American Psychiatric Association

TASK
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REPORT
18

TARDIVE DYSKINESIA

Task Force Reports

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TARDIVE DYSKINESIA

Report of the American Psychiatric Association Task Force on Late Neurological Effects of Antipsychotic Drugs

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PREFACE

The past two decades have produced almost revolutionary changes in the pattern of care of psychiatric patients. Important features of this revolution are a strikingly decreased prevalence of psychiatric hospitalization, the phasing out of many public mental institutions, the early return of psychotic patients to home and work, the development of open psychiatric units in general hospitals, and an increased reliance on local community and outpatient treatment facilities even for patients with severe or psychotic illnesses such as schizophrenia and manic or depressive disorders, many of whom are treated effectively by physicians without specialized training in psychiatry as well as by psychiatrists. These changes almost certainly are the result of a complex interplay among new forms of medical treatment of psychiatric patients, administrative decisions, social and philosophic changes in medicine, and cultural and historical factors that are still poorly understood.

Among these factors, the introduction of effective and relatively safe new antipsychotic medications that are useful in schizophrenia, paranoid disorders, mania and some severe forms of depression, and certain neuropsychiatric disorders, and the rise of the new discipline of psychopharmacology since the early 1950s have surely had an important effect. This era was opened by the introduction of reserpine and chlorpromazine (Thorazine) into the treatment of severely disturbed psychiatric patients in 1952. The new antipsychotic psychopharmaceuticals lead to rapid control of psychotic symptoms and behavior and have profound preventive effects, both of a direct pharmacologic type and by prevention of some untoward complications of prolonged institutionalization.

While the present report deals only with an important toxic neurological side-effect associated with prolonged use of the antipsychotic, or so-called neuroleptic, agents, it is important to emphasize at the outset that the use of neuroleptic drugs has had extremely beneficial direct effects on patient care. In addition, it has also helped to draw psychiatry even closer to the rest of medicine, has encouraged more careful differential diagnosis, and has gained support for biomedical approaches in psychiatry which complement psychosocial theories and therapies.

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CHAPTER I

INTRODUCTION

Tardive dyskinesia

This Task Force Report deals with the late dyskinetic neurologic disorders, commonly referred to as "tardive dyskinesia," which are associated with the prolonged use of the presently available antipsychotic drugs. We will review the clinical features, evaluation, differential diagnosis, epidemiology, neuropathology, pathophysiology and pharmacology, prevention, and management of this condition.

Antipsychotic drugs produce several distinctive transient and more prolonged or even irreversible extrapyramidal neurologic syndromes. Acute dyskinesias, akathisia, and parkinsonism were all recognized soon following the introduction of phenothiazines into clinical practice in the 1950s. The neurological effects of these agents in animals and man justified the term *neuroleptic,* which was coined in Europe to describe them—a term that meant "affecting the nervous system," but that also implied "mimicking neurologic disorders." Transient extrapyramidal reactions occurred early in treatment, subsided with reduction in drug dosage, and were often regarded as desirable aims or indications of effective antipsychotic therapy (1, 2).

The first clinical reports recognizing the occurrence of persistent dyskinesias following prolonged treatment with phenothiazines were published in the late 1950s (3, 4). Thereafter, a number of reports appeared describing the occurrence of similar persistent dyskinesias, nearly always among chronic psychiatric patients, in the course of treatment with phenothiazine antipsychotic drugs (5-9). Initial reports emphasized the orofacial distribution of the dyskinesia and referred to it as a "bucco-linguo-masticatory syndrome" (4, 5); it was later referred to as "terminal extrapyramidal insufficiency syndrome" (10). The now commonly used term, "tardive dyskinesia" (late and persistent dyskinesia), was introduced by Faurbye and his colleagues in 1964 (11). The subject has been extensively reviewed (12-14) with regard to clinical description (11, 15-17), pathophysiology (18-20), pharmacology (13, 14, 19, 21), and management (13, 14, 22).

Tardive dyskinesia (TD) was initially regarded as a complication of antipsychotic drug therapy largely restricted to elderly, chronically

institutionalized, frequently brain-damaged patients receiving prolonged drug treatment. In recent years, however, the status of tardive dyskinesia as a more general public health problem of major proportions, which may interfere with the ultimate rehabilitation of the patient in the community, has been given strong emphasis (23, 24).

Prior to more detailed discussions of specific aspects of tardive dyskinesia, it may be helpful to provide a brief overview of the current understanding of the major actions of the neuroleptic drugs on the nervous system and to outline the several other extrapyramidal disorders associated with their use.

Introductory comments on the antipsychotic drugs

Antipsychotic agents include compounds proven effective in the management of a broad range of psychotic symptoms and particularly useful in the treatment of schizophrenia and mania. Nearly all produce neurological effects in animals and in humans. The evidence that this class of substances has real and selective antipsychotic effects in schizophrenia and other disorders marked by abnormalities of thought associations, perceptions, and beliefs is now overwhelming (25). Antipsychotic drugs are rarely, if ever, *curative,* although they are highly effective in hastening remissions of acute psychotic illnesses and also seem to prevent later exacerbations of psychotic symptoms. Since their effects in truly chronic and relentless psychoses such as schizophrenia are not always obvious, a judicious clinical evaluation of the sometimes limited benefits and long-term neurological risks is required.

Although the antipsychotic drugs also calm excited, agitated, or manic behavior, they are not merely a special kind of sedative; and their older appellation "tranquilizers" is a misnomer. The regular association between antipsychotic effects and extrapyramidal effects suggested the term *neuroleptic* for this class of drugs. However, the recent description of experimental agents that are relatively free of acute neurological toxicity supports the conclusion that the more general and hopeful term *antipsychotic* is to be preferred while the search for safer and more selective drugs is pursued. Throughout this report the two terms, neuroleptic and antipsychotic, will be used more or less interchangeably. However, it should be made clear that the former term is less general and comprehensive, although it is appropriate for all antipsychotic agents available in current American medical practice, as they all also produce neurologic effects.

Early antipsychotic agents

The earliest antipsychotic drugs were the phenothiazines and the *Rauwolfia* alkaloids, notably reserpine (1952-53), although the usefulness of lithium salts for the management of excited or manic patients had been described earlier (1949). The first antipsychotic phenothiazine, chlorpromazine (Largactil), was developed in France in 1952 and introduced into American medicine as Thorazine in 1954. At the present time, American practice accepts more than a dozen neuroleptic drugs of scientifically demonstrated clinical value for the treatment of psychoses (Table 1; Figures 1 and 2). These include the phenothiazines of low mg-potency (but *not* low efficacy) (with aliphatic or piperidine side-chains in their chemical structures) which have a relatively greater tendency to induce sedation, hypotension, and other autonomic side-effects; the high-potency piperazine phenothiazines, which have relatively greater effects on extrapyramidal function; the *non*-phenothiazine tricyclic compounds (thioxanthenes and dibenzazepines); the butyrophenones and their still-experimental analogues, the orally relatively long-acting diphenylbutylpiperidines; an indolone; and the now rarely-used *Rauwolfia* alkaloids.

Although the antipsychotic or neuroleptic drugs represent a wide variety of chemical structures, their pharmacology and spectrum of activity are remarkably similar (25). Thus, the antipsychotic agents in current use in this country all regularly produce a variety of presumably extrapyramidal disorders of the control of posture, muscle tone, and movement. A crucial question is whether the almost routinely encountered neurologic ("neuroleptic") effects of the antipsychotic drugs are essential to their actions. The fact that several effectively antipsychotic drugs have relatively little tendency to induce acute neurologic reactions (dystonias, parkinsonism, and restlessness) now strongly challenges the inevitability of the association of neurologic and antipsychotic effects. Such drugs include thioridazine (Mellaril) and clozapine and sulpiride (both experimental agents); their existence offers some hope that better antipsychotic agents with diminished neurologic side-effects can be developed. Thioridazine does produce extrapyramidal effects but appears to be among the least likely to do so of currently available agents. Unfortunately, it does produce other autonomic and metabolic side-effects, and its maximum daily dose is limited to 800 mg/day due to reports of potentially irreversible and sight-damaging retinal toxicity (retinitis pigmentosa). Clozapine is of great theoretical interest as its extrapyramidal side-effect risk is extremely low, but its present status is in great doubt due

TABLE 1

Equivalent Doses of Commonly Used Antipsychotic Agents, by Chemical Type

Generic Name	*Commercial Name*[a]	*Approximate Equivalent Dose (mg)*[b]
Phenothiazines		
Aliphatic		
Chlorpromazine	Thorazine, etc. (generic)	100
Triflupromazine	Vesprin	30
Piperidines		
Mesoridazine	Serentil	50
Piperacetazine	Quide	15
Thioridazine	Mellaril	90-100
Piperazines		
Acetophenazine	Tindal	20
Fluphenazine	Prolixin, Permitil	2[c]
(esters)		ca. 0.5-0.7
Perphenazine	Trilafon	10
Trifluoperazine	Stelazine	5
Thioxanthenes		
Aliphatic		
Chlorprothixene	Taractan	65-100
Piperazine		
Thiothixene	Navane	3-5
Dibenzazepines		
Loxapine	Loxitane, Daxolin	15
Clozapine	(Leponex, experimental)	60
Butyrophenones		
Haloperidol	Haldol	2-3
Droperidol	Inapsine (for injection)	1-2
Diphenylbutylpiperidines		
Pimozide	(Orap, experimental)	ca. 0.5-5.0
Penfluridol	(experimental)	2 (1 week dose)[c]
Fluspirilene	(experimental)	—
Indolones		
Molindone	Moban, Lidone	8
Rauwolfia		
Reserpine	Serpasil, etc. (generic)	1-2

a) Trade names in parentheses are not yet licensed in the U.S. Many other agents used elsewhere are not available in the U.S. The commercial preparations are available as soluble salts (most are hydrochlorides; Loxitane or Daxolin is a succinate). Other agents that are not commonly em-

to its association with agranulocytosis. Both of these agents are strongly anticholinergic; sulpiride is not.

An important fact (or artifact) is that the methods of screening new substances for potential antipsychotic utility have essentially involved seeking neurologic reactions in laboratory animals because there are no satisfactory animal tests for psychosis. This impasse, coupled with current conservatism of the system for development and testing of new agents, particularly in the United States, has contributed to a repeated "rediscovery" of agents with very similar actions and limitations over the past 25 years.

Actions of neuroleptic-antipsychotic drugs

In the past, a number of mechanisms have been proposed to explain the actions of the antipsychotic drugs. They differ from most other depressants of the central nervous system (CNS) in several ways. Thus, they have limited ability to induce generalized sedative effects or coma until enormous overdoses are taken; in addition, tolerance to their antipsychotic effects is unknown, and addiction virtually does not occur. Unlike sedatives, they have been reported to have greater ability to diminish conditional behavioral responses than to depress unconditional responses. They may have a selective ability to dampen the neurophysiologic effects of peripheral stimuli on the forebrain, while inhibiting to a much lesser extent the effects of stimulating

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ployed now or are less effective in the treatment of psychoses are not included, e.g., butaperazine (Repoise), carphenazine (Proketazine), mepazine (Pacatal), promazine (Sparine), and thiopropazate (Dartal). Droperidol (Inapsine) is an extremely potent neuroleptic, now used mainly as a preanesthetic or coanesthetic agent i.m. or i.v., although it has powerful antipsychotic-sedative effects that might be useful in psychiatric emergencies too. In addition, prochlorperazine (Compazine) and thiethylperazine (Torecan), while having typical neuroleptic (and some antipsychotic) effects, are mainly employed as antiemetic agents. Reserpine and other amine-depleting agents are inferior antipsychotic drugs but are sometimes used in the management of tardive dyskinesia. While the other tabulated drugs vary by over 100-fold in *potency*, they are very similar in their clinical *efficacy*.

b) Data are summarized as averages from several sources, some of which vary greatly. These numbers are only an approximate guide, and dosage for each patient must be established by the clinical response. In switching from high doses of one agent to a dissimilar one, it is well to proceed gradually over several days to decrease the risk of side effects from the newly introduced drug. It is also important to realize that these equivalent doses are *not therapeutic doses* (which are typically several times higher).

c) Injectable fluphenazine esters are used in doses of 25-100 mg every one to four weeks. Long-lasting diphenylbutylpiperidines (experimental in the U.S.) can be used once weekly; penfluridol can be used as two percent of a *weekly* dose of chlorpromazine (i.e., 40 mg/week can replace 2,100 mg/week of chlorpromazine).

Adapted from Baldessarini (1977) (25); Davis JM: Comparative doses and costs of antipsychotic medication. Arch Gen Psychiatry 33:858-861, 1976; and Simpson G (personal communication, 1979).

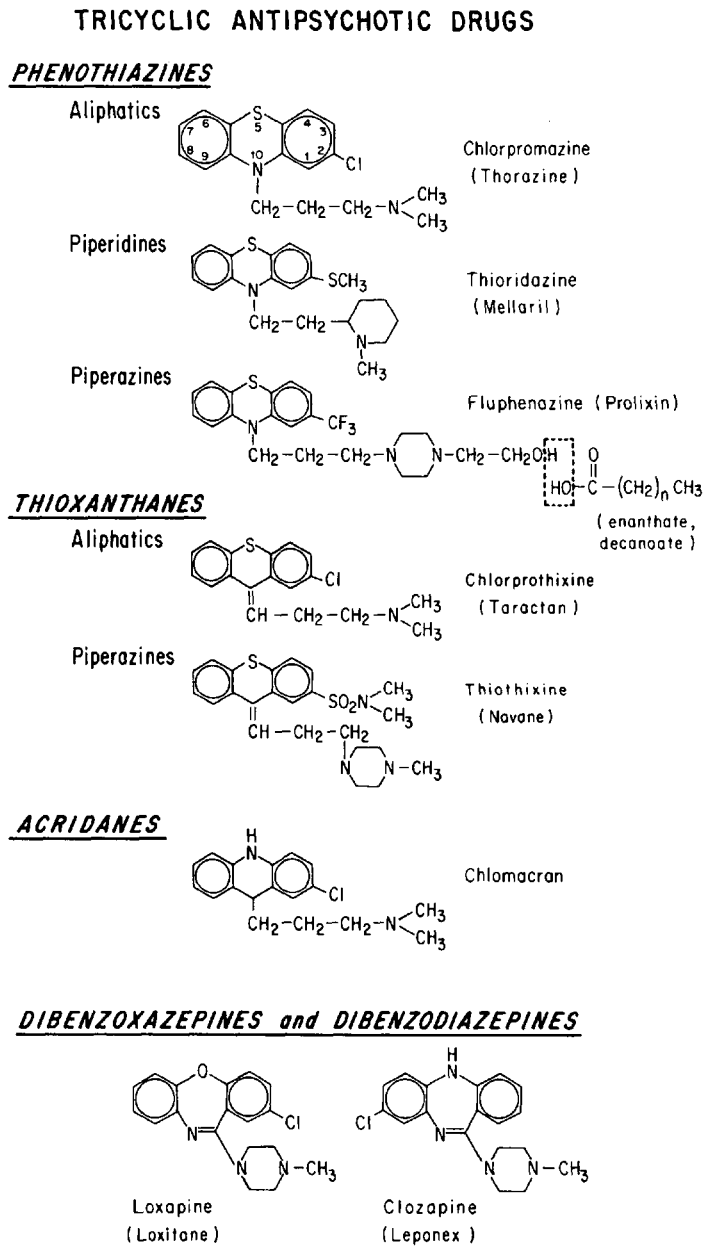


Figure 1. *Tricyclic Antipsychotic Agents* (from Baldessarini, 1977 [25]).

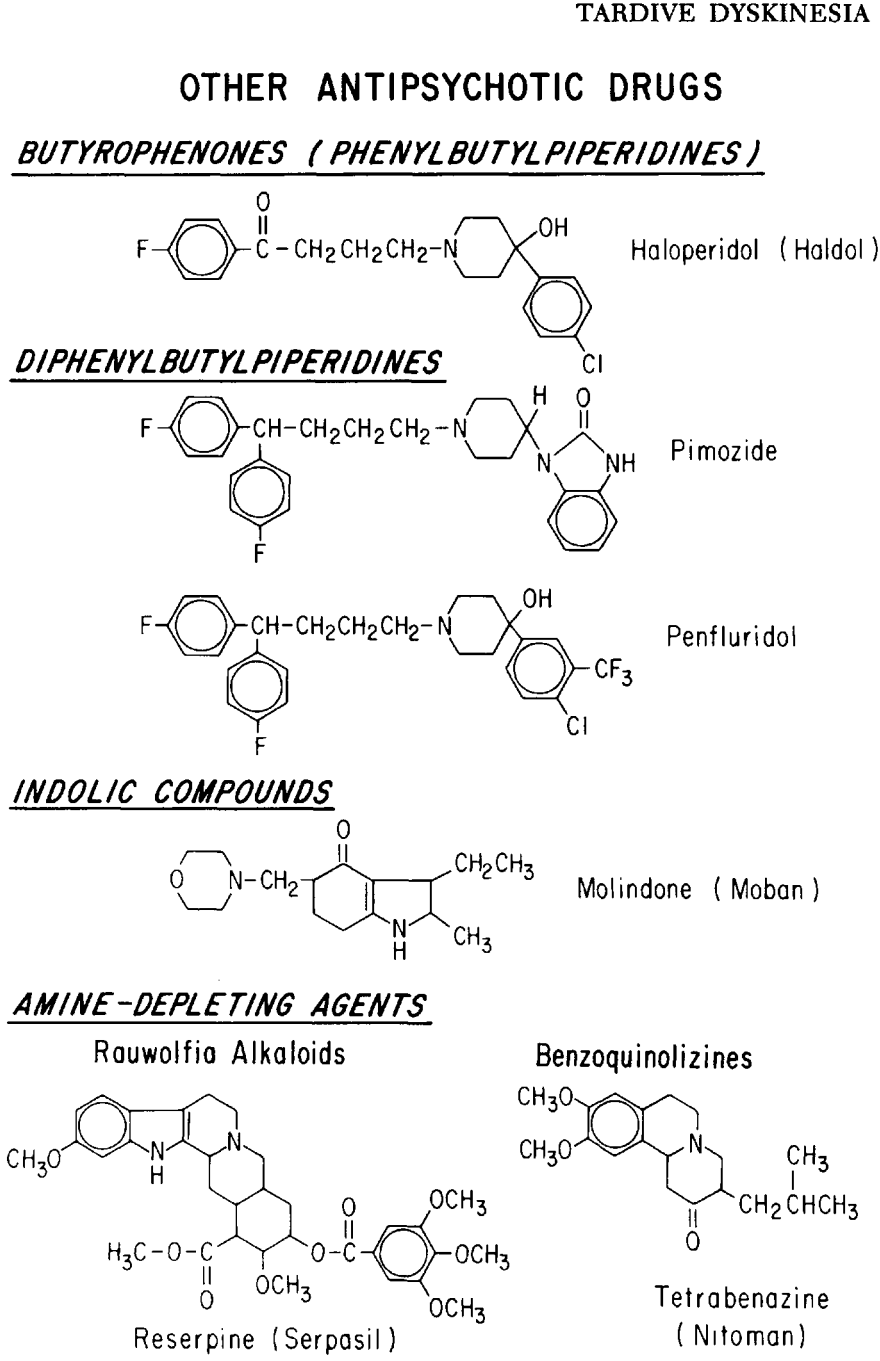


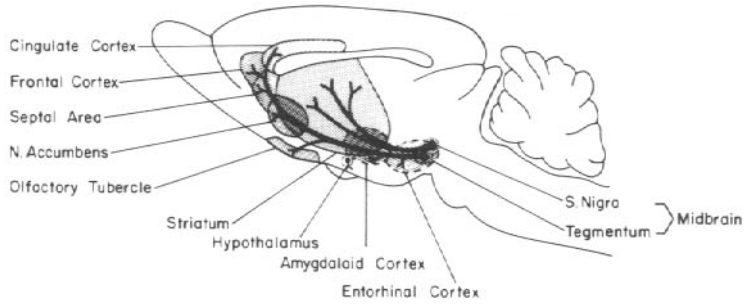
Figure 2. *Other Antipsychotic Agents* (from Baldessarini, 1977 [25]).

electrodes placed in the brain-stem. In addition to these distinctions from sedatives, antipsychotic drugs have striking inhibitory effects on autonomic and motoric expressions of arousal and strong affect in animals, presumably mediated by actions in the limbic forebrain and hypothalamus. The cellular and biochemical events underlying these behavioral and physiologic actions, however, have remained obscure until recently.

It was proposed by European pharmacologists as long ago as the early 1960s that the neurologic, and possibly also the antipsychotic, effects may reflect the ability of neuroleptic drugs to interfere with synaptic transmission in the brain mediated by dopamine (26). This suggestion arose largely from the observation that among the biochemical consequences of giving a neuroleptic drug to an animal, there was a consistent increase in levels of the metabolites of dopamine but variable effects on the metabolism of other candidate neurotransmitters. The possible importance of dopamine was given strong support by early histochemical studies of the normal distribution of amine-containing neurons in the mammalian brain, which indicated a preferential distribution of dopamine fibers between midbrain and the basal ganglia (notably, the nigroneostriatal tract) and within the hypothalamus. More recently, anatomists have come to appreciate the existence of other dopamine projections from midbrain nuclei to forebrain regions which are associated with the limbic system and probably not primarily with the extrapyramidal motor system, as well as to temporal and prefrontal cerebral cortical areas closely interlinked with the limbic system (Figure 3). A somewhat simplistic, but attractive, concept has been that many extrapyramidal neurologic effects of the antipsychotic drugs may be mediated by antidopamine effects in the basal ganglia and that some of their antipsychotic effects may be mediated by the antagonism of "dopaminergic" neurotransmission in the limbic system, hypothalamus, and cortex. The latter supposition has been given indirect general encouragement by repeated "natural experiments" that have associated psychotic mental phenomena with lesions of the temporal lobe and other portions of the limbic system.

In recent years, a large body of data has accumulated to support the theory that the antagonism of dopamine-mediated synaptic neurotransmission is an important action of antipsychotic-neuroleptic agents. Their effects on dopamine systems are summarized in Table 2. Thus, antipsychotic agents, but not their nonantipsychotic congeners, are reported to increase the rate of production of dopamine metabolites (notably, dihydroxyphenylacetic and homovanillic acids), the rate of conversion of the precursor amino acid tyrosine through dopa to dopamine and its metabolites, and the firing rate of presumably

DOPAMINE PROJECTIONS: RAT BRAIN



DOPAMINE PROJECTIONS: HUMAN BRAIN

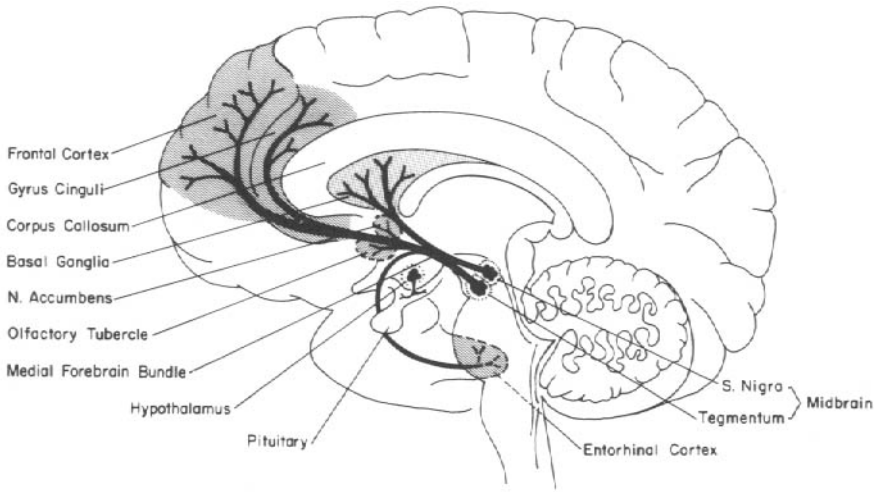


Figure 3. *Dopamine-Containing Neurons in the Mammalian Brain.*

The major systems involving dopamine are: the *nigrostriatal* pathway from the zona compacta of the midbrain substantia nigra to the neostriatum (caudate-putamen); *mesolimbic* projections from midbrain tegmentum through the lateral hypothalamus to limbic structures, including the septal nuclei (e.g., nucleus accumbens septi) and olfactory tubercle; and related *mesocortical* projections, also arising in midbrain, and projecting particularly to prefrontal and temporal areas of the cerebral cortex; there is also a *tuberoinfundibular* dopamine-containing (TIDA) system within the hypothalamus. The upper scheme is based on extensive studies in rat, but the anatomy is very similar in man, as depicted in the lower diagram.

TABLE 2

Effects of Neuroleptic Drugs on Dopamine (DA) Neurons in the Brain

Secondary or Indirect Effects:

- DA metabolism increased acutely (increased tyrosine hydroxylation and metabolite production)
- Midbrain cell firing increased acutely

Primary or Direct Effects:

- Plasma prolactin increased in rat and man in proportion to behavioral or clinical potency of neuroleptic
- Behavioral actions of systemically administered DA agonists blocked (eg, L-dopa, apomorphine, amphetamine)
- Self-stimulation through electrodes in DA-rich forebrain regions blocked in rat
- Arousal in response to local injections of DA agonists in forebrain DA target areas blocked in rat
- Iontophoretic effects of DA (but not of cyclic AMP) blocked in caudato-putamen (striatum) of rat
- DA-sensitive adenylate cyclase in forebrain (striatal) homogenates blocked
- Binding of tritiated neuroleptics to membranes in forebrain homogenates antagonized with potency corresponding closely to behavioral and clinical effects

dopamine-containing neuronal cell bodies in midbrain. These effects have been interpreted as secondary or compensatory responses of plastic and adaptive neuronal systems attempting to maintain homeostasis in the face of what is assumed to be a primary interruption of synaptic transmission at the dopamine terminals in the caudate nucleus, septal nuclei, and cerebral cortex. Figure 4 shows the metabolic arrangements at such synapses.

Evidence that a crucial primary event may be the blockade of postsynaptic dopamine receptor sites includes the ability of small doses of antipsychotic agents to block behavioral or neuroendocrine effects of dopamine agonists. Examples are stereotyped gnawing behavior in the rat induced by the putative direct dopamine agonist, apomorphine, possibly acting at the caudate nucleus; the locomotor excitement induced by the injection of dopamine into the nucleus accumbens septi of the limbic system; or the prolactin-decreasing response to apomorphine or L-dihydroxyphenylalanine (L-dopa, the immediate precursor of dopamine), believed to be mediated by hypo-

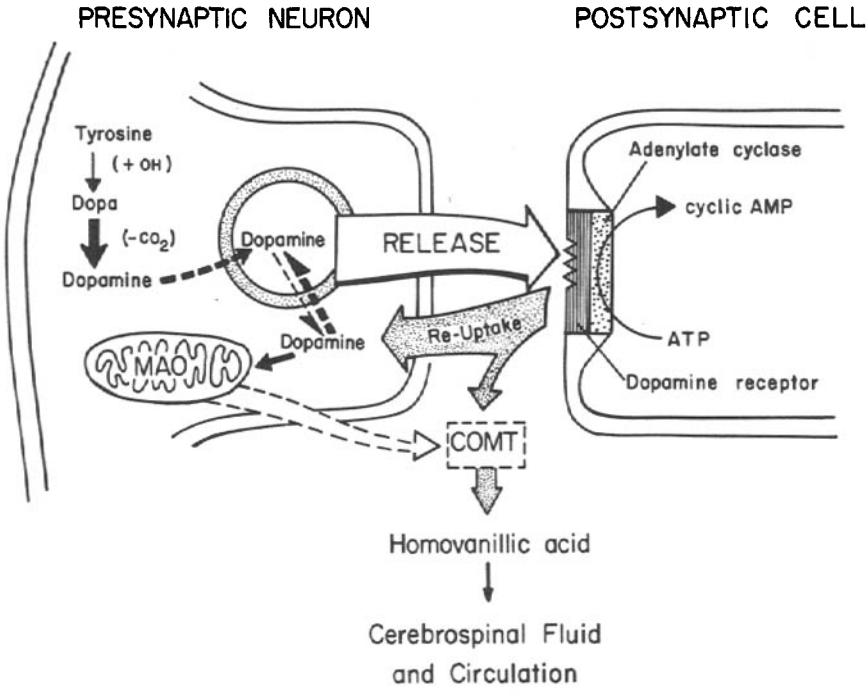


Figure 4. *Metabolism at Dopamine Synapse in the Brain.*

Dopamine is formed from L-tyrosine by hydroxylation (the rate-limiting step) to L-dihydroxyphenylalanine (dopa), which is rapidly decarboxylated. Dopamine is stored in presynaptic vesicles (shaded circle), from which release occurs into the synaptic cleft by neuronal depolarization in the presence of calcium. The released amine has a postsynaptic effect, possibly mediated by a recognition molecule (receptor) associated with adenylate cyclase that converts adenosine triphosphate (ATP) to adenosine-3′,5′-cyclicmonophosphate (cyclic AMP), which may, in turn, exert biochemical effects leading to altered neurophysiological sensitivity in the receptive cell. The neurotransmitter is inactivated largely by efficient high-affinity reuptake into the presynaptic terminals; excess dopamine that is not stored can be metabolized by monoamine oxidase (MAO) in the mitochondria and catechol-*O*-methyltransferase (COMT), largely extra-neuronal, to produce homovanillic acid from dihydroxyphenylacetic acid, an intermediary metabolite; the metabolites are removed in the cerebrospinal fluid and venous circulation by a probenecid-sensitive uptake, largely at the choroid plexus.

thalamic or pituitary dopamine receptors. Such "tests" have been proposed as screening methods to detect even more agents of the kinds already available.

More direct evidence of a receptor blockade has been provided by the antagonism of an apparently selectively dopamine-sensitive adenylate cyclase in homogenates of caudate or limbic tissue, and the interference with electrophysiological responses to dopamine iontophoretically applied to receptive cells in the caudate nucleus—a blockade overcome by presumed circumvention of the receptor sites on the cell surfaces by iontophoresed cyclic-AMP analogues (see 19 and Figure 4). A more recent development is the application of radioligand binding assays using homogenates of mammalian caudate nucleus and low concentrations (nanomolar or 10^{-9}M) of intensely radioactive [^{3}H]-dopamine, [^{3}H]-labeled neuroleptic drugs (haloperidol or spiroperidol), or [^{3}H]-apomorphine. Pharmacologic evidence supports the suggestion that the binding of these ligands to brain tissue represents, at least partially, an interaction with a dopamine "receptor" site. Correlations between the *in vitro* potency of antipsychotic drugs of all types to interfere with the binding of such ligands and estimates of their potency to block the effects of dopamine agonists in animals or to produce clinical benefits in psychotic patients (26, 27) are impressive.

Analogues or isomers of the antipsychotic drugs which are clinically inactive lack this potent antagonistic effect against ligand binding. It is particularly interesting that two antipsychotic agents (thioridazine and clozapine) with relatively weak acute neurologic side-effects seem to have antidopamine effects in the ligand-binding assays which correlate closely with their clinical potencies (26, 27). Although their relative lack of extrapyramidal toxicity has been explained by a countervening antimuscarinic (antiparkinsonism?) action of these two drugs, this explanation is not satisfactory for a similar drug, sulpiride (see 20). Analogous approaches have led to the suggestion that hypotensive and sedative effects of the less potent phenothiazines may correspond to their relatively strong antagonistic effects at central and vascular alpha-noradrenergic receptors (28).

Although these findings together strongly support the theory that antipsychotic agents interfere with the actions of dopamine as a synaptic neurotransmitter in the brain, they do not prove that antidopamine effects are either necessary or sufficient for antipsychotic efficacy. They strongly suggest, however, that some of the extrapyramidal neurologic effects of this class of agents may be produced by antagonism of dopamine, largely on the basis of analogy to the demonstrated loss

of dopamine in the caudate nucleus, and the beneficial responses to its precursor, L-dopa, in idiopathic parkinsonism.

Neurologic side-effects of neuroleptic drugs

The common and sometimes troublesome neurologic side-effects of most antipsychotic drugs represent a unique constellation of syndromes not associated with other psychotropic agents. These reactions can be subdivided into four or five categories, as are outlined in Table 3. Other classes of psychotropic drugs, including sedatives (e.g., barbiturates), tranquilizer-antianxiety agents (e.g., benzodiazepines such as diazepam [Valium]), and even tricyclic antidepressants and lithium salts are more likely to express toxic effects in the CNS, especially on overdosage, with generalized depressant effects, toxic delirium, and eventually coma and death. The antidepressants are likely to produce additional atropine-like signs and symptoms on acute overdose. The monoamine oxidase (MAO) inhibitors, as well as the classical stimulants (notably, amphetamines), are more likely to produce toxic states of excitement, hypertension, and eventually collapse on acute overdosage.

Thus, for the antipsychotic agents, CNS toxicity is expressed in several characteristic syndromes. Except for parkinsonism, the pathophysiology of these reactions is still poorly understood, although it is suspected that effects on dopamine-mediated systems in the basal ganglia are involved (Table 3). These syndromes are as follows:

a) Acute dystonias (12) occur within the first few days of treatment and are most likely to be associated with the more potent neuroleptics (see Table 1). They involve hyperkinesias of the branchiomeric musculature of the neck, mouth, and tongue; may include opisthotonos or oculogyric crises; and appear to be somewhat more likely in younger, male patients. The pathophysiology of the condition remains obscure, in part due to the wide and inconsistent variety of agents reported to be of benefit in this reaction (12). It has been reported that the period of maximum risk for neuroleptic-induced dystonias is during the phase of most rapid decrease of blood levels of the drug (29). This observation may provide a clue to the physiologic basis of the reaction. The main clinical problem with this syndrome is to recognize it and not to ascribe it to a seizure disorder, tetany or tetanus, or "hysteria." Treatment by injection of an antiparkinsonism agent is usually dramatically effective; diphenhydramine (Benadryl, 25 or 50 mg given intramuscularly or 25 mg intravenously) and benztropine

TABLE 3

Neurological Side-Effects of Neuroleptic-Antipsychotic Drugs

Reaction	*Features*	*Maximum Risk*	*Proposed Mechanism*	*Treatment*
Acute dystonia	Spasm of muscles of tongue, face, neck, back; may mimic seizures; *not* hysteria	1-5 d	Unknown	Antiparkinsonism agents are diagnostic and curative (i.m. or i.v., then p.o.)
Parkinsonism	Bradykinesia, rigidity, variable tremor, mask-facies, shuffling gait	5-30 d	DA-blockade	Antiparkinsonism agents help (p.o.)
Akathisia	Motor restlessness; *not* anxiety or agitation	5-60 d	Unknown	Reduce dose or change drug; antiparkinsonism agents or benzodiazepines may help
Tardive dyskinesia	Oral-facial dyskinesia; choreo-athetosis	mos.-yrs. (worse on withdrawal)	DA-excess?	Prevention best; treatment unsatisfactory
"Rabbit" syndrome	Perioral tremor (late Parkinson variant?)	mos.-yrs.	Unknown	Antiparkinsonism agents may help

mesylate (Cogentin, 2 mg given intravenously) are currently popular choices. If dystonic reactions recur frequently, abnormal calcium metabolism might be present.

b) Drug-induced parkinsonism (12) is similar to other forms of the disease, except that tremor is less prominent. The onset of the syndrome is usually after the first week of treatment but within the first month (see Table 3). There appears to be some "tolerance" to this effect, as the signs usually fade away over two or three months with a decreasing requirement for antiparkinsonism medications. Antipsychotic agents with higher milligram potency induce parkinsonism and the dystonic reactions with greater frequency than less potent agents, while the latter tend more often to induce sedation and autonomic effects (see Table 1). Severe akinetic, catatonic reactions and mutism have also been associated with relatively high doses of potent antipsychotics, such as the piperazine phenothiazines and thioxanthenes, and the butyrophenones. With such severe reactions, a temptation is to suspect worsening functional psychosis and give even higher doses of the offending agent, although improvement usually follows reduction in its dosage. The antiparkinsonism agents, including anticholinergics or amantadine (Symmetrel), may also help.

There are now a variety of agents used for the treatment of idiopathic as well as drug-induced parkinsonism, and the differential effectiveness of various classes of agents provides strong support for the theory that dopamine deficiency (and perhaps a relative excess of cholinergic function) in the basal ganglia is an important aspect of the pathophysiology of both forms of the syndrome. In addition, there is excellent neuropathological and postmortem neurochemical evidence of this dopamine deficiency in idiopathic parkinsonism. Antiparkinsonism drugs used in psychotic patients (L-dopa is too likely to produce agitation for routine use in such patients) are listed in Table 4. Most of these drugs (except amantadine [Symmetrel]) are strongly antimuscarinic (atropine-like), so they can induce the syndrome of anticholinergic poisoning—restless agitation, confusion, disorientation, perhaps seizures and hyperthermia, dry and sometimes flushed skin, tachycardia, sluggish and at least moderately dilated pupils, decreased bowel sounds, and often acute urinary retention. These effects are probably due to peripheral and central anticholinergic actions of these potent muscarinic blocking agents (30). This syndrome is best managed by removal of the offending agent and the use of physostigmine (eserine, Antilirium)—the only commonly available centrally as well as peripherally active reversible anticholinesterase agent (30). It can be seen from Table 5 that the antiparkinsonism and tricyclic anti-

TABLE 4

Equivalent Doses of Antiparkinsonism Agents

Generic Name	*Trade Name*	*Usual Dose Range (mg/day)*
amantadine	Symmetrel	100-300
benztropine	Cogentin	1-6
biperiden	Akineton	2-6
diphenhydramine	Benadryl	25-100
ethopropazine	Parsidol	5-0
orphenadrine	Disipal, Norlex	300
procyclidine	Kemadrin	6-20
trihexyphenidyl	Artane, etc. (generic)	5-15

These agents are commonly prescribed orally three times a day to provide the total daily adult doses stated above. Benztropine (2 mg) and diphenhydramine (25-50 mg) are commonly used intramuscularly or intravenously to reverse acute dystonic reactions to antipsychotic agents. Amantadine has recently been used to treat drug-induced parkinsonism and catatonia; it is relatively expensive and may lose effectiveness in a few weeks; overdoses may respond to physostigmine. Diphenhydramine and orphenadrine are antihistaminic and anticholinergic; ethopropazine is a strongly anticholinergic phenothiazine; the other agents are atropine-like. Most are available as soluble hydrochlorides. From Baldessarini, 1977 (25).

depressant drugs are among the most potent centrally active anticholinergic agents used in medicine. In addition, it can be seen that among antipsychotic drugs with relatively less tendency to induce acute extrapyramidal reactions, clozapine and thioridazine are relatively strongly anticholinergic (Table 5). The potential to induce CNS toxicity is only one of the problems associated with antiparkinsonism agents which indicates caution in their use with psychotic patients being treated with neuroleptics, or especially with antidepressant agents.

