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Neuropathologic Findings after Neuroleptic Long-Term Therapy

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There are several theories explaining the main tranquilizing action and side effects of neuroleptic (NL) and related antipsychotic drugs that are thought to act on dopamine (DA) receptor sites in brain (12,14,29,56, 93).

1. The receptor–blockage hypothesis states that the NL drugs specifically attach to striatal DA receptors (90,93), thus inhibiting DA-sensitive adenyl cyclase (44), increasing the firing rate of DAergic nigral neurons, and accelerating DA turnover and synthesis (2,28,68). There is no simple and direct quantitative relationship, however, between any of these NL actions and their antipsychotic potencies (79).

2. As the strionigral GABA-ergic system is suggested to influence the nigrostriatal DA-ergic systems (7), NL-induced decrease of γ-aminobutyric acid in strionigral neurons may result in decreased inhibition of DA-ergic nigrostriatal neurons and thus activate the turnover of DA in the striatum (47).

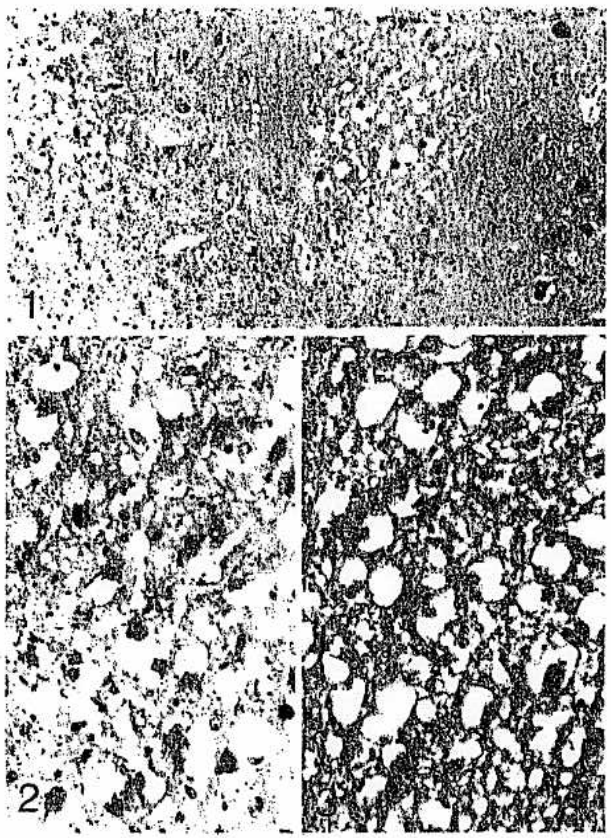
3. The coupling–blocking hypothesis of NL action recognizes that the NLs are fat-soluble and surface-active drugs that accumulate in cell membranes (78) blocking nerve membrane impulses, enhancing the spontaneous release of the transmitter, or modulating the coupling between impulses and neurosecretion (23). There is recent evidence of a direct correlation between the antipsychotic activity of NL drugs and their ability to block the presynaptic impulse-coupled release of DA (79). Whatever the mechanism of NL inhibition of DA release, a presynaptic site of NL action in the small striatal DA neuron terminals might explain many of the chronic NL effects in brain (79), which also have been related to a state of denervation hypersensitivity of postsynaptic DA receptors with a resulting increase in DA-ergic activity (12,40,48,87,93).

Although clinical and experimental data on both acute intoxication and chronic treatment with NL drugs suggest some morphologic changes in the central nervous system (CNS), the problems of chronic brain damage due to long-term NL therapy and of the kind of lesion accounting for the clinical syndromes [e.g., parkinsonism and tardive and persistent dyskinesias (6,19,22, 48,71)] are poorly understood.

The results of neuropathologic studies after both acute intoxication and prolonged treatment with NL drugs are controversial, and surprisingly little is known of the anatomic substrate of drug-induced encephalopathies (31,43,72).

ACUTE INTOXICATION

After acute intoxication with NL drugs, CNS changes in both man and experimental animals



FIGS. 1 and 2. Localized status spongiosus with astroglial swelling and mild neuronal damage in Westphal–Edinger nuclei after fatal overdosage of nialamide. H. & E. Fig. 1, ×90. Fig. 2, ×250.
FIG. 3. Severe spongy changes with neuronal and axonal changes in inferior olive after acute fatal intoxication with thioridazine. C. V. ×250.

include cerebral edema and nonspecific neuronal changes, including reversible neuronal swelling and vacuolation, often superimposed on by secondary anoxic and vasocirculatory lesions (for review, see 13,25,43,58). Necroses of the cerebral gray matter with gliovascular reaction found in a cerebral biopsy of an infant 9 months after accidental poisoning with chlorpromazine (CPZ) were attributed to chronic hypoxia (5). In one case of acute fatal intoxication with thioridazine (Melleril®, 6,000 mg), and in two cases of acute death following

overdoses of nialamide, a monoamine oxidase (MAO) inhibitor, given in doses of 1,500 mg/day, we observed localized spongy changes of the neuropil with astroglial swelling and neuronal damage in both the Westphal-Edinger nuclei (Figs. 1 and 2) and inferior olives (Fig. 3). Similar changes experimentally induced in dogs by heavy dosing and chronic application of MAO inhibitors were attributed to a vasoconstrictor action of serotonine in the brain, with associated edema (70,91).

