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Persistent Dyskinesia

By GEORGE E. CRANE

The first three cases of tardive dyskinesia were described in a brief communication by Schonecker (1957), and in the following ten years some 600 new cases were reported in 37 papers. Since the literature up to 1967 has been reviewed by Ayd (1967a) and myself (1968a), this communication will deal mainly with the publications of the last five years. I will also report a few personal observations of the last two years, hitherto unpublished.

Frequency of Tardive Dyskinesia (Literature 1967–71)

Since 1967, 60 papers and two workshops (1967, 1969) have been concerned directly or indirectly with the problem of tardive dyskinesia. The number of patients reported in the literature of the last five years is approximately 1,200, or double that of the previous ten years. (Duplications and questionable data are not included in this figure.) Some authors have published single case reports, while other investigators have gathered data on hundreds of patients.

The incidence of tardive dyskinesia varies from one-half of 1 per cent to 40 per cent of the populations surveyed by 17 investigators (Table I). This discrepancy can be attributed to a number of reasons, of which the definition of the syndrome, the type of patient population, the methods used in obtaining information and, above all, the clinical assessment of symptoms, play a major role. Some studies reporting a low incidence include only cases of oral dyskinesia (Dynes, 1970; Lehmann *et al.*, 1970; Turunen and Achte, 1967) or extremely severe cases (Roxburgh, 1970). The large survey by Hoff and Hoffmann (1967) is based on heterogeneous populations from 14 institutions, with many physicians contributing inconsistent data. (The incidence of tardive dyskinesia in this study ranges from 0 to 8 per cent.) Villeneuve *et al.* (1969) admittedly may have missed a large number of patients with dyskinesia because their collection of material depended on questionnaires distributed to several ward physicians, and on hospital records which might have been incomplete. The study by Eckman (1968) provides insufficient information to permit an evaluation of his data. Among studies reporting a high incidence of dyskinesia, one finds Greenblatt's study (1968) which consists exclusively of geriatric subjects, and the investigation by Kennedy *et al.* (1971) on patients receiving relatively high doses of trifluperazine for a number of years. Similarly, two of my studies (1968b, 1970) are on patients who for six months were treated with large doses of chlorpromazine or trifluperazine. Hippius and Lange (1970), and Brandon *et al.* (1971), may have also included subjects with motor disorders unrelated to drugs, judging from the high incidence of motor abnormality in the untreated control sample. The same may be true of Fann's (1972) study.

The question has often been raised whether the chronicity of a disease and/or institutionalization with attendant emotional and physical deprivation is responsible for motor abnormalities. Prior to 1967, two surveys (Degkwitz *et al.*, 1966; Pryce and Edwards, 1966) showed that the incidence of dyskinesia in patients with a history of drug treatment was considerably higher than in similar patients who never were exposed to neuroleptic agents. A third study (Demars, 1966) failed to detect a difference between the two groups. Since then, a number of studies comparing abnormal movements in treated and untreated patients have appeared in the literature (Table I). In nine investigations the incidence of tardive dyskinesia was higher in the drug-treated than in the non-treated sample, but in the survey by Brandon *et al.*

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TABLE I

Frequency of dyskinesia in treated and untreated patients (1967–71)

	No. of patients with neuroleptics	% dyskinesia	No. of patients with no neuroleptics	% dyskinesia
Brandon (1971)	625	24	285	19
Crane (1967)	182	14		
Crane (1968b)	305	24		
	379 s	28		
Crane (1970)	127 s	27		
Crane (unpub.)	926	17	46	2
Degkwitz (1967a, b)	1,209	22	912	1·5
			1,500 g	1
Dynes (1970)	1,200 o	8		
Eckman (1968)	804	3		
Edwards (1970)	184 o	19		
Fann (1972)	204	36		
Greenblatt (1968)	52 g	39	101 g	2
Heinrich (1968)	554	17	201	3
			110 g	2
Hippius (1970)	531	32	137	14
Hoff (1967)	10,000	·5		
Kennedy (1971)	63 s	40		
Lehmann (1970)	350 o	6·5		
Paulson (1968)	500	10		
Roxburgh (1970)	120 s	2		
Siede (1967)	404 g	11	235 g	1
Turunen (1967)	400 o	6		
Villeneuve (1969)	3,280 o s	2		

o = Oral dyskinesia only.
g = Geriatric.
s = Selected.

