

Parallels between Neuroleptic Effects and Lethargic Encephalitis: The Production of Dyskinesias and Cognitive Disorders

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A retrospective examination of lethargic encephalitis finds many parallels with neuroleptic effects. The encephalitis, like the neuroleptics, produced an acute continuum of cognitive disorders from emotional indifference through apathy and onto a rousable stupor. It also produced similar acute dyskinesias, including akinesia, akathisia, dystonia, oculogyric crises, and tremors. The encephalitis also caused similar chronic effects, including dementia and psychosis, and somewhat different persistent dyskinesias. The chronic motor and cognitive disorders, like those associated with the neuroleptics, were often delayed in onset. An acute, severe episode of lethargic encephalitis also finds a parallel in the neuroleptic malignant syndrome. These parallels are probably due to a common site of action in the basal ganglia. They provide a model for understanding many neuroleptic effects and alert us to the probability of persistent cognitive deficits, including dementia, from neuroleptic treatment. © 1993 Academic Press, Inc.

Increasing concern is being shown about acute and persistent cognitive deficits associated with neuroleptic therapy. Thus far the literature has lacked a comprehensive model or framework for explaining the source, nature, and course of these deficits. Parallels between the effects of lethargic encephalitis and neuroleptic treatment offer a potential model based on a common site of impact in the basal ganglia and associated structures, resulting in both motor and cognitive disorders. These close parallels draw our attention to the probability of persistent cognitive dysfunction following chronic neuroleptic treatment.

LETHARGIC ENCEPHALITIS

Lethargic encephalitis (LE, encephalitis lethargica, von Economo's disease, and epidemic encephalitis) was identified by von Economo in

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the winter of 1916–1917 in Vienna. The pandemic was most severe in Europe and North America, with cases reported throughout the world. Over a decade, the disease afflicted more than a million people and caused hundreds of thousands of fatalities (Ravenholt and Foege, 1982). The last epidemic was reported in 1926 (Matheson Commission, 1939) and the disease largely disappeared by 1930. The infectious nature of LE was demonstrated with its transmission to monkeys, but the presumed viral agent was never isolated or identified.

Manifestations of the disease varied greatly from case to case and epidemic to epidemic; but the syndrome frequently included lethargy or a rousable stupor, various cognitive and behavioral abnormalities, and dyskinesias, among them hyperactivity, tremor, chorea and athetosis, dystonia, and Parkinsonism (Abrahamson, 1935; Brill, 1959; von Economo, 1931; Ward, 1986). Neurological symptoms due to involvement of the basal ganglia¹ were far more common than those associated with the cerebral cortex.

The disease could result in complete recovery or, in approximately 25% of the cases, death (Jubelt & Miller, 1989). Often it became chronic without any period of recovery. At other times, the patient seemed to recover; but months or years later developed postencephalitic disorders afflicting both the mental faculties and motor control, most frequently Parkinsonism. On occasion, postencephalitic states seemed to develop in the absence of a recognized acute phase (von Economo, 1931, p. 112).

Good reasons exist to compare lethargic encephalitis effects with those of neuroleptic drugs. The encephalitis caused a much broader spectrum of acute and chronic symptoms than those associated with neuroleptics; not all manifestations of the infectious disease will be found in neuroleptic-treated patients. *However, nearly all the cognitive and motor disorders commonly associated with neuroleptic treatment were also commonly associated with lethargic encephalitis.*

Some empirical research was carried out on cognitive function in post-encephalitic cases (e.g., Worster-Drought and Hardcastle, 1924–1925); however, it was not sufficiently extensive for comparative purposes. Evaluation of cognitive dysfunction from LE will draw on clinical observations and perspectives.

In the early years of the epidemic, some clinicians mistakenly diag-

¹ The term basal ganglia includes several large gray masses of neurons embedded in the lower parts of each cerebral hemisphere, including the striatum. The striatum is made up of the caudate and the lenticular nuclei, the latter being divided into the putamen and the globus pallidum. When the term basal ganglia is used in this review, it will also include the substantia nigra which sends afferent dopaminergic fibers to the striatum via the nigrostriatal pathway. Damage to the dopaminergic neurons of the substantia nigra affects the striatum. The basal ganglia are interconnected with the reticular activating system, the limbic system, and the frontal cortex (Alheid, Heimer & Switzer, 1990).

nosed LE as dementia praecox or schizophrenia, and even referred to it as "epidemic schizophrenia" (Wyatt, Kirch, & De Lisi, 1989, p. 720). von Economo (1931, p. 133) observed that confusions between encephalitis and schizophrenia occurred "in the days preceding our knowledge of encephalitis lethargica." These confusions affected the concept of schizophrenia in the early 20th Century. Sarbin (1990) observes that many of Kraepelin's and Bleuler's patients diagnosed with dementia praecox and schizophrenia were in reality displaying postencephalitic neurological symptoms.

