus, dysarthria characterized the clinical picture. The effects described for the two cases of Cohen and Cohen (1974) were even more detrimental: severe dementia, opsoclonus, and cerebellar-parkinsonism-like traits. In the first case reported by Juul-Jensen and Schou (1973), pathogenic complications resulted from heart failure and phenylhydantoin medication, whereas their second case, and that of Goldwater and Pollock (1976), resembled the typical intoxication picture.

Our observations on a female patient with long-term damage after three phases of lithium intoxication present some new aspects, including the first neuropathological description of such a case.

Case Report

The female patient, whose father had suffered from depression, died at the age of 61. At the age of 27 she suffered her first depression following the birth of her first child. The second depression occurred at the age of 33 after the birth of her second child. Tabe 1 summarizes the clinical course and treatment given after the first symptoms in 1944 until the start of the lithium therapy in 1969. Between 1944 and 1958 convulsive therapy was given.

High doses of neuroleptic therapy resulted in the appearance of extrapyramidal symptoms which disappeared on dose reduction or after Biperiden administration. On several occasions records show an anaemia with a raised erythrocyte sedimentation rate, caused by metrorrhagia (myoma of the uterus was diagnosed).

Before the long-term therapy with lithium salts, examination of kidney function gave normal values. The lithium serum concentration was monitored regularly in the first weeks, later at intervals of a few months. The values ranged from 0.82 to 1.18 mEq/l (optimum values 0.6–1.5 mEq/l). Between 1969 and 1974, lithium carbonate treatment was supplemented with thymoleptic and neuroleptic medication (3×50 mg Imipramine, $2–3 \times 100$ mg Perazine) respectively when depressive and manic symptoms became aggravated. In January 1974 the lithium serum level rose to 1.58 mEq/l without any clinical side effects.

Retrospectively, the *first,* slight signs of an *intoxication* probably developed at the end of May 1974 during a manic phase. Her complaints of weakening concentration were at first attributed to her psychosis. But the patient steadily grew slower, showed a raised tone of the adductors and a sort of spastic gait. The patient was very tired and complained of "stinging pains" in the region of the heart during strain (Table 2a).

The lithium serum concentration was 1.16 mEq/l. The skin was extraordinarily dry and exfoliated. Hormone assays, however, showed no signs of thyroid hyperactivity. T 3 and T 4 assays, as well as the total gonadotropin excretion, were normal. The ECG showed signs of a first degree atrioventricular block with slight disorder of left ventricular repolarization. The possibility of a myocarditis was considered. Renal function was normal. Serum sodium 135 mEq/l, potassium 3.9 mEq/l. At the reappearance of depressive states, lithium therapy was continued and supplemented by thymoleptics and neuroleptics. The lithium serum concentration ranged from 0.95 to 1.0 mEq/l.

Table 1. Course of treatment between 1944 and 1969 (D = depression; M = mania; + = dose unknown)

Course of Cyclothymia	Convulsion Therapy	Amitriptyline	Imipramine	Chlorpromazine	Levomepromazine	Promethazine	Thioridazine	Perazine	Pernhenazine	Chlorprothixene	Prothipendyl	Haloperidol	Side Effects
		Antidepressives (in mg)				Neuroleptics (in mg)							
1944 D	5x1 Electro shock												
1950 D	6x1 Electro shock												
D_z	6x1 Pentetrazol-Shock												
1954 D	38 Insulin subcoma (12-50 E)												
1957 D				2x50		2x50							
1958 D	17x1 Electro shock			2x50		2x50							
1959 M						2x50 4x50 2x100							
D			3x50										
1960 M			3x50			3x25 3x50		3x50	3x8-12 100				Parkinsonoid
1961 D			3x50	3x100		3x50 3x50	100	3x50 3x50	100 3x8				Parkinsonoid
1962 M			+			+	+			3x100		1.5	Anaemia
1963 M												1.5	Hyperthyreoidism
1964 M										3x50			Parkinsonoid
1965 M				3x50					+				Anaemia by Metrorrhagia
							3x50						
		3x50								1x50			
1966 M		+	+				3x100						
1967 D		+								+			
M			2x25							3x50			
D		+		+									
D			2x25	4x25									
D			2x25									1.5	
M												+	
M				3x100		3x25							
1968 D		+					+						
D		+								+			
D/M		3x50					3x100					1.5	
1969 D		3x50									3x80		

A *second phase of intoxication* developed at the beginning of October 1974 at a dose of 1668 mg lithium acetate (Quilonum), combined with 3 × 100 mg Perazine, with diarrhea, nausea, and a rise in temperature. During the preceeding weeks, the patient had complained of very great thirst. The maximum *lithium serum concentration* was *2.02 mEq/l.* Lithium medication was stopped. Nevertheless, within 48 h, the patient developed a non-paralytic strabismus, slow, slurred, and stumbling speech, and akinesia with rigor of both arms, restricted eye movement, and hyper-reflexia. Sometimes the tongue was convulsively protruding. The patient became disorientated, incontinent, and at times showed a clearly reduced state of consciousness. The EEG revealed moderate to grave overall changes (Table 2b). The number of cells in the CSF was normal, while the total protein concentration was slightly elevated (41 mg%, with 13mg% globulin, and 28 mg% albumin). The erythrocyte sedimentation rate was greatly increased at

126/136 mm/h. Bone marrow aspiration did not reveal any abnormal pathological findings. The blood pressure values ranged from 120/80 to 180/110 mm Hg. The ECG showed a sinus rhythm with left axis deviation of the QRS vector, and diffuse disorders of repolarization. The T 4 level was normal, the T 3 slightly diminished. There was neutrophilia (13000) with a slight "shift to the left", haemoglobin 10.7 g%, albumin 3.1 g%, α_1-globulin 5.8%, α_2-globulin 11.8%, β-globulin 12.1%, γ-globulins 18.5%, cholesterol 131 mg/100 ml, potassium 3.4 mEq/l. Dehydration at first developed, disappearing after fluid intake. Subsequently, a distinct diabetes insipidus became apparent, with an excretion rate greater than 5 l/day, and a urinary specific gravity of 1.003–1.008. During a 12-h period with no fluid intake, a urinary concentration with a specific gravity of 1.016 was attained. The symptoms improved within 2 weeks. The disturbances of consciousness, the ataxia and coordination disorders disappeared. Some parkinsonism-like symptoms remained, including diminished facial movements, static tremor of the head, right hand and leg, a small-stepping ataxia gait, and hyper-reflexia, especially on the right side of the body. Clinically, encephalitis was suspected. The small-stepping gait was still apparent in January 1975, the reflexes were dextro-accented, the speech was always somewhat slurred, and the finger-nose test revealed an intention tremor.

