

Manganese and Niacin in the Treatment of Drug-Induced Dyskinesias

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It is well documented that the antipsychotic medications, i.e., the pheno-thiazines and butyrophenones, offer considerable risk of permanent injury to the liver, skin, cornea, bone marrow, heart, and especially to the nervous system. Tardive dyskinesia, a prolonged and sometimes permanent extrapyramidal syndrome, has been reported in up to 50 percent of patients over age 60 who have been treated with neuroleptics for over three years (Crane, 1973).

Tardive dyskinesia is differentiated from the immediately occurring extrapyramidal symptoms that accompany phenothiazines by the fact that it occurs after prolonged exposure or after withdrawal of the neuroleptic. Rigidity and akathisia are prominent symptoms of the immediate extrapyramidal syndrome, and dystonias and oculogyric crises are less frequent manifestations. The immediate extrapyramidal syndrome is easily controlled by reducing the dose of neuroleptic or adding an anticholinergic antiparkinson agent to the medication regime.

Tardive dyskinesia is dominated by disturbed movements, just as the name

1974.

implies. If the rhythm is rapid it is considered a chorea. If slow moving it is called athetosis. If prolonged spasms occur the dyskinesia is called dystonia. In tardive dyskinesia choreiform movements are the type most commonly seen. In addition many cases with dyskinesia of the lingual-facial-buccal type occur. These exhibit movements of the facial muscles, grimacing, chewing, tongue-thrusting, blinking, and eyelid closure. In addition there may be involuntary laughing or crying, but without feelings, i.e., automatism.

Patients with tardive dyskinesia are usually incapacitated or exhausted by the severity of their symptoms. The only complete relief is in sleep. The least excitement, even a minor pleasure, causes a flare-up. Many patients are forced into social isolation in order to avoid this. In many cases they suffer complete boredom due to a concomitant impairment of concentration and memory that precludes all but the simplest mental tasks.

Tardive dyskinesia is unresponsive to treatment with the usual anticholinergic antiparkinson agents. Symptoms are not improved by lowering the dose of neuroleptic. In fact they are usually first noticed when the dose is reduced. This may account for the confusion in diagnosis, especially in outpatient

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practice, where tardive dyskinesia is likely to be mistaken for anxiety, hysteria, or relapse into psychosis.

Naturally the doctor is tempted to simply raise the dose of the neuroleptic and maintain the patient indefinitely this way because this will often ease the symptoms at first. However the dyskinesia will eventually break through in spite of high doses of neuroleptic medication or in fact because of it. Treatment with neuroleptics may suppress tardive dyskinesia, but at the same time this causes it and makes it worse.

Over 2,000 cases of prolonged or permanent neurologic damage, tardive dyskinesia, had been reported in the world literature by mid-1973. Dr. George Crane reviewed the literature in 1968 (Crane, 1968) and brought attention to the magnitude of this problem: "An educated guess would be that some two to three percent of patients on an antipsychotic medication for more than three years are seriously impaired neuro-logically."

In May, 1973, the Food and Drug Administration issued a drug bulletin (FDA Drug Bulletin, 1973) testifying to a rate of occurrence of tardive dyskinesia of 20 percent in older, institutionalized, chronically ill patients and admitting that perhaps 3 to 6 percent of patients in a mixed psychiatric population receiving neuroleptics exhibit some symptoms of dyskinesia.

The FDA recommended that physicians minimize the use of neuroleptics in chronically ill patients and in all patients over age 50 and advised that many patients can be maintained for long periods without antipsychotic drugs. They also advised that neuroleptics be discontinued at the first sign of abnormal oral or lingual movements or other possible manifestations of tardive dyskinesia. The bulletin acknowledged that the symptoms appear to be irreversible in some patients and that there is no known treatment.

The occurrence of immediate extrapyramidal symptoms due to treatment with

neuroleptics is so commonplace that it has become routine to prescribe anticholinergic-type antiparkinson agents along with the antipsychotic drugs. Antiparkinson drugs, such as benztropine mesylate (Cogentin), trihexyphenidyl (Artane), or procyclidine (Kemadrin) usually attenuate the immediate extrapyramidal symptoms, but they definitely increase the risk of tardive dyskinesia (Kiloh et al., 1973; Crane, 1968). In addition they sometimes interfere with treatment of psychosis by aggravating hostility reactions (Singh and Smith, 1973), and in some cases they cause a toxic, confusional state (Ananth and Jain, 1973).