Discussing the differential diagnosis, Brill (1959, p. 1168) observes, "the emotional reaction is shallow and often dull and apathetic" in encephalitic patients, "but it does not resemble schizophrenia . . ." Ward (1986, p. 219) confirms that "a picture closely resembling schizophrenia was unusual," and adds, "Comparisons between the phenomenology of encephalitis lethargica and schizophrenia suggested that basal ganglia pathology might be the basis of schizophrenia, but such generalizations tend to be far-fetched" (p. 221). Indeed, "Encephalitis is clearly recognizable in necropsy material whereas schizophrenia is not" (Boardman, 1990, p. 185).²

In this paper, it is suggested that the more accurate comparison is between LE and neuroleptic treatment, both of which damage the basal ganglia and produce similar acute and chronic clinical syndromes.

EARLY COMPARISONS BETWEEN THE NEUROLEPTIC AND THE ENCEPHALITIC EFFECTS

Psychiatrists and neurologists working in the 1950s often had firsthand experience with patients from the earlier LE epidemic and were able to

² The finding of extrapyramidal motor disorders in preneuroleptic clinical descriptions of schizophrenia has led some researchers to conclude that at least some motor disorders are the product of schizophrenia rather than the neuroleptics (Waddington & Crow, 1988). As already noted, these preneuroleptic era cases were probably misidentified examples of lethargic encephalitis or other coincident diseases of the basal ganglia or associated structures (also see, for example, Appel, Myers, & Morris, 1958, p. 549). The cases were almost always state mental hospital patients who were exposed to a wide variety of potentially brain-damaging contingencies, including epidemic diseases, malnutrition, trauma, or toxic therapies. As noted in the text, there is no known connection between schizophrenia and basal ganglia disease. When damage to the basal ganglia and surrounding structures is identified on autopsy, a diagnosis other than schizophrenia is made. The same confusion originally occurred between schizophrenia and general paresis before the Wassermann test (Bellak, 1948, p. 88). The question of whether or not tardive dyskinesia is almost always the result of neuroleptic treatment, rather than a mental disorder, is largely answered by a recent controlled study involving the elderly. Older people are considered most susceptible to spontaneous dyskinesias; but during a 24-month period, more than 40% of a neuroleptic-treated group (65 years or older) developed tardive dyskinesia, while none of the controls did so (Yassa, Nastase, Camille, & Belzile, 1988).

compare its effects to those of the neuroleptics. Delay and Deniker, who pioneered the psychiatric use of neuroleptics in France in the 1950s, recognized certain similarities between LE and the new drugs (Delay, Deniker, & Thuillier, 1957).

It is certain that the observation of "cerebral accidents" due to prochlorperazine brings back to life an entire pathology observed as sequelae of lethargic encephalitis, especially in the preparkinsonian excito-motor phase, where abnormal movements and mental states dominated. (p. 509).

In a retrospective published in 1970, Deniker explained:

It was found that neuroleptics could experimentally reproduce almost all the symptoms of lethargic encephalitis. In fact, it would be possible to cause true encephalitis epidemics with the new drugs . . . Furthermore, it might have been feared that these drugs, whose actions compares with that of encephalitis and parkinsonism, might eventually induce irreversible secondary neurological syndromes. (1970, pp. 160, 163).

Other clinicians and researchers became aware of parallels between the effects of the viral disease and the medication (Paulson, 1959). In a 1957 symposium, Haase (1959, p. 199) drew comparisons between LE and neuroleptic effects. Haase also compared the neuroleptic effect to the "analogous syndromes of encephalitis lethargica" and postulated a common lesion in the striatum of the basal ganglia (cited in Kline, 1959, p. 472). Brill (1959) also recognized similarities between LE and the neuroleptics, "which, in full doses, can reproduce many of the most outstanding features of the chronic encephalitic syndrome" (p. 1166), including Parkinsonian rigidity, masked facies, tremor, restlessness, oculogyric crises, dystonias, and "the rousable stupor of acute encephalitis" (p. 1167). Hunter, Earl, and Thornicroft (1964) also recognized similarities and suggested that neuroleptic-treated patients suffer from a "chemically induced" encephalitis.

SIX PARALLEL EFFECTS

At least six parallels between both the acute and the persistent effects of neuroleptics and LE can be drawn: (1) *acute* extrapyramidal reactions or dyskinesias, including Parkinsonism, akathisia, dystonia, chorea, athetosis, and tremors; (2) *acute* cognitive dysfunctions such as apathy, disinterest, and reduced arousal; (3) *chronic* (irreversible) motor disorders, including tardive dyskinesia, tardive akathisia, and tardive dystonia; (4) *chronic* (irreversible) cognitive dysfunctions, including dementia, anosognosia, and deactivation³; (5) the close resemblance between neuroleptic

³ The term deactivation will be used to designate a continuum of phenomena variously described as disinterest, indifference, diminished concern, blunting, lack of spontaneity,

malignant syndrome (NMS) and an acute episode of LE; (6) the common site of action in the basal ganglia.