Nonspecific neuronal changes in the striatum, substantia nigra, hypothalamus, and cerebral cortex of experimental animals after application of high doses of NL drugs are often unrelated to clinical signs (73), and their separation from artifacts may be difficult. Ultrastructural demonstration of increased glycogen in astroglia and dendrites of hypothalamus and globus pallidus after therapeutic doses of CPZ and trifluoperazine (haloperidol) (50–52) are suggested to result from blockage of glycolysis and oxidative processes (24). Neuronal swelling with dilated endoplasmic reticulum (ER), increase in the number of mitochondria and profiles of granular ER (4) and of microvesicles in dendrites and presynaptic terminals are related to a partial—probably reversible—blockage of rapid axonal transport induced by CPZ and other tranquilizers (23). Increased pinocytosis of capillary endothelial cells after intracisternal application of CPZ indicates disorders of the blood-brain barrier (24).

In vitro application of CPZ and antidepressant drugs induces neuronal swelling with dilatation of the ER and mitochondria, and accumulation of concentric multilamellated dense bodies (MLB), often related to rough ER or resulting from stimulation of the lysosomal system with accumulation of phospholipids (10,35,36). Although similar MLBs were observed after chronic phenothiazine treatment in rats and in a human biopsy case after acute CPZ intoxication (5), these changes were not seen in human brains after chronic CPZ treatment (36). Similar changes induced by a variety of drugs [e.g., LSD, chloroquine, and antidepressant and anorexic drugs (3,49,60,61,76,85)] are thought to result from impairment of phospholipid turnover, thus representing some kind of experimental lipidosis.

CHRONIC EXPERIMENTS

Neuropathologic studies after long-term administration of phenothiazines and related drugs, summarized in Table 1, revealed nonspecific neuronal changes, neuronal loss, and gliosis in cerebral cortex, limbic system, brain stem, and cerebellar nuclei, with changes in the glioneuronal ratio in dentate nuclei and superior olives (38). Neuronal hyperchromia in cerebral cortex is associated with increase in the RNS content, accumulation of glycogen, and decreased activities of oxidative enzymes (77), some of these changes being dose dependent (81). Neuronal changes and gliosis in the limbic system (20,81) could be related to a blockage of DA receptors in the (meso)limbic system that project to the hypothalamus and nucleus accumbens septi (67,86).

Electron microscopic studies in rabbits with extrapyramidal syndromes after prolonged application of CPZ and haloperidole showed synaptic changes in the pallidum and hypothalamus (53–55,88) that were considered the results of partial blockage of glycolysis and/or axonal transport. Increased cytoplasmic membranes in the presynaptic axons of the globus pallidus (54) are probably related either to the interaction of phenothiazines with synaptosomal membranes (18) or to hyperplasia of the smooth ER resulting from disorders in the physiologic remodeling of synapses seen in a large variety of conditions (83). Changes of the postsynaptic dendrites with deposition of granular and fibrillar material, shrunken boutons embraced by astroglia, and vacuolation of presynaptic axon terminals in the hypothalamus (55) are similar to antegrade axonal degeneration following neuritic transection (1,82) and to degeneration of striatal boutons after experimental damage to the substantia nigra with degeneration of the DA-ergic nigroneostriatal pathway (39,46). Changes in the glioneuronal ratio (38) and synaptic changes in the brainstem, therefore, are tentatively related to chronic "biochemical denervation" of striatal DA- or GABA-ergic neuronal systems.

HUMAN NL ENCEPHALOPATHY

Neuropathologic experience in man after long-term NL treatment is still limited, and its results are controversial (see Table 2). A suggested increase of mortality in schizophrenic patients after prolonged NL treatment (64) needs further statistical confirmation. The majority of the morphologic CNS changes reported in the literature are nonspecific or related to normal aging, extraneural disease, or agonal and postmortem phenomena.

