Brain Damage, Dementia and Persistent Cognitive Dysfunction Associated With Neuroleptic Drugs:
Evidence, Etiology, Implications

Peter R. Breggin

Center for the Study of Psychiatry and George Mason University

Several million people are treated with neuroleptic medications (major tranquilizers or antipsychotics) in North America each year. A large percentage of these patients develop a chronic neurologic disorder – tardive dyskinesia – characterized by abnormal movements of the voluntary muscles. Most cases are permanent and there is no known treatment. Evidence has been accumulating that the neuroleptics also cause damage to the highest centers of the brain, producing chronic mental dysfunction, tardive dementia and tardive psychosis. These drug effects may be considered a mental equivalent of tardive dyskinesia. Relevant data are derived from human autopsies, brain imaging (CT, MRI and PET scans), neuropsychological tests, and clinical research. That the neuroleptics can damage higher brain centers is confirmed by their known neurotoxicity and neurophysiological impact, animal autopsies, and a comparison to diseases that mimic neuroleptic effects, such as Huntington's chorea and lethargic encephalitis. Patients and the public should be informed of the danger of both tardive dyskinesia and tardive dementia. The mental health professions should severely limit the use of neuroleptics and develop safer and better alternatives to these dangerous substances.

The neuroleptics, also known as major tranquilizers or antipsychotics, are among the most widely used drugs in psychiatry. In the United States and Canada alone, millions of adults and children receive these medications in general hospitals, private and public mental hospitals, board and care homes, institutions for the developmentally disabled, nursing homes, prisons, clinics and private practice. While the medications are most often advocated for patients diagnosed as schizophrenic or manic, they are in fact widely used as a method of social control. In many institutions, most of the inmates will be receiving them (Breggin, 1983).

It is now widely recognized that the neuroleptics frequently produce a largely irreversible neurological disease, tardive dyskinesia, in a significant number of patients. New evidence is accumulating that the same drugs can also cause persistent damage or dysfunction to the highest centers of the brain, resulting in irreversible intellectual and emotional impairments, including tardive dementia and tardive psychosis. These effects may be viewed as the mental equivalent to tardive dyskinesia.

Although concerns about neuroleptic-induced damage to the highest centers of the brain have been voiced for more than a decade (Marsden, 1976), it was not until 1983 that the subject was analyzed in depth (Breggin, 1983, pp. 110–146). Since then, a considerable amount of relevant evidence has been published. In the first part of this article, I will review evidence of cognitive deficits, dementia and atrophy in neuroleptic-treated patients. In the second part I will explore the etiology.

The term dementia will be used as defined in the *Diagnostic and Statistical Manual of Mental Disorders* (third edition, revised, American Psychiatric Association [APA], 1987) [DSM-III-R]: "The essential feature of Dementia is impairment in short- and long-term memory, associated with impairment in abstract thinking, impaired judgment, other disturbances of higher cortical function, or personality change" (p. 103). The DSM-III-R states "As in all Organic Mental Syndromes, an underlying causative organic factor is always assumed" (p. 103). Acute drug-induced disorders that can cause brain damage and impair mental function, such as neuroleptic malignant syndrome or toxic psychoses, will not be considered in this article which deals with more gradually evolving persistent brain damage and dysfunction associated with chronic exposure to neuroleptics.

Reliance upon the neuroleptics for the treatment of acute schizophrenia is almost universal in psychiatry and most psychiatrists use them as the first line of treatment in these cases (see any recent textbook of psychiatry, for example, Nicholi, 1988; or Talbott, Hales, and Yudofsky, 1988). Occasional criticism of their use has been made (Breggin, 1983; Cohen and Cohen, 1986; Mosher and Burti, 1989). I have documented that the neuroleptics have no specific ameliorative effect on any mental disorder and that they are non-specific brain-disabling agents that perform a chemical lobotomy, in part through disruption of dopamine neurotransmission in the limbic and frontal lobe pathways (Breggin, 1983). The drugs do not cure a disorder but instead flatten the emotions, produce disinterest or apathy, and enforce docility. In a controlled study, Mosher and Burti (1989) demonstrated that almost all patients undergoing their first schizophrenic episode can be treated more successfully without neuroleptics than with them.

Terms like schizophrenia and schizophreniform, based on DSM-III or DSM-III-R, are used largely without reservation in most of the studies reviewed,

and I have adopted this language for convenience in communicating. Several fundamental assumptions behind this classification – including the disease model – create a bias toward believing that a supposedly medical disease, schizophrenia, has caused the physical disorders found in the brains of these patients. This built-in bias should not distract us from properly evaluating the etiology of the damage. In my own opinion, schizophrenia is neither genetic nor physical in origin (Breggin, in press). The lay term, madness, is more appropriate to this psychosocial phenomenon. I have suggested alternative explanations elsewhere (Breggin, 1980d, in press).

Evidence from Studies of Drug-Treated Patients

Background: Tardive Dyskinesia

In a large percentage of patients the neuroleptic medications produce a neurologic disorder called tardive dyskinesia [TD]. The disease, characterized by abnormal involuntary movements, can manifest itself after a few weeks or months. More commonly it develops after six months to two years or more of treatment. In the majority of cases it is irreversible and there is no effective treatment. If it is detected early and the medications are discontinued, an estimated 20-50% of patients may greatly improve or recover (APA, 1980). However, a recent report indicated that among patients with persistent TD, followed for a period of 5 years, 82% showed no overall significant change, 11% improved, and 7% became worse (Bergen, Eyland, Campbell, Jenkings, Kellehear, Richards, and Beumont, 1989).

TD often begins with uncontrolled movements of the face, including the tongue, lips, mouth and cheeks; but it can start with almost any group of muscles. The most common early sign is a quivering or curling of the tongue. Tongue protrusions and chewing movements are also common, and can become serious enough to harm teeth. The hands and feet, arms and legs, neck, back and torso can be involved. The movements displayed are highly variable, and include writhing contortions, tics, spasms, and tremors. The person's gait can be badly impaired. More subtle functions can be affected and are easily overlooked: respiration (involving the diaphragm), swallowing (involving the pharyngeal and esophageal musculature), the gag relflex, and speech (Yassa and Jones, 1985). The movements disappear during sleep. They sometimes can be partially suppressed by willpower and frequently are made worse by anxiety. They can vary from time to time.

Many cases of TD appear to be relatively mild, often limited to movements of the tongue, mouth, jaw, face, or eyelids. Nonetheless, they are disfiguring and often embarrassing. A rare case is totally disabling and patients have been known to commit suicide (Yassa and Jones, 1985).

There is increasing awareness of two related variants of TD, tardive dystonia and tardive akathisia. Tardive dystonia involves "sustained involuntary twisting movements, generally slow, which may affect the limbs, trunk, neck, or face" (Burke, Fahn, Jankovic, Marsden, Lang, Gollomp, and Ilson, 1982, p. 1335). It can produce cramp-like, painful spasms that temporarily prevent the individual from carrying out normal activities. Tardive akathisia involves a feeling of inner tension or anxiety that drives the individual into restless activity, such as pacing (Jeste, Wisniewski, and Wyatt, 1986).

Recognition of TD's existence became widespread in 1973 with the publication of reports by George Crane and by the American College of Neuropsycopharmacology–Food and Drug Administration Task Force. In the same year, the *Physician's Desk Reference* (*PDR*, see Thorazine) began to include persistent dyskinesias among neuroleptic side-effects and reports began to flood the psychiatric literature.

In 1980 the APA produced a detailed analysis of the disease in its *Task Force Report: Tardive Dyskinesia*. It made clear that TD is a serious, usually irreversible, untreatable, and highly prevalent disease resulting from therapy with the neuroleptics. The *Task Force* estimated the prevalence rate for TD in routine treatment (several months to two years) as *at least* 10–20% for *more than minimal disease*. For older and chronically exposed patients, the rate was at least 40% for more than minimal disease. A recent study of elderly nursing home patients found that 41% developed tardive dyskinesia over a period of only twenty-four months and that none fully recovered (Yassa, Nastase, Camille, and Belzile, 1988). While long-term studies have found a spontaneous dyskinesia prevalence of 1–5% in the elderly, none of the non-drug treated controls developed spontaneous dyskinesias during the two years.

As high as the *Task Force* rates are, a number of studies indicate that the rates may in fact be still higher, especially in older and long-term patients for whom the prevalence may exceed 50% (see APA, 1980, Table 9, p. 50; reviewed in Breggin, 1983). Furthermore, there is general agreement in the literature that for unknown reasons the overall rates of tardive dyskinesia have been increasing in recent years (Jeste and Wyatt, 1980, p. 27); this suggests that the *Task Force* figures have been eclipsed by increasing rates.

As an exception to the usually higher prevalence estimates, Jeste and Wyatt (1982) estimated a prevalence rate of only 13%; but they obtained this lower estimate by two most unusual manipulations of the data. First, they excluded all minimal and mild cases, and included only moderate and severe ones (pp. 22–23), even though most studies indicate that the great majority cases are in fact minimal or mild (APA, 1980, p. 45). Thus they excluded most cases from consideration. Second, the authors assumed that one-fourth of the remaining cases did not have drug-induced dyskinesias (p. 32), even though they themselves cite studies indicating that the pre-drug era rate of dyskinesias

was as low as 0.5% (p. 16). Without their severe pruning of the data, the prevalence rates derived from Jeste and Wyatt's data would surpass 25% by a considerable amount. On the other hand, even a rate of 13% for a moderate to severe treatment-induced neurological disease constitutes an iatrogenic disaster.

Children are susceptible to a particularly virulent form of TD with truncal involvement that can interfere with posture and locomotion (Breggin, 1983; Gualtieri and Barnhill, 1988; Gualtieri, Quade, Hicks, Mayo, and Schroeder, 1984; Gualtieri, Schroeder, Hicks, and Quade, 1986).

In 1985 the Food and Drug Administration (FDA) took the unusual step of setting specifically worded requirements for a warning in association with all neuroleptic advertising ("Neuroleptics," 1985). In a wholly unprecedented move, in the same year the APA sent out a warning letter about the dangers of tardive dyskinesia to its entire membership.

Various authors have noted that cases of dyskinesia were reported among psychiatric patients prior to the neuroleptic era. However, the APA's *Task Force on Tardive Dyskinesia* (1980, pp. 47–48), as well as Jeste and Wyatt (1982, pp. 15–20), and others have concluded that the particular syndrome of TD is a product of the drug era. TD is recognized as a disease produced by neuroleptics in all contemporary textbooks of psychiatry (e.g., Nicholi, 1988; Talbott, Hales, and Yudofsky, 1988).

It is difficult to determine the total number of TD cases. Van Putten (see Lund, 1989) recently estimated 400,000–1,000,000 cases in the United States. My own estimate is higher, ranging in the several millions (Breggin, 1983). It is no exaggeration to call tardive dyskinesia a widespread epidemic and possibly the worst medically-induced castastrophe in history.

Neuroleptic-Induced Persistent or Permanent Damage to the Highest Centers of the Brain

Evidence is accumulating that there are higher-brain and mental function equivalents to TD in the form of damage in the limbic system and frontal lobes, with associated persistent mental dysfunction.

Brain Atrophy and Associated Mental Deficits from Brain Imaging Studies

In one of the earliest studies attempting to measure cerebral atrophy in neuroleptic-treated schizophrenic patients, Sabuncu, Sabacin, Saygill, Kumral, and Ornek (1977) used pneumoencephalography (PEG) to show enlarged ventricles. Other PEG studies have demonstrated similar findings, but we shall focus on the newer and more sophisticated brain imaging techniques.

Many studies involving computerized axial tomography (CT scans) of

schizophrenic patients, nearly all of them neuroleptic-treated, have found enlarged lateral ventricles and sometimes enlarged sulci, indicating shrinkage or atrophy of the brain. The ventricles tend to expand in proportion to tissue shrinkage within the confines of the skull. The sulci deepen or enlarge when there is shrinkage of the cerebral cortex. Enlargement of the lateral ventricles is the most common finding in CT studies of drug-treated schizophrenic patients.

Johnstone and his colleagues (Johnstone, Crow, Frith, Husband, and Kreel, 1976; Johnstone, Crow, Frith, Stevens, Kreel, and Husband, 1978) were among the first researchers to show increased ventricular size on CT scan of schizophrenic patients. They also found mental impairment on the *Withers and Hinton Test* and the *Inglis Paired Association Learning Test*. Weinberger, Cannon-Spoor, Potkin, and Wyatt (1980) and Weinberger, Torrey, Neophytides, and Wyatt (1979) found increased ventricular size in schizophrenic patients, nearly all of whom had been treated with drugs. Jeste, Wagner, Weinberger, Reith, and Wyatt (1980) found no difference on a CT scan between a TD group and a matched control group of neuroleptic-treated patients without TD. Both groups were chronic inmates (mean duration 33.5 years) with many years of neuroleptic therapy. Famuyiwa, Eccleston, Donaldson, and Garside (1979) found cerebral atrophy on CT scan in schizophrenic patients with and without TD, and also found an increased rate of dementia compared to controls, especially among TD patients. On the *Withers and Hinton* and the *Inglis Paired Association Learning Test* they found increased mental dysfunction. Golden, Moses, Zelazowski, Graber, Zatz, Horvath, and Berger (1980) found brain atrophy on CT scan in neuroleptic-treated schizophrenics and correlated it with mental dysfunction on the *Luria-Nebraska* battery.

DeMeyer, Gilmore, DeMeyer, Hendrie, Edwards, and Franco (1984) found that third ventricle size was correlated with both length of illness and length of neuroleptic treatment. In a second study, DeMeyer, Gilmore, Hendrie, DeMeyer, and Franco (1984) reviewed the CT literature on measurements of brain tissue density rather than ventricular size, and found several studies which demonstrated a loss of density in drug-treated schizophrenics. In their own research they found a loss of density among neuroleptic-treated schizophrenic patients compared to unmedicated hospital controls, as well as a direct correlation with mental impairment as measured by psychological tests.