Signs of a *third phase of intoxication* became obvious at the end of January 1975. During the preceding 6 days, the medication of 1.668 mg lithium acetate had been continued, always with serum concentrations below 0.75 mEq/l. The day before hospitalization, the patient again developed a rise in temperature, paroxysmal tachycardia, bursts of perspiration, kinetic restlessness, chewing movements, slurred speech, and uncoordinated fiddling movements. The ECG showed sinus tachycardia and a left axis deviation, with unspecific repolarization disorders in the right precordium. The patient was not responsive on admittance. The *lithium serum concentration* was found to be *0.50 mEq/l.* The erythrocyte sedimendation rate was 30/55 mm/h. Blood pressure fluctuated greatly, from 195/110 to 130/75 mm Hg. Lithium medication was stopped immediately, and overall consciousness improved within 4 days. The patient, however, was markedly non-responsive. The rigor of the arms, the hyper-reflexia, the instability of gait, and the slurred speech improved only slightly.

Following this last phase of intoxication, the patient no longer received lithium medication prior to death in 1978. The treatment during the last 3 years of life was restricted to thymoleptics and neuroleptics. During the depressive phases a dose of 3×100 mg Thioridazine or 2×100 mg Clozapine was used and during the manic phases a dose of 3×50 mg Imipramine combined with 3×12.5 mg Clozapine. Symptoms of an organic psychic syndrome with slight dementia persisted. The kinetic restlessness of the fingers, a constant smacking of the lips, a severe speech strammer, rigor of the arms and an instability of gait lasted; improvements were minimal and even then fluctuated. The EEG showed moderate to severe overall changes, interspersed by 4–7 waves per second. During the following years tetanic cramps of the hands and legs occurred occasionally, likewise revolving of the tongue, grimacing, and a more or less marked nystagmus. Akineton medication did not bring about any remarkable improvements. A slight diabetes insipidus persisted.

The patient died of heart failure associated with angina tonsillaris and temperatures of up to 41.2° C. In the terminal phase, there were signs of renal insufficiency (urea 64, urea nitrogen 30, creatinine 1.9 mg/dl, non-protein nitrogen 42.1).

Neuropathological Results

Post-mortem examination had to be restricted to the brain. The neuropathological examination revealed, macroscopically, a slight hydrocephalus internus, especially of the anterior horns of the lateral ventricles, associated with a rounding off of the ventricular angles. The temporal and insular cortices appeared somewhat small. There was slight arteriosclerosis of the basal arteries and darkly stained nuclei-regions in the dorsolateral parts of the medulla oblongata. Microscopically, the Nissl substance of the giant cortical nerve cells was, for the most part, stained only