Chronic liver damage may induce hepatic encephalopathy with occurrence of Alzheimer type II astroglia. Drug-induced agranulocytosis and coagulation disorders may induce cerebral

TABLE 1. *CNS morphology in animals following long-term administration of NLs*

Author (ref. no.)	Animal	Drugs	Dosage/day (mg/kg)	Duration	CNS changes	Location
Kemali et al. (45)	Rabbit	CPZ, reserp.	7.5	12 d	Neuronal lesion. gliosis	Basal ganglia, hypothalamus
Roizin et al. (75a)	Rat, monkey	CPZ	12.5	8 mo	Chromatolysis, neuronophagia, gliosis	Diffuse
Guyeniseman (37)	Rat	CPZ	5.0	30 d	Neuronal lesion	Diffuse
Palmer & Noel (70)	Dog	MAO-inhibitors	5–35	3 mo	Focal neuronal loss, spongy necrosis, gliosis, myelin damage	Inf. olives, cerebellar nucl., caud. nucl.
Mackiewicz & Gershon (63)	Guinea pig	CPZ	10	4–13 wk	Neuronal lesion, gliosis, capill. hyperplasia	Reticular formation
Cazzullo et al. (15)	Rabbit	CPZ	Clin. dose	12 mo	Neuronal swelling	Brainstem
Dom (20)	Rat	Haloper.	Ther. dose	4 mo	Gliosis	Limbic system
Worden et al. (91)	Dog	MAO-inhibitors	?	wk	Stat. spong., neuron. loss, myelin lesion	Inf. olives, Cerebell. nuclei
Romasenko & Jacobson (77)	Rat	Trifluoper.	20	4 wk	Neuron. hyperchromasia, RNS, AcPase, SDH*	Cerebral cortex
Sommer & Quandt (81)	Rabbit	CPZ Prothioop.	3–16.7	6 mo	Neuron. loss, gliosis, glycogen increase	Cortex, Ammon's horn Glob. pallidus
Koizumi & Shiraishi (54,55)	Rabbit	CPZ Haloper.	2.0 15	2–5 mo	Presyn. axon degen. Postsyn. dendrite	Hypothalam. Dent. nucl., sup. olive
Hackenberg & Lange (38)	Rat	CPZ	10–15	6–8 wk	Neuron. degeneration, neuron. loss, gliosis (diffuse)	

* RNS, ribonucleic acid; AcPase, acid phosphatase; SDH, succinic dehydrogenase.

TABLE 2. *Morphology of human brains following long-term NL therapy*

Author (ref. no.)	No. cases	Drug	Dosage (mg/d)	Duration	Dyskinesia	Autopsy	Neuropathology
Ayd (6)	1	CPZ	400	4 yr	–	Ac. death	Neuron. swelling bas. ggl.
Bom (9)	1	Megaph.	400	17 d	–	Ac. death	Neuron. swelling striatum
Grünthal & Bühl (34)	1	Perph.	550	13 d	Perioral	Pneum.	Edema, chromatolysis inf. olivary neurons
Roizin et al. (75)	17	CPZ	50–1200 mg	3–6 mo	Parkinson	?	Lipofuscinosis (general), cortical neuronophagia (4 cases)
Forrest et al. (27)	1	CPZ Trifluoper.	?	? yr	–	?	Neuronophag. putamen depigmentation nigra
Greiner & Nicolson (30)	12	CPZ	225	0.4–9 yr	–	Increas. melanine	Generalized lipofuscinosis
Hunter et al. (41)	1	CPZ	1–200	2.5 yr	Perioral	Pneum.	Gliosis striatum, thal., mild nigral lesion
Same	1	CPZ Trifluoper.	Same 10	6 yr 6 mo	Perioral	Pneum. Liver dm.	Moderate nigral lesion
Same	1	Same	Same	6 yr	Perioral	Myoc. inf.	Nigrostrial myelin damage
Christensen et al. (17)	28 (21) 28	CPZ Thior. Reserp.	75–600 mg	1–40 mo	Perioral	?	27/28 nigral lesion 25/28 brainstem gliosis 7/28 nigral lesion
		Same	Similar	1–43 mo	–	?	4/28 brainstem gliosis
Eijk-Bots (25)	1	Thiop.	20	? mo	Perioral	Shock	Edema, lipofuscinosis
Personal series (31,33,43)	14	CPZ Var. NL	Ther. dose	3–11 yr (int)*	Hyperkin. (9) Akinetic (5)	Pneum. Bolus	8/14 caudate lesions 2/13 pallid. lesion
Same	14	Similar	Similar	2–11 yr	None	Similar	5/14 caudate lesion

* Int = intermittent.

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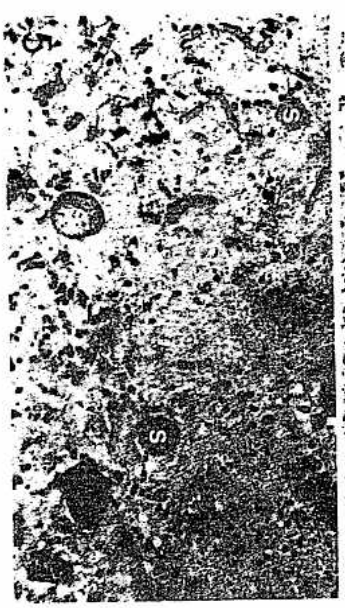


FIGS. 4 and 5. Severe increase in glial pigment and numerous axonal spheroids (S) in the reticular zone of substantia nigra of schizophrenic man aged 65 without dyskinesia. C. V. Fig. 4, ×90. Fig. 2, ×280
FIG. 6. Terminal axonal swellings (x, *arrows*) in globus pallidus of schizophrenic woman on long-term NL treatment. Bodian's silver impregnation. ×560.

edema, microhemorrhages, capillary thromboses with microcirculation disorders, and ischemic lesions. Frequent cerebral edema in psychiatric autopsy material can only rarely be related to chronic psychopharmacotherapy (26). Frequent but nonspecific phenomena are chromatolysis and increased lipid in neurons and other visceral organs (13,26,30,75).