Other problems include the added complexity and expense of polypharmacy and some tendency toward dependence on these sometimes euphoria-inducing agents, which may add to the difficulty in discontinuing them. While the antiparkinsonism agents are sometimes given prophylactically to avoid acute extrapyramidal effects of antipsychotic agents, this practice is often unnecessary, and it is a matter of clinical judgment to evaluate the urgency of indications and contraindications for their use.* Furthermore, sound practice includes the attempt to withdraw these drugs gradually after several weeks, and

*A recent unpublished review on this topic by Drs. T. Jellinek, G. Gardos, and J.O. Cole (1980) points out that prolonged use of antiparkinsonism agents may be indicated for some patients maintained on neuroleptics to control akinesia or akathisia that may be uncomfortable and reduce the

certainly within four to 12 weeks after the onset of an acute extrapyramidal reaction, due to tolerance to the neuroleptics, which typically develops within that time with respect to acute dystonias and even parkinsonism (see Table 3).

c) Akathisia—motor restlessness, fidgeting, pacing, "restless legs," and the drive to move about—is a common early motor symptom complex of obscure pathophysiologic basis. This syndrome, like other extrapyramidal reactions, should not be mistaken for increasing psychotic anxiety or agitation or treated by increasing the dose of an antipsychotic drug. It can sometimes be managed by reducing the dose or changing to a different chemical class of antipsychotic agents. Antiparkinsonism drugs may have a beneficial effect, as may anxiolytic-sedative agents with putative muscle-relaxing properties, such as diazepam (Valium) or oxazepam (Serax). Unfortunately, many cases respond poorly to treatment, and a clinical decision must be made to weigh the distress of the akathisia against the need for antipsychotic medication. This reaction may persist or reoccur indefinitely, even though it is usually said to have its peak incidence on a similar time scale to that of parkinsonism (see Table 3). Tolerance to akathisia seems less likely than to dystonic and parkinsonism reactions.

d) Tardive dyskinesia (late and persistent dyskinesia) is the late-developing extrapyramidal syndrome that has led to a reappraisal of the benefits and risks of uninterrupted and indefinitely prolonged neuroleptic drug therapy (12-24), and that is the subject of this report. As will be discussed later in more detail, the syndrome consists of involuntary or semivoluntary movements of a choreiform (tic-like) nature, sometimes with an athetotic or dystonic component. These classically affect the tongue, facial, and neck muscles but often also affect the extremities, digits, and muscles that control posture and sometimes those used in breathing. Early signs of tardive dyskinesia are movements of the tongue or extremities. Oral-lingual-masticatory movements are common, especially in older patients; it is usual to find abnormalities of posture and at least subtle choreiform movements of the fingers as well, especially in younger patients. The movements of tardive dyskinesia are much less voluntary and purposeful and more classically choreoathetotic than the stereotyped mannerisms and

acceptance of antipsychotic agents. In addition, abrupt withdrawal of antiparkinsonism agents can produce apparent withdrawal reactions, including dysphoria, agitation, physical discomforts, and even hallucinations. Even after several weeks, there may be increased akinesia and depressed mood. The effects seem to occur more rapidly on withdrawal of trihexyphenidyl (Artane) or biperiden (Akineton) than benztropine (Cogentin). Many members of the Task Force have noted that chronically psychotic patients are especially reluctant to give up these anticholinergic agents.

TABLE 5

Antimuscarinic Potency of CNS Agents

Agent	EC_{50}(nM)[a]	K_d(nM)[b]
scopolamine	0.3	—
atropine	0.4	0.4
trihexyphenidyl (Artane)	0.6	—
benztropine (Cogentin)	1.5	0.2
amitriptyline (Elavil, etc.)	10	25
doxepin (Sinequan)	44	57
nortriptyline (Aventyl)	57	250
imipramine (Tofranil, etc.)	78	100
protriptyline (Vivactil)	—	62.5
desipramine (Norpramin, etc.)	170	62.5
clozapine (Leponex)	26	3.3
thioridazine (Mellaril)	150	60
promazine (Sparine)	650	60
chlorpromazine (Thorazine, etc.)	1,000	2,000
triflupromazine (Vesprin)	1,000	—
acetophenazine (Tindal)	10,000	4,000
perphenazine (Trifalon)	11,000	4,000
fluphenazine (Prolixin)	12,000	2,000
trifluoperazine (Stelazine)	13,000	20,000
haloperidol (Haldol)	48,000	7,000
prochlorperazine (Compazine)	—	40,000
iproniazid (Marsilid)	100,000	—
nialamid (Niamid)	100,000	—
phenelzine (Nardil)	100,000	—

a) Data are half-maximally effective concentrations (EC_{50}) of drugs that compete for the binding to tissue of the labeled test agent, ^{3}H-QNB—an avid and selective muscarinic antagonist, [^{3}H]-3-quinuclidinylbenzilate—as estimated in rat brain homogenates. Concentrations are in units of nM (nanomolar, or 10^{-9}M). Adapted from Baldessarini, 1977 (25), based on data of Snyder, Yamamura, and Greenberg, 1974 (33) and 1977 (34).

b) From data of Richelson and Divenetz-Romero, 1977 (35) and Richelson (personal communication, 1979), based on the potency of the test drugs in blocking the formation of cyclic guanosine-3′,5′-cyclic-monophosphate (cyclic GMP) by carbamylcholine (a stable acetylcholine analogue), using cultured mouse neuroblastoma cells. Data are reported as dissociation constants (K_d in units of nM).

The two methods are best compared by the rank-order of potencies, disregarding the absolute values obtained. Smaller numbers indicate *greater* potency.

posturing that occur spontaneously in schizophrenia (12). The signs of TD usually become worse if the antipsychotic agent is withdrawn and can be suppressed, at least temporarily, by readministering a neuroleptic drug or an amine-depleting agent. Since the remainder of this report details many aspects of this condition, it will not be discussed further at this point.

e) "Rabbit" syndrome (31)—perioral tremor—is another reaction associated with neuroleptic drugs which usually occurs late in therapy. This timing has led to its (probably erroneous) classification with the tardive dyskinesias. It may represent an atypical and localized variant of parkinsonism since the rate of the mouth movements is similar to more typical parkinsonian limb tremors and the reaction sometimes responds favorably to treatment with antiparkinsonism agents (31).

Other CNS effects of antipsychotic drugs

In addition to these more specific neuroleptic-induced neurologic syndromes, other effects of antipsychotic drugs on the CNS have also been described. They include the following.

a) Seizures: There is some evidence that neuroleptic drugs, and perhaps especially low-potency phenothiazines, slightly increase the incidence of seizures in epileptic patients, while the piperazines and haloperidol may have somewhat less tendency to do this. As yet, there are few helpful data to guide the clinician in the selection of a specific agent least likely to have this effect. Usually clinical judgment is required to balance the patient's need for antipsychotic medication with his need for anticonvulsants, and the dosage of the latter may need to be increased.

b) "Hypothalamic crises": Antipsychotic agents, and particularly chlorpromazine, have also been associated with severe reactions that are marked mainly by hyperthermia but that may also include sweating, drooling, tachycardia, dyspnea, seizures, and unstable blood pressure. Similar rare reactions have been ascribed to the tricyclic antidepressants.

c) Acute intoxication: In contrast to almost all other central nervous system depressants, the antipsychotic agents' lethality on acute overdose and their potential for inducing deep and prolonged coma and respiratory depression are limited. That is, they have a very high therapeutic index (ratio of toxic or lethal dose to effective dose). The half-maximal lethal doses (LD_{50}) for most of these agents are not

known. Patients have survived ingestions of many grams, and it is virtually impossible to commit suicide by taking an overdose of an antipsychotic agent (32). On the other hand, it is essential to consider the possibility of more lethal and treatable forms of acute intoxication, since ingestions are often mixed. For example, the patient may also have taken barbiturates or agents with important central anticholinergic activity, such as the tricyclic antidepressants, antiparkinsonism drugs, or thioridazine. Dialysis can be used to remove barbiturates, but it is not useful in removing antipsychotic or antidepressant medications because of their strong binding to protein and lipids. The reversible anticholinesterase agent physostigmine (eserine or Antilirium) can be administered for the central anticholinergic syndrome (30). Attempts to induce vomiting after overdoses of antipsychotic agents may be unsuccessful, owing to their antiemetic effects. One indication of the antipsychotic agents' limited toxicity and addiction potential is the fact that large quantities of these drugs can be prescribed with relative impunity, even for patients with impaired judgment or little impulse control.

In conclusion, the currently available antipsychotic agents virtually all carry some risk of inducing early or late neurological toxic effects. Most of these can be managed with antiparkinsonism agents or by thoughtful and conservative use of the available neuroleptics as we await the development of more selectively antipsychotic agents.

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CHAPTER II

CLINICAL DESCRIPTION, DIFFERENTIAL DIAGNOSIS, AND METHODS OF EVALUATION

Description

Tardive dyskinesia (TD) is an involuntary movement disorder that may appear after several months of treatment with antipsychotic drugs. It may be either permanent or transient and is characterized by a variable mixture of orofacial dyskinesia, chorea, athetosis, dystonia, tics, and facial grimacing. Orofacial and lingual dyskinesia and dystonia are traditionally considered the most characteristic and well recognized features of TD. Typically insidious in onset, such movements may initially be detectable only as mild forward-backward (snail-like contraction) or lateral tongue movements when the patient is asked to hold his mouth wide open with the tongue lying on the floor of the mouth. In some patients, however, tic-like movements of the lips or face or frequent blinking (1) are earlier signs of TD. Later, more obvious protruding, twisting, and curling movements of the tongue; pouting, puckering, sucking, or smacking lip movements; retraction of the corners of the mouth (bridling), bulging of the cheeks, and various forms of chewing or lateral movements of the jaw may occur individually or in various combinations. Blepharospasm, brief upward deviations of the eyes, arching of the eyebrows, and a variety of facial grimaces may also occur.

In patients over age 50 orofacial dyskinesia frequently appears first and often remains the most conspicuous feature of the syndrome, although when looked for carefully, involuntary movements of the extremities and trunk are usually apparent as well. Restless, choreiform, and athetotic distal movements of the limbs, including twisting, spreading, and flexion-extension "piano-playing" movements of the fingers; tapping motions of the feet; and dorsiflexion movements of the great toe are common at all ages. Abnormal movements of the extremities are often more extreme in younger individuals in whom dystonic postures of extension, abduction, or adduction of the arms as well as ballistic movements may occur. Postural disturbances of the neck and trunk may include torticollis, retrocollis, exaggerated truncal lordosis, rocking and swaying, shoulder shrugging, and rotary or thrusting pelvic movements. Dyskinetic disturbances of respiratory rhythm may be

observed, including periodic tachypnea, irregular respiratory rate, and grunting. In adults, cases in whom severe and disabling axial dystonia is the predominant disturbance have usually but not exclusively involved individuals under 50 years of age (2). A syndrome resembling TD has also been reported in children when antipsychotic drugs are withdrawn, characterized predominantly by chorea of the extremities, athetosis, myoclonus, and hemiballism (3, 4). TD has also been reported in 20 percent of an inpatient population of mentally retarded children who were receiving prolonged treatment with neuroleptic drugs (5). In contrast to elderly individuals, children are rarely said to exhibit orolingual dyskinesia, although facial tics are common.

TD resembles other choreoathetotic syndromes in that movements typically worsen with emotional stress, decrease with drowsiness or sedation, and disappear in sleep. Repetitive voluntary motor activity in other body parts, concentration on fine motor tasks, and attempts to inhibit one portion of the dyskinesia may enhance the movements but often have variable effects. Patients are frequently unaware of their movements following the onset of milder forms of TD with relatively mild dyskinesias of the face or fingers. Failure to complain of more severe dyskinesia, however, appears to be more common in patients with chronic psychosis or dementia than in younger individuals with less severe psychiatric disorders. Only on rare occasions does orofacial dyskinesia interfere with speech, eating, or respiration or produce oral ulcerations (6-9). On the other hand those patients with severe dystonia of the neck, trunk, and extremities can be severely disabled as a result of their abnormal movements.

Clinical course

TD may appear after as little as three to six months or, rarely, even a shorter period (10) of treatment with antipsychotic drugs, although in most published studies dyskinesia has been observed for the first time after two years of treatment. Onset usually occurs insidiously while the patient is still receiving drugs (11) but also may characteristically occur for the first time following reduction or discontinuation of treatment (12). Estimates of the prevalence of tardive dyskinesia have been extraordinarily variable; as will be clarified in Chapter III, apparent prevalence rates are easily inflated when mild or questionable cases, transient dyskinesias, or other neurological disorders are counted or when populations at high risk of spontaneous dyskinesias (such as the elderly) are evaluated. Thus, estimates range from more probable rates

of around ten to 20 percent to a few surveys reporting as high as 40 percent or more.

Neurologically asymptomatic patients may develop dyskinesia for various periods of time upon discontinuation of treatment with antipsychotic drugs (13). The incidence of irreversible dyskinesia under these circumstances is not known, but is almost certainly lower than the total of all dyskinesias, and probably not more than a few percent. It is likely that hypokinetic or frankly parkinsonian effects of antipsychotic drugs frequently mask the signs of TD, thereby delaying its recognition and apparent time of onset (12).

Despite earlier suggestions to the contrary (13), the fact that TD is sometimes irreversible is well documented (14) and generally accepted (15). Unfortunately, on the basis of available information, prognosis for recovery is not known and nearly impossible to predict in individual cases. As might be expected, short-term drug withdrawal studies (11, 16, 17) indicate frequent increases in severity of TD attributable to the "unmasking" effect of neuroleptic withdrawal. Particularly in cases of generalized dyskinesia, early phases of rapid progression from mild to severe dyskinesia are often observed but are so commonly associated with drug withdrawal that natural evolution may be obscured. Once dyskinesia is well established, it is usually either static, quite frequently with superimposed rapid or daily fluctuations, or shows slow and steady improvement over a period of months to years provided that neuroleptic drugs continue to be withheld.

In recent years there has been increasing awareness that sudden withdrawal of antipsychotic drugs may be followed by self-limited dyskinesia that lasts for several days or weeks before subsiding (18-23) and is most commonly associated with abrupt discontinuation of relatively high doses of the more potent neuroleptic agents. This form of tardive dyskinesia has been referred to as "withdrawal dyskinesia" (22, 23). In children, in fact, late dyskinesias have been largely, although not exclusively (5), restricted to this situation and have been referred to as "withdrawal emergent symptoms" (4). Because in childhood cases drugs have usually been reintroduced for psychiatric indications within several weeks or months (4, 5) it is presently uncertain whether these dyskinesias would remain permanent if antipsychotic drugs were discontinued.

The relationship of transient "withdrawal dyskinesia" in adults to more persistent forms of dyskinesia is obscure. As already discussed, a certain proportion of dyskinesias appearing for the first time during drug withdrawal subside within several days to weeks and may be referred to as "withdrawal dyskinesia." On the other hand, some patients show a slower disappearance of dyskinesia extending over

several months following drug withdrawal. Although it is possible that the latter dyskinesia is a transitional form between transient withdrawal dyskinesia and permanent dyskinesia, the precise relationship among dyskinesias that differ only in duration following drug withdrawal has not been formally studied.

Most studies of the natural course of TD following drug withdrawal have been carried out among chronically institutionalized patients, often of advanced age, with very prolonged exposure to antipsychotic drugs and with widely varying periods of follow-up. In studies of chronic populations results have generally been unfavorable (Table 6). In the largest available single study—of 273 patients with TD free of antipsychotic drugs for seven to ten months—

TABLE 6

Remission of Dyskinesia Following Drug Termination

Investigators (Ref.)	*Patients Total*	*Number remitted*	*Percent remitted*	*Follow-up period (months)*
Hershon et al., 1972 (28)	23	0	0	4
Hunter et al., 1964 (6)	13	0	0	3-18
Paulson, 1968 (26)	33	0	0	3
Edwards, 1970 (17)	19	1	5	ca. 12
Crane, 1971 (27)	39	3	8	6-24
Degkwitz, 1969 (11)	273	52	19	7-10
Uhrbrand and Faurbye, 1960 (24)	17	6	35	4-22
Turunen and Achté, 1967 (25)	26	10	38	?
Yagi et al., 1976 (30)	19	10	53	12-24
Jeste et al., 1979 (89)	21	12	57	3-13*
Quitkin et al., 1977 (29)	12	11	92	1-24

*Not drug-free for more than three months, but followed up to one year.

The overall weighted average of remission rates in all studies is 21.2 percent, although it seems clear that most recent studies have even higher rates. If another study providing preliminary unpublished results of J. Doller-Wojcek, A.J. Gelenberg, R. Labrie, and M. Berg is included (remission was observed in 54 percent of 13 patients after six-18 months, but exposed to neuroleptic drugs for unspecified periods during that time), the overall rate of apparent remission is over 22 percent.

Two other studies are also instructive: Mehta D, Mehta S, Mathew P: Tardive dyskinesia in psychogeriatric patients: a five-year follow-up: J Am Geriatr Soc 25:545-547, 1977 found that only 2/13 cases in elderly patients remitted (15 percent, while 31 percent improved), although most continued to require neuroleptics; Itoh H, Yagi G: Reversibility of tardive dyskinesia. Folia Psychiat Neurol Japon 33:43-54, 1979 found that only 2/19 cases improved within a few months of diagnosis, but 9/14 (64 percent) were clearly improved (none totally remitted) within five years on reduced or no neuroleptic treatment. When the data from these two studies are pooled, there is a highly significant relationship between improvement and age ($r = -0.75$, $p < 0.001$), so that younger patients appear to have a better prognosis for eventual improvement, especially if neuroleptic treatment can be avoided.

dyskinesias disappeared in 19 percent, were reduced in another 19 percent, and remained unchanged in 50 percent (11). Although two smaller studies (22, 23) have shown disappearance of dyskinesia in about 35 to 40 percent of patients after several months of follow-up, the remainder have shown disappearance in zero to ten percent (6, 17, 26-28). While a general conclusion regarding prognosis in this group of patients is difficult to extract from the available data, it would appear that as a conservative estimate TD may be expected to be permanent in up to 50 percent of patients.

The relevance of studies of older chronic populations to the prognosis of TD in younger patients is open to question. TD is being identified earlier in relatively young outpatient populations, who may have a more favorable prognosis. In one recent study of 12 outpatients with TD, eight of them age 30 or less were identified four to 16 weeks after the onset of dyskinesia (29). Dyskinesia remitted entirely within two to 26 weeks in 11 of the 12 patients after reduction or discontinuation of drugs. In another study, ten of 19 patients with TD remitted within two years (six within six months); most of these were under age 30 and had been treated with antipsychotic drugs for less than one year (30). Although it is currently uncertain whether early dyskinesias appearing while patients are still on antipsychotic drugs or transient withdrawal dyskinesias constitute a potentially reversible phase in the evolution of TD, these reports of reversal of dyskinesia in 50 to 90 percent of such patients indicate the need for a more hopeful attitude, vigorous early diagnosis, and, where appropriate, prompt discontinuation of antipsychotic drug treatment.

Since many patients with chronic psychosis worsen after discontinuation of antipsychotic drugs, it may not seem reasonable to terminate therapy in a significant proportion of patients with TD. It would, therefore, be important to know the natural course of TD in patients who continue to receive antipsychotic drugs. Prospective study of the natural course of TD in patients who remain on neuroleptic drugs has not been carried out, and retrospective studies have shown mixed results (31). In one study 40 percent of patients continuing to receive antipsychotic drugs at a fixed dose following the appearance of TD showed disappearance of dyskinesia after 18 months (32). In another study severity of dyskinesia was said to increase in patients receiving high doses of trifluoperazine for six months compared with a group receiving lower doses during this period, although increased sensitivity to milder forms of dyskinesia by the investigators conducting the study may have accounted for the findings (33). In a different group of chronically institutionalized psychiatric patients exhibiting primarily orofacial dyskinesia who participated in several clinical

trials of neuroleptic agents over a period of one year, there was no change in severity of dyskinesia 18 months following the start of these trials (34). On the basis of the available retrospective data it is not possible to state the prognosis of TD in patients remaining on neuroleptic drugs. It is our impression, however, that in the vast majority of cases TD remains fairly static or, in some cases, may be suppressed by the hypokinetic effects of the neuroleptic drugs.

One other clinical factor to be considered is whether there is evidence that the neurological or mental status of patients exposed to neuroleptic drugs for prolonged periods is altered other than in the manifestations of tardive dyskinesia. We have uncovered no evidence to suggest that generalized toxic or degenerative changes occur in CNS function; for example, there is no convincing evidence that dementia might result from prolonged neuroleptic treatment.*

Differential diagnosis

The diagnosis of TD should be considered in any patient displaying orofacial dyskinesia, facial grimacing, chorea, athetosis, dystonia, or tic-like disturbances who has been taking phenothiazines, thioxanthenes, butyrophenones, high doses of reserpine, or other neuroleptic-antipsychotic agents for a period of at least several months. Onset in association with a recent reduction in dose or discontinuation of treatment with a neuroleptic drug is typical of TD and should immediately suggest the diagnosis. On the other hand, since neuroleptic drugs may suppress a variety of dyskinesias it must be appreciated that this "unmasking" effect need not be restricted to TD. Differential diagnosis should be considered and caution exercised to avoid incorrectly attrib-

*One recent report noted small differences in computerized cranial tomograms and in tests of intellect between schizophrenics with and without TD (Famuyiwa OO, Eccleston D, Donaldson AA, Garside RF: Tardive dyskinesia and dementia. Br J Psychiatry 135:500-504, 1979). In addition, there has been some speculation about the possibility that the mental status might be impaired in other ways, supported in part by laboratory evidence that dopamine receptors of limbic as well as extrapyramidal regions may become more sensitive after prolonged exposure to these agents (see Chapter IV). Thus, it has been suggested recently that psychosis may worsen or show tolerance to the effects of antipsychotic drugs in some cases ("tardive" or "supersensitivity psychosis") (e.g., Chouinard G, Jones BD: Neuroleptic-induced supersensitivity psychosis: clinical and pharmacologic characteristics. Am J Psychiatry 137:16-21, 1980). While such a phenomenon might occur, its frequency and possible clinical significance remain unclear and require further critical study. The extraordinary complexity and opportunity for artifacts which can be encountered in evaluating changes in psychopathology in association with prolonged neuroleptic treatment have been emphasized recently by J.M. Smith and L.T. Kucharski ("Tardive Dyskinesia, Social Functioning, and Psychopathology," a manuscript submitted for publication, kindly made available as a personal communication from Dr. Smith, 1980).

uting persistent extrapyramidal symptoms to TD in all patients with a pre-existing psychiatric disorder. In Wilson's disease, Huntington's chorea, and several other disorders (Table 7) psychiatric symptoms followed by neuroleptic treatment may precede the appearance of dyskinesia, thereby obscuring correct diagnosis.

TD must be distinguished from other syndromes induced by neuroleptic drugs (see Chapter I). This is sometimes made difficult by the not infrequent coexistence of more than one drug-related syndrome. Tremor, defined as a regular, rhythmic oscillation of a body part around a fixed point, is the only hyperkinetic movement disorder that appears to be unrelated to TD. This is instead a reversible sign that is frequently but not always associated with some degree of parkinsonian bradykinesia or rigidity. The "rabbit syndrome" is a late-onset neuroleptic-induced syndrome characterized by rhythmic tremor-like movements of the mouth and jaw resembling chewing movements of a rabbit. This reaction may be unassociated with other generalized signs of parkinsonism but differs from TD in its rapid reversibility when neuroleptic drugs are discontinued and its favorable response to anticholinergic treatment (35). Akathisia (motor restlessness) is a reversible disorder sometimes also appearing relatively late in treatment which usually differs from TD in its prominent subjective somatic discomfort often centered in the lower extremities (see Chapter I). It should be noted, however, that akathisia may sometimes lack this subjective component, and similar phenomena frequently do accompany tardive dyskinesia.

Acute dyskinesias appearing immediately following administration of antipsychotic drugs are usually characterized by dystonic and spasmodic muscle contractions usually involving neck and truncal musculature. Not infrequently, however, milder forms may be restricted to face, tongue, or extremities (36), making a distinction on the basis of physical appearance alone difficult. In the use of long-acting "depot" esters of fluphenazine (Prolixin), such acute dyskinesias may appear recurrently following each injection of drug and may be confused with a late and, therefore, potentially irreversible dyskinesia.

A problem that occasionally arises in the diagnosis of TD is that patient populations receiving prolonged treatment with antipsychotic drugs are heavily weighted with chronic schizophrenia, institutionalization, advanced age, edentulism, and organic brain damage. Since these factors themselves often contribute to the presence of involuntary movement disorders, particularly involving the face and mouth, difficulty in diagnosis may arise. A number of movement disorders have been described in schizophrenia, for example, which may resemble extrapyramidal disturbances (37). These include repetitive, pur-

TABLE 7

Differential Diagnoses to Consider in Evaluating Tardive Dyskinesia

- Neuroleptic withdrawal-emergent dyskinesias or other transient acute dyskinesias associated with neuroleptics (see Table 3)
- Late and persistent "classical" tardive dyskinesia itself*
- Stereotyped movements of schizophrenia*
- Spontaneous oral dyskinesias of advanced age or senility*
- Oral dyskinesias related to dental conditions or prostheses
- Idiopathic torsion dystonia
- Focal dystonias (oromandibular dystonia, blepharospasm, spasmodic torticollis) and "habit spasms" (tics)
- Huntington's disease*
- Gilles de la Tourette's syndrome
- Wilson's disease (hepato-cerebral-lenticular degeneration due to abnormal copper metabolism), manganism and other heavy metal intoxications*
- Fahr's syndrome or other disorders with calcification of the basal ganglia
- Postanoxic, postencephalitic, encephalitic, or extrapyramidal syndromes*
- Rheumatic (Sydenham's) chorea ("St. Vitus' Dance")
- Drug intoxications (L-dopa, amphetamines, less commonly anticholinergics, antidepressants, lithium, phenytoin)*
- CNS complications of systemic metabolic disorders (e.g., hepatic or renal failure, hyperthyroidism, hypoparathyroidism, hypoglycemia, vasculitides)*
- Brain neoplasm (thalamic, basal ganglia)

*Both psychiatric disorder and dyskinesia may be present.

poseless, stereotyped movements of the face and virtually all portions of the body, manneristic distortions of purposeful activity, and a variety of miscellaneous tic-like disturbances. These phenomena were predominantly described in earlier accounts of catatonic schizophrenia (38, 39) but occasionally appear in contemporary descriptions of schizophrenic patients as well (40-42).

Although some stereotyped movements may resemble orofacial dyskinesias, they usually lack the rhythmic character of most dyskinesias. By contrast with chorea or athetosis, stereotyped motor activity of the limbs is often characterized by repetitive handling and manipulatory activity often more closely resembling ordinary volitional behavior and sometimes is associated with relevant thought content or apparent psychological significance. It is unlikely that true chorea or athetosis ever occurs in untreated schizophrenia unassociated with neurologic disease. Although classical descriptions of "athetoid ataxia" (38) and "parakinesia" (43) seem to resemble chorea closely, Bleuler (39) claimed never to have observed chorea in schizophrenia. He attributed the high incidence described by others to differences in definition. It is indeed likely that many choreoathetotic signs described in the older literature occurred as a result of undiagnosed organic neurological disease, sometimes of postencephalitic origin (44). More recent studies (42, 45) indicate that true chorea or athetosis is rare in chronic psychiatric populations in the absence of organic neurological disease.

The issue can be raised whether TD is distinctive from the orofacial dyskinesias that are occasionally observed in elderly or chronically institutionalized patients not exposed to neuroleptic drugs. Oral dyskinesias in elderly individuals have been described in association with structural brain damage (46) and edentulism (47). Although formerly a low prevalence (less than two percent) of such dyskinesia was reported from geriatric facilities in which antipsychotic drugs are not widely used (11, 48), a recent survey of elderly institutionalized patients, most of whom were demented but not treated chronically with antipsychotic drugs, found an incidence of 37 percent (46). Although spontaneous cases of this type may be indistinguishable in appearance from TD, the association with dementia and the usual restriction to the face and mouth without involvement of the trunk and extremities (46) may help to differentiate them from TD.

Blepharospasm and oromandibular dystonia (49, 50) occurring alone or together may also appear spontaneously in the absence of neuroleptic drug exposure, dementia, or other signs of neurologic disease. The peak age of onset is in the sixth decade; it is sometimes very slowly progressive with subsequent involvement of neck, trunk, or

extremities; and it may in fact be a limited form of torsion dystonia (50). Since this disorder may be indistinguishable in appearance from TD, differentiation requires knowledge of lack of neuroleptic drug exposure prior to its appearance. This is particularly important since many patients with spontaneous dyskinesias of this type also receive neuroleptic drugs in an effort to suppress the abnormal movements.

The only drug other than neuroleptic agents which regularly produces orofacial dyskinesia together with chorea, athetosis, and dystonia is L-dopa. Since this drug is used primarily in patients with pre-existing Parkinson's disease, no problem in differential diagnosis from TD should arise. Amphetamines may produce prominent chewing behavior, repetitive stereotyped movements (51, 52), or chorea (53), particularly in patients with pre-existing neurological disorders (51) or Gilles de la Tourette's syndrome (54) or as a result of gross abuse of the drugs (51, 53). Anticholinergic drugs (55-57), tricyclic antidepressants with anticholinergic properties (58-61), and phenytoin (62) may also produce transient choreoathetotic dyskinesias on rare occasions, but apparently only in the context of pre-existing extrapyramidal disease, TD, brain damage, or following acute overdosage.

Many individual manifestations of TD are similar in appearance to those that occur in a number of other spontaneous extrapyramidal disorders. A disorder to which TD is frequently compared is Huntington's disease (63). Since, in Huntington's disease involuntary movements sometimes appear after the onset of behavioral disturbances or psychosis, a problem in diagnosis may arise. Aside from clues afforded by the family history, progressive course, and associated dementia, Huntington's disease is usually characterized by more jerky and unpredictable movements with less repetitive and stereotyped appearance, greater incorporation of movements into normal activity, lack of facial involvement, and greater postural and gait disturbance. Abnormal tongue movements in Huntington's chorea are usually less extreme and tend to be choreic (sudden and jerky) rather than athetotic (continuous, slow, and twisting) as in TD. As a result, Huntington's chorea is characterized by inability to maintain prolonged tongue protusion unlike most patients with TD, who usually have little difficulty with this maneuver.

In some patients the combination of movement disorders which may occur in a patient with TD is unique and unlikely to be produced by any other single extrapyramidal disorder with the exception of encephalitis lethargica, which currently does not occur, or certain forms of torsion dystonia (dystonia musculorum deformans) (64). Interestingly, the frequent observation that young patients with tardive dyskinesia often show severe involvement of the trunk and extremities

while older individuals tend to show more restricted orolingual involvement is similar to the effect of age on the topographic distribution of motor disturbances in torsion dystonia and is perhaps exemplified by focal dystonias such as oromandibular dystonia (50). Features helpful in differentiating these syndromes, in addition to the drug-history, are the usually progressive course of both torsion dystonia and oromandibular dystonia (50) contrasted with the static or slowly resolving pattern seen in TD and, where present, the positive family history in torsion dystonia.

In some patients with TD, facial tics and grimacing are particularly prominent and may resemble those seen in Gilles de la Tourette's syndrome, a disorder in which myoclonic jerks and minor degrees of chorea are sometimes also observed (65). Although irregular respiratory patterns sometimes associated with noises and grunts may occur in TD, the frank coprolalia and other vocal utterances associated with Gilles de la Tourette's syndrome are absent. In virtually all cases, the presence of childhood onset without antecedent antipsychotic drug exposure will correctly identify Gilles de la Tourette's syndrome.

Miscellaneous disorders that should be considered in differential diagnosis are Wilson's disease and chronic manganese poisoning and other heavy metal intoxications, particularly in view of the associated psychiatric and neurologic features in some of these conditions. Acquired hepatocerebral degeneration in which orofacial grimacing may be particularly prominent, postanoxic and postencephalitic extrapyramidal syndromes, and extrapyramidal syndromes associated with calcification of the basal ganglia should also be considered. Miscellaneous vascular, endocrinologic, and metabolic disorders such as central nervous system vasculitis, hyperthyroidism, hypoparathyroidism, and hypoglycemia may also produce choreoathetotic syndromes but are more likely to be associated with transient rather than chronic movement disorder. Brain tumor is a very rare cause of hyperkinetic dyskinesia, but on occasion neoplasms of the thalamus or basal ganglia may be associated with involuntary movements.

With increased awareness of TD, there is likely to be an increasing tendency to attribute extrapyramidal signs that appear while a patient is receiving antipsychotic drugs to the drugs themselves. In the case of patients with uncommon neurologic disorders presenting initially with psychiatric manifestations, there is a good possibility that dyskinesia will either appear for the first time or even be precipitated after exposure to antipsychotic drugs, thus leading to an erroneous diagnosis of TD (66). A particularly helpful clue in the diagnosis of TD is that, except for the time of initial onset and the period during or shortly after withdrawal from antipsychotic drugs, TD does not appear

to be a progressive disorder. Extrapyramidal signs that should not be expected to accompany TD (unless antipsychotic drugs are still being administered or have recently been discontinued) include tremor, rigidity, bradykinesia, and abnormal facial expression. Other neurologic signs that should also strongly suggest an alternative diagnosis include ataxia and other signs of cerebellar dysfunction, weakness, abnormal reflexes, sensory disturbances, dementia, and urinary incontinence. A reasonable list of studies that should be done in investigating a presumed case of TD would include evaluation by a neurological consultant, chemistry profile, thyroid function studies, liver function tests, sedimentation rate, serum ceruloplasmin, urinary copper, electroencephalogram, and in selected cases a CT scan.*

Methods of evaluating and rating tardive dyskinesia

Clinicians need to observe patients carefully for evidence of dyskinesia, to record the presence or absence of suspicious or clearly abnormal movements, and to take such observations into account in planning and monitoring antipsychotic drug therapy in patients requiring such medication. The time-honored method for recording such observations is by simple descriptive anecdotal notes in the patient's clinical record. However, research in tardive dyskinesia has led to the development of a variety of evaluative procedures, some of which are easily applicable in the routine clinical care of patients (68) (Table 8).

Some methods involve electronic instrumentation. These include electromyography of muscle areas showing dyskinesia (69); the use of a balloon placed in the mouth or taped between the fingers and connected to a pneumatic transducer (70); accelerometers and other electrical transmitters attached to wrist or ankle (71), fingers (72), or other body parts (73); and electronic recording of speech (71). Most of these measures are best applied to the assessment of one or two specific body areas and, although sensitive and probably reliable, are not readily usable in ordinary clinical practice. A simpler quantitative method,

*The related possibility that biological characteristics of patients with tardive dyskinesia may help to distinguish them from other patients, or even provide clues to reasons for individual variations in susceptibility to TD, remains too sparsely evaluated to permit review at this time. Nevertheless, some studies of this kind are being pursued, and there are preliminary indications that patients with tardive dyskinesia may have somewhat lower activity of monoamine oxidase in blood platelets or higher activity of plasma dopamine-betahydroxylase than other schizophrenics (67). In addition, studies to evaluate individual pharmacokinetics and neuroleptic drug metabolism in such patients are currently underway (Drs. D. Jeste and B. Cohen, personal communications, 1979).

TABLE 8

Summary of Methods of Assessment of Tardive Dyskinesia

TECHNIQUE	*VALIDITY*	*RELIABILITY*	*SENSITIVITY*	*COMPREHENSIVENESS*	*PRACTICALITY*	*REFERENCES*
Electromechanical or visual instrumentation	uncertain	high	high	limited	limited	69-79
Frequency counts or duration of tongue extension*	good	good	high	limited	good	20, 69, 78, 80-82
Global ratings	probably good	variable or uncertain	limited	poor	good	17, 69, 93-96
Multiple-item ratings	usually good	variable, can be excellent	variable	excellent	good after raters well trained	16, 28, 31, 32, 69, 83-88, 90, 91, 97-101 (see Appendix)

Modified after Gardos et al., 1977 (68).

*While the usefulness of timing tongue-extension has been claimed by some investigators, such alterations can be complex and confusing: Typically, the athetotic component in a choreoathotic dyskinesia tends to have little effect on ability to protrude the tongue (commonly found in TD), while chorea tends to diminish this ability (as commonly found in Huntington's disease, for example).

namely movement counting, requires only a readily identifiable countable movement, such as tongue protrusion, chewing, or foot tapping, and a watch (80, 81). Although this approach can be reliable, it has the disadvantage of being restricted to only a few discrete movements in what may be a more extensive dyskinesia.

Global judgment of degree of severity of dyskinesia is simple but neither reliable nor useful in monitoring shifts in the severity or pattern of specific movements. A reasonable compromise between precise electronic evaluation of isolated features of tardive dyskinesia and gross global assessments is the Abnormal Involuntary Movements Scale (AIMS) developed at the National Institute of Mental Health (83, 90, 91; see Appendix). It includes severity ratings on a multi-point scale for six body areas (face, lips, jaw, tongue, trunk, and arms and legs) as well as ratings of severity, incapacitation, and patient's awareness of the movements. This rating method has been used widely in clinical studies of the treatment of tardive dyskinesia and can also be used for routine clinical care. Other more detailed multi-item rating scales also exist which document individual movements such as tongue protrusion, toe movements, retrocollis, etc. These permit the recording of a more complete picture of the presence and intensity of several discrete movements. A typical scale of this kind is the Simpson Dyskinesia Rating Scale (84, 85; see Appendix). It consists of 33 items (plus space for adding other less common movements not listed) and has been applied in several clinical trials of experimental treatments for tardive dyskinesia. Other rating scales of this type include those developed by Crane (16) and expanded by Smith et al. (86), by Heinrich et al. (31), and by a British group (28, 86).

Both the AIMS and the more detailed multi-item scales are useful to both clinicians and researchers for rating and recording the status of tardive dyskinesia. Reliability for such scales between trained raters is good for total scores and scores for specific body areas. On the Simpson Dyskinesia Scale, the reliability of individual items is less satisfactory than total scores for general body areas (such as face, neck and trunk, extremities) among raters who are not rigorously trained and highly experienced. Moreover, individual patients on stable medical regimens may show marked fluctuations in the intensity and distribution on dyskinetic movements over time, in part due to shifting levels of attention, arousal, or anxiety, but sometimes for no obvious reason (88). Drowsiness tends to suppress movements; and, similar to most extrapyramidal disorders, the signs of tardive dyskinesia disappear during sleep. Attempts to enlist the patient's cooperation in distracting maneuvers or in deliberate attempts to suppress specific

movements can have variable effects on the intensity of the movements.

The main purpose for any of these evaluative techniques is to heighten awareness of the signs of tardive dyskinesia among psychiatrists and their colleagues and to foster careful clinical observation and documentation. Written descriptions or standard rating sheets can be used. A standard form, such as the AIMS, or the counting of specific movements (20) can be used in a reasonably consistant manner adequate for assessing a patient's dyskinesia at different points in his clinical course by most psychiatrists, nurses, or other clinicians who observe patients with TD over time.