Because dyskinesias have become such an accepted part of psychiatric treatment, the occurrence of tardive dyskinesia is often overlooked and almost always underappreciated by medical and nursing personnel. To illustrate: I admitted the most severe case of tardive dyskinesia that I have ever seen to a psychiatric ward, at a first-class general hospital in order to safely evaluate possible benefits of treatment with *Rauwolfia*. The nursing staff described this man only in terms of social withdrawal and mood depression. There was not a word about the obvious and persistent adduction-abduction movements of his lower extremities, or the peculiar grimacing, chewing, and tongue-thrusting that contorted his face most of the time and especially whenever he was approached, spoken to, or involved in any task other than reading or watching television.

To my amazement the personnel could not seem to comprehend the disorder or empathize with the incredible suffering of the patient. Imagine the alienation such patients experience in relation to their peers, who can only interpret these indescribable movements as manifestations of madness. But the unkindest cut of all is to find that this disorder is commonly diagnosed as anxiety or hysteria by physicians and psychiatrists. Sometimes there are years of wasted time and expense devoted to treating dyskinesia or akathisia by increasing the

medication in order to suppress the "nervousness," or with psychotherapy to "get at the underlying cause."

In any case, lack of proper diagnosis puts the onus on the patient: that the symptoms mean that he is neurotic or disturbed and acting out some mental or emotional conflict. Such an interpretation, often made by the patient himself, is destructive to self-esteem and thus aggravates the sense of loss and grief. This inevitably leads to an increase in confusion, agitation, and despair. Such a super-anxiety state activates the dyskinesic movements and thus compounds the vicious cycle.

Until now the patients with tardive dyskinesia have been suffering in confused helplessness while the facts about cause and lack of cure are slowly becoming known. It is no wonder that immediate extrapyramidal symptoms are the most common reason that our patients refuse antipsychotic medications. If knowledge of the perils of tardive dyskinesia were more widespread there might be even more resistance by patients and greater caution by their physicians. As Dr. Crane has pointed out to the medical community, "the risk of being sued for not recognizing tardive dyskinesia until it is too late will increase considerably, as demonstrated by recent court cases."

In 1973 I found eight patients with tardive dyskinesia out of 70 schizophrenic patients in my own outpatient private practice of psychiatry. In the first six months of 1974 I encountered seven additional cases. This suggests roughly a 10 percent rate of occurrence among my schizophrenic patients and 2 percent in my practice at large.

With the earlier of these cases, having tried antiparkinson agents and Rauwolfia to no avail, I recalled that phenothiazines are potent chelators of manganese (Borg and Cotzias, 1972). I also recalled that manganese is found in high concentration in the extrapyramidal system. I reasoned that phenothiazines might chelate manganese, thus binding it

electrochemically, and that this might make manganese unavailable for some presumed function as an enzyme activator. It seemed plausible that by providing extra dietary manganese the deficiency would be corrected and the dyskinesia might thereby improve.

I did not have long to wait before a young man (case #5) consulted me because of dyskinesia due to fluphena-zine enanthate (Prolixin). This had been administered over two months earlier at a university psychiatric service in two doses of 100 mg, intramuscular, a week apart, plus 30 mg orally for four days and 45 mg for four days. He still exhibited mask-like facial expression, Parkinson's posture and gait, and severe tremor and rigidity of the extremities. These symptoms had persisted in spite of previous treatment with diphenhydramine (Benadryl), diazepam (Valium), and nicotinamide (1,000 mg, t.i.d.). Manganese chelate, 10 mg, t.i.d., was now started. After one day the tremor and rigidity were much improved. After two days he was entirely free of dyskinesia. There was no recurrence.