Lawson, Waldman, and Weinberger (1988) studied twenty-seven schizophrenic patients with the CT and with neuropsychological batteries, including the *WAIS* and *Halstead-Reitan*. They found enlarged ventricles or cortical atrophy in twelve of the patients. Their study revealed a significant correlation between cognitive impairment on the psychological batteries and brain

damage. The patients with cerebral abnormalities averaged more than nine years in duration of illness with long-term exposure to neuroleptics and other psychotropic drugs. As in other studies, no correlation was found between the damage and the degree of schizophrenic pathology. Also in 1988, Shelton, Karson, Doran, Pitkar, Bigelow, and Weinberger found prefrontal atrophy in schizophrenics.

Thus far nearly all studies demonstrating cerebral atrophy involved patients heavily treated with neuroleptics, and sometimes with electroshock and other brain-disabling regimens (see Breggin, 1979, for a review of brain damage from electroshock). Two studies that have evaluated relatively young and relatively untreated patients have found enlarged ventricles, and several others have not.

Weinberger, DeLisi, Perman, Targum, and Wyatt (1982) reported enlarged ventricles in seven of thirty-five (20%) of "first-episode schizophreniform disorders." Of these seven with abnormalities, five had scans within two weeks of their initial exposure to neuroleptic drugs, the other two within four weeks. The study found a similar rate of ventricular enlargement in chronic schizophrenic patients (four of seventeen or 23.5%). Twelve patients in their experimental group had already been given CT scans "because of a suspicion of 'organicity.' " This could raise questions about the composition of the group, but only one of twelve had enlarged ventricles. There was no correlation between ventricular enlargement and duration of treatment or illness. The investigators labelled their CT criteria as "suggestive of CNS abnormality."

Schulz, Koller, Kishore, Hamer, Gehl, and Friedel (1983) studied 15 teenage patients, including twelve schizophrenic and three schizophreniform. The patients had been ill for less than two years. Of the fifteen patients, eight were found to have enlarged ventricles. Ten of the patients had never received neuroleptics, and six of these had enlarged ventricles. As in Weinberger et al. (1982), there was no correlation between length of treatment or illness and CT abnormalities.

The above two studies are frequently cited as conclusive evidence that enlarged ventricles are found in untreated patients and that therefore the abnormalities are not due to medication. Anticipating more extensive discussion ahead, three points can be made.

First, other studies of young schizophrenics do not find abnormal CT findings. Tanaka, Hazama, Kawahara, and Kobayashi (1981) found no ventricular enlargement or cortical atrophy in thirty-two patients ages 21–40, while they did find abnormalities in patients aged 41–60. Benes, Sunderland, Jones, LeMay, Cohen, and Lipinski (1982) found no abnormalities in a group with a mean duration of illness of 1.1 years. Jernigan, Zatz, Moses, and Cardellino (1982) found no abnormalities in a group that ranged from age 23 to 58. Iacono, Smith, Moreau, Beiser, Fleming, Lin, and Flak (1988) studied 85 individuals experiencing a first psychotic episode. They ranged in age from 15 to 40 years.

There was no enlargement of lateral ventricles and no succal expansion, and therefore no confirmation of the findings of Weinberger et al. (1982) and Schulz et al. (1983). The authors did find an unexplained enlargement of the third ventricle in their patients which they did not feel they could attribute to schizophrenia. Second, the total numbers of patients in the two studies are small, with only ten patients who were never exposed to neuroleptics (Schulz et al., 1983). Third, a disorder associated with ventricular enlargement and cerebral atrophy, sometimes leading toward dementia, is likely to be progressive. Weinberger et al.'s (1982) finding of similar rates in first-episode schizophreniform patients and chronic schizophrenics would seem unlikely. More frequently, studies have found increasing rates among patients exposed to a longer duration of treatment and illness. All of the patients in Weinberger et al. (1982) and one-fifth of the patients in Schulz et al. (1983) were schizophreniform. This diagnosis means the patients had one acute episode of six months or less duration without deterioration and without recurrence. It seems especially improbable that CNS pathology involving enlarged ventricles would cause this short-lived disorder with good outcome.

A study by Nyback, Weisel, Berggren, and Hindmarsh (1982) is occasionally cited as indicating that relatively young and untreated patients suffer from enlarged ventricles and brain atrophy. The abstract for the paper described the subjects as "relatively young patients with acute psychoses" (p. 403). However, it turns out that "relatively young" meant under the age of forty-five, typically with multiple hospitalizations. Similarly, "acute psychosis" did not indicate a first episode, but merely that the patients were actually psychotic at the time of the study.

Recently, magnetic resonance imaging (MRI) has begun to replace the CT scan for determining brain tissue density. A 1988 MRI study by Kelsoe, Cadet, Pickar, and Weinberger confirms the general findings on many CT studies. So does an unpublished study by Andreasen and her colleages (cited in Andreasen, 1988). In the eight studies reviewed by Kelsoe et al. (1988), a few showed no abnormalities, and the majority showed a variety of somewhat inconsistent abnormalities. However, the weight of the studies leans toward a finding of atrophy in the brains of neuroleptic-treated schizophrenic patients. Surprisingly few studies have attempted to correlate CT scan findings with the presence of TD. Bartels and Themelis (1983) found abnormalities in the basal ganglia of TD patients; but overall the results have been mixed and inconclusive (see Goetz and van Kammen, 1986).

Recently the positron emission tomography (PET scan) has been used to measure the metabolic rate and blood flow of various parts of the brain. This instrument can detect dysfunction before it necessarily manifests as gross pathology. From the earliest studies, there has been a somewhat consistent finding of hypoactivity in the frontal lobes and frontal cortex of neuroleptic-

treated schizophrenics (Buchsbaum, Ingvar, Kessler, Waters, Cappelletti, van Kammen, King, Johnson, Manning, Flynn, Mann, Bunney, and Sokoloff, 1982; Farkas, Wolf, Jaeger, Brodie, Christman, and Fowler, 1984; Wolkin, Angrist, Wolf, Brodie, Wolkin, Jaeger, Cancro, and Rotrosen, 1988 [reviewed in Andreasen, 1988]; Wolkin, Jaeger, Brodie, Wolf, Fowler, Rotrosen, Gomez-Mont, and Cancro, 1985). However, not all reports confirm the finding of frontal hypoactivity (Gur, Resnick, Alavi, Gur, Caroff, Dann, Silver, Saykin, Chawluk, Kushner, and Reivich, 1987; Gur, Resnick, Gur, Alavi, Caroff, Kushner, and Reivich, 1987). There has been no consistent correlation with atrophy on CT scans. In each study, the patients had long histories of neuroleptic treatment prior to being removed temporarily for the PET scans.

The PET has been used to study specific parts of the brain in which the neuroleptics are known to produce dysfunction by blockade of the dopamine neurotransmitter system, including the basal ganglia (see ahead). A variety of studies show that the basal ganglia of neuroleptic-treated patients can develop dopamine related abnormalities (Farde, Wiesel, Halldin, and Sedvall, 1988).

PET studies of untreated schizophrenic patients have been contradictory (reviewed by Andreasen, 1988). One PET study involving unmedicated patients found no frontal hypoactivity (Sheppard, Gruzelier, Manchanda, Hirsch, Wise, Frackowiak, and Jones, 1983). It included a dozen patients, six who had never received any neuroleptics, and four who had received between 1 and 4 single doses. Neither PET, MRI nor CT scan studies are as yet conclusive concerning the existence of brain abnormalities prior to neuroleptic treatment. One CT scan project was specifically developed for the purpose of evaluating lifetime intake of neuroleptics. Lyon, Wilson, Golden, Graber, Coffman, and Bloch (1981) found a correlation between lifetime intake and shrinkage of the posterior but not anterior quadrants of the brain. The study has a relatively small sample of sixteen patients; but as a preliminary study, it points the way toward a much neglected area of research.

In summary, mounting radiological evidence from PET, MRI and CT scans confirms the presence of chronic brain dysfunction (PET scans) and brain atrophy (MRI and CT scans) in neuroleptic-treated schizophrenic patients. The total number of relevant CT scan studies is estimated to be over 90 (Kelsoe, Cadet, Pickar, and Weinberger, 1988), most of which show damage. Other studies implicate the total lifetime amount of neuroleptic intake (DeMeyer, Gilmore, DeMeyer et al., 1984; Lyon et al., 1981), but that is not a frequently replicated finding. There is some indication that early in their disorder and their treatment, patients tend not to display CT scan abnormalities; and that later in the disorder and treatment, the abnormalities become more frequent. There is insufficient data to determine whether or not cerebral atrophy or other abnormalities are consistently found in TD,

although some researchers have found electroencephalographic evidence that the cerebral cortex is afflicted (Koshino, Hiramatsu, Isaki, and Yamaguchi, 1986).

In published series, the percentage of drug-treated schizophrenic patients with atrophy on CT scan varies from zero to over 50%. It is premature to establish a prevalence rate for any particular group of patients, but the reported rates are substantial, typically in a range of 10-40%. Independently, Andreasen (1988) recently reviewed the literature and found a very similar range of 6-40%, using the criterion of two standard deviations larger than the control mean. Andreasen noted that higher rates were reported with increasing severity and length of illness. This would also correlate with length and intensity of treatment with neuroleptics.

A number of the CT scan studies we have reviewed found a correlation between atrophy and persistent cognitive deficits or frank dementia (DeMeyer, Gilmore, Hendrie et al., 1984; Famuyiwa et al., 1979; Golden et al., 1980; Johnstone et al., 1976; Lawson et al., 1988). This material is reviewed next.

Clinical studies and neuropsychological tests for persistent cognitive deficits and tardive dyskinesia. Evidence for mental deterioration in association with neuroleptic therapy has been mounting. An earlier review (Breggin, 1983) disclosed that many patients with TD are also suffering from severe mental deterioration (e.g., Edwards, 1970; Hunter, Earl, and Thornicroft, 1964; Rosenbaum, 1979). Often the data had to be culled from charts and footnotes because most of the studies relegated this correlation to obscurity within the article. Other studies concluded, without evidence, that the brain damage must have pre-dated the TD.

Ivnik (1979) observed that many TD patients at the Mayo Clinic were demented and decided to investigate the problem by studying one case in detail using a battery of neuropsychological tests before and after termination of neuroleptic therapy. Ivnik took the position that the dementia observed frequently among TD patients at the Mayo Clinic was not permanent – this one case tended to clear up partially upon discontinuation of the drug. However, partial clearing without complete recovery is expected in dementia after the causative agent has been removed. The patient remained severely and permanently mentally impaired on psychological tests.

A national research project evaluated brain dysfunction caused by polydrug abuse, including street drugs (for a more detailed analysis, see Breggin, 1983). Using the *Halstead-Reitan*, the study unexpectedly uncovered a significant correlation between generalized brain dysfunction and total lifetime psychiatric drug consumption in schizophrenics (Grant, Adams, Carlin, Rennick, Judd, Schooff, and Reed, 1978; Grant, Adams, Carlin, Rennick, Lewis, and Schooff, 1978). More than one quarter of the neuroleptic-treated patients had persistent brain dysfunction. The statistical analysis related the chronic brain dysfunc-

tion more to the lifetime neuroleptic intake than to the schizophrenia: "Neuropsychological abnormality was associated with greater antipsychotic drug experience" (Grant, Adams, Carlin, Rennick, Lewis, and Schooff, 1978, p. 1069). Indeed, schizophrenic patients who abused street drugs rather than taking neuroleptics showed no correlation between schizophrenia and increased brain dysfunction. None of the patients had been exposed to neuroleptics for more than five years.

In an unpublished version of the paper presented at a professional meeting (Grant, Adams, Carlin, Rennick, Judd, and Schooff, 1978), the authors underscored the connection between tardive dyskinesia and cognitive deficits, and warned in their concluding sentence, "It is also clear that the antipsychotic drugs must continue to be scrutinized for the possibility that their extensive consumption might cause general cerebral dysfunction" (p. 31). The version published in *Archives of General Psychiatry* (Grant, Adams, Carlin, Rennick, Lewis, and Schooff, 1978) warned of the possibility of long-term cognitive deficits associated with neuroleptic use, but in somewhat less threatening language. However, the danger was wholly expurgated from the *American Journal of Psychiatry* version (Grant, Adams, Carlin, Rennick, Judd, Schooff, and Reed, 1978). The misleading correlation with schizophrenia was highlighted, and the more important relationship with extent of psychiatric drug use was buried out of sight in the statistical analysis. The several warnings about cognitive deficits from neuroleptic use were edited out. This appears to have been part of a successful attempt to keep vital information from reaching the profession and the public. I have never seen the studies cited in a discussion of brain damage and dysfunction from neuroleptics.

More recently, a clinical study of hospitalized drug-treated patients found many suffering from mental deterioration typical of a chronic organic brain syndrome (Wilson, Garbutt, Lanier, Moylan, Nelson, and Prange, 1983). The mental abnormalities correlated positively with TD symptoms measured on the AIMS. In addition, length of neuroleptic treatment correlated with three measures of dementia — unstable mood, loud speech and euphoria. The authors stated: "It is our hypothesis that certain of the behavioral changes observed in schizophrenic patients over time represent a behavioral equivalent of tardive dyskinesia, which we will call tardive dysmentia" (p. 188). However, these symptoms are typically part of a more encompassing organic brain syndrome, including the cognitive deficits found in many studies, and the term tardive dementia would seem more appropriate. The tendency in the literature, perhaps in search of a euphemism, has been to use the term tardive dysmentia even when a fullblown dementing syndrome is being described.

In addition the *Schizophrenia Bulletin* has published several articles with commentaries discussing neuroleptic-induced "tardive dysmentia" (Goldberg, 1985; Jones, 1985; Mukherjee, 1984; Mukherjee and Bilder, 1985; Myslobodsky, 1986).

Jones distinguished between two types of permanent brain damage from such drugs – one producing apathy and the other euphoria. Goldberg pursued a similar line of reasoning and reviewed the literature.

We have already noted that many CT scan studies of brain atrophy have reported additional findings of cognitive loss on neuropsychological testing. However, the correlation is not wholly consistent (Goetz and van Kammen, 1986). Zec and Weinberger (1986) reviewed the subject at length. Using the *Withers and Hinton Test*, Johnstone's initial positive correlation between CT scan abnormalities and mental dysfunction was not confirmed by some later studies. However, the *Luria-Nebraska* and *Halstead-Reitan* batteries, considered among the most sensitive for detecting brain damage and dysfunction, do tend to indicate a relationship between ventricular enlargement and neuropsychological deficits. Overall, the trend is definitely toward a correlation between CT scan indices of atrophy and neuropsychological indices for persistent cognitive dysfunction and dementia.