(1971) this difference was not statistically significant. Two factors may account for the authors' failure to demonstrate a clear-cut relationship between neuroleptics and the motor disorder. First, the population at risk was defined as having had three or more months of pharmacotherapy. Since most investigators agree that dyskinesia seldom develops within a year of drug exposure, the drug-treated sample may have been diluted by a number of low-risk subjects. Second, the authors subdivided their sample of dyskinetic patients according to the severity of symptoms, but did not provide a breakdown by severity in their comparative analyses of treated and untreated patients. This is unfortunate, because mild and doubtful dyskinesias of the mouth (60 per cent in the survey) cannot be properly assessed in patients with organic brain disorder or dementia. Adequate information was provided only for 14 patients with the most severe dyskinesia. Indeed, all 14 patients had a history of drug treatment, although in two the appearance of symptoms might have antedated the administration of neuroleptics.

One may argue that chronic psychiatric patients who do not receive drug therapy in the United States, the United Kingdom or Western Europe are a selected group, since it is customary for such patients to be subjected to chemotherapy at one time or another. On the other hand, drugs are seldom prescribed to chronic mental patients in Turkish hospitals. There I examined some 150 males from wards housing chronic, mostly schizophrenic patients. Of those who had been given drugs only occasionally or never, none manifested symptoms consistent with tardive dyskinesia. A sample of Turkish

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patients was then matched for age, sex, and diagnosis with a heavily treated group from a U.S. hospital. The difference between samples with regard to tardive dyskinesia was highly significant.

Abnormal movements, however, including the characteristic oral-facial syndrome, have been known to occur in a variety of physical conditions (Critchley, 1970). Two French papers (Delay *et al.*, 1967; Graux *et al.*, 1969) have reported cases resembling those of drug-induced dyskinesias, but the patients either suffered from massive neurological disease, or had been treated with neuroleptics. Appenzeller and Biehl (1967) described ten cases of oral dyskinesias in geriatric patients, but their symptomatology was different from that of the drug-induced condition. A variety of drugs, including amphetamines (Brandon *et al.*, 1971; Eveloff, 1968; Mattson and Calverly, 1968) and L-Dopa (Papavasiliou *et al.*, 1969); ill fitting dentures (Sutcher *et al.*, 1971); anoxia (Brandon *et al.*, 1971); thyrotoxicosis (Fidler *et al.*, 1971); hepatic disorder (Ettinger and Currant, 1970) may cause involuntary movements in all areas of the body, including the mouth. Except for the well-known dyskinesias induced by L-Dopa, all these conditions appear to be infrequent. Furthermore, motor disorders associated with neurological diseases can be easily identified, as they have characteristics of their own in most instances. Other conditions subside once the offending agent is removed or the underlying condition is corrected. More problematic are the dyskinesias associated with mental disease. Recently, Yarden and Di Scipio (1971) have reported motor abnormalities in 18 newly admitted schizophrenic patients. These patients, however, manifested choreiform movements as well as the classical mannerisms and stereotypies of schizophrenia. Jones and Hunter (1969), who made a thorough study of abnormal motility in a long-term hospital population, found mainly repetitive, semi-voluntary movements and rituals in the chronic schizophrenics, who had never received drugs.

In conclusion, the high incidence of involuntary movements in drug-treated populations, and the relative rarity of such abnormalities in similar untreated populations provide compelling evidence to indicate that tardive dyskinesia is related to the use of phenothiazines or similar agents.