Another young man (case #7) was treated with fluphenazine (Prolixin), 30 mg per day, orally for 10 months in a state hospital for his second schizophrenic episode. During his previous hospitalization of six months' duration, four years earlier, he was treated with chlorpromazine, 150 mg, q.i.d. In each illness he had taken LSD beforehand. He had terminated fluphenazine and trihexyphenidyl (Artane) nine weeks earlier, but still had parkinsonian posture, mask-like facies, and moderate tremor of the thumb and forefinger. On a low dose of manganese chelate, 6.4 mg per day, in a multivitamin, he showed no improvement in two weeks. However when the dose was increased by the addition of manganese chelate, 5 mg, t.i.d., providing a total of 21.4 mg of manganese per day, he showed overnight improvement in posture and gait and more gradual improvement in facial expression. Mental dullness and flat affect did not improve until he was treated with nicotinic acid, 250 mg t.i.d.,

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three months later.
Table 1 summarizes my observations in 15 cases.

TABLE 1

Case*	DIAGNOSIS	SEX	AGE	DRUG	DURATION AVG. DOSE	DYSKINESIA	Mn HAIR	RESULT/Mn	RESULT/B3
1.	Neurotic Depression	61 Male		Thioridazine	1 1/2 yr.	Oral, Buccal Glossal Akathisia	0.2	Much improved Cured Much improved	Improved
2.	Paranoid Schizophrenia	46 Male		Chlorpromazine Haloperidol	15 yr. 200mg/d 2 yr. 10mg/d	Eyelid Closure Akathisia Oral	0.6	Improved Improved Improved	
3.	Neurotic 150mg/d	70 (arms)		Thioridazine	11 yr.	Tremor	0.4	Improved Depression	Fern.
4.	Anxiety 75mg/d	25 Cervical		Thioridazine Cured	5vr.	Glossal	0.4	Cured Disorder	Male
5.	Paranoid 45mg/d 100mgIMx2	20 Rigidity		Fluphenazine Cured	12 days	Tremor	1.0	Cured Schizophrenia	Male
6.	Schizoaffective improved Fern. improved Oral Haloperidol 1 54 yr.	39		Chlorpromazine Haloperidol	16 yr. 400mg/d 1 mg	Tremor Akathisia Tremor	0.6	Improved Improved Unchanged Improved	Much Much Unchanged Improved
7.	Paranoid Schizophrenia Chlorpromazine 600 mg	23 Male		Fluphenazine Chlorpromazine	1 54 yr. 30mg/d	Tremor Rigidity Cured	0.3	Cured	
8.	Schizoaffective Male Haloperidol Thiothixene 15 mg/d	28		Chlorpromazine Haloperidol Thiothixene	7yrs. 200 mg/d 7 days 3mos. 15 mg/d	Akathisia	0.3	Cured	
9.	Schizoaffective Male Akathisia	25		Fluphenazine	7yr. 20 mg/d	Tremor Rigidity	0.6	Cured Cured Cured	
10.	Paranoid Schizophrenia Mesoridazine Thiothixene 40 mg/d	18 Male 54 yr. 150 mg/d		Fluphenazine	54 yr. 75mg/wk 54 yr.	Tremor Rigidity	0.2	Unimproved Unimproved Cured Cured	
11.	Manic 10 mg/d	50		Fluphenazine	10yr.	Tremor	0.6	Cured Depressive	Male
12.	Paranoid 25 mg/wk Trifluoperazine 20 mg/d	22 Rigidity		Fluphenazine Trifluoperazine	3mos. 2yrs.	(Tremor) Akathisia	0.3	Schizophrenia Improved	Male

TABLE 1 Continued

13.	Schizophrenia (Undiff.)	30 Fem.	Fluphenazine 125mg/wk	54 yr.			
	Haloperidol				1/2 yr.		
		110mg/d	Chlorpromazine	3 yrs.			
		300mg/d					
14.	Schizoaffective	36 Fem.	Trifluoperazine	9yrs.		Tremor 0.6	Cured
				5		Akathisia	Improved
						Oral 0.2	Much Improved
						Akathisia	
15.	Paranoid Schizophrenia	38 Fem.	Trifluoperazine	5yrs.			
				8 mg/d			

The tabulation shows that in 15 cases of tardive dyskinesia treated with manganese, seven (46 percent) were cured outright (#4, #5, #7, #8, #9, #11, #13). Three (20 percent) cases were much improved (#1, #6, #12). Four (27 percent) were improved (#2, #3, #14, #15), and only one (7.7 percent) was unimproved after treatment with manganese (#10).