ACUTE EXTRAPYRAMIDAL REACTIONS

Several extrapyramidal symptoms manifested themselves in the acute phase of LE. These so closely paralleled the various motor disorders routinely produced by neuroleptic medications that they can be discussed together.

LE patients frequently suffered from compulsive hyperactivity, an "irritative hyperkinetic form" of the disease (Haase, 1959). von Economo (1931) considered the "hyperkinetic form" the second most frequent acute manifestation of the disease. This hyperactivity was typically associated with a subjective feeling of extreme tension or anxiety, what von Economo described as "general mental unrest and ceaseless motor activity" (p. 36). An identical hyperkinesia, called akathisia, is very common in drug-treated patients. In a sample of 110 patients, Van Putten (1975) found a rate of 45% "some time during the course of their treatment" (p. 45). Van Putten, May, and Marder (1974) found that akathisia developed in 75% of patients after 1 week of receiving a daily 10-mg dose of haloperidol.

During the onset of the disease, LE patients commonly developed a Parkinsonian syndrome, including psychomotor retardation, akinesia, masked facies, tremor, and a characteristic shuffling gait. von Economo (1931) considered this "amyostatic-akinetic" form the third most frequent acute manifestation of the disease. In chronic postencephalitic states, the Parkinsonian syndrome was by far the most common. A very similar Parkinsonian syndrome is also common during acute and prolonged neuroleptic therapy and can probably be induced in any patient with sufficiently high doses. Some phases of the viral epidemic were more marked by akinesia and others by hyperkinesia, with a considerable crossover (von Economo, 1931). Similarly, according to Van Putten (1975), "59% of [neuroleptic-treated] patients with akathisia concomitantly experienced akinesia, parkinsonian tremor, or dystonia" (p. 45).

Frequently, acute encephalitic patients developed dystonias: painful, tonic spasms of the voluntary muscles. Oculogyric crises—spasmodic eye deviations lasting for minutes or hours—were among the most common dystonias (von Economo, 1931). Dystonias are more rare during neuroleptic treatment and usually occur within the first days or weeks. However, when drug-induced dystonias do develop, they are often oculogyric. Delay et al. (1957) reported disabling "hypertonic" dystonias, in-

reduced emotional reactivity, reduced motivation or will, apathy, and, in the extreme, a rousable stupor.

cluding eye deviations, in response to prochlorperazine, a neuroleptic that is especially prone to produce them. They compared these reactions to similar reactions reported by Marinesco, Radovici, and Draganesco (1925) in association with LE. Paulson (1959) attributed the occurrence of oculogyric crises in both encephalitis and drug treatment to dysfunction of the basal ganglia.

In summary, the two most common dyskinesias associated with routine neuroleptic therapy—Parkinsonism and akathisia—were also among the most frequently associated with the early or acute stages of LE. Dystonias, including oculogyric crises, while more common in LE, are also occasionally found in neuroleptic treatment.

A CONTINUUM OF ACUTE COGNITIVE DYSFUNCTIONS

A continuum of deactivation was reported as a consistent and prominent feature of LE, ranging from disinterest through a rousable stupor, and was the subject of considerable discussion. The same continuum was cited as the primary effect of neuroleptic treatment by pioneers in the field, but in recent years has received insufficient attention.

von Economo (1931) noted that when roused from the stupor, many LE patients were docile and obeyed commands, without displaying gross cognitive dysfunction (p. 27).

If aroused, they wake up quickly and completely, are oriented and fully conscious, and can reply sensibly to questioning; they are fully aware of the situation, carry out all requests promptly, get up if asked to do so and walk about, but, left to themselves, soon drop back to sleep. (p. 27).

In his section discussing “Psychological Disorders,” von Economo spoke of two basic dysfunctions generally found in LE: “disturbances of will,” characterized by a “dynamic lack of impulse,” and “Changes of ‘humor,’” with “indifference” and “lack of emotion” (p. 162). Abrahamson’s 1920 descriptions of the effects of viral encephalitis, reprinted in his posthumous book, *Lethargic Encephalitis* (1939), also cover the continuum from disinterest through rousable stupor.

Irritability both to internal and external stimuli diminishes, and the vital tone of the afflicted host lessens. . . . He may display neither conscious nor unconscious initiative. . . . Yet from the depth of this seeming slumber, he may respond immediately when questioned and his short but coherent answers show no loss either of memory or of orientation. . . . There is a complete lack of emotional expression. . . . The face, waxen and corpse-like, remains an impassive and inscrutable mask. . . . In other words, sensory stimuli stream into the brain and the brain ignores them. . . . [And] volition is practically suspended. (pp. 32–44)

Abrahamson and von Economo both believed that the cognitive dysfunction were part of a unitary syndrome that included motor inhibition or slowing. In effect, patients lost the will to move. In connecting the

loss of will and diminished movement, von Economo referred to “akinesia” (p. 159), a term now used in psychiatry to describe the similar neuroleptic effect that includes both motor slowing and apathy (Van Putten, May, & Wilkins, 1980). For his part, Abrahamson used the term “psychomotor inertia” (p. 40), nearly identical to the phrase commonly used in contemporary psychiatric rating scales, i.e., the BPRS’ “psychomotor retardation.”