Clinical Considerations

The bucco-lingual masticatory syndrome and the motor abnormalities of the trunk and extremities were described in great detail by Sigwald and Degkwitz prior to 1967 (Crane, 1968a). More recently, efforts have been made to provide a better clinical definition of these conditions. At a symposium held in Bethesda, Maryland, the use of the terms 'choreiform', 'myoclonic', 'dystonic' was questioned by Baker (1969), and in the discussion that followed most participants agreed that the drug-induced neuroleptic syndrome has unique characteristics. In a study in cooperation with Naranjo (Crane and Naranjo, 1971), all neurologic symptoms observed in drug-treated patients were subdivided into 16 major categories, and the term 'complex dyskinesia' was used to describe the more typical manifestations of tardive dyskinesia. A factor analysis yielded three symptom clusters: the first consistent with parkinsonism; the second with the classical tardive dyskinesia; and the third characterized by postural disorder and dyskinesia of the upper extremities. In England, Kennedy *et al.* (1971), using comparable analytic methods, have reported similar findings.

Syndromes resembling Huntington's chorea, dystonia musculorum deformans, various tics, and other degenerative diseases of the basal ganglia have been reported also (Crane, 1972a). Harenko (1967) described retrocollis as an irreversible and fatal complication of neuroleptics in very old patients. Grahmann (1967) attributed to drugs a severe brain disorder which he called psychopharmacotoxic encephalopathy. A case of permanent torticollis was reported by Angle and McIntire (1968) in a brain-damaged child who took an overdose of various neuroleptics. Postural disorders and dystonias are not uncommon in long-term hospital populations, but in the absence of adequate clinical records the role neuroleptics play in these disorders remains uncertain. A well documented case of permanent dystonia attributable to triflu-

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perazine is described in Appendix I. In this unusual case, there was a progression from parkinsonism to dystonia. A similar sequence of events can be observed in the more common forms of tardive dyskinesia. Crane and Naranjo (1971) showed that tardive dyskinesia increased, while pseudo-parkinsonism diminished, in a sample of patients at the end of a six-month drug-free period. Further studies have provided additional evidence that patients with pseudo-parkinsonism are more likely to develop tardive dyskinesia as the result of drug withdrawal than patients who are neurologically intact (Crane, 1972b). Similarly, Hippius and Longemann (1970), who administered L-Dopa intravenously to patients with tardive dyskinesia, observed an aggravation of this disorder only in subjects who also had parkinsonian features. Degkwitz (1969) and Degkwitz *et al.* (1970), on the other hand, could not find a close parallelism between a reduction of pseudo-parkinsonism and the appearance of hyperkinetic movement when neuroleptics were replaced by placebo. The data by the German authors were not analysed statistically.

Tardive dyskinesia and pseudo-parkinsonism can co-exist, but as a rule patients exhibiting severe manifestations of the former seldom show the latter syndrome, and vice versa (Heinrich *et al.*, 1968; Crane, 1969).

In conclusion, tardive dyskinesia is a well-defined neurological condition which the clinician should not have great difficulty in differentiating from parkinsonism, naturally occurring diseases of the basal ganglia, or functional psychomotor disorders. Other drug-induced conditions resembling diseases of the central nervous system seem to occur occasionally.

Characteristics of Patients with Dyskinesia

According to early findings, textbooks, and reviews (Duvoisin, 1968; Klein and Davis, 1969; Di Mascio and Shader, 1970; Ayd, 1967a 1967b), tardive dyskinesia is more likely to occur in females, in the elderly, and in brain-damaged patients. There is considerable disagreement regarding these statements in the more recent literature. In seven studies (Degkwitz, 1967; Heinrich *et al.*, 1968; Kennedy *et al.*, 1971; Turunen and Achte, 1967; Villeneuve *et al.*, 1969; Lehmann *et al.*, 1970; Brandon *et al.*, 1971), females are found to be more frequently affected; but according to four other reports (Crane, 1968c; Crane, 1970; Hippius and Lange, 1970; Fann *et al.*, 1972) they are not, to a significant degree. In general, age seems to be an important contributing factor to tardive dyskinesia, but two authors (Heinrich *et al.*, 1968; Kennedy *et al.*, 1971) disagree. These discrepancies may be due to complex interactions between drug treatment and the characteristics of the populations studied by the several investigators. For instance, in a selected sample of patients under 56 years of age, I found that age was positively related to dyskinesia only in subjects receiving very high doses of Stelazine (Crane, 1970). Pre-existing brain damage, previous treatment with EST, or insulin coma do not seem to play a role, according to Greenblatt *et al.* (1968), Heinrich *et al.* (1968), Degkwitz (1969), Brandon *et al.* (1971), and Fann *et al.* (1972). Edwards (1970), who in a previous study (Pryce and Edwards, 1966) had reported no difference in this respect between brain-damaged and non-damaged patients, found a highly significant difference between the two groups by using a more refined technique of assessing brain disorder and by carefully matching patients for important variables.