Not included in the tabulation were the observations that indicate that those cases which showed prompt response to manganese also showed complete response: there were four cases of literally overnight cure (#5, #8, #11, #13). These were all completely cured. In nine others a definite improvement occurred in two to five days (#1, #2, #3, #4, #6, #7, #9, #12, #14). These were cured (#4, #7, #9), or much improved (#1, #6, #12), or improved (#2, #3, #14). Case #15 was rated improved because withdrawal dyskinesia did not recur as it had before. All of the dramatic results were in patients age 50 or under. On the other hand there were two cases under age 40 that were resistant. One of these (#6) responded dramatically with mood elevation, mental clarity, and reduced tremor to the addition of niacinamide. The other (#10) experienced a dramatic cure within hours of starting on niacin. This case had been resistant to manganese and all other medication at outpatient doses, responding only to heavy sedation with diazepam and diphenhydramine when hospitalized.

Let me describe this case in greater detail. The patient was an 18-year-old

Oculogyric 0.7 Cured Much improved

schizophrenic college student whose dyskinesia appeared while he was under treatment for six months with fluphenazine, mesoridazine, and thiothixene in a state hospital. Tremor and akathisia had been suppressed by increasing the doses. Two weeks after withdrawal from the weekly injection of 75 mg of fluphenazine enanthate the dyskinesia emerged. Two weeks later, after discontinuing mesoridazine and thiothixene, the dyskinesia erupted full force with severe tremor of the extremities and severe rigidity. Manganese was of no benefit at a dose of up to 80 mg per day. Then, after 10 weeks without improvement, there was complete and sustained relief within three hours of a single, oral dose of niacin, 500 mg. The niacin flush reaction frightened the patient so that he delayed three days before taking a second dose. During this time the dyskinesia partially recurred. The second dose of niacin produced a complete cure.

My observations indicate that niacin at doses of 100 - 500 mg was of significant benefit in treating the dyskinesia in three of these 15 cases (#1, #10, #13). In another case (#7) niacin improved mental acuity, but it was not started until after the dyskinesia had already recovered with manganese treatment. Niacinamide had a similar but less dramatic effect in two cases (#6, #15). The reason for this possible disparity may lie in the well-known flush response which occurs in conjunction with niacin, but not niacinamide.

It is known that the niacin flush

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response usually disappears upon repeated administration of large doses of niacin. This suggests that niacin may deplete tissue stores of substances that mediate vasodilation, e.g., bradykinin, histamine, and prostaglandins (Kunin, 1974). This could account for the calming effect that niacin often exerts: since histamine and prostaglandins modulate action of neurotransmitters in the brain, their depletion might have a sedative effect. This would reduce input into the disordered extrapyramidal system. The occasional benefit of niacinamide could derive from a related mechanism for niacinamide is known to exert a significant antihistamine effect including the actual inhibition of release of histamine from mast cells (Bekier and Maslinski, 1974). Cotzias noted that niacinamide protected mice from L-Dopa-induced dyskinesia. However when he tested it in six patients with parkinsonism no benefits were found (Cotzias et al., 1972). He did not test niacin, however. On the other hand, if niacin happens to increase the activity of prostaglandins, which is likely during the initial flush response, this could further increase cholinergic activity.

Prostaglandins increase the release of acetylcholine at cholinergic nerve terminals (Sanner, 1974). This could explain the immediate improvement in dyskinesia after treatment with niacin. Furthermore the E type prostaglandins inhibit the release of norepinephrine from adrenergic nerves, and this could diminish the tremorigenic effects of the adrenergic inputs into the striatum. It seems likely that the combination of these effects would produce a significant benefit both by decreasing the tremorigenic effects of adrenergic stimulation and also by augmenting cholinergic activity.