In conclusion, tardive dyskinesia can present with a variety of signs of neurological dysfunction, including involuntary movements of the mouth or extremities. These movements are typically choreoathetotic and have a wide range of severity. Perhaps more than 25 percent remit spontaneously over a few months after discontinuing treatment. Methods of evaluation of tardive dyskinesia have included some attempts to use electromechanical recording of specific movements and videotaping patients for research and clinical training purposes, but most clinical studies have employed one or more rating scales as are illustrated in the appendix. One of the most commonly used in the U.S. is the NIMH-devised AIMS scale. The differential evaluation of patients with suspected tardive dyskinesia includes consideration of other neurologic reactions induced by neuroleptic drugs, as well as the several other neurologic conditions that can lead to abnormal involuntary movements as summarized in Table 7.

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CHAPTER III

EPIDEMIOLOGY OF TARDIVE DYSKINESIA

Tardive dyskinesia has been reported in patients exposed to virtually all of the phenothiazines (1), to thioxanthenes (2, 3), and to a butyrophenone (4) but has only rarely been associated with exclusive exposure to reserpine (5-7) or molindone. TD has recently been reported after exposure to a tricyclic antidepressant associated with prolonged exposure to a neuroleptic drug or α-methyldopa (8, 9). Assessment of the relative incidence of tardive dyskinesia following specific drugs is difficult since most patients have been exposed to many drugs by the time of its appearance. The potent piperazine phenothiazines, which have a high incidence of acute extrapyramidal side effects, have sometimes been reported to produce tardive dyskinesia earlier and more frequently than other less potent phenothiazines (5, 10), although this increased risk associated with the more potent neuroleptics is only weakly supported by the results of other more recent surveys (11-13).

An association risk of TD with exposure to injectable preparations of fluphenazine has been suggested in several surveys (14-17). Tardive dyskinesia has also occasionally been reported following exclusive exposure to thioridazine, a piperidine phenothiazine with a relatively low incidence of early extrapyramidal effects (18), and thus far virtually not at all with other experimental agents that have very little propensity to induce acute extrapyramidal effects (dystonias, akathisia, parkinsonism), such as clozapine (19) and sulpiride (20). It has also been reported in association with metoclopramide, an agent used in gastrointestinal disorders, which also has neuroleptic activity and has some ability to suppress the signs of TD (21).

Prevalence of tardive dyskinesia

The reported prevalence of tardive dyskinesia in chronic, institutionalized patients as well as partially hospitalized patients and outpatients has varied between 0.5 and 65 percent; a mean value of about 20 percent can be estimated from surveys including tens of thousands of psychiatric inpatients (12, 13, 22-30). Differences in definition of the syndrome, patient populations, methods of case ascertainment, and

neurological assessment make an accurate statement concerning prevalence virtually impossible (1, 13, 22, 27, 31). As a very rough estimate, currently at least ten to 20 percent of patients in mental hospitals and at least 40 percent of elderly, chronically institutionalized or outpatients exhibit more than minimal signs of probable tardive dyskinesia attributable to or associated with neuroleptic drug treatment (13, 22, 31). Of these cases, perhaps 25 to 50 percent are potentially reversible (see Chapter II). In addition, it is likely that differences in prevalence rates occur among different kinds of patients, in different clinical settings, and among different countries or regions, although these aspects of the epidemiology of TD have not yet been studied systematically.*

Although tardive dyskinesia had formerly been considered to be less common among outpatient populations and in acute psychiatric units or private hospitals, an increasing number of cases are now being reported in these groups as well (4, 33-36). A few surveys have placed such prevalence rates with the highest formerly obtained among chronic inpatients (25, 26), while others indicate that the problem may be less prevalent in such settings (35, 37).

*There was an impression among several European and Canadian neuropsychiatrists whom we interviewed that prevalence rates for tardive dyskinesia in their areas may be lower than those typically reported in this country in recent years. A recent survey of schizophrenics in a community treatment program in Hungary revealed only mild forms of dyskinesia, with a prevalence rate of about 16 percent. These patients were characterized as having stable regimens of moderate doses of neuroleptics, common use of ECT in acute phases of exacerbation, and vigorous use of antiparkinsonism agents (Gardos, G: Personal communication, 1979). One hypothesis is that this difference may in part reflect the use of lower average doses of neuroleptic agents than are commonly used here (e.g., Refs. 20, 22, 26 of Chapter II; 41). Another recent survey of more than 3,000 patients at risk in the Bordeaux region of France revealed prevalence rates well below ten percent (Berger P, Yesavage J: Personal communication, 1979). This rate is much lower than earlier rates reported elsewhere in France of about 18 percent (32) or elsewhere in Europe, of 17 percent (13). Further data from informal surveys in several Far Eastern countries, where much lower doses of neuroleptics are used (or are tolerated) than in the U.S. or even Europe, provided by Dr. C.P. Chien, suggest that the prevalence of tardive dyskinesia there may be as low as two to three percent (Ref. 18, Chapter II). Published results of studies in Japan (averaging about 13 percent; see Ref. 34 of Chapter II) are less consistent with such a dose-prevalence relationship since prevalence rates there have been reported to be similar to those reported in France in 1975 (32), even though average doses used were much lower than are usual in Western countries. These latter results are difficult to assess as differences in tolerance to the CNS effects of the neuroleptics may exist between Europeans and Asians. Furthermore, Drs. H. Itoh and G. Yagi of Japan have recently noted that most cases of even severe and long-persistent tardive dyskinesia among Japanese patients, especially the younger males, showed evidence of spontaneous improvement over five years of follow-up, whether or not neuroleptic treatment was stopped or merely used episodically in small doses (unpublished data reported at the VI World Congress of Psychiatry, Honolulu, Hawaii, 1977). More systematic comparisons of prevalence rates and prescribing practices among regions and among countries are clearly needed in order to pursue some of the interesting hypotheses suggested by the informal comments made by our foreign colleagues.

Range of severity of TD

The wide range of severity and clinical significance of the signs of tardive dyskinesia are emphasized in two recent surveys of American patients (31, 38) in which about two-thirds had only mild dyskinesia; another one-fourth to one-third had moderately severe, clinically significant dyskinesia, while fewer than 15 percent had widespread, severe, disabling, or disfiguring degrees of abnormality. Such results emphasize the great difficulty in arriving at firm data concerning the overall prevalence of tardive dyskinesia, or concerning the levels of severity of abnormal movements, on which to arrive at a fair estimate of the clinical significance of the problem.

Some further information on these points is provided by very recent surveys using the NIMH Abnormal Involuntary Movements Rating Scale (AIMS, see Appendix) in a New York State hospital population, which revealed that prevalence rates of minimal abnormalities exceeded 60 percent, while the prevalence of moderate abnormalities was close to 30 percent and of severe impairment less than ten percent (31, 37; Figure 5). Another study, which counted only clear-cut or relatively severe cases in a similar population, reported a prevalence rate of only 11 percent (27).

While prevalence rates are influenced by the level of severity accepted for making the diagnosis (standards for which are currently virtually non-existent), the nature of the population at risk may also influence the rates observed. For example, a very recent survey in a private psychiatric hospital in New York, in which chronic cases of psychosis given prolonged hospitalization are relatively infrequent, indicated that evidence of tardive dyskinesia, even among patients at risk over age 50, was found in only seven percent; and the movements proved to be persistent after prolonged withdrawal of the neuroleptics in only four percent of the population at risk (35). This result is consistent with the hypothesis that the risk of TD may rise with greater drug exposure (time or total dose over time) in more severe and chronic cases of schizophrenia or other psychoses. A potentially important, but very tentative, suggestion that arose from the last study was that persistence of dyskinetic movements may have correlated with an interrupted pattern of exposure to the neuroleptic agents. This curious result, of uncertain significance (and possibly related to total duration of exposure to drugs), should now be pursued in larger prospective studies.

The wide range of severity illustrated in these several studies indicates the potentially misleading conclusions that might be drawn

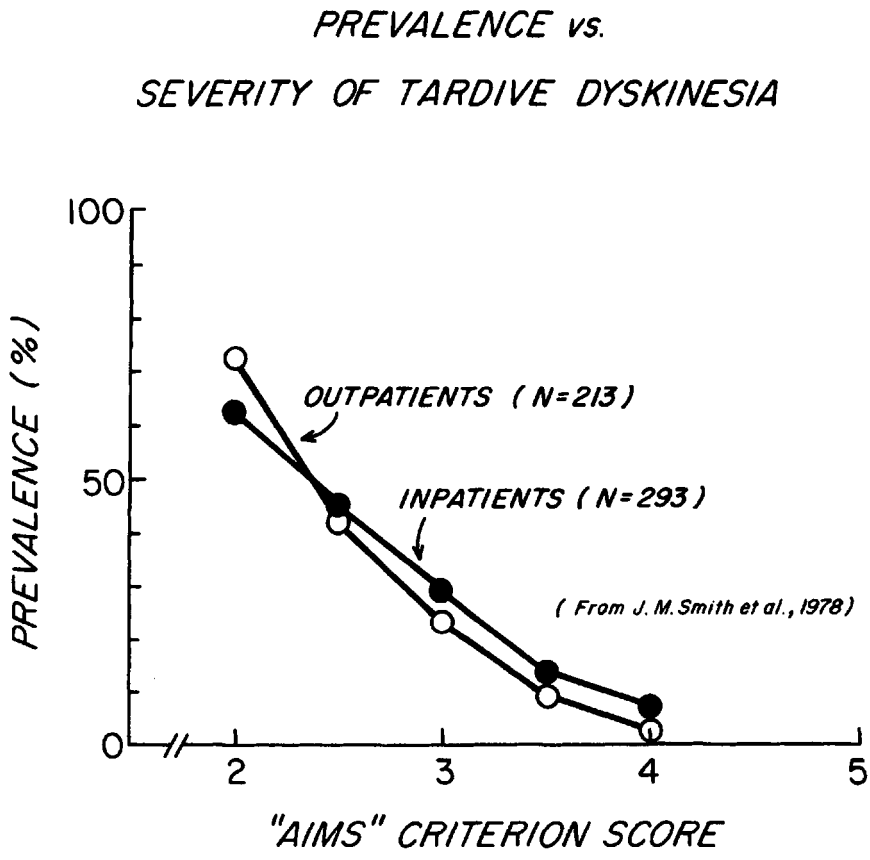

Figure 5. *Apparent Prevalence of Tardive Dyskinesia vs. Severity*

Data were obtained, and summarized with permission, from Dr. J. M. Smith and his colleagues at the Harlem Valley Psychiatric Center in Wingdale, New York (31, 37, 40). They indicate similar trends for a total of 506 psychiatric patients (schizophrenics exposed to various neuroleptics for prolonged periods) in that the "prevalence" decreased as the criterion of severity increased when the AIMS rating scale was used (see Chapter II and Appendix I). Their overall estimate of prevalence of dyskinetic movements likely to be accepted as clinically significant (criterion of mean score of 2.5 or higher in at least one body area) was 42 percent for this population (see also Table 9).

from epidemiologic surveys in which global prevalence rates typically obscure the relative infrequency of severe and disabling abnormalities and may *incorrectly* suggest a specter of grotesque incurable dyskinesias in large numbers of patients treated with antipsychotic drugs.*

Predisposing factors

Evidence of an etiologic role of neuroleptic drugs in tardive dyskinesia is mainly epidemiologic. At the present time this evidence is substantial (1, 29, 30, 39) although it is likely that "host" susceptibility factors are also important. Comparative studies of treated and untreated patients within the same institution (10, 42) and in institutions where drugs were used freely compared with those in which they have been used very little (11, 43-45) have disclosed a significantly higher incidence of persistent dyskinesias in neuroleptic-treated patients. Other epidemiologic data further reinforce the conclusion that exposure to neuroleptic drugs in a susceptible subject is a crucial factor in the production of tardive dyskinesia. For example, one study indicated that dyskinesia was two to three times more prevalent in psychiatric patients receiving neuroleptic drugs regardless of their diagnosis and that the dyskinetic symptoms that were found were much milder in the untreated cases (10). Furthermore, it was noted that as few as one percent of 2,000 elderly patients in nursing homes receiving little or no neuroleptic medication had signs of this disorder (6). It has also been reported that while only two percent of American geriatric patients not receiving neuroleptic medications had signs of dyskinesia, there was a 20-times greater prevalence (40 percent) among drug-treated patients (45). However, a more recent European survey found a 37 percent incidence of *spontaneous* orofacial dyskinesias unrelated to neuroleptic drugs in a geriatric and nursing home population, only some of whom had signs of dementia (46).** Finally, in a study compar-

*The high prevalence rates for tardive dyskinesia suggested by some recent studies (e.g., 25, 26) may in part reflect the current sensitivity of many investigators to the problem, possibly leading to a misleading lumping of indubitable cases with other very mildly or questionably abnormal movements, rather than a true increase in incidence in the 1970s. If incidence really has increased recently (*not* proven), other hypotheses might also be considered. Although an association with the use of higher average daily doses of neuroleptics, and especially the more potent neuroleptics, in recent years is possible, direct attempts to demonstrate a correlation between dose and prevalence rates have not been convincing. Another more speculative possibility is that other factors, such as an occult toxin or infectious agent, might be involved.

**This impression has been further supported by a recent unpublished study of dyskinesias among elderly unmedicated nursing home residents in New Jersey: see Garber, RS: Tardive dyskinesia. Psychiatric News 14(9):2, 1979.

ing drug-treated American schizophrenic patients with a matched group of Turkish patients not treated with neuroleptic drugs tardive dyskinesia occurred in 25 percent of the former and none of the latter (11).

Other important data bearing on the suspected etiologic role of neuroleptic drugs in tardive dyskinesia would be prevalence rates of chronic dyskinesias prior to the neuroleptic era. Unfortunately, systematic studies on this point are virtually non-existent, although some suggestive information is available. In reviews of the neurological findings of typical schizophrenic patients, comments about their well-known odd posturings, grimacing, and various repetitive stereotyped movements are found (47); but reports of frank choreoathetoid dyskinetic movements of the branchiomeric musculature, typical of tardive dyskinesia, are rare (25, 48). In one older study of neurological symptoms before the introduction of neuroleptic therapy, choreiform dyskinesia was found only occasionally among schizophrenic patients, although dyskinetic orofacial movements were commonly observed in patients with a variety of forms of overt or presumed damage to the central nervous system (e.g., senility, paresis, encephalitis, alcoholism and liver disease, and other dementias) (49).

Tardive dyskinesia is usually first recognized after at least two years of treatment with a neuroleptic drug (10, 22, 50), although onset within the first six months of drug exposure has been reported (6, 10) and we have recently encountered a *few* cases in which the syndrome was diagnosed within three months of exposure. Attempts to determine the amount of drug exposure necessary to produce the disorder have been inconclusive (22, 27, 28), and evidence of an association with the average dose or total amount of neuroleptics is weak and inconsistent (12). Thus, although some studies have reported on association with the duration of drug treatment, drug dosage, or total amount of drug (18, 42, 51), others have failed to confirm these correlations (17, 23, 25, 52, 53), or have found a *negative* correlation with total amount of drug exposure (14). Several reports have recently emphasized the occasional but dramatic occurrence of persistent (at least days or weeks) dyskinesia following exposure to unusually large (4), but even to rather small (33, 54, 55), doses of neuroleptics for relatively short periods of time. (See also Chapter II on the course of TD.)

Factors predisposing to tardive dyskinesia have been widely discussed. There is no evidence that the specific underlying psychiatric disorder plays any role in predisposition, although a recent very tentative suggestion is that depression may contribute somewhat to risk (56, 57). Furthermore, although the point has not been studied formally, there is no evidence that the rather common pre-existing spontaneous hyperkinetic movement disorders associated with chronic

psychoses, including stereotyped movements and catatonic phenomena in schizophrenia (47), have any relationship to subsequent appearance of tardive dyskinesia. The majority of cases have been reported in patients with chronic schizophrenia, prolonged or repeated affective illness, a variety of dementias or mental retardation (10, 12, 27, 43, 58-60), or even pre-existing movement disorders—evidently reflecting the fact that these patients are most often given prolonged treatment with neuroleptic drugs.* Importantly, however, tardive dyskinesia also occurs in non-psychotic patients treated with neuroleptic agents for psychoneurosis, gastrointestinal disturbances, chronic pain syndromes, or personality disorders (4, 10, 33, 34, 43, 50, 61). Tardive dyskinesia has also been reported in medically ill patients treated with drugs that are not antipsychotic but which may affect the extrapyramidal motor system. These drugs include non-phenothiazine antihistamines (62) and metoclopramide (63). Moreover, one can expect that the antiemetic phenothiazines thiethylperazine (Torecan) and prochlorperazine (Compazine), which are both typical neuroleptics (34, 64), carry a risk of producing tardive dyskinesia. Although it has been suggested that tricyclic antidepressants (which are phenothiazine and thioxanthene analogs) may also be associated with TD, the evidence is weak. Virtually all such cases that have been reported have also involved neuroleptic or other probably antidopamine agents (such as α-methyldopa) and, sometimes, ECT as well (8, 9).**

While appropriate prospective studies have not been done, there is presently no evidence that tardive dyskinesia occurs with a higher incidence in patients who previously manifested acute drug-induced extrapyramidal reactions (1, 12, 65). On the other hand, a history of drug-induced parkinsonism is reported to occur with increased frequency in patients who subsequently develop TD (66); this could simply reflect their exposure to relatively high doses of antipsychotic drugs, or a tendency to emphasize this aspect of the history by the patients or those evaluating them once the question of TD has been raised. Similarly, one recent survey found an association with prior treatment with antiparkinsonism drugs in a population of geriatric patients in a mental hospital who reportedly had not been exposed to greater total amounts of neuroleptics than a matched comparison

*While prolonged treatment with a neuroleptic drug such as haloperidol has, rarely, led to added dyskinesia during the treatment of Gilles de la Tourette's syndrome (80), there are yet evidently no comparable reports in Huntington's disease, another condition often treated with neuroleptic agents for many years. Gilles de la Tourette's syndrome, itself, has been reported to occur in schizophrenia after prolonged exposure to a neuroleptic drug (as well as after exposure to dopamine-agonistic stimulants) (82).

**It is not known whether ECT adds to the risk of TD during treatment with neuroleptics, but TD associated with ECT itself is unknown.

group (67). While the significance of this association is unclear, evidence that antiparkinsonism or other anticholinergic agents may *themselves* contribute to risk of tardive dyskinesia is not convincing (see also Chapter IV regarding cholinergic mechanisms in TD).

Although early reports (10, 61, 68, 69) emphasized a relationship with brain disease, with rare exceptions (17, 70), studies of the past decade seriously question an association of tardive dyskinesia with preceding neurologic disease (12, 23, 26, 43, 52), electroconvulsive therapy (12, 27, 43, 52, 68), or frontal leukotomy (10, 52, 68). Several reports have claimed an association with advanced age (and thus possibly with senile brain changes) (10, 12, 27, 31, 52) and female sex (25, 27, 31, 68, 71) (see Table 9). Although middle aged males may have slightly more severe dyskinesia (72), elderly females may have especially severe abnormal movements (31, 37, 40) (Table 9). Since there is now evidence that older laboratory animals show greater supersensitive responses to dopamine agonists after treatment with neuroleptics (25, 73), since brain levels of dopamine and other neurotransmitters diminish with age (see Chapter IV), and since very elderly persons commonly have "spontaneous" or idiopathic abnormal involuntary movements of the mouth and tongue (46), it may be that the

TABLE 9.

Relation of Prevalence and Severity of Tardive Dyskinesia Ratings by Age and Sex

AGE	*MALES (246)*			*FEMALES (260)*		
(years)	*Prevalence (%)*	*Severity*	*N*	*Prevalence (%)*	*Severity*	*N*
< 40	20	3.4	(51)	12	3.5	(34)
40-49	36	5.1	(39)	30	4.3	(27)
50-59	39	6.6	(31)	47	5.5	(55)
60-69	54	7.2	(59)	59	8.1	(76)
≥ 70	39	5.3	(66)	66	8.8	(68)
Means	38	5.5	—	45	6.1	—

Data for severity are mean total scores on the AIMS scale, and for prevalence (overall mean = 42 percent) are the percent of patients with a mean rating (*two* raters) of 2.5 or higher in at least one body area on the same scale (See Chapter II and Appendix 1); and N = numbers of schizophrenic patients evaluated (total N = 506, 213 of whom were outpatients and 193 of whom were hospitalized in a New York State institution). Results with schizophrenic inpatients and outpatients were similar and are pooled as weighted means. Data were obtained with permission of the authors from Dr. J. M. Smith and his colleagues (31, 37, 40) and re-analyzed. The data suggest a general increase in prevalence and severity with age (except in males over 70) and possibly slightly greater severity in males aged 40-60.

aging brain presents increased risk for neuroleptic-related late and persistent dyskinesias, especially of the oral region.

Moreover, there is a growing clinical impression that the pattern of persistent dyskinesias may vary with age and to some extent with sex. Thus, younger patients (especially males) may have somewhat greater likelihood of generalized dystonic and choreoathetotic syndromes (1) with a relatively greater chance for eventual remission after discontinuation of neuroleptic agents (74, 75). Older patients (especially females) may have a somewhat greater predisposition to oral-buccal-lingual-masticatory dyskinesias and more risk of prolonged exposure to neuroleptics (75); they commonly have such movements spontaneously in the senium (1), with a possibly reduced chance for eventual remission even after medication has been discontinued for many months (74, 76). However, these suggested trends are not clear-cut and are poorly supported by the data available at this time (59). Indeed, a few epidemiologic studies have suggested that advanced age (26, 42, 71) and female sex (23, 26, 43, 51) are *not* significantly correlated with the development of tardive dyskinesia.

In view of the complex characteristics of chronically treated patient populations, the precise contribution of brain damage or senility and advanced age to individual susceptibility to TD remains problematic. It is clear, however, that tardive dyskinesia is not restricted to the elderly. Many cases have been reported in young adults, and even in the pediatric population (77-80)—the latter are reversible in many, but not all, instances (60, 81).

In conclusion, epidemiologic studies support an association, but do not prove a simple causal relationship, between the use of neuroleptic drugs and the development of persistent or relatively transient forms of tardive dyskinesia—either generalized choreoathetotic syndromes or more localized involuntary oral-facial movements. While there is some suggestive evidence that prolonged exposure or large total amounts of drug, and especially of the more potent neuroleptics, may be a contributing factor, this is not well established. The relationship of risk with the size of average doses is extremely weak.

Factors that contribute to individual susceptibility are also not yet clearly demonstrated. Older patients, and perhaps especially elderly females, may be at somewhat higher risk and have a somewhat poorer prognosis for eventual remission following prolonged removal of the suspected offending agents. On the other hand, a most compelling conclusion from epidemiologic studies is that specific predictors of

risk (such as age, sex, type of drug and dose, history of acute reversible extrapyramidal symptoms, or use of antiparkinsonism agents) do not reveal consistently important or clinically useful risk factors, with the possible exception of advanced age. Moreover, it is clear that similar exposure to neuroleptics neither produces tardive dyskinesia in all patients nor exempts any groups (as defined by age, drug history, etc.) from risk.

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CHAPTER IV

PATHOPHYSIOLOGY AND ETIOLOGY OF TARDIVE DYSKINESIA

At the present time, it seems clear that the prolonged use of antipsychotic (neuroleptic) drugs can lead to the development of late dyskinetic disorders that may be either transient or persistent (1). Evidence that antipsychotic drugs are directly responsible for tardive dyskinesia is mainly epidemiologic but appears to be quite convincing (2-5). TD has been reported in patients exposed to virtually all of the phenothiazines (although relatively infrequently with piperidines such as thioridazine [2]), occasionally a thioxanthene (6, 7) or a butyrophenone (8, 9), but has only rarely been associated with exclusive exposure to reserpine (10, 11). While similar involuntary movement disorders occur in various known or presumed brain disorders, repeated exposure to neuroleptic agents by itself is probably adequate to induce the syndrome of tardive dyskinesia. Although the association between neuroleptic agents and late transient or persistent dyskinesias is now quite clear, the mechanisms by which these drugs might induce such neurotoxic actions remain unknown (11, 12).

Classical neuropathologic studies

The prolonged and sometimes irreversible course of TD strongly suggests that permanent structural alterations of the brain may be responsible for this disorder. However, neuropathologic studies following acute or prolonged administration of antipsychotic drugs in laboratory animals (13-16) have not convincingly and consistently demonstrated specific or localized pathologic changes in the brain beyond those that might be produced secondarily by the diverse systemic effects of these drugs (17, 18). A report (19) of an 18 percent reduction of neuronal cell counts in the neostriatum of rats treated for one year with perphenazine enanthate is of uncertain significance since gliosis and degenerative changes of remaining neurons were not present. Moreover, subsequent studies using much larger doses of perphenazine enanthate for six months had no effect on cell counts in the neostriatum or substantia nigra (20, 21). Similarly, nine months of

treatment of rats with flupenthixol resulted in only small and equivocal cell losses in portions of the striatum (22).

Human neuropathologic studies have been few and sometimes limited in design as regards including tissue from age-matched control subjects, using quantitative and objective methods (as for cell-counting), and inappropriately including patients with known progressive dementing neurologic diseases (e.g. Huntington's disease) that occasionally can be confused with schizophrenia with a movement disorder (23, 24), and failing to consider degenerative effects of aging (23, 25, 26). In man, postmortem neuropathologic changes following prolonged neuroleptic treatment in patients without extrapyramidal syndromes have usually consisted of scattered areas of neuronal degeneration and gliosis in the basal ganglia and other brain regions without convincing localization (17, 27). Individual patients with drug-induced parkinsonism or tardive dyskinesia have been reported to have abnormalities in the globus pallidus and putamen (28), caudate nucleus and substantia nigra (29), and inferior olive (30). Hunter et al. (25) reported no significant neuropathologic abnormality in three patients with TD, although two of these showed, among other lesions, neuronal degeneration in the substantia nigra which was believed to be consistent with their advanced age. In one of the few neuropathologic studies of a large number of patients with tardive dyskinesia, Christensen et al. (26) reported neuronal degeneration and gliosis of the substantia nigra in 27 of 28 brains from elderly patients (mean age, 74 years) with chronic oral dyskinesias, 21 of which were attributed to antipsychotic drugs. Only seven of 28 control brains matched for age and psychiatric diagnosis, but lacking a history of dyskinesia, showed similar changes. Other careful and controlled neuropathologic studies of large numbers of patients with TD are still rare, but several have failed to replicate these findings, especially among younger patients, while one found evidence of degenerative changes in the caudate nucleus (23).

Since prolonged administration of perphenazine enanthate to rats reportedly produced no changes in cell counts or morphology in the substantia nigra (20, 21), and since degenerative changes of the basal ganglia and midbrain occur in some elderly individuals without TD (23), it has been suggested that pre-existing nigral changes, unrelated to the effects of neuroleptic drugs and possibly accompaniments of aging, predispose in some way the subsequent appearance of tardive dyskinesia (20, 26). In view of the fact that even in several other extrapyramidal neurologic diseases, relatively moderate or apparently absent light-microscopic histopathologic changes occur, it should probably not be surprising that to date conventional neuropathologic

studies as well as computerized axial tomography (CAT scanning) of the brains of such patients (31) have not revealed obvious structural defects in TD.* Although one Turkish group reported pneumoencephalographic evidence of cortical atrophy (without dementia) in 11 of 30 chronic schizophrenics under the age of 50 exposed to prolonged neuroleptic treatment (and in several other patients treated with antidepressants for prolonged periods) (33), this observation is quite surprising as it is not consistent with earlier neurologic evaluations of chronic schizophrenics; it requires further critical evaluation. Electron microscopic studies of postmortem brain tissue in TD have scarcely been initiated up to this time (23).

Very recently, newer biochemical approaches have been made to the problem of post-mortem changes in the brain tissue of patients exposed to neuroleptic drugs, including assays of neurotransmitter concentrations, activities of their synthesizing enzymes, and of the binding of radio-labeled ligands to their presumed receptor sites. These studies have grown out of the dopamine supersensitivity hypothesis. They will be discussed in the following section.

Dopamine mechanisms

Several clinical observations have indicated that the syndrome of tardive dyskinesia may be associated with a pathophysiologic state of relative dopaminergic overactivity. Thus, it tends to worsen on withdrawal of the antipsychotic-neuroleptic drugs, which are believed to be antagonistic to dopamine receptors (34-46) and may also have a lesser effect of antagonizing the release of this central synaptic neurotransmitter (47). Furthermore, TD often resembles the dyskinesias and tic-like disturbances produced by L-dopa in patients with Parkinson's disease and the dyskinesias and tics produced by amphetamines (48) or other stimulants (indirect dopamine agonists) in some patients with underlying brain dysfunction or tic disorders (49), or in amphetamine addicts (50). Moreover, administration of d-amphetamine (51) or of L-dopa, the immediate precursor of dopamine, usually exacerbates tardive dyskinesia (52-55), although low doses (56) or repeated treatment (57) with dopamine agonists may have apparently paradoxical beneficial effects. The fact that TD may be suppressed by treatment with drugs that deplete or block the action of dopamine,

*Recent observations made with semi-quantitative analysis of CAT scan radiographs raise the possibility that subtle changes in cerebroventricular size or cortical thickness may occur in some chronically psychotic patients, not necessarily with TD (32).

such as tetrabenazine, reserpine, phenothiazines, and butyrophenones (58, 59), as well as alpha-methyl-*p*-tyrosine (53, 54), provides additional support for a state of relative excess of dopaminergic function in the central nervous system. Since improvement after use of anti-dopaminergic agents may occur without the appearance of clinically significant parkinsonism (58), it is not clear that the benefits are due solely to the superimposition of a hypokinetic state.

Denervation or disuse supersensitivity: behavioral evidence supporting the concept

One possible mechanism to account for the apparent functional overactivity of central dopaminergic mechanisms in TD is the development of denervation or disuse supersensitivity of dopamine receptors (59-66). Since drugs responsible for tardive dyskinesia appear to produce pharmacologic blockade of transmission at dopamine-mediated synapses, disuse supersensitivity mediated by alterations of receptors may be a long-term consequence of their use. There is a good deal of experimental evidence to support the occurrence of synaptic supersensitivity in the CNS in general (67-69) and in striatal dopamine-mediated synapses in particular (11, 12, 67). (See Table 10.)

A number of behavioral studies lend support to the existence of this phenomenon. After unilateral destruction of the nigrostriatal tract in rats (70) or the striatum in mice (71, 72), L-dopa or low doses of the putative direct dopamine-receptor agonist apomorphine produced contralateral turning behavior consistent with enhanced sensitivity of the denervated striatum. Intracerebroventricular administration of 6-hydroxydopamine to newborn rats resulted in the appearance of stereotyped behavior at three months following doses of apomorphine found to be ineffective in control rats (73). Stereotyped behavioral responses to apomorphine were also increased by 6-hydroxydopamine-induced nigrostriatal lesions in adult rats (74). Furthermore, the administration of L-dopa or apomorphine to monkeys pretreated with intraventricular or intracaudate 6-hydroxydopamine resulted in the appearance of abnormal lip and tongue movements, chorea, dystonia, and hemilballism that did not appear in animals given a control injection (75).

Further behavioral evidence accumulated in several animal species in recent years (76) indicates that prolonged administration of antipsychotic drugs (57, 66, 67, 77-91) or other agents (67) antagonistic to dopamine, followed by their discontinuation, also produces a behavioral state of increased responsiveness to dopamine agonists. These effects appear to represent the development of functional

supersensitivity to dopamine in the brain, and this state persists for at least several weeks (67, 77, 90). The duration of supersensitivity may to some extent parallel the duration of pretreatment with a neuroleptic agent (76). Additional studies reveal that prolonged exposure of animals to a neuroleptic agent leads to a prolonged (weeks) requirement for increased doses of the same agent ("tolerance") (92) or a dissimilar neuroleptic agent ("cross-tolerance") (78) to block the behavioral effects of apomorphine.

It has also been noted recently that repeated treatment with a neuroleptic agent led to increasing tolerance toward the ability of the same or dissimilar neuroleptics to block electrically-induced self-stimulation of the brain through an electrode in the nigrostriatal pathway of the rat (93). Moreover, on discontinuation of treatment, there was a marked and prolonged (more than one month) increase in the self-stimulation response (93). The development of increased rates of self-stimulation during treatment with neuroleptics has also been noted in the frontal cortex, but tolerance to neuroleptic blockade may not develop as fully in the nucleus accumbens (93, 94)—a region currently considered to be mainly "limbic" rather than extrapyramidal in function and suspected of being an important site of mediation of the antispychotic effects of neuroleptic drugs (46, 95, 96).

Inconsistent with this hypothesis, however, is some recent evidence strongly suggesting that limbic supersensitivity can follow prolonged neuroleptic pretreatment. This evidence arises from evaluations of behavior by local injection of dopamine into the nucleus accumbens (80, 97), by self-stimulation elicited by an electrode placed in the same area (94), or by the elicitation of locomotor activity with low systemic doses of apomorphine (97). It is also evident that accumbens supersensitivity to a direct dopamine agonist follows lesioning of accumbens dopamine terminals by local microinjections of 6-hydroxydopamine (97), sometimes given after protection of norepinephrine cells by desmethylimipramine (98). The development of tolerance to neuroleptic-blockade of self-stimulation induced by an electrode in the frontal cortex (93, 94) also seems to fail to support a crucial role of cortical dopamine projections in the mediation of antipsychotic effects of these drugs. These findings suggesting limbic or cortical tolerance or supersensitive dopamine responses apparently fail to support a dopamine hypothesis for antipsychotic drug action (46) because tolerance to these drugs in their clinical use in the psychoses and gradual worsening of psychosis (97) ("tardive psychosis") are unknown, although this possibility has been the topic of some recent speculation (99). (See also footnote, p 28)

TABLE 10

Summary of evidence supporting development of dopamine (DA) receptor supersensitivity following denervation or disuse of dopamine systems[a]

Experimental Observations	*References*
A. *AFTER LESIONING DA PROJECTIONS* (electrolytically or with 6-hydroxydopamine)	
1. *Increased behavioral responses*	
a. Turning contralateral to lesion with direct DA agonist[b]	(70–72,98)
b. Turning ipsilateral to lesion with indirect agonist[b]	(70)
c. Increased stereotyped behavior to direct, but decreased to indirect DA agonists	(73,74)
2. *Increased biochemical responses*	
a. Increased sensitivity of DA-sensitive adenylate cyclase in brain to direct DA agonists	(135,137)
b. Increased binding of tritiated neuroleptic drugs in forebrain	(141,147,148,166)
3. *Increased neurophysiologic responses to direct DA agonists in forebrain*	(124–126)

B. *AFTER PROLONGED NEUROLEPTIC TREATMENT* (or use of other anti-DA agents)

1. *Increased behavioral responses*

a. Tolerance to same or dissimilar neuroleptic in blockade of behavioral responses to DA agonists	(78,92)
b. Increased arousal with amphetamine after withdrawal of neuroleptic	(90,91)
c. Increased stereotyped responses to DA agonists after withdrawal of neuroleptic	(67,76,81,83–85, 88–91,104,139)
d. Tolerance to neuroleptic blockade of self-stimulation in nigrostriatal system, followed by increased responses after neuroleptic withdrawn	(93,94)

2. *Increased biochemical responses*

a. Increased sensitivity of DA-sensitive adenylate cyclase to DA agonists	(110,140)
b. Increased binding of tritiated neuroleptic drugs in forebrain[c]	(110,141,142,145, 149–154,169,283)

3. *Increased neurophysiologic responses to direct DA agonists in forebrain* (127,128)

[a]Further details and references can be found in Muller and Seeman (1978) (76), and Baldessarini and Tarsy (1979) (282).

[b]It is interesting to note that a case of human responses of a very similar kind has recently been reported in unilateral parkinsonism, by Trabucchi et al, 1979.

[c]Note that while studies of postmortem human brain tissue demonstrating increased binding of ^{3}H-neuroleptics to membrane preparations have usually been interpreted as an aspect of the pathology of schizophrenia, such changes, at least in part, may be due to prior treatment with neuroleptics.

These several behavioral observations concerning responses after repeated exposure to neuroleptic drugs in animals do, overall, seem to be consistent with the phenomenon of increased sensitivity to dopamine, possibly mediated by increased sensitivity of post-synaptic receptor and effector mechanisms in response to disuse (or frank denervation) of dopamine-mediated synapses. Such behavioral experiments have led to applications with potential practical and clinical significance. Thus, they have been applied in a growing number of studies aimed at predicting the clinical efficacy of experimental therapeutic approaches to the dyskinesias. Many examples of the application of this strategy will appear later in this review. However, as one intriguing example of this approach, it has been reported recently that lithium given simultaneously with prolonged neuroleptic treatment in the guinea pig (100) or rat (101, 102) can prevent the evolution of supersensitive behavioral responses to dopamine agonists, although it probably cannot block them once they are developed (100). Furthermore, lithium treatment can prevent the increased binding of labeled neuroleptic drugs to presumed receptor sites in brain tissue (101).

Lithium salts have little effect on tardive dyskinesia, although it is not known whether lithium might have a protective effect in man if given with neuroleptics before tardive dyskinesia develops. A second practical point to be emphasized arises from the growing behavioral or biochemical evidence demonstrating impressive regional differences in the extrapyramidal and limbic effects of typical neuroleptic agents and those "atypical" antipsychotic agents (such as clozapine and sulpiride) with less tendency to induce neurological side-effects. An implication of such observations is that they may permit the detection of new experimental agents that act selectively on limbic or cortical tissues, permitting the development of new drugs that are selectively antipsychotic and less neurotoxic than existing neuroleptics (45, 93, 97).

Disuse supersensitivity: behavioral results that may not be consistent with the hypothesis

There are several recent observations that provide further insights into the characteristics of tissue responses to agents that interact with catecholamine-mediated synaptic transmission in the CNS. One type of observation questions the requirement of prolonged exposure to neuroleptics to induce supersensitivity. There are recent studies demonstrating biochemical and behavioral evidence of clear increases in this sensitivity after even a single dose of a neuroleptic (103, 104)—increases that may persist for many hours or even several days (104), and which are prevented by drugs that block protein synthesis

(105). Such rapid changes in catecholamine receptor sensitivity are not unprecedented, as diurnal changes of considerable physiological significance have been documented in the β-adrenergic receptors of the pineal gland, evidently as a reflection of diurnal changes in availability of norepinephrine from sympathetic fibers innervating this organ (106).

Even more puzzling observations are seemingly paradoxical *increases* in responsiveness to dopamine after prolonged (107-109) or even brief (104) exposure to certain dopamine agonists. This phenomenon remains to be rationalized in light of other recent studies that indicate that dopamine supersensitivity induced by neuroleptics can be prevented or reversed by treatment with an agonist or precursor such as L-dopa (110). The sensitivity-enhancing effect of agonists (amphetamine and apomorphine have most commonly been studied) may reflect *presynaptic* actions of such drugs as amphetamine and apomorphine which reduce the synthesis, turnover, and release of dopamine (111, 112), possibly at lower doses than required for postsynaptic effects (104-114). Amphetamine, at least, can exert this effect for many hours after its initial dopamine-enhancing and behaviorally stimulating actions (113).