Several studies in addition to Wilson et al. (1983) have reported an association between TD symptoms and generalized mental dysfunction. Itil, Reisberg, Huque, and Mehta (1981) found a clinical profile of severe organicity in TD patients. Waddington and Youssef (1986) found a correlation between TD and intellectual impairment, as well as blunted affect and poverty of speech, but attributed it to the underlying schizophrenia. Struve and Willner (1983) found a loss of abstract reasoning in TD patients compared to neuroleptic treated controls without TD. In a study of patients with affective disorder and TD, Wolf, Ryan, and Mosnaim (1982) found evidence of dementia: "relatively intact IQ scores but significant impairment in performing tasks of immediate memory and new learning abilities are similar to the findings of investigations of patients with Huntington's chorea" (p. 477). DeWolfe, Ryan, and Wolf (1988) found a strong correlation between cognitive deficits, including memory impairment, and facial tardive dyskinesia. They suggested that the degree of deficit was related to total lifetime intake of neuroleptics in patients with facial dyskinesias.

Wade, Taylor, Kasprisin, Rosenberg, and Fiducia (1987) pointed out that Huntington's and Parkinson's diseases might provide a model for tardive dyskinesia, including the development of cognitive impairments (see ahead, as well as Koshino et al., 1986; and Breggin, 1983, for similar discussions). They studied 54 manic or schizophrenic patients with tardive dyskinesia. Using a vareity of tests that had demonstrated cognitive deficits in patients with Parkinson's and Huntington's diseases, they found similar cognitive impairments in the tardive dyskinesia cases. Individuals with more severe TD had more severe cognitive losses. They concluded that the tardive dyskinesia was one expression of a larger "chronic neuroleptic-induced neurotoxic process" (p. 395).

Reports by Gualtieri and his colleagues (Gualtieri and Barnhill, 1988; Gualtieri, Quade, Hicks, Mayo, and Schroeder, 1984; Gualtieri, Schroeder, Hicks, and Quade, 1986) indicated that many institutionalized children and young adults go through a period of worsening of their psychiatric symptoms after withdrawal from neuroleptics. This occurs in developmentally disabled patients in whom there is no complicating schizophrenic process. The researchers attribute the withdrawal problems to a drug-induced dementing process. Some patients stabilize or improve if kept medication free, but others seemed permanently worsened by the medications, and like adult cases, require increased medication to control their drug-induced symptoms. Gualtieri and Barnhill (1988) discuss the various explanations and conclude that the most likely hypothesis is that the neuroleptics impair higher mental function. They point out that "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). They believe that the dementia results from damage to the basal ganglia that is also found in TD (see below). Gualtieri and Barnhill declare that "neuroleptic treatment is considered by enlightened practitioners in the field to be an extraordinary intervention" (p. 137) requiring serious justification. In summary, a convincing body of literature indicates that patients treated long-term with neuroleptics develop persistent cognitive deficits and dementia.

There is another source of clinical evidence for damage to higher brain centers in patients suffering from TD: clinical reports of denial or anosognosia among TD patients. A review of the literature disclosed that most tardive dyskinesia patients do not complain about their symptoms and will even refuse to admit their existence when confronted with them (Alexopoulos, 1979; Breggin, 1983; DeVeaugh-Geiss, 1979; Smith, Kuchorski, Oswald, and Waterman, 1979; Wojcik, Gelenberg, LaBrie, Mieske, 1980). Myslobodsky, Tomer, Holden, Kempler, and Sigol (1985) found that 88% of the TD patients "showed complete lack of concern or anosognosia with regard to their involuntary movement" (p. 156). The study also found some indication for cognitive deficits in these patients. Myslobodsky (1986) reported "emotional indifference or frank anosognosia of abnormal movements" (p. 1) in 95% of TD patients. He concluded that the most probable cause was "some form of cognitive decline associated with dementia disorder, probably owing to some neuroleptic-induced deficiency within the dopaminergic circuitry" (p. 4). As Myslobodsky suggests, the denial of obvious symptoms of brain dysfunction can be a telltale sign of chronic damage to the highest centers of the brain. It is found, for example, in severe brain disease caused by alcoholism (Wernicke's encephalopathy) or syphillis.

Overall, there is increasing evidence that long-term use of neuroleptics produces or is strongly associated with persistent cognitive deficits and demen-

tia in a significant but as yet undetermined percentage of patients, and that
tardive dyskinesia patients are especially afflicted, perhaps in the majority
of cases.

Tardive psychosis. Some reports have indicated that some neuroleptic-treated
patients develop drug-induced tardive psychoses that can become more severe
than their original psychiatric disorders (Chouinard and Jones, 1980;
Chouinard and Jones, 1982; Chouinard, Jones, and Annable, 1978; Csernan-
sky and Hollister, 1982; also see news reports by Jancin, 1979 and "Supersen-
sitivity Psychosis," 1983). Tragically, patients can require lifetime medication
for a disorder that could have had a much shorter natural history.

The authors of two studies (Chouinard and Jones, 1980; Csernansky and
Hollister, 1982) believe that the exacerbation of psychotic symptoms after
removal from the drugs is due to brain damage from the drugs. They have
labelled the disease tardive psychosis to underscore its parallel with TD. It
can be irreversible and, like TD, can require ever-increasing drug doses to
suppress the drug-induced symptoms.

At present, tardive psychosis is considered a controversial clinical entity,
and the number of studies is insufficient to determine a prevalence. Although
Chouinard and Jones (reported in "Supersensitivity Psychosis," 1983) have
found a prevalence of 30–40%, Hunt, Singh, and Simpson (1988) reviewed
the charts of 265 patients and located 12 probable and no definite cases of
tardive psychosis.

Tardive psychosis overlaps clinically with the more established entity of
tardive dementia. Studies by Gualtieri and his colleagues (1984, 1986) indicate
that their patients suffer from a mixture of increased dysphoria, psychotic
symptomatology, and dementia.

Clinicians have become increasingly aware of the difficulty of removing
patients from neuroleptics, in part because of what appears to be tardive
psychosis. Withdrawal from the drugs also can produce transient or persistent
dyskinesias, dysphoria, and autonomic imbalances, resulting in nausea and
weight loss. These reactions to neuroleptic withdrawal have led to debate
over classifying these medications as addictive (Breggin, 1989a, 1989b).

Direct examination of the brain. There are surprisingly few autopsy reports
following chronic neuroleptic therapy and they have been somewhat in-
conclusive (reviewed in the following: Bracha and Kleinman, 1986; Breggin,
1983, pp. 103–105; Brown, Colter, Corsellis, Crow, Frith, Jagoe, Johnstone,
and Marsh, 1986; Jeste, Iager, and Wyatt, 1986; Rupniak et al., 1983). However,
several studies have demonstrated the expected pathological changes from
neuroleptic treatment: cellular loss or degeneration in the basal ganglia. The
term basal ganglia will be used to indicate the striatum (caudate, putamen
and globus pallidus), plus the substantia nigra — areas known to be strongly
affected by the neuroleptics (see below).

There is autopsy evidence that the neuroleptics can damage the basal ganglia, areas potentially critical in the production of both TD and tardive dementia. As early as 1959, Roizin, True, and Knight reported postmortem degeneration in the basal ganglia of a few neuroleptic-treated patients and correlated these findings with related neurologic dysfunctions caused by the drugs. Forrest, Forrest, and Roizin (1963) reported an autopsy evaluation of one case of long-term neuroleptic treatment which demonstrated neuronal loss in the cerebral cortex and degenerative changes in the substantia nigra. The most striking alterations were in the putamen of the basal ganglia. The patient had also been given shock treatment.

Gross and Kaltenbach (1968) found evidence from three autopsies of irreparable damage to the caudate nucleus. They suggested that neuroleptic treatment may cause reversible tissue lesions and lead to irreparable damage of the caudate nucleus. Christensen, Moller, and Faurbye (1970) found a considerably higher degree of cell degeneration in the substantia nigra, as well as other pathological findings, in patients with TD compared to their controls. Jellinger (1977) reviewed the literature, and in his own research he found "damage to large neurons in the caudate nuclei with increased satellitosis and slight glial reaction in 46%" (p. 38) of patients subjected to chronic neuroleptic therapy. The percentage of patients with pathological changes was higher among those suffering from tardive dyskinesia (57% versus 37.5%). The afflicted areas were among those most directly affected by neuroleptics.

Brown et al. (1986) performed postmortem examinations on 41 schizophrenic patients. They found that, compared to controls, the patients' brains were lighter in weight (by 6%) and displayed ventricular enlargement associated with temporal lobe atrophy. The authors believed that their findings substantiate the atrophy found on CT scans. They stated "There were no significant effects of insulin, phenothiazine treatment, or electroconvulsive therapy on the results reported herein" (p. 38) but gave no supporting data. The conclusion contradicts evidence indicating cell death and degeneration from insulin treatment (see Breggin, 1979, p. 137; Kalinowsky and Hippius, 1969, pp. 288–289), as well as from shock therapy (Breggin, 1979, pp. 38–62). According to a table in Brown et al. (1986, p. 38), 23% had shock treatment, 28% had insulin therapy, and 41% had neuroleptic treatment. A note indicated that the frequency of shock treatment might be under-estimated. How many patients had combined treatment was not indicated.

Since the patients had a mean length of illness of 31 years and had died in the hospital, many during the era before de-institutionalization, most or all were probably long-term inmates who would have been subjected to numerous other stresses that might have caused brain damage, including head trauma and undetected disease. It would appear that nearly all the patients were subjected to so many damaging stresses that it would be impossible to

attribute the findings to schizophrenia or to rule out other causes, including treatment (see Marsden, 1976, for similar observations on brain damage found among chronic inmates). Finally, as Brown et al.'s (1986) review chart indicated, the only modern postmortem study of *drug-free schizophrenics* (Wildi, Linder, and Costoulas, 1967) found no brain atrophy.

Hunter, Blackwood, Smith, and Cumings (1968) concluded that they could find no pathology in three postmortem studies of neuroleptic-treated patients. However, all three individuals did have pathological changes in the substantia nigra which were interpreted as normal due to aging in two cases and dismissed as of unknown etiology in the other case. All three subjects were elderly, complicating the interpretation of the findings. Arai, Amano, Iseki, Yokoi, Saito, Takekawa, and Misugi (1987) found neuronal degeneration in the cerebellar dentate nucleus, rather than the basal ganglia, in four cases of oral TD.

Although inconclusive, postmortem findings tend to confirm the effects expected from neuroleptic treatment: deterioration in the basal ganglia and substantia nigra, plus more generalized pathology. Animal research also strongly suggests permanent brain damage from neuroleptic treatment (see below).

In a recent review of structural changes in the brain associated with TD, Krishnan, Ellinwood, and Rayasam (1988) concluded "In summary, neuropathological, CT, and MRI studies reveal neuroanatomical and physicochemical changes in the brain of TD patients, but the exact nature and significance of these changes remain an enigma" (p. 173). However, while the specific changes associated with TD do remain something of a puzzle, the finding of pathological changes of various kinds associated with neuroleptic therapy in general seems increasingly well-established, and many of the studies do localize the findings in the basal ganglia, where the greatest impact can be anticipated.

Summary of Evidence from Human Studies

Substantial evidence confirms the presence of persistent cognitive deficits, brain dysfunction, dementia and brain damage — especially atrophy — among neuroleptic-treated patients. The most consistent and convincing body of evidence has been produced by the new brain imaging techniques (CT, MRI and PET scans). A range of 10–40% of patients afflicted with brain damage is most consistently reported. The rates seem to increase with duration of treatment and the age of patient.

Numerous clinical and neuropsychological studies have reported persistent cognitive dysfunction, tardive psychosis and tardive dementia among neuroleptic-treated schizophrenic patients. Tardive dementia is becoming an in-

creasingly recognized syndrome. There is some postmortem evidence of basal ganglia deterioration, as well as generalized neuropathology. Brain atrophy has also been found in at least one recent postmortem study of these patients, although few studies exist. Various kinds of pathology have also been found in association with TD, sometimes localized in the basal ganglia.

Overall, the evidence presented from brain imaging, clinical evaluations, neuropsychological testing, and human postmortems indicates that the neuroleptics are the probable cause of the cognitive dysfunction and brain damage found in many patients. Our analysis continues with further evidence pertaining to etiology and a discussion of the implications of these findings for the mental health professions.

Neuroleptics as the Cause

As reviewed in the preceding section, data from human studies indicate that the neuroleptics are the cause of damage to the higher brain and to the mind reported in various research studies. This section will explore a more definitive answer to the question "Is neuroleptic medication or schizophrenia the cause of persistent mental dysfunction and brain damage found in many neuroleptic-treated patients?"

The Lessons of Lethargic Encephalitis and Subcortical Dementia

The neuroleptic drug effect as clinically observed closely mimics the effects of lethargic encephalitis (encephalitis lethargica or von Economo's disease) as reported during and after World War I. Both the neuroleptics and the viral disease produce mental apathy and indifference, plus various acute dyskinesias, including Parkinson's syndrome, dystonias and tremors. The encephalitis epidemic, which afflicted tens of thousands, was well-known to neurologists and psychiatrists in the 1950s, including Delay and Deniker in France, who were among the first to use the neuroleptics for psychiatric purposes. In a 1970 retrospective, Deniker observed:

> It was found that neuroleptics could experimentally reproduce almost all symptoms of lethargic encephalitis. In fact, it would be possible to cause true encephalitis epidemics with the new drugs. Symptoms progressed from reversible somnolence to all types of dyskinesia and hyperkinesia, and finally to parkinsonism. The symptoms seemed reversible on interruption of the medication. (p. 160)

While the symptoms initially seemed reversible, Deniker realized that they were turning out to be permanent in some cases:

> Furthermore, it might have been feared that these drugs, whose action compares with that of encephalitis and parkinsonism, might eventually induce irreversible secondary neurological syndromes. Such effects cannot be denied: it has been known for some years that permanent dyskinsias may occur. . . . (p. 163)

The parallel between lethargic encephalitis and neuroleptic toxicity was remarkable in several respects. Both groups of patients initially displayed apathy or disinterest, followed by the onset of various dyskinesias; and then in both groups of patients, after a delay, the dyskinesias sometimes became permanent. In regard to lethargic encephalitis, many patients seemed to recover, only to relapse into devastating neurological disorders years later. Many cases of Parkinson's disease were traced, years later, to an earlier exposure of lethargic encephalitis. While Parkinson's disease was the most common "tardive" or delayed motor disorder associated with lethargic encephalitis, other dyskinesias more similar to drug-induced TD (see below) were also known to develop.