In order to understand why manganese supplementation is therapeutic in tardive dyskinesia I surveyed the results of spectrographic mineral assays of hair samples from these patients. Analysis by atomic

absorption spectrophotometry revealed a mean content of manganese in the hair of my patients at large to be 0.8 parts per million (ppm). However for the dyskinesia patients it was only 0.46 ppm,* nearly 50 percent less. Dietary supplementation with manganese is usually followed by an increase in the level of manganese in the hair (Kunin, unpublished data), where it is bound to melanin (Cotzias et al., 1964). Thus white (unpigmented) hair has very low manganese levels. Aside from this, hair biopsy is a reflection of the degree or absence of manganese surplus (Rosen-stock et al., 1971).

These observations lend some credence to the idea that phenothiazine treatment chelates and thus removes manganese from availability by sequestering the ion in an electrochemical bond. I speculate that a deficiency state may be induced in susceptible or borderline deficient patients. Deficiency would be most pronounced in the extrapyramidal system because phenothiazines accumulate there, perhaps because of the rather high concentration of divalent mineral ions, e.g., manganese, copper, iron, and magnesium, that are chelated or complexed to the catechol and indole molecules that abound there as neurotransmitters and related intermediary and degradation products.

Melanin, a degradation product of tyrosine and dopamine metabolism, is known to attract manganese and, as noted above, the manganese in hair is present mostly in association with melanin. There is undoubtedly some manganese stored in the substantia nigra with the melanin deposits that build up there; however, it is copper that reigns as the predominant mineral cation of the substantia nigra, because of its essential role in tyrosine and dopamine metabolism (Hornykiewicz, 1972; Friede, 1966).

Manganese is actually found in greatest concentration in the corpus striatum (Hornykiewicz, 1972), probably related

* 0.54 if earlier sample value of 1.3 ppm is taken for case #15.

to the great concentration of acetylcholine within the caudate and putamen. Manganese is a potent activator of the acetylcholine - restoring enzyme, choline-acetyl-transferase, also called choline-acetylase (Miller, 1973; Pfeiffer and Iliev, 1972), so that alteration in the availability of manganese might affect striatal function through its effect on acetylcholine synthesis.

In addition to its presumed action on the enzyme choline-acetylase it is possible that manganese exerts further cholinergic action by activating the enzyme, arginase. In this case an increase in conversion of arginine to urea, a reaction that requires arginase and manganese, would produce greater amounts of ornithine. Ornithine is believed to be part of the binding protein by which acetylcholine is stored at the nerve terminals (Whittaker, 1973). Thus, greater amounts of ornithine may indicate a greater ability to store and release acetylcholine.

Borg and Cotzias (1972) were the first to report that phenothiazines form free radicals with manganic (trivalent) ions in vitro. They were impressed by the parallel effects of phenothiazines and manganese in causing psychic effects and parkinsonism, and they postulated that phenothiazines might concentrate manganese in the melanin-rich areas of the substantia nigra (Cotzias, 1962).

If phenothiazines do actually concentrate manganese in the substantia nigra, this might inhibit the activity of copper-dependent enzymes, such as tyrosine hydroxylase and dopa-decarboxylase. The rationale for this is in the well-verified antagonism between manganese and copper. Specifically one would expect a decrease in conversion of tyrosine to dopamine. On the contrary a build up of dopamine in the substantia nigra is what actually happens (Horny-kiewicz, 1972a; Nyback et al., 1967); however, this may be due to feedback mechanisms rather than cation interference and enzyme inhibition.

In 1956 Comens reported that hydralazine (Apresoline), then much in vogue as an

antihypertensive medication, chelates manganese and causes a clinical deficiency in some patients (Comens, 1956). He suggested that this might account for the frequent lupus erythematosus syndrome associated with hydralazine therapy. Lupus can be prevented if manganese is given before treatment with hydralazine in birds and dogs, and manganese prevents in vitro formation of LE cells. Patients with lupus have benefited by manganese therapy (Davies, 1972).

However, the formation of a chelation bond with manganese does not necessarily cause deficiency. Quite the contrary occurs in the case of tetracycline, which also chelates manganese. The administration of tetracycline will prevent signs of manganese deficiency in experimental animals on an otherwise manganese-deficient diet by increasing efficiency of intestinal absorption. In humans this phenomenon of increased absorption (Cotzias, 1962a) may account for the hypoglycemia tendency that often complicates the long-term use of tetracyclines. Manganese lowers blood sugar levels, perhaps through its action as activator of pyruvate carboxylase.