Alternatively, apomorphine and other newer dopamine agonists may be "partial agonists" at dopamine receptors, possibly leading to a net reduction in effects in competition with the natural agonist, dopamine (115, 116). Apomorphine might also act by selectively reducing sensitivity of presynaptic receptors to dopamine, thus facilitating the turnover and release of dopamine (104, 117). The paradoxical effect of dopamine agonists to induce further supersensitivity indicates a need for a cautious approach to recently suggested therapeutic approaches to tardive dyskinesia (and even schizophrenia) using low doses of dopamine agonists (notably L-dopa or apomorphine) for their apparent antidopamine effects (56) or by gradually increased and repeated exposure to dopamine agonists such as L-dopa in the hope of "resuppressing" dopamine receptors and thus diminishing their sensitivity (57). Since it has recently been found that, in contrast to apomorphine itself (90), long-acting ester "prodrugs" of apomorphine (116) induce *tolerance* to their behavioral and dopamine-turnover suppressing effects (117), they may suppress dopamine receptor sensitivity, and so be potentially useful for the treatment of TD or even of psychoses.

Another feature of dopamine supersensitivity that must be considered in the attempt to evaluate animal models of mechanisms underlying TD is the differential ability of various classes of neuroleptics to induce supersensitivity. Since certain "atypical" antipsychotic drugs

(notably thioridazine, clozapine, and sulpiride) are relatively less likely to induce *acute* extrapyramidal effects in patients, or presumably analogous actions in animals (such as inducing catalepsy or antagonizing dopamine receptor agonists), it has been suggested that they may produce tardive dyskinesia less often than other neuroleptic agents. This prediction seems to be supported by clinical experience with thioridazine compared with many other antipsychotic agents, although this point has not been evaluated critically. Clozapine and sulpiride have not been associated with tardive dyskinesia, although they are experimental drugs and have not yet been used for prolonged periods in many patients. The ability of one or more of these agents, after repeated administration, to induce behaviorally supersensitive responses (83-85) to a dopamine agonist such as apomorphine (or tolerance to dopamine turnover-enhancing actions of neuroleptics [86, 87]) has been reported, but this appears to be an inconsistent or relatively weak capability (81, 82, 86). Moreover, the suggestion that these "atypical" agents have less impact on the extrapyramidal motor system because of relatively strong anticholinergic actions (118) is probably not entirely correct. They may simply have regional selectivity, with a preference for limbic dopamine receptors (119). Thus, while thioridazine and clozapine are strongly anticholinergic (their antimuscarinic potencies approach those of tricyclic antidepressants [118], and they can induce a toxic state similar to atropine poisoning on overdosage [120]), sulpiride is not especially anticholinergic (121). Furthermore, the biochemical and behavioral actions of the "atypical" antipsychotic agents are not mimicked by combining a more typical neuroleptic with a centrally active antimuscarinic agent (80, 81-82), nor is there any clinical evidence that anticholinergic-antiparkinsonism agents tend to diminish the risk of TD (2). Rather, there are some speculations that they might even increase the risk (65, 122), based largely on the tendency of anticholinergic drugs to worsen existing signs of tardive dyskinesia (2, 65, 122). In addition, anticholinergic agents may (81-83) or may not (67) increase dopamine supersensitivity induced by neuroleptics.

While denervation or disuse supersensitivity is a reasonable explanation of much of the above evidence indicating enhanced behavioral effects of dopamine agonists following treatment of animals with neuroleptics, the synaptic mechanisms by which the phenomenon is produced remain open to question. The enhanced responses to apomorphine, which is believed to act primarily directly on dopamine receptors (67, 123), and the persistence of the enhanced behavioral responses for at least several weeks in most of these studies (67, 76, 77)

suggest that changes in receptor sensitivity rather than in presynaptic metabolism of dopamine may account for the findings.

Disuse supersensitivity: neurophysiological and biochemical evidence

Several studies have attempted to identify changes in the postsynaptic sensitivity to dopamine following denervation more directly than in behavioral experiments. In neurophysiological studies, destruction of dopamine-containing neurones of the nigrocaudate pathway of cats with intraventricular (124) or intranigral 6-hydroxydopamine (39, 125, 126) or repeated pretreatment with haloperidol (127, 128) all produced a significant increase (as much as 100-fold [126]) in the sensitivity of caudate neurons to microiontophoretically applied dopamine. However, in one of these studies (129) electrolytic lesions of the ventral tegmentum (which reduced levels of all caudate biogenic amines) depressed rather than enhanced the effect of microiontophoretically applied dopamine upon caudate neurons. Several biochemical approaches have also been employed.

A biochemical strategy to detect possible receptor changes produced by denervation has been the study of dopamine-sensitive adenylate cyclase in denervated brain regions, based on the proposal that hormone-sensitive cyclase activity reflects receptor stimulation (37, 130). An increase in adenylate cyclase response to norepinephrine in rat cerebral cortex in 6-hydroxydopamine-pretreated (131-133) as well as reserpine-pretreated (134) animals has been demonstrated, but the effect of 6-hydroxydopamine is sometimes inconsistent and may not bear a close relationship to small changes in binding of β-receptor labeling agents (133). Unilateral destruction of the nigrostriatal tract (135-137) and prolonged treatment of the rat with trifluoperazine or haloperidol (112, 138, 139) have been reported to induce an increase in responsiveness of dopamine-sensitive adenylate cyclase in some preparations of neostriatal tissues which may reflect supersensitivity of dopamine receptors. However, these effects of drugs or even lesions on catecholamine-sensitive adenylate cyclase reactions have usually been relatively small (two- to ten-fold increase in agonist potencies) (133-135) and in some instances have not been found at all in the striatum (137, 139, 140). In spite of failure to demonstrate supersensitivity consistently by this method, the possibility remains that alteration of the dopamine receptor occurs at some other point in the receptor or "effector" mechanisms which may not be adequately reflected in changes of adenylate cyclase activity.

In another biochemical test, it has been noted that prolonged

treatment with a neuroleptic drug altered the ability of a dopamine agonist to depress the synthesis rate and turnover of dopamine in rat corpus striatum. This pretreatment led to a greater dopamine turnover-inhibiting effect of a dopamine agonist alone and enhanced the ability of such an agonist to block the dopamine-depleting effect of α-methyltyrosine (84). These observations have been considered to be consistent with supersensitivity to dopamine of central receptors believed to modulate the neurophysiologic and biochemical activity of nigrostriatal dopamine neurons (84).

In yet another biochemical approach to the study of receptors, several groups have recently reported the labeling of dopamine receptors in mammalian brain (41, 42) with tritiated dopamine or apomorphine, and haloperidol or spiroperidol, which might label distinct agonist and antagonist states of the receptor, respectively (141), or more likely, similar but different binding sites (142-145). It has been found very recently that kainic acid, which selectively destroys many "GABAergic" and cholinergic neurons in the caudate nucleus believed to be receptive to dopamine, reduces the binding of the radioligand ^{3}H-haloperidol markedly and almost completely removes the activity of dopamine-sensitive adenylate cyclase (146). These observations support the idea that both biochemical measures reflect, at least in part, changes occurring at post-synaptic dopamine receptors. In rats, 6-hydroxydopamine-induced lesions of dopamine-containing neurons in the substantia nigra led to enhanced binding of some of these labeled ligands (147-150), presumably to dopamine receptors, but, inconsistently, increased (148) or decreased (151) labeling by ^{3}H-apomorphine (possibly a selective presynaptic agent). Decreases have also been observed with tissue from brains of patients with Parkinson's disease (151). Increases have also followed prolonged treatment with neuroleptic drugs (110, 152, 153). Moreover, these changes have recently been found to correlate well with the degree of behavioral supersensitivity to apomorphine appearing in the same animals (139, 147) and to be prevented by simultaneous treatment with the dopamine precursor L-dopa (110). Further support for the usefulness of this approach was obtained by the survey of changes in the level of labeling with a variety of tritiated putative receptor-labeling ligands following prolonged treatment of the rat with haloperidol (154, 155). Thus, there was a significant increase in binding to presumed dopamine or neuroleptic sites in striatal and limbic tissue, although not in pituitary tissue (154, 155), and little change in binding to serotonin, norepinephrine (α-receptor), or acetylcholine (muscarinic) sites in the brain (154). The latter result regarding muscarinic sites seems inconsistent with a recent report of enhanced behavioral

responsiveness to atropine and decreased responsiveness to physostigmine in haloperidol-pretreated mice, consistent with a *diminished* sensitivity of central muscarinic acetylcholine receptors (156).

Other recent data, in addition to increases in binding site density of dopamine-receptor labeling ligands, also suggest the involvement of macromolecular mechanisms in supersensitivity to dopamine agonists following pretreatment with antidopamine agents. In one study, protein synthesis inhibitors prevented induction of such supersensitivity by α-methyltyrosine (105). This result is paralleled by the ability of cycloheximide, an inhibitor of protein synthesis, to block the CNS denervation supersensitivity to serotonin agonists after lesioning with a selective serotonin-neuron toxin (157). It has also been suggested recently that a Ca^{++}-binding protein activator of dopamine-sensitive adenylate cyclase (calmodulin) may contribute to the supersensitivity to dopamine induced by typical neuroleptics (but not by clozapine or the inactive isomer of butaclamol) (158).

Thus, the various biochemical studies reviewed provide strong supporting evidence of possible receptor-macromolecular changes in neuronal membranes that might underlie the behavioral supersensitivity to dopamine that follows prolonged exposure to neuroleptics. This and other ways in which apparent overactivity of dopamine systems might occur are summarized in Table 11.

Attempts to evaluate the disuse supersensitivity concept in man

Some of the newer biochemical approaches to the study of receptors of neurotransmitters and transmitter levels in the brain have begun to be applied to postmortem studies of neuropathology in human brain tissue. For example, the report that dopamine levels in

TABLE 11

Ways in which apparent functional overactivity of dopamine (DA)-mediated neurotransmission might occur

1. Increased synthesis or release of DA
2. Increase of DA receptors or "effectors"
3. Decreased feedback modulation of DA cells (eg, by GABA or substance P) [a]
4. Decreased activity of parallel antagonistic systems (eg, cholinergic) [b]

[a] Such a situation may occur in Huntington's disease in which DA is not over-abundant but GABA is deficient in postmortem brain, while potent neuroleptics are therapeutic (63,168,229).

[b] Just the opposite may occur in Parkinson's disease, in which DA is deficient in postmortem brain, but anticholinergic agents are often therapeutic; whereas in tardive dyskinesia cholinergic agents or anti-DA drugs may help (1,2).

the basal ganglia normally decrease with advancing age (159) may contribute to increased sensitivity of dopaminergic mechanisms to neuroleptic agents. Such increased sensitivity may predispose older patients to tardive dyskinesia and may somehow contribute to an increased likelihood of long-lasting oral-facial dyskinesias. Interestingly, older rats seem to be more susceptible to development of supersensitivity to dopamine agonists after treatment with neuroleptic drugs (160, 161). Older rats are also more sensitive to extrapyramidal behavioral effects of such drugs (A. Campbell and R.J. Baldessarini, unpublished observations, 1980).

It has also been reported recently (162), but not confirmed (142, 143), that dopamine levels or those of its metabolite homovanillic acid may be increased in the brains or CSF of chronic schizophrenic patients, almost all of whom have been exposed to prolonged treatment with neuroleptic-antipsychotic drugs. Dopamine-sensitive adenylate cyclase activity was not different from normal in one postmortem study of brain tissue of similar patients (163). In the brains of patients with Huntington's disease (164, 165) and Parkinson's disease (164, 166), receptor-labeling techniques with radioactive ligands have been applied recently. In Huntington's disease, the number of ^{3}H-neuroleptic binding sites per mg of tissue or protein sampled from the basal ganglia was reported to be decreased more than 50 percent (165)—a finding that is consistent both with a post-synaptic location of many dopamine receptors on cholinergic or GABAergic neurons (146) and with the degenerative loss of such cells in Huntington's disease (164). In parkinsonian caudate nucleus tissue, ^{3}H-neuroleptic binding sites were also somewhat diminished in one study (167), but increased in another, suggesting the presence of denervation supersensitivity (151). While the first observation may seem to contradict the prediction that a loss of nigrostriatal dopamine, as occurs in Parkinson's disease (168), would increase the density or efficiency of dopamine receptors, it may reflect the modern prolonged treatment of such patients with L-dopa or other dopamine agonists (167).

More recently, it has been reported that the basal ganglia and limbic tissues of chronic schizophrenic patients contain increased binding sites for some (^{3}H-labeled neuroleptics), but not all (^{3}H-apomorphine, which may label presynaptic sites preferentially [142, 151]) of the currently employed radioactive ligands proposed to label dopamine receptors (142, 144, 169). This phenomenon, if it can be replicated (and results from two other laboratories using ^{3}H-spiroperidol seem to be disconfirmatory [170, 171]), may reflect changes induced by prolonged treatment with antipsychotic agents, although in a few patients said not to have been exposed to such

treatments, there was a similar increase in binding of radioactive haloperidol or spiroperidol (142, 169).

Another strategy aimed at the evaluation of possible supersensitive dopamine receptor mechanisms in patients has been the study of endocrine responses believed to be regulated in part by small tuberoinfundibular dopamine-containing neurons of the hypothalamus that influence the function of the anterior pituitary or adenohypophysis. Most of these studies have included assays of blood levels of prolactin or growth hormone in schizophrenic subjects with or without signs of tardive dyskinesia after prolonged exposure to antipsychotic drugs. These studies compared basal levels or responses to a dopamine agonist in such subjects with normal controls. The results of this approach in animals or man have not supported a dopamine supersensitivity hypothesis in tardive dyskinesia (51, 172–175). On the other hand, one need not expect this approach to be productive since it has been demonstrated repeatedly that hypothalamic dopamine neurons are peculiarly unable to develop tolerance to the dopamine-turnover enhancing (176) and endocrine altering (e.g. prolactin-increasing) (177, 178) actions of neuroleptic drugs, whereas evidence of tolerance to their dopamine antagonistic effects in the forebrain is abundant (e.g., 78, 92). Since, elsewhere in the CNS, receptor supersensitivity is commonly associated with increased tolerance to the prolonged antagonism of dopamine's actions (104), although almost never in the tuberoinfundibular system (84), the neuroendocrine approach may not be an appropriate one for the evaluation of changes in the dopamine receptor. In addition to this theoretical objection, artifacts due to effects of residual neuroleptic drugs in the brain are extremely hard to eliminate in experiments of this type. Interestingly, it has recently been noted that increased binding of ^{3}H-haloperidol after prolonged neuroleptic treatment in rats was found in striatal, but not in pituitary, tissues (179).

One other clinical approach to the evaluation of central effects possibly mediated by dopamine has been the measurement of nausea-producing threshold doses of intravenous apomorphine in normals and drug addicts compared with chronic schizophrenic subjects (not necessarily with TD) previously exposed to neuroleptics. Again no differences were found (180).

Although denervation or disuse supersensitivity may be produced experimentally in animals and may be an important mechanism in transient and reversible clinical forms of tardive dyskinesia, especially in younger patients (2), it seems improbable that this mechanism alone is responsible for the development of the more persistent forms of TD. The usually prolonged and frequently irreversible course of the syn-

drome seems inconsistent with a relatively transient, purely pharmacologic state of disuse supersensitivity.* It suggests instead that significant structural or other neurotoxic changes have taken place, possibly at the postsynaptic receptor, and are related to known effects of neuroleptic agents on cell membranes or cellular respiratory mechanisms, for example (182, 183). One might also speculate that antipsychotic drugs may interfere with synaptic transmission of some unidentified "trophic" factor, thereby producing alterations in the postsynaptic membrane analogous to those described after denervation of the neuromuscular junction (184). Available clinical approaches to the detection of supersensitive responses to dopamine agonists *in vivo*, or to the demonstration of altered dopamine receptors in brain tissue, have so far not produced convincing support of the disuse supersensitivity hypothesis for TD, though clearly such studies are still at a very preliminary state of development.

Presynaptic mechanisms

Although alterations in postsynaptic receptor mechanisms in the nigrostriatal system have generally received greater attention, the possibility that prolonged exposure to neuroleptics may permanently alter presynaptic mechanisms is also worthy of consideration. A possible explanation for the apparent increase in dopamine activity in tardive dyskinesia might be its increased availability through the well-known increase of dopamine turnover in response to neuroleptic drugs (34, 35). This biochemical response is paralleled by an increase in the firing rate of dopamine neurons in the midbrain on acute systemic administration of these agents (38). These effects seem to represent acute, possibly adaptive or compensatory responses to the blockade of dopamine-mediated synaptic transmission by neuroleptic agents. However, in animal experiments, accelerated turnover of dopamine in response to neuroleptic drugs is reported to be only a transient effect, at least in the caudate nucleus and to some extent in portions of the limbic system, although not in the hypothalamus (92, 176, 185-187). In some studies prolonged treatment of the rat with neuroleptic agents was actually associated with decreased striatal dopamine turnover 24 hours following termination of the neuroleptic treatment (186, 187). There is currently some debate as to whether

*Recent very prolonged studies of neuroleptic treatment in the rat, equivalent to several years of treatment in man, indicate that supersensitivity to dopamine agonists can evolve *even while treatment continues* (i.e., a net increase and not merely return to pretreatment baseline), and that some changes can persist for the human equivalent of many months or even years (181). These observations are thus a much more compelling model of TD than similar short-term studies have been.

"atypical" antipsychotic drugs such as clozapine and sulpiride induce tolerance to their dopamine turnover-enhancing effects, and especially whether they do so in the mesolimbic and mesocortical systems. Evidently they can do so if *large* doses are used; the effects are most evident in the nigrostriatal system (86, 87). In man, however, there is evidence that increases in the lumbar cerebrospinal fluid (CSF) levels of homovanillic acid (HVA, a major metabolite of dopamine and presumably an index of dopamine turnover) persist during several months of treatment with neuroleptic agents (188-190), although diminishing elevations have been observed after the first few weeks of treatment (190-192).

Attempts to evaluate dopamine turnover in patients with TD include several studies of dopamine metabolites in the lumbar CSF that have yielded conflicting results. In three studies, the rise of lumbar CSF concentrations of HVA measured after probenecid (to block its exit into the venous blood) was normal (192-194); and levels of 3′,5′ (cyclic) adenosinemonophosphate (cyclic AMP), production of which is stimulated by catecholamines in CNS tissue, were normal or somewhat depressed (194). In addition, CSF levels of HVA failed to distinguish children with neuroleptic withdrawal-emergent dyskinesias (195). In another study (196) dopamine turnover, as estimated by this probenecid method, as well as by the response of HVA levels in the CSF to haloperidol treatment, was diminished in patients with tardive dyskinesia. Chase (196) suggested that low CSF levels of HVA in these patients might either reflect structural changes in dopamine neurons or functional responses to altered sensitivity of dopamine receptors.

It has been suggested (197) that increased sensitivity to dopamine in TD might occur because of impaired presynaptic reuptake and inactivation of dopamine, either due to pre-existing subclinical disease of the nigrostriatal system (26) or toxic effects of neuroleptic drugs insufficient to produce extrapyramidal signs but sufficient to interfere with reuptake mechanisms. According to this hypothesis, however, one might expect choreoathetotic dyskinesias to occur early in the course of nigrostriatal damage associated with idiopathic Parkinson's disease, but this does not occur. It has been reported recently that treatment with chlorpromazine may even increase the numbers of presynaptic vesicles in some neurons (198), sites in which neurotransmitter molecules may be stored.

Several recent studies of the effect of prolonged administration of neuroleptic drugs on presynaptic dopamine metabolism have produced somewhat conflicting results but are worthy of consideration. As already discussed, in at least two studies, prolonged administration of neuroleptics to rats led to a reduction in dopamine turnover in the

basal ganglia but not in limbic areas or cerebral cortex when measured 24 hours following discontinuation of the treatment (186, 187). In addition, Velley et al. (199) have shown that prolonged treatment of newborn rats with a neuroleptic agent led to reduced dopamine synthesis and turnover in the striatum at 40 days of age. Although this reduction in dopamine turnover could be explained on the basis of supersensitivity of dopamine receptors leading to feedback inhibition of nigrostriatal activity (92), a direct effect of neuroleptics on dopamine neurons could not be excluded (199). In contrast to studies of the effect of sustained and prolonged exposure to neuroleptic agents to decrease dopamine turnover, one study found that upon termination of long-term administration of penfluridol, a hyperkinetic syndrome appeared in the rat together with evidence of increased receptor sensitivity and an increased rate of dopamine turnover (200). Another similar study failed to find an increase in dopamine turnover after prolonged treatment with haloperidol, and in addition found increased sensitivity to the dopamine turnover-reducing action of apomorphine—another effect that may be mediated by supersensitive receptors (201). The above animal studies, involving relatively brief exposure to neuroleptics (weeks) and carried out under varying circumstances, are subject to several interpretations. At present they must be regarded as of uncertain relevance to an understanding of TD in patients exposed to antipsychotic agents for many months or years. Newer studies of very prolonged treatment of laboratory animals with neuroleptic agents may better model the pathophysiology of TD.*

An additional presynaptic mechanism to be considered is that nigrostriatal neurons may contain dopamine-sensitive *auto*receptors important for feedback inhibition of nigrostriatal dopamine activity (104, 202, 203). Recently, evidence has been presented that the dendrites of dopaminergic neurons in the substantia nigra contain dopamine (204), apparently in a releasable form (205, 206). It has been suggested that these dendrites may mediate self-inhibition of dopamine neurons at dendro-dendritic synapses (205-207). However, this concept fails to account for observations that, although intravenously administered neuroleptics reversed the inhibitory effect of dopamine agonists on nigral firing rates, chlorpromazine applied directly to dopaminergic neurons in the substantia nigra had little or no effect and did not block the inhibitory action of dopamine (202, 208). Moreover, the observation that lesions that remove most of the dopamine-sensitive adenylate cyclase from midbrain did not injure nigrostriatal neurons (but removed GABA and substance P) further

*See Trabucchi M, Albizzati MG, Frattola L, Scarlato G: Hemiparkinsonism, a human model for studying dopaminergic supersensitivity. Arch Neurol 36:246-249, 1979.

calls this hypothesis into serious question (209), although the dendrites may modulate the activity of other nearby cells in the substantia nigra.

The observation that low doses of apomorphine depressed locomotor activity while high doses increased it has been explained on the basis of activation of dopamine autoreceptors (location, e.g., in the nigra or striatum, not specified) such that motility changes produced by apomorphine may reflect a balance between presynaptic and postsynaptic effects (203, 210). The observation that, unlike the dyskinesia-enhancing effect of L-dopa (211), apomorphine (56) and several other dopamine agonists (212) may suppress tardive dyskinesia and other forms of choreoathetosis (56, 116) can be interpreted along similar lines. Whether prolonged administration of neuroleptic drugs might damage this hypothetical self-regulatory system, thereby leading to inappropriately increased dopaminergic activity, is unknown.

Two other presynaptic mechanisms should also be considered. One is the phenomenon of neuronal "sprouting" following partial neuronal lesions that leave the perikaryon intact, and which has been observed in central catecholamine neurons following both electrolytic (213) and 6-hydroxydopamine-induced lesions (214). A second mechanism is suggested by evidence that partial lesioning of nigrostriatal neurons leads to increased dopamine turnover in the remaining cells (215). Whether these experimental phenomena, the clinical relevance of which is uncertain, can contribute to an understanding of the pathophysiology of tardive dyskinesia is only speculative at present. The phenomenon of sprouting and excessive regeneration might now be approached neuropathologically in postmortem studies of the brain by the application of recently developed immunohistochemical techniques to visualize central dopamine projections (216).

Other neurotransmitters

The possibility that changes in other neuronal systems may account for dopamine sensitivity or offer independent contributions in tardive dyskinesia has not been widely studied. For example, tardive dyskinesia could represent toxic or destructive effects on striatal interneurons on which dopamine usually exerts an inhibitory effect, which in turn may have a physiological feedback influence on nigrostriatal dopamine neurons or serve as an output pathway for nigrostriatal projections (217). Such interneurons may utilize acetylcholine (ACh) (218, 219) or gamma-aminobutyric acid (GABA) (111, 220) or a peptide

such as substance P (209) as their neurotransmitter. A similar phenomenon has been suggested to occur in Huntington's disease (160, 165, 167, 219). Although postmortem biochemical and histochemical studies of neuronal systems that utilize ACh or GABA are now feasible (162, 165, 167, 219, 221–223), they have not yet been reported in brains from patients with tardive dyskinesia. Such studies in patients with chronic schizophrenia who have also received long-term treatment with neuroleptic drugs so far reveal little consistent evidence for deficiency in enzymes used in the metabolism of ACh (221, 223).

There are postmortem studies which suggest that GABA levels (222) or the activity of the enzyme that produces GABA (glutamic acid decarboxylase, GAD) may be decreased in several brain areas of chronic schizophrenics exposed to antipsychotic drugs (160, 221, 222), although other very recent reports failed to confirm a decrease of GAD (224-226) or of binding of ^{3}H-GABA (226). If centrally effective agonists of GABA become available for clinical use (227–230), they might be worthy of trial in tardive dyskinesia, particularly in light of these recent neuropathological findings (160, 221) and the evidence that neurons utilizing GABA as a neurotransmitter may have inhibitory effects on nigrostriatal dopamine neurons (111, 231, 232). Sodium valproate has recently been claimed to be of moderate but inconsistent benefit in various dyskinesias and may be such a GABA-facilitating agent (230, 233).

So far there is little evidence for deficits in other neurotransmitter systems or of benefits of agents that modify their action in patients with TD, with the possible exception of ACh-potentiating drugs (2, 11).

There is considerable clinical, animal behavioral, physiologic, and biochemical evidence for a reciprocal functional relationship between dopaminergic and cholinergic mechanisms in the basal ganglia (231, 234). Among extrapyramidal disorders, this relationship is most apparent in idiopathic Parkinson's disease (235) and neuroleptic-induced parkinsonism (236). In animal behavioral models of both hypokinetic and hyperkinetic motor activity, anticholinergic drugs are known to potentiate several effects of dopamine agonists (234, 237, 238). Moreover, this reciprocal relationship is illustrated by biochemical studies that demonstrate both dopaminergic regulation of striatal cholinergic activity (239-241) and cholinergic regulation of striatal dopaminergic activity (242-244). In addition to the above findings, recent studies suggest that there may also be cholinergic regulation of nigrostriatal dopaminergic activity at the level of the substantia nigra (202, 245).

With regard to the first of these mechanisms, acute blockade of dopamine neurotransmission by antipsychotic drugs increases the turnover and release of acetylcholine within the striatum, while dopamine agonists exert the opposite effects (239, 241), suggesting that the nigrostriatal dopamine system may exert an inhibitory effect on striatal cholinergic interneurons (246). Viewed in terms of this possible relationship, the effect of a dopamine antagonist to disinhibit (facilitate) activity in striatal cholinergic neurons may be mimicked by administration of a cholinergic drug while, conversely, the inhibitory effect of a dopamine agonist on striatal cholinergic activity may be mimicked or potentiated by an anticholinergic drug. By the same token, the effect of a dopamine agonist or antagonist may be blocked by cholinergic or anticholinergic drugs, respectively (see 234 for further discussion). It has recently been reported that repeated treatment with a neuroleptic drug can *diminish* behavioral effects believed to be mediated by central muscarinic ACh receptors (156). This result is consistent with the view that some diminution of ACh function may contribute to apparent functional overactivity of dopamine. In addition, prolonged treatment with a neuroleptic agent may also modify noradrenergic mechanisms in the CNS (247).

Although, as previously noted, a reciprocal balance between dopaminergic and cholinergic effects in the basal ganglia is evident in spontaneous and drug-induced parkinsonism (235, 236), evidence for a similar relationship in choreiform disorders in general, and tardive dyskinesia in particular, has been less consistent (2, 11). When neuroleptics are withdrawn, as drug-induced parkinsonism becomes less prominent, signs of TD increase (3). When anticholinergic drugs are used to treat drug-induced parkinsonism in patients also manifesting tardive dyskinesia, reduction of parkinsonism is associated with a reciprocal increase in severity of tardive dyskinesia (248, 249)—an effect that is not surprising in view of the worsening effect of anticholinergic-antiparkinsonism agents in Huntington's chorea (250) and TD (251), and their occasional capacity to induce dyskinesias in Parksinson's disease (252, 253). While oral administration of anticholinergic drugs frequently, though inconsistently, worsens tardive dyskinesia (54, 122), attempts to produce improvement with intravenous physostigmine, a centrally active anticholinesterase, have, as in the case of Huntington's disease, produced mixed results. Two studies (251, 254) reported mild improvement in TD, but in other studies (54, 255) no consistent beneficial effects were observed following intravenous physostigmine. It is possible that the effect of drugs given intravenously may simply not parallel their oral activity or exert sufficiently

long-lasting effects. Thus, for example, intravenous anticholinergic drugs have variously been reported to produce some worsening in TD (251) or no consistent change (256, 257). It has been suggested that a provocative pharmacologic test might reveal early (and hopefully more readily reversible) stages of tardive dyskinesia, such as by the use of a test dose of an antiparkinsonsim agent (256). However, this does not yet seem to be a useful clinical approach.

Since physostigmine depends for its cholinergic activity on the presence of intact endogenous cholinergic neurons, its variable effects in tardive dyskinesia might be on the basis of damage to cholinergic neurons or receptors (see 160), as is possibly the case in Huntington's disease (162, 258, 259). The fact that in preclinical studies cholinergic mechanisms have been described which either facilitate or inhibit dopaminergic activity (231, 234) may offer yet another explanation for ambiguous effects of cholinergic drugs in choreiform syndromes, depending on the functional balance that is obtained between these potentially opposite effects. It is also possible that clinical attempts to demonstrate cholinergic responsiveness in tardive dyskinesia have been limited simply by the relatively small number of practical and effective centrally active cholinergic drugs that are available. Efforts at the treatment of TD by oral administration of large doses of presumed acetylcholine precursors such as dimethylaminoethanol (deanol) (260) and choline (254, 261, 262) or lecithin (263), although not dramatically or consistently effective or convincingly demonstrated to increase brain levels of acetylcholine (264), are worthy of continued study. Also worth investigation is the suggestion that an orally centrally active reversible anticholinesterase agent, tetrahydro-aminoacridine (THA) (265), may have antidopamine effects in the rat (266).

The possibility has been raised that administration of anticholinergic drugs may increase the incidence of tardive dyskinesia (65, 122) by altering the threshold for appearance of these movements (65). At present there is little evidence to support this assumption although it seems clear that oral anticholinergic drugs generally worsen the syndrome once it has already appeared. Possibly relevant is the observation that the enhanced sensitivity to apomorphine produced by prolonged neuroleptic treatment in animals is only slightly (82, 83) and inconsistently (67) enhanced by the simultaneous administration of an anticholinergic agent. A contributory role of anticholinergic drugs has also been considered in attempts to address the question of whether acute extrapyramidal effects of neuroleptic agents are strongly associated with the later development of tardive dyskinesia. Such an association would also be consistent with the hypothesis that both the early and late extrapyramidal disorders depend on direct or indirect

effects of the blockade of dopamine receptors, respectively. An association between drug-induced parkinsonism and tardive dyskinesia was suggested in at least one study (267), although it has also been reported that TD also occurs in some patients without previous parkinsonism (64, 268), and it is clear that the majority of patients experiencing acute neuroleptic-induced extrapyramidal reactions never go on to develop tardive dyskinesia. One suggestion to explain the apparently inconsistent correlation of early and late neurological signs takes note of microiontophoretic electrophysiological studies of the caudate nucleus which have disclosed two populations of neurons, respectively inhibited or facilitated by dopamine (269). Thus, in order to explain the appearance of TD without previous parkinsonism, Klawans has proposed that these two receptors may not be equally susceptible to blockade with antipsychotic drugs (64, 65). Electrophysiological evidence to support such a differential response has been presented (270) but has not always been confirmed in subsequent studies (39), although a growing body of physiological and pharmacological data that supports such a concept has been reviewed recently (269).

Experimental neuroleptic dyskinesias

An important experimental test of the drug-etiology theory of tardive dyskinesia would be to reproduce the neurological phenomena in laboratory animals following prolonged administration of neuroleptic drugs. Attempts to reproduce tardive dyskinesia in animals generally have had only limited success. Oral dyskinesias have been produced in monkeys by prolonged administration (months) of antipsychotic drugs (271-273). In five out of 15 Rhesus monkeys fed large doses of chlorpromazine daily for up to nine months, buccolingual dyskinesias, biting behavior, and self-destructive acts occurred which were maximal several hours after each dose but ceased when chlorpromazine was discontinued (272). In another study (273), two of six Rhesus monkeys treated with haloperidol for six months developed choreoathetosis and oral dyskinesias which, in one case, persisted for six months after cessation of treatment. More recently, three Cebus monkeys developed buccolingual and some limb dyskinesias following prolonged treatment with haloperidol (274, 275). These reactions in Cebus monkeys had many descriptive and pharmacologic similarities to clinical TD. They differed from acute dystonias, which also occur in Cebus monkeys (276) and the baboon (277) and are typically reversible with antiparkinsonism agents. The Cebus model of TD is currently undergoing intensive study for new therapeutic approaches

to clinical TD (275). Although some dyskinesias produced in these studies more closely resemble the acute dyskinesias (dystonias) seen early in the treatment of patients with antipsychotic agents, others appear to be a valid animal model for tardive dyskinesia. A possibly less relevant model of TD is the production of striking and grotesque oral-facial dyskinesias after repeated treatment of Rhesus monkeys with a combination of chlorpromazine and an amphetamine, or the opioid methadone, which is not known to be associated clinically with late dyskinesias despite prolonged use in addict rehabilitation programs (278).

Smith and Davis (279) have reported an emergence of spontaneous, as well as enhanced dopamine agonist-induced, stereotyped behavior during administration of very high doses of haloperidol to rats for a period of two months. As in the case of the primate studies, this effect was a transient one that followed each dose of neuroleptic and did not appear during the final withdrawal period. It may have more similarity to the acute dystonic reactions to antipsychotic drugs seen in human patients (1). Furthermore, more recent studies in rats treated weekly for nine months with a long-lasting, potent experimental neuroleptic agent (flupenthixol in oil) (280), or with an orally administered soluble neuroleptic (181, 281) revealed minimal neurological impairment during or at the end of this prolonged treatment.

In general, an open-minded attitude concerning the etiology of tardive dyskinesia is appropriate at this time (282, 283). More work can and should be done to study the possible relationship of drug effects and the tardive dyskinesia syndrome. More epidemiological studies in countries where antipsychotic drugs are still not extensively used or are used in consistently different doses than in the United States would be helpful. Transient and more persistent dyskinesias that occur following treatment with neuroleptic-antipsychotic agents may represent a syndrome or reaction pattern and not necessarily a single disease with a unitary pathophysiology. In addition, similar conditions can occur independently in association with senile brain changes and many other overt or presumed states of CNS disease. However, when tardive dyskinesia occurs during the treatment of psychosis with antipsychotic drugs, usually there are no organic, metabolic, or neurological factors found on clinical examination which might contribute to the development of dyskinesias, although this question deserves further study. More attempts should be made to reproduce the dyskinetic phenomena by prolonged administration of drugs to otherwise normal animals, as well as to animals with selective brain lesions,

compromised cerebral circulation, or old age, and to make maximum use of the newer primate models of the disorder. In addition to further studies of patients and living animals, there is a need for further carefully controlled neuropathologic studies in animals and man following prolonged exposure to neuroleptic agents. Classical neurohistology may now be complemented by the use of chemical assays of transmitters and their metabolites, as well as biochemical and immunohistological assays of neuron-specific enzymes and the new assays of neurotransmitter receptors with intensely radioactive ligands. Such methods might be applicable to postmortem human brain tissue for a more direct evaluation of the various hypotheses that denervation supersensitivity occurs in striatal dopamine receptors, that presynaptic changes appear in nigrostriatal or other neuronal systems, or that degeneration of striatal interneurones may occur.

In conclusion, although the etiology of tardive dyskinesia remains unknown, there is considerable clinical pharmacologic evidence to suggest that a functional overactivity of extrapyramidal mechanisms mediated by dopamine is an important aspect of its pathophysiology. An explanation for the prolonged and even irreversible course of many cases of tardive dyskinesia awaits further research, although it suggests that irreversible neurotoxic or degenerative effects of neuroleptic agents may occur.

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CHAPTER V

CLINICAL INDICATIONS FOR PROLONGED NEUROLEPTIC TREATMENT

Introduction

In current American medical practice, neuroleptic agents are used for short-term treatment of acute psychotic episodes or for sustained "maintenance" or preventive therapy. Short-term use can reasonably be defined as treatment of less than six months' duration. The risk of persistent neurologic sequelae in this period of time appears to be very small (except in rare cases of unusually sensitive patients, or perhaps with unusually high dosages). The primary indication for short-term use of a neuroleptic drug is acute psychosis, including *a*) first clinical presentation or exacerbations of schizophrenia; *b*) paranoid states and other acute psychotic episodes of uncertain types (idiopathic psychoses in which a categorical diagnosis is not possible); *c*) mania, when lithium alone is not adequate; *d*) in the control of agitation or psychosis in organic mental syndromes; and *e*) as an adjunctive therapy in severe depressions with psychotic symptoms (see Table 12). These short-term indications are outside the scope of the present report but are discussed in detail elsewhere (1-6); some are discussed along with long-term treatment below.

In short, the neuroleptic drugs are used clinically in virtually any form of psychosis, although these practices remain largely empirical and not always based on controlled studies, with the notable exceptions of acute phases of schizophrenia and allied idiopathic psychoses and psychotic mood disorders. For example, in severe manic excitement when acute control is of primary clinical importance, neuroleptics typically are required in addition to a lithium salt, due to the delayed onset of action of lithium. Evidence of the effectiveness of tricyclic antidepressants alone in depressions with prominent psychotic symptoms is mixed; therefore, some of these patients may be found empirically to benefit from the temporary addition of a neuroleptic agent. For depression, whether or not complicated by psychotic symptoms, antidepressant drugs and electroconvulsive therapy (ECT) remain the basic medical therapies, with ECT being the most rapid means of achieving remission.

TABLE 12

Indications for short-term use of neuroleptics

- Acute psychotic episodes
- Exacerbation of schizophrenia
- Acute reduction of manic excitement when the onset of lithium's action is too slow
- Adjunctive therapy for depressions with prominent psychotic symptoms or when antidepressants or ECT alone may not be successful
- For agitation in delirium, dementia, or severe mental retardation while seeking to identify and treat the primary basis of the problem
- In certain chronic degenerative or idiopathic neuropsychiatric disorders with dyskinesias such as Huntington's disease and Gilles de la Tourette's syndrome
- Childhood psychoses
- Miscellaneous medical indications, notably nausea and vomiting

Other indications for short-term use of neuroleptic drugs which are widely accepted (although not firmly grounded on controlled studies) include states of agitation secondary to acute or chronic brain syndromes, the latter including dementia and mental retardation. There are other occasional non-psychiatric uses of neuroleptic drugs, including for preoperative sedation, adjunctive uses in general anesthesia, and control of nausea or vertigo. They may also be used in the control of neurological or psychiatric manifestations of certain unusual disorders, such as Huntington's disease and Gilles de la Tourette's syndrome, as well as in the psychoses of childhood. Short-term treatment with neuroleptics has also been used in clinical psychiatric practice in empirical attempts to ameliorate the symptoms of a variety of neurotic and characterologic disorders. This latter form of pharmacotherapy has not been adequately tested in controlled scientific studies to permit generalizations or conclusions. In general, the use of antipsychotic drugs, even for short periods of time, often remains a matter of critical clinical judgment regarding individual cases when research data or long clinical experience is not available to guide clinical decisions.