Table 2a, b. Course of treatment around the three intoxication phases 1974–1975

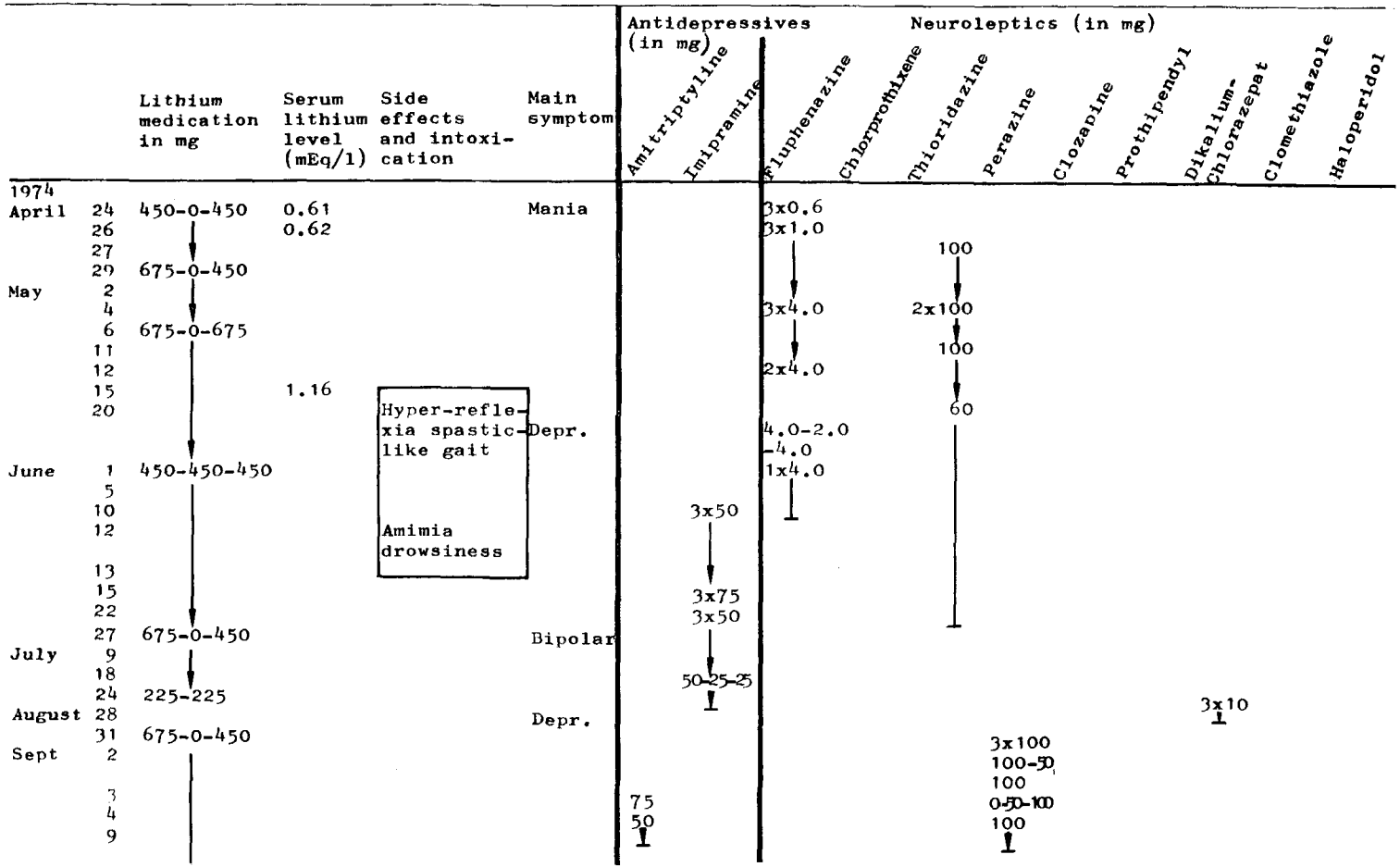
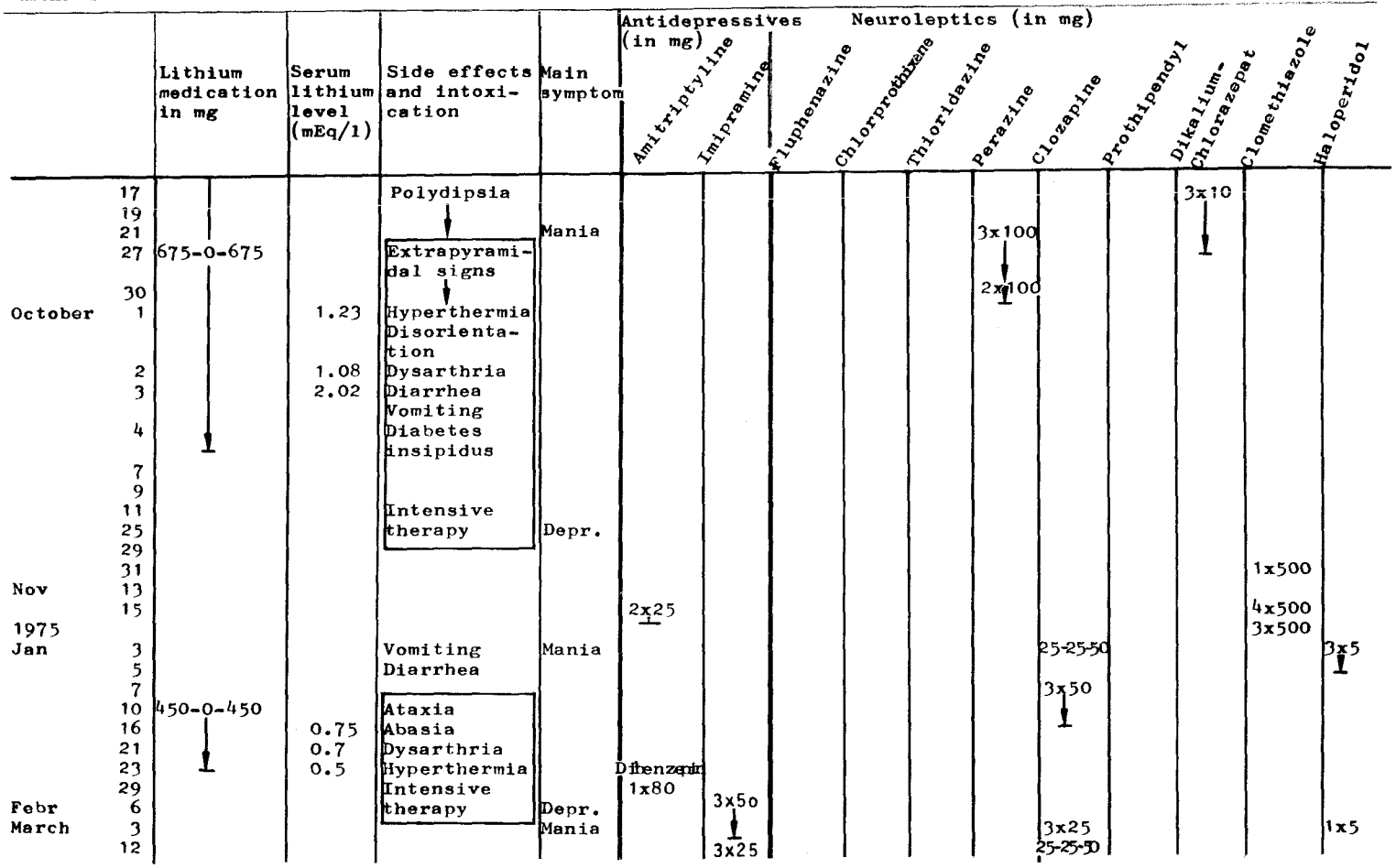


Tabelle 2b


Lithium medication in mg
Serum lithium level (mEq/l)
Side effects and intoxication
Main symptom
Antidepressives (in mg)
Neuroleptics (in mg)
Amitriptyline
Imipramine
Fluphenazine
Chlorprothixene
Thioridazine
Perazine
Clozapine
Prothipendyl
Dikalium-Chlorazepat
Clomethiazole
Haloperidol
17
19
21
27
30
October 1
2
3
4
7
9
11
25
29
31
Nov 13
15
1975
Jan 3
5
7
10
16
21
23
29
Febr 6
March 3
12
675-0-675
450-0-450
1.23
1.08
2.02
0.75
0.7
0.5
Polydipsia
Extrapyramidal signs
Hyperthermia
Disorientation
Dysarthria
Diarrhea
Vomiting
Diabetes insipidus
Intensive therapy
Vomiting
Diarrhea
Ataxia
Abasia
Dysarthria
Hyperthermia
Intensive therapy
Mania
Depr.
Depr.
Mania
3x10
3x100
2x100
1x500
4x500
3x500
2x25
25-25-50
3x50
3x5
Dibenzepin 1x80
3x50
3x25
25-25-50
1x5