In a survey of approximately 350 patients from chronic hospital wards, I made an attempt to relate the frequency of tardive dyskinesia to age, sex, duration of continuous hospitalization, current treatment, and disorders of the central nervous system (Crane, 1971b). The only variable that was positively related to dyskinesia at a high level of significance was age (Appendix II). The findings, however, do not invalidate Edwards' (1970) conclusions regarding predisposition of brain-damaged individuals to abnormal motility, because my definition of brain disorder was based on standard diagnostic criteria, while Edwards used a more sophisticated approach.

In summary, various factors seem to contribute to the development of tardive dyskinesia in drug treatment, but one must agree with Brandon *et al.* (1971) that the use of neuroleptics is not sufficient to cause this complication.

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Onset and Evolution of Symptoms

In 1967, Ayd stated that the earliest onset of tardive dyskinesia was between three and six months after the beginning of drug therapy. Subsequent papers have added little to our knowledge of the evolution of this disorder. Degkwitz *et al.* (1967) reported that 9 out of 247 dyskinetic patients developed overt symptoms in less than six months of treatment. In the series of Turunen and Achte (1967), dyskinesia became apparent in two patients who had received neuroleptics for only four months. In a sample of 28 geriatric subjects, who are particularly vulnerable to drug effects, I found the presence of moderate dyskinesia in two, six months after the beginning of neuroleptic treatment (Appendix III). In the majority of investigations (Degkwitz *et al.*, 1967; Turunen and Achte, 1967; Heinrich *et al.*,1968; Lehmann *et al.*, 1971; Kennedy *et al.*, 1971), dyskinesia has been diagnosed in subjects who had been on drugs for over two years. These patients may have had the disorder long before it was recognized, because it is seldom reported in the hospital records; hence the necessity of repeated examinations.*

Efforts have been made by several authors to determine the amount of drug intake which is necessary to produce the disorder (Degkwitz and Wenzel, 1967; Heinrich *et al.*, 1968; Lehmann *et al.*, 1970; Turunen and Achte, 1967; Hippius and Lane, 1970; Crane, 1968b; Kennedy *et al.*, 1971; Brandon *et al.*, 1971). This task presents unsurmountable difficulties, because in order to properly evaluate the cumulative effects of drugs one must take into consideration the types of neuroleptics prescribed, the trend of drug administration, the continuity of treatment, and the use of ancillary medication. It is understandable that the results should have been inconclusive. The question whether certain neuroleptics are more likely to produce dyskinesia than others is largely unanswered, since the majority of patients are treated with a multitude of such agents. I know of three patients who developed the syndrome (see Appendix I) on average doses of trifluperazine only. On the other hand, drugs with weaker neuroleptic action like thioridazine (Kurland and Turek, 1969; and a personal observation) and non-phenothiazines like reserpine (Degkwitz, 1969) can also produce persistent abnormal movements.

The fact that tardive dyskinesia may be present in a latent form while the patient is on drugs adds to the problem of assessing the effects of drug exposure. This interesting observation was made in earlier studies and has been amply confirmed by case reports (Kennedy, 1969; Roxburgh, 1970) and by systematic studies (Degkwitz *et al.*, 1968; Eckman, 1968; Hoff and Hoffmann, 1967; Crane and Naranjo, 1971). According to recent reports, five to approximately 40 per cent of asymptomatic patients develop dyskinesia upon discontinuation of treatment (Degkwitz *et al.*, 1968; Eckman, 1968; Hoff and Hoffman, 1967; Hershon *et al.*, 1972).