Although antipsychotic drugs are used to treat a variety of acute illnesses and are sometimes given for periods longer than six months in illnesses other than schizophrenia, it is important to emphasize that

there is very little information about most of these uses which comes from controlled clinical trials. It is a possibly surprising and unsettling fact that *compelling scientific evidence for the long-term effectiveness of antipsychotic drugs exists only for schizophrenia.* Even in schizophrenia, few trials have evaluated patients for more than one year, and there is little information about the relationship of dosage to long-term effectiveness. A related problem is that it has become increasingly clear that many (probably *most*) patients with acute psychotic illnesses of brief onset do not go on to develop chronic or frequently relapsing illnesses (7). Such patients may be given a diagnosis such as "acute schizophrenia," "schizoaffective schizophrenia," or "good-prognosis schizophrenia," which may be taken as an indication for prolonged use of a neuroleptic drug by analogy to (chronic) schizophrenia, although neither the identity of such conditions as schizophrenia nor the efficacy of neuroleptics against their future relapses is proven.

Prolonged use (more than six months) of a neuroleptic drug requires careful evaluation of indications and risks; such use is currently best supported with controlled clinical trials for maintenance treatment in chronic psychotic disorders (mainly schizophrenia) in which the patient, although improved, is not symptom-free and is at probable risk of exacerbation or acute worsening of that chronic illness (sometimes loosely referred to as "relapse," although *prophylactic efficacy against truly relapsing or intermittent psychoses is still not proven*). A summary of well-established, possible, and more questionable long-term indications for neuroleptic agents is provided in Table 13. A review of these indications and related matters follows.*

Summary of controlled long-term studies in schizophrenia

Data available from well designed studies show a marked reduction of the exacerbation rates for drug-treated versus placebo-treated

*Our intent in reviewing the available information concerning controlled clinical research on the long-term use of antipsychotic drugs is to summarize what is known and to encourage further research in areas where more information is needed. With regard to the need for further research, it is common for scientifically controlled studies to follow, rather than to lead, the clinical use of medicines. Thus, clinical reports of new uses for already-approved drugs are often the impetus for further controlled studies. This pattern of development in experimental therapeutics is a well-established fact for many agents, including the antipsychotic drugs. It should not be construed as either dangerous or undesirable that uses lacking strong prior scientific demonstration are sometimes undertaken thoughtfully in individual cases, with special care to balance demonstrated benefits against potential risks in the *long*-term use of an antipsychotic agent.

TABLE 13

Possible indications for continuous long-term use of neuroleptics (for more than six months)

Primary indications
Schizophrenia
Paranoia[a,b]
Childhood psychoses[a,b]
Some degenerative or idiopathic neuropsychiatric disorders (notably, Huntington's disease and Gilles de la Tourette's syndrome)[b]
Secondary indications
Extremely unstable manic-depressive or other episodic psychoses (rare)[b]
Otherwise unmanageable behavior symptoms in dementia, amentia, or other brain syndromes[a,b]
Questionable indications
Chronic characterological disorders with neurotic or "borderline" characteristics[a,b]
Recurrent mood disorders[a,b]

[a]Efficacy has not been adequately demonstrated in controlled studies.

[b]Long-term neurological safety has not been demonstrated.

It is important to clarify that there may be times when a neuroleptic drug is used in the short-term management of exacerbations and crises of chronic or recurrent conditions such as those outlined above. Moreover, there may be justifications for even more prolonged uses based on clinical judgment in individual cases and objective demonstration of important benefits. It is also important to clarify that clinical research has not yet provided compelling support for long-term uses in cases other than chronic schizophrenia, nor has it provided evidence that such uses are contraindicated. Clinicians are left to rely on their evaluations of individual patients and on their clinical experience as further research data continue to be gathered and assessed. Thus, the recommendations provided above can only be viewed as tentative and are based on an attempt to balance the available research literature and clinical experience.

patients with schizophrenia (3, 8). The overall mean "relapse" rate with various lengths of follow-up using different kinds and doses of antipsychotic agents in 30 controlled studies has been 16 percent, versus 58 percent of nearly 3,500 patients randomly assigned to an active drug or inactive placebo following initial recovery from an acute phase of chronic schizophrenia, or a difference of three-to-four-fold (highly significant statistically: $p < 10^{-100}$). Table 14 summarizes virtually all of the available reports of double-blind controlled studies of

TABLE 14

Rate of exacerbation of schizophrenia with and without antipsychotic drugs

Authors	*Year*	*(Ref.)*	*Drug*	*Daily Dose (mg CPZ)*[a]	*Numbers of Patients*			*Relapse Rates (%)*		
					Placebo	*Drug*	*Total*	*Placebo*	*Drug*	*Savings*
Zeller et al.	1956	(45)	Chlorpromazine	ca. 300(?)	33	23	56	68	14	54
Shawver et al.	1959	(42)	Chlorpromazine	200	40	40	80	18	5	13[b]
Diamond & Marks	1960	(20)	Phenothiazines	470	20	20	40	70	25	45[b]
Blackburn & Allen	1961	(13)	Phenothiazines	ca. 320	14	25	39	57	12	45[b]
Gross & Reeves	1961	(26)	Phenothiazines	—	73	36	109	58	14	44
Schiele et al.	1961	(41)	Phenothiazines	900,990,1225	20	20,20,20	80	70	10,10,10	60[b],60[b],60[b]
Adelson & Epstein	1962	(10)	Phenothiazines	—	90	191	281	90	49	41
Freeman & Alson	1962	(22)	Chlorpromazine	220	46	48	94	28	12	16[b]
Troshinsky et al.	1962	(43)	Chlorpromazine	175	19	24	43	63	4	59[b]
Whitaker & Hoy	1963	(44)	Perphenazine	240	26	13	39	39	8	31[b]
Caffey et al.	1964	(14)	Phenothiazines	160,375	171	89,88	348	44	15,5	30[b],40[b]
Kinross-Wright & Charalampous	1965	(31)	Fluphenazine	250	20	20	40	70	5	65[b]
Garfield et al.	1966	(23)	Phenothiazines	ca. 600	18	9	27	31	11	20
Melnyk et al.	1966	(34)	Phenothiazines	ca. 350	20	20	40	50	0	50[b]
Englehardt et al.	1967	(21)	Chlorpromazine	200	142	152	294	30,31	15,20	15[b],11[b]
Morton	1968	(35)	Phenothiazines	—	20	20	40	70	25	45
Prien et al.	1968/69	(36,46)	Chlorpromazine	300,2000	189	188,189	566	42	21,15	21[b],27[b]
Prien et al.	1969	(37)	Trifluoperazine	430,2290	107	105,113	325	56	20,20	36[b],36[b]
Baro et al.	1970	(12)	R-16341 (Exptl.)	—	13	13	26	100	0	100
Rassidakis et al.	1970	(38)	Various drugs	—	43	41	84	58	34	24
Clark et al.	1971	(17)	Pimozide	—	10	9	19	70	44	26
Leff & Wing	1971	(32)	Phenothiazines	250	12	18	30	83	33	50[b]

Hershon et al.	1972	(27)	Trifluoperazine	490	32	30	62	28	7	21[b]
Hirsch et al.	1973	(28)	Fluphenazine	ca. 130	38	36	74	66	8	58[b]
Hogarty & Goldberg	1973/74	(29,30)	Chlorpromazine	275	182	192	374	68,80	30,48	38[b],32[b]
Gross	1975	(25)	Trifluoperazine, Pimozide	ca. 500,—	20	20,21	61	62	50,19	15[b],46
Clark et al.	1975	(16)	Thioridazine, Pimozide	ca. 200,—	10	15,14	39	56	14,17	42[b],39
Chien	1975	(15)	Fluphenazine	ca. 170,400	15	16,16	47	87	38,12	49[b],75
Andrews et al.	1976	(11)	Chlorpromazine	ca. 220	17	14	31	35	7	28[b]
Rifkin et al.	1977/78	(39,40)	Fluphenazine	300,ca.450	19	24,19	62	68	8,5	63[b],63[b]
Total or Means ± SEM					1479 (43%)	1971 (57%)	3450 (100%)	55.0±3.6	17.5±2.1	39.6±3.1

Most of the available controlled studies are included. They involve nearly 3,500 patients diagnosed by various methods, presumably randomly assigned to an inactive placebo (43 percent) or to continued antipsychotic drug treatment (57 percent); various drugs and doses used (but note that studies not involving phenothiazines are rare); followed for times usually ranging from a few months to one year; diagnosed as "relapsed" by various criteria (typically, gross psychotic decompensation or rehospitalization). Most of the studies have been reviewed and summarized previously by Davis (8). The mean rate of clinical worsening overall was 55.0 percent (range = 18 to 100 percent) versus 17.5 percent (range = zero to 50 percent) for patients treated with placebo versus drug (most often a phenothiazine, given in daily doses ranging from the equivalent of less than 200, to nearly 2,000 mg of chlorpromazine). If these data are corrected by weighting each study according to the number of subjects, the weighted means are 54.2 percent and 23.4 percent, respectively, for a difference of nearly three-fold. These differences are highly significant statistically: Even a simple t-test (with N = 30 studies) indicates $p < 0.0001$, but when the statistics are evaluated by pooling data across studies by methods described elsewhere (47-49) and reviewed by Davis (8), p is less than 10^{-10} (when N = 3,450 subjects). Other studies have given further support for these conclusions but did not collect or present data in a form to permit their addition to this table (18, 24, 33, 51, 53, 54). If the studies involving neuroleptics at known or closely estimated doses are considered separately, the mean relapse rate with treatment at *less* than the daily equivalent of 500 mg of chlorpromazine (mean dose = 273 mg) was 18 percent, while this rate was 11 percent at higher doses (mean = 827 mg). Doses above 1,000 mg appear to be no better than 300-600 mg (10, 36, 37, 46); an approximately half-maximally effective dose may be less than 250 mg/day (see Fig. 8).

[a]mg CPZ = mg equivalent to chlorpromazine (see Baldessarini, 1977, p. 20 [3], and Rifkin et al. 1977 [39]).
[b]Data used to plot the 30 points in Figure 8.

maintenance treatment of schizophrenia by antipsychotic drugs for more than one month (9-46, 50, 51). These trials were carried out in state, federal, and private inpatient and outpatient facilities in the United States, England, or Europe. The fair consistency of these results, despite the wide variety of settings, patients, definitions of exacerbation, and choices and doses of drugs, is quite compelling in a general way. Nevertheless such studies have several important limitations and leave many questions unanswered.

The studies summarized in Table 14, while providing strong general support for the efficacy of prolonged neuroleptic treatment of chronic schizophrenia, have several characteristics that limit the generalizations that can be drawn from them. Thus the fact that there is a 14 percent difference in the numbers of patients assigned to active drug (57 percent) or inactive placebo (43 percent) suggests that these assignments may not have been perfectly random and possibly that some "sicker" patients ended up remaining on active medication. If such an artifact influenced the results, it might have worked *against* the drug:placebo differences demonstrated. A second characteristic is that the range of results reported varied widely: 18 to 100 percent "relapse" on placebo versus zero to 50 percent on neuroleptic. In part, this variance for patients maintained on drug may reflect the dose of drug given (as is discussed below in regard to Figure 8) or differences in the severity of illness in various groups of patients. Duration of follow-up is another important variable, as the risk of relapse increases with time for at least a year (9, 29, 30; see Figure 6).

The sources of variability of relapse for the placebo-treated patients, however, are more limited, including duration of follow-up and severity of illness or definitions of "relapse" used, as well as diagnostic criteria. The fact that many studies found relapse rates on placebo in excess of 50 percent within four to six months makes it uncertain whether the effect of neuroleptic treatment is truly "prophylactic," as is often assumed, or whether it represents continued treatment of actively and severely ill patients. A corollary of this observation is that a crucial factor limiting the numbers of studies longer than one year must surely be the high rate of relapse of severely ill patients when taken off antipsychotic medication for even a few months. It is important to emphasize that most of these results pertain to severely chronically ill patients, lest the unwarranted conclusion be drawn that it is unwise to attempt to diminish or interrupt drug treatment of *all* psychotic patients. A further indication of the severity of illness of some of the patients studied (or of the limitations of maintenance treatment) is the fact that up to 50 percent of patients given drug still relapsed. On the other hand, this maximum reported rate and the mean

relapse rate on active drug treatment of 17.5 percent should not obscure the fact that relapse on drug was as low as zero percent in some studies, suggesting that some schizophrenic patients may be more strongly affected by antipsychotic drugs than others. Moreover, a wide range of severity of illness must be represented in the studies cited since, although 55 percent relapsed on placebo, nearly half (45 percent) did not—again indicating that not all psychotic patients require prolonged neuroleptic treatment.

Another serious limitation of the available studies is that few types of antipsychotic drugs other than phenothiazines have evidently been adequately evaluated for their long-term protective effects (at least 28 of the 30 studies summarized in Table 14, or 93 percent, involved phenothiazines). Thus it would be useful to have more data regarding the long-term effectiveness of thioxanthenes, butyrophenones, and more recently introduced (e.g., loxapine and molindone) or experimental agents (diphenylbutylpiperidines, sulpiride, etc.). It may also be possible in future research to define better which patients or conditions account for the range of zero to 50 percent relapse on medication, as the optimal matching of patients and neuroleptic regimens is of crucial clinical importance for optimal treatment and the avoidance of neurologic toxicity.

Unanswered questions, in addition to the identification of which patients have the most favorable responses to which drugs, include questions about optimal doses and routes of administration for what length of time and in what pattern of use (e.g., divided versus single daily doses, continuous versus intermittent administration). The available research literature provides at least some suggestions about several of these questions. Thus, in addition to the evidence just discussed that not all psychotic patients, and not even all those diagnosed as "chronic schizophrenic," are equally vulnerable to clinical worsening without antipsychotic medication, there is evidence that all patients do not relapse at the same time and that the pattern of exacerbation is, to some extent, orderly and predictable.

Time-course of relapse in schizophrenia

When data available from the few studies reporting cumulative rates of "relapse" over many months of follow-up treatment with a neuroleptic drug or a placebo are reviewed collectively, a strikingly similar pattern emerges from the majority of studies, as noted previously in a critical review of most of these studies by Davis (8) (see Figure 6). Thus, during the first year at least, the probability of relaps-

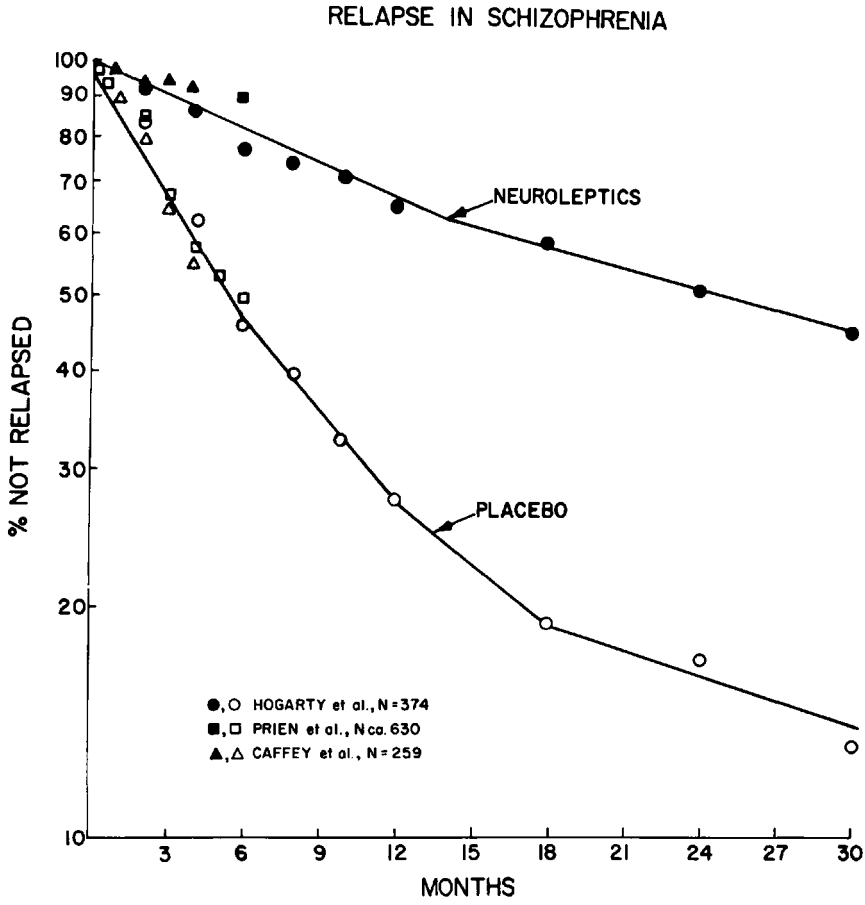

Figure 6. *"Relapse" rates in schizophrenia*

Original data are from studies by Caffey et al. (14), Prien et al. (46), and Hogarty and his colleagues (9, 29, 30, and personal communication). The data of Prien et al. (46) were adjusted by excluding an additional 35 patients who had been treated, prior to a switch to a placebo, with apparent success at doses *less* than the equivalent of 300 mg/day of chlorpromazine (19.6 percent of the total of 178 subjects, only about 10 percent of whom relapsed within six months on placebo).

ing appears to increase approximately linearly when expressed by plotting semilogarithmically the percentage of patients remaining stable versus time. That is, the *rate* of relapse, or proportion of previously stable patients falling ill per month (or other unit of time), is quite steady. This rate for the data depicted in Figure 6 is about seven to 15 percent (say, ten percent) per month for placebo treatment versus one to three percent per month for active drug treatment, or about a five-fold difference. Moreover, the correlation between the logarithm of the rate versus the time at which it is measured (during the first six to 12 months of follow-up) is very high ($r > 0.9$ in all studies for both treatments). Data from other studies also suggest that the risk of clinical worsening of schizophrenia or of rehospitalization follows a logarithmic function, increasing as time passes, and most clearly during the first year (e.g., see 18). The course of relapse may, to some extent, reflect the slow removal of neuroleptic drugs from the body (50-52), at least during early weeks following discontinuation of treatment, although it seems more likely to reflect the natural history of schizophrenia.

One of the rare studies to evaluate schizophrenic patients for more than two years following random assignment to a neuroleptic drug or a placebo is that of Hogarty and his colleagues (9, 29, 30) (although at least one other group has followed schizophrenic outpatients for nearly ten years [21, 53, 54]). Their results suggest (but do not prove, due to the uncertain influence of the "drop-out" of some subjects from the study) that the rate of relapse may slow somewhat after the first year of followup (Figure 6). This suggestive trend is more apparent among patients given an inactive placebo. Even if this pattern of diminishing risk of relapse after the first year is valid, it might not represent a characteristic of all chronic schizophrenic patients. Thus, it is possible that patients called "chronic schizophrenics" are an admixture of subtypes with "good" versus "poor" prognoses, or of those with truly chronic versus more intermittent conditions (including misdiagnosed recurrent severe mood disorders or intermittent atypical psychoses of uncertain diagnostic type). Another very prolonged study further supports the same impression qualitatively. That is, the work of Rosen, Engelhardt et al. (21, 53, 54) indicates a clear diminution of the relapse rate after one year of follow-up (Figure 7), although they found a remarkably low maximum rate of rehospitalization, even on placebo (about 30 percent), with virtually no change between the end of the first and fourth years. One of the practical hypotheses suggested by these considerations is that not all patients *called* schizophrenic may require equal amounts or durations of antipsychotic drug treatment.

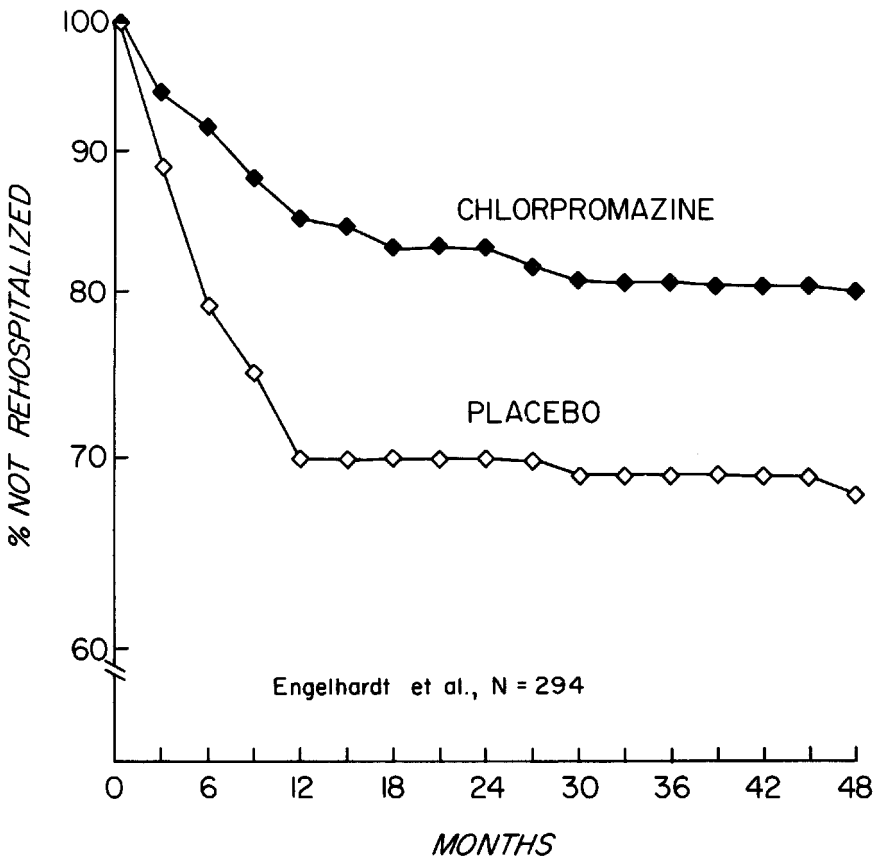

Figure 7. *"Survival" rates in schizophrenia versus time*

Original data are from a study by Engelhardt et al. (21) in the late 1960s presented as "survival" or non-relapse, as in Figure 6. Note the striking dissimilarity to the results in Figure 6 in that only 30 percent of placebo-treated patients diagnosed "chronic schizophrenic," with at least a year of illness prior to index hospitalization, required rehospitalization in a public mental health facility in Brooklyn, New York, within one year (versus only 15 percent of patients given a small dose of chlorpromazine, 200 mg). Moreover, there were few additional relapses in either group for up to four years of follow-up, suggesting that the drug added little after the first year. These results are also at marked variance with the mean relapse rate on placebo of 55 percent in 30 studies summarized in Table 14. These results may suggest either marked diagnostic heterogeneity or unusually high local tolerance of psychopathology outside of the hospital.

Which psychotic patients require maintenance neuroleptic treatment?

Unfortunately, clinically useful guidelines concerning the probable requirement for sustained drug treatment are not yet firmly established, although it is likely that factors predicting a generally favorable prognosis in psychotic illnesses (such as relative acuteness of onset of psychosis after adolescence, effective premorbid personality, prominence of affective features and sustained social relationships, relatively intact cognitive functions, and rapid and virtually full recovery) may also predict greater tolerance of *removal* of an antipsychotic drug (54-57; see also 1, 3, 7). At least one study (46) indicates that the requirement of neuroleptic dosage *prior* to random assignment to a placebo is a good predictor of the risk of relapse within the subsequent six months, in that patients previously requiring the equivalent of more than 500, 300 to 500, less than 300, or 0 mg of chlorpromazine per day relapsed on placebo within six months as follows: 57, 45, 18, and six percent, respectively (other studies have failed to find such a correlation; see 46). While this phenomenon has been suggested as evidence of "tardive" or "supersensitivity" psychosis, perhaps due to drug-induced supersensitivity of forebrain dopamine receptors (58, 59), it seems much more likely to reflect the degree of severity of illness prior to removal of the drug (60; see also Chapter IV).

An important caveat concerning investigations of the type discussed above is that entry into most studies has presupposed a requirement for, or responsiveness to, antipsychotic medication. This criterion may thus introduce a bias in favor of both the efficacy of neuroleptic treatment (Table 14) and the appearance of fairly uniform rates of relapse (Figure 6). An important clinical conclusion is that not all schizophrenic patients require continuous maintenance treatment with doses of neuroleptics as high as may be required for the management of more acute phases of illness. Some may even do well for periods at least as long as many months on no medication at all. To reiterate the important conclusion already discussed: The research evidence supporting a preventive action of sustained neuroleptic treatment in chronic schizophrenia (even as strong as it is [8, 61; Table 14]) should not be taken to endorse the commitment of all psychotic patients to automatic, routine, and uninterrupted treatment with high doses of a potentially toxic class of drugs indefinitely.

It must be emphasized that while the discussion about prolonged treatment with neuroleptics has been concerned so far with schizophrenia, the term "schizophrenia" in the United States has sometimes

been extended to include not only classical "poor prognosis" or "chronic" schizophrenia but also acute psychoses of uncertain type, many cases of manic-depressive disorder, severe "adolescent turmoil," and even severe personality disorders that do not have objective psychotic features (7, 62-67). Within the context of this report, the term schizophrenia is taken to refer to a chronic, poorly remitting psychotic illness lacking prominent affective or organic features (7, 63, 67-71). Using this definition, it is not possible to diagnose schizophrenia from a single psychotic episode with confidence unless the family history is positive for schizophrenia and a premorbid history documents a gradual onset of psychotic symptoms for more than six months prior to initial contact. However, when a patient presents for the first time with psychotic symptoms, the past history and family history are usually not convincing enough to establish a definitive diagnosis. In such instances it is preferable to defer the diagnosis of schizophrenia until the patient can be observed for at least several months.

Many follow-up studies of patients who present with acute psychotic symptoms have found that the great majority either remit or develop clinical features of an affective disorder (7, 65, 66). Only a minority of patients presenting initially with acute psychotic symptoms are found later to actually suffer from chronic schizophrenia. It is prudent, therefore, to use the adequately descriptive but more open-ended term, *acute psychosis* (of undetermined type), for a single, and especially a first, psychotic episode. The patient can then be treated symptomatically with a neuroleptic agent without a commitment to indefinitely prolonged or uninterrupted neuroleptic therapy. The danger in using the term "schizophrenia" following an isolated psychotic episode is that the term might be taken to imply that indefinitely prolonged neuroleptic therapy is warranted, regardless of the later course of the illness. Thus, a very broad definition of the term schizophrenia may indirectly encourage prolonged use of neuroleptic therapy in cases where it may not be required, and so increase the risk of tardive dyskinesia.

To re-emphasize this clinically crucial point, the usefulness of prolonged "maintenance" treatment with antipsychotic drugs is well supported only for chronic schizophrenia, and then only for rather brief periods of follow-up (rarely more than one year). In patients for whom a clear diagnosis and prognosis may not be possible, particularly following a first episode of acute psychosis in a formerly relatively stable personality, a reasonable practice may be to plan to continue treatment with a neuroleptic drug for no longer than a few months following adequate recovery and to reserve longer "main-

tenance" therapy for cases in which the past history or current psychotic mental status strongly indicate it.

Despite the considerable amount of information about rates and probabilities of exacerbations in schizophrenia, there is a need for more data about the interactions between antipsychotic drugs and the natural history of exacerbation itself. Can patients reliably be selected who will require sustained treatment? Are there clinically useful early signs of impending exacerbation? If so, does reinstituting or increasing neuroleptic therapy minimize further symptomatic worsening? Can criteria be established to guide the selection of optimum timing, doses, and duration of such interventions? Information of this nature would allow for the more rational management of prolonged neuroleptic therapy for chronic psychosis.

Maintenance dosage requirements in schizophrenia

One other specific deficiency in the current state of knowledge is that there are few studies of dose requirements for the maintenance phase of neuroleptic therapy. A study by Clark and associates comparing the efficacy of three maintenance doses of chlorpromazine found that a daily dose of 600 mg was associated with better results than 300 or 150 mg (72). Other studies have supported this impression. In one by Caffey and his colleagues (73), 348 schizophrenics were assigned to placebo, low and intermittent doses of a phenothiazine, or sustained and higher doses; relapse rates at four months were 44 percent, 15 percent, and five percent, respectively. In work by Prien et al. (46), already discussed, in a National Institute of Mental Health (NIMH)-sponsored collaboration among seven state mental hospitals involving more than 600 chronic schizophrenics, random assignment to 0, 300, or 1,900 mg of chlorpromazine a day resulted in relapse rates of 40, 13, and six percent, respectively, within six months. The actual acceptance and taking of medication may also have an effect on the risk of relapse. Thus, DelGiudice and his collaborators (18), in a 16-month study of 88 chronic schizophrenics treated with presumably equivalent doses of oral or injected fluphenazine, found relapse rates of 80 percent and 36 percent, respectively, by the end of the first year. On the other hand, a recent study by Hogarty et al. (19) found no significant differences in relapse on oral or injected fluphenazine during the first year of outpatient follow-up.

While such studies suggest that there may be a dose-response relationship in the maintenance phase of neuroleptic treatment, such a relationship cannot yet be defined precisely. Nevertheless, doses

effective in long-term treatment appear to be similar to or somewhat lower than the low-to-moderate doses required for more acute phases of psychosis (1). This impression is supported further by a graphic analysis of data provided in Table 14 which permits correlations between the dose of neuroleptic and the reduction in "relapse" rates in chronic schizophrenia due to neuroleptic agents (Figure 8). Thus, doses equivalent to less than 300 mg of chlorpromazine daily appear to be nearly maximally effective in some studies, and at doses between 100 and over 2,000 mg, there is no obvious dose-effect relationship (Figure 8). Moreover, at least two studies indicate that doses as low as 200 and 360 mg/day yielded exacerbation rates of only five percent (42) and zero percent (34), respectively. Studies involving doses below the equivalent of 500 mg/day (18 percent mean relapse) were nearly as effective as those with doses above 500 mg/day (11 percent relapse); in addition there was little difference in outcome above, versus below, the median dose of 310 mg/day (see Table 14 and Figure 8). Data of this kind are not available for thioxanthenes, butyrophenones, or other newer neuroleptics (with the notable exception of the experimental diphenylbutylpiperidine pimozide [16, 17, 25]), as most of the reported work has involved phenothiazines. Other studies have not confirmed significant differences in the long-term protective effects of the daily equivalent of 300 versus 1,600-2,000 mg of chlorpromazine (36, 37, 74). Nevertheless, as such studies may have compared *adequate* with *excessive* doses, it remains possible that doses that may be only marginally effective in acute phases of psychosis (1) may be adequate for the long-term maintenance of some schizophrenic patients.

This important question clearly deserves further study in view of the suspicion that there may be a relationship between the amount of total exposure to neuroleptics and tardive dyskinesia (see Chapter III). Even though the latter point is not well supported scientifically, clinical wisdom strongly suggests that if daily doses equivalent to about 300 mg of chlorpromazine (or less) are found to be adequate for many patients, higher doses should be used for prolonged periods only when poor results are obtained with lower doses *and* objective gains are demonstrated with higher doses.

Limitations and problems associated with neuroleptic maintenance treatment in schizophrenia

In the early years of introduction of the antipsychotic drugs, their acceptance as something more than mere "tranquilizers" was only

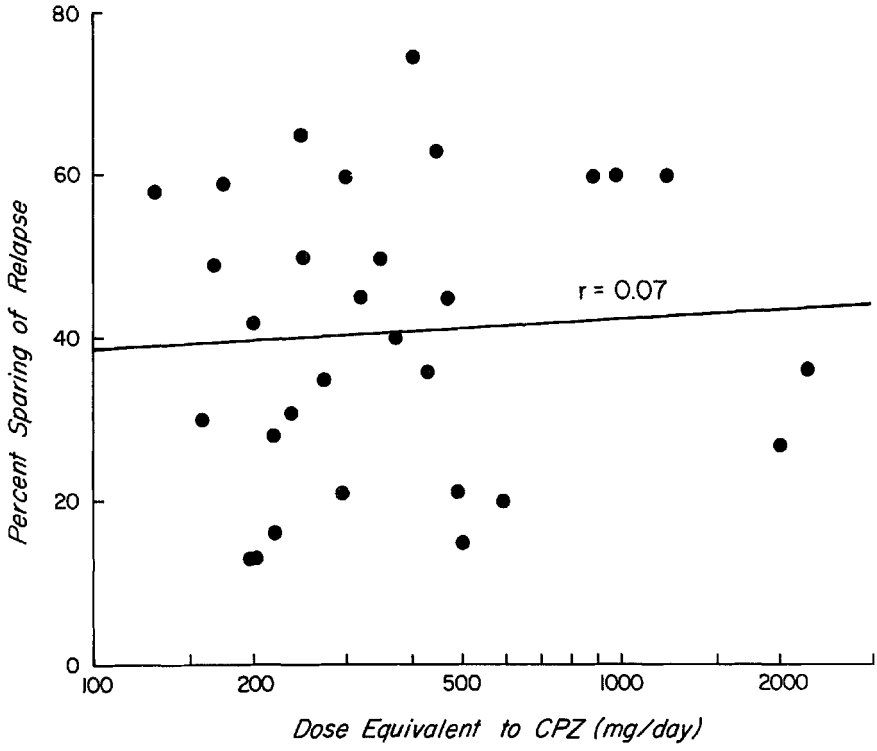

Figure 8. *"Relapse" rates in schizophrenia versus daily maintenance dose of neuroleptic*

Data are taken from Table 14 (indicated by [b]) for studies involving phenothiazines for which information on average dose given permits conversion to the approximately equivalent amount (mg) of chlorpromazine (see Table 1). There was an insignificant relationship between relapse rate on medication versus log dose (r = 0.02) and, as shown here, between the "sparing of relapse due to drug" (relapse rate on drug minus relapse rate on placebo) and log dose (r = 0.07). Moreover, the mean sparing effect at doses below and above the median (310 mg/day) is not different (38 ± 5 percent versus 44 ± 5 percent, respectively). Overall, this display suggests that the available data do not indicate added benefit at doses above 100 to 300 mg/day.

gradual, and the result of accumulation of a mass of compelling research data. An implication of the term "tranquilizer" was that overt signs of agitation were being suppressed, with little modification of the "underlying disease process" or the course of the illness, schizophrenia. Clearly, the evidence previously summarized indicates that not only is the early relief of symptoms and overt signs of psychosis to be expected, with early discharge and return to active participation in the community, but also the level of function is improved in schizophrenic patients treated with neuroleptic drugs, at least over periods of follow-up of a year or so. Whether the availability of antipsychotic drugs has truly modified the life-long pattern of adaptation in schizophrenia in comparison with the best treatments available before their introduction in 1952 is less certain (75).

The introduction of the neuroleptic drugs into American medical practice in the mid-1950s occurred at a time of unusual enthusiasm and optimism about intensive psychotherapy, milieu therapies, and other efforts at rehabilitation of psychotic patients. For a time, it was unclear whether these points of view would emerge as complementary or competing. A minority view seems to have persisted which held that the early suppression of signs and symptoms of psychosis somehow prevented the patient from "working through a growth-promoting experience," which was hypothesized to lead to "more fundamental characterological change" than could be obtained with "mere symptom suppression" alone. While this interesting hypothesis has had occasional anecdotal encouragement, it has never been subjected to rigorous scientific study (76). A more salutary majority view seems to have been that there is no fundamental competition between pharmacotherapy and efforts to understand patients psychosocially and to hasten their maximum recovery by all means available.

The minority view has recently shown signs of revival, in part encouraged by the problem of tardive dyskinesia and other probable toxic effects of the neuroleptic agents in common current use. Aspects of this view are highlighted in several recent essays and treatment proposals (77-79). Since such discussions are provoking healthy debate and a much-needed reassessment of past applications of medical technology in psychiatry, they are very useful. In the rush to enjoy the benefits of the new technology, it is possible that some of its problems and limitations have been underemphasized. Many of these limitations, and the frankly meager data base on which the long-term use of neuroleptic drugs has evolved, have already been reviewed. In addition, several writers have in the past pointed out negative effects of antipsychotic drugs, and the need, as with all medical treatments, to critically balance benefits and undesirable effects. Undesirable effects

include excessive sedation, possible impairment of some cognitive functions, and often-overlooked neurologic side-effects, as well as other more difficult-to-define subjective discomforts (79-84).

Some well-informed critics have also suggested the possibility of mindless routinization of neuroleptic therapy to the point of near-abandonment of thoughtful, critical, and continuous evaluations of each patient (83, 84). In the current era of increased demands for standardization and regulation of medical practice by the profession, by the law, and by consumers and society in general (85-87), consideration of the limitations and problems of antipsychotic drug therapy is especially germane.

To the extent that critics of drug-treatment of schizophrenia emphasize the risks of side-effects and toxicity of antipsychotic drugs, and the fact that many patients do not seem to require indefinitely sustained and uninterrupted medication, they are in close accord with much of the discussion already presented in this report. In addition, it is valid to point out that most of the outcome assessments made in the long-term evaluation of schizophrenic patients have been frankly crude, with an emphasis on the most easily measured changes, such as grossly psychotic behavior or the need for increased medication or hospital care. In fact, regarding the effects of all treatments of psychosis on finer levels of cognitive, psychological, and social function, little has been subjected to controlled scientific study. On the other hand, extensions of critical comments to suggest that antipsychotic drugs may not only be unnecessary for most patients at some times during their illnesses but may be positively harmful, in the sense of making psychosis worse or impairing full recovery, must be judged to be unproven at the present time. A number of methodological problems are apparent in most of the small number of studies which are sometimes cited as evidence supporting the latter hypothesis.

Methodological problems in some studies of experimental therapeutics of schizophrenia

For any study in experimental therapeutics to be valid, a control group is compared against the experimental group. Patients must be randomly *assigned to and remain in* each group, and unbiased assessment must be made periodically to evaluate clinical progress. Lacking random assignment, differences in outcome might be due to biased assignment of patients with dissimilar prognoses to different treatments. It has already been pointed out that the tendency for more

patients to end up on drug than on placebo in the studies summarized in Table 14 may suggest a bias in which sicker patients might receive active medication; if so, this bias would, however, probably work *against* the reported difference in relapse rates for the two groups (if indeed patients with a better prognosis are overrepresented in the placebo groups). In the interpretation of studies comparing antipsychotic medications versus a placebo, other forms of nonpharmacologic treatment, psychotherapy, or even simple custodial care and kindness, one must be especially wary of this type of *bias of assignment,* as well as certain other methodologic pitfalls.