Lesions of substantia nigra with depigmentation and neuronal loss occasionally seen in drug-induced dyskinesia (17,27,41) are *not* considered significant in view of the advanced age of most of these patients, the average age in the dyskinesia material of Christensen et al. (17) being 74 years. Reduction in the number of melanin-containing neurons in elderly subjects has been shown by semiquantitative and automatic counting procedures (16,69) but was not observed in a personal series I conducted of 28 autopsy cases after prolonged NL treatment where the average age at death was 56 years (see discussion below).

Axonal swellings ("spheroids") in the reticular zone of substantia nigra (Figs. 4 and 5) and globus pallidus (Fig. 6), described in some cases of drug-induced dyskinesia (32,33), are also considered age-dependent changes *unrelated* to NL treatment. "Dystrophic" axonal changes represent a nonspecific and experimentally reproducible degenerating phenomenon of the neuron, the intensity of which in some constantly affected sites of the human CNS is clearly related to age without relation to any basic disease (42). However, the occurrence of dystrophic axons in the reticulata nigrae has been shown to be significantly ele-

vated in Parkinson's disease and chronic alcoholism (42). This latter condition and advanced age are suggested to be responsible for the presence of these axonal changes in some elderly patients with drug-induced dyskinesia.

Diffuse gliosis in the striatum and thalamus, and mild chronic degeneration of myelin of questionable significance in the pallidonigral system were observed in phenothiazine-induced dyskinesia (41). Christensen et al. (17) reported gliosis in the brainstem in 25 of 28 brains with drug-induced dyskinesia, a condition rarely seen in age-matched controls. However, these changes, which in combination with damage to substantia nigra were considered to account for the clinical syndromes, were not confirmed by other investigators (31–34).

Damage to large neurons in the *caudate nucleus* with increased glial satellitosis, occasional neuronophagia, and mild gliomesenchymal reaction in the brains of patients with dyskinesia was reported by Gross et al. (31–34). These changes, observed in the striatum of other patients who died after prolonged treatment with CPZ and triflupromazine (27,74) but not seen in normal controls, were taken to be related to the drug-induced clinical syndrome.

PERSONAL INVESTIGATIONS

In order to further elucidate this problem, a histologic study of 28 brains following long-term NL treatment with persistent extrapyramidal symptoms in 14, was performed. The series included 16 men and 12 women, ranging in age from 21 to 74 years (average 56.1 years). There were 24 schizophrenics, four depressives, and two organic psychoses to whom NL and tranquilizers had been administered for, on the average, 5 years (range from 2 months to 11 years), although in most of the patients intermittent treatment was given. The drugs administered were CPZ, trifluoroperazine, chlorprothixen, reserpine, thioridazine, tricyclic antidepressants, and tranquilizers, alone or in combination. Fourteen patients developed extrapyramidal disorders with rigid akinetic parkinsonism in five and choreiform or perioral hyperkinesias in nine (Table 3). The duration of dyskinesia ranged from 4 months to 7 years. The average age at death was 54.3 years; the average duration of drug treatment was 5 years. The control group included 14 patients with an average age at death of 57.8 years who never developed extrapyramidal symptoms in the course of NL medication with an average duration of 4.4 years (Table 4).

The *pathologic changes* in brains of both groups consisted of:

1. nonspecific lesions related to age or lethal basic disease, e.g., cerebral edema, atrophy, atherosclerosis, lipid deposition in the neurons, and dystrophic axons in substantia nigra (Figs. 4 and 5), globus pallidus, and Goll's nucleus;

2. incidental findings unrelated to NL treatment, e.g., two cases of abortive Fahr's syndrome (mineralization of the basal ganglia), and lipoma of the hypothalamus;

3. no observed damage to substantia nigra and gliosis in the brainstem although this had been previously reported;

4. changes in the *caudate nucleus*, in 13 cases, i.e., 46% of the total series, with swelling of large neurons, increased glial satellitosis, and occasional neuronophagia, associated with slight proliferation of astroglia and preservation of small neurons (Figs. 7–11). These changes were usually conspicuous in the rostral two-thirds of the caudate nucleus with almost bilaterally symmetrical intensity, but were rarely seen in the caudal part of the nucleus. Similar, much less pronounced, changes in the putamen and globus pallidus were seen in five of the affected cases, but were never observed in other subcortical nuclei or in the cerebral cortex. In some cases, multiple terminal axonal swellings in the globus pallidus next to swollen neurons with central chromatolysis or ballooned cytoplasm (Fig. 6) were noted. All these changes were unrelated to general autopsy findings and to the cause of death, basic lethal disorder, or duration of agonia (Tables 3 and 4).