There was a still more menacing potential parallel between the viral disease and the drug-induced disease. Many of the post-encephalitic patients, after an apparent recovery, later went on to develop severe psychoses and dementia (Abrahamson, 1935; Matheson Commission, 1939). Thus, the completion of the parallel between lethargic encephalitis and neuroleptic effects awaited the discovery that in addition to TD, tardive psychosis and tardive dementia could follow the exposure to neuroleptics.

The parallel between the medication effects and the viral encephalopathic effects was not proof that the medications would also produce mental deterioration; but it sounded a warning that similar mechanisms and hence similar adverse outcomes were possible. This concern was raised early by Paulson (1959), who wrote:

> The sequelae of encephalitis include many muscular, psychic and autonomic responses; and most of the neurologic complications from the penhothiazines are within the range of post-encephalitic parkinsonism. (p. 800)

Paulson remarked that no "permanent lesions" had yet been discovered to correspond with the "muscular, psychic and autonomic responses"; but his concern was justified.

The same year, Brill (1959) also commented on the similarity between lethargic encephalitis and the neuroleptics "which, in full doses, can reproduce many of the most outstanding features of the chronic encephalitic syndrome. . ." (p. 1166). Brill pointed out that both the viral disease and the drug reaction produce similar neurological and mental effects, including "the rousable stupor of acute encephalitis." Apparently unimpressed with initial reports of persistent dyskinesias, Brill believed that the neuroleptic effects were "controllable, reversible, and nonprogressive." A few years later, Hunter et al. (1964) again noted the parallel between the epidemic viral disease and the drug effect, and suggested that the neuroleptics cause a chemically induced encephalitis.

Given the clinical similarity between the impact of lethargic encephalitis

and that of the neuroleptics, we may wonder about similarities in brain pathology produced by each. Brill (1959) summarized the autopsy findings of patients suffering from lethargic encephalitis (see also Abrahamson, 1935; Brodal, 1969). Cell loss was marked in the basal ganglia and especially the substantia nigra, where the damage, according to Brill, "is outstanding and may be seen by inspection, even in gross freshly cut specimens" (p. 1165).

The hardest hit areas in lethargic encephalitis, the cells of the basal ganglia and the substantia nigra, are also the areas most affected by the neuroleptic medications in the production of TD. The substantia nigra and the basal ganglia (the caudate and putamen) constitute the nigra-striatal pathway. This pathway contains dopamine neurons whose function seems irreversibly affected by neuroleptics in the development of TD (see below). As reviewed earlier, these regions are sometimes found damaged in autopsies of neuroleptic-treated patients, as well as in neuroleptic-treated animals (see ahead).

We have already seen that lethargic encephalitis sometimes caused dementia as well as dyskinesias. A number of other diseases which cause dyskinesias also tend to produce dementia. Huntington's chorea, whose dyskinesias somewhat mimic TD, typically results in severe mental deterioration. The most characteristic pathology is found in the basal ganglia (caudate and putamen), with less severe loss of tissue in the frontal and temporal lobes (Adams and Victor, 1985). Postmortem findings in Huntington's disease resemble those found in postmortem studies of some neuroleptic-treated patients, but are more severe (Brown et al., 1986). Based on a review of pertinent literature and their own electroencephalographic studies, Koshino et al. (1986) come to the same conclusion as we do:

> The EEG similarities of TD and Huntington's chorea were discussed, and a suggestion was made that not only the basal ganglion, but also the cerebral cortex, could be involved in development of TD. (p. 34)

Parkinson's disease, which affects motor control, is also frequently associated with a gradually developing loss of mental faculties, sometimes leading to dementia. Like neuroleptic treatment, Parkinson's disease often produces a blunting or slowing of emotional responsiveness. The characteristic lesions of Parkinson's disease are found in the substantia nigra (Adams and Victor, 1985).

The association of mental deterioration with diseases of the basal ganglia and substantia nigra led to the concept of subcortical dementia (Huber and Paulson, 1985). According to this formulation, a type of dementia can arise from damage to the basal ganglia and surrounding structures rather than to the cerebral cortex. Patients with subcortical dementia are very similar to those with cortical dementia, except that they tend to be more depressed and apathetic, without as much evidence of impairment to higher cortical

functions, such as speech. Patients with subcortical dementia display a slowing of mental operations and progressive memory impairment. Although Huber and Paulson do not make the connection, we will suggest that subcortical dementia is one more probable mechansim for the production of persistent mental dysfunction and deterioration by the neuroleptics, although there are other probable mechanisms as well (see below).

An important lesson may be learned from lethargic encephalitis, as well as from subcortical dementia in other diseases, such as Huntington's and Parkinson's diseases. Long-term pharmacological alteration in dopamine neurotransmission in the basal ganglia and substantia nigra has the potential risk of producing not only movement disorders but serious and potentially irreversible cognitive dysfunction, including dementia. These observations are extremely relevant in deciding whether the neuroleptics can cause persistent mental dysfunction and brain damage in medicated patients.

Neuroleptic Neurotoxicity

Deniker (1970, 1971) indicates that he and Delay were well aware of the neurotoxicity of the first neuroleptics. Many references in the literature also refer to the "neurotoxicity" of the drugs (e.g., DiMascio and Shader, 1970; Famuyiwa et al., 1979; van Sweden, 1984). In routine treatment, most patients demonstrate one or another manifestation of neurotoxicity, including Parkinson's syndrome, dystonia, akathisia and tremors. The disinterest, apathy and lethargy that develop more or less in proportion to dosage can also be attributed to toxic reactions (Breggin, 1983).

Occasional severe reactions to the drugs, such as neuroleptic malignant syndrome, closely mimic the described acute phase of the once-feared lethargic encephalitis. The neuroleptic malignant syndrome includes signs of severe central nervous system intoxication with extreme dyskinesias, hypertonicity of muscles, impaired consciousness, hypertension, and instability of the autonomic nervous system (Guze and Baxter, 1985; Levenson, 1985). It is fatal 10–20% of the time. The occurrence of such an extremely toxic reaction in even a small percentage of patients – an estimated 1–2% or less – again suggests the damaging potential of these drugs.

The adverse effects of neuroleptics on many biochemical processes in the brain, including protein synthesis, mitochondrial activity and membrane structure, and most enzymes are described in a substantial body of work (Matsubara and Hagihara, 1968; Teller and Denber, 1970). Various neurotransmitter systems are affected, including dopamine, gamma-aminobutyric acid (GABA) and acetylcholine (APA, 1980, pp. 75–79). Protein synthesis is maximally inhibited in the basal ganglia (Sellinger and Azcurra, 1970), a finding consistent with evidence from many sources demonstrating the impact of

neuroleptics on that region of the brain (see below). Although attention will be focused on blockade of dopaminergic neurons, it should not be forgotten that the neuroleptics disrupt many processes in the brain. We should anticipate that many untoward effects of these drugs will escape our attention due to the complexity of their effects and the difficulty of detecting them with our present methods. The generalized neurotoxic impact of the neuroleptics provides another warning about potential dangers to the functioning of the brain and mind.

Neuroleptics, Tardive Dyskinesia, and Dopamine Neurons

TD is produced partly as a result of neuroleptic-induced chronic inhibition of dopaminergic neurons in area A9 of the substantia nigra. These A9 neurons project to the striatal nuclei (caudate and putamen) where they stimulate the release of dopamine. Following neuroleptic blockade of A9 neurons, post-synaptic dopamine receptor targets in the striatum undergo a compensatory increase in both the numbers of dopamine receptors and their sensitivity. This dopamine receptor supersensitivity or hyper-reactivity in the striatum produces TD (Chiodo and Bunney, 1983; Jenner and Marsden, 1983; Jeste, Iager, and Wyatt, 1986). Of recent interest, neuroleptic blockade of dopamine receptors in the putamen has been demonstrated on PET scan (Farde, Wiesel, Halldin, and Sedvall, 1988).

The dopamine model for TD indicates why the initial impact of the neuroleptics mimics Parkinson's disease (motor slowing), while the delayed effects (hyperkinesias) of the drugs mimic Huntington's chorea. The characteristic lesions of Parkinson's disease are found in the substantia nigra (Adams and Victor, 1985). The substantia nigra is the site of the dopamine neurons whose function is rapidly inhibited by the neuroleptics. The characteristic lesions of Huntington's chorea are found in the striatum [caudate and putamen] (Adams and Victor, 1985). The striatum is where the delayed supersensitivity of TD results from chronic neuroleptic inhibition. This emphasizes a point we have already noted: neuroleptic effects parallel neurological diseases which produce both motor impairment and severe cognitive dysfunction.

The neuroleptic threat to the highest mental centers becomes apparent when it is realized that dopaminergic neurons susceptible to similar neuroleptic inhibition are found in the highest centers of the brain, including the meso-limbic system and cortex, which regulate emotional and mental activities. The bodies of these neurons originate in the ventral midbrain tegmentum (A10) and project axons to limbic and cortical structures, including the nucleus accumbens, septal nuclei, amgydala, and frontal and cingulate cortex, where they stimulate the release of dopamine (Adams and Victor, 1985; Chiodo and Bunney, 1983; White and Wang, 1983).

Marsden (1976) was one of the few to point to the danger of irreversible neuroleptic-induced damage — similar to tardive dyskinesia — in the highest centers of the brain. He observed in a letter to *Lancet*, " If long-term neuro-leptic therapy can cause an apparently permanent change in striatal dopamine-receptor action, then one must assume that the same can occur in the meso-limbic cortical dopamine receptors" (p. 1079).

Animal research has confirmed that supersensitivity of dopamine recep-tors develops in the meso-limbic and cerebral cortical areas, much as it does in the striatum (Chiodo and Bunney, 1983; White and Wang, 1983) and that it can become chronic after termination of neuroleptic treatment (Jenner and Marsden, 1983; Rupniak, Jenner, and Marsden, 1983).

While tardive dyskinesia is difficult to reproduce in animals, Gunne and Haggstrom (1985) have been able to create both acute and irreversible dyskinesias in monkeys and rats. With persistent dyskinesias, they demon-strated evidence of irreversible biochemical changes in the basal ganglia and related areas (substantia nigra, medial globus pallidus, and nucleus sub-thalamicus). The changes were thought to reflect suppression of the dopamine system with a corresponding hyper-reactivity or supersensitivity. The authors found that a limbic component of the dopamine systems was involved.

Many researchers have remarked on the relationship between inhibition of the meso-limbic and cortical dopamine system and the clinical production of blunting or apathy (White and Wang, 1983; reviewed in Breggin, 1983). Lehmann (1975), who introduced the neuroleptics into North America in 1954, offered this straightforward observation:

> Neuroleptic drugs are characterized by their effects on the ascending reticular activating formation, which result in reduced reactivity to external and internal stimuli and in de-creased spontaneous activity. Furthermore, their effects on the limbic system lead to blun-ting of emotional arousal. . . . (p. 28)

That the neuroleptics currently suppress the activity of neurons in area A10, with their projections to higher brain centers, is confirmed clinically by the disinterest, indifference or apathy which the neuroleptics produce in routine clinical usage. As previously analyzed in detail (Breggin, 1983), this impact closely parallels the clinical effect of surgical disruption of the limbic system fibers by lobotomy and newer forms of psychosurgery. It is no exaggeration to label the impact of the neuroleptics a chemical lobotomy.

In summary, dopamine neurons play a major role in the functioning of basal ganglia, limbic and cerebral cortical regions, and are critical in the highest mental life of the individual. Evidence from human and animal research con-firms that neuroleptics suppress dopamine neurotransmitter systems. The im-pact of the neuroleptics on the mind can be explained by inhibition of these neuronal systems. Finally, animal experimentation reveals that chronic neuro-leptic treatment affects the limbic-cortical system much as it does the striatum,

with the production of a persistent reactive supersensitivity of the dopamine receptors. From such observations, we can expect a limbic and cortical equivalent of tardive dyskinesia, capable of causing persistent cognitive deficits, tardive dementia and brain atrophy in neuroleptic-treated patients.

In addition, some dopamine neurons in the substantia nigra (A9) project to the cortex rather than to the striatum. These neurons are blockaded by the neuroleptics, and dysfunction in these cortical projections can be expected to have a negative impact on the highest mental functions. Furthermore, it has been known for some time that the striatum itself is not a purely motor area and that it is involved with higher mental functions (e.g., Adams and Victor, 1985; Brodal, 1969). There are multiple interconnections between the striatum, limbic system and cerebral cortex. Gualtieri and Barnhill (1988) have recently confirmed these observations:

> Persistent TD is probably the consequence of irreversible striatal damage. But the corpus striatum is responsible for more than motor control; it is a complex organ that influences a wide range of complex human behaviors. No disease that afflicts striatal tissue is known to have only motor consequences; Parkinson's disease and Huntington's disease are only two examples. [citations deleted] (p. 150)

Underscoring the relationship between the striatum and mental function is the fact that the striatum is closely related in mammalian evolution to the development of the highest centers of the brain. The striatum increases in size parallel with the development of the cortex. The caudate and putamen of the striatum evolve from the telencephalon, the most anterior segment of embryonic development, which also gives rise to the cerebral hemispheres, including the frontal lobes and cerebral cortex. The striatum is also interconnected with the reticular activating system with its key role in the arousal and the overall emotional energy level of the individual.

Damage to the striatum and related structures, if severe enough, would be expected to produce persistent cognitive deficits and dementia, including the subcortical dementia described by Huber and Paulson (1985) [see above].

Thus, there are several related mechanisms for the development of neuroleptic-induced persistent cognitive dysfunction, tardive psychosis and tardive dementia: damage to dopamine neurons and supersensitivity of dopamine receptors in meso-limbic and cortical regions, and similar damage and dysfunction in the striatum itself, with its rich interconnections with the highest portions of the brain. It would seem inevitable that the neuroleptics would cause permanent harm to the higher mental functions, including lobotomy-like apathy or indifference.

