Postoperative visual deprivation would leave the animal with old but still serviceable representations that could provide for function until compensatory mechanisms take effect.

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14. Cortical lesions were made by subpial aspiration with a fine pipette. Anteromedial lesions were located in the region that Leonard (*9*) identified as the projection field of the lateral dorsomedial nucleus. Dorsolateral lesions had approximately the same rostrocaudal limits but began medially 2 mm from the midline. Electrolytic lesions in the superior colliculus were at coordinates derived from L. J. Pellegrino and A. J. Cushman, *A Stereotaxic Atlas of the Rat Brain* (Appleton-Century-Crofts, New York, 1967).
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16. There were four sensory tests. In the vision test, the rat faced a semicircular wall and a sucrose pellet on a wand was introduced from the rear and moved slightly for 5 seconds. The initial side was chosen at random, and the test was repeated at random intervals until the rat responded or it was clear that it could not respond. In the audition test, scratching and tapping sounds were made outside one wall of the enclosure and then the opposite wall. In the vibrissae test the tips of the whiskers were stroked with a swab stick. In the toe pinch test a swab stick was pressed against the outermost toe of one forepaw and then the other. The vibrissae test normally elicits vigorous head turning and sniffing; the toe pinch test, withdrawal of the limb. The inattentive animal fails to respond or may respond toward the opposite side. On each test, a strong response scored 2, a weaker response 1, and no response 0. The scores were summed over 3 days to give a weekly orienting score. Circling was tested by placing the animal in its home cage atop an elevated platform and counting the number of ipsiversive and contraversive turns in 2 minutes.
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Spontaneous Orofacial Dyskinesia and Dopaminergic Function in Rats After 6 Months of Neuroleptic Treatment

Abstract. *A syndrome of spontaneous orofacial dyskinesia was identified in groups of rats treated for 6 months with a wide range of neuroleptic drugs. Phenothiazines, thioxanthenes, and substituted benzamides were particularly likely to induce the syndrome. It was observed in the presence of a functional blockade of dopamine receptors and endured for at least 2.5 months after drug withdrawal. There was no relation between the syndrome and changes in striatal dopamine receptors, as indexed by the binding of tritiated spiperone and tritiated* cis*(Z)-flupenthixol. The syndrome parallels several of the features of clinical tardive dyskinesia, whose pathophysiology thus may not involve changes in the characteristics of striatal dopamine receptors.*

The abnormal, involuntary movements of the orobuccolingual area seen in some schizophrenic patients have been termed tardive dyskinesia. This disorder, which is generally believed to emerge as a late-onset side effect of several years of treatment with neuroleptic drugs (*1*, *2*), may be traceable to striatal dopaminergic hyperfunction, possibly through the supersensitivity of dopamine (DA) receptors in the basal ganglia (*1*). When neuroleptics are given to rodents for weeks, subsequent withdrawal rapidly and reliably results in enhanced perioral stereotypies on challenge with DA agonists and increased striatal binding of tritiated neuroleptic ligands; however, rodents so treated do not show enduring spontaneous orofacial dyskinesia (*1*, *3*). The clinical syndrome can emerge during ongoing treatment with neuroleptics. Withdrawal of these drugs, while sometimes exacerbating existing dyskinesia or unmasking latent dyskinesia, is not always required for its manifestation.

Not all schizophrenics develop dyskinesia. Those who do have usually received neuroleptics for several years. It can appear despite continuing antipsychotic activity and functional blockade of at least some forebrain DA receptors (*1*). Thus, the rodent perioral stereotypies induced in previous studies are at variance with several characteristics of the clinical syndrome. We describe here the characteristics of spontaneous orofacial dyskinesia that emerged during treatment of rats with a range of neuroleptic drugs for periods constituting a substantial proportion of their adult lifespan.

