Tardive Dyskinesia: Biological Mechanisms and Clinical Aspects

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Chapter 10

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A remarkable change has taken place in the past 10 years, a change that coincides with physicians' growing concern over the problem of tardive dyskinesia (TD). The prescription of neuroleptic drugs had declined markedly for mentally retarded patients and child psychiatry patients. At one time, not long ago, neuroleptics like thioridazine and haloperidol were widely prescribed to children who were hyperactive or emotionally unstable; neuroleptics were virtually the only psychotropic prescribed for retarded people with any behavior problem at all. This practice seems to have changed. Neuroleptic treatment is considered by enlightened practitioners in the field to be an extraordinary intervention, one that is not to be undertaken for mild disorders where other treatments may be more effective. For children, the only acceptable indications are schizophrenia and severe cases of Tourette's syndrome (TS) (1). For retarded people, the only accepted indications are schizophrenia, TS, and some severe cases of self-injurious behavior (2, 3).

The reasons for this change of view are:

1. The realization that only limited therapeutic success is to be gained from neuroleptic prescription in these populations;
2. The discovery of intelligent alternatives to neuroleptics—the psychotropic anticonvulsants, calcium channel blockers, beta-blockers, and lithium; and
3. The discovery of high rates of TD in these patient groups (3).

A third group of patients, victims of closed head injury (CHI) with "neurobehavioral sequelae" are a relatively new patient population. In contrast to child psychiatry and mental retardation, the field of CHI does not have a history of neuroleptic overuse; the prevailing attitude in that young and emerging field has always been

one of "therapeutic nihilism"—emphasizing rehabilitation, deemphasizing pharmacology. CHI patients represent a third group for whom neuroleptics are "relatively contraindicated" (4).

TARDIVE DYSKINESIA IN CHILDREN

Anecdotal reports of neuroleptic-induced movement disorders have appeared in the literature for quite some time (5, 6). Systematic investigations concerned with the epidemiology and course of TD in children are a more recent phenomena, however (7). The reasons for this delayed interest are myriad, derived perhaps from the notion that children were relatively safe from irreversible neuroleptic effects (8); that small neuroleptic doses posed few risks; or that in severe psychiatric disease, no alternative treatments were available or considered. The present application of TD as a public health problem has helped to revise this attitude.

Clinical investigations of TD follow a predictable trend. Early studies focused on case descriptions, and then came studies of incidence and prevalence. Subsequent epidemiologic work focuses on prevention and reducing morbidity. Prevention studies try to define at-risk populations; try to solidify diagnostic processes and the justification for neuroleptic treatment; emphasize trial drug withdrawals and low-dose treatment techniques; and try to find alternatives to neuroleptic treatment. The development of sophisticated "at risk" strategies and of alternative treatment approaches has been complicated in child psychiatry by relative weakness of neuropsychiatric research in the field. Relative unawareness of advances in biological and psychopharmacological treatments by child psychiatrists and pediatricians has probably compounded the problem of TD in this population.

Part of the difficulty, however, lies in the complexity of TD. Attempts to map the pathophysiology of TD have yielded ambiguous results. Neuroleptic-induced dopaminergic supersensitivity is too simple a model and fails to explain the existence of persistent dyskinesia. Other ambiguous factors include the varying effects of cholinergic drugs, the occasional favorable responses to dopamine agonists (9), and inconsistent results from attempts to manipulate the gamma-aminobutyric (GABA) receptor (10).

In addition, the variability of dyskinetic movements in response to manipulation of neuroleptics confounds the issue. Breakthrough dyskinesias seem different from withdrawal dyskinesias, mainly in terms of persistence and perhaps severity (5, 7, 11). In children, the unanswered question is why there is a preponderance of withdrawal or transient dyskinesias relative to the incidence of persistent dyski-

nesias. The simplest explanation is that cumulative exposure in children is rarely sufficient to induce a persistent TD syndrome. But that is only a hypothetical explanation. The possibility of an interaction between age and neuroleptic toxicity cannot be discounted; such an interaction would also explain why, at the other end of the spectrum, elderly people appear to be more vulnerable to severe and persistent TD.

The description of childhood TD has undergone an evolution. The repertoire of movements was initially described as more centrifugal in distribution, involving predominantly peripheral dystonic and choreiform-like movements (12). With greater systematic experience, this topographical distribution has been modified to overlap the pattern of adult TD (5, 7).