TABLE 3. *CNS changes following long-term NL therapy with extrapyramidal disorders*

Case no.	Age. sex	Clinical diagnosis	Duration NL Th. (yr/int)*	Extrapyr. symptoms		Autopsy	Neuropathology findings		
				Parkinson.*	Hyperkinesia		Caud.	Pallid.	Others
11/66	55. M	Schizo.	3	+	Perioral	Bolus death	++	–	Edema
18/67	50, M	MDP[a] alc. chron.	4	+ +	Perioral	Myoc. Inf.	++	–	Edema
23/67	40, F	Schizo.	3	+ +	Choreif.	Pneumonia	+	–	Cer. atrophy
17/68	48, F	Schizo.	5	+ +	Perioral	Pneumonia	–	–	Abort. Fahr's dis.
26/68	51, M	Schizo.	4	+ +	Dyskinet.	Nephritis	++	+	Cer. atrophy
5/69	55, M	Involl. psych.	8	+ +	Perioral	Card. decomp.	+	–	Vasc. encephalop.
20–69	55, F	Schizo.	11	+ +	Perioral	Pneumonia	++	–	Bil. lobotomy
348–70	56, M	Schizo.	11	–	Choreoathet.	Pneumonia	–	–	Hydroceph. int.
388–70	70, M	Schizo.	9	–	Choreif. + tremor	Pneumonia	++	–	–
18/63	38, M	Hebephr.	2 yr	++	–	Pneumonia	–	–	Edema
56/65	66, M	Vasc. dementia	4	++	–	Pneumonia	–	–	Pontine dystrophy
16/67	44, M	Hebephr.	9	++	–	Pulm. edema	+	–	Edema
16/68	56. M	Schizo.	5	+ +	–	Bolus death	+	+	–
182–72	66, F	Schizo.	11	++	–	Pneumonia	–	–	Abort. Fahr's dis.

*Yr/int = years/intermittent application.
*+ = slight; ++ = moderate.
[a]MDP = manic–depressive psychosis.

TABLE 4. *CNS changes following long-term NL therapy without extrapyramidal symptoms*

Case no.	Age, sex	Clinical diagnosis	Duration NL Th.	Autopsy	Neuropathology findings		
					Caud.[b]	Pall.	Others
22/63	65, M	Schizo., alc.	3 yr	Tuberc., myoc. inf.	++	–	–
17/65	70, M	Schizo.	7 yr/int[a]	Pneumonia	+	–	Diff. cer. atroph.
42/65	29, M	Schizo. suic.	6 yr/int	Shock, aort. stab.	+	–	Cerebr. edema
3–68	65, M	Schizo. suic.	5 yr/int	Pneum. shock	+	–	Atherosclerosis II
49–69	60, M	Depression	2 mo	Tuberculosis	+	–	Diff. gliosis
22/67	40, F	Schizo.	3 yr	Bronchopneum.	–	–	Neuron. lipidosis
275–69	56, F	Schizo.	6 yr/int	Hem. cystitis	–	–	Cerebr. edema
434–70	21, M	Schizo.	1 yr	Pneumonia	–	–	Cerebr. edema
14–71	69, F	Depression	2 yr	Pneumonia	–	–	–
66–71	72, F	Mixed psych.	2 mo	Enteritis, pneum.	–	–	Cerebr. edema (mild)
389–71	74, F	Schizo. defect.	6 yr/int	Hypertension	–	–	Lipoma hypothalamus
14–72	66, F	Schizo.	6 yr/int	Tuberculosis	–	–	Cerebr. edema
78–72	68, F	Schizo.	8 yr/int	GI carcinoma	–	–	Cerebr. edema
177–72	60, F	Schizo. defect.	7 yr/int	Pulm. embolism	–	–	Edema (mild)

[a] Yr/int = years/intermittent application
[b] + = slight; ++ = moderate.

As these lesions in the caudate nuclei were only observed in 4% of an age-matched control group of psychotics without long-term NL treatment and in less than 2% of a large neuropathologic routine group of patients, they were tentatively considered significant. Caudal lesions of this type were seen in nine of 14 cases, i.e., 57% of the dyskinesia group, and in only five of 35 cases, 7% of the cases without extrapyramidal disorders (Table 2). Although these changes were more pronounced in cases with choreiform and perioral hyperkinesias than in akinetic parkinsonism and controls, there was no definite correlation between the intensity of the morphologic changes and the clinical syndrome.