One such methodologic problem can be appreciated by considering the results of a hypothetical study. In this study, a group of young, acutely psychotic patients (diagnoses not certain) are carefully assigned at random to one of two treatment groups, half receiving antipsychotic medication with no other active interventions and half assigned to a psychosocial treatment program without medication. The change in clinical rating scores over the following several months demonstrates a marked average improvement (say by 100 points) in patients treated with medication, as compared with those treated with the alternative method (who, let us say, improved by only 25 points). Thus, there is a 75-point difference in the short-term improvement between the two groups, strongly favoring drug-treatment. Now, in a second long-term follow-up phase of the study, patients in both groups are evaluated at regular intervals while receiving more-or-less at random whatever treatment the community or institution provides. After several years patients who were treated initially without drugs may subsequently improve, say, by another 50 points to a total of 75 points above the starting level. The group who received drugs initially may or may not continue to receive drugs regularly and show partial deterioration of perhaps 25 points (to a level only 75 points above their starting level). Data derived from such a study can now lead to deceptive conclusions: It might be claimed that patients who improve initially without drug treatment do as well (or poorly) in the long run as those treated initially with drugs alone. Furthermore, one could interpret such observations as suggesting that patients who receive drugs initially do worse than those who receive the alternative treatment, since they tend to worsen after initial improvement, while the comparison group undergoes slow but steady improvement. In contrast to this interpretation, it seems quite possible that the later improvement of the group treated initially without drugs may be due to the combination of spontaneous remission (i.e., probably not chronic schizophrenics after all) or the later uncontrolled addition of drug treatment.

Since strong evidence exists for the short-term efficacy of antipsychotic drugs, and there is little scientific support yet for the efficacy of psychotherapy in psychosis, a prudent conclusion would be that the latter interpretation is much more probable. Whether that conclusion is accepted or not, it is clear that such a study certainly has *not proven* the "greater benefits" of the alternative initial therapy. In short, this hypothetical study depicts the fallacy of mistaking the "washing-out" of early effects in the controlled phase of a study *during an uncontrolled follow-up phase* for demonstration of "equiefficacy" of two treatments, or even the "superiority" of the treatment that was less effective in the early controlled phase of the study.

Another methodologic artifact can result from an investigation that employs the same design, granting the assumption that neuroleptic drug treatment is the most efficacious treatment of acute psychoses. That is, patients treated without drugs initially deteriorate to such a degree that many require drugs on an emergency basis or are dropped from the study. Thus, bias is introduced if patients with less severe illness or a better prognosis come to predominate among the survivors of non-pharmacologic early treatment and a relatively greater number of sicker patients remain in the drug-treated group. When both groups are compared later, in the long run the placebo group may show an apparently better outcome because the poorer-prognosis patients were dropped from the study artifactually. A related problem is that some studies of this type have been plagued by low yields of numbers of subjects completing the entire study, not only raising questions about biased survivalship through the study, but also about the great statistical risks in attempting to draw conclusions from apparent differences between small samples, especially when the conclusions are picked out retrospectively and not subjected to rigorous, independent, prospective verification.

All of these types of artifacts should be avoided if a study is to yield valid conclusions. While these methodologic issues may seem obvious, they are highlighted because of their pertinence to literature that includes several studies sometimes cited to support the lack of differences among treatments of schizophrenia, or even of the supposed worsening or "psychotoxic" effect of antipsychotic drugs. Many such discussions appear to be flawed by one or more of these problems, by excessively broad diagnostic criteria that confuse the terms "psychosis" and "schizophrenia," or by failure to differentiate changes in the clinical features of schizophrenia with social and administrative attitudes about the management of psychotic patients (e.g., see 54, 55, 61, 75, 78, 79).

Use of antipsychotic drugs in psychoses other than schizophrenia

In addition to the use of neuroleptic drugs in the treatment of schizophrenia, they are also used in the treatment of a variety of other conditions. The empirical use of neuroleptics in mania, paranoid disorders, and acute psychoses of uncertain type is widely employed in clinical practice. For mania and other acute psychotic illnesses, including paranoid states, neuroleptics appear to be useful for controlling symptoms and hastening remission. In mania, neuroleptics are often used early in the treatment course since lithium typically requires seven to ten days to exert clinical effects (88); this use is well documented in many studies (88-97). Nevertheless, other than for early control of symptoms, lithium salts rather than neuroleptics are the drugs of choice for prolonged treatment of recurrences of manic-depressive illness (98).

Except for short-term use in mania, the use of neuroleptics in other acute psychotic illnesses has evidently not been well evaluated by controlled scientific trials, although these uses are widely accepted on an empirical basis in clinical practice. One possible exception to this generalization may be the use of antipsychotic drugs in the management of psychotic or other severe behavioral disorders of childhood (the relationship of these to adult psychotic syndromes remains problematic and uncertain), for which a few controlled studies (mostly short-term) exist (99-109). Often the dose of a neuroleptic drug can be reduced and then discontinued after a few months in such disorders when remission has been achieved. Neuroleptic therapy beyond a few months after recovery from acute psychosis is usually not necessary clinically, nor is its hypothetical "prophylactic" effectiveness supported by a single controlled, prospective study. If psychotic symptoms continue in an acute illness despite vigorous neuroleptic treatment for several months, or if symptoms recur when the dose is reduced, the patient should be re-evaluated diagnostically for the possibility that the acute presentation represented an early phase of schizophrenia, an organic mental syndrome, or another chronic illness.

It is important to re-emphasize the conclusion that *there are no studies of maintenance neuroleptic treatment in psychotic disorders other than schizophrenia,* not even in manic-depressive illness. Therefore, maintenance use of neuroleptic medications in such conditions is now based upon clinical judgment alone.

Organic neuropsychiatric syndromes

Neuroleptic medications have been reported to be beneficial in treating mentally retarded patients who have prominent psychotic symptoms, stereotyped motor activity, or assaultive behavior. Some of this literature has been reviewed by Prien (110). The efficacy of such short-term treatment is supported by some, but not all, controlled studies and by a larger number of uncontrolled trials. A collection of representative articles from this literature is provided (111-130). The prolonged use of neuroleptics in such cases, however, has not been well investigated; therefore, guidelines must be tentative.

Some mentally retarded patients have prominent psychotic symptoms including hallucinations, delusions, incoherent thinking, and bizarre behavior. Accordingly, there is abundant clinical experience indicating that neuroleptic drugs are effective in treating such patients, and they are widely used in this population on empirical grounds. Since there are virtually no long-term studies of the benefits and problems attending the prolonged use of neuroleptics in this way, the decision for such treatment is based on clinical assessment of the individual patient. This assessment includes consideration of the patient's mental status and previous response to neuroleptics, as well as responses and risks associated with alternative treatment modalities. When neuroleptic agents are used for retarded patients, the more potent agents may interfere less with cognitive function but more with motor function. Doses should be minimized as soon as possible, especially when sedative and other neurologic side effects seem to add more to the retarded patient's problems than to his comfort and safety. In cases of retardation with disruptive or assaultive behavior, there is no evidence that neuroleptic drugs have a "prophylactic" effect to prevent future behavioral outbursts. Thus, while maintenance neuroleptic medication cannot be recommended for this group, single doses of neuroleptics may be warranted in individual episodes to prevent harm to the patient or others.

Neuroleptics have also been used in the treatment of demented patients who are assaultive or who have prominent psychotic symptoms. It seems clear that neuroleptic drugs do have a short-term beneficial effect in reducing psychotic symptoms or controlling agitated or assaultive behavior in elderly demented patients (110, 131-134). Often the effective (or *tolerated*) dose of neuroleptic in demented (especially elderly) patients seems, from clinical experience, to be considerably smaller than dosages used for young schizophrenics (87) and is often required for shorter periods of time, although controlled long-

term studies to verify these clinical impressions have not been conducted. In general, the use of neuroleptic medication in the elderly and the demented should be as brief and as conservative as possible in order to minimize the risk of neurologic and autonomic side effects (especially confusion and hypotension). Moreover, one must remain open to the possibility that impressive benefits may not always be apparent (134).

Neuroleptic medications have been found to reduce neurologic and psychiatric symptoms in several other neuropsychiatric conditions, particularly in those with prominent choreic or other dyskinetic components, such as Gilles de la Tourette's syndrome (135-142) and Huntington's disease (143-145), or other forms of dyskinesia (146-148), as well as "habit spasms" ("simple tics") or stuttering (149, 150). These agents have also been employed successfully in other neuropsychiatric syndromes as diverse as alcoholic withdrawal or alcoholic psychoses (138, 151), amphetamine psychosis (152), or withdrawal from opioid narcotics (153), as well as nausea, vomiting, or "hiccups" due to various causes (6, 154-156). Unfortunately, there are very few studies of long-term treatment in any of these neuropsychiatric syndromes (138, 141, 143, 150). There is some evidence that neuroleptic medications fail to alter the long-term course of those illnesses, especially the tendency toward relentless progression in Huntington's disease (143). Furthermore, cases of Tourette's syndrome with probable superimposed tardive dyskinesia have been reported in a few patients maintained on neuroleptic medications for prolonged periods of time (see footnote, page 49). Thus, the risk of TD must be weighed against clinical improvement in neuropsychiatric as well as chronically psychotic patients in the decision to maintain them on a neuroleptic drug.

Depression

For depression uncomplicated by psychotic symptoms, clear advantages to treating the acute episode with antidepressant drugs or ECT are their well-demonstrated efficacy (1, 3) as well as the apparently low risk of tardive dyskinesia with short-term (and probably even long-term) use of these modalities (see Chapter III, page 49). The routine use of neuroleptics for typical cases of depression is probably not warranted unless alternative treatments have been found to be ineffective (157-160). There are evidently no studies of long-term treatment with neuroleptic agents for the prevention of recurrent depression in either unipolar or bipolar manic-depressive illness or for

the treatment of other forms of prolonged mood disorders. Considering the lack of such evidence and the risk of tardive dyskinesia, there is currently no scientific basis for the prolonged use of neuroleptic drugs in such patients.

Moreover, a special problem is posed by the evidently rather widespread use of perphenazine-amitriptyline combinations that provide inflexibly fixed ratios of the two agents (Etrafon, Triavil), as well as the recent introduction of thioridazine (Mellaril) in the treatment of mixed anxiety and depression, especially in outpatients with disorders of relatively mild severity. While there is evidence that such agents are more effective than an inactive placebo for short-term use (161-167), there is no evidence that they are more useful in the maintenance therapy of affective disorders than a tricyclic antidepressant or lithium salt alone (98). However, the risk of TD with such preparations is evident, and their availability may tend to encourage uncritical diagnostic evaluation of difficult patients.

The treatment of depressed patients with psychotic symptoms has not been studied adequately. ECT is a highly effective and rapid treatment for depressive disorder, both with and without psychotic symptoms (see *APA Task Force Report on Electroconvulsive Therapy,* 1978). A few clinical trials of antidepressant medications and neuroleptics alone or in combination have been performed with depressed patients of various types and severities. They suggest that neuroleptic agents may be especially useful clinically in cases of depression with prominent agitation or psychotic features (158, 159, 168-199). At least two additional studies have reported high response rates to combined neuroleptic and tricyclic antidepressant therapy in severe depression with psychotic symptoms; however, both studies were retrospective and lacked control groups treated with antidepressants or ECT alone and so do not provide comparisons of the relative efficacy of different treatments (200, 201). Several studies of various designs have suggested that ECT is superior to tricyclic antidepressants alone in such agitated or delusional, severely depressed patients (202-207). However, a well-designed critical, prospective study comparing ECT alone, antidepressant alone, and antidepressant plus neuroleptic therapy has evidently not been done. Thus, there is no consensus about the preferred treatment of patients with severe depression characterized by agitation and psychotic symptoms.*

*The current controversy over the relative efficacy of antidepressant and antipsychotic drugs and of ECT in the management of severe depression with psychotic or delusional characteristics is beyond the scope of this report but is discussed in the *APA Task Force Report on ECT* (1978, pp 13-30) and by Nelson and Bowers (1978 [201]).

When ECT is not successful, is clinically contraindicated, or is not accepted by a patient, treatment with an antidepressant alone or in combination with a neuroleptic drug may be necessary, on empirical grounds, in psychotic depression. In such a case, the risk of tardive dyskinesia is not a prominent concern unless the antipsychotic agent is continued for many months. Since there are no data to permit a critical evaluation of the comparative efficacy of neuroleptics versus antidepressants in preventing relapses of psychotic depression, prolonged use of neuroleptic medications for patients following recovery from severe depression with psychotic features *does not have scientific support* as a preventive treatment. While clinical experience with individual patients may occasionally demonstrate a need to continue a neuroleptic medication past the acute episode if the patient's clinical condition deteriorates when the dose of neuroleptic drug is reduced, this is not often necessary. An antidepressant drug alone is often adequate treatment in such cases.

Neuroses and character disorders

Neuroleptic medications have been used to treat patients diagnosed as troubled by obsessive-compulsive neurosis, anxiety neurosis, "borderline" syndrome or "pseudoneurotic schizophrenia," or other "characterological" disorders or chronic dysphoria. Studies of the short-term use of neuroleptic drugs for such patients exist. Many are deficient in the definition of the syndromes being treated or in their design as scientifically controlled experiments. Some indicate that neuroleptic drugs may be helpful in some cases, and further, that effective doses may be lower than those typically employed for antipsychotic effects (208-236). However, *virtually no controlled studies of the prolonged use of neuroleptics in such cases are yet available,* despite the fact that many of these conditions follow a chronic course. Furthermore, even in the available brief studies, the performance of neuroleptic drugs was sometimes unimpressive or no better than a placebo (235-249), a sedative-tranquilizer (242), or an antidepressant (241, 250, 251). A recent uncontrolled report of the use of various drugs in so-called "borderline" patients (252) suggests that intermittent use of low doses of antipsychotic agents may be especially helpful in patients with evidence of mild, and especially intermittent, psychosis. This report (252) also reviewed evidence that can be taken to suggest that some such patients may be selectively benefitted by antianxiety or antidepressant agents, no doubt reflecting the diagnostic uncer-

tainty of this group of patients and the probable inclusion of those with more classical neuroses, mood disorders, or mild schizophrenia.

Thus, the use of neuroleptic drugs in neurotic or other patients without clear-cut psychoses is probably best reserved for individual cases for whom alternative modes of treatment (including non-pharmacologic therapies) have failed and a brief trial of a neuroleptic agent has demonstrated clearly beneficial effects that are lost when the drug is discontinued, or when the risks (intoxication, abuse, overdoses) and ineffectiveness (tolerance) of prolonged use of sedatives are a predominant consideration, especially with impulsive or sociopathic patients. Nevertheless, it must be emphasized that the status of antipsychotic-neuroleptic agents as "tranquilizers," especially in comparison to the proven short-term efficacy and relative safety of the benzodiazepine sedative-tranquilizers (1, 3, 6, 253), is not at all secure based on the evidence already cited. Moreover, the long-term usefulness of any drug in chronic neurotic or characterologic disorders remains unproven.

In conclusion, the evidence that neuroleptic drugs are effective in acute psychoses of various kinds is excellent, although the best data exist for acute phases of schizophrenia and for mania. Neuroleptic agents also have a place in various neuropsychiatric disorders—notably, in the syndromes of Huntington and of Gilles de la Tourette. The usefulness of these agents in depression as a secondary or adjunctive treatment is also fairly well supported, but indications among the neuroses and characterological disorders are poorly supported at the present time. For all of these conditions, however, there is little scientific support for the efficacy of long-term uses, with the *single notable exception of chronic schizophrenia.* Moreover, the risk of late neurologic toxicity, including tardive dyskinesia, in any prolonged use can be assumed.

Even in schizophrenia, very few drugs have been evaluated; and the most numerous studies, which involve phenothiazines, have rarely followed patients for more than six to 12 months, although "relapse" rates may diminish at times later than one year. There is also little information concerning dose-effect relationships. A dose-protective effect relationship cannot be demonstrated at daily doses between the equivalent of 100 and 2,000 mg of chlorpromazine, and there is evidently little added benefit with doses above 300 mg/day. Thus, the prolonged use of neuroleptic drugs (for more than a few months) in conditions other than schizophrenia (and perhaps a few unusual neuropsychiatric conditions such as Huntington's disease) requires care-

ful balancing of objectively demonstrated benefits against the risks involved in individual patients by an exercise of critical clinical judgment, discussion with the patient and his family, and the use of the lowest effective doses as determined empirically for each patient.

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CHAPTER VI

PREVENTION AND TREATMENT

There are currently no consistently effective therapies for patients with persistent drug-induced dyskinesia.* To date, much of the available literature on drug therapies consists of case reports or small series of cases in uncontrolled trials. Such studies are suspect for several reasons. Early signs of dyskinesia may diminish spontaneously after antipsychotic drugs are stopped. Patients with tardive dyskinesia sometimes show waxing and waning of their movements independent of drug therapy. Most dyskinesia patients can modify their dyskinesias to some extent voluntarily, and extrapyramidal signs are notoriously dependent on the level of arousal of the patient. Bias toward finding a new therapy can affect both patients and observers. Nonspecific sedative effects may also reduce dyskinesia a bit. It is therefore hard to place much weight on uncontrolled studies.

Controlled studies present a different problem. These have usually been carried out with chronic institutionalized schizophrenic patients whose dyskinesias may be longstanding and perhaps unusually resistant to treatment. Probably, the ideal way to demonstrate the efficacy of a drug therapy in persistent dyskinesia would be a double-blind, placebo-controlled study in outpatients with dyskinesia that has persisted for one or more years. Several studies of this sort, all showing efficacy, would be most impressive. If the drug were also effective in double-blind placebo-controlled studies in more chronic inpatients, this evidence would be even more compelling. No currently proposed drug therapy has fulfilled these criteria. In fact, the only drugs other than dopamine antagonists which have shown evidence of even partial efficacy in single controlled studies are choline, lioresal, sodium valproate (1-3), and perhaps apomorphine (4).

Other problems must be considered in evaluating drug therapies in this area. There is some evidence that movements can "break through" suppression by a dyskinesia-suppressing drug, at least in the cases of the dopamine antagonists, haloperidol and tetrabenazine (5). On the other hand, a recent case report (6) describes a case of very

*The current status of experimental therapeutics in TD and problems associated with its investigation have recently been critically reviewed by MacKay and Sheppard (Pharmacotherapeutic trials in tardive dyskinesia. Br J Psychiatry 135:489-499, 1979).

severe, life-threatening tardive dyskinesia that had been well controlled for a year on 20 mg of haloperidol without recurrence of symptoms. Long-term studies, in contrast to the studies of only several weeks' duration which are common in the present literature, are needed. Since the majority of patients with persistent dyskinesia also have persistent schizophrenia, a useful anti-dyskinesia therapy must either have antipsychotic properties as well or must be well tolerated when given along with an antipsychotic drug. At the very least, the drug should not aggravate psychotic symptoms. However, these ideal requirements will have to await a far better therapy than we now have.

Most drugs that have been tried in tardive dyskinesia are known or presumed to affect either dopaminergic or cholinergic systems in the brain, directly or indirectly. In the indirect group are several drugs that have been proposed to increase the activity of the inhibitory neurotransmitter amino acid γ-aminobutyric acid (GABA) and, presumably, inhibit dopaminergic activity at the same time. Other drugs—lithium carbonate, cyproheptadine, manganese salts—are less easily classified. The drugs having demonstrated effects on specific systems will be reviewed first.

Drug Treatments

Dopamine Blocking Agents

A commonly discussed hypothesis is that the pathophysiology of tardive dyskinesia is based on overactivity or hypersensitivity of dopamine receptors in the nigrostriatal system (see Chapter IV). Drugs that block dopamine receptors, such as the neuroleptic agents, not only can cause persistent dyskinesia but can block or suppress existing tardive dyskinesia as well as other forms of choreoathetosis such as Huntington's disease. Some patients show the first signs of dyskinesia only when such drugs are stopped, and others show an exacerbation of a pre-existing dyskinesia when these drugs are stopped.

Several open or partially controlled studies report suppression of dyskinesia when the patient's previous antipsychotic medication is given in increased dosage. The effect has been reported for several antipsychotic drugs, including perphenazine (7), thiopropazate (8-12), thioproperazine (13), chlorpromazine (14), and haloperidol (10, 15). The antidyskinetic effect of haloperidol was reportedly reversed by an anticholinergic-antiparkinsonism agent (16). One controlled study of pimozide, a potent and selective dopamine receptor blocker available in Europe, showed this neuroleptic drug to be more effective than

placebo in suppressing dyskinesia (17). A second placebo-controlled study found thiopropazate to be superior to placebo in decreasing oral movements in TD (18).

Papaverine, a smooth muscle relaxant derived from opium, has been reported to have some dopamine blocking effect (19), although its actions remain obscure. It has been reported to improve both L-dopa-induced dyskinesia and tardive dyskinesia in open or single-blind studies (20, 21). In a cross-over study in which patients received either papaverine for six weeks and then no drug for six weeks, or vice versa, using blind raters, papaverine had a barely detectable effect, differing from no drug only in the group receiving this drug in the first six weeks of the study (22). It also caused parkinsonian side effects, which may reflect its putative antidopamine actions and may have contributed to the observed antidyskinetic effects.

Clozapine, another antipsychotic drug formerly in general use in Europe, until its use was recently curtailed due to its apparent bone marrow toxicity, is claimed to have minimal neurological side effects and almost never to have caused tardive dyskinesia, to date, although at least one case has recently been reported (23). It has been reported to have relatively weak dopamine blocking activity in the basal ganglia but more in the mesolimbic dopamine system, and it is clearly effective as an antipsychotic (24-26). In several uncontrolled studies (22, 27-29), it has been found to ameliorate tardive dyskinesia. In other more recent controlled studies, this conclusion has not been supported (16, 30), although clozapine was found to have an antidyskinetic effect in some patients with Huntington's chorea (30) and to have *anti*parkinsonism effects (16). Whether it is antidyskinetic by virtue of blockade of post-synaptic dopamine receptors, as other antipsychotics are believed to do, or by action on presynaptic dopamine receptors, or, while controlling the psychosis by some mechanism other than dopamine blockade, merely allows non-persistent dyskinesias to gradually fade away spontaneously is unclear. The drug's alleged propensity for causing bone marrow depression or agranulocytosis, tachycardia, fever, hypersalivation, oversedation, and convulsions make it less than an ideal candidate to replace other antipsychotics (16, 22, 27, 30), although it had offered some hope of being a useful antipsychotic for patients who have already developed tardive dyskinesia. The drug had been available to clinical investigators on a limited basis to treat selected patients until recently. Clozapine's continued association with agranulocytosis (30) makes it's future availability for even limited use in dyskinetic patients unlikely. Nevertheless, other drugs similar to clozapine which are effectively antipsychotic but have little extrapyramidal toxicity are being sought at the present time. Agents that are

antipsychotic, but not "neuroleptic," may make possible the treatment of schizophrenia with little risk of persistent dyskinesia.

Dopamine depleting drugs

Tetrabenazine and reserpine have both been observed to decrease dyskinetic movements. These drugs deplete amine stores from nerve terminals. There are five positive uncontrolled (31-33) studies and partially controlled (9, 34) studies that suggest that tetrabenazine reduces dyskinetic movements. This synthetic investigational compound is not generally available in the United States. Reserpine has also been reported to improve dyskinesia. It does so in doses of 0.75 to 5 mg a day (35-37), which are close to those formerly employed for antipsychotic effects in the early 1950s (37, 38). When such high doses of reserpine have suppressed dyskinesia, the dose could then sometimes be lowered without recurrence of TD (39). It may be especially effective in patients who are not receiving other antipsychotic drugs (35, 36).

It is hard to tell whether reserpine offers any advantage over newer and more effective neuroleptic drugs. Used alone, the drug has about as high an incidence of acute neurological side effects as chlorpromazine (37, 38) and other undesirable side effects as well (especially sedation, dysphoria, nasal congestion, hypotension, and diarrhea). Although only a few cases of persistent dyskinesia have been reported with reserpine alone (40-42), the drug has not been widely used in schizophrenia for about 20 years, and its relative benignity in this regard is uncertain. Moreover, even though reserpine has been shown to be more effective than placebo, it is less effective than phenothiazine antipsychotics in schizophrenia (37). Thus, it remains an option for use in dyskinesia patients without clear superiority over other approaches.

Dopamine agonists

Since persistent dyskinesia may be associated with supersensitivity of dopamine receptors, dopamine agonists should exacerbate the condition. Recent evidence opens this simplistic prediction to question. Although apparent disuse supersensitivity of the dopamine system in the basal ganglia may be produced experimentally in animals by neuroleptic treatment and may be an important mechanism in the more transient and reversible forms of late neuroleptic-induced dyskinesias ("withdrawal dyskinesias"), it remains uncertain whether this reversible pharmacological mechanism is responsible for more persistent late dyskinesias (see Chapter IV). Recently, there has been interest in the possibility that some dopamine agonists may exert "paradoxical" effects whereby behavioral and motor syndromes nor-

mally produced or exacerbated by such agents may actually be suppressed when the drugs are administered in low or repeated doses. Although most of the experimental evidence has been accumulated in animal studies, there have been indications that similar phenomena may occur in human clinical conditions as well.

When administered in high doses to man, dopamine agonists such as L-dopa and amphetamine produce choreoathetotic dyskinesias that are similar to those that occur in tardive dyskinesia. However, the apparently "paradoxical" observations in man which suggest that under certain circumstances some dopamine agonists may suppress, rather than increase, dyskinesias include the following:

1) Apomorphine (a putative direct agonist of dopamine receptors) has been reported to suppress L-dopa-induced dyskinesias in patients with Parkinson's disease (43).

2) Apomorphine reduces chorea in patients with Huntington's disease (44) and in tardive dyskinesia (4), as well as acute dystonias induced by neuroleptics, Gilles de la Tourette's syndrome, and wry neck (45).

3) Apomorphine and piribedil (another antiparkinsonism agent with an active metabolite that may be a dopamine agonist) have both been reported to suppress TD (4, 46, 47).

4) Methylphenidate, which releases presynaptic stores of catecholamines, including dopamine, may suppress rather than increase TD in some patients (48), although it worsens it in most patients.

5) Amantadine, which reportedly releases central catecholamines and may also be a mild agonist at dopamine receptors, has been reported to abolish tardive dyskinesia, although long-term studies have found no significant effect (49). Its beneficial effects in parkinsonism are similarly short-lived (49).

6) An older, uncontrolled study of a monoamine oxidase (MAO) inhibitor, isocarboxazid 80 mg/day, reported that this drug, which would be expected to increase the availability of dopamine and other amines in the brain, paradoxically improved dyskinesia (50).

7) Recent unpublished work (22) suggests that a low single dose of Sinemet (5/50 or 10/100 mg, respectively, of a peripheral decarboxylase inhibitor and L-dopa) decreased dyskinetic movements in four out of seven drug-free psychotic patients, while a higher dose increased dyskinesia in the same patients. Two patients showed no change in dyskinesia at any dose, while one additional patient with dyskinesia of very recent onset (one month) showed increased dyskinesia on the lowest dose of Sinemet.

8) On a different basis, Alpert and Friedhoff (51, 52) have treated at least seven patients with persistent dyskinesia with L-dopa in grad-

ually increasing amounts up to 6 gm per day. Neuroleptic drugs were discontinued in all patients for three months prior to initiating this novel L-dopa therapy. The rationale of this regimen is to attempt to reverse presumed dopamine receptor hypersensitivity. Transient increases in psychiatric symptoms were observed in some patients after step-wise increases in L-dopa dosage. Four patients were unable to complete the trial, two because of side effects and two for administrative reasons. The remaining three showed excellent or good results. The two with excellent results have been followed off all drugs for two years and continue to do well psychiatrically as well as neurologically.

In summary, it is clear at this point that the effects of dopamine agonists in persistent dyskinesia appear to be complex. Moderate doses generally worsen dyskinesia, while very low or repeated doses may ameliorate the condition. Mechanisms that might be involved in these paradoxical effects of dopamine agonists include the possibilities that various dopamine agonists may have additional actions at other sites, may be only partial agonists or mixed agonist-antagonists, or may stimulate presynaptic dopamine receptors that might functionally inhibit the availability of dopamine to its postsynaptic receptors.

Anticholinergic drugs

There is a general impression that anticholinergic drugs either increase or have no effect on persistent dyskinesias (53). The effects of such drugs have been clearly shown for biperiden in a study employing blind raters (54). Patients with both parkinsonism and dyskinesia often show a reduction in parkinsonism and an increase in dyskinesia when an antiparkinsonism drug is given (55). An anticholinergic agent can reverse the antidyskinetic effects of a neuroleptic drug (16). Intravenous anticholinergic drugs usually worsen dyskinesia (56, 57), but occasional patients with persistent dyskinesia have been reported to improve after 2 mg of intravenous benztropine (57, 58). Although it had been suggested that a challenge dose of a drug such as benztropine might provide a useful predictive test for early or latent tardive dyskinesia, the marked variability of response seems to preclude this approach (57).

All that one can say at present is that patients who develop dyskinesia while given both antipsychotic drugs and antiparkinsonism drugs may show decreased dyskinesia when the antiparkinsonism drugs are stopped, but that occasional patients may respond favorably (and unpredictably) to such drugs. It is not known whether patients showing decreased dyskinesia after intravenous benztropine would show continued benefit from prolonged oral therapy with this drug, as this possibility has evidently never been tested.

Cholinergic drugs

Physostigmine, a potent, short-acting or reversible cholinesterase inhibitor, is a commonly employed cholinergic agonist used to study the effects of presumably increased cholinergic function on persistent dyskinesia. To date, such studies have yielded inconsistent results (59, 60), although some studies have found temporary suppression of dyskinesia in some patients (58, 60-62) at doses ranging from 1 to 3 mg given intravenously. Since physostigmine sometimes elicits either sedation or mild stimulation as well as nausea and vomiting, its effects on dyskinesia may not all be through direct cholinergic influences on the control of movements.

Deanol is another putative cholinergic drug. It is marketed as a mild stimulant (Deaner) at doses up to 300 mg a day. It has also been used extensively in tardive dyskinesia at doses up to several grams a day with only minimal side effects (typically, gastrointestinal distress). Sixteen available reports of its use have been reviewed in detail by Casey (63); most of these involve uncontrolled studies. Only three small double-blind studies involving a total of only 29 patients have been reported, and these gave unimpressive results. Two studies (61, 64) showed no drug-placebo differences, and one other found a difference only in orofacial movements (22). Two other recent controlled cross-over studies of deanol and placebo, not covered in Casey's review (63), were equivocal. In the first, all patients were taken off antipsychotic drugs and most showed some modest amelioration of dyskinesia on deanol, but no worsening on placebo (65). In the second, four of the five patients with tardive dyskinesia were drug-free; only one showed more decrease in dyskinesia on deanol than on placebo (66). Casey's own study gave the most promising results (58). He gave deanol in doses of 800-2,000 mg a day to six patients with persistent dyskinesia. The three patients whose dyskinesia had improved with physostigmine also improved with deanol; the other three worsened on deanol, suggesting that physostigmine might provide a useful test to predict responsiveness to deanol or other cholinergic agents (58). In this study, only bucco-lingual dyskinesia and dyskinesia in one other body area (fingers) were measured. The possibility remains that some patients may respond to high doses of deanol. There is still some doubt as to whether, and by what mechanism, deanol increases brain choline and acetylcholine levels (67).

Data on the use of choline itself to affect brain acetylcholine appear to be more promising. Wurtman and his colleagues have reported that choline raises brain acetylcholine in animals (68) and have completed a double-blind placebo-controlled cross-over study of choline

(150 to 200 mg/kg per day for two weeks) in 20 chronically hospitalized psychotic patients with persistent dyskinesia. Only one patient worsened, and nine showed improvement—movement reductions of 41 to 84 percent (1). Three patients showed mild cholinergic side effects. Depression has been reported in some patients treated with high doses of oral choline (69). Choline-treated patients also can develop an unpleasant fishy odor. Davis et al. (70) and Tamminga et al. (61) have observed a little improvement in a few patients with TD given choline in doses of 8 to 20 gm a day, but Gelenberg, Growdon, and colleagues have recently reported more encouraging results with choline and its usual dietary precursor, phosphatidylcholine (lecithin) (71-73). Longer term studies of choline and lecithin (the most important natural dietary source of choline) are currently in progress (71). This work was facilitated by the use of similarly large doses of choline in hepatitis 20 years ago without adverse effects.

Sedatives and "GABA-ergic" agents

Because of some recent evidence that drugs which activate brain systems involving gamma-amino-butyric acid (GABA) as a neurotransmitter have an inhibitory effect on dopaminergic systems (74), there is a recently increasing interest in such agents as treatments of persistent dyskinesia.

Benzodiazepines may activate GABA-ergic systems (75), and two newer drugs on the market in Europe, baclofen (Lioresal), a muscle relaxant, and sodium valproate, an anticonvulsant, may also affect GABA-ergic systems. Baclofen, a structural analogue of GABA, has been studied as a presumed GABA-ergic drug, but the available data (76, 77) suggest that this is probably not the case. Sodium valproate is a weak inhibitor of GABA-transaminase, an enzyme that destroys GABA (76) and appears to increase GABA in the brain (3).

Diazepam (at a low dose of 4 mg a day) has been reported to be as effective as tetrabenazine in reducing dyskinetic movements; both drugs produced sedation (33). Another open study reported diazepam (4-30 mg daily) to produce marked improvement without sedation in three dyskinetic patients (78). Intravenous diazepam (10 mg) caused marked acute reduction in dyskinesia in a 14-patient study (79). Chlorazepate also has been reported to reduce dyskinesia in seven of 12 patients in doses of 15-45 mg daily (80). Clonazepam, a newer benzodiazepine marketed as an anticonvulsant, has also been reported to reduce acute dyskinesia due to antipsychotic drugs (81). In a study of clonazepam in tardive dyskinesia patients, improvement occurred in 11 of 18 patients at doses up to 4 mg daily; but drowsiness, ataxia, and confusion were observed in elderly patients (82). Other work

further suggests that an antidyskinetic effect occurs with clonazepam, and that side effects can be minimized by more gradual dosage increments (22).

Sodium valproate has been subjected to a double-blind cross-over study in chronic dyskinetic patients at a dose of 900 mg a day (3). The drug was superior to placebo in reducing rigidity, akathisia, akinesia, and dystonic spasms (undefined) but was only marginally superior to placebo for orofacial dyskinesia. Since improvement continued temporarily in some patients after receiving the active drug when they were given a placebo, the duration of placebo treatment may have been too short to demonstrate a clear difference. More confusingly, a few patients who had not improved when on the drug also improved after being shifted to placebo.

Baclofen, in a similar double-blind cross-over study (2), was more impressive, leading to a two-thirds reduction in dyskinesia on the average at a dose increased to 60 mg a day. Fifteen of the 20 patients studied showed clear improvement on drug; none improved on placebo. In this study, all patients continued to receive antipsychotic medication. Baclofen has been observed to markedly worsen psychosis in drug-free schizophrenic patients (83). Therefore, its use in drug-free schizophrenics with TD seems unwise. Moreover, a more recent controlled trial failed to support a therapeutic effect of baclofen for TD (84).

Still another putative GABA-agonist, muscimol, has recently been reported to be of consistent benefit in tardive dyskinesia, usually without inducing sedation, in a small controlled trial (85). Unfortunately, this agent, too, is probably excessively psychotomimetic for routine use in already-psychotic patients (85).

Phenobarbital, a barbiturate with anticonvulsant properties, was reported to abolish dyskinesia in a single patient (86). Methohexital sodium (Brevital) given intravenously reduced dyskinetic movements briefly in three patients (61); this effect appeared to be related to sedation, since activating the patients abolished the drug-related reduction in dyskinesia.

At present, it is hard to evaluate this area. The effects reported are interesting. The benzodiazepines are readily available, generally safe, and can be employed as an interim treatment that will probably not aggravate the underlying schizophrenia and may or may not provide limited benefit for dyskinesia. These drugs can be viewed as providing mildly helpful and encouraging non-specific effects; they can be employed in tardive dyskinesia in the absence of more specific or effective agents. Controlled studies of their efficacy are urgently needed. Of the newer drugs, trials of the efficacy of baclofen in tardive

dyskinesia are now ongoing in this country. The possible GABA-enhancing actions of benzodiazepines or baclofen, while suggested by some pre-clinical research data, remain unproven (87). Moreover, their non-specific sedative or anti-anxiety effects may be confounded with effects on GABA-ergic mechanisms. Muscimol, a more clearly effective GABA-ergic drug, has been tried in the dyskinesia of Huntington's chorea without evident effect (88).

Lithium

Lithium salts are effective in manic excitement and as a maintenance therapy in recurrent affective disorders. The mechanism of action of lithium remains unknown. Uncontrolled studies of one (89) and six patients (90), respectively, reported clear benefit in tardive dyskinesia. The six improved patients studied by Reda et al. (90) were the only subjects to complete the study of an initial group of 20 patients with persistent dyskinesia. Gerlach et al. studied 20 similar patients in a placebo-controlled cross-over study. Plasma lithium levels were raised to over 0.8 m Eq/L (91). Patients received each treatment for three weeks. Five patients were dropped from the study because of side-effects or their refusal to continue. The duration of bucco-lingual-masticatory dyskinesia had ranged from two months to five years. The modest (25 percent) reduction in movements with lithium treatment was statistically significantly different from the dyskinesia rated during placebo treatment; lithium generally had some tranquilizing effect in these patients, whose other drug therapy was unchanged. In five patients, cerebrospinal fluid levels of the dopamine metabolite, homovanillic acid (HVA) and the serotonin end-product, 5-hydroxyindoleacetic acid (5-HIAA) were measured after pre-treatment with probenecid (to block exit of these metabolites from the CSF compartment) under both study treatments. Four patients showed a drop in HVA when given lithium; 5-HIAA was unchanged (91).

Simpson et al. studied ten elderly patients with chronic dyskinesias in an open study (92) at plasma lithium levels between 0.6 and 1.2 mEq/L; no patient improved. Since all patients in this pilot study continued to receive antipsychotic medications, a placebo-controlled cross-over study in elderly patients free of antipsychotic drugs for at least four weeks was carried out next (92). In this second study, patients spent six weeks on each treatment. No differences were observed between lithium and placebo. A single case report (93) describes marked worsening of tardive dyskinesia in a single patient at plasma levels of lithium around 2.0 mEq/L on two occasions; lower plasma levels did not aggravate the dyskinesia.

Cyproheptadine

This antihistamine drug was reported by Goldman to improve persistent dyskinesia strikingly in several outpatients (94). An open trial in five more chronic hospitalized patients at a comparable dose (8 mg a day) had little effect (22). Only two patients improved even slightly, and one of these continued to improve for several weeks after the six-week trial of cyproheptadine.

A summary of pharmacologic treatments that have been evaluated in tardive dyskinesia is provided in Table 15.

Non-drug treatment

Biofeedback

Albanese and Gaarder (95) reported on the treatment of two cases of persistent dyskinesia using biofeedback of muscle tension from the masseter muscles by activating sounds and a visual meter. Both patients apparently "learned" over nine or ten sessions to stop chewing movements entirely; since in both cases the dyskinesia was of relatively recent origin (one or five months, respectively), the three-month period of biofeedback treatment with no control group may have coincided with a spontaneous waning of the dyskinesia of the sort reported by Quitkin et al. (96). Pilot work at McLean Hospital using a similar technique (C. Swett, unpublished observations) has resulted in some decrease in dyskinetic movements, particularly during treatment sessions.