More recently, Ward (1986) confirmed the characteristic continuum of cognitive disorder in association with LE, including “subjective feelings of marked lassitude” and a general “lack of initiative” (p. 217). Ward also notes the lack of clinically apparent cognitive deficits.

A very similar continuum of cognitive dysfunction was reported in the earliest clinical descriptions of the neuroleptic effect. In 1952 Delay and Deniker described for the first time the effect of chlorpromazine when given in relatively small doses. The effect varied from indifference to the rousable stupor. Later, Deniker (1970) more fully appreciated the central role of drug-induced *indifference*.

But the impact of the most significant finding was not immediately recognized. It was the characteristic psychomotor indifference that chlorpromazine caused in treated subjects. Later, it was classified as akinesia. (p. 158).

Other investigators quickly pinpointed indifference as the main clinical effect of the drug. The first description of this effect in the North American literature was by Lehmann and Hanrahan (1954) who focused on “emotional indifference.” They observe, “Patients receiving the drug become lethargic” (p. 230). The first British report, by Anton-Stephens (1954), states:

Psychic indifference. This is perhaps the characteristic psychiatric response to chlorpromazine. Patients responding well to the drug have developed an attitude of indifference both to their surroundings and their symptoms best summarized by the current phrase “couldn’t care less.” (p. 550)

Textbooks from the beginning of the neuroleptic era also focused on the production of indifference or disinterest as the primary drug effect. For example, in *Modern Clinical Psychiatry*, Noyes and Kolb (1958) commented: “If the patient responds well to the drug, he develops an attitude of indifference both to his surroundings and to his symptoms” (p. 654). From Germany, Flugel identified what he called “the akinetic–avolitional syndrome” as key to the neuroleptic effect (Kline, 1959, p. 466).

Jarvic (1970) summarized that neuroleptics produce indifference and “taming” in every species of animal studied. Lehmann (1975) suggested that neuroleptic treatments result primarily “in reduced reactivity to external and internal stimuli and in decreased spontaneous activity” and in “blunting of emotional arousal” (p. 28). Without elaborating on it, he used the phrase “deactivation of the CNS” (p. 32) to describe the overall

effect. Emerich and Sanberg (1991) noted that neuroleptics produce many types of dysphoria, including "cognitive blunting" and a "paralysis of volition" (p. 201). A number of authors have observed the apathy so frequently associated with long-term neuroleptic treatment (Van Putten & May, 1978; Van Putten et al., 1980). There are many discussions of psychomotor slowing, often without specifically addressing the deactivation component. Baldessarini (1985) states that "Nearly all of the neuroleptic agents used in psychiatry can diminish spontaneous motor activity in every species of animal studied, including man" (p. 394). More specifically, he notes that "Exploratory behavior is diminished, and responses to a variety of stimuli are fewer, slower, and smaller . . ." (p. 394). Consistent with this, Breggin (1983a, pp. 56-59, 1991) has taken the viewpoint that neuroleptic-induced disinterest and lethargy are nonspecific for any particular diagnostic group of patients. Like many earlier clinicians and researchers, he believes that deactivation is largely responsible for the clinical effect of the neuroleptics.

CHRONIC MOVEMENT DISORDERS

Victims of LE frequently developed irreversible postencephalitic motor complications, of which Parkinsonism was the most common. Sometimes the Parkinsonism persisted continuously from the acute into the chronic stage, and sometimes it appeared years later after seeming recovery from an acute attack.

As early as 1959, Paulson observed:

When used in therapeutic doses, phenothiazines may never permanently injure the central nervous system. Their innocence, however, may be difficult to prove to a patient who develops idiopathic Parkinsonism years after having had identical symptoms as a side-effect of tranquilization. (p. 801)

There are few reports in the literature about irreversible Parkinsonism associated with neuroleptic therapy; but little attempt has been made to evaluate the possibility.⁴ Cases of persistent Parkinsonism have been reported following neuroleptic malignant syndrome (see ahead).

As another chronic residual of the viral disease, von Economo (1931, p. 107) noted "irritative phenomena," including "cases of hemichorea and also of general chorea, others reminiscent of athetosis, cases of torticollis, torsion-spasms, and tics." Similarly, in their discussion of chronic effects of LE, Noyes and Kolb (1958) also noted:

Tremors, tics, myotonias, and athetoid and choreiform movements are frequently observed. In addition to these dyskinesias and hyperkinesias, there may be parox-

⁴ Most long-term neuroleptic patients are undergoing drug treatment while being evaluated for persistent dyskinesias, and it is *assumed*, perhaps wrongly, that the frequent findings of akinesia and Parkinsonism is merely the result of the on-going treatment.

ysmal symptoms such as disturbances in rate and rhythm of respiration, also gasping and yawning. (p. 171).