Electron microscopic studies performed on formalin-fixed and osmium-postfixed autopsy material of the caudate nucleus and globus pallidus of two patients with late dyskinesias following prolonged treatment with CPZ and other NL drugs (cases 348–70 and 388–70, Table 3) gave the following preliminary results: in addition to considerable postmortem changes and nonspecific neuronal and astroglial changes including lipofuscin accumulation, there were neuronal processes and mildly enlarged axons with a variety of altered organelles including mitochondrial, multigranular bodies (MB) with accumulation of glycogen, and concentric multilamellar bodies and loose membranous whorls (Fig. 12). These "myelin bodies" resembled those observed in degenerating and dystrophic axoplasm (42,57) and in neurons of aging brain (74) rather than the drug-induced MLBs (10,49,60,61,76).

The pathogenesis of the changes in the caudate nuclei following prolonged NL treatment and their relation to the biochemical effects of NL drugs are obscure. The possible mechanisms underlying the caudate lesions, which are believed to represent the only constant light microscopic findings in drug-induced dyskinesia, could be the following.

1. Nonspecific damage to the large caudate neurons associated with increased glial satellitosis, and occasional neuronophagia are consistent with some chronic sublethal neuronal lesions, e.g., as seen in chronic denervation.

2. Although ultrastructural data indicate nonspecific neuronal changes and axonal

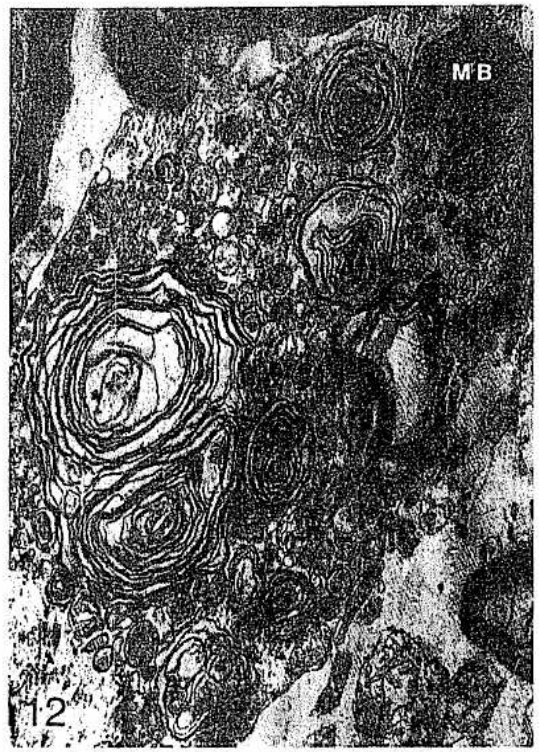
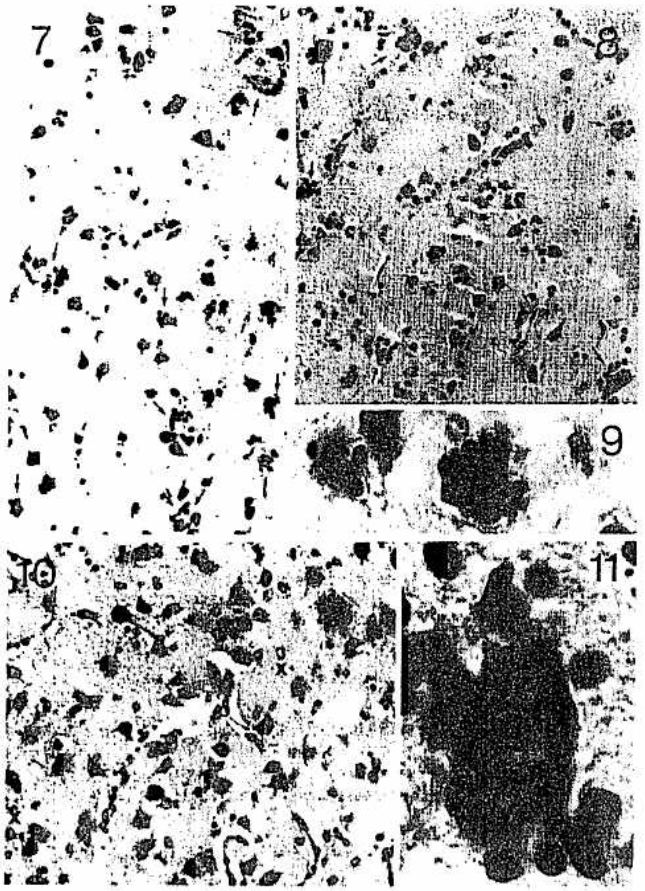


FIG. 12. Enlarged axon in caudate nucleus of schizophrenic patient on prolonged NL treatment, showing increased number of mitochondria, some MB and many concentric MLB and loose-lamellated whorls. ×10,000.

degeneration, some similarities with experimental striatal changes following prolonged NL administration (53–55) and lesion of the nigrostriatal pathway (7,39) indicate that these changes may be the results of chronic biochemical denervation in some striatal neuronal systems.