Various neurochemical studies of childhood psychopathology intimate a high incidence of dopaminergic dysfunction (11, 13). The introduction of neuroleptics may not only affect immediate risks but potential, long-term maturational changes. Reduced serum estrogen levels in prepubertal children may also have some undefined effect on dopamine neurotransmission and receptor sensitivity (14).

One additional question remains unanswered. What are the long-term effects of disruption of neurotransmittor systems in the maturing organism? Does the fact that TD in children is usually transient actually mean that they have really escaped a debilitating disorder? The question is whether early neuroleptic exposure may lead to a latent weakness in dopamine systems such that degenerative changes will appear in later years. Precedents exist: kindling effects in temporal lobe epilepsy, postpoliomyelitis deterioration, postencephalitic Parkinson's disease, and late-onset psychosis following CHI.

TD in the Mentally Retarded

Although neuroleptics are commonly prescribed for developmentally disabled patients, they are usually misapplied. Most surveys of large populations have revealed similar findings:

1. Neuroleptic use ranges from 19 percent to roughly 25 percent of institutional and community-based patients. Ten years ago the rate was about 50 percent (2).
2. Most patients lack a clear psychiatric diagnosis (less than 6 percent in institutions, less than 3 percent in community settings (15, 16).
3. Many patients are treated with relatively large doses or in situations involving polypharmacy (15, 17, 18).

4. Many treatment programs are carried on for extended periods of time without careful monitoring (3, 5, 17, 18).

These practices have created a large pool of patients who are at high risk for TD. On the basis of available data, rates for TD may exceed 34 percent of patients on chronic neuroleptic treatments (3, 5). This figure falls within the ranges associated with neuroleptic treatment in nonhandicapped psychiatric populations (19). It is not clear whether severe or persistent dyskinesias are more common in the developmentally disabled.

Several risk factors may be involved in the development of TD in the developmentally disabled. At this point, total cumulative dose appears to correlate most clearly with the emergency of TD (3, 7, 10). The prescribing patterns noted earlier may surely heighten this factor. A higher incidence of encephalopathy associated with severe developmental disorders may also influence vulnerability (3, 20).

The retarded population displays an increased rate of behavioral abnormalities such as hyperactivity, aggression, self-injurious behavior, and stereotypies, as well as high rate of institutionalization. It is likely that rates of neuroleptic treatment are high, especially by poorly trained physicians who do not appreciate the availability of alternative treatments. In many of these clinical situations, neuroleptics have been considered front-line treatment (17).

As the level of intellectual function and communication skills diminishes, the reliability of psychiatric diagnoses tends to follow suit (21). Low IQ may also affect a physician's assessment of emerging extrapyramidal symptoms, in particular, akathisia. A patient's poor verbal skills combined with an unusual akathisia may prompt the unwitting physician to increase the neuroleptic dose. Such a pharmacologic tail-chase will only increase the patient's eventual risk of developing TD by guaranteeing continued neuroleptic use at increasing doses, while potential warning signs of TD are suppressed. More troublesome is the relative lack of reported breakthrough dyskinesias on maintenance neuroleptics (3). These emergent symptoms (particularly vermicular tongue movements and choreiform hand movements) alert clinicians to the presence of TD. Such harbinger symptoms may signal the need to reduce or to discontinue neuroleptics and presumably reduce the risk for more severe persistent dyskinesia. Lacking this signal, clinicians must episodically reduce the dose of neuroleptics. Even with this approach, dyskinetic movements may emerge only after a lag of between 1 to 4 weeks (3, 7). The mentally retarded patient may have some difficulty tolerating this lag. Many patients will show significant behavior deterioration

off the drug, even if it has not been particularly beneficial in the first place, with dramatic increases in premedication behaviors, or the emergence of new "rebound" symptoms (3, 22–24). This vulnerability requires special strategies for management, intense environmental structure, behavioral management, and sometimes the resumption of the offending neuroleptic drug.

COURSE OF TARDIVE DYSKINESIA IN MENTALLY RETARDED ADULTS

A more critical concern, once tardive dyskinesia has been diagnosed, is the course of tardive dyskinesia in individuals who continue on neuroleptic treatment.