Despite opinions to the contrary (Kline, 1968), several publications prior to 1967 have provided considerable evidence to suggest that neurologic symptoms persist after a prolonged drug-free period (Crane, 1968a). More recent studies have supplied additional data to support this contention (Degkwitz, 1969; Dynes, 1970; Lee, 1967; Singer and Wong, 1970). The period of observation after removal of drugs is important, because in some cases, particularly in subjects under 50, symptoms tend to disappear over a period of several months (Degkwitz, 1969; Turunen and Achte, 1967) or to diminish after an initial increase (Crane *et al.*, 1969). An early diagnosis of dyskinesia and subsequent withdrawal of medication may also contribute to a recovery from the disorder. In a large percentage of patients, however, symptoms are unchanged after months or years following discontinuation of all neuroleptics (Edwards, 1970; Crane, 1971a).

Less information is available on the evolution of dyskinesia in patients who continue to receive neuroleptics. In Heinrich's (1968) follow-up study, approximately 40 per cent of patients

* In a survey of chronic patients, I found that 184 had no neurologic symptoms attributable to drugs. One year later 18 patients exhibited very definite dyskinesia. The records showed that 6 patients had been on neuroleptics from 10 to 14 years, 9 for at least 5 years, and 3 for 3 years. Age ranged from 26 to 73. Drug therapy had been continuous between assessments.

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became symptom-free after 15 months of unchanged drug therapy.

Degkwitz *et al.* (1966), and more recently other investigators (Kennedy, 1969; Roxburgh, 1970; Klawans and McKendall, 1971), have observed that the use of neuroleptics reduces or suppresses motor abnormality, which develops after drug withdrawal. An increase of dosage may have similar effects in dyskinetic patients who continue to receive neuroleptics. One must keep in mind that phenothiazines and related drugs mask overt symptoms, but at the same time may increase the patients' vulnerability to such drugs. I had an opportunity to observe patients (from two collaborative studies sponsored by the National Institute of Mental Health) who had been treated with chlorpromazine and trifluperazine at two-dose levels. I found that patients who had been exposed to large doses of the two agents for six months manifested significantly more dyskinesia than the control subjects after they were returned to routine drug therapy (Crane, 1968b, 1970).

Other Studies

There are two reports on post-mortem findings. Christensen *et al.* (1970) described gliosis in the brain stem of 28 patients with oral dyskinesia, but Hunter *et al.* (1968), found no specific lesions in three brains obtained from similar patients. By means of stereotaxic procedures, Nashold (1969) was able to localize the pathology underlying the oro-facial-lingual syndrome in the central tegmental region. Nashold, who has had considerable experience with stereotaxic surgery in this general area of the brain for the relief of intractable pain, observed a patient complaining of involuntary complex facio-oral movements in association with painful sensations. This prompted the author to produce lesions in the central tegmentum and subthalamic area in a patient with similar motor manifestations, which had been caused by large doses of chlorpromazine and haloperidol. The results were quite satisfactory in this and three additional patients with severe drug-induced dyskinesias. Thus, the malfunctioning area seems to lie in the upper brain stem, but so far gross anatomical lesions in the brain or its vascular system have been ruled out.