A few years ago, these descriptions of persistent neuroleptic sequelae by von Economo and by Noyes and Kolb would have varied somewhat from our understanding of neuroleptic-induced sequelae. More recently attention has been given to irreversible hyperactivity (tardive akathisia) and irreversible torsion spasms (tardive dystonias) caused by neuroleptics (e.g., Gualtieri & Sovner, 1989; Burke, Fahn, Jankovic, Marsden, Lang, Gollomp, & Ilson, 1982), and the two syndromes are now finding their way into neurology textbooks (Fahn, 1989). Thus neuroleptic-induced tardive dyskinesia, tardive akathisia, and tardive dystonia are paralleled in the chronic disorders produced by encephalitis lethargica.

Tardive dyskinesia is a frequent sequela of neuroleptic therapy. The American Psychiatric Association's (1980) task force on tardive dyskinesia concluded that more than minimal signs of the disease are found in at least 40% of older patients on long-term neuroleptic treatment. More recent studies are disclosing higher rates than earlier studies, and Schatzberg and Cole (1986, p. 99) remark that 50–60% of chronically institutionalized patients display dyskinesias. Studies by Gualtieri (Gualtieri & Sovner, 1989) have found rates of 13–14% for tardive akathisia in institutionalized developmentally disabled persons with a history of neuroleptic treatment.

In summary, both LE and neuroleptic treatment result in high rates of chronic dyskinesias, with Parkinsonism more common as the aftermath of the viral disease, while tardive dyskinesia and tardive akathisia are more frequent following neuroleptic treatment.

CHRONIC COGNITIVE DYSFUNCTIONS

Several chronic cognitive disorders resulted from LE and are now found in association with long-term neuroleptic treatment.

Dementia and Persistent Cognitive Impairment

Dementia was among the most common chronic manifestations of the LE. Many of the Parkinsonian patients may have suffered from varying degrees of cognitive dysfunction and dementia. Harvey (1986) reports that Parkinsonism is associated with dementia in 20–80% of cases, depending upon the criteria. According to Yahr (1989), some authorities consider dementia “an intrinsic characteristic of the disease, increasing in severity as it progresses” (p. 662). Yahr himself concludes that “it does appear that a number of cognitive, perceptual, and memory deficits are present” in Parkinson's disease (p. 662).

The intellectual deficits in Parkinsonism patients have been somewhat hard to measure, because the dementia is dominated by pathology in the

basal ganglia rather than the cerebral cortex. This results in so-called subcortical dementia (Huber and Paulson, 1985) with fewer overt intellectual deficits. Like postencephalitic patients, those with subcortical dementia display more apathy and depression than euphoria, and social judgment is characteristically spared.

As a result of the more minimal intellectual deterioration, observers like von Economo and Abrahamson may have been less likely to describe the patients as obviously demented. Furthermore, it is plausible that the finding of postencephalitic dementia was considered too commonplace to merit much attention compared to the more dramatic psychomotor retardation and deactivation syndrome. Nonetheless, von Economo did describe cases of more typical dementia with "confusion," "delirium," and "para-amentia." He also compared the patients' mental condition to that of neurosyphilis, toxic states, and other disorders commonly associated with generalized intellectual dysfunction. Abrahamson (1935) reported that the typical akinetic syndrome sometimes deteriorated into frank dementia: "This state may pass away leaving confusion, faulty orientation and memory loss of the Korsakoff type" (p.35).

According to von Economo, an irreversible hypomanic syndrome resembling "moral insanity" was frequently seen, especially in younger patients. Usually it was moderate in degree: the patients became "more talkative, importunate, impertinent, forward, and disrespectful; they lack inhibition; they often become troublesome and antisocial and display a tendency to outbreaks of emotion" (1931, p. 128). The cases could develop progressively from the acute phase of encephalitis or appear at a later date. The clinical picture, in retrospect, seems like mild to moderate dementia with euphoria.

Do the neuroleptics cause parallel permanent changes in cognitive function? Evidence for neuroleptic-induced cerebral cortical atrophy, persistent cognitive dysfunction, and dementia has recently been discussed by a number of authors (e.g., Breggin, 1983a, 1990, 1991; Jones, 1985; Myslobodsky, 1986; and Gualtieri & Barnhill, 1988). In concluding that neuroleptic treatment frequently causes atrophy and dementia, Breggin (1990) reviewed brain scan studies, clinical evaluations, psychological testing, animal and human postmortem findings, and parallel models from other diseases of the brain, such as Parkinsonism and Huntington's chorea. Rates of cerebral atrophy in neuroleptic-treated patients range from 10 to 40%, and tend to correlate with life-time drug exposure.