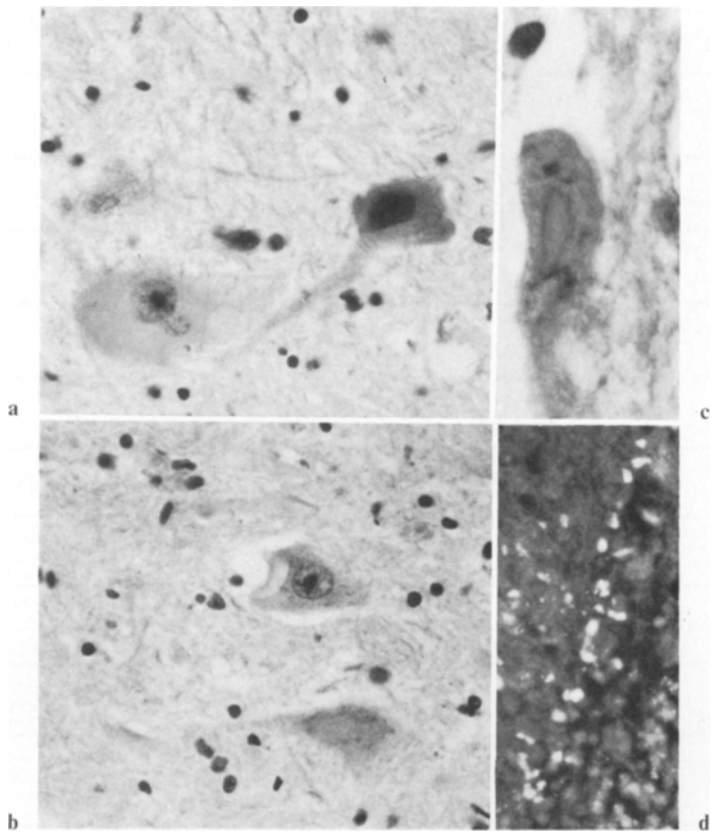
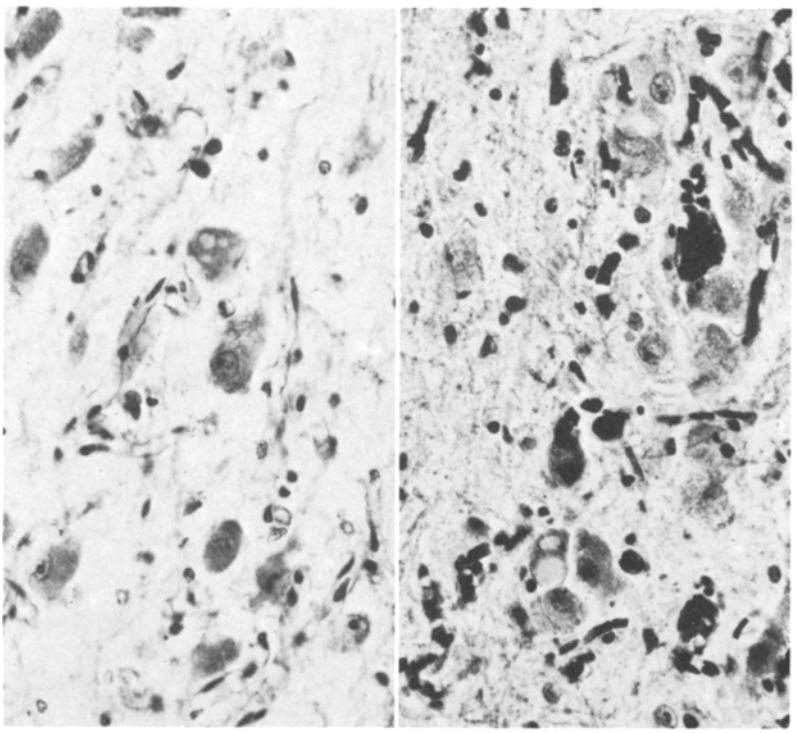


Fig. 1. **a** Cytoplasmic vacuoles, nuclear protrusions, and shrinkage of the nerve cells in the nuclear regions at the bottom of the fourth ventricle (HE 875×). **b** Cytoplasmic inclusions (Hirano-type) in nerve cells of the nucleus of the hypoglossal nerve (HE 350×), and **c** in the substantia nigra (HE 875×). **d** Strong autofluorescence of the Bergmann glia cells (140×) in the cerebellum.

very faintly. The extraordinarily large content of lipopigment in the cortical nerve cells, and especially that of the thalamic nerve cells, the giant nerve cells of the neostriatum, and the nerve cells of the dentate nucleus and olives, was striking. Fluorescent microscopy showed pigments with an intense autofluorescence, which were PAS positive. Fine PAS-positive granules and autofluorescent material was also visible in the glia cells of the grey matter of these regions, especially in the molecular layer of the putamen. The typical age-associated characteristics of layer IIIa/b as described by Braak (1979) were not found, i.e., the transition of lipopigment granules from the pericaryon over the axon-hilloc to the somato-near portions of the axon. Coarser pigment fragments, which can be found with ceroid-lipofuscinosis, were not observed in the histochemical reactions, nor in the fluorescence-optic examinations. The autofluorescence was most distinct when the non-stained sections were embedded with fluorochrome, whereas staining with thioflavine led to a decrease in fluorescence.



a b

Fig. 2. Cytoplasmic vacuolization in the nerve cells of the supraoptic nucleus (Mallory 350×)

In the first and second layers of the temporal cortex, there was a light spongy loosening of the tissue. In the cortex, however, there was no definite loss of nerve cells. Isolated nerve cells of the hippocampus showed a strong positive cytoplasmic PAS reaction. There were a few isolated binucleated nerve cells in the thalamus. In the Bodian preparations, neither the fibril changes expected in Alzheimer's disease, nor senile plaques could be found. There were merely some very fine, fibrous condensations in the insular cortex. A slight decrease in nerve cell content was seen in the nucleus ruber. There was a distinct proliferation of astrocytes, with occasional Alzheimer II type glia, especially in the dorsolateral region. The nerve cells of the substantia nigra contained normal cell pigment and were well preserved. Occasionally, oval or elongated Hirano bodies, and small eosinophilic cytoplasmic inclusions could be seen (Fig. 1 c). Axonal swellings were rarely observed. Neither in the zona reticularis nor in the zona compacta were there any glial proliferations. The nerve cells of the supra-optic nucleus and, to a lesser degree, those of the lateral geniculate bodies often had cytoplasmic vacuoles (Fig. 2). Siderophages could be found lightly scattered throughout the infundibular stalk.