Male Sprague-Dawley rats (250 to 450 g) were treated continuously through their drinking water (*4*) with the butyrophenone haloperidol, the phenothiazines fluphenazine and trifluoperazine, the thioxanthene piflutixol, or the substituted benzamide metoclopramide. Other rats were given 0.2-ml intramuscular injections of fluphenazine as the decanoate (25 mg/ml in oil) or of oil vehicle alone at 2- to 3-week intervals (*5*). The doses selected were proportionate to those used clinically (Fig. 1) (*6*). Spontaneous behavior was observed both in animals that continued to receive neuroleptics and in animals from which the drugs were withdrawn (*4*). Striatal tissue was removed to assay the specific binding of [^{3}H]spiperone (0.8 n*M*) and [^{3}H]*cis*(Z)-flupenthixol (2 n*M*) (*7*).

A syndrome of spontaneous perioral movements was noted in the animals. These movements, while similar to chewing, were not directed onto physical material. A prominent characteristic was a grating sound produced as the teeth were drawn across one another by lateral jaw movements. This sound was the most reliable index of the syndrome when assessed by an experimenter with no knowledge of the treatment history, and the syndrome was judged to be present or absent on the basis of this auditory criterion.

During the sixth month of treatment the prevalence of spontaneous orofacial dyskinesia was 2.5 times higher in the groups treated with fluphenazine, trifluoperazine, piflutixol, or metoclopramide (mean prevalence, 53 percent; $N = 62$) than in the matched controls (mean prevalence, 21 percent; $N = 55$) [χ^2 (1) = 12.20, $P < .01$] (Fig. 2). The syndrome occurred slightly less frequently in haloperidol-treated rats (18 percent; $N = 45$) than in their matched controls (23 percent; $N = 70$). After completing these behavioral studies, we withdrew the neuroleptics. Seven to eleven days later, striatal binding of [^{3}H]spiperone was equally elevated in animals that had received haloperidol, fluphenazine, piflu-

tixol, or metoclopramide (Mann-Whitney U test, $P < .05$) (Fig. 1). This indicates that a representative of each of the four classes of neuroleptics used induced similar degrees of DA receptor blockade and masked DA receptor supersensitivity at the given doses.

The syndrome of spontaneous orofacial dyskinesia persisted in the animals that had been given 6 months of treatment with trifluoperazine and piflutixol. There was no diminution of the syndrome after drug withdrawal, and further increases in prevalence over controls were noted (Fig. 3). After the final behavioral assessments (2.5 months after withdrawal of trifluoperazine and 1 month after withdrawal of piflutixol), the binding of [^{3}H]spiperone and [^{3}H]*cis*(Z)-flupenthixol to striatal tissue was indistinguishable from that in control animals (Fig. 3).

Functional DA receptor blockade, indicated by antagonism of stereotyped behavior induced by subcutaneous apomorphine (0.15 mg/kg), endured until drug withdrawal for all neuroleptics except metoclopramide (*5, 8, 9*). The syndrome thus appears not to have a dopaminergic basis, since (i) it was independent of the state of functional DA receptor blockade and of masked DA receptor supersensitivity during neuroleptic treatment, (ii) it occurred in the absence of any spontaneous stereotyped behavior that would indicate net dopaminergic hyperfunction, and (iii) it endured long beyond the decline of DA receptor supersensitivity after drug withdrawal. This hypothesis holds for receptor binding indices of proposed multiple dopaminergic sites (*10*), as [^{3}H]spiperone labels predominantly the D_2 receptor and [^{3}H]*cis*(Z)-flupenthixol principally the D_1 site (*7, 9, 10*). The neuronal basis of the syndrome cannot yet be specified.

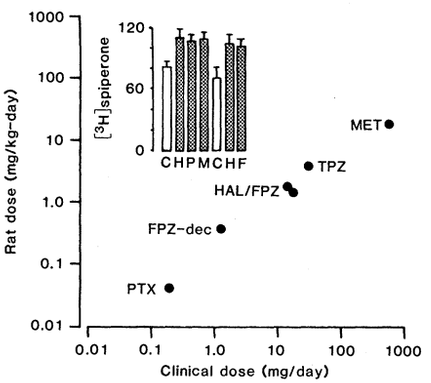

Fig. 1. Relation between doses of neuroleptics given to rats for 6 months and doses used clinically in man. All neuroleptics were given by drinking water, except fluphenazine decanoate (*FPZ-dec*), which was given intramuscularly once every 3 weeks (the dose indicated is 1/21 the intramuscular dose). Age-matched control groups are maintained drug-free under otherwise identical conditions. Piflutixol, *PTX*; haloperidol, *HAL*; trifluoperazine, *TPZ*; metoclopramide, *MET*. Inset: striatal binding of [^{3}H]spiperone (femtomoles per milligram of protein) in control animals (*C*) and those given haloperidol (*H*), piflutixol (*P*), fluphenazine (*F*), and metoclopramide (*M*). Data are means ± standard errors for five to nine animals per group.