Does the resumption of neuroleptic treatment necessarily mean that the disorder will grow worse, or is the course of the disorder variable or idiosyncratic? The literature is silent on this point, since most tardive dyskinesia research has been done in patients examined at a single point in time. Further, if neuroleptic withdrawal is not a part of a patient evaluation for tardive dyskinesia, the masking effect of maintenance neuroleptic treatment may obscure the proper assessment of severity of dyskinesia. The only prospective longitudinal study of tardive dyskinesia of which the authors are aware has not yet gathered data sufficient to address the question of course (25). In one study of TD patients maintained off neuroleptics, no appreciable symptom reduction was noted after 12 months, and the authors concluded that the disorder is for the most part unremitting (26). This is at variance with clinical experience that seems to suggest that improvement in symptoms of TD may sometimes occur, even years after the disorder is originally diagnosed. There is one study from a Danish sample, not yet published, that suggests that TD may remit even in patients who continue a neuroleptic treatment (D. Casey, personal communication, 1984). In a 2-year follow-up study by Yassa, Nair, and Schwartz (27), most TD patients (66 percent) showed no change, while equal proportions improved (18 percent) or worsened (16 percent). However, neuroleptic masking effects may compromise this finding. Paulson, Rizvi, and Crane (28) reexamined institutionalized retarded children 4 years after an original drug withdrawal trial and found no change in TD in six children; four displayed more severe dyskinesias, and five had improved. However, the patients' medication status in the interval between observations and during the follow-up period was not stated.

One aspect of our research was to measure the occurrence of dyskinetic movements during a second neuroleptic drug withdrawal in 12 mentally retarded individuals who had been involved in a similar

withdrawal 3 years previously (7). It was hypothesized that the severity of dyskinetic movements in the second withdrawal would increase following continued treatment and would be associated with each subject's increment in lifetime cumulative dose of neuroleptic drug.

Subjects were eight male and four female profoundly retarded, long-term residents of a state mental retardation facility who had participated in a previous study (7). The 12 residents were on the average 30.7 years old (range = 22–41 years), had mean IQs of 11 (range = 10–23) and mean Vineland Social Quotients of 10.2 (range = 4–25). All subjects had a continuous, lengthy neuroleptic history prior to the original study and did not have other conditions (for example, cerebral palsy) which might produce abnormal involuntary movements. At the start of the original and the present studies respectively, 12 of 12 and 8 of 12 subjects were receiving neuroleptic medication. Each resident's cumulative neuroleptic history before the first study and average daily dose in a comparable period before each study is presented in Table 1. The medications were prescribed for aberrant behaviors such as aggression, self-injury, property destruction, or noncompliance. Each subject lived in a 24-hour residential treatment unit with 15 to 25 similarly functioning individuals and received several hours of adaptive skill training each day. Prior to the second withdrawal, four subjects were receiving thioridazine, three haloperidol, one thiothixene, and four not any psychoactive medication at all. All subjects were healthy and on no intercurrent medication.

Three psychologists rated location and severity of dyskinetic movements using the Abnormal Involuntary Movement Scale (AIMS) (29). Raters were trained in a fashion similar to a previous study, using videotapes, "live" observation of individuals with dyskinetic movements, and discussion of practice ratings to clarify disagreements. Practice ratings continued until all three observers independently and simultaneously agreed on the specific location of each subject's dyskinetic movements with no difference greater than one unit of severity (none, minimal, mild, moderate, severe). Reliability was also checked with a rater (the first author) who had conducted examinations in the original study (7). The four raters agreed on location and severity of 93 percent of items with a difference of 1 or less and the remaining 7 percent of items showed a difference of 2. The three psychologists showed agreement in this observation similar to that initially established.