It is clear that good results with dyskinesia were associated with manganese doses of at least 15 mg and up to 60 mg per day. At doses above 60 mg per day of manganese chelate, two patients (#1, #10) were more tremulous and also noted an excessive salivation. These effects reversed within a few days after withdrawal of the manganese. So it appeared that manganese, in doses above 60 mg per day, may have aggravated dyskinesia. However, this is not certain inasmuch as these were the two worst cases to begin with.

There were no other adverse effects of manganese noted in these patients. However, in many other cases in my practice at large I have observed manganese to be a potent aphrodisiac. This has proved of significant therapeutic value in the treatment of sexual impotence in men and frigidity in women. At a dose of 15 to 30 mg per day

there is often a marked increase in libido and sexual performance in both sexes.

Rodier (1955) called attention to a syndrome of sexual stimulation followed by impotency in 83 percent of his cases of manganese poisoning in Moroccan miners. Of course these more damaging effects were only seen at much higher doses and over a much longer time. His patients averaged over two years' exposure to toxic levels of airborne particles of manganese before their psychiatric and neurological symptoms erupted. In my practice I have had only two cases, not in this series, in which manganese had to be discontinued because it provoked sexual unrest in schizophrenics. The agitation and obsessive preoccupation receded within a few days' time. I have seen no cases in which impotency or loss of sexual performance or feeling was associated with manganese treatment.

The three common syndromes of extrapyramidal dysfunction associated with neuroleptics are only partially understood. For example, dystonias that occur immediately after medication are probably caused by overproduction of dopamine and acetylcholine as an initial response to the receptor-blocking action of the drug (Markham et al., 1974; Trabucchi et al., 1974).

On the other hand, the immediate drug-induced parkinson syndrome is best explained in terms of imbalance between the dopamine-blocking effects of the drugs and their acetylcholine-blocking effects. If the acetylcholine blockage is dominant, extrapyramidal symptoms are negligible (Snyder et al., 1974).

Thus thioridazine, which is a strong acetylcholine blocker, is associated with weak extrapyramidal symptoms. Halo-peridol, a very weak acetylcholine blocker, induces severe extrapyramidal symptoms. The range of acetylcholine effects is over a thousandfold between haloperidol and clozapine, a new phenothiazine with almost nil extrapyramidal effects.

The effect of clozapine, which has strong

dopamine and acetylcholine blocking activity, may turn out to be neurotoxic in some patients. Cohen and Cohen (1974) recently reported on four cases of acute encephalopathy following combined lithium and haloperidol, which together decrease norepinephrine and acetylcholine and block dopamine activity (Flemenbaum, 1974). Benztro-pine may have aggravated this tragic outcome in three of their cases by synergistic increase of the acetylcholine-blocking action of lithium. With norepinephrine, acetylcholine, and dopamine receptors blocked, intercellular communication is almost totally disrupted and both cyclic AMP and cyclic GMP activity in the cells is reduced (Forn et al., 1974; Weight et al., 1974).

Tardive dyskinesia occurs as the dopamine blockade is withdrawn and the striatal dopamine receptor sites are vacated by termination of the neuroleptic (Klawans, 1974). The receptor cells behave in a manner akin to denervation hypersensitivity, perhaps caused by sprouting of new dendrites in reaction to the blocking effect of the neuroleptic. Sprouting of new terminals to replace damaged or necrotic ones is known to account for denervation hypersensitivity in both central and peripheral synapses (Goodman and Gilman, 1965; Markham et al., 1974). Reinnervation can even proceed with terminals from adjacent pathways, but with different chemical transmitters. Such regrowth can place serotonergic or adrenergic terminals in place of the previous dopamine receptors. Understandably the coordination of activities in these neuronal circuits is disrupted. "Noise" in the extrapyramidal system is expressed as dyskinesia.

In addition there is an immediate dopamine hypersensitivity when the nigra-striatal pathway is injured and therefore not caused by dendritic sprouting. Ohye (1970) demonstrated increased rate of firing of cells in the putamen by application of the dopamine precursor, L-Dopa, after interruption of the nigra-striatal pathway. So it is possible that another mechanism of tardive dyskinesia

is related to damage to the nigra-striatal pathway by the prolonged neuroleptic blockade of the dopamine receptors (Markham et al., 1974; Klawans, 1974).