The most prominent alterations, however, were found in the *cerebellar cortex*: The granule layer was diminished slightly to severely (Fig. 3 a), according to location. The Purkinje cell content was likewise strongly decreased. Many empty

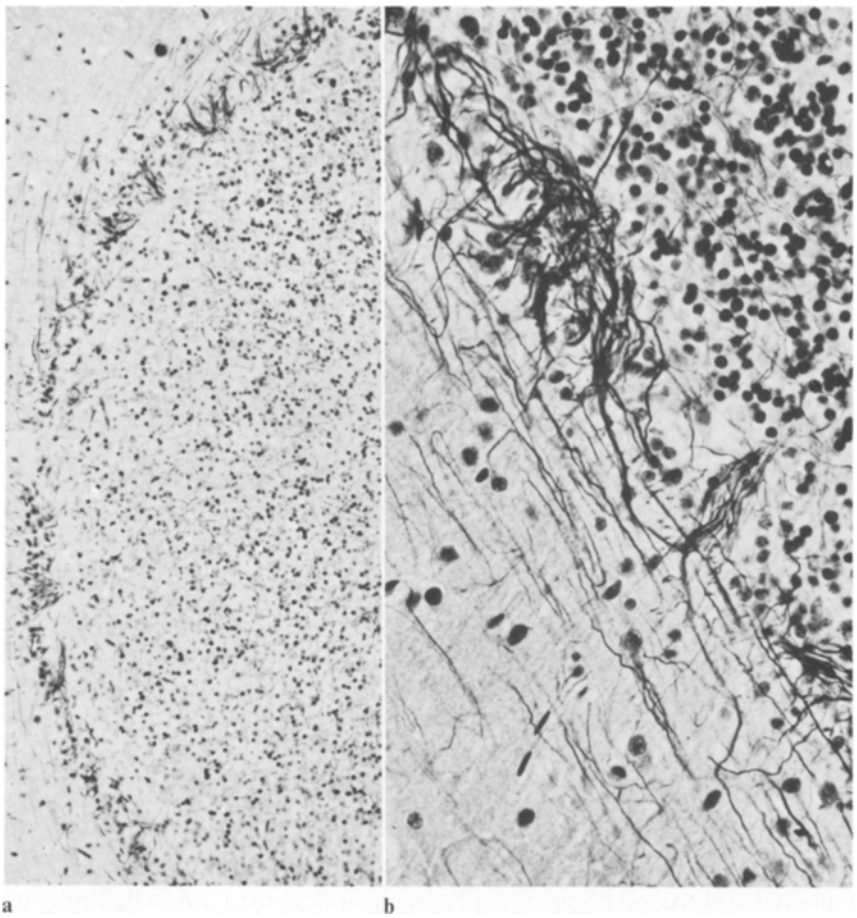


Fig. 3 a, b. Cerebellar cortex: **a** distinct loss of granule cells, **b** numerous empty baskets (Bodian: **a** 35×, **b** 350×)

baskets could be seen in the Bodian preparations (Fig. 3 b). There were often torpedo-shaped or morningstar-shaped swellings of the dendrites of the Purkinje cells (Fig. 4) within the molecular layer. In many cases, mere "shadows" of the Purkinje cells remained, but their dendrites appeared to be surrounded in a normal fashion by distinctly impregnated climbing fibres. In Golgi preparations, the dendrites of the Purkinje cells seemed to have lost a great portion of their spines, some of the dendrites often appeared "naked" over long stretches (Fig. 5). Small axonal swellings could be found repeatedly throughout the granule cell layer close to the Purkinje cell layer. The number of glia cells was increased markedly in the molecular layer. The same may be said for the level of the Purkinje cells. Here, the glia cells were sometimes binucleate and rich in cytoplasm. While the Purkinje cells revealed very littly storage of lipopigment, there was a distinct fluorescence in the cell layer of Bergmann (Fig. 1 d).

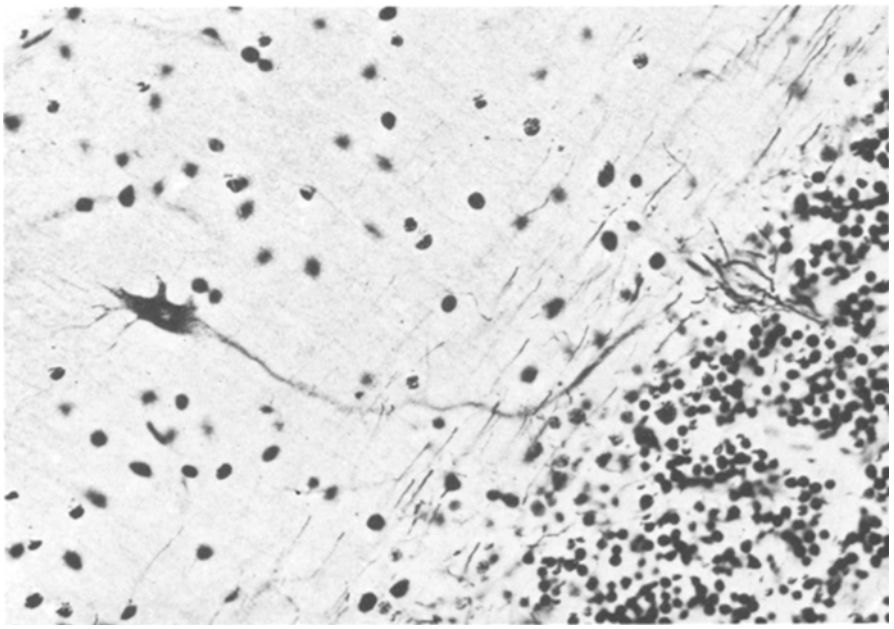


Fig. 4. Cerebellar cortex: Molecular layer with swollen dendrites of Purkinje cells (Bodian 250×)

The dentate nucleus showed a considerable proliferation of glia, but no clearly degenerating nerve cells (Fig. 6). Similarly in the inferior olive the nerve cells again contained much lipopigment. Eosinophilic cell inclusions could be found in some of the nerve cells in the nuclear regions of the dorsolateral medulla, particularly in the hypoglossal nerve nuclei (Fig. 1 b). The nerve cells of the locus caeruleus contained many nucleoli and much granular nucleolic substance. A number of nerve cells in the nuclear regions at the bottom of the fourth ventricle possessed striking protrusions of their nuclei (Fig. 1 a), chromatolysis, and cytoplasmic inclusions. Others appeared shrunken or showed signs of ischaemic cell damage. Alzian-blue staining showed no evidence for an increased content of mucopolysaccharides.