Structural Damage to the Brain from Neuroleptic Exposure

We have briely reviewed evidence for permanent biochemical changes (dopamine supersensitivity) as a result of neuroleptic treatment in animals. There is corresponding evidence for permanent damage to nerve cells.

related to the inhibition of its functions noted by physiologists. Coln (1975) found a reduction in the nuclear volume of cortical brain cells in rats two months after the termination of a four week treatment period with haloperidol. No attempt was made to localize the damage beyond the cerebral cortex.

Reviews of animal studies can be misleading. For example, the *APA Task Force Report on TD* (APA, 1980) stated that "neuropathologic studies following acute or prolonged administration of antipsychotic drugs to animals have not convincingly and consistently demonstrated specific or localized pathological changes in the brain. . ." (p. 57). The report listed as evidence the four studies which we have reviewed in the above paragraph. Despite the APA interpretation, all four studies were convincing and consistent in one important aspect: the finding of widespread, severe, and irreversible changes in the form of neuronal damage and death.

Moreover, while the studies listed by the *Task Force* did not show consistent *localized* damage in the anticipated area, the basal ganglia, the duration of the exposure to the neuroleptics was very brief, varying from a single dose to thirteen weeks of treatment. Of great importance, animal studies with longer durations of exposure to neuroleptics – one year (Pakkenberg, Fog, and Nilakantan, 1973) and 36 weeks (Nielsen and Lyon, 1978) – showed the expected neuronal deterioration in the basal ganglia. These findings establish the capacity of the neuroleptics to produce permanent changes in basal ganglion function after chronic administration.

Not all rat studies show permanent damage. A follow-up by the Pakkenberg group (Fog, Pakkenberg, Juul, Bock, Jorgensen, and Andersen, 1976) found no irreversible changes in the rat brain with shorter duration treatments of 4 to 6 months, and concluded that the time factor was key. Similarly, Gerlach (1975) found no changes after 6 and 12 months treatment, and concluded "it may be assumed that the neuroleptics may exert an irreversible neurotoxic effect on the nigro-striatal system" (p. 53), but that the effect required aging or lengthier exposures, and that many changes might take place that were not discernable by light microscope.

In summary, most animal studies report irreversible neuronal damage, including cell death, after relatively brief exposure to neuroleptics. After longer exposure to the neuroleptics, the expected localization of damage in the basal ganglia and substantia nigra is often found. These findings in animal studies are especially striking considering the relatively short durations of treatment as well as the relatively low doses in some reports. One year is considered "long-term." Human subjects are often exposed to the neuroleptics for many years, sometimes for decades, and sometimes in very high doses. Furthermore, it is well-known that the brains of small rodents tend to be much more resistant to damage from most toxic agents than that of larger mammals.

Some human autopsy studies, reviewed earlier, have found evidence of basal

ganglia deterioration and atrophy of the brain in neuroleptic-treated patients, as well as more generalized neuropathology, and are consistent with the animal reports. However, postmortem reports concerning humans have been surprisingly infrequent and somewhat inconsistent (Arai, Amano, Iseki, Yokoi, Saito, Takekawa, and Misugi, 1987; reviewed in Bracha and Kleinman, 1986; Brown et al., 1986; Rupniak Jenner, and Marsden, 1983).

Findings that the neuroleptics can permanently damage the brain structure of animals, often in the expected regions of neuroleptic impact, constitute convincing evidence that neuroleptics are the cause of the cognitive deficits and dementia found in neuroleptic-treated schizophrenic patients.

Tardive Psychosis, Tardive Dementia, and Senile Psychosis

The identification of tardive psychosis, previously discussed, bolsters more solid evidence that the neuroleptics can produce persistent cognitive dysfunction. The authors of these studies (Chouinard and Jones, 1980; Csernansky and Hollister, 1982) assign causation to the neuroleptics rather than to schizophrenia. The association of tardive psychosis with length of drug treatment and with drug withdrawal is convincing. Also, these patients frequently suffer from an organic brain syndrome, which is known to be caused by toxic drug reactions but not by schizophrenia.

Since generalized cognitive dysfunction and dementia are typically caused by an organic insult to the brain, such as toxic medication, authors of cognitive dysfunction and dementia studies usually identify the neuroleptics, rather than schizophrenia, as the probable cause (see preceding review, including DeWolfe et al., 1988; Goldberg, 1985; Grant, Adams, Carlin, Rennick, Lewis, and Schooff, 1978; Grant, Adams, Carlin, Rennick, Judd, and Schooff, 1978; Gualtieri and Barnhill, 1988; Gualtieri, et al., 1984, 1986; Ivnik, 1979; Jones, 1985; Myslobodsky, 1986; Wade et al., 1987; Wilson et al., 1983).

Psychosis in old age sometimes appears spontaneously in association with movement disorders, and the correlation between the two is probably related to deterioration of the dopamine system in the brain (Lohr and Bracha, 1988). While these disorders are produced by aging rather than by medication, the finding adds further confirmation to the fact that abnormalities of the dopamine system cause both movement disorders and mental dysfunction, and alerts us that we may reasonably expect the same untoward combination as a result of neuroleptic therapy, which also causes disturbances in dopamine neurotransmission.

Brain Imaging Studies

Studies based on the CAT, MRI and PET scans, as well as the PEG (Part I), did not prove very useful in distinguishing between schizophrenia and

neuroleptics as the cause of findings of atrophy in neuroleptic-treated schizophrenics. Authors of these studies were divided in their conclusions concerning etiology, some favoring schizophrenia (Golden et al., 1980; Johnstone, Crow, Frith, Husband, and Kreel, 1976; Johnstone, Crow, Frith, Stevens, Kreel, and Husband, 1978; Shelton et al., 1988; Weinberger et al., 1979, 1980) and others favoring neuroleptics (DeMeyer, Gilmore, DeMeyer, Hendrie, Edwards, and Franco, 1984; DeMeyer, Gilmore, Hendrie, DeMeyer, and Franco, 1984; Famuyiwa et al., 1979; Sabuncu et al., 1977). Famuyiwa et al. suggested that if their findings were born out by other studies, "radical changes in drug treatment policy are indicated" (p. 504).

Sometimes claims were made that one or another study showed atrophy in unmedicated or relatively unmedicated schizophrenics; but the review disclosed that some of these studies were inadequate or misinterpreted and that the greater number of studies failed to find atrophy in schizophrenics early in their treatment. The arguments used in favor of a schizophrenic etiology by some authors of brain imaging studies will be further evaluated in the following section.

Schizophrenia as the Cause

Are there any competing reasons or evidence to bolster the alternative view that schizophrenia is the cause? Weinberger (1984) and others have argued that neuroleptics are not the cause of the brain atrophy and associated cognitive losses. The main basis for their argument is the presumed lack of correlation between lifetime intake of neuroleptics and the degree or presence of atrophy and cognitive changes. However, researchers have no direct measurement of lifetime intake of neuroleptics as a separate variable. Instead, they measure the length of psychiatric disorder, and assume that total exposure to neuroleptics increases with the duration of the psychiatric disorder.

The argument has serious flaws. First, it can be used equally well against schizophrenia as a cause. If there is no correlation between duration of psychiatric disorder (the variable actually being measured!) and the damage, then it seems unlikely that the psychiatric disorder is the cause.

Second, their premise is not wholly correct. Supporters of schizophrenia as the cause of the atrophy sometimes cite one or two studies (Schulz et al., 1983; Weinberger et al., 1982) in defending their position that untreated schizophrenics also display atrophy. We have reviewed these studies and found that they are not convincing and they are contradicted by several others (Benes et al., 1982; Iacono et al., 1988; Jernigan et al., 1982; Tanaka et al., 1981). Another study cited occasionally as demonstrating atrophy in relatively untreated patients (Nyback et al., 1982) turned out to involve patients under age forty-five, many with multiple hospitalizations and many years of treat-

ment. Besides, the argument does not shed much light on the cause of the brain disorders, since either neuroleptic exposure or schizophrenia would presumably take time to produce its damaging effect.

Third, although a good correlation has never been made between lifetime neuroleptic ingestion and tardive dyskinesia, we know that neuroleptics cause tardive dyskinesia (APA, 1980; Fann et al., 1980; Jenner and Marsden, 1983; Jeste and Wyatt, 1982). It is therefore no surprise that it is proving difficult to make a more exact correlation between lifetime neuroleptic ingestion and atrophy or dementia.

Overall, investigators who assume that schizophrenia is the cause of brain atrophy and persistent cognitive losses do not offer convincing evidence or rational justification. On the other hand, there is a very cogent reason to believe that the atrophy found on CT scans cannot be the product of schizophrenia. Brain atrophy is far more accurately and definitively evaluated on direct postmortem pathological examination than on CT scan. The actual pathology, if it exists, can more easily be identified and accurately measured by direct observation and microscopic studies. Yet no consistent finding of brain atrophy was made in hundreds of autopsy studies performed on schizophrenics prior to the use of neuroleptics.

From the perspective of Adams and Victor (1985, p. 1150), the CT studies of the schizophrenic brain are so inferential as to be of dubious merit without confirmatory postmortem pathological studies. I believe that the mounting evidence from a combination of CT, MRI, and PET brain scans does indicate an abnormality of the brain that corresponds with many other findings we have reviewed. If the CT scans prove inconclusive, as Adams and Victor suggest, the remaining evidence would nonetheless confirm the existence of chronic cognitive dysfunction and dementia caused by neuroleptics. More pertinent, the relative insensitivity of the CT scan underscores the importance of the failure to detect similar findings on autopsy in the pre-neuroleptic era.

The search for a consistent finding as obvious as brain atrophy had been ruled out by direct postmortem pathological examination in the pre-neuroleptic days. Weinberger and Kleinman (1986) estimated that by 1950 more than 250 studies had claimed to find a gross pathological defect in schizophrenia and "the overwhelming majority of these claims were either never replicated, unreplicable, or shown to be artifacts." The task proved so frustrating that "the effort stalled in the 1950s" (p. 52).

Based on pre-neuroleptic studies, Noyes and Kolb's *Modern Clinical Psychiatry* (1958, pp. 387–389) reviewed the failure to find a consistent neuropathological problem of any kind, let alone one so gross as atrophy of the brain, and concluded that "the present trend of opinion" attributes schizophrenia to "a faulty reaction to life situations." Again drawing on pre-neuroleptic studies, in *The*

American Handbook of Psychiatry (1959), Arieti found that hopes for a neuropathology of schizophrenia "have remained unfulfilled" (p. 488). Later textbooks would not bother to mention the possibility of gross pathological changes in the brains of schizophrenics, since the question had been laid to rest by the repeated failure to find any (e.g., Nicholi's *The Harvard Guide to Modern Psychiatry*, 1978). When the *Task Force on Tardive Dyskinesia* (APA, 1980) made a brief reference to the initial CT scan findings of brain atrophy in neuroleptic-treated patients, it remarked, "this observation is quite surprising as it is not consistent with earlier neurologic evaluations of chronic schizophrenics; it requires further critical evaluation" (p. 59).

In reply to the question "do schizophrenic patients have cerebral atrophy, dilated ventricles, neurological deficits, dementia?", Lidz (1981) observed that

> . . . [F]or 100 years investigators have reported a neuropathological or physiopathological cause of schizophrenia. The trouble is that no such findings have been replicated. If the patient suffers from dementia, the diagnosis is not schizophrenia. (p. 854)

Lidz went on to link the CT scan studies to other fervent attempts by the same investigators to find a physical basis for schizophrenia. Lidz instead recommended taking into account the impact of medications and shock treatment on the brain.

The failure to obtain consistent findings of cerebral atrophy on postmortem examination prior to the drug era strongly indicates that the recent findings of atrophy on CT scans are the result, not of schizophrenia, but of some new threat to the brain of schizophrenics. The only relevant new threat is the widespread use of the neuroleptic drugs which are already known to cause one brain disease, tardive dyskinesia.

Other reasons to doubt that schizophrenics have a deteriorating brain disorder have been reviewed by Manfred Bleuler in his book *The Schizophrenic Disorders* (1978). Bleuler's analysis provides some of the basis for the following summary. First, organic disorders characterized by brain atrophy and dementia are not usually reversible. To the contrary, they are most often progressive. Yet it is well-documented by Bleuler and others that many schizophrenic patients improve over time; up to one-third or one-half show significant recovery over the years.

Second, a dementing disorder, once it has progressed, would rarely if ever clear up spontaneously. Yet clinical observations abound concerning the ability of some schizophrenics to respond to acute emergencies, such as a fire in the hospital, with temporary displays of great clarity and responsibility. As Eugen Bleuler (1924) put it, "A highly excited, especially a confused, patient, may appear entirely normal from one minute to the next, only to fall back after hours or days into the previous condition" (p. 435).

Third, Manfred Bleuler reminds us, schizophrenic patients do not show

any classic signs of illness; they tend to become psychotic in the bloom of life. Over time, they do not tend to show the physical signs of deterioration usually associated with progressive neurological losses, such as premature aging, infirmity, seizures or neurological signs and symptoms. They die of the same diseases that afflict normal people. In following 208 patients for decades, Bleuler found that most of them remained in generally good health "in spite of advanced age" (p. 450).

Fourth, schizophrenic patients do not suffer from the typical signs of the earlier stages of a dementing disorder, including short-term memory problems. They are usually easy to distinguish, for example, from victims of Alzheimer's disease, multi-infarct dementia, and the dementias associated with Parkinson's disease, Huntington's chorea or multiple sclerosis. As M. Bleuler (1978) put it, "In the schizophrenic psychoses, however, the old intellectual competence, warmth, and emotional depth are discernable behind every serious state of morbidity, time and time again" (p. 453).

Fifth, schizophrenic communications suggest a very different process than the mental deterioration associated with a generalized brain disease leading to atrophy and dementia. The schizophrenic's intellectual functions do not deteriorate but rather become misdirected or psychologically and spiritually deranged. Schizophrenics often speak in unusual and complex metaphors dealing with psychological and spiritual conflicts over the meaning of love, life or God. Often they display enormous passion around the concept of their own presumed evil or exalted nature. Quite frequently only one or two specific false ideas (delusions) will appear in an otherwise normal mental life, and they will be defended with intellectual vigor and a high degree of mental acuity indicating that overall brain function itself is normal.