In summary it would appear that the dopaminergic system acts in opposition to the cholinergic system and that a balance of dopaminergic and cholinergic influence in the striatum is necessary for normal movement to occur. It may be that by increasing the manganese level the activity of the enzyme, choline-acetylase, is enhanced. This would increase the level of acetylcholine in the striatum, thus counterbalancing the dopaminergic hypersensitivity that would inhibit striatal cholinergic neurons in tardive dyskinesia.

In support of this is the finding that treatment with Deanol (dimethyl-aminoethanol, Miller, 1974) is of benefit in cases of L-Dopa-induced dyskinesia. Just recently it has been reported of value in tardive dyskinesia as well (Miller, 1974a; Casey and Denney, 1974). (In case #6 Deanol was beneficial, but in case #1 it was not.)

Also relevant is McGeer's (McGeer et al., 1973) demonstration of reduced levels of choline-acetylase in Huntington's chorea, a congenital disorder that causes symptoms similar in appearance to those in tardive dyskinesia. That the levels of glutamic decarboxylase and therefore of gamma amino butyric acid, a well-known inhibitory transmitter, are also reduced, intrigues us further about the biochemical complexity of dyskinesia.

Feedback mechanisms contribute to the complexity of extrapyramidal function. For instance, increased acetylcholine activity of the striatum is known to evoke greater production of dopamine in the substantia nigra. Evidently this is part of a feedback process since injection of acetylcholine into the substantia nigra (of rats) increases dopamine output (Hornykiewicz, 1972b). So if manganese does really increase acetylcholine activity in the striatum it is possible that

overdose would worsen the dyskinesia by causing a feedback increase in production of dopamine. Indeed, I did notice increased tremor in two patients who received over 60 mg per day of manganese chelate (#1, 10). In addition I observed sialorrhea (increased salivation), an indication of possible peripheral cholinergic overactivity in case #1 and in a parkinsonian patient not included in this series.

There are additional mechanisms by which manganese could operate. In the first place, in vitro manganese (divalent) has been observed to inhibit acetylcholine release at the neuromuscular junction, more precisely at the presynaptic terminals of motor nerves (frog), (Meiri and Rahamimoff, 1972; Balnave and Gage, 1973). These are nicotinic acetylcholine terminals, not identical with the muscarinic type found in the central nervous system. At higher concentrations of calcium more manganese was needed to achieve the same inhibition. This suggests that manganese may compete for a common site with calcium on the presynaptic membrane. This competitive inhibition by manganese appears to be about 20 times more potent than similar inhibition by magnesium ion!

The results of such inhibition of acetylcholine activity are observed as an inhibition of neuromuscular transmission. Clinically this is manifest as myasthenia. The Eaton-Lambert Syndrome is a naturally occurring disorder of acetylcholine release leading to attacks of weakness. In a recent case report by Drs. Gutman and Takamori (1973), a patient with this disorder was treated with intramuscular magnesium sulfate, 2 g (equivalent to 474 mg of magnesium) at 9 a.m. and 3 p.m. The second injection caused a two-hour seige of weakness to the point of dyspnea. A third injection at 9 p.m. caused generalized weakness and bulbar paresis requiring a mechanical respirator for two days.

It appears from this dramatic case report that there could be some inhibition of acetylcholine release with higher doses of manganese, especially in susceptible patients. An equimolar dose

of manganese comparable to the 474 mg dose of magnesium would be over 1,000 mg, but divided by 20 to allow for the greater inhibitory effect of manganese as compared to magnesium the equivalent dose would only be 50 mg. This may be adequate to provide some relief of dyskinesia by inhibition of neuromuscular activity at the peripheral acetylcholine receptors at the neuromuscular junction in some patients. Absorption of orally administered manganese chelate is supposed to be greater than inorganic forms.

Another mechanism by which manganese could operate involves its ability to inhibit the activating effect of ferrous iron on catecholamine activity. Manganese induces a 50 percent reduction in iron-activated norepinephrine uptake in rat brainstem (Sawami et al., 1974). In addition an inhibition of catecholamine binding with human serum albumin was observed due to manganese (Sawami et al., 1974). Manganese has also been shown to reduce the effects of catecholamines on smooth muscle in guinea pigs, ostensibly by interfering with calcium fluxes (Strubett et al., 1973).