Discussion

Our case appears to be the first neuropathological report of long-term damage after lithium intoxication. Pathological descriptions of the human brain after acute lithium intoxication exist so far with relatively meager and non-uniform findings. In 1950, Roberts reported the case of a 57-year-old patient suffering from a chronic mania. She died after 9 days of lithium therapy (20 g, 3 × daily), with signs of intoxication for the 9 days (vomiting, confusion, ataxia, seizures). Autopsy of the brain did not reveal any pathological findings. In 1954, Glesinger described the case of a 45-year-old male patient, with a 10-day period of intoxication with seizures. Autopsy revealed some slight lymphocyte and leukocyte infiltrations about hyperemic capillaries in the brain, giving rise to a questionable encephalitis.

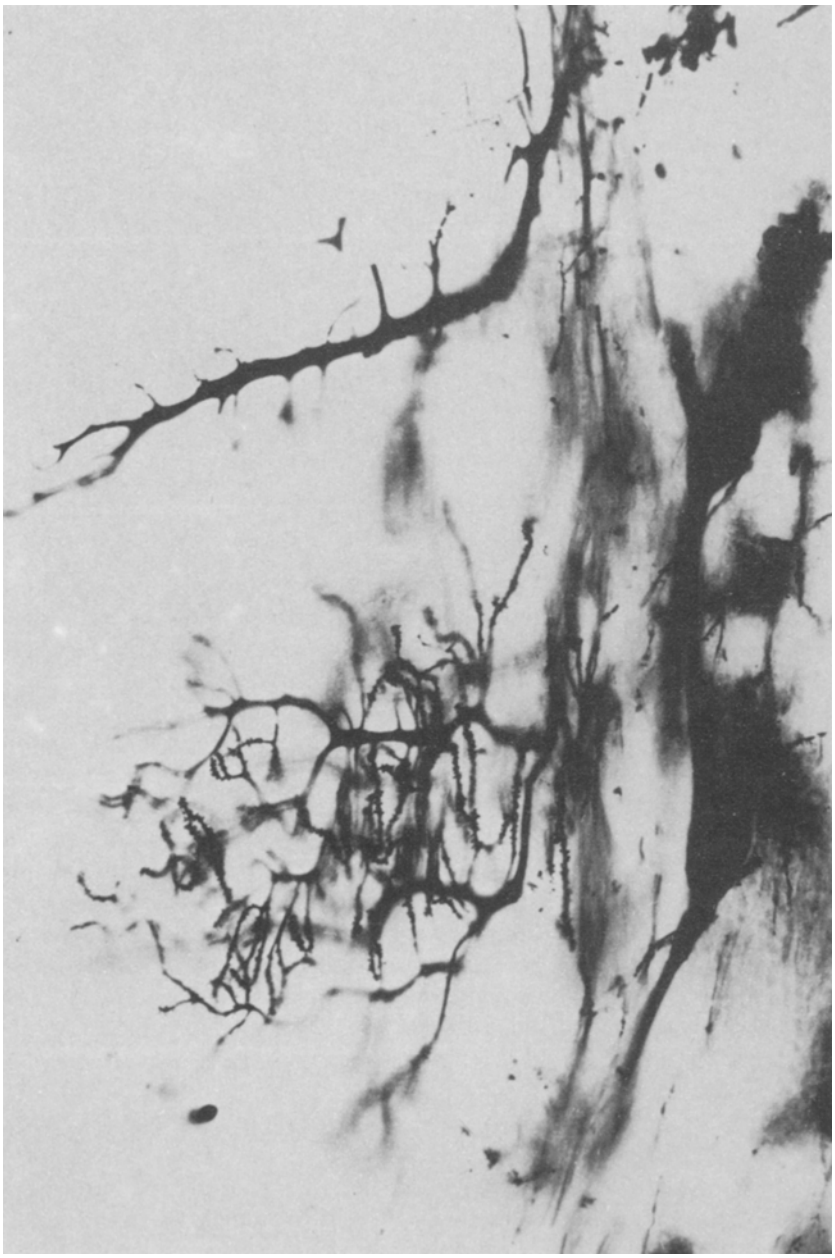


Fig. 5. Cerebellar cortex: Loss of dendritic spines and naked dendrites of Purkinje cells (Golgi preparation ca. 1,800×)

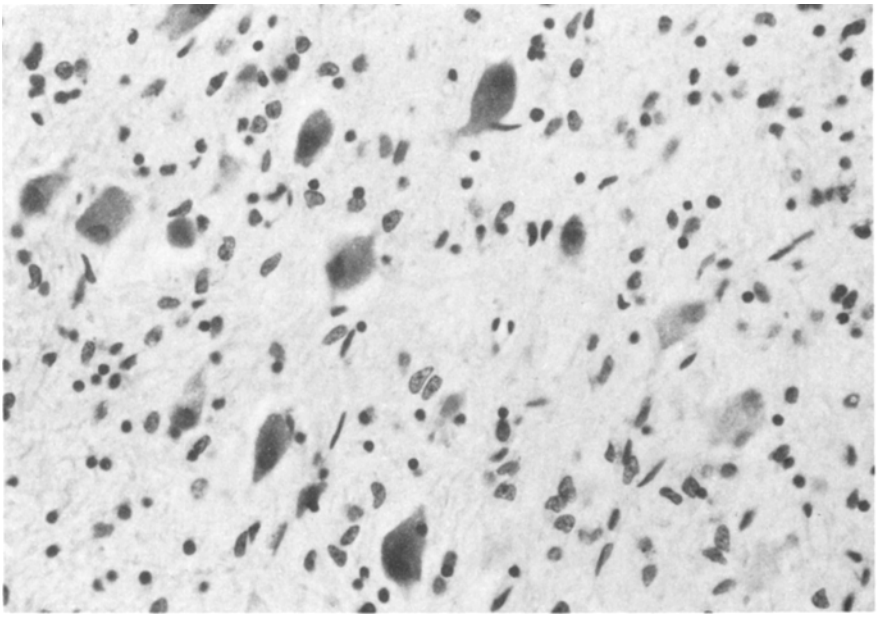


Fig. 6. Proliferation of glia cells in the dentate nucleus (HE 150×)