There have been some interesting speculations as to the role played by dopamine in tardive dyskinesia. Biochemical studies have shown that there is no deficit of this neuro-hormone in patients with tardive dyskinia (Klawans and McKendall, 1971; Pind and Faurbye, 1970) or with hyperkinetic conditions, like Huntington's chorea (Hornikiewicz, 1968). It has been established also that the levels of dopamine in animal brains are not lowered by the administration of neuroleptics (Pletscher, 1969). Klawans and McKendall (1971), among others, have suggested that the blockage of receptors by phenothiazines causes a phenomenon akin to denervation, which in turn produces a hypersensitivity of specific receptors. This is in keeping with the observation that L-Dopa aggravates tardive dyskinesia (Klawans and McKendall, 1971; Hippius and Longemann, 1970) and Huntington's chorea (Barbeau, 1968), while alphamethylparathyrosine, which interferes with the synthesis of dopamine, may have the opposite clinical effect (Chase, 1971). Rubovitz *et al.* (1972) have attempted to provide experimental support for these theoretical considerations. Guinea pigs were treated with chlorpromazine for several months and were then injected with amphetamine. (This agent provokes stereotyped movements by acting directly or indirectly on dopaminergic receptors.) Stereotyped activity was substantially greater in animals pre-treated with chlorpromazine than in controls which had not received the phenothiazine.

These experimental data obviously need confirmation. Further long-term clinical observations are also essential in order to provide a satisfactory and comprehensive explanation for the many puzzling features of the drug-induced neurological disorders.

Treatment

Agents that deplete cells of dopamine (reserpine, Villeneuve and Boszormenyi, 1970; Sato *et al.*, 1971; tetrabenazine, McCallum, 1970) or interfere with its action (alphamethyldopa, Villeneuve and Boszormenyi, 1970; Villeneuve *et al.*, 1970) have been administered to patients

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with tardive dyskinesia with apparent success. MAO inhibitors (Bucci, 1971) have also been used for reasons that are not entirely clear. Greenblatt *et al.* (1970) report trials with penicillamin, but little information is available on the treatment with this substance, which has considerable toxicity. Lately, the use of amantadine has been the object of some controversy. Two clinicians (Dynes, 1970; Crane, 1971c) observed no therapeutic effects on 31 patients, while two groups of investigators (Vale and Espejel, 1971; Decker *et al.*, 1971) have claimed excellent responses in a total of eight patients. Pyridoxine, which promptly controls motor disorders due to L-Dopa, was also used in the hope that it would be equally effective in tardive dyskinesia; the results were entirely negative (Crane *et al.*, 1970; Paulson, 1971; Dynes, 1970).

On theoretical grounds there is no justification for the use of anticholinergics in tardive dyskinesia, because extrapyramidal hyperkinesias are characterized by a preponderance of dopaminergic and not of cholinergic activity. Bordeleau *et al.* (1967) have shown that a shift from parkinsonism to tardive dyskinesia may occur as the result of anticholinergic treatment. Klawans and McKendall (1971) have made a similar observation in an elderly female. As indicated earlier, neuro-surgery has been used successfully by Nashold (1969) in four patients, but it is quite clear that this procedure is reserved for the most severe cases. A number of authors (Degkwitz and Wenzel, 1967; Kennedy, 1969; Roxburgh, 1971; Carruthers, 1971) have advocated the re-administration of neuroleptics, particularly thiopropazate, in patients who develop dyskinesia following the discontinuance of such drugs. Common sense suggests that this should be done with extreme caution, because the risk of causing further damage to the brain is a very real one. Finally, Ayd (1970) forcefully recommends that patients be taken off neuroleptics periodically. This procedure is feasible, because the psychopharmacologic literature has shown that most patients on long-term drug therapy do not deteriorate mentally if the administration of such agents is discontinued for a few days or even several months. Ayd's approach is medically sound, too, because the withdrawal of medication may reveal the presence of latent neurological disorder (Crane, 1972c).

As Hershon *et al.* (1972) say, the primary concern of the physician should be the prevention of these side-effects, because 'once they have developed, there is little or no chance of reversing the process caused by years of perhaps unnecessary and thoughtless medication.'

Summary

This is a review of the literature on tardive dyskinesia from 1967 to 1971. The paper is divided into the following sections: (a) Reported frequency of this disorder in patient samples treated with neuroleptics and in samples of subjects never exposed to drugs; (b) clinical characteristics of tardive dyskinesia and its relation to other extrapyramidal disorders; (c) factors predisposing to this disorder; (d) onset and evolution; (e) anatomical and biochemical studies; (f) therapy of tardive dyskinesia.