Electroconvulsive treatment (ECT)

ECT has been evaluated in very few patients in an uncontrolled or only partially controlled manner. The tentative impression made by the available data is that ECT is probably not helpful as a treatment for tardive dyskinesia, but, importantly, it probably does not worsen the condition either, thus leaving open the possibility of its use for the treatment of some psychiatric conditions when TD is also present (97).

Neurosurgical treatment

Heath has used electrodes applied to the surface of the rostral vermis of the cerebellar cortex to deliver continuing rhythmic stimuli from an external pacemaker to alter pathological behavior and epileptic seizures in seriously disturbed psychiatric patients (98). In the course of these clinical studies, he has noted concurrent improvement

TABLE 15

The differential pharmacology of tardive dyskinesia (References)

Agents that may partially suppress tardive dyskinesia

- Dopamine antagonists
  - [a]Apomorphine (in low dose) (4, 45-47)
  - Butyrophenones (5)
  - Clozapine (27-29)
  - Papaverine (mechanism uncertain) (19-21)
  - Phenothiazines (7-14, 18)
  - Pimozide (17)
- Amine-depleting agents
  - Reserpine (35-37, 120-123)
  - Tetrabenazine (31-34)
- Blockers of catecholamine synthesis
  - Alpha-methyltyrosine (108, 109)
- Blockers of catecholamine release
  - Lithium salts (efficacy and mechanisms uncertain) (89-92)
- Cholinergic agents
  - Choline and Lecithin (phosphatidylcholine) (1, 61, 69-71)
- Miscellaneous Agents
  - Baclofen (postulated GABA mechanism unproven) (2, 83, 84)
  - Benzodiazepines (33, 78-80)
  - Clonazepan (22, 81, 82)
  - Valproate (postulated GABA mechanism unproven) (3)

Agents with variable, negligible, or uncertain effects[b]

- [b]Alpha-methyldopa (35, 36, 107, 120)
- Amantadine (49)
- Antihistamines (110, 111)
- Barbiturates (61, 86)
- Benzodiazepines (112-114)
- Cyproheptadine (22, 95)
- [b]Deanol (22, 57, 58, 61, 63-66)
- Isocarboxazid (50)
- Methylphenidate (48)
- Penicillamine (107)
- [b]Physostigmine (60-62)
- Pyridoxine (vitamin B_6) (116-118)
- Tryptophan (113, 118)

Agents that typically worsen tardive dyskinesia

- Anticholinergic agents
  - Antiparkinsonism agents (e.g., benztropine, has complex effects) (53-58)
- Dopamine agonists (22, 44, 54)
  - Amphetamines (46)
  - L-DOPA (may have opposite effect in small repeated doses) (22, 51, 52)
- Other Agents
  - Phenytoin (106)

of dyskinesia in some patients. It is unclear whether this improvement is a result of the stimulation or of the withdrawal of antipsychotic drugs.

Other attempts at the modification of tardive dyskinesia by the production of lesions rather than the application of electrodes have been less successful. Bilateral thalamotomy has been tried in one patient with only temporary reduction of movements (99). Unilateral and bilateral lesions in the region of the red nucleus and the prerubral field of Forel have been undertaken in three patients by Nashold (100) with partial abolition of movements in two cases; the area chosen for these lesions is one in which electrical stimulation occasionally elicits complex orofacial movements.

Dental treatment

Clinical experience suggests that occasional patients with oro-bucco-lingual dyskinesia attribute their tongue and jaw movements to irritating or ill-fitting dentures and that removal of dentures will sometimes reduce or abolish such movements. Although most patients with persistent dyskinesia have either no dental abnormalities or are edentulous and not wearing dentures, occasional patients may benefit from dental procedures such as better fitting dental prosthetic appliances (101, 102). However, tardive dyskinesia is more likely to interfere with the wearing of dentures than to benefit from their adjustment (103).

Clinical management of drug-related dyskinesia

A practicing physician will sometimes observe dyskinetic movements (see Chapter II on clinical description and evaluation) in a patient treated with antipsychotic drugs or soon after these have been discontinued, either because they are no longer clinically needed or in an attempt to see if a "covert" dyskinesia had been suppressed by maintenance antipsychotic medication. At that point, what should the clinician do? If the oral-lingual or choreoathetotic dyskinesia appears to be tardive dyskinesia, the patient's clinical condition should be described in detail and the patient should, in most cases, be evaluated neurologically to rule out alternative diagnoses.

[a]Note that while apomorphine is usually classed as a dopamine-agonist, it has complex mixed actions, may antagonize dopamine at low doses, and has clear antidyskinetic effects. For other references, see also Tarsy and Baldessarini (1976) (119).

[b]Some agents (such as α-methyl-dopa, deanol, and physostigmine) have been reported to be of some benefit in some studies.

Assuming that no other diagnosis is likely and a dyskinesia related to antipsychotic drugs is presumed to be present, then all antipsychotic medication should ideally be withheld indefinitely in the expectation that the dyskinesia may fade away, slowly or rapidly. Typically, if the dyskinesia has appeared during antipsychotic drug therapy, there is a chance that it may worsen temporarily when the drug is stopped. If the dyskinesia initially worsens but later fades away over a four to eight week period, it can be considered a transient or so-called "withdrawal" dyskinesia. If it continues relatively unchanged for two or more months off drugs it can be considered to be a "persistent" tardive dyskinesia, although even such dyskinesias may eventually diminish or disappear after many months. The distinction between "withdrawal" and "persistent" dyskinesias is somewhat arbitrary and may well represent the ends of a continuum. Thus, lack of early improvement in the dyskinesia does *not* necessarily mean that eventual improvement will not occur over many months or even years, nor is it safe to assume that eventual persistent TD cannot follow reinstitution of neuroleptic therapy after apparently full recovery from a transient dyskinesia.

If the patient is likely not to require further treatment with antipsychotic drugs because the illness under treatment was a neurosis, anxiety state, depression, or a personality disorder, then the problem is relatively simple. The patient's psychiatric symptoms should be treated with other safe and possibly more appropriate drugs or with non-drug therapies. For example, antidepressants and antianxiety agents are unlikely to aggravate the dyskinesia. If the dyskinesia, even though painless, causes subjective distress or impaired function, a low dose of a benzodiazepine (e.g., 5 mg of diazepam or 1 mg of clonazepam two or three times a day) may both reduce the dyskinesia somewhat and reduce anxiety secondary to the dyskinesia. An occasional case may be helped by antiparkinsonism drugs. Although most cases of tardive dyskinesia are worsened by anticholinergic agents, Casey's recent experience with TD patients leads him to guess that about 20 percent may be *helped* by drugs like benztropine (D. Casey, personal communication, 1978).

In the rare patient with very severely disabling and distressing dyskinesia, it may be reasonable to try drugs such as reserpine and haloperidol in an attempt to suppress the dyskinesia. In the absence of clear evidence about the theoretical risk of dyskinesia-worsening long-term effects of such treatment, a dopamine-depleting agent such as reserpine (up to 1-5 mg a day) *may be* a more benign dyskinesia-suppressing drug than potent dopamine receptor blocking agents such as haloperidol and the piperazine tricyclic antipsychotic agents (see

Table 1 in Chapter I). At present, it is neither clear that such continued antidopamine treatment (which seems intuitively irrational) will aggravate tardive dyskinesia in the long run nor that such treatment is safe. Nevertheless, in some very severe cases with disfiguring and incapacitating tardive dyskinesia, this approach may be clinically unavoidable, and it is sometimes quite effective.

Patients who, because of frequent exacerbations of psychotic illness, appear to require continued long-term antipsychotic therapy, should be re-evaluated diagnostically. In some cases, the history, in retrospect, may indicate affective features during psychotic episodes, with good adjustment or full recovery between episodes on maintenance antipsychotic drugs. Clearly, such patients deserve a trial on lithium carbonate at adequate blood levels of lithium (0.8-1.2 mEq/L), as they may have an episodic manic-depressive illness or other atypical recurrent psychosis in which recurrent episodes may be prevented or ameliorated by lithium.

For the occasional dyskinetic patient with recurrent atypical manic-depressive illness or other recurrent psychoses that do not respond to lithium, electroconvulsive therapy (ECT) for the acute episodes should be considered as an alternative to re-exposing the patient with dyskinesia to antipsychotic drugs. ECT also provides a reasonable alternative for dyskinetic patients with severe recurrent "psychotic" or "agitated" depressions, which may in the past have responded best to antipsychotics alone or to antidepressant-antipsychotic drug combinations.

For clearly schizophrenic patients with continuing signs of psychotic defects, who appear to need maintenance antipsychotic drugs because of the demonstrated severity and rapidity of their previous exacerbations off drugs, a more complex situation exists. Ideally, one would like to recommend that all patients with dyskinesia be kept off antipsychotic drugs forever, but often this is clinically neither wise nor feasible. Nevertheless, in such cases the issue must be faced, and indications for continued antipsychotic therapy in the presence of dyskinesia should be clearly documented in detail in the clinical record.

If discontinuation of antipsychotic drugs is not feasible, reducing the dosage may be a reasonable alternative. The risks of exacerbation of psychosis following dosage reduction are presumably less than after complete discontinuation of a neuroleptic agent, although the extent of the risk is not predictable and must be evaluated empirically for each patient. To complicate matters, the timing of psychotic exacerbation after discontinuation of an antipsychotic drug reported in research studies appears to be almost randomly distributed over many months

or several years (104); see also Figure 6 in Chapter V. It is also probable that exacerbation in response to dosage reduction may similarly be delayed and unpredictable. If a patient's psychiatric condition worsens after reduction of dosage or withdrawal of maintenance antipsychotic drug therapy, the clinical justification for continuing antipsychotic medication in the face of dyskinesia is greatly strengthened. As with neuroleptic-free patients, benzodiazepines may have a mild ameliorative action on dyskinesia in patients on maintenance antipsychotic drugs. They can safely be tried and can help to sustain hope as time passes and the chance of spontaneous remission of the dyskinesia increases.

In patients given maintenance treatment with antipsychotic drugs, dyskinesia may worsen if antiparkinsonism drugs are also given simultaneously. Therefore, the patient should be re-evaluated without antiparkinsonism drugs. As noted above, occasionally dyskinesia improves with such drugs; in other cases, the redevelopment of bradykinesia and rigidity (i.e., parkinsonism *added* to tardive dyskinesia) may give the potentially misleading impression that the dyskinesia has improved on discontinuation of the antiparkinsonism drugs. In patients with both parkinsonism and TD, treatment is especially difficult: Drugs that improve one disorder usually worsen the other. In such cases, a prolonged period off all neuroleptic drugs may be particularly valuable.

If a patient develops dyskinesia after a change to a new antipsychotic agent, it would seem sensible to return the patient to the drug that seemed to be better tolerated in the past. It is also possible, but by no means proven, that thioridazine (Mellaril), due to its somewhat lower incidence of acute neurological side-effects and apparent *relative* infrequency of reported association with tardive dyskinesia, might be better tolerated by patients who have developed tardive dyskinesia during treatment with a high-potency neuroleptic.

It is hard to predict whether changing to an antipsychotic agent that is dissimilar to those used previously will make a difference either in the dyskinesia or the psychosis. Some chronic schizophrenic patients who have been stable on an old familiar drug relapse when their medication is changed to a presumably equivalent dose of another drug (105). The reasons for this are obscure, although they probably include psychological as well as pharmacologic aspects. As already noted, dyskinesia, as well as psychosis, in chronic patients may wax or wane even when constant moderate dosages of a neuroleptic are given. Since it is by no means clear that continuing neuroleptic treatment in the face of either recent or long-standing tardive dyskinesia will worsen the dyskinesia, patients with tardive dyskinesia who

require continued antipsychotic drug therapy should be carefully followed. Progressive worsening of previously mild dyskinesia may cause the clinician to reassess the relative risks and benefits of antipsychotic drug therapy. Such a worsening may even make hospitalization for drug withdrawal and more detailed neurological evaluation a sensible next step.

Some practical suggestions for the avoidance and management of TD are provided in Table 16 and Figure 9 (pp 169 and 172).

In summary, although many clinical reports about a variety of therapies for tardive dyskinesia are available and have been reviewed (see Table 12), none has yet been either thoroughly studied or proven to be safe and effective. Of the available approaches, stopping all antipsychotic medication indefinitely seems to be the theoretically ideal treatment. Unfortunately, for many patients, this is not a feasible alternative. Several newer investigational therapies are said to be based on partially demonstrated increases of brain cholinergic activity (choline, lecithin, deanol), unproven increases of GABA-ergic activity (benzodiazepines, baclofen, sodium valproate), or reduced dopaminergic activity (dopamine blocking drugs, such as the potent neuroleptics themselves, or dopamine depleting drugs, such as reserpine).

It is likely that tardive dyskinesia is a heterogeneous group of disorders having a variety of anatomical, neuropathological, and pathophysiological bases, corresponding to the varieties of natural history and responses to treatment. No treatment to date uniformly benefits all signs of dyskinesia in patients, and most treatments studied cause only slight to moderate benefit in only a proportion (rarely more than half) of the patients studied, and then sometimes only in some of their movements.

In the long run, the best available "treatment" of tardive dyskinesia continues to be the use of conservative but effective dosage regimens on clear-cut indications (continuing objective evidence of manifestations of chronic psychosis and their *responsiveness* to treatment). Antipsychotic drugs are to be avoided in patients who do not clearly need them or when they are not required or effective, as we await the development of improved antipsychotic drugs that lack neurological side effects.

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CHAPTER VII

SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

Summary of Chapters I-VI

Introduction

The past two decades have produced revolutionary changes in the practice of psychiatry and in psychiatric research. Particularly striking changes have occurred in the pattern of care of psychotic and other severely disturbed patients. The introduction of effective antipsychotic drugs in the early 1950s contributed to the changes in clinical management of such patients and to the administrative changes leading to diminished emphasis on long-term care in mental institutions. The antipsychotic drugs lead to rapid control of psychotic symptoms and behavior in a wide variety of psychotic illnesses and can have useful long-term preventive or ameliorative effects, although these have been scientifically verified only in schizophrenia.

Virtually all of the antipsychotic agents in use in current American medical practice also exert undesirable neurological effects, contributing to the acceptance of the term *neuroleptic* to describe this class of drugs. Most of the early neurological effects (dystonias, parkinsonism, akathisia or motor restlessness) are spontaneously reversible or are more-or-less adequately managed by the temporary addition of an antiparkinsonism drug. It has been realized in recent years, however, that certain neurological effects may occur later. They include abnormal movements, usually of a choreoathetotic or dystonic type. These late reactions are referred to as *tardive* (late and gradually appearing) *dyskinesia*. They can be so mild as to escape notice or can be severely disabling. In an uncertain proportion of cases, these movements seem to persist, at least for many months, and perhaps indefinitely, even when the suspected offending agent is removed. Their occurrence in association with long-term use of neuroleptic agents has become a cause of increasing concern to the medical profession and the general public.*

*E.g., see Steinmann, M: The Catch-22 of antipsychotic drugs. The New York Times Magazine, March 18, 1979, pp 114-121.

Clinical Description, Differential Diagnosis, and Clinical Evaluation

Tardive dyskinesia is manifested by a wide variety of involuntary movements including orofacial dyskinesia, chorea, athetosis, dystonia, tics, and facial grimacing, but excluding rhythmic tremor. The severity and extent of dyskinesias range from isolated orolingual dyskinesia to widespread and sometimes disabling dystonia, with some indication that age may influence the topographic distribution of involuntary movements—oro-lingual movements being especially common in the elderly. Tardive dyskinesia may appear after months or years of treatment with neuroleptic drugs and often worsens during or following drug withdrawal. In some cases dyskinesias that initially are manifested during drug withdrawal subside within several days to weeks and are referred to as withdrawal dyskinesias. It is possible, although unproven, that these represent an early and reversible form of tardive dyskinesia. Prognosis is difficult to predict in individual cases, but tardive dyskinesia has been irreversible in many patients; in younger populations with shorter drug exposure and prompt termination of treatment, the prognosis may be considerably better.

Differential diagnosis includes schizophrenic stereotypies, reversible neuroleptic syndromes, and dyskinesias induced by other drugs. In addition, one should consider Huntington's disease, Wilson's disease, generalized or focal forms of idiopathic torsion dystonia, oral dyskinesias associated with advanced age, chronic hepatic encephalopathy, postanoxic or postencephalitic states, basal ganglia calcification, Gilles de la Tourette's syndrome, endocrine or metabolic disorders that produce involuntary movements, and neoplastic diseases of the brain. Although vigilance for early identification of tardive dyskinesia is essential, it is important not to overlook other disorders in which psychiatric symptoms and involuntary movements may coexist with no relationship to tardive dyskinesia. Once identified, efforts to rate severity of tardive dyskinesia in at least a semiquantitative manner are useful for future management. A number of quantitative methods were reviewed, the most practical of which are multiple item rating scales topographically arranged by body area.

Epidemiology

Epidemiologic studies strongly support an association between the use of neuroleptic drugs and the development of persistent or relatively transient forms of tardive dyskinesia. While there is some evidence that prolonged exposure or exposure to large total amounts of drug may be a contributing factor, this is not established, and a correlation with the size of average doses is extremely weak. Older

patients, and possibly females, may be at higher risk and may have a somewhat poorer prognosis for eventual remission following prolonged removal of the suspected offending agents; the aging brain may present an increased risk for neuroleptic-related tardive dyskinesias, especially of the oral region. On the other hand, specific predictors of risk (such as type of drug and dose, timing of exposure, prior experience of acute reversible extrapyramidal symptoms, use of antiparkinsonism agents, or sex) do *not* reveal *clinically useful* risk factors (with the possible exception of advanced age) that might guide medical practice. Moreover, it is clear that similar exposure to neuroleptics neither produces tardive dyskinesia in all patients, nor are any groups (as defined by age, drug history, etc.) exempt from risk.

The precise prevalence rates of tardive dyskinesia are nearly impossible to specify as there is no currently accepted standard of diagnosis. It seems probable, based on the available data, that clinically appreciable cases, including transient dyskinesias and cases of only moderate severity, occur in perhaps ten to 20 percent of patients exposed to neuroleptic drugs for more than a few months. These rates may more than double in the elderly. Fortunately, an increasing number of cases are being reported which appear to undergo spontaneous remission within a period of months after removal or decreased dosage of the suspected offending agent: Perhaps one-quarter to one-half of cases remit within a year.

Etiology

An open-minded attitude concerning the etiology of tardive dyskinesia is still called for. More work can and should be done to study the possible relationship of neuroleptic drug effects and the tardive dyskinesia syndrome. More epidemiological studies in countries where antipsychotic drugs are still not used extensively would be helpful. Dyskinesias follow treatment with neuroleptic-antipsychotic agents after various lengths of time, manifesting various anatomical patterns and showing varying degrees of persistence. Therefore, they may not represent a single disease with a unitary pathophysiology. While similar dyskinesias can occur independently in association with senile brain changes and many other overt or presumed states of CNS disease, usually there are no organic, metabolic, or neurological factors found on clinical examination that might contribute to the development of neuroleptic-related tardive dyskinesias. More attempts should be made to reproduce the dyskinetic phenomena by prolonged administration of drugs to intact animals, as well as those with selective brain lesions, compromised cerebral circulation, or old age, and to make greater use of newer primate models of the disorder. There is also a

need for further carefully controlled neuropathologic studies in animals and man following prolonged exposure to neuroleptic agents, using classical neurohistology and electron microscopy as well as newer techniques such as chemical assays of transmitters and their metabolites, biochemical and immunohistological assays of neuron-specific enzymes, and labeling assays for neurotransmitter and drug receptors. Such methods are applicable to postmortem human brain tissue for a more direct evaluation of current pathophysiologic hypotheses concerning the response of the brain to prolonged exposure to neuroleptic drugs and the development of tardive dyskinesia.

At the present time, the conclusion seems inescapable that an important and relatively selective action of the antipsychotic-neuroleptic drugs is to block the actions of dopamine as a neurotransmitter in various regions of the CNS. Acute extrapyramidal and sustained neuroendocrine side-effects of these agents (such as increased secretion of prolactin) are almost certainly, in part at least, reflections of this action in the basal ganglia and hypothalamus or pituitary, respectively. Antipsychotic effects may further in part reflect antidopamine effects in limbic or cortical portions of the forebrain, although this hypothesis remains highly tentative. There is also excellent evidence that prolonged exposure to antidopamine drugs can lead to a variety of secondary or partially compensatory adjustments in the physiology and biochemistry of dopamine neurons and other cells with which they interact in the animal or human CNS. Among these adjustments, some tend to increase the effectiveness of dopamine as a neurotransmitter, particularly in the basal ganglia. These effects may help to explain the clinical observation that the risk of acute clinical extrapyramidal reactions diminishes in time, as the risk of tardive dyskinesia increases.

Another crucial source of support for a "dopamine supersensitivity" hypothesis in tardive dyskinesia is the now considerable amount of clinical pharmacologic evidence suggesting that a functional overactivity of extrapyramidal mechanisms mediated by dopamine is an important aspect of the clinical pathophysiology of tardive dyskinesia. An explanation for the prolonged and even irreversible course of some cases of tardive dyskinesia awaits further research, especially as it suggests that irreversible neurotoxic or degenerative effects of neuroleptic agents may occur, although these have not been convincingly demonstrated in postmortem neuropathological studies of animal or human brain tissue.

While the precise pathophysiology of tardive dyskinesia remains uncertain, the study of neurological, behavioral, and endocrinological effects of the neuroleptic agents on the CNS has contributed to an

improved understanding of their actions, at least equal to that of many other drugs used in medicine. Moreover, insights arising from studies of the antidopamine effects of the antipsychotic drugs in various brain regions promise to lead the way to a more rational basis for developing new, less neurotoxic, but effectively antipsychotic agents.

Clinical indications for prolonged neuroleptic treatment

A review of the literature demonstrates the efficacy of maintenance neuroleptic medication in preventing psychotic relapse in chronic schizophrenics. In approximately 30 controlled studies, it has been found that 55 percent of nearly 3,500 patients who received a placebo relapsed, in contrast to only 18 percent of patients given prolonged maintenance therapy and followed from several months to several years. Most studies have followed patients for less than one year, although there are some suggestions that "relapse" rates may diminish after the first year. The maximally effective doses of neuroleptic drugs during so-called "maintenance" treatment of schizophrenia may be lower than the effective doses used for the treatment of more acute phases of the illness. That is, many schizophrenic patients can evidently be maintained adequately for many months on doses below the equivalent of 300 mg a day of chlorpromazine. Even in schizophrenia, very few drugs other than phenothiazines have been evaluated adequately.

There are some reports of controlled studies (or a large amount of clinical experience) to support the efficacy and safety of neuroleptic drugs for conditions other than schizophrenia, including acute psychoses of uncertain types, mania, paranoid states, psychotic-agitated depression, some organic mental syndromes, and other neurological conditions with psychotic symptoms and disorders of movement (such as the syndromes of Huntington and Gilles de la Tourette), as well as miscellaneous medical indications (such as nausea and vomiting, and use in anesthesia). Nevertheless, there are virtually *no controlled studies* of long-term or "maintenance" uses of these drugs in those conditions. Such uses remain a matter of clinical judgment in individual cases.

Treatment and management of tardive dyskinesia

Although many clinical reports about a variety of therapies for tardive dyskinesia are available and have been reviewed (see Table 15 in Chapter VI), none has yet been either thoroughly studied or proven to be both safe and effective. Of the available approaches, stopping all antipsychotic medication indefinitely seems to be the theoretically ideal treatment. Unfortunately for many chronically disturbed

patients, this is not a feasible alternative. Several newer investigational therapies are said to be based on partially demonstrated increases of brain cholinergic activity (choline, lecithin, deanol), unproven increases of GABA-ergic activity (benzodiazepines, baclofen, sodium valproate), or reduced dopaminergic activity (dopamine blocking drugs, such as the potent neuroleptics themselves, or dopamine depleting drugs, such as reserpine). It is likely that tardive dyskinesia is a heterogeneous group of disorders having a variety of anatomical, neuropathological, and pathophysiological bases, corresponding to the varieties of natural history and responses to treatment. No treatment to date uniformly benefits all signs of dyskinesia in all patients, and most treatments studied cause only slight to moderate benefit in only a proportion (rarely more than half) of the patients studied, and then sometimes only in some of their movements.

At the present time, the best available means of dealing with the problem of tardive dyskinesia continues to be the use of conservative but effective dosage regimens of neuroleptics on clear-cut indications (continuing objective evidence of manifestations of chronic psychosis and their *responsiveness* to treatment). Antipsychotic drugs are to be avoided in patients who do not clearly need them or when they are not required or effective. The development of improved antipsychotic drugs that lack neurological side effects may be the best means of avoiding the problem in the long run. Such research is strongly encouraged.

Conclusions and Recommendations

Introduction

Psychiatric chemotherapy must be based on rational guidelines that include: objective diagnosis of the illness to be treated; consideration of the patient's past clinical history and response to treatment; an analysis of the risk:benefit ratio of any prospective agent for that patient; and a plan of action based on whether treatment is for an acute episode, sustained therapy of an active condition, or prevention of possible reactivation of a successfully treated condition. These criteria are especially pertinent in decisions regarding sustained, continuous use (more than six to 12 months) of neuroleptic medications, since such treatment carries a risk of the development of tardive dyskinesia.

Diagnosis

Rational treatment in psychiatry, as in general medicine, is based on careful diagnosis. Until recently, there was a tendency in the

United States to use the term "schizophrenia" excessively broadly, almost as a synonym for "psychosis" or "severe psychiatric disorder." There is now a growing realization that the diagnosis of schizophrenia has probably been given to many patients who would now be considered to suffer from affective disorders, acute psychoses of uncertain types, or personality disorders. Since diagnosis guides therapy, acceptance of a broad definition of "schizophrenia" and of corresponding broad indications for prolonged neuroleptic therapy in cases other than chronic psychosis almost certainly entails an increased risk of tardive dyskinesia when it might be avoided by the use of alternative treatments. During the past decade, the practical as well as theoretical importance of rigorous psychiatric diagnosis has become increasingly recognized in this country. The resurgence of careful differential diagnosis began in academic centers and is a concern of the American Psychiatric Association, as witnessed by the current revision of its *Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III).*

It is also important to emphasize that a wide range of severity of abnormal movements that may be called tardive dyskinesia is encountered clinically. This fact complicates the definition and diagnosis of tardive dyskinesia. One of the difficulties arising from currently heightened awareness of tardive dyskinesia is greater sensitivity to minor degrees of abnormal movements, some of which may not be related to neuroleptic drug use and do not represent tardive dyskinesia. These abnormalities include very minor movements that may be difficult to distinguish from habit spasms, other tics of unknown cause, psychotic mannerisms, or even normal movements (e.g., in association with ill-fitting dentures). A major problem in diagnosing tardive dyskinesia is determining the baseline of spontaneous (not neuroleptic-induced) dyskinetic movements in normal populations, the geriatric population, and the schizophrenic population—the latter two groups apparently having a greater incidence of relatively minor spontaneous movement abnormalities.

Indications for neuroleptics: short-term

In current American medical practice, neuroleptic medications are used for short-term treatment of acute psychotic episodes or for sustained "maintenance" or preventive therapy. Short-term use can reasonably be defined as treatment of less than six months' duration. The risk of persistent neurologic sequelae in this period of time appears to be very small (except in rare cases of unusually sensitive patients, or perhaps with unusually high dosages). The primary indication for short-term use of a neuroleptic drug is acute psychosis, includ-

ing *1*) first clinical presentation or exacerbations of schizophrenia; 2) paranoid states and other acute psychotic episodes of uncertain types (idiopathic conditions in which a categorical diagnosis is not possible); 3) mania, since lithium alone is typically not adequate for rapid reduction of manic excitement; *4*) certain cases of toxic or organic psychosis; 5) childhood psychoses; and 6) as an adjunctive therapy in severe depressions with psychotic symptoms (see Table 12 in Chapter V). For manic excitement when acute control is of primary clinical importance, neuroleptics typically are required in addition to lithium due to the latter's delayed onset of action. Evidence of the effectiveness of tricyclic antidepressants alone in depressions with prominent psychotic symptoms is mixed; therefore, some of these patients may be found empirically to benefit from the temporary addition of a neuroleptic agent. For depression, whether complicated by psychotic symptoms or not, antidepressant drugs and electroconvulsive therapy remain the basic medical therapies, with ECT being the most rapid means of achieving remission in very severe depression.

Other indications for short-term use of neuroleptic drugs include states of acute agitation occurring in acute or chronic brain syndromes, the latter including dementia and mental retardation. Serious consideration should be given to the risks and benefits of neuroleptics in comparison to other drug treatments or non-pharmacologic management. In these two conditions, as with any psychotic or agitated state associated with cerebral dysfunction, patients are at greater risk for drug-induced delirium, but this risk may be less prominent with neuroleptic drugs than with sedatives. There are other occasional non-psychiatric uses of neuroleptic drugs, including preoperative sedation, adjunctive uses in general anesthesia, control of nausea or vertigo, the treatment of pain, as well as in the control of neurological or psychiatric manifestations of certain unusual disorders, such as Huntington's disease and Gilles de la Tourette's syndrome. Finally, short-term treatment with neuroleptics has also been used in clinical psychiatric practice in empirical attempts to ameliorate the symptoms of a variety of neurotic or characteriologic disorders. The differential indications for this latter form of pharmacotherapy have not been adequately developed in controlled studies to permit generalizations or conclusions; therefore, this use remains a matter of critical clinical judgment with individual cases.

Indications for neuroleptics: long-term

Prolonged use (more than six months) of neuroleptic medications requires careful evaluation of indications and risks (see Table 13 in Chapter V). Such use is typically for maintenance treatment in chronic

psychotic disorders (mainly, schizophrenia) in which the patient, although improved, is not symptom-free. Sometimes prolonged neuroleptic treatment is used in Huntington's disease or Gilles de la Tourette's syndrome, although the *long-term* efficacy and risk of such therapy require further study. An important clinical consideration during prolonged exposure to neuroleptics for any reason is the risk of toxic effects, principally tardive dyskinesia. Although the physician is always responsible for the therapy given, the burden of justification for recommending prolonged use of neuroleptics rests especially heavily on the psychiatrist.

Any treatment has four potential outcomes: complete remission, partial relief, no effect, or clinical worsening. Maintenance neuroleptic treatment must be considered in light of these possible outcomes. Documentation of the continued indications *and effectiveness* of this treatment should be reviewed periodically and stated in the patient's records at least every three to six months, with regular reconsideration of the benefits and the risk of development of tardive dyskinesia in each case. At those times the patient's neurological and psychiatric status should be recorded. If there is no evidence of tardive dyskinesia, this observation should be noted, as it constitutes a significant negative finding. Other practical aspects of the prolonged use of neuroleptics are summarized in Table 16.

In general, maintenance treatment with neuroleptics is supported by scientifically sound data *only for schizophrenia.* Commitment of a patient to prolonged treatment with neuroleptics requires more than one acute psychotic episode without full return to optimal prepsychotic status, objective evidence of continuing psychosis, or good recovery but frequent recurrences that suggest the likelihood of further recurrences. In addition, it is recognized that some cases of mania or depression with recurrent psychotic symptoms occur for whom neither lithium nor an antidepressant alone is an effective maintenance therapy and for whom a clinical decision to try neuroleptic therapy might be considered. When long-term use of neuroleptics is contemplated, the possible benefits must be carefully weighed against the potential complications, especially in view of the fact that there are almost no scientifically compelling data to support the prolonged use of neuroleptics in psychiatric disorders other than schizophrenia.

Management of prolonged neuroleptic therapy

Even for schizophrenia, for which maintenance treatment has strong research support, deliberate and sustained effort must be made to maintain patients on the *lowest effective amount of drug* and *to keep the treatment regimen as simple as possible.* After a first acute

TABLE 16

Suggested Guidelines for the Avoidance and Management of Tardive Dyskinesia

1. Consider indications for prolonged neuroleptic therapy carefully; indications (chronic psychosis) should be serious, with objective evidence of benefit.

2. Seek alternative therapies in neuroses and mood and character disorders.

3. Use lower doses in elderly patients and children, strive for minimum effective doses, avoid multiple drugs, and remove antiparkinsonism agents as soon as possible.

4. Advise patients and families of risks and benefits; arrive at a mutual decision when use of neuroleptic exceeds one year. Note discussion and agreement in clinical record.

5. Examine patient regularly for early signs of choreoathetosis and oral-lingual dyskinesia. Consider alternative neurologic diagnoses.

6. Reevaluate and document indications and response at least every three to six months and attempt to reduce dose.

7. At earliest sign of dyskinesia, lower the dose, change to a less potent agent, or ideally stop treatment; await remission as long as psychiatric status permits.

8. Treat dyskinesia with benign agents first (diazepam, deanol, choline, or lecithin in high doses, possibly lithium); stay alert to new experimental therapies, if only to bide for time and offer hope. Reinstitute neuroleptics only as an extreme measure for disabling dyskinesias, using lowest doses feasible.

psychotic episode of any type has clinically remitted, a neuroleptic drug should be given in decreasing doses and can usually be safely discontinued within a matter of months. This recommendation is especially pertinent as it is rarely possible to diagnose schizophrenia with confidence based upon a single psychotic episode. It is becoming increasingly clear that many acute psychoses eventually prove to be episodes of manic-depressive illness, which has not been demonstrated scientifically to benefit from prolonged maintenance neuroleptic treatment. Also, dose-response data, even in schizophrenia, are very sparse, although it is widely suspected that dosage requirements for maintenance therapy are probably lower than in management of more acute phases of the illness.

Increasing the dose of a neuroleptic in a schizophrenic patient can be supported only when lesser doses do not lead to clinical improvement but higher doses appear to be effective. The presumption in such therapy is that the degree of added benefit is being thoughtfully balanced by the clinician against the possible additional risk of developing long-term complications.

For schizophrenic patients, neuroleptic treatment is typically only *partially* successful: This fact, ironically, is probably the main reason schizophrenia is the most common indication for prolonged neuroleptic treatment. Unfortunately, a curative treatment of schizophrenia does not exist. Presently, an aggressive medical approach is the most efficacious treatment available for schizophrenic patients, especially for those who have limited support systems in the community. Yet, some schizophrenic patients appear to respond undramatically, or not at all, to antipsychotic drugs. Before maintenance therapy is recommended for a schizophrenic patient, there should be reasonable evidence that the antipsychotic drug has helped improve the patient's symptoms and social adjustment. In cases where neuroleptic medications have not provided at least partial objective benefit, their continued uninterrupted use must be seriously questioned.

For the special case of chronically hospitalized schizophrenics, at least yearly, and preferably, twice yearly re-evaluations off neuroleptic medications are recommended. The dose of medication should be reduced by approximately ten percent every three to seven days until totally discontinued or until clear signs of clinical worsening intervene. The patient should remain off treatment for at least two weeks if his clinical status permits and if clinical experience in the recent past does not suggest that such a trial is excessively dangerous. Such periodic evaluations serve two purposes: *a*) to detect "withdrawal" dyskinesia (Chapter II), which may be a prodromal but reversible phase of tardive dyskinesia; and *b*) to allow the clinician to decide whether continued neuroleptic use is necessary. This practice may also be tried in selected outpatients. However, the ubiquitous and critical shortage of adequate aftercare systems often does not permit such trials, because without medication and without close follow-up to detect early clinical signs of worsening, there is a high risk of relapse, which often has serious—in some instances, life-threatening—health and social consequences. The hospital setting, however, does provide such close monitoring, and occasionally outpatients or day-hospital patients may be readmitted to conduct such periodic re-evaluations. Even if such a trial with less medication has been unsuccessful within the past year, it still should be reconsidered at regular intervals and seriously attempted for most patients—the potential benefits outweighing the

possible risks and the natural reluctance of those caring for more-or-less stable chronically ill patients to "rock the boat."

Prevalence of tardive dyskinesia

Both the medical profession and the public should be aware that some recent epidemiological studies suggesting a very high prevalence of tardive dyskinesia probably reflect an increasing sensitivity to minor degrees of possible movement abnormality. In addition, although some early studies suggested that prevalence of spontaneous buccolinguomasticatory movement abnormalities was relatively low in geriatric patients not treated with drugs, more recent studies show rates close to those found in neuroleptic-medicated patients (see Chapter III). At present, it is impossible to say whether patients showing a slightly increased hyperactivity of the tongue and slight choreic movements of the fingers do or do not have tardive dyskinesia. Some abnormalities of posture and movement were reported in schizophrenia prior to the use of neuroleptics. There is no agreement at the present time concerning criteria to be used to diagnose tardive dyskinesia. The available epidemiologic studies have applied different criteria and have reported vastly different prevalence rates ranging from less than ten percent to more than 50 percent (see Chapter III). Even if the "true" prevalence of tardive dyskinesia is between ten and 20 percent of patients treated with neuroleptic drugs for more than a year, and even if half of these may remit spontaneously, the problem is clearly a significant one. Moreover, even mild choreoathetosis, if due to neuroleptic treatment, is a valid cause of concern and encourages the development of safer and more selective antipsychotic drugs. On the other hand, considering the present state of knowledge, it would be a distortion and misrepresentation of the data to conclude that serious and profoundly disabling degrees of irreversible dyskinesia are a common occurrence in standard practice.

Management of tardive dyskinesia

If a patient develops dyskinesia during a trial of reduced dosage of a neuroleptic, or while fully medicated, the theoretical treatment of choice is discontinuation of neuroleptics (see Figure 9). The available data suggest that tardive dyskinesia is often reversible if neuroleptics are withdrawn, especially early in its course, although some cases may require many months to improve (see Chapters II and III). A dilemma is presented when a patient's psychosis exacerbates after neuroleptic treatment is stopped and tardive dyskinesia is also present. In this situation, the clinician, with the patient and family, must weigh the risk of psychiatric worsening, which may be seriously life-disrupting

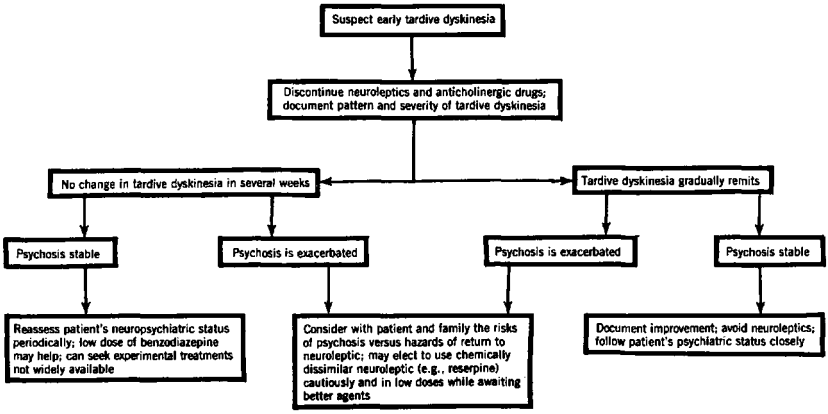

Figure 9. *Recommended scheme of management of tardive dyskinesia (TD)*

or even life-threatening, against the risk of tardive dyskinesia. Since tardive dyskinesia seems not to be a relentlessly progressive neurologic disorder, it may be prudent to continue neuroleptic therapy temporarily if the psychiatric indications are sufficiently compelling. Although there is little scientific evidence to support the practice, some psychiatrists rely on the less potent neuroleptic drugs with relatively less tendency to induce acute extrapyramidal effects in such situations. Clozapine had also been used in this way, due to its low incidence of acute and late neurologic side-effects, but this experimental agent has been withdrawn by its manufacturer because of serious toxic effects. Other safer agents are being sought, but none is yet available in American practice (see Chapter VI). Recently proposed experimental treatments, notably attempts to increase brain cholinergic function with deanol, choline, or lecithin, are worthwhile as they do not seem to worsen psychosis and theoretically might be expected to benefit psychosis as well as dyskinesia. Moreover, attempts to provide such treatments (their still-experimental status makes it difficult to avail a patient of them except in academic centers) offer a hopeful and positive approach to clinical management while the clinician and patient await a spontaneous remission of tardive dyskinesia over a period of many weeks or even months following discontinuation of neuroleptic treatment. Although increasing the dose of a potent neuroleptic may "mask" or suppress the dyskinetic movements, this tactic carries the theoretical risk of causing further neurologic insult. Nevertheless, this step is sometimes taken when the dyskinetic problem is severely incapacitating (similar to the practice of treating Huntington's disease or Gilles de la Tourette's syndrome).