During each weekly examination, the rater and the subject were alone in a quiet room. The AIMS examination procedure (29) was

followed as closely as the adaptive level of the subject permitted. Raters were assigned randomly to observe subjects each week and were not aware of any subject's current or past medication status. After a variable baseline, subjects were withdrawn from medication in a double-blind fashion. After withdrawal subjects were off med-

Table 1. Occurrence of Dyskinetic Movements During a Second Neuroleptic Drug Withdrawal in 12 Mentally Retarded Individuals

Group, subject	Sex	Cumulative dose before first study[a] (g)	Mean daily dose at withdrawal (mg)	Mean total AIMS score
Group 1: Medication increased				
2	F	5,804	a. 1,000	a. 2.2
			b. 2,750	b. 7.0
3	M	562	a. 75	a. 0.6
			b. 200	b. 5.0
7	F	4,177	a. 150	a. 2.8
			b. 190	b. 4.0
11	M	62	a. 75	a. 0.0
			b. 237	b. 0.9
Group 2: Medication decreased				
1	M	3,956	a. 60	a. 17.8
			b. 40	b. 11.1
8	F	3,474	a. 300	a. 7.3
			b. 130	b. 4.5
10	M	1,133	a. 225	a. 0.6
			b. 137	b. 0.0
12	F	3,209	a. 750	a. 12.4
			b. 683	b. 4.0
Group 3: Medication discontinued				
4	M	45	a. 50	a. 0.0
			b. 0	b. 0.1
5	M	11,188	a. 300	a. 7.5
			b. 0	b. 5.5
6	M	316	a. 150	a. 0.0
			b. 0	b. 1.2
9	F	160	a. 75	a. 0.0
			b. 0	b. 0.0

Note. AIMS—Abnormal Involuntary Movement Scale. a. = first withdrawal. b. = second withdrawal.

[a]Chlorpromazine equivalent.

ication from 1 to 15 weeks. Subjects 10 and 11 were not withdrawn from medication because of staff concerns about aberrant behavior.

The criteria for diagnosing TD were those recommended by Gualtieri et al (30). Three additional cases of TD were noted in the second withdrawal (Subjects 3, 6, and 11) in addition to the six cases reported in the original trial (Subjects 1, 2, 5, 7, 8, and 12). Five subjects (2, 3, 6, 7, and 11) displayed more severe dyskinetic movements after the second withdrawal. These subjects, except for Subject 6, received neuroleptics at a mean daily oral dose greater than a similar period prior to the first withdrawal (see Table 1). Subject 6 was not returned to a neuroleptic after the first withdrawal but showed a small increase in dyskinetic movements. Four subjects (1, 5, 8, and 12) displayed less severe movements during the second withdrawal; these individuals received lower doses of neuroleptic medication between studies. Three subjects (4, 9, and 10) did not display dyskinetic movements in either withdrawal trial.

These withdrawal data were categorized into three groups based on neuroleptic status between studies: medication increased (Group 1), decreased (Group 2), and discontinued (Group 3). Mean total AIMS data were analyzed using a 3×2 analysis of coveriance (Group $\times$ Trial) with cumulative lifetime neuroleptic dose prior to the first withdrawal as the covariate. This analysis, which was statistically controlled for cumulative dose, was not significant for main group effects but yielded the following for the interaction terms: $F(2, 8) = 3.81$, $p < .07$. A post-hoc Newman-Keuls analysis revealed significant differences for the following comparisons: Group 2, Trial 1 versus Group 1, Trial 1 ($p < .01$); Group 2, Trial 1 versus Group 1, Trial 2 ($p < .05$); Group 2, Trial 1 versus Group 3, Trial 1 ($p < .05$); Group 2, Trial 1 versus Group 3, Trial 2 ($p < .01$); and Group 2, Trial 1 versus Group 2, Trial 2 ($p < .05$). Salient aspects of the Newman-Keuls comparisons are as follows: 1) Group 2, the individuals with the highest cumulative neuroleptic history, had significantly more severe dyskinetic movements than Groups 1 or 3 during the first trial. 2) Group 2 showed a significant decrease in severity of movements between withdrawal trials. 3) Differences between groups during the second withdrawal trial were nonsignificant. And 4) Group 1 was the only group that showed an increase between trials in severity of dyskinesia with a trend toward statistical significance.

The results of this second withdrawal trial indicated that 9 of 12 individuals met the tardive dyskinesia movement criteria, 3 more than in the first trial. Within-subject comparisons revealed that five subjects displayed more severe movements, four subjects displayed

movements that were less severe, and three subjects did not display any dyskinetic movements in the second or in the first withdrawal trial.