3. The phenothiazines and related NL drugs are thought to act by blocking DA receptor sites, thus chemically denervating DA receptors of the striatal afferents, which are most probably the small and medium spiny neurons (7,46), whereas dendrites originating from the sparse population of larger caudate neurons are believed to send their axons to the substantia nigra (84), thus forming a strioneostriatal loop system. The prominent changes in the large caudate neurons after prolonged NL treatment, therefore, might result from *in-*



FIGS. 7 and 8. Increased satellitoses (*arrows*) and mild glial reaction in left (Fig. 7) and right (Fig. 8) caudate nuclei of schizophrenic man aged 55 with persistent dyskinesia. C. V. Both figures, ×90.
FIG. 9. Satellitosis around large neuron and small glial nodule in caudate nucleus of same patient. C. V. ×540.
FIG. 10. Occasional glial satellitosis and mild glial reaction (x) in caudate nucleus of schizophrenic man aged 65 on long-term NL therapy without dyskinesia. C. V. ×240.
FIG. 11. Glial satellitosis around large caudate neuron in same patient. C. V. ×1,500.

direct damage, although the selective vulnerability of the large striatal neurons to different noxae is well established (65).

Although biochemical and experimental data are in favor of some relationship between hyperkinesia and lesions in the caudate nuclei (59), the clinical significance of the caudate changes after long-term NL treatment remains to be elucidated. The similarities between NL-induced dyskinesias and those following levodopa therapy of parkinsonism have been emphasized (12,48), both disorders probably being related to excessive inhibition of the striatal DA neurons. So far, however, no anatomic substrate of the levodopa-induced syndrome has been found (21,92). The question remains, therefore, why some patients on chronic NL treatment develop parkinsonism or tardive dyskinesia with or without caudate lesions, whereas others on equal or even higher doses do not show any extrapyramidal disorders even in the presence of some anatomic changes in the caudate nuclei.

Alternative Diagnoses to NL Encephalopathy

Clinical problems may arise from the "masking" of extrapyramidal degenerative disorders, e.g., Huntington's chorea, by NL treatment, and from difficulties in the clinical distinction between drug-induced encephalopathies and organic brain disease, including Creutzfeldt-Jakob disease and Huntington's chorea.

Long-term NL treatment may inhibit the clinical manifestation of Huntington's chorea, as observed in a demented woman aged 63, presenting with schizophrenia, who received intermittent NL treatment for 11 years without developing hyperkinesia. At autopsy, the brain showed the characteristic features of Huntington's chorea, without pallidal lesions often associated with rigid akinetic forms of this disease (11). This is in keeping with clinical experience indicating favorable influence of NL drugs on Huntington's chorea (40,80), which is morphologically characterized by loss of small striatal neurons (11) with preserved striatal DA receptors, and no or very little decrease in striatal DA content (8).

Although NL-induced dyskinesia usually differs from Huntington's chorea, NL-induced encephalopathy may be occasionally mimicked by the latter disease showing initial psychotic features with delayed development of extrapyramidal symptoms (33,89). We observed three cases of Huntington's chorea, confirmed at autopsy, that had been clinically interpreted as chronic schizophrenia with NL-induced dyskinesia. Later, positive family histories of Huntington's chorea were found in two of these patients. Any causal relationship to or triggering of Huntington's chorea, a hereditary degenerative disease, by NL treatment, however, can be strictly denied.

Cerebral Phlebitis

A rare type of *cerebrovascular lesion* should be mentioned that may or may not be related to prolonged NL treatment. Moore and Brook (66) reported two cases of young girls who had received NLs and/or anticonvulsive drugs over an extended period of time and who were found dead without any preceding acute illness. The outstanding pathologic finding was a segmental nodular, occasionally annular intraadventitial lymphomonocytic infiltration of the meningeal and intracerebral veins without arterial and parenchymatous involvement or extracerebral vascular disease. Similar inflammatory reaction of cerebral veins was mentioned in an epileptic who had been "allergic" to antiepileptic drugs (66). We observed this type of *"cerebral segmental nodular phlebitis"* in four patients, three of whom had received long-term NL treatment. A man aged 65 with organic psychosis who developed