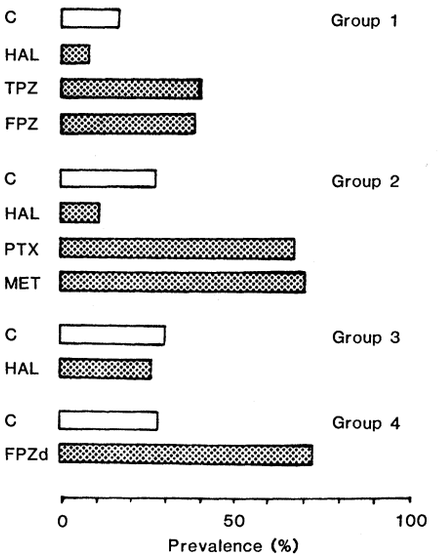

Fig. 2. Prevalence of spontaneous orofacial dyskinesia after 6 months of neuroleptic treatment (while drug administration continued). The syndrome was determined to be either present or absent during a 10-minute observation period in which the rats were placed individually in large plastic cages similar to the group home cage. Prevalence is expressed as the percentage of animals in each group (N = 8 to 32) exhibiting the syndrome. No spontaneous stereotypy was observed, suggesting no spontaneous hyperdopaminergic behaviors.

Several characteristics of tardive dyskinesia were apparent. Spontaneous orofacial dyskinesia emerged only during prolonged neuroleptic treatment and in the presence of functional blockade of DA receptors. It endured and increased long after neuroleptic withdrawal. Also, the syndrome was present in a small percentage of control animals. Thus a tardive neuroleptic component in both animals and man appears to be superimposed on a baseline prevalence that may reflect a combination of predisposing aging and disease processes (*2, 11, 12*); neuroleptics may act to enhance this predisposition. However, two features of the present rodent syndrome appear to conflict with some conventional views on tardive dyskinesia, namely its apparent independence from dopaminergic hyperfunction and the failure of continuing haloperidol treatment to promote the syndrome. Some authors have proposed that neuroleptic-induced DA receptor supersensitivity is too short-lived to explain the persistent forms of tardive dyskinesia (*13*). While dyskinetic features can be influenced by manipulations of dopaminergic function (*1*), this need not imply abnormal striatal dopaminergic function in their pathophysiology. Basal ganglia from the brains of schizophrenics who were movement-disordered do not show greater binding of [^{3}H]spiperone or [^{3}H]*cis*(Z)-flupenthixol than tissue from schizophrenics who were free of such symptoms (*12*). This is in agreement with our animal data.

The failure of haloperidol to promote the syndrome in three separate groups (Fig. 2) is not necessarily in conflict with the presence of dyskinesia in patients receiving haloperidol. Such patients have almost invariably received substantial treatment with other neuroleptics and antiparkinsonian agents. Therefore, while there are few substantive data to indicate that any oral neuroleptic, including haloperidol, is more or less likely to promote tardive dyskinesia (*1, 14*), studies are required of patients who have received prolonged therapy with haloperidol alone (*15*). Tardive dyskinetic movements in primates given long-term treatment with haloperidol are also not common, and when present appear to reflect a particular species sensitivity (*16*). They appear to be more reliably induced by nonbutyrophenones (*16, 17*), as reported here. Regarding particular modes of neuroleptic treatment, we found intramuscular injections of flu-