One may draw the following conclusions from these results. First, dyskinetic movements may persist over time regardless of change in neuroleptic status. This was evident in all seven subjects who were returned to a neuroleptic after the first withdrawal study. Subjects 5 and 6 who displayed dyskinesias in the first withdrawal and were not returned to a neuroleptic still showed movements in the second study. These results replicate the frequently reported finding that neuroleptic-induced dyskinesias persist over time (31). Second, severity of dyskinetic movements may change over time in the same direction as the increase or decrease of neuroleptic dosage, independent of prior cumulative exposure. Group 1 subjects, with the lowest prestudy 1 cumulative dose history, received increased dosages of neuroleptics between studies and were the only group to show an increase in the severity of dyskinetic movements. Subjects in Group 2 received lower doses of neuroleptics between studies and showed a decrease in severity of movements. While these results do not necessarily contradict the importance of lifetime cumulative dose as predictor for occurrence of tardive dyskinesia (7, 31), the data do suggest that severity of dyskinetic movements at a specific point in time may be related more to the recent history of neuroleptic dose rather than to a lifetime exposure or duration of treatment. They represent indirect support of a dopamine supersensitivity hypothesis of TD (10).

It is not possible to draw strong conclusions from a study of only 12 patients. Further, data from mentally retarded patients may not be generalized to patients of normal intelligence; the prevalence of TD, its severity, and perhaps also its course may be more problematic in the former group (7). This application of a serial neuroleptic withdrawal method is unique in the TD literature, however, and demands careful attention. TD may not remit spontaneously in retarded patients, and continued treatment, especially with high doses, may make it worse. On the other hand, if continued neuroleptic treatment is necessary, the application of low doses may prevent the aggravation of TD.

WHY NEUROLEPTIC USE SHOULD BE AVOIDED IN CLOSED HEAD INJURY

Each year, there are more than 800,000 serious cases of CHI in the United States. Ninety percent of the victims survive their injury (only 10 percent survived 10 years ago). Fifty to ninety thousand people

suffer injuries that leave severe residual symptoms or deficits. Since the majority of CHI victims are young (peak incidence is between ages 18 and 24), the cumulative number of such patients will continue to rise, year by year, for a long time to come. (Figures are from the National Head Injury Foundation.)

Even mild head injuries may result in significant symptoms: the so-called "post-concussive syndrome." Many mild head injuries are never reported. Most physicians fail to relate psychological problems to a mild head injury; the tendency, then, is to underestimate the extent of the problem. The actual number of CHI patients is probably much higher than we have ever believed.

Brain injury will necessarily lead to a wide range of symptoms and deficits. As a general rule, the severity of the injury will determine the severity of outcome. Some of the problems of CHI patients are attributable to the specific focus of damage. More commonly, however, residual problems are the consequence of diffuse cortical damage or of damage to axial brain structures that modulate cortical function. Since anterior, frontal, and temporal lobe structures are most frequently damaged in CHI, many of the sequelae are referable to these structures. It is believed that the shear forces that damage axial or subcortical structures in CHI are probably responsible for problems in memory, attention, emotional regulation, and arousal (32, 33). It is this combination of specific cortical damage and diffuse subcortical damage that renders the CHI patient a unique specimen.

Advocates insist that the clinical needs of CHI patients are different from those of other patients, and in this contention they are probably correct. CHI patients are not like stroke patients, or developmentally handicapped patients, or psychiatric patients; they are different, and unique. Physicians and therapists who were originally trained with other patient groups soon discover that major adjustments in therapeutic approach are necessary when the sequelae of CHI are at issue. So it is, too, when pharmacological approaches are brought to bear.

The following is a typical neuroleptic scenario for CHI patients: A patient is treated with intramuscular and then with oral haloperidol, to control agitation and assaultiveness during emergence from coma. The drug is almost inadvertently continued for months after discharge from the hospital. Then the patient appears for evaluation at a rehabilitation facility, anergic, depressed, and apathetic, with fine and gross motor coordination problems and deficits in attention, memory, and emotional control. The neuroleptic is withdrawn, and there is immediate improvement in all of these areas.

This is a typical example of short-term benefit for an appropriate indication—acute agitation—turning into inappropriate long-term

treatment. The more intelligent course would have been to gradually taper the neuroleptic after the patient's emotional state was stable for a couple of weeks. Neuroleptics should usually be tapered, not withdrawn abruptly. Abrupt withdrawal from neuroleptics may precipitate seizures (34); abrupt withdrawal can also be the occasion for prompt relapse with severe behavior problems. Stepwise reduction by 25 percent decrements over 4 weeks usually averts such problems.