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APPENDIX I

Case Report

Patient D.L., Jewish, married, with one child, developed a psychotic episode with persecutory and depressive features at age 34. She received EST with some mental improvement, but relapsed and was treated with trifluperazine in doses not exceeding 12 mg./day on an ambulatory basis. Minor neurological symptoms occurred at the beginning of treatment, but the first serious extrapyramidal manifestations became apparent some ten months after the initiation of drug therapy. These consisted of blinking, later accompanied by a 'staring expression', 'mouth half open', grimacing, and 'shaking'. A few weeks later, the patient became severely disabled by

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a massive motor syndrome, and this was tentatively attributed to the use of trifluperazine. The diagnosis was substantiated by extensive laboratory procedures which seemed to rule out conditions like Wilson's disease, Huntington's chorea, or dystonia musculorum deformans.

When she came to my attention three and a half years after the onset of her symptoms, she exhibited a massive postural disorder of the axial musculature, of the upper extremities, particularly on the left, and lesser symptoms in the lower extremities. She could walk without support for a few steps, but had obvious difficulty in maintaining a normal postural relation of the trunk or neck to the rest of her body. In certain sitting positions, over-extension of her neck and arching of her back would cause her to fall backward.

The left upper extremity was in a stiff, extended position at the elbow, with inward rotation and a 90 degree flexion of the hand. Efforts to flex her elbow would aggravate all symptoms. In addition, there were rotatory movements of the head to the left, tics of the lips, side to side movements of the chin, and choreic movements in various parts of her body. When she opened her mouth on command, a thrust of her tongue became noticeable. Clonic extensory movements as well as tremor of her fingers were almost continuous. Reflexes were exaggerated, with a powerful clonus on percussion of the left Achilles' tendon. There was little change in her condition when she was seen again in six months.

In summary, the picture was one of a severe encephalopathy with a predominance of dystonic features. The diagnosis of drug-induced extrapyramidal disorder was based on the complexity of the syndrome, the presence of oral dyskinesia, and the sequence of events in the course of drug therapy.

APPENDIX II*

Dyskinesia (D) in 398 patients by Age, Sex, Continuous Hospitalization, Current Treatment Level (in CPZ Equiv.), Diagnosis of Organic Brain Disorder (CNS)

		No. of patients with D	No. of patients with no D	%
Age	<44	6	120	4·7
	−54	9	84	9·7
	−65	16	105	13·2
	+65	19	39	32·7
	$\chi^2 = 29{\cdot}1$, 3 df. $p < {\cdot}001$			
Sex	M	27	210	11·4
	F	23	138	14·3
	$\chi^2 = {\cdot}63$, 1 df. n.s.			
Continuous hospitalization	−2 yrs.	6	64	8·6
	−5 ,,	4	67	5·6
	−10 ,,	8	62	11·4
	+10 ,,	32	155	17·1
	$\chi^2 = 7{\cdot}7$, 3 df. n.s.			
Current treatment level ..	−100 mg.	18	127	13·3
	−400 mg.	23	127	15·3
	+400 mg.	9	94	8·7
	$\chi^2 = 2{\cdot}3$, 2 df. n.s.			
CNS	Present	12	77	13·5
	Absent	38	271	18·2
	$\chi^2 = {\cdot}1$, 1 df. n.s.			

* This is part of a table which was included in a presentation at the Annual Meeting of the Amer. Psychiat. Assn. (Crane, 1971b).

APPENDIX III

Incidence of Tardive Dyskinesia in Three Samples of Patients Over 65

I: Never treated
II: Treated for six months
III: Treated for over 5 years with neuroleptics

	N	Treatment years	Average	Sex M	Current* drug level	Doubtful	No. of patients with dyskinesia	
							Moderate	Severe
I	28	0	73	17	0 mg.	2	0	0
II	28	½	69	7	86 mg.	2	2	0
III	28	+5	71	4	80 mg.	2	4	4

* In mg. of chlorpromazine equivalent/day.

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