Wilson, Garbutt, Lanier, Moylan, Nelson, and Prange (1983) for example, found mental abnormalities consistent with an organic brain syndrome in tardive dyskinesia patients. The severity of cognitive disability correlated with the severity of tardive dyskinesia symptoms. Some studies have correlated persistent cognitive dysfunction with tardive dyskinesia and with life-time intake of neuroleptics (DeWolfe, Ryan, & Wolf,

1988). Famuyiwa, Eccleston, Donaldson, and Garside (1979), and many others, have found cerebral atrophy as measured on a computerized tomography (CT) scan among neuroleptic-treated patients. Often the atrophy is associated with cognitive dysfunction. Gualtieri and Barnhill (1988) concluded:

In virtually every clinical survey that has addressed the question, it is found that TD patients, compared to non-TD patients, have more in the way of dementia.
(p. 149)

I have evaluated several cases of long-term neuroleptic patients with hypomanic syndromes similar to those described by von Economo—mildly euphoric individuals who display superficial joviality, poor judgment, rambling talkativeness, and sometimes an inappropriate tendency to move too close to the examiner. Wilson, Garbutt, Lanier, Moylan, Nelson, and Prange (1983) have described a similar neuroleptic-induced syndrome that they call dysmentia, consisting of “unstable mood, loud speech, and [inappropriately close] approach to the examiner.” It is probably a variant of hypomanic dementia. Euphoria, as well as apathy, can result from frontal lobe damage and dysfunction (Bradley, Daroff, Fenchel, & Marsden, 1991, p. 84; see below).

In summary, there is evidence that varying degrees of dementia resulted from LE and that persistent cognitive dysfunction and dementia also result from long-term neuroleptic treatment. Usually, the dementia associated with the neuroleptics is of the subcortical variety with apathy and relatively little disturbance of higher cortical function. In addition, a hypomanic dementia was also identified as a consequence of LE and can also be found after prolonged neuroleptic treatment.

Anosognosia

Anosognosia—denial of dysfunction after physical damage to the higher centers of the brain—is frequently found in tardive dyskinesia. One-half or more of tardive dyskinesia patients deny the existence or severity of their involuntary movements (Breggin, 1983a, pp. 115–117; DeVeauh-Geiss, 1979; Myslobodsky, 1986). Some tardive dyskinesia victims will be able to identify symptoms of the disease in other patients but not in themselves (Smith, Kuchorski, Oswald, & Waterman, 1979). Anosognosia is said to be usually associated with damage to the parietal, nondominant hemisphere. However, patients with generalized brain disease, such as neurosyphilis and chronic alcoholism or Korsakoff’s syndrome, will often deny their impairments and confabulate. My experience coincides with that of Fisher (1989) who states that anosognosia “may qualify as one of the general rules of cerebral dysfunction” (p. 128).

The presence of anosognosia in tardive dyskinesia patients tends to confirm the existence of generalized cerebral dysfunction. It can be diffi-

cult, however, to distinguish anosognosia from the indifference or disinterest produced by neuroleptic treatment.

In the literature on LE, no references to anosognosia have been located. The specific symptom was probably obscured by the generalized apathy displayed by so many of the patients.

Deactivation and the Frontal Lobe Syndrome

von Economo (1931) and other observers noted that many LE patients lapsed into chronic apathy or indifference, often in association with Parkinsonian psychomotor retardation. This chronic deactivation is also common among tardive dyskinesia patients. Myslobodsky (1986) points out that many observers have wondered why so many tardive dyskinesia patients "develop signs of emotional indifference" and that no satisfactory explanation has been forthcoming. As already noted, Van Putten and May (1978) and Van Putten et al. (1980) have described the apathy that is characteristic of many long-term neuroleptic patients. These outcomes are probably best understood as a sometimes irreversible deactivation, compounded with anosognosia.

Deactivation can result from dysfunction in either the frontal lobes and limbic system (as an aspect of frontal lobe syndrome) or the basal ganglia (as an aspect of subcortical dementia). Adams and Victor (1989) divide the manifestations of frontal lobe syndrome into (1) cognitive and intellectual changes, such as loss of abstract reasoning and planning, (2) personality deterioration, and (3) "impairment or lack of initiative and spontaneity" (p. 333) or deactivation, which they call the most common effect of frontal lobe disease. Stuss and Benson (1986, 1987) ascribe two basic functions to the anterior portion of the frontal lobes: "sequence, set, and integration," and "drive, motivation, and will" (1986, p. 241). The "most common alteration is apathy" (p. 242). The activation function appears to depend upon medial frontal structures.