Agitation, explosiveness, emotional instability, disorganization, and psychosis in CHI patients are not necessarily confined to the immediate post-recovery period. They may be persistent symptoms of CHI. In such instances, neuroleptics may be indicated, although they may not always be effective. Relatively short trials of two or three neuroleptics, in succession, ought to be sufficient to determine whether treatment is going to be successful, and if it is not successful, it is common sense to withdraw the patient from neuroleptics, reestablish a baseline, and try some other approach. Low to moderate doses are usually sufficient to establish whether a neuroleptic will be useful. High-dose treatment is rarely, if ever, necessary. It seems trite to warn against long-term treatment with an ineffective medication, but with neuroleptics, the pattern is too common to ignore.

Tourette's syndrome may be the consequence of CHI, and low-dose neuroleptics are occasionally helpful. Low dose neuroleptics may actually enhance cognitive performance, for example, in attentional tasks (7), probably a presynaptic stimulant-like effect (3).

Low-potency neuroleptics like thioridazine (Mellaril) and chlorpromazine (Thorazine) tend to be sedating, and thioridazine in particular is a strongly anticholinergic neuroleptic. It also appears that the neuroleptic chlorpromazine may impair short-term memory at doses below those required to cause motor impairment (35). Such drugs probably should be avoided in CHI patients. The high-potency neuroleptics are less sedating and are preferred when a neuroleptic is required. Representatives of this class include fluphenazine (Prolixin), trifluoperazine (Stelazine), and haloperidol (Haldol). Haloperidol commonly causes dysphoria, however. High-potency neuroleptics are more likely to cause acute extrapyramidal reactions and the neuroleptic malignant syndrome.

Neuroleptics can lower the seizure threshold. Pimozide and fluphenazine are two neuroleptics least likely to do so. Haloperidol and thioridazine are among the most likely to lower the seizure threshold (34, 36).

Do neuroleptics compromise the recovery process for CHI patients? Yes, if one extrapolates from the preclinical studies and from

human studies of neuroleptic-induced anhedonia (37), dysphoria (38), and cognitive and motor impairment (39). Yes, indeed, if one is guided by the prevailing belief that deficits in dopaminergic neurotransmission are central to the pathophysiology of CHI. One is thus inclined to consider neuroleptics relatively contraindicated in CHI patients, except for those subjects with neuroleptic-responsive psychosis, hallucinosis, mania, Tourette's syndrome, assaultiveness, or agitation. The key is to determine whether the symptoms are indeed "neuroleptic responsive," that is, that the drugs exert dramatic clinical effects when no other treatment will work as well; that their efficacy is established at a "minimal effective dose"; and that their continued clinical utility is assessed at reasonable intervals, say, every 6 months, by gradually tapering the dose. There is nothing "rational" about long-term large-dose neuroleptic treatment for CHI patients.

The issue is not only even the negative cognitive or motor effects of neuroleptics, or their tendency to "blunt" the personality of treated patients. It is only in small part influenced by their serious side effects: dysphoria, pseudo-parkinsonism, dystonia, tardive dyskinesia, hyperthermia, and the "neuroleptic malignant syndrome," photosensitivity, cholestatic jaundice, hypotension. It is in its largest dimensions defined by their limited utility in the long-term management of CHI patients, and the superior effects to be won by more carefully selected psychotropic treatments. Neuroleptics may be the best and only drug treatment for schizophrenia, but they are usually a poor third to carbamazepine and lithium for patients whose symptoms are a consequence of "organic" brain disorder.

Preexisting brain damage is sometimes listed as a risk factor for tardive dyskinesia. The clinical evidence is equivocal on this point, but the research is suggestive (40). Long-term neuroleptic treatment in CHI patients requires careful monitoring for TD.

A Behavioral Analog of TD

The question of a behavioral "analog" of TD is a good example of the limitations of inferential research. The idea is that chronic neuroleptic treatment may also afflict "higher" areas of brain and that dementia, psychosis, and/or emotional instability may be the consequence of suprastriatal neuroleptic effects. Terms like "supersensitivity psychosis" and "tardive dysmentia" have been coined to capture the phenomenon, and there are animal models of postsynaptic receptor supersensitivity in the mesolimbic dopamine system. The notion is not supported by any direct evidence; it is only a surmise based on indirect evidence.