Chapman and Lewis (1972) described normal macroscopic and microscopic findings for the brain of a 41-year-old female patient with a similar 2-week history of acute illness. In the case of Amdisen et al. (1974), severe disturbances of cardiac rhythm and status epilepticus developed lasting several days, leading via a deep coma to the clinical picture of an intravital brain death. Accordingly, the brain was necrotic. Furthermore, there were signs of a peri- and myocarditis and of tubular damage in the kidney. This author could find only one other, somewhat more detailed, neuropathological description by Jakob (1978). A 44-year-old woman had died in a state of delirium after a 3-day period of intoxication. Histologically, Jakob described a strong glial reaction of astrocytes in the cortex and white matter, furthermore, a spongy dystrophic tissue reaction with an accent at the border of cortex and white matter, in the thalamus, in the midbrain, and in the cerebellum. H. Jakob generously provided me with the preparations, so that I could reexamine them. The alterations in this case of intoxication proved to be minor. Clear parallels between these observations on acute cases to date and our own examinations cannot be drawn.

In our case three temporally separated phases of intoxication had developed. The clinical picture, as described above, corresponds well to the ones described in numerous publications (see reviews by Schou et al. 1974; Dempsey and Meltze 1977; Fieve 1978; Reisberg and Gershon 1979). It was not until the second phase of intoxication that the connection with the lithium medication was recognized. An increased risk had been indicated by the age and sex of the patient (van der Velde 1971; Len Tseng 1971), and by the heavy additional neuroleptic and thymoleptic medication over many years (Degkwitz et al. 1976). Seizures, similar to those

reported by McCawley et al. (1975) did not occur in our case. The convulsive therapy induced with electro- or Pentetrazol-shocks as well as the subcutaneous insulin treatment were not followed by brain alterations.

The symptomatology of intoxication points to functional disorders of the cerebellum (ataxia and coordinational disturbances), of the cranial nerve nuclei (strabismus, disturbed eye motility, nystagmus), and of the basal ganglia (akinesia, rigor, tremor, choreiform hyperkinesis). Pathophysiologically, the signs of parkinsonism in particular implicate functional disorders of the neurotransmitters in the dopaminergic and cholinergic systems. It is interesting that the third intoxication appeared under conditions of low-dose medication and a normal serum lithium level (0.5–0.75 mEq/l). This is evidence against the concept that changes in lithium tolerance do not appear during long-term lithium therapy. Numerous results from animal research are available that could be used to explain the clinical effects of lithium. Unfortunately, these are not without contradictions. The following principles of effect probably play an important role during lithium treatment:

1. The Electrolyte Effect

Lithium cations can displace sodium ions and can also take the place of calcium and magnesium ions. Lithium thus influences the reactions dependent on Ca^{++} and Mg^{++}, e.g. the Mg^{++} dependent adenylate cyclase with the corresponding effects on reabsorption in the proximal tubules and the clinical picture of diabetes insipidus (Forrest et al. 1974; Martinez-Maldonado et al. 1975). According to Birch and Goulding (1975), lithium also interferes with the Mg^{++}-ADP reaction, and according to Bishop and Gill (1971) it inhibits the DNA-nuclease and polymerase.

2. The Effect on Neurotransmitter Metabolism

Generally, lithium exerts an inhibitory influence on the catecholaminergic system (Schildkraut 1973; Jope 1979). More specifically, the following explanations are given for this phenomenon:

a) Under the supposition that electrical impulses were occurring (Corrodi et al. 1967), lithium stimulates the uptake of noradrenaline into the synaptosomes (Colburn et al. 1967). This concentration of noradrenaline in the intraneuronal storage vesicles does not, however, lead to a corresponding increase at the noradrenaline receptors. To explain this, Schildkraut proposes the hypothesis that lithium does not substitute for the role of Ca^{++}, which is normally involved in bringing the storage organelles to the synaptic cleft and in the subsequent extraneuronal excretion of the noradrenaline. Instead, the storage vesicles empty their contents intraneuronally. Noradrenaline is then broken down via deamination by the monoamine oxidase, which is present to excess. This would result in a relative increase in the metabolites of the intraneuronal deamination pathway, and a relative decrease in the metabolites of the extraneuronal o-methylation pathway (Iversen and Bloom 1970; Schildkraut 1973). The Mg^{++} dependent ATPase, which is probably involved in the release of noradrenaline into the synaptic cleft, is probably also inhibited by the increase in intracellular Li^{+}. Thus, despite an

increase in noradrenaline metabolism, there is a deficit of noradrenaline at the receptor.

b) The *serotonin* metabolism is also affected: In the acute phase, lithium leads to an increased intraneuronal uptake of tryptophane. Due to excess activity of the tryptophane hydroxylase, this leads to an increase in serotonin synthesis and release. Under long-term lithium administration, the tryptophane uptake remains elevated. However, there is a decrease in the activity of the tryptophane hydroxylase via a feedback from the over-saturated serotonin receptor. There is thus a decreased serotonin production (Mandell and Knapp 1978). According to Sheard and Aghanjanian (1970), serotonin metabolism is elevated, but the release of serotonin from the postsynaptic receptors is not. Under long-term lithium administration, Ho et al. (1970) found that the turnover rate in the hypothalamus was distinctly decreased; it was increased only in the cerebellum.

c) The *dopamine* content of the tubero-infundibular neurons was found to be increased after lithium treatment (Corrodi et al. 1969). Other researchers, however, could not find any definite alterations in noradrenaline or dopamine metabolism in the brain (Ho et al. 1970; Bliss and Ailon 1970). In man, lithium leads to a normalization of the dopamine excretion, which is increased during mania (Messiha et al. 1970). It has a stabilizing effect on the increased sensitivities of the dopamine receptors during mania (Bunney et al. 1979).

d) The *GABA* content of the region of the hypothalamic nuclei, and to a lesser extent that of the amygdaloid nucleus was found to be elevated (Gottesfeld et al. 1971). The corresponding values in other regions of the brain were unchanged. This effect outlasted cessation of treatment by 1 week.

e) Finally, the behaviour of *choline* and *acetylcholine* under lithium treatment deserves to be mentioned. Under long-term treatment, there was an increased choline uptake, and therefore an increase in acetylcholine synthesis, especially in the striatum (Jope 1979). Lithium stimulates the high affinity choline transport, but apparently does not directly affect the synthesis of acetylcholine.