These points do not rule out the future discovery of a subtle biochemical cause for schizophrenia, but they do tend to rule out schizophrenia as the cause of a more gross neurological disorder leading to brain atrophy and dementia. There is almost no reason to believe that findings of brain atrophy and dementia are caused by schizophrenia, while there is considerable reason to indict neuroleptic therapy.

Other Causes of Mental Deterioration and Brain Damage

Mental deterioration in psychiatric patients, especially long-term mental hospital inmates, can be produced in a variety of ways, lending confusion to attempts to find definite causes in any particular case.

First, long-term stays in custodial mental hospitals and nursing homes can result in severe and partially irreversible losses in mental capacity on a purely psychosocial basis. Second, when psychoactive drugs suppress mental function over a long period of time, the individual may fail to develop or lose

intellectual function without damage to the brain. Those who deal with the developmentally retarded have been especially concerned about permanent maturational suppression resulting from neuroleptic therapy (extensive reviews in Kuehnel and Slama, 1984; Plotkin and Rigling, 1979; also see Breggin, 1983; Hartlage, 1965).

Third, mental losses and even brain disease in chronic psychiatric patients can result from a variety of covert physical causes, as Marsden (1976), Jellinck (1976) and others have noted. These causes include malnutrition and poor medical care through self-neglect or staff-neglect, head trauma from beatings, poor sanitation, and unrecognized chronic disease. Many chronic patients are extreme abusers of cigarettes, alcohol, caffeine, and street drugs.

Due to the passage of time and inadequate or lost records, many chronic patients may be the unsuspected recipients of one or more physical treatments that might cause brain damage, such as metrazol, insulin and electric shock; psychosurgery; and various toxic agents used in psychiatry in previous decades (Breggin, 1979, 1980a, 1980b, 1980c).

Many studies that have been cited as linking schizophrenia to brain damage or dementia (e.g., Brown et al., 1986; Jeste et al., 1980; Johnstone et al., 1976, 1978; Waddington and Youssef, 1986) have drawn their subjects from among chronic patients. They cannot truly separate the effects of schizophrenia from the many other stresses in the lives of these patients.

Discussion

The term dysmentia has been used occasionally in the literature when referring to the generalized brain disorder associated with prolonged exposure to the neuroleptics. This coinage seems unnecessary, since the patients in question typically have dementia as defined in DSM-III-R. That the dementia is iatrogenic in origin should not lead us to cloud the picture with a misleading euphemism.

At present, among some authorities, there is an apparent reluctance to give consideration to the increasing evidence that the neuroleptics cause persistent cognitive deficits, dementia and brain atrophy. For example, no textbook or other source brings together the broad spectrum of evidence compiled and analyzed in this review. It took psychiatry twenty years to recognize tardive dyskinesia as an iatrogenic illness, although it afflicted a large portion of hospitalized patients (Gelman, 1984, p. 1753). Resistance to dealing adequately with tardive dyskinesia continues (Brown and Funk, 1986; Wolf and Brown, 1987). An even greater reluctance to recognize tardive dementia and brain atrophy is likely, since the damage is still more catastrophic. Furthermore, it is easier to overlook cognitive defects and dementia than to ignore dyskinesias, and easier as well to mistakenly attribute the deficits to the patient's psychiatric disorder.

A final word of caution is necessary concerning agents such as clozapine that do not cause as many acute dyskinesias as do other neuroleptics. Clozapine produces a typical neuroleptic suppression and reactive supersensitivity in A10 dopaminergic neurons that project fibers into the meso-limbic system and cerebral cortex (Chiodo and Bunney, 1983). We should not be lulled into using such drugs more freely on the unconfirmed hope of causing fewer cases of tardive dyskinesia. Because of their specificity for A10 neurons, these neuroleptics are probably an equal or greater threat in producing persistent cognitive deficits, dementia and atrophy.

Conclusion and Suggestions

There is convincing evidence to indicate that long-term treatment with neuroleptic medication frequently produces persistent cognitive deficits, dementia and atrophy of the highest centers of the brain. In addition, there is some evidence that neuroleptics also produce a reactive tardive psychosis. There is little or no reason to believe that schizophrenia causes any of these adverse effects, especially dementia and brain atrophy.

The most consistent information on prevalence has been generated by brain scans which measure brain atrophy. We can estimate a prevalence of 10–40% among neuroleptic-treated patients, increasing with duration of treatment and age.

Even if the rate turns out to be in the lower range, we are confronted with an epidemic of iatrogenic brain damage of large proportions with serious consequences. Millions of patients, some with tardive dyskinesia and some without, have developed drug-induced damage to the higher brain and mental processes. The following steps are proposed.

First, the threat of neuroleptic-induced persistent cognitive deficits, tardive dementia and brain atrophy should be recognized in the PDR and in drug company advertising.

Second, along with TD, persistent cognitive deficits, tardive dementia and brain atrophy should become part of the standard informed consent warning given to patients and their families before the initiation of neuroleptic treatment. The general public should also be warned about the dangers of these widely used medications.

Third, psychiatric textbooks (Nicholi, 1988; Talbot et al., 1988) and reviews should no longer relegate discussions of the issue to sections on schizophrenia and instead place them in their appropriate context among neuroleptic side effects. If textbooks and reviews consider the subject controversial, they should nonetheless present the problem as one of great importance.

Fourth, future research should focus directly on neuroleptic-induced damage to the brain and mind.

Fifth, the health professions are obliged to find and implement methods for the rehabilitation of persons suffering from iatrogenic brain damage from all sources. As a part of this, the growing movement surrounding the rehabilitation of head injury victims should be extended to encompass patients injured by neuroleptic treatment.

Sixth, the threat of damage to the highest centers of the brain constitutes one more reason for a thoroughgoing re-evaluation of the assumptions behind the use of neuroleptics. Every effort must be made to curtail their use.

Seventh, more attention should be given to non-pharmacological treatment alternatives utilizing professionals (Breggin, 1980d; Karon and Vandenbos, 1981; Mosher and Burti, 1989; Walkenstein, 1972) as well as those utilizing self-help groups (Chamberlin, 1978; Low, 1950; Zinman et al., 1987).

Finally, the patient's right to refuse treatment, well-established in general medicine, should be more thoroughly extended to psychiatry. The best safeguard against the abusive prescription of medication is a voluntary psychiatry based on informed consent.

Never before in history has the psychiatric and medical profession been confronted with an iatrogenic tragedy of such proportions as the neuroleptic-induced epidemic of tardive dyskinesia, persistent cognitive deficits, tardive dementia, and brain atrophy. It is time for the profession to take responsibility for the damage it is inflicting on millions of patients throughout the world.

References

Abrahamson, I. (1935). *Lethargic Encephalitis*. New York: privately published.

Adams, R.D., and Victor, M. (1985). *Principles of neurology*. New York: McGraw-Hill.

Alexopoulos, G.S. (1979). Lack of complaints in schizophrenics with tardive dyskinesia. *Journal of Nervous and Mental Diseases, 167*, 125–127.

American College of Neuropsychopharmacology–Food and Drug Administration Task Force. (1973). A special report: Neurological syndromes associated with antipsychotic drug use. *Archives of General Psychiatry, 28*, 463–467.

American Psychiatric Association. (1980). *Task force report: Tardive dyskinesia*. Washington, D.C.: APA.

American Psychiatric Association. (1985). *Task force on tardive dyskinesia: Letter to the membership of the Association*. Washington, D.C.: APA.

American Psychiatric Association. (1987). *DSM-III-R*. Washington, D.C.: APA.

Andreasen, N.C. (1988). Brain imaging: Applications in psychiatry. *Science, 239*, 1381–1388.

Arai, N., Amano, N., Iseki, E., Yokoi, S., Saito, A., Takekawa, Y., and Misugi, K. (1987). Tardive dyskinesia with inflated neurons of the cellular dentate nucleus. *Acta Neuropathologica (Berlin), 73*, 38–42.

Arieti, S. (1959). Schizophrenia: Other aspects; psychotherapy. In S. Arieti (Ed.), *American handbook of psychiatry, I* (pp. 455–484). New York: Basic Books.

Bartels, M., and Themelis, J. (1983). Computerized tomography in tardive dyskinesia. Evidence of structural abnormalities in the basal ganglia system. *Archive für Psychiatrie and Nervenkrankheiten, 233*, 371–379.

Benes, F., Sunderland, P., Jones, B., LeMay, M., Cohen, B.M., and Lipinski, J.F. (1982). Normal ventricles in young schizophrenics. *British Journal of Psychiatry, 141*, 90–93.

Bergen, J.A., Eyland, E.A., Campbell, J.A., Jenkings, P., Kellehear, K., Richards, A., and Beumont, J.V. (1989). The course of tardive dyskinesia in patients on long-term neuroleptics. *British Journal of Psychiatry, 154,* 523–528.

Bleuler, E. (1924). *The textbook of psychiatry.* New York: Macmillan.

Bleuler, M. (1978). *The schizophrenic disorders: Long-term patient and family studies.* New Haven: Yale University Press.

Bracha, H.S., and Kleinman, J.E. (1986). Postmortem neurochemistry in schizophrenia. *Psychiatric Clinics of North America, 9,* 133–141.

Breggin, P.R. (1979). *Electroshock: Its brain-disabling effects.* New York: Springer.

Breggin, P.R. (1980a). Disabling the brain with electroshock. In M. Dongier and E. Wittkower (Eds.), *Divergent views in psychiatry* (pp. 247–271). Hagerstown, Maryland: Harper and Row.

Breggin, P.R. (1980b). Psychosurgery as brain-disabling therapy. In M. Dongier and E. Wittkower (Eds.), *Divergent views in psychiatry* (pp. 302–326). Hagerstown, Maryland: Harper and Row.

Breggin, P.R. (1980c). Brain-disabling therapies. In E. Valenstein (Ed.), *The psychosurgery debate: Scientific, legal and ethical perspectives* (pp. 467–505). San Francisco: W.H. Freeman.

Breggin, P.R. (1980d). *The psychology of freedom: Liberty and love as a way of life.* Buffalo: Prometheus.

Breggin, P.R. (1983). *Psychiatric drugs: Hazards to the brain.* New York: Springer.

Breggin, P.R. (1989a). Addiction to neuroleptics? [letter]. *American Journal of Psychiatry, 146,* 560.

Breggin, P.R. (1989b). Dr. Breggin replies [follow-up letter on addiction to neuroleptics]. *American Journal of Psychiatry, 146,* 1240.

Breggin, P.R. (1991, in press). *Toxic psychiatry.* New York: St. Martins.

Brill, H. (1975). Postencephalitic states or conditions. In S. Arieti (Ed.), *American handbook of psychiatry* (pp. 1163–1174). New York: Basic Books.

Brodal, A. (1969). *Neurological anatomy.* New York: Oxford University Press.

Brown, P., and Funk, S.C. (1986). Tardive dyskinesia: Barriers to the professional recognition of an iatrogenic disease. *Journal of Health and Social Behavior, 27,* 116–132.

Brown, R., Colter, N., Corsellis, J., Crow, T.J., Frith, C.D., Jagoe, R., Johnstone, E.C., and Marsh, L. (1986). Postmortem evidence of structural brain changes in schizophrenia. *Archives of General Psychiatry, 43,* 36–42.

Buchsbaum, M.S., Ingvar, D.H., Kessler, R., Waters, R.N., Cappelletti, J., van Kammen, D.P., King, A.C., Johnson, J.L., Manning, R.G., Flynn, R.W., Mann, L.S., Bunney, W.E., and Sokoloff, L. (1982). Cerebral glucography with positron tomography. *Archives of General Psychiatry, 39,* 251–259.

Burke, R.E., Fahn, S., Jankovic, J., Marsden, C.D., Lang, A.E., Gollomp, S., and Ilson, J. (1982). Tardive dystonia: Late-onset and persistent dystonia caused by antipsychotic drugs. *Neurology, 32,* 1335–1346.

Chamberlin, J. (1978). *On our own: Patient-controlled alternatives to the mental health system.* New York: Hawthorn.

Chiodo, L.A., and Bunney, B.S. (1983). Typical and atypical neuroleptics: Differential effects of chronic administration on the activity of A9 and A10 midbrain dopaminergic neurons. *Journal of Neuroscience, 3,* 1607–1619.

Chouinard, G., and Jones, B. (1980). Neuroleptic-induced supersensitivity psychosis: Clinical and pharmacologic characteristics. *American Journal of Psychiatry, 137,* 16–21.

Chouinard, G., and Jones, B. (1982). Neuroleptic-induced supersensitivity psychosis, the "hump course," and tardive dyskinesia. [letter]. *Journal of Clinical Psychopharmacology, 2,* 143–144.

Chouinard, G., Jones, B., and Annable, L. (1978). Neuroleptic-induced supersensitivity psychosis. *American Journal of Psychiatry, 135,* 1409–1410.

Christensen, E., Moller, J.E., and Faurbye, A. (1970). Neuropathological investigation of 28 brains from patients with dyskinesia. *Acta Psychiatrica Scandinavica, 46,* 14–23.

Cohen, D., and Cohen, H. (1986). Biological theories, drug treatments, and schizophrenia: A critical assessment. *Journal of Mind and Behavior, 7,* 11–36.

Coln, E.J. (1975). Long-lasting changes in cerebral neurons induced by drugs. *Biological Psychiatry, 10,* 227–264.

Crane, G. (1973). Clinical psychopharmacology in its 20th year. *Science, 181,* 124–128.

Csernansky, J., and Hollister, L.E. (1982). Probable case of supersensitivity psychosis. *Hospital Formulary, 17,* 395–399.

DeMeyer, M.K., Gilmore, R., DeMeyer, W.E., Hendrie, H., Edwards, M., and Franco, J.N. (1984). Third ventricle size and ventricular/brain ratio in treatment-resistant psychiatric patients. *Journal of Operational Psychiatry, 15,* 2–8.

DeMeyer, M.K., Gilmore, R., Hendrie, H., DeMeyer, W.E., and Franco, J.N. (1984). Brain densities in treatment resistant schizophrenic and other psychiatric patients. *Journal of Operational Psychiatry, 15,* 9–16.

Deniker, P. (1970). Introduction to neuroleptic chemotherapy into psychiatry. In F. Ayd and B. Blackwell (Eds.), *Discoveries in biological psychiatry* (pp. 155–164). Philadelphia: Lippincott.