Much of what we know about the frontal lobe syndrome comes from studying the effects of psychosurgery, whose primary clinical effect is the production of deactivation or what Kalinowsky (1973, p. 20) called "diminished concern." Anosognosia is also common in postpsychosurgery patients who frequently deny they have been operated on, despite the evidence of surgical scars or burr holes (Breggin, 1981). My clinical experience indicates that most elements of the frontal lobe syndrome, including deactivation, are also produced by stereotactic procedures, such as cingulotomy, amygdalotomy, and thalamotomy, that impair the limbic system.

As already described, pioneers in the use of neuroleptics almost uniformly cited deactivation as the main clinical effect of neuroleptics (see above). Because of this, clinicians often referred to the neuroleptics as a

chemical lobotomy (Haase, 1959, p. 206). Bleuler (1979) observed that long-term neuroleptic use "also often dampens the vitality and the initiative of the person" (p. 301). He concluded, "So we see that long-term maintenance with neuroleptics is fraught with some of the same disadvantages that are ascribed to lobotomies" (p. 301).

Although there is little direct evidence, it is probably as Bleuler suggests, that long-term exposure to neuroleptics can produce an irreversible frontal lobe syndrome with deactivation. The syndrome would seem an inevitable consequence of the permanent dysfunction of dopaminergic neurons that frequently results from neuroleptic treatment (see below). Some of these neurons (from the ventral tegmentum) project to the limbic system and frontal lobes. Others (from the substantia nigra) project to the striatum where they also interconnect with the limbic system as well as with the reticular activating system (Alheid, Heimer, & Switzer, 1990).

Psychosis

Somewhat infrequently, postencephalitic patients developed schizophrenic-like psychoses, including confusion, hallucinations, and delusions (Brill, 1959). As discussed earlier, the syndrome was relatively easy to distinguish from schizophrenia.

Neuroleptic-treated patients have been reported to develop tardive psychoses (Jones, 1985; Chouinard, Jones, & Annable, 1978). I have noted these reactions on occasion when a patient quickly decompensates during the process of withdrawing from neuroleptics. These psychoses can sometimes be distinguished from the patients' premedication psychotic disorder which tends to return, if at all, several months after drug withdrawal. At present, tardive dementia is probably a more clearly discernable syndrome than tardive psychosis.

ACUTE ENCEPHALITIS AND THE NEUROLEPTIC MALIGNANT SYNDROME

Attention has been increasingly focused on an especially severe reaction, NMS, which occurs in a small percentage of neuroleptic-treated patients. A review of 24 episodes of NMS in 20 patients by Rosebush and Stewart (1989) found that most cases fit the following cluster of symptoms: delirium, a high fever with diaphoresis, unstable cardiovascular signs, an elevated respiratory rate, and an array of dyskinesias, including tremors, rigidity, dystonia, and chorea.

Patients spoke little during the acute illness and later reported that they had found themselves unable to express their anxiety and feelings of doom. Almost all patients were agitated shortly before developing NMS, suggesting to the authors that they were undergoing akathisia. The white blood cell count was elevated in all cases, dehydration was common, and

lab tests showed a broad spectrum of enzymatic abnormalities. While this series had no deaths, the authors note that 20–30% of untreated cases reportedly die. This mortality rate corresponds with that of LE.

There seems to be nothing about acute NMS to distinguish it from an acute, severe episode of LE, except for the fact of antecedent neuroleptic therapy. Although Rosebush and Stewart provide insufficient data to draw exact parallels, their NMS patients also suffered similar chronic impairments to those reported in LE patients. Of the 20 patients, 14 continued to have “extrapyramidal symptoms or mild abnormalities of vital signs and muscle enzymes at the time of discharge” (p. 721); but we are not told how many of the 14 specifically had persistent extrapyramidal signs. In a striking parallel with LE, three patients displayed persistent Parkinsonian symptoms until they were lost to follow up. One patient, who had mild cognitive impairment prior to NMS, developed a persistent worsening of her dementia.

Recognition of the similarities between acute LE, severe LE, and NMS can help us in evaluating cases of NMS, sharpening awareness of possible persistent sequelae. The parallels may someday help elucidate the mechanisms of both.

LE AND NEUROLEPTIC IMPACT ON THE BASAL GANGLIA

While LE afflicted all regions of the brain, including the frontal cortex, there was consistent agreement that the most marked pathology was located in the basal ganglia and especially the substantia nigra (von Economo, 1931; Brill, 1959; Ward, 1986). According to Brill (1959), “The involvement of the substantia nigra is outstanding and may be seen by inspection, even in gross freshly cut specimens” (p. 1165).

There is also general agreement that the basal ganglia are most directly affected by the neuroleptics. As Thacker, Ferraro, Hare & Tamminga (1988) summarize, “basic research suggests that . . . all mammalian brains treated chronically with neuroleptic drugs develop DA [dopamine] receptor supersensitivity in the striatum” (p. 199) (also see Rupniak, Jenner, & Marsden, 1983). These striatal changes are due, at least in part, to the suppression or inactivation of dopaminergic neurons originating in the substantia nigra (White and Wang, 1983).