In general, it must be emphasized that the effects of short-term lithium medication differ markedly from those of long-term medication for these examination of neurotransmitter systems.

3. Glucose transport is increased, as well as glycogen synthesis in brain and muscle (Vendsborg and Rafaelsen 1973; Plenge et al. 1970). Rafaelsen et al. (1978) explain these effects on intermediary metabolism by hypothesizing a chain of effects from the carbohydrate metabolism via electrolyte anomalies to disturbances in amine metabolism. They propose that the main effect of lithium lies in a stabilization of the membrane, and they believe that correspondingly the basic defect of the manic-depressive psychoses is a malfunctioning of the cell membrane. Irrespective of these speculative hypotheses, we must ask ourselves to what extent the pathophysiological data may be correlated to the neuropathological findings.

In our case, the predominant alterations were those of the cerebellar cortex. The varying degree of necrosis of granule cells and the patchy damage to the Purkinje cells, together with the swelling of nerve cell axons, can all be regarded as the morphological equivalent to the ataxic symptoms and disturbances of coordination. The enforced glia cell reaction in the dentate nucleus also fits this

picture, even though there was no distinct nerve cell damage in this region. With its interneuronal connections, the cerebellum represents a system of inhibitory neurons, whose principle transmitter is GABA (Ito and Yoshida 1966; Eccles 1969). Those authors engaged in research on GABA metabolism during lithium treatment did find a concentration of GABA in the hypothalamus and amygdaloid nucleus, but no abnormal findings in the cerebellum (Gottesfald et al. 1971), only that the serotonin turnover rate was increased (Ho et al. 1970). With respect to our neuropathological findings in the cerebellar cortex the work of Siggins and Schultz (1979) is of special interest: in rat experiments these authors showed a significant reduction of spike activity of the Purkinje cells during long-term lithium therapy using doses corresponding to psychopharmacological doses.

The symptoms of the extrapyramidal motor system, especially in association with long-term damage after lithium intoxication, led us to expect corresponding alterations in the nigro-striatal system. Neither the striatum nor the pallidum were markedly altered, and no clear pathological findings could be established in the substantia nigra. The eosinophilic cytoplasmic inclusions and the Hirano bodies of some of the nerve cells must be considered as physiological in the case of a 61-year-old woman. Dispersion of pigment was not remarkably increased. Only the nucleus ruber, like the inferior olives, showed a proliferation of glia cells. There is thus a discrepancy between the clinical picture and the light-microscopical findings. Similarity, there was no observable light-microscopical damage to the nerve cells, that could correspond to the expected elevation of dopamine and acetylcholine metabolism under lithium medication, as can be found for example in the cases of paralysis agitans or the postencephalitic parkinsonism.

In the little available animal research on lithium intoxication, corresponding alterations could also not be found. Akai et al. (1977) identified using electron microscopy an injured endoplasmic reticulum and expanded cisternae in the nerve cells of putamen and thalamus, cortex, and medulla oblongata. The Golgi complexes were atypical. In these experiments on apes, the presynaptic vesicles often showed increased osmiophilic properties or were incrusted in their membranes by points and spikes. In the putamen, in particular, there were unusually large presynaptic vesicles with invaginations of the border membranes and a tendency for the spherical vesicles to stick to the dense synaptic clefts. The latter were often covered with dense osmiophilic material. The dense-core vesicles in the presynaptic cells were also often pathologically altered, as were the other intraneuronal organelles and the mitochondria. Since the dense-core vesicles are thought to be involved in the catecholamine metabolism, a correlation can be made here to the lithium-induced alterations of catecholamine metabolism mentioned above.

In Edelfors' (1975) research with experimental animals, the highest lithium concentrations were found in the nuclear regions of the hypothalamus. In these areas, Akai et al. (1977) have also discovered using electron microscopy, marked damage to cell organelles. In addition to the already mentioned gliosis in the nucleus ruber in our case, we found cytoplasmic vacuoles in various nerve cells of the supra-optic nucleus, the lateral geniculate bodies, and furthermore siderophages in the infundibular stalk. Damage to the nerve cells of the supra-optic nucleus, the infundubulum, and the hypophyseal gland had also been reported

from animal research by Ellman and Gan (1973). Cytoplasmic vacuoles were found in cultured nerve cells grown in lithium-containing medium (Whetsell jr. and Mire 1970). This damage may have a similar pathophysiological origin to our case, which also revealed some cytoplasmic inclusions in some of the nerve cells in the cranial nerve nuclei.

In view of the above-mentioned disturbances to noradrenaline metabolism when using lithium, we paid special attention to the Raphe nerve cells, but could not find any clear deviations from the standard. Strong parallels could be drawn between the apes of Akai et al. (1977) and the findings established in our case, with regard to the heavy loading with lipofuscin pigment of the nerve cells. Akai et al. even described some finger-print patterns in their complexes of lipopigment. The nerve cells of our case were also very lipophilic. Here, however, the age of the patient must be taken into consideration. We did not find the lipopigment-filled processes of the pyramidal cells of layers III a/b as described by Braak (1979). On the other hand, the coarsely granulated pigment inclusions normally seen in the ceroidlipofuscinosis were also missing. The question whether a correlation between lithium intoxication and a lipopigment content that goes beyond the norm for age is indeed indicated here, but requires further research. Even Akai et al. did not commit themselves to an answer this question. Instead they explained the enrichment of lipofuscin pigment as a combination of effects from nutritional factors, ageing, and lithium ions.

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