Deniker, P. (1971, October 6). Deniker recounts to symposium discovery of chlorpromazine. *Psychiatric News,* p. 6.

DeVeaugh-Geiss, J. (1979). Informed consent for neuroleptic therapy. *American Journal of Psychiatry, 136,* 959–962.

DeWolfe, A.S., Ryan, J.J., and Wolf, M.E. (1988). Cognitive sequelae of tardive dyskinesia. *Journal of Nervous and Mental Disease, 176,* 270–274.

DiMascio, A., and Shader, R.I. (1970). *Clinical handbook of psychopharmacology.* New York: Science House.

Edwards, H. (1970). The significance of brain damage in persistent oral dyskinesia. *British Journal of Psychiatry, 116,* 271–275.

Famuyiwa, O.O., Eccleston, D., Donaldson, A.A., and Garside, R.F. (1979). Tardive dyskinesia and dementia. *British Journal of Psychiatry, 135,* 500–504.

Fann, W.E., Smith, R.C., Davis, J.M., and Domino, E.F. (Eds). (1980). *Tardive dyskinesia.* New York: SP Medical and Scientific Books.

Farde, L., Wiesel, F.-A., Halldin, C., and Sedvall, G. (1988). Central D2-dopamine receptor occupancy in schizophrenic patients treated with antipsychotic drugs. *Archives of General Psychiatry, 45,* 71–76.

Farkas, T., Wolf, A.P., Jaeger, J., Brodie, J.D., Christman, D.R., and Fowler, J.S. (1984). Regional brain glucose metabolism in chronic schizophrenia. *Archives of General Psychiatry, 41,* 293–300.

Fog, R., Pakkenberg, H., Juul, P., Bock, E., Jorgensen, O.S., and Andersen, J. (1976). High-dose treatment of rats with perphenazine enanthate. *Psychopharmacology, 50,* 305–307.

Forrest, F.M., Forrest, I.S., and Roizin, L. (1963). Clinical, biochemical and post mortem studies on a patient treated with chlorpromazine. *Revue Agressologie, 4,* 259–265.

Gelman, S. (1984). Mental hospital drugs, professionalism, and the constitution. *Georgetown Law Journal, 72,* 1725–1784.

Gerlach, J. (1975). Long-term effect of perphenazine on the substantia nigra in rats. *Psychopharmacologia (Berlin), 45,* 51–54.

Goetz, K.L., and van Kammen, D.P. (1986). Computerized axial tomography scans and subtypes of schizophrenia: A review of the literature. *Journal of Nervous and Mental Disease, 174,* 31–41.

Goldberg, E. (1985). Akinesia, tardive dysmentia, and frontal lobe disorder in schizophrenia. *Schizophrenia Bulletin, 11,* 255–263.

Goldberg, T.E., Weinberger, D.R., Berman, K.F., Pliskin, N.H., and Podd, M.H. (1987). Further evidence for dementia of the prefrontal type in schizophrenia. *Archives of General Psychiatry, 44,* 1008–1014.

Golden, C.J., Moses, J.A., Zelazowski, M.A., Graber, B., Zatz, L.M., Horvath, T.B., and Berger, P.A. (1980). Cerebral ventricular size and neuropsychological impairment in young chronic schizophrenics. *Archives of General Psychiatry, 37,* 619–623.

Grant, I., Adams, K.M., Carlin, A.S., Rennick, P.M., Judd, L.L., and Schooff, K. (1978). *The collaborative neuropsychological study of polydrug users.* Minneapolis: Unpublished paper delivered at the International Neuropsychological Association.

Grant, I., Adams, K.M., Carlin, A.S., Rennick, P.M., Judd, L.L., Schooff, K., and Reed, R. (1978). Organic impairment in polydrug users: Risk factors. *American Journal of Psychiatry, 135,* 178–184.

Grant, I., Adams, K.M., Carlin, A.S., Rennick, P.M., Lewis, J.L., and Schooff, K. (1978). The collaborative neuropsychological study of polydrug users. *Archives of General Psychiatry, 35,* 1063–1074.

Gross, H., and Kaltenback, E. (1968). Neuropathological findings in persistent hyperkinesia after

DeMeyer, M.K., Gilmore, R., DeMeyer, W.E., Hendrie, H., Edwards, M., and Franco, J.N. (1984). Third ventricle size and ventricular/brain ratio in treatment-resistant psychiatric patients. *Journal of Operational Psychiatry, 15,* 2–8.

DeMeyer, M.K., Gilmore, R., Hendrie, H., DeMeyer, W.E., and Franco, J.N. (1984). Brain densities in treatment resistant schizophrenic and other psychiatric patients. *Journal of Operational Psychiatry, 15,* 9–16.

Deniker, P. (1970). Introduction to neuroleptic chemotherapy into psychiatry. In F. Ayd and B. Blackwell (Eds.), *Discoveries in biological psychiatry* (pp. 155–164). Philadelphia: Lippincott.

Deniker, P. (1971, October 6). Deniker recounts to symposium discovery of chlorpromazine. *Psychiatric News,* p. 6.

DeVeaugh-Geiss, J. (1979). Informed consent for neuroleptic therapy. *American Journal of Psychiatry, 136,* 959–962.

DeWolfe, A.S., Ryan, J.J., and Wolf, M.E. (1988). Cognitive sequelae of tardive dyskinesia. *Journal of Nervous and Mental Disease, 176,* 270–274.

DiMascio, A., and Shader, R.I. (1970). *Clinical handbook of psychopharmacology.* New York: Science House.

Edwards, H. (1970). The significance of brain damage in persistent oral dyskinesia. *British Journal of Psychiatry, 116,* 271–275.

Famuyiwa, O.O., Eccleston, D., Donaldson, A.A., and Garside, R.F. (1979). Tardive dyskinesia and dementia. *British Journal of Psychiatry, 135,* 500–504.

Fann, W.E., Smith, R.C., Davis, J.M., and Domino, E.F. (Eds). (1980). *Tardive dyskinesia.* New York: SP Medical and Scientific Books.

Farde, L., Wiesel, F-A., Halldin, C., and Sedvall, G. (1988). Central D2-dopamine receptor occupancy in schizophrenic patients treated with antipsychotic drugs. *Archives of General Psychiatry, 45,* 71–76.

Farkas, T., Wolf, A.P., Jaeger, J., Brodie, J.D., Christman, D.R., and Fowler, J.S. (1984). Regional brain glucose metabolism in chronic schizophrenia. *Archives of General Psychiatry, 41,* 293–300.

Fog, R., Pakkenberg, H., Juul, P., Bock, E., Jorgensen, O.S., and Andersen, J. (1976). High-dose treatment of rats with perphenazine enanthate. *Psychopharmacology, 50,* 305–307.

Forrest, F.M., Forrest, I.S., and Roizin, L. (1963). Clinical, biochemical and post mortem studies on a patient treated with chlorpromazine. *Revue Agressologie, 4,* 259–265.

Gelman, S. (1984). Mental hospital drugs, professionalism, and the constitution. *Georgetown Law Journal, 72,* 1725–1784.

Gerlach, J. (1975). Long-term effect of perphenazine on the substantia nigra in rats. *Psychopharmacologia (Berlin), 45,* 51–54.

Goetz, K.L., and van Kammen, D.P. (1986). Computerized axial tomography scans and subtypes of schizophrenia: A review of the literature. *Journal of Nervous and Mental Disease, 174,* 31–41.

Goldberg, E. (1985). Akinesia, tardive dysmentia, and frontal lobe disorder in schizophrenia. *Schizophrenia Bulletin, 11,* 255–263.

Goldberg, T.E., Weinberger, D.R., Berman, K.F., Pliskin, N.H., and Podd, M.H. (1987). Further evidence for dementia of the prefrontal type in schizophrenia. *Archives of General Psychiatry, 44,* 1008–1014.

Golden, C.J., Moses, J.A., Zelazowski, M.A., Graber, B., Zatz, L.M., Horvath, T.B., and Berger, P.A. (1980). Cerebral ventricular size and neuropsychological impairment in young chronic schizophrenics. *Archives of General Psychiatry, 37,* 619–623.

Grant, I., Adams, K.M., Carlin, A.S., Rennick, P.M., Judd, L.L., and Schooff, K. (1978). *The collaborative neuropsychological study of polydrug users.* Minneapolis: Unpublished paper delivered at the International Neuropsychological Association.

Grant, I., Adams, K.M., Carlin, A.S., Rennick, P.M., Judd, L.L., Schooff, K., and Reed, R. (1978). Organic impairment in polydrug users: Risk factors. *American Journal of Psychiatry, 135,* 178–184.

Grant, I., Adams, K.M., Carlin, A.S., Rennick, P.M., Lewis, J.L., and Schooff, K. (1978). The collaborative neuropsychological study of polydrug users. *Archives of General Psychiatry, 35,* 1063–1074.

Gross, H., and Kaltenback, E. (1968). Neuropathological findings in persistent hyperkinesia after

neuroleptic long-term therapy. In A. Cerletti and F.J. Bove (Eds.), *The present status of psychotropic drugs* (pp. 474–476). Amsterdam: Excerpta Medica.

Gualtieri, C.T., and Barnhill, L.J. (1988). Tardive dyskinesia in special populations. In M.E. Wolf and A.D. Mosnaim (Eds.), *Tardive dyskinesia: Biological mechanisms and clinical aspects* (pp. 135–154). Washington, D.C.: American Psychiatric Press.

Gualtieri, C.T., Quade, D., Hicks, R.E., Mayo, J.P., and Schroeder, S.R. (1984). Tardive dyskinesia and other clinical consequences of neuroleptic treatment in children and adolescents. *American Journal of Psychiatry, 141,* 20–23.

Gualtieri, C.T., Schroeder, R., Hicks, R., and Quade, D. (1986). Tardive dyskinesia in young mentally retarded individuals. *Archives of General Psychiatry, 43,* 335–340.

Gunne, L.M., and Haggstrom, J. (1985). Experimental tardive dyskinesia. *Journal of Clinical Psychiatry, 46,* 48–50.

Gur, R.E., Resnick, S.M., Alavi, A., Gur, R.C., Caroff, S., Dann, R., Silver, F.L., Saykin, A.J., Chawluk, J.B., Kushner, M., and Reivich, M. (1987). Regional brain function in schizophrenia, I: A positron emission tomography study. *Archives of General Psychiatry, 44,* 119–125.

Gur, R.E., Resnick, S.M., Gur, R.C., Alavi, A., Caroff, S., Kushner, M., and Reivich, M. (1987). Regional brain function in schizophrenia, II: Repeated evaluation with positron emission tomography. *Archives of General Psychiatry, 44,* 126–129.

Guze, B.H., and Baxter, Jr., L.R. (1985). Neuroleptic malignant syndrome. *New England Journal of Medicine, 313,* 163–164.

Hartlage, L.C. (1965). Effects of chlorpromazine on learning. *Psychological Bulletin, 64,* 235–245.

Huber, S.J., and Paulson, G.W. (1985). The concept of subcortical dementia. *American Journal of Psychiatry, 142,* 1312–1317.

Hunt, J.I., Singh, H., and Simpson, G.M. (1988). Neuroleptic-induced supersensitivity psychosis: Retrospective study of schizophrenic inpatients. *Journal of Clinical Psychiatry, 49,* 258–261.

Hunter, R., Blackwood, W., Smith, M.C., and Cumings, J.N. (1968). Neuropathological findings in three cases of persistent dyskinesia following phenothiazine medication. *Journal of the Neurological Sciences, 7,* 263–273.

Hunter, R., Earl, C.J., and Thornicroft, S. (1964). An apparently irreversible syndrome of abnormal movements following phenothiazine medication. *Proceedings of the Royal Society of Medicine, 57,* 24–28.

Iacono, W.G., Smith, G.N., Moreau, M., Beiser, M., Fleming, J.A.E., Lin, T., and Flak, B. (1988). Ventricle and sulci size at onset of psychosis. *American Journal of Psychiatry, 145,* 820–824.

Itil, T.M., Reisberg, B., Huque, M., and Mehta, D. (1981). Clinical profiles of tardive dyskinesia. *Comprehensive Psychiatry, 22,* 282–290.

Ivnik, R.J. (1979). Pseudodementia in tardive dyskinesia. *Psychiatric Annals, 9,* 211–218.

Jancin, B. (1979, January). Could chronic neuroleptic use cause psychosis? *Clinical Psychiatry News,* p. 1.

Jellinck, E.H. (1976). Cerebral atrophy and cognitive impairment in chronic schizophrenia. *Lancet, 2,* 1202–1203.

Jellinger, K. (1977). Neuropathologic findings after neuroleptic long-term therapy. In L. Roizin, H. Shiraki, and N. Grčević (Eds.), *Neurotoxicology* (pp. 25–45). New York: Raven Press.

Jenner, P., and Marsden, C.D. (1983). Neuroleptics and tardive dyskinesia. In J.T. Coyle and S.J. Enna (Eds.), *Neuroleptics: Neurochemical, behavioral and clinical perspectives* (pp. 223–254). New York: Raven Press.

Jernigan, T.L., Zatz, L.M., Moses, J.A., and Cardellino, J.P. (1982). Computed tomography in schizophrenics and normal volunteers. I: Fluid volume. *Archives of General Psychiatry, 39,* 765–770.

Jeste, D.V., Iager, A.C., and Wyatt, R.J. (1986). The biology and experimental treatment of tardive dyskinesia and other related movement disorders. In P.A. Berger and H.K. Brodie (Eds.), *Biological psychiatry* (pp. 535–580). New York: Basic Books.

Jeste, D.V., Wagner, R.L., Weinberger, D.R., Reith, K.G.R., and Wyatt, R.J. (1980). Evaluation of CT scans in tardive dyskinesia. *American Journal of Psychiatry, 137,* 247–248.

Jeste, D.V., Wisniewski, A.A., and Wyatt, R.J. (1986). Neuroleptic-associated tardive syndromes. *Psychiatric Clinics of North America, 9,* 183–192.

Jeste, D.V., and Wyatt, R.J. (1982). *Understanding and treating tardive dyskinesia.* New York: Guilford Press.