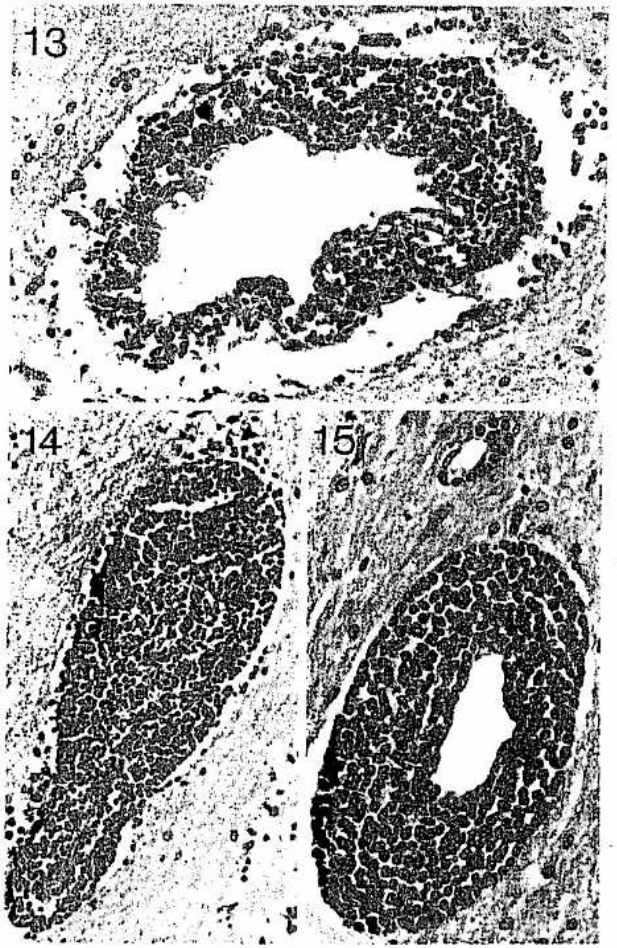


FIG. 13. Adventitial monocytoid infiltration in striatal vein. H. & E. ×250.
FIGS. 14 and 15. Mural and adventitial lymphoid infiltration of small veins in thalamus (Fig. 14) and globus pallidus (Fig. 15). H. & E. Fig. 14, ×250. Fig. 15, ×360.

dyskinesia after 8 years of intermittent administration of phenothiazines died from myocardial infarction. The brain, in addition to a small old cystic infarction in the striatum, disclosed disseminating lymphocytic infiltration of the cerebral veins without meningeal or parenchymal involvement. In a schizophrenic woman aged 30 who for at least 10 years received combined NL treatment without dyskinesia and who died in acute catatonia, disseminated phlebitis was seen in the striatum, thalamus, hypothalamus, amygdaloid nucleus, and medulla oblongata (Figs. 13,14,15). Similar phlebitic lesions in the white matter and basal ganglia were observed in a 52-year-old schizophrenic woman who, after several years of treatment with NL and antiepileptic drugs, died in an acute coma. Thorough histologic review of other tissues of the body failed to uncover any lesions of the extracerebral vasculature or of the cerebral arteries. The explanation for the singular involvement of the brain (the spinal cord was not available for study), with the escape of other tissues of the body, is not forthcoming, nor is there any manifest explanation for the sole attack on the veins to the exclusion of the arteries. No definite conclusion about the type of cerebral phlebitis observed after prolonged treatment with phenothiazines and anticonvulsive drugs being a form of sensitization to autoimmune reaction can be reached. However, the appearance of intramural segmental or annular phlebitis in the brain and meninges has been observed in other conditions, e.g., in demyelinating disorders including multiple sclerosis (62), indicating immune activity on the CNS. A study of similar cases could assist in clarifying the relationship between the clinical data and pathology findings.

The same applies for the pathogenetic elucidation of other neuropathologic findings after long-term NL therapy including the reported changes in the caudate nuclei that may or may not represent some morphologic substrates for drug-induced dyskinesia. We can guess that, under certain circumstances, NL treatment primarily causes reversible structural and ultrastructural changes in certain extrapyramidal systems that later progress to irreversible damage, particularly in caudate nucleus. However, this guess can only be proved if these findings are reproduced in larger autopsy material and correlated with experimental ultrastructural and biochemical data.

SUMMARY

Biochemical and experimental electron microscope data on the effects of NL drugs indicating a blockage of the postsynaptic DA receptors or of the presynaptic DA release in the striatum and electron microscope data on synaptic changes probably resulting from partial blockage of glycolysis and of rapid axonal transport with disorders of the physiologic remodeling of synaptosomes suggest the possibility of permanent structural CNS lesions following prolonged administration of phenothiazines and tranquilizers. Changes in the glioneuronal ratio and degeneration of boutons in brainstem are tentatively related to chronic biochemical denervation. The majority of changes described in human brains after long-term NL treatment with or without dyskinesia are nonspecific or related to normal aging (nigral lesions, axonal dystrophy) and lethal disease. A neuropathologic study of 28 cases following prolonged NL treatment, with persistent hyperkinesia in 14, disclosed damage to large neurons in the caudate nuclei with increased satellitosis and slight glial reaction in 46%. The incidence of these changes was higher in the dyskinesia group (57%) than in cases without extrapyramidal disorders (37.5%), but there was no correlation between the intensity of the morphologic changes and the clinical syndromes. The pathogenesis of the caudate

lesions and their relation to the biochemical effects and clinical side effects of NLs are obscure. A rare type of isolated cerebrovascular lesion observed after prolonged NL and anticonvulsive treatment is cerebral segmental nodular phlebitis which may represent some form of autoimmune reaction to these drugs.

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