The fundamental problem is how to demonstrate a connection

between neuroleptics and cortical dysfunction when cortical dysfunction of one sort or another characterizes a large proportion of the patients who are treated with neuroleptics to begin with. How can one draw inferences based on the expected natural history of neuroleptic-treated patients when the conditions for which drugs are most commonly prescribed are known to have an extremely variable course, and when the patients are often compelled to spend their lives in degrading circumstances that may of themselves lead to psychological deterioration? Even were one to demonstrate dopamine receptor proliferation in human brains, in frontal cortex or the limbic system, the natural question would be whether this was the consequence of the drugs or of the primary disease that afflicted the patient. There is no clearer demonstration of the limitations of TD research than this; if one cannot cultivate a no-treatment control group, the definitive answer will always be elusive.

There are several alternative strategies that may be mounted to deal with the question. Considering the alternative approaches is an interesting lesson in the scientific method.

Alternative 1 is to ignore the problem. After all, it is a hard question to test, and any result will be contested anyway. There are other research priorities.

This is not a bad idea. After all, the demonstration of a "higher" neuroleptic effect should not enjoin practitioners to greater caution with respect to neuroleptic treatment than they currently exercise in the face of TD or the neuroleptic malignant syndrome.

However, there is a problem with alternative 1: We miss an opportunity to surmount a scientific challenge simply because it is difficult. We lose an opportunity to learn how neuroleptics affect the dynamics of neural systems. These might be theoretical questions today, but they may have practical importance years hence, when antipsychotics that do not work on striatal receptors are developed, and the need to measure their long-term psychological impact is upon us.

Alternative 2 is to assume that neuroleptics do affect higher cortical centers. After all, why shouldn't they? Simply place the burden of proof on those who maintain that neuroleptics have no long-term psychological effects. This is not an extreme position. 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 (41). It is the interpretation of these data that is at issue—whether one presumes that the neuroleptic caused dementia, or that dementia predisposed patients treated with neuroleptics to develop TD, or that some kind of interaction is operating. Is there

a reason to suppose that one interpretation is preferred?

It is our opinion that the first interpretation is not tenable and that the truth of the matter probably rests with the second or the third. The reasoning behind this opinion is as follows: Patients with "organic" brain disease have not been shown to be at greater risk for TD than patients with "functional" disorders. The prevalence of TD in retarded people is probably no higher than in schizophrenic patients (1, 3). In contrast, patients with affective disorders may be at greater risk to develop TD than any other clinical group (42, 43).

The high prevalence of persistent TD in elderly populations suggests an interaction between antipsychotic drug neurotoxicity and some pharmacodynamic elements intrinsic in the aging process (8).

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 (44, 45). No disease that afflicts striatal tissue is known to have only motor consequences; Parkinson's disease and Huntington's diesease are only two examples.

This approach sidesteps the issue of mesocortical and mesolimbic damage and emphasizes the psychological importance of straital damage. It is an interesting approach because it generates a testable hypothesis: that TD patients, compared to non-TD patients, will have specific neuropsychological impairment in tests known to be sensitive to striatal lesions, delayed response, for example (46). A research strategy like this will only be effective, however, if it is linked to a prospective study design. If the hypothesis were tested in a design that identified patients in a point-prevalence survey, there would be no way of distinguishing between drug-induced striatal effects of predrug deficits in striatal function that predisposed patients to the development of TD.

It is likely that the best way to approach the question of whether dopamine receptor proliferation in human brains is the consequence of the drug or the primary disease will be to look for specific psychological or behavioral changes in primates treated with long-term neuroleptics. Here the research is simplified considerably by the possibility of comparing neuroleptic-treated animals to untreated controls. If a specific behavioral syndrome were to be demonstrated in primates with TD, then the model of that syndrome could be investigated in humans with and without TD. The strategy is still indirect, but less so than strategies relying exclusively on human populations.

The lesson of science is that as simple questions are addressed, more complicated questions arise. Scientists only succeed, it seems,

in making work for new generations of scientists. As we begin to acquire some fundamental epidemiological information about TD, we are left with the imperative to advance our knowledge in areas that are less explicit and more complex. As we master the methods to study the epidemiology of TD, we are left with the challenge of untangling the neuropsychology of the disorder.

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