Johnstone, E.C., Crow, T.J., Frith, C.D., Husband, J., and Kreel, L. (1976). Cerebral ventricular size and cognitive impairment in chronic schizophrenia. *Lancet*, 2, 924–926.

Johnstone, E.C., Crow, T.J., Frith, C.D., Stevens, M., Kreel, L., and Husband, J. (1978). The dementia of dementia praecox. *Acta Psychiatrica Scandinavica*, 57, 305–324.

Jones, B.D. (1985). Tardive dysmentia: Further comments. With commentary by S. Mukherjee and R.M. Bilder. *Schizophrenia Bulletin*, 11, 87–190.

Kalinowsky, H., and Hippius, H. (1969). *Pharmacological, convulsive and other somatic treatments in psychiatry.* New York: Grune and Stratton.

Karon, B., and Vandenbos, G. (1981). *The psychotherapy of schizophrenia: The treatment of choice.* New York: Jason Aronson.

Kelso, Jr., J.R., Cadet, J.L., Pickar, D., and Weinberger, D.R. (1988). Quantitative neuroanatomy in schizophrenia: A controlled magnetic resonance imaging study. *Archives of General Psychiatry*, 45, 533–541.

Koshino, Y., Hiramatsu, H., Isaki, K., and Yamaguchi, N. (1986). An electroencephalographic study of psychiatric inpatients with antipsychotic-induced tardive dyskinesia. *Clinical electroencephalography*, 17, 30–35.

Krishnan, K.R.R., Ellinwood, Jr., E.H., and Rayasam, K. (1988). Tardive dyskinesia: Structural changes in the brain. In M.E. Wolf and A.D. Mosnaim (Eds.), *Tardive dyskinesia: Biological mechanisms and clinical aspects* (pp. 165–178). Washington, D.C.: American Psychiatric Press.

Kuehnel, T.G., and Slama, K.M. (1984). Guidelines for the developmentally disabled. In K.M. Tardiff (Ed.), *The psychiatric uses of seclusion and restraint* (pp. 87–102). Washington, D.C.: American Psychiatric Press.

Lawson, W.B., Waldman, I.N., and Weinberger, D.R. (1988). Schizophrenic dementia: Clinical and computed axial tomography correlates. *Journal of Nervous and Mental Disease*, 176, 207–212.

Lehmann, H.E. (1975, Summer). Psychopharmacological treatment of schizophrenia. *Schizophrenia Bulletin*, pp. 25–45.

Levenson, J.L. (1985). Neuroleptic malignant syndrome. *American Journal of Psychiatry*, 142, 1137–1145.

Lidz, T. (1981). Psychoanalysis, schizophrenia, and the art of book reviewing [letter]. *American Journal of Psychiatry*, 138, 854.

Lohr, J.B., and Bracha, H.S. (1988). Association of psychosis with movement disorders in the elderly. *Psychiatric Clinics of North America*, 11, 61–68.

Low, A.A. (1950). *Mental health through will-training.* Winnetka, Illinois: Willett.

Lund, D.S. (1989, May). Tardive dyskinesia lawsuits on increase. *Psychiatric Times*, p. 1.

Lyon, K., Wilson, J., Golden, C.J., Graber, B., Coffman, J.A., and Bloch, S. (1981). Effects of long-term neuroleptic use on brain density. *Psychiatric Research*, 5, 33–37.

Mackiewicz, J., and Gershon, S. (1964). An experimental study of the neuropathological and toxicological effects of chlorpromazine and reserpine. *Journal of Neuropsychiatry*, 5, 159–169.

Marsden, C.D. (1976). Cerebral atrophy and cognitive impairment in chronic schizophrenia. *Lancet*, 2, 1079.

Matheson Commission (1939). *Epidemic encephalitis.* New York: Columbia University Press.

Matsubara, T., and Hagihara, B. (1968). Action mechanism of phenothiazine derivatives on mitochondrial respiration. *Journal of Biochemistry*, 63, 156–164.

Mosher, L.R., and Burti, L. (1989). *Community mental health: Principles and practice.* New York: Norton.

Mukherjee, S. (1984). Tardive dysmentia. A reappraisal. *Schizophrenia Bulletin*, 10, 151–152.

Mukherjee, S., and Bilder, R.M. (1985). Commentary. *Schizophrenia Bulletin*, 11, 189–190.

Myslobodsky, M. (1986). Anosognosia in tardive dyskinesia: "Tardive dysmentia" or "tardive dementia"? *Schizophrenia Bulletin*, 12, 1–6.

Myslobodsky, M.S., Tomer, R., Holden, T., Kempler, S., and Sigol, M. (1985). Cognitive impairment in patients with tardive dyskinesia. *Journal of Nervous and Mental Disease*, 173, 156–160.

Neuroleptics to cary FDA class warning. (1985, May 17). *Psychiatric News*, p. 1.

Nicholi, A.M. (Ed.). (1978). *The Harvard guide to modern psychiatry.* Cambridge, Massachusetts: Belknap.

Nicholi, A.M. (Ed.). (1988). *The new Harvard guide to psychiatry.* Cambridge, Massachusetts: Belknap.

Nielsen, E.G., and Lyon, M. (1978). Evidence for cell loss in corpus striatum after long-term treatment with a neuroleptic drug (flupenthixol) in rats. Psychopharmachology, 59, 85–89.

Noyes, A.P., and Kolb, L.C. (1958). Modern clinical psychiatry (Fifth Edition). Philadelphia: Saunders.

Nyback, H., Weisel, F.-A., Berggren, B.-M., and Hindmarsh, T. (1982). Computed tomography of the brain in patients with acute psychoses and healthy volunteers. Acta Psychiatrica Scandinavica, 65, 403–414.

Pakkenberg, H., Fog, R., and Nilakantan, B. (1973). The long-term effect of perphenazine enanthate on the rat brain. Some metabolic and anatomical observations. Psychopharmacologia (Berlin), 29, 329–336.

Paulson, G.M. (1959). Phenothiazine toxicity, extrapyramidal seizures, oculo-gyric crises. Journal of Mental Science, 105, 798–802.

PDR: Physicians' Desk Reference. (1973). Oradell, New Jersey: Medical Economics.

PDR: Physicians' Desk Reference. (1978). Oradell, New Jersey: Medical Economics.

Plotkin, R., and Rigling, K. (1979). Invisible manacles: Drugging mentally retarded people. Stanford Law Review, 31, 637–678.

Popova, E.N. (1967). On the effect of some neuropharmacological agents on the structure of neurons of various cyto-architectonic formations. Journal für Hirnforschung, 9, 71–89.

Roizin, L., True, C., and Knight, M. (1959). Structural effects of tranquilizers. Research Publications of the Association for Research in Nervous and Mental Disease, 37, 285–324.

Romasenko, V.A., and Jacobson, I.S. (1969). Morpho-histochemical study of the action of trifluoperazine on the brain of white rats. Acta Neuropathologica (Berlin), 12, 23–32.

Rosenbaum, A.H. (1979). Pharmacotherapy of tardive dyskinesia. Psychiatric Annals, 9, 205–210.

Rupniak, N.M.J., Jenner, P., and Marsden, C.D. (1983). The effect of chronic neuroleptic administration on cerebral dopamine receptor function. Life Sciences, 32, 2289–2311.

Sabuncu, N., Sabacin, S., Saygill, R., Kumral, K., and Ornek, T. (1977). Cortical atrophy caused by long-term therapy with antidepressive and neuroleptic drugs: A clinical and experimental study. In L. Roizin, H. Shiraki, and N. Drcevic (Eds.), Neurotoxicology (pp. 149–158). New York: Raven Press.

Schulz, S.C., Koller, M.M., Kishore, P.R., Hamer, R.M., Gehl, J.J., and Friedel, R.O. (1983). Ventricular enlargement in teenage patients with schizophrenic spectrum disorder. American Journal of Psychiatry, 14, 1591–1595.

Sellinger, O.Z., and Azcurra, J.M. (1970). The breakdown of polysomes and the stimulation of protein synthesis in cerebral mechanisms of defense against seizufes. In A. Lajtha (Ed.), Protein metabolism of the nervous system (pp. 519–532). New York: Plenum.

Shelton, R.C., Karson, C.N., Doran, A.R., Pickar, D., Bigelow, L.B., and Weinberger, D.R. (1988). Cerebral structural pathology in schizophrenia: Evidence for selective prefrontal cortical defect. American Journal of Psychiatry, 145, 154–163.

Sheppard, G., Gruzelier, J., Manchanda, R., Hirsch, S.R., Wise, R., Frackowiak, R., and Jones, T. (1983). O positron emission tomography scanning of predominantly never-treated acute schizophrenic patients. Lancet, 24, 1448–1452.

Smith, J.M., Kuchorski, M.A., Oswald, W.T., and Waterman, M.A. (1979). A systematic investigation of tardive dyskinesia inpatients. American Journal of Psychiatry, 136, 918–922.

Sovner, R., DiMascio, A., Berkowitz, D., and Randolph, P. (1978). Tardive dyskinesia and informed consent. Psychosomatics, 19, 172–177.

Struve, F.A., and Willner, A.E. (1983). Cognitive dysfunction and tardive dyskinesia. British Journal of Psychiatry, 143, 597–600.

Supersensitivity psychosis thought to often follow withdrawal of neuroleptics after extended use. (1983, September 1). Psychiatric News, p. 39.

Talbott, J.A., Hales, R.E., and Yudofsky, S.C. (Eds.). (1988). Textbook of psychiatry. Washington, D.C.: American Psychiatric Press.

Tanaka, Y., Hazama, H., Kawahara, R., and Kobayashi, K. (1981). Computerized tomography of the brain in schizophrenic patients. Acta Psychiatrica Scandinavica, 63, 191–197.

Teller, D.N., and Denber, H.C.B. (1970). Mescaline and phenothiazines: Recent studies on subcellular localization and effects upon membranes. In A. Lajtha (Ed.), Protein metabolism of the nervous system (pp. 685–698). New York: Plenum.

van Sweden, B. (1984). Neuroleptic neurotoxicity: Electro-clinical aspects. *Acta Neurologica Scandinavica, 69,* 137–146.

Waddington, J.L., and Youssef, H.A. (1986). Late onset involuntary movements in chronic schizophrenia: Relationships of "tardive" dyskinesia to intellectual impairment and negative symptoms. *British Journal of Psychiatry, 149,* 616–620.

Wade, J.B., Taylor, M.A., Kasprisin, A., Rosenberg, S., and Fiducia, D. (1987). Tardive dyskinesia and cognitive impairment. *Biological Psychiatry, 22,* 393–395.

Walkenstein, E. (1972). *Beyond the couch.* New York: Crown.

Weinberger, D.R. (1984). Computed tomography (CT) findings in schizophrenia: Speculation on the meaning of it all. *Journal of Psychiatric Research, 18,* 477–490.

Weinberger, D.R., Cannon-Spoor, E., Potkin, S.G., and Wyatt, R.J. (1980). Poor premorbid adjustment and CT scan abnormalities in chronic schizophrenia. *American Journal of Psychiatry, 137,* 1410–1414.

Weinberger, D.R., DeLisi, L.E., Perman, G.P., Targum, S., and Wyatt, R.J. (1982). Computed tomography in schizophreniform disorder and other acute psychiatric disorders. *Archives of General Psychiatry, 39,* 778–783.

Weinberger, D.R., and Kleinman, J.E. (1986). Observations on the brain in schizophrenia. In A. Frances and R. Hales (Eds.), *American Psychiatric Association Annual Review* (Volume 5, pp. 42–67). Washington, D.C.: American Psychiatric Association.

Weinberger, D.R., Torrey, E.F., Neophytides, H.N., and Wyatt, R.J. (1979). Lateral ventricular enlargement in chronic schizophrenia. *Archives of General Psychiatry, 36,* 735–739.

White, F.J., and Wang, R.Y. (1983). Differential effects of classical and atypical antipsychotic drugs on A9 and A10 dopamine neurons. *Science, 221,* 1054–1056.

Wildi, E., Linder, A., and Costoulas, G. (1967). Schizophrenia and involutional cerebral senility. *Psychiatry and Neurology, 154,* 1–26.

Wilson, I.C., Garbutt, J.C., Lanier, C.F., Moylan, J., Nelson, W., and Prange, Jr., A.J. (1983). Is there a tardive dysmentia? *Schizophrenia Bulletin, 9,* 187–192.

Wojcik, J.D., Gelenberg, A.J. LaBrie, R.A., and Mieske, M. (1980). Prevalence of tardive dyskinesia in an outpatient population. *Comprehensive Psychiatry, 21,* 370–380.

Wolf, M.E., and Brown, P. (1987). Overcoming institutional and community resistance to a tardive dyskinesia management program. *Hospital and Community Psychiatry, 38,* 65–68.

Wolf, M.E., Ryan, J.J., and Mosnaim, A.D. (1982). Organicity and tardive dyskinesia. *Psychosomatics, 23,* 475–480.

Wolkin, A., Angrist, B., Wolf, A., Brodie, J.D., Wolkin, B., Jaeger, J., Cancro, R., and Rotrosen, J. (1988). Persistent cerebral metabolic abnormalities in chronic schizophrenia determined by positron emission tomography. *American Journal of Psychiatry, 142,* 564–571.

Wolkin, A., Jaeger, J., Brodie, J.D., Wolf, A., Fowler, J., Rotrosen, J., Gomez-Mont, F., and Cancro, R. (1985). Low frontal glucose utilization in chronic schizophrenia: A replication study. *American Journal of Psychiatry, 145,* 251–253.

Yassa, R., and Jones, B. (1985). Complications of tardive dyskinesia: A review. *Psychosomatics, 26,* 305–313.

Yassa, R., Nastase, C., Camille, Y., and Belzile, L. (1988). Tardive dyskinesia in a psychogeriatric population. In M.E. Wolf and A.D. Mosnaim (Eds.), *Tardive dyskinesia: Biological mechanisms and clinical aspects* (pp. 123–134). Washington, D.C.: American Psychiatric Press.

Zec, R.F., and Weinberger, D.R. (1986). Relationship between CT scan findings and neuropsychological performance in chronic schizophrenia. *Psychiatric Clinics of North America, 9,* 49–61.

Zinman, S., Howie the Harp, and Budd, S. (1987). *Reaching across: Mental health clients helping each other.* Riverside, California: California Network of Mental Health Clients.