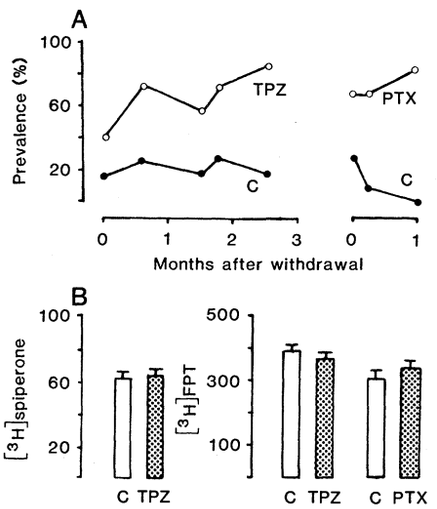

Fig. 3. (A) Prevalence of orofacial dyskinesia after withdrawal from 6 months of treatment with trifluoperazine (*TPZ*) or piflutixol (*PTX*). (B) Striatal binding of [^{3}H]spiperone and [^{3}H]*cis*(Z)-flupenthixol (*[^{3}H]FPT*) (femtomoles per milligram of protein) in the same animals, which were killed immediately after the behavioral assessments. Data are means ± standard errors for three to ten animals per group.

phenazine decanoate to be slightly more potent in promoting orofacial dyskinesia than oral treatments. Several investigators recently noted that tardive dyskinesia may be significantly more common in patients who have received intramuscular fluphenazine decanoate than in those who had received oral treatments (*18*).

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Treehoppers Transfer Parental Care to Ants: A New Benefit of Mutualism

Abstract. *Female treehoppers (*Publilia reticulata *Van Duzee) modify their parental care behavior in the presence of ants. Females with untended young remain with their original brood, but females from ant-tended colonies readily desert their first brood and produce additional clutches. Care by female treehoppers, in the absence of ants, increases the probability that a colony will produce some survivors, but ant attendance greatly increases the number of surviving nymphs.*

Mutualisms between ants and honeydew-producing insects have generally been described in terms of benefits to insects that are directly associated with the ants (*1*). Females of some species of treehoppers (Homoptera: Membracidae), which remain with their young, change their behavior in the presence of ants—either abandoning broods earlier (*2*) or later than usual (*3*). I present evidence that females that abandon nymphs may be abdicating parental care to the ants; these females can then produce additional broods and thus increase their total fitness. Because females are apparently exploiting mutualists and benefiting from their activities without direct interaction, this response may provide a new class of mutualistic benefits. To determine whether treehoppers receive such indirect benefit, I examined the effects of ant attendance on female parental behavior and the consequences of ant attendance and parental care on juvenile survival in the North American treehopper, *Publilia reticulata*.

Publilia reticulata is a membracid which commonly feeds on ironweeds (*Vernonia* spp.) throughout the eastern and midwestern United States. In the spring, females, which have overwintered as adults, mate and oviposit a clutch of about 50 eggs into the midrib of a leaf. Although some females may produce additional clutches, there is only a single generation per year. Nymphs complete their 40- to 50-day development period feeding in aggregations on the natal plant. Both adult and immature forms produce honeydew, which is highly attractive to ants. At the study site in central New Jersey (*4*), seven species of ants were found tending colonies of *P. reticulata* (*5*). Females of *P. reticulata*, in common with some other species of treehoppers (*6*), exhibit parental care by remaining with egg masses and young nymphs. This behavior has been shown in other species to protect egg masses from parasitoids (*7*), maintain nymphal aggregations (*8*), and deter predators (*9*).

In a field study in the summer of 1981,

Table 1. The effect of ant care and parental care on survival of *Publilia reticulata*. Results for mean colony size and mean number of survivors per clutch were analyzed by using the Newman-Keuls test, and results for colonies producing survivors were analyzed by Fisher's exact test; results with the same letter did not differ at the .05 level.

Treatment group	Colonies (*N*)	Colony size	Colonies with survivors		Total nymphs (*N*)	Nymphs surviving		Survivors per clutch
			N	%		*N*	%	
No ants								
No females	8	48.8 ± 14.3 A	2	25 A	390	12	3.1	1.5 A
Females	15	45.4 ± 6.5 A	10	67 A, B	681	73	10.7	4.9 A
Ants present								
Brood 1	37	47.3 ± 7.4 A	29	78 B	1751	475	27.1	12.8 B
Brood 2	12	32.8 ± 4.3	10	83 B	393	167	42.5	13.9 B