While there is a consensus that the neuroleptics impair neurotransmission in the basal ganglia, the nature and existence of related neuropathological lesions remain less certain. Cadet and Lohr (1989) review a variety of physiological changes in neuroleptic-treated animals, as well as post-mortem anatomical changes in tardive dyskinesia patients. They conclude, “We agree with the suggestion that these drugs may be responsible for degenerative changes in the basal ganglia . . .” (p. 181; see also Breggin, 1983a). Those few postmortem studies of tardive dyskinesia pa-

tients that are available usually show increased degeneration in the substantia nigra (Roizin, True, & Knight, 1959; Hunter, Blackwood, Smith, & Cumings, 1968; Christensen, Moller, & Faurbye, 1970; Jellinger, 1977). Other postmortem studies of schizophrenic patients have found increased dopamine receptor density in the basal ganglia (caudate and putamen) (reviewed in Hyde, Casanova, Kleinman, & Weinberger, 1991). Nearly all of these patients had been exposed to neuroleptics.

Another review (Breggin, 1990, pp. 447–450) focused on animals exposed to neuroleptic treatment and found consistent reports of basal ganglia pathology after several weeks or months. For example, Neilsen and Lyon (1978) documented cellular loss in the striatum of rats after 36 weeks and concluded “The results further suggest that persistent irreversible anatomical changes can follow long-term neuroleptic treatment” (p. 85). Pakkenberg, Fog and Nilakantan (1973) found basal ganglia degeneration in rats after 1 year of drug exposure.

Brain scan studies (CT and magnetic resonance imaging) of tardive dyskinesia patients have disclosed neuropathology, sometimes in the basal ganglia (Bartels & Themelis, 1983; Besson, Corrigan, Cherryman, & Smith, 1987). However, no consistent pattern has emerged from the limited number of studies (Rama Krishnan, Ellinwood, & Rayasam, 1988, p. 173).

Yahr (1989) observed that the dementia associated with Parkinsonism probably requires mesocortical, as well as striatal, dopamine deficits. Neuroleptic-induced dopamine depletion also afflicts both the nigrostriatal and the mesocortical or limbic projections, probably contributing to the production of both tardive dyskinesia and tardive dementia. Jenner and Marsden (1983, p. 234), for example, found that cerebral dopamine receptors became hyperactive after 6–12 months of continuous neuroleptic administration in rats and that the overactivity is associated with the development of abnormal behaviors.⁵

Gualtieri and Barnhill (1988) conclude that tardive dyskinesia is associated with dementia, and that the source of both problems, as is the case with Parkinson's disease and Huntington's chorea, is most likely lesions in the basal ganglia.

DISCUSSION

Probably because of their common impact on the basal ganglia, neuroleptic effects parallel many of the core symptoms reported in LE. In the acute phase, both produce a deactivation continuum from indifference to

⁵ Although the permanence of most cases of tardive dyskinesia points to a corresponding irreversible hyperactivity of dopamine receptors, it has not been demonstrated in the animal brain. However, animals are also less prone to develop tardive dyskinesia, and may therefore be less susceptible than humans to persistent receptor changes.

a rousable stupor, as well as a variety of dyskinesias, including akinesia, akathisia, dystonia, oculogyric crises, and tremors. In the persistent or chronic phase, they both cause cognitive disorders, including dementia, and a variety of motor disorders. However, Parkinsonism dominates the aftermath of LE while tardive dyskinesia and tardive akathisia are most common after neuroleptic therapy.

It was well-known in the 1950s that LE had frequently produced irreversible neurological and cognitive sequelae, and that the neuroleptics mimicked the epidemic disease; but the threatening implications were not recognized or heeded. It would be 2 decades before psychiatry generally acknowledged tardive dyskinesia (Crane, 1973) and even longer before the American Psychiatric Association (1980) officially addressed it. Organized psychiatry and individual practitioners continue to give insufficient attention to the problem (Brown & Funk, 1986; Cohen & McCubbin, 1990). Furthermore, many psychiatric textbooks still fail to mention tardive dystonia and tardive akathisia.

Meanwhile, even less attention is being given to the danger of permanent cognitive disorders from neuroleptic treatment. Yet these disorders were predictable from the parallels with LE that were identified by Delay, Deniker, Brill, and others. Cognitive disorders were also predictable through an understanding of basal ganglia dysfunction, which was available long before the neuroleptics came into use. von Economo (1931) and Abrahamson (1935) delved into the relationship between basal ganglia disease and chronic cognitive dysfunction in publications during the early phases of the LE epidemic, 1917–1920. Modern functional neuroanatomy confirms the interconnections between the basal ganglia, the reticular activating system, and the limbic system and frontal lobes (Alheid et al., 1990). The evidence strongly suggests that the neuroleptics produce their most common and important effects by causing a brain disorder that closely parallels LE with persistent motor and cognitive dysfunction, including dementia.

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