Physician-patient relationship

Good practice necessitates that the psychiatrist sustain rapport with patients at risk of developing tardive dyskinesia. Furthermore, the psychiatrist should attempt to *educate* the patient as to the nature of his illness, the potential benefits of available treatments, and their potential adverse results. Early in the treatment of a severely disturbed patient such education may be limited by virtue of the patient's psychosis or confusion. At these times, family members or other persons close to the patient can be involved in such discussions. The need to review the treatment plan and its potential benefits and risks with the patient and his family becomes especially significant when prolonged neuroleptic therapy is considered or if tardive dyskinesia has already developed.

Although the routine use of signed and witnessed consent documents to protect the interests of the patient and the physician during prolonged neuroleptic therapy has been proposed, there are many serious problems with this approach. First, there are marked differences between established pharmacological treatments and invasive surgical, diagnostic, or experimental procedures for which this type of formal documentation of consent is often (but not always) used. While the latter typically involve brief acute risks during a patient's care for which limited procedural consent can meaningfully be given, pharmacologic treatments of chronic disorders are likely to be continued and modified repeatedly over extended periods of time. Written consent would, therefore, not be feasible unless given in a blanket fashion, making it a potentially meaningless formal exercise. Furthermore, it tends to introduce a potentially detrimental adversary quality to the physician-patient relationship. Finally, it is a precedent-setting step to routinely require written consent to institute an accepted nonexperimental medicinal therapy. Based upon these considerations, routine signing and witnessing of written consent for neuroleptic therapy is not recommended.* On the other hand, good practice does require that the physician note in the records that the indications and risks of prolonged neuroleptic treatment have been carefully considered and reviewed with the patient or family.

*J. Vaccarino, J.D., has recently emphasized that even when informed consent is necessary, the documentation can be done with or without "forms," that a signature on a form does not guarantee freedom from legal action, and that "informed consent" fundamentally requires a face-to-face discussion of the issues by doctor and patient (see Vaccarino J: Consent, informed consent and the consent form. N Engl J Med 289:455, 1978).

Need for further research

A review of the present state of the medical treatment of severe chronic psychiatric disorders leaves many unanswered questions and underscores the need for further basic and applied research. An urgent need is the development of effective antipsychotic drugs that do not have the long-term risk of inducing tardive dyskinesia. This requires the development by academic and industrial pharmacologists of better drug screening tests (e.g., animal models that are not dependent upon drug-induced extrapyramidal effects) (Chapter IV). Clozapine and sulpiride are examples of experimental drugs that seem to be effective antipsychotic agents with few acute or late extrapyramidal effects. Unfortunately, experimental trials with clozapine have been discontinued due to its association with agranulocytosis, and sulpiride is not available in the United States. Safer analogues of these or similar drugs are now being considered; their rapid development and clinical testing are strongly encouraged.

While we await the availability of more nearly ideal antipsychotic drugs, many questions still need to be answered about the use of the presently available neuroleptic drugs. For example, more controlled treatment studies are needed comparing the efficacy of ECT, antidepressants, neuroleptics, and various combinations of these treatments in severely depressed patients. The long-term safety and effectiveness of neuroleptics in manic-depressive patients or others with episodic psychoses who cannot be managed with lithium alone need to be studied. Although neuroleptics have sometimes been used for neuroses, character disorders, and "borderline" patients, these uses remain a matter of clinical judgment; and more research studies of such cases are encouraged. Another research area in need of strong support includes various attempts to optimize the use of available agents for specific patients. Thus, more information on dose:response relationships in man is required for all antipsychotic agents, especially to support the clinical impression that effective maintenance doses may be lower than those required for acute exacerbations of psychosis. In addition, efforts to apply available and still-evolving methods of analysis of drug metabolism and pharmacokinetics to routine clinical use are badly needed. While neuroleptic pharmacotherapy has greatly advanced patient care, it must be continually improved, and its clinical use must be based on sound research data.

Postgraduate education

Although further research is required to address the many areas of uncertainty already discussed, much is already known which has a

bearing on the safe and effective use of antipsychotic drugs in clinical practice. Our survey of North American psychiatric training centers (see Appendix II) indicates that the majority provide some training in clinical psychopharmacology to residents and practicing physicians. These aspects of postgraduate and continuing medical education are to be strongly encouraged and given even greater support to ensure that the best possible care will continue to be available to the most severely ill psychiatric patients.

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APPENDICES

APPENDIX I
CLINICAL RATING SCALES FOR TARDIVE DYSKINESIA

For educational purposes, as well as for training researchers in the use of rating methods, several films or videotapes are available, including a comprehensive film on extrapyramidal effects of neuroleptic drugs edited by Dr. Frank Ayd of Baltimore; a set of training tapes prepared for NIMH by Dr. N. Schooler; and a film illustrating various forms of tardive dyskinesia by Drs. D. Tarsy, R. Granacher, and R.J. Baldessarini of Boston. These can be obtained at the following addresses:

Dr. Frank J. Ayd, Jr.
912 West Lake Avenue
Baltimore, Maryland 21210

Dr. Nina Schooler
Psychopharmacology Branch
National Institute of Mental Health
5600 Fishers Lane
Rockville, Maryland 20857

Dr. Ross J. Baldessarini
Mailman Research Center
McLean Hospital
115 Mill Street
Belmont, Massachusetts 02178

Following are two rating scales to be used in the assessment of tardive dyskinesia. The Abnormal Involuntary Movement Scale (AIMS) was developed at the National Institute of Mental Health. The Rockland (Simpson) Scale was developed at the Rockland Research Institute. References to the use of these methods are provided in Chapter II.

AIMS
EXAMINATION PROCEDURE

Either before or after completing the Examination Procedure observe the patient unobtrusively at rest (e.g., in waiting room).

The chair to be used in this examination should be a hard, firm one without arms.

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1. Ask patient whether there is anything in mouth (i.e., gum, candy, etc.) and if there is, to remove it.

2. Ask patient about the *current* condition of his/her teeth. Ask if patient wears dentures. Do teeth or dentures bother patient *now*?

3. Ask whether patient notices any movements in mouth, face, hands, or feet. If yes, ask to describe and to what extent they *currently* bother patient or interfere with activities

4. Have patient sit in chair with hands on knees, legs slightly apart, and feet flat on floor. (Look at entire body for movements while in this position.)

5. Ask patient to sit with hands hanging unsupported. If male, between legs, if female and wearing a dress, hanging over knees. (Observe hands and other body areas.)

6. Ask patient to open mouth. (Observe tongue at rest within mouth.) Do this twice.

7. Ask patient to protrude tongue. (Observe abnormalities of tongue movement.) Do this twice.

* 8. Ask patient to tap thumb, with each finger, as rapidly as possible for 10–15 seconds; separately with right hand, then with left hand. (Observe facial and leg movements.)

9. Flex and extend patient's left and right arms (one at a time). (Note any rigidity separately.)

10. Ask patient to stand up. (Observe in profile. Observe all body areas again, hips included.)

* 11. Ask patient to extend both arms outstretched in front with palms down. (Observe trunk, legs, and mouth.)

* 12. Have patient walk a few paces, turn, and walk back to chair. (Obverse hands and gait.) Do this twice.

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* Activated movements

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
ALCOHOL, DRUG ABUSE, AND MENTAL HEALTH ADMINISTRATION
NATIONAL INSTITUTE OF MENTAL HEALTH

ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS)

STUDY	PATIENT	PERIOD	RATER	HOSPITAL

PATIENT'S NAME

RATER

DATE

INSTRUCTIONS: Complete Examination Procedure (next page) before making ratings.
MOVEMENT RATINGS: Rate highest severity observed. Rate movements that occur upon activation one *less* than those observed spontaneously.

Code: 0 = None
1 = Minimal, may be extreme normal
2 = Mild
3 = Moderate
4 = Severe

		(Circle One)
FACIAL AND ORAL MOVEMENTS:	1. Muscles of Facial Expression e.g., movements of forehead, eyebrows, periorbital area, cheeks; include frowning, blinking, smiling, grimacing	0 1 2 3 4
	2. Lips and Perioral Area e.g., puckering, pouting, smacking	0 1 2 3 4
	3. Jaw e.g., biting, clenching, chewing, mouth opening, lateral movement	0 1 2 3 4
	4. Tongue Rate only increase in movement both in and out of mouth, NOT inability to sustain movement	0 1 2 3 4

EXTREMITY MOVEMENTS:	5. Upper *(arms, wrists, hands, fingers)* Include choreic movements, (i.e., rapid, objectively purposeless, irregular, spontaneous), athetoid movements (i.e., slow, irregular, complex, serpentine). Do NOT include tremor (i.e., repetitive, regular, rhythmic	0 1 2 3 4
	6. Lower *(legs, knees, ankles, toes)* e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot	0 1 2 3 4
TRUNK MOVEMENTS:	7. Neck, shoulders, hips e.g., rocking, twisting, squirming, pelvic gyrations	0 1 2 3 4
GLOBAL JUDGMENTS:	8. Severity of abnormal movements	None, normal 0 Minimal 1 Mild 2 Moderate 3 Severe 4
	9. Incapacitation due to abnormal movements	None, normal 0 Minimal 1 Mild 2 Moderate 3 Severe 4
	10. Patient's awareness of abnormal movements Rate only patient's report	No awareness 0 Aware, no distress 1 Aware, mild distress 2 Aware, moderate distress 3 Aware, severe distress 4
DENTAL STATUS:	11. Current problems with teeth and/or dentures	No 0 Yes 1
	12. Does patient usually wear dentures?	No 0 Yes 1

INSTRUCTIONS FOR ROCKLAND RESEARCH INSTITUTE (SIMPSON) CLINICAL RESEARCH RATING SCALE FOR TARDIVE DYSKINESIA*

This scale is well suited for clinical or research purposes. In addition, an abbreviated scale that may be simpler for clinical use is described on page 192. The examination routine is similar for both the full form (pp. 188-191) or the short form (p. 192).

Patients may be examined one at a time or in pairs. Pairs have the advantage in that the examiner can rate each patient "unawares." Thus, the dyskinetic movements may be diminished or even absent when the patient's attention is focused on the examiner or when the patient is aware of being rated. Talking to one patient while rating the other produces a more accurate rating. If only one patient is present, the examiner should engage in conversation or have someone else talk to him while the examiner rates him.

Observation begins when the patient walks into the room. Observe whole body movements with particular attention to the limbs. Wrist and finger movements not readily observable by other procedures can frequently be seen when the subject is walking. Similarly, abnormalities of gait give clues to other dyskinetic phenomena.

The patient should sit in a chair with a firm armrest and remove his shoes and socks. The hands should be placed on the knees and hang loosely. The feet should be placed slightly apart, flat on the floor.

To examine the tongue, have the patient open his mouth wide and protrude his tongue. This should be done at least twice, and a good light is essential to see the tongue movements. Another procedure to bring out buccolingual movements is to distract the patient by asking him to count up to ten or 20 in his mind, tap with his hands, count his fingers, or flap his hands. The tongue is observed within the buccal cavity while this procedure is being carried out. Eye tremor can be demonstrated with the eyes gently closed and if need be the same reinforcing procedures as are carried out during evaluation of the tongue. In order to rate trunk movements, the patient should be asked to stand still for at least one minute and then to walk away from and toward the examiner.

*This material was kindly provided by Dr. Simpson, and a report on this method is in the press: Simpson GM, Lee JH, Zoubok B, Cole JO, Gardos G: A rating scale for tardive dyskinesia. Psychopharmacology (in press, 1980).

To elicit dyskinetic movements that are not evident at rest, the following distracting maneuvers are suggested: The patient is asked to stand with his arms straight out in front of him with his wrists bent at 90 degrees to his arms. This should be in a relaxed position. He should be told to close his eyes gently and open his mouth, keeping his tongue within the buccal cavity. This position should be held for about 30 seconds. The patient can be spoken to at this time in order to distract him. Tongue and finger movements are watched for; slight forward and backward movements of the fingers of a choreoathetoid nature are easily distinguishable from tremor. If no finger movements are noted, the patient can be told to close his mouth and be engaged in conversation while his arms remain extended with wrists flexed and his eyes remain closed.

In examining the feet, the patient is sitting; while talking to the patient, reinforcing or distracting movements, either slapping his hand on his knees or rapidly tapping his fingers with his thumbs, can be added. One watches for movement at the ankle joint and contracting and relaxing movements of the toes, as well as any tapping movements. Trunk and arm movements are rated while the patient is walking, and also while he is standing. Whatever distractive maneuvers are used during the first examination should be noted and used consistently in subsequent examinations, especially during a research study. A minimum of ten minutes should be spent with each patient at each examination.

ROCKLAND RESEARCH INSTITUTE (SIMPSON) TARDIVE DYSKINESIA RATING SCALE: DEFINITIONS

FACE

1) *Blinking of Eyes*—Repetitive and more or less continuous or in bursts. To be distinguished from tics, which occur episodically.
2) *Tremor of Eyelids*—Isolated tremor, more frequently bilateral but can occur unilaterally. Usually seen when eyes are closed. Fine in character.
3) *Tremor of Upper Lip (Rabbit Syndrome)*—Fine, rapid tremor confined to the upper lip.
4) *Pouting of the Lower Lip*—A thrusting out of the lower lip.
5) *Puckering of Lips*—Drawstring or pursing action of the lip.
6) *Smacking of Lips*—Brisk separation of lips which produces a sharp sound.
7) *Chewing Movement*—Self-explanatory.
8) *Sucking Movement*—Self-explanatory.
9) *"Bon Bon" Sign*—Tongue movement within the oral cavity which produces a bulge in the cheek, giving the impression that the patient has a hard candy pocketed in his cheek. Occasionally a repetitious sweeping movement of the tongue over the buccal lining which also pushes out the mouth.
10) *Tongue Protrusion*—Clonic–a rhythmic in and out movement of the tongue; tonic–a continuous protrusion of the tongue; "fly catcher"–a sudden shooting out of the tongue from the mouth at irregular episodes.
11) *Tongue Tremor*—Fine tremor observed with the mouth open and tongue within the buccal cavity.
12) *Choreo-athetoid Movements of the Tongue*—A rolling, worm-like movement of the tongue muscles without displacement of the tongue from the mouth. The tongue may rotate on its longitudinal axis. Observed when the mouth is opened.
13) *Facial Tics*—Brief, recurrent, stereotyped movement involving relatively small segments of the face.

14) *Grimacing*—A repetitive, irregularly occurring distortion of the face. A complex movement involving large segments of facial muscles.

Other—Write in items such as unusual bucco-lingual movements, blepharospasm, repetitive sounds, or grunting, etc.

NECK AND TRUNK

15) *Head Nodding*—Slower than tremor, may or may not be rhythmic. Can occur horizontally or vertically.
16) *Retrocollis*—Overextension of the neck as a result of which the head is bent backward. Can occur with or without rigidity of the muscles of the neck and shoulder.
17) *Spasmodic Torticollis*—Tonic, prolonged contracture of sternocleidomastoid on one side resulting in a downward and lateral fixation of the chin. The head may be bent laterally.
18) *Torsion Movements*—Twisting undulant movements of the upper or lower part of the trunk (shoulder or hip girdle) resulting from mobile, spastic movements of the axial and proximal muscles. The movements are not fast, and they involve large portions of the body. Increased lordodic posturing may be present, sometimes with backward bending toward one side, more or less constantly.
19) *Axial hyperkinesia*—A front-to-back hip rocking movement. Resembles copulatory movements. Differs from the rocking movement, in which the upper torso has to-and-fro movement.
20) *Rocking Movements*—A rhythmic to-and-fro movement of the upper torso which occurs from a repeated bending of the spinal column in the lumbar region. Different from Axial Hyperkinesia where the hips move to-and-fro.

Other—(Write-in)

EXTREMITIES

21) *Ballistic Movements*—Sudden, fast, large amplitude swinging movements occurring most often in the arms and less frequently in the legs. One or both sides may be involved.

Choreo-athetoid Movements

22) *Choreiform Movements*—In fingers, wrists, arms. Variable, purposeless, coarse, *quick* and jerky movements that begin suddenly and show no rhythmicity. They vary in distribution and extension.
23) *Athetoid Movements*—In fingers, wrists, arms. Continuous rhythmic, *slow,* writhing, worm-like movements. They almost invariably appear together with choreiform movements.
24) *"Finger Counting" or "Pill-Rolling"*—Rhythmic rubbing of the thumb against the middle and index finger.
25) *Carressing Face and Hair*—Gives the impression of an absent-minded or nervous mannerism; may appear to be purposeful.
26) *Rubbing of Thighs*—Hands rub the outside or tops of thighs. Sporadic and non-rhythmic.

Other—(Write-in)

27) *Rotation and/or Flexion of the Ankles*—Self-explanatory.
28) *Toe Movements*—Slow rhythmic retroflexion, usually of the big toes, although other toes can also be involved.
29) *Stamping Movements* (Standing)—Weight is shifted back and forth from one foot to the other when patient stands.
30) *Stamping Movements* (Sitting)—Flapping or tapping of the whole foot on floor when the patient is sitting or may comprise an alternate toe and heel tapping.
31) *Crossing and uncrossing legs*—Self-explanatory.
32) *Restless Legs*—Constant leg movement; jiggling of legs, of foot when leg is crossed; may involve rapidly moving knees apart and together.
33) *Holokinetic Movements*—Extensive, jerky, rapid, abrupt, awkward, gross movements of large parts or entire body. The movement may appear to be somewhat goal directed and only moderately coordinated. May begin in response to a stimulus or spontaneously.
34) *Akathisia*—An inability to sit or stand still. (The verbal expression of inner restlessness is not required here.)

Other—(Write in)

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Patient Name				
Patient Study #				
Date Form Completed	MO.	DAY	YR.	

ROCKLAND (SIMPSON)
Clinical Research

TARDIVE DYSKINESIA
RATING SCALE

ITEMS	Absent	Questionable	Mild	Moderate	Moderately Severe	Very Severe
FACE						
1. Blinking of eyes	0	1	2	3	4	5
2. Tremor of eyelids	0	1	2	3	4	5
3. Tremor of upper lip (Rabbit Syndrome)	0	1	2	3	4	5
4. Pouting of the (lower) lip	0	1	2	3	4	5
5. Puckering of lips	0	1	2	3	4	5
6. Smacking of lips	0	1	2	3	4	5
7. Chewing movements	0	1	2	3	4	5

8.	Sucking movements	0	1	2	3	4	5
9.	Bon Bon sign	0	1	2	3	4	5
10.	Tongue protrusion	0	1	2	3	4	5
11.	Tongue tremor	0	1	2	3	4	5
12.	Choreoathetoid movements of the tongue	0	1	2	3	4	5
13.	Facial tics	0	1	2	3	4	5
14.	Grimacing	0	1	2	3	4	5
	Other (describe) _____	0	1	2	3	4	5
	Other (describe) _____	0	1	2	3	4	5

NECK & TRUNK

15.	Head nodding	0	1	2	3	4	5
16.	Retrocollis	0	1	2	3	4	5
17.	Spasmodic Torticollis	0	1	2	3	4	5
18.	Torsion movements (trunk)	0	1	2	3	4	5
19.	Axial Hyperkinesia	0	1	2	3	4	5
20.	Rocking movement	0	1	2	3	4	5
	Other (describe) _____	0	1	2	3	4	5
	Other (describe) _____	0	1	2	3	4	5

	Absent	Questionable	Mild	Moderate	Moderately Severe	Very Severe
EXTREMITIES (Upper)						
21. Ballistic movements	0	1	2	3	4	5
22. Choreoic movements - Fingers, wrists, Arms	0	1	2	3	4	5
23. Athetoid movements - Fingers, wrists, Arms	0	1	2	3	4	5
24. Pill Rolling movements	0	1	2	3	4	5
25. Caressing or rubbing face and hair	0	1	2	3	4	5
26. Rubbing of thighs	0	1	2	3	4	5
Other (describe) _____	0	1	2	3	4	5
Other (describe) _____	0	1	2	3	4	5
EXTREMITIES (Lower)						
27. Rotation and/or Flexion of ankles	0	1	2	3	4	5
28. Toe movements	0	1	2	3	4	5

29. Stamping movements - Standing	0	1	2	3	4	5
30. Stamping movements - Sitting	0	1	2	3	4	5
31. Crossing, uncrossing legs - Sitting	0	1	2	3	4	5
32. Restless Legs	0	1	2	3	4	5
Other (describe) _____	0	1	2	3	4	5
Other (describe) _____	0	1	2	3	4	5

ENTIRE BODY

33. Holokinetic Movements	0	1	2	3	4	5
34. Akathisia	0	1	2	3	4	5
Other (describe) _____	0	1	2	3	4	5
Other (describe) _____	0	1	2	3	4	5

COMMENTS:

_____

Investigator

ROCKLAND RESEARCH INSTITUTE (SIMPSON)

ABBREVIATED DYSKINESIA RATING SCALE

Patient _____ # _____ Date _____ Time _____ am pm

Setting _____ Study # _____ Rater # _____ Period _____

FACIAL AND ORAL MOVEMENTS	RATING*
1. Periocular area (blinking of eyes, tremor of eyelids)	1 2 3 4 5 6
2. Movements of the lips (Pouting, Puckering, Smacking)	1 2 3 4 5 6
3. Chewing movements	1 2 3 4 5 6
4. Bonbon sign	1 2 3 4 5 6
5. Tongue protrusion	1 2 3 4 5 6
6. Tremor and/or choreoathetoid movements of the tongue	1 2 3 4 5 6
7. OTHER (describe) _____	1 2 3 4 5 6
NECK AND TRUNK	
8. Axial hyperkinesis (patient standing)	1 2 3 4 5 6
9. Rocking movements	1 2 3 4 5 6
10. Torsion movements	1 2 3 4 5 6
11. OTHER (describe) _____	1 2 3 4 5 6
EXTREMITIES	
12. Movements of fingers and wrists	1 2 3 4 5 6
13. Movements of ankles and toes	1 2 3 4 5 6
14. Stamping movements	1 2 3 4 5 6
15. OTHER (describe) _____	1 2 3 4 5 6
ENTIRE BODY	
16. Akathisia	1 2 3 4 5 6
17. OTHER (describe) _____	1 2 3 4 5 6

*RATING: 1 - absent
2 - questionable
3 - mild
4 - moderate
5 - moderately severe
6 - severe

TOTAL SCORE:

ROCKLAND RESEARCH INSTITUTE

TARDIVE DYSKINESIA DEFINITIONS

(ABBREVIATED SCALE)

FACIAL AND ORAL MOVEMENTS

1) *Periocular area (blinking of eyes, tremor of eyelids)*

a) *Blinking of eyes*

Repetitive or continual involuntary shutting and opening of eyes (distinguish from tics which occur episodically).

b) *Tremor of eyelids*

Isolated fine tremor more frequently bilateral but can occur unilaterally. Usually seen when eyes are closed (not too tightly).

Rate the increase in frequency and extent of these movements. Movements should be observed separately but can be rated together or separately as the case may be.

1 = absent
2 = questionable
3 = 7-10 blinks per 30 seconds
4 = 11-13 blinks per 30 seconds
5 = almost continuous
6 = continuous and incapacitating

---

2) *Movements of the lips (Pouting, Puckering, Smacking*

a) *Pouting*

A thrusting out of the lower lip.

b) *Puckering*

Drawstring or pursing action of the lips.

c) *Smacking*

Brisk separation of lips which produces a sharp sound.

Rate the increase in frequency and extent of these movements. Movements should be observed separately but can be rated together or separately as the case may be.

1 = absent
2 = questionable
3 = occasional during observation period
4 = frequently during observation period
5 = almost continuously
6 = continuously

---

3) *Chewing Movement* - Self explanatory.
Make sure that the patient does not have chewing gum or candy in his mouth.

Rating based on the frequency and degree of interference with normal chewing activities.

1 = absent
2 = questionable
3 = occasional chewing movements
4 = frequent chewing movements
5 = almost continuous chewing
6 = continuous chewing which interferes with normal eating and articulation.

---

4) *Bon-Bon Sign*
Tongue movement within the oral cavity which produces a bulge in the cheek giving the impression the patient has a hard candy pocketed in his cheek. Occasionally a repetitive sweeping movement of the tongue over the buccal lining which also pushes out the mouth. (Distinguish from choreoathetoid movements of the tongue.)

Rating based on the frequency and degree at which the tongue pushes against the cheek within the oral cavity.

1 = absent
2 = questionable

3 = occasionally
4 = obvious most of the time
5 = almost continuous
6 = continual sweeping movements involving whole cheeks and buccal cavity.

---

5) *Tongue Protrusion*
   a) *Clonic* - a rhythmic in and out movement of the tongue.
   b) *Tonic* - a continuous protrusion of the tongue.
   c) *Fly Catcher* - a sudden shooting out of the tongue from the mouth at irregular episodes.

Rating based on the frequency, degree and duration of tongue protrusion in and out of the mouth cavity.

1 = absent
2 = questionable
3 = occasional protrusion of tongue
4 = frequent protrusion
5 = almost continuous protrusion of the tongue
6 = pronounced protrusion with swollen tongue as if it has no room in the mouth.

---

6) *Tremor and/or choreoathetoid movements of the tongue.*
   a) *Tremor* - Fine rapid to slow tremor observed with the mouth open and tongue within the buccal cavity.
   b) *Choreoathetoid movements of the tongue* - Rolling, worm-like movement of the tongue muscles without displacement of the tongue from the mouth. The tongue may rotate on its longitudinal axis. Observed when the mouth is open.

Both movements should be observed separately but could be rated together as the case may be. (Distinguish from Bon Bon sign which is continual irregular movements within the oral cavity with the mouth closed.)

Rating based on the intensity and frequency of the tongue movements.

1 = absent
2 = questionable
3 = Brief and occasional worm-like tongue movements.
4 = tongue moves several times in all directions on its longitudinal axis
5 = almost continuous rolling
6 = continuous and incessant twisting, folding and rolling all over the oral cavity so that the underside of the tongue is exposed.

---

7) Other - write in items as the "Rabbit" Syndrome, a fine, very rapid tremor of the upper lip (5 per second). Tics or grimacing.

NECK AND TRUNK

8) *Axial Hyperkinesis* (patient standing).
A front to back hip rocking movement. Resembles copulatory movements. Differs from the rocking movement where it is the upper torso which has to and fro movement.

Rating is based on the frequency and range of the movements of the pelvis when standing.

1 = absent
2 = questionable
3 = seen occasionally
4 = seen most frequently
5 = almost continuous long range movements of the pelvis
6 = continuous swinging of the pelvis

---

9) *Rocking Movements*
Continuous or episodic rhythmic to and fro or side-to-side movement of the upper torso which occurs from a repeated bending of the spinal column in the lumbar region while sitting. (Distinguish from axial hyperkinesia where the hips move to and fro while standing).

1 = absent

2 = questionable
3 = occasional to and fro movements
4 = episodic movements with small range
5 = almost continuous to and fro movements with small range
6 = continuous to and fro movements with large range.

---

10) Torsion Movements
Twisting undulant movements of the upper or lower part of the trunk (shoulder or hip girdle). The movements are not fast and they involve large portions of the body. More or less constantly altered posture or twisting of the trunk may be seen.

Rating based on frequency and intensity.

1 = absent
2 = questionable
3 = occasional
4 = episodic
5 = almost continuous - small range
6 = continuous twisting of large portions of the body.

---

11) Other
Write in items such as head nodding, retrocollis and torticollis.

EXTREMITIES

12) Movements of Fingers and Wrists -
Irregular, purposeless, coarse, jerky (non-rhythmic and rhythmic) movements (guitar playing) which begin suddenly and may last for brief period or may be continuous; may involve few fingers or whole hand and wrist. Wrist movements are more rhythmic and occasional jerky and worm-like. Both invariably appear together.

Rating based on frequency and intensity.
1 = absent
2 = questionable
3 = seen occasionally in few fingers - low in intensity

4 = seen most of the time during observation involving the whole hand with marked intensity
5 = continuous worm-like movements involving all the fingers of whole hand
6 = continuous, worm-like irregular movements of the whole hand and wrist

---

13) *Movements of Ankles and Toes*
Involves rotation and flexion of ankles. Slow range, irregular coarse involuntary movement of toes, episodic or continuous.

Rating based on intensity and frequency.

1 = absent
2 = questionable
3 = seen occasionally
4 = seen most of the time during observation, ankle rotating and flexing
5 = almost continuously
6 = seen continuously with marked intensity

---

14) *Stamping Movements*
Flapping or tapping of whole foot on the floor either in sitting or standing.

Rating based on intensity and frequency.
1 = absent
2 = questionable
3 = seen only few times
4 = seen most of the time
5 = almost continuously
6 = seen continuously

---

15) *Other*
Write in such as pill rolling-like movements (these are classical pill rolling movements but involve repetitive movement of the thumb across several fingers), carressing or rubbing of face and/or hair.

ENTIRE BODY

16) Akathasia

Involuntary restlessness (may be continuous or may be observed as outbursts of activity) with inability to sit or stand still. (Verbal expression of inner restlessness is not required here.)

Rating based on the frequency and intensity of restlessness.

1 = absent
2 = questionable
3 = infrequent jiggling
4 = pacing, jiggling most of the time
5 = pacing up and down; continuous jiggling
6 = unable to sit and stand still

---

17) Other

Write in items such as holokinetic movements, i.e. extensive, abrupt, gross movements of large parts or entire body.

APPENDIX II

SUMMARY OF INTERNATIONAL SURVEY ON NEUROLEPTIC DRUG THERAPY

Questionnaires concerning local teaching and practice regarding the use of antipsychotic-neuroleptic drugs were sent to approximately 100 correspondents. These included every chairman of a medical school department of psychiatry in the United States and senior psychiatrists in many other teaching hospitals and public (federal and state) and private psychiatric institutions. In addition, the Task Force received responses from several Canadian medical schools and interviewed several European and Far Eastern psychiatrists informally. The following institutions responded in writing to our questionnaire:

Responding Institutions (N = 42)

USA Medical Schools (34)

Baylor University
Boston University
Bowman-Gray Medical College
Chicago Medical School
Columbia University
Creighton University
Harvard University
Johns Hopkins University
Mayo Clinic
Medical College of Ohio at Toledo
New York Medical College
Stanford University
SUNY-Stonybrook
Temple University
Tufts University
Tulane University
Univ. of Alabama
Univ. of Arizona
Univ. of California at San Francisco

Univ. of Cincinnati
Univ. of Colorado
Univ. of Kansas
Univ. of Michigan
Univ. of Minnesota
Univ. of Oregon
Univ. of Pennsylvania
Univ. of Rochester
Univ. of So. Carolina
Univ. of So. Florida
Univ. of Tennessee
Univ. of Texas at Dallas
Univ. of Texas at San Antonio
Univ. of Wisconsin
Washington University

USA Other Institutions (2)

North Dakota State Hospital System
USPHS-NIMH

Canada (N = 6)

Dalhousie University
Laval University
McGill University
McMaster University
University of Ottawa
University of Western Ontario

The following summaries review responses that are sufficiently clear to permit analysis.

Concerning clinical indications for neuroleptic drugs, 48 percent of the 33 respondents commenting believed that local practice commonly extended use of these agents to conditions *other than* acute, chronic, or recurrent psychosis, severe agitated depression, and some neurologic conditions (e.g., Huntington's disease, Gilles de la Tourette's syndrome, and some other organic mental syndromes); 31 percent disagreed; and 21 percent did not present a clear statement. Furthermore, 27 percent offered unsolicited specific criticisms of local practices, which they characterized as including excessive doses or duration of use; acceptance of questionable indications, including rou-

tine use of neuroleptics for "neuroses, character disorders and borderline states, mild depressions, persistent anxiety (especially when the risk of abuse of sedative-tranquilizers seems high), hysteria, and stuttering"; excessive doses and questionable indications among elderly patients in nursing homes; and a tendency for doses for the more potent neuroleptics to be on the rise. In addition, "product-insert" indications for some specific neuroleptic products currently permitted by the U.S. Food and Drug Administration were criticized as being excessively broad.

Regarding the sharing of information with patients and their families on the risk:benefit estimates for prolonged neuroleptic therapy in specific cases, 58 percent of 42 responding psychiatrists stated that good medical practice required such discussions; 25 percent disagreed; 17 percent did not take a clear position, and 12 percent of the letters stated conflicting opinions of respondents from the same city or institution. In contrast, only 11 percent favored some form of written consent for prolonged neuroleptic therapy (of more than one year), while 70 percent did not (19 percent of the responses were unclear).

Concerning recognition and management of tardive dyskinesia, some psychiatrists (12 percent) suspected that many colleagues underdiagnose or sometimes fail to recognize the problem. On the other hand, 17 percent claimed that the problem is rare or greatly exaggerated. On specific local practices regarding the medical management of tardive dyskinesia, several expressed concern about the lack of clearly effective treatments, although 62 percent outlined some form of locally accepted conservative management or active treatment proposals. There was some emphasis on prevention and on hopeful temporarizing while awaiting spontaneous remission, as well as frequent awareness of many of the newer experimental treatments already reviewed in this text. However, the variety of responses or failure to comment (38 percent) suggest that a clear and widely accepted plan of management may not exist at the present time.

Regarding education in psychopharmacology, fully 76 percent of those questioned stated that their institutions offered some form of postgraduate education in psychopharmacology, although 12 percent of these efforts were rated inadequate or unsatisfactory and 12 percent of respondents spontaneously encouraged further efforts as a means of improving local practice.

In summary, our survey indicated a widespread awareness and concern about the problem of tardive dyskinesia. It further suggested that neuroleptics are not uncommonly overused on questionable indi-

cations and in excessive doses and durations and that there was little common agreement of a clear plan of action for the management of tardive dyskinesia. A bare majority (58 percent) favored discussing the risks and benefits involved in prolonged neuroleptic therapy with patients or their relatives and noting such discussions in their records; a clear majority (70 percent) were not in favor of a signed form to document such informed consent. Nearly all psychiatric training programs and institutions surveyed (nearly all were departments of medical schools or teaching hospitals) offered postgraduate educational programs in clinical psychopharmacology as well as training for medical students and psychiatric residents, although a few believed their efforts to be inadequate. The overall impression left by this survey was that the present *Task Force Report on Tardive Dyskinesia* is timely and that the information it contains should be helpful to practicing American psychiatrists.

APPENDIX III

GLOSSARY

akathisia: Motor restlessness; literally "inability to sit"; a common neurologic effect of neuroleptic drugs.

amines (including dopamine, catecholamines and others): Organic compounds containing the amino group ($-NH_2$).

antipsychotic drugs: Agents used primarily for the treatment of acute psychosis and long-term management of schizophrenia. Also called *neuroleptics.* The older terms "major tranquilizers" and "ataractic" (antianxiety) drugs are obsolete and misleading.

"blind" conditions: Experimental conditions, commonly used in evaluating a medical treatment or procedure in which patients ("single blind") or patients and treatment providers ("double blind") are kept unaware of which alternative treatment (commonly, active versus placebo medications) is given.

catecholamines: Biologically active hormones produced ("biogenically") in nerve or adrenal cells and containing an amino group ($-NH_2$) and a catechol moiety (two adjacent hydroxyl [$-OH$] groups on a benzene ring).

chorea: Quick, tic-like, irregular, spasmodic involuntary movements.

dementia: Organic mental impairment of intellect.

dopamine: A catecholamine: *di*hydr*oxyp*henethyl*amine* formed from the precursor amino acid L-dopa, or *di*hydr*oxyp*henyl*a*lanine.

dystonia: Tonic overactivity of muscle; torsion and writhing of body parts that can be induced by neuroleptic drugs.

Gilles de la Tourette's syndrome (also "Tourette's" disease): A neuropsychiatric syndrome of unknown cause, marked by involuntary choreic movements and vocal utterances and ejaculation of expletives.

Huntington's disease: Chronic, progressive, degenerative, hereditary chorea with late dementia.

limbic system: A neuroanatomical concept involving several deep structures of the forebrain that mediate olfaction and many visceral and emotional functions; may be an important site of action of antipsychotic drugs.

neuroleptic: A term implying specific effects on the nervous system; antipsychotic drugs with effects on emotional responses as well as effects that mimic neurological disorders such as Parkinson's disease.

nigrostriatal tract: An important dopamine-containing neural pathway in the brain arising from the pars compacta of the midbrain substantia nigra and projecting to the corpus striatum (especially the caudate nucleus) or basal ganglia; this pathway degenerates in Parkinson's disease and is believed to be an important site of action of neuroleptic drugs.

parkinsonism: A neurological disorder of the control of muscle tone, posture, and movement marked by slowing, rigidity, coarse tremor, inexpressive face, and shuffling gait, as an idiopathic primary neurologic disease (Parkinson's disease) or as an effect of neuroleptic drugs.

placebo: A pharmacologically inert imitation of an active medication commonly used in a controlled scientific test of an experimental treatment.

psychosis: A severe psychiatric or neurological disorder in which there is impaired ability to think, reason, understand, and behave adaptively; delusions, hallucinations, or mood changes may be present; confusion and memory loss may or may not be present; major subtypes include schizophrenia, paranoia, manic-depressive illness, and organic mental syndromes (delirium and dementia).

"rabbit" syndrome: Perioral tremor sometimes appearing late in neuroleptic therapy but probably a variant of parkinsonism rather than tardive dyskinesia.

receptor: Presumed site of specific interaction between a drug or hormone molecule and tissue leading to a biological action; *not* necessarily identical to an experimentally observed "binding site."

schizophrenia (formerly *dementia praecox*, now obsolete): A severe psychiatric disorder of unknown etiology characterized by psychotic mental disorganization, classically having a gradual onset in adolescence and a chronic course, sometimes with periods of exacerbation and improvement. As used in this report, this term is *not* meant as a synonym for "psychosis" or "severe psychiatric disorder."

tardive dyskinesia: Late or slowly-evolving movement disorder associated with prolonged use of neuroleptic drugs that may be restricted to oral-lingual-facial movements or involve more widespread chorea, athetosis, and dystonia, typically following a prolonged course.