Since catecholamine activity aggravates tremor the foregoing effects could inhibit dyskinesia. Note that amphetamine, which increases catecholamine activity, causes choreiform tremor (Klawans and Weiner, 1974). Thyroid can also aggravate chorea, by "activating catecholamines. In case #2, the severe tremor of the upper extremities was much improved after a nontoxic benign thyroid nodule was removed. Presumably the operation of subtotal thyroidectomy reduced thyroid output.

Finally manganese may benefit dyskinesia by reducing dopamine activity in the substantia nigra, after all. Bonilla demonstrated just such an effect in rats that were treated with manganese chloride in their drinking water (equivalent to 70 mg per day of manganese, Bonilla and Diez-Ewald, 1974).

The use of manganese at toxic levels as a therapy is not exactly what I had in mind at

the beginning, but it may turn out to be of value in those cases, such as case #1, where L-Dopa aggravates the dyskinesia, hence indicating dopamine hypersensitivity. Manganese, by reducing dopamine production, might exert a beneficial effect in the long run. Pentschew (1966) was first to suggest using manganese toxicity to treat parkinsonism by correcting a disequilibrium between the striatum and the substantia nigra. Manganese is not very toxic and the severe cases of toxicity have been mostly among miners who have built up tissue levels of manganese in their lungs, which are then released in uncontrolled fashion leading to neurotoxicity in months or years after the exposure is terminated. In medical practice a degree of control is possible for the dose could be titrated and monitored by measuring urinary homovanillic acid (HVA) excretion as a reflection of dopamine production (Hornykiewicz, 1972c).

When all else fails, heavy sedation with large doses of diazepam and diphenhydramine has been the most reliable treatment to control the symptoms of tardive dyskinesia. Phenothiazine analogs, such as thiopropazate (Dartal, Curran, 1973), and tetrabenzazine (Swash et al., 1972), and some butyrophenones, including haloperidol, have been recommended recently. I believe that these may carry some risk of aggravating the disorder.

It is not generally recognized as yet that haloperidol can cause tardive dyskinesia. The fact that this occurred in cases #1, #2, and #6 indicates that this is not rare at all. In fact, my observations indicate that haloperidol is at least as toxic to the extrapyramidal system as is fluphenazine. Trifluoperazine has been considered the prime offender, but I suspect this is only because it has been around longer and used more extensively-

Perhaps the most intriguing possibility that emerges from these observations and speculations is that manganese may have prophylactic value in preventing tardive dyskinesia and perhaps immediate parkinsonism and dystonias as well.

The dramatic speed of recovery in about half of these cases is highly suggestive of true manganese deficiency. Such dramatic results have often been associated with correction of nutritional deficiencies. If these cases are, indeed, truly manganese deficient, then simple manganese supplementation may prove quite gratifying in preventing both the extrapyramidal syndrome and tardive dyskinesia.

I realize that some of these cases represent withdrawal dyskinesia without permanent damage to the extrapyramidal system, especially those cases that had only a few large doses of depot fluphenazine enanthate. However, exposure to dopamine-blocking agents need not be prolonged for years nor at high dose to be seriously toxic (Simpson, 1973; Thornton and Thornton, 1973). The Cohens' cases developed severe, irreversible, generalized encephalopathy within a week of combined haloperidol-lithium treatment! So, it is very possible that dendritic sprouting may occur within a few weeks under the prolonged and powerful influence of depot fluphenazine. It seems to me entirely plausible that withdrawal dyskinesia is a form of tardive dyskinesia.

More important is the fact that these were among the cases that responded dramatically to manganese treatment. It is possible that by treating the withdrawal type of tardive dyskinesia with manganese, it may be possible to prevent the occurrence of chronic tardive dyskinesia. A controlled study of manganese supplementation in conjunction with phenothiazine treatment of schizophrenia is indicated. I hope that this paper will encourage such a study.

ADDENDUM

An intriguing development in support of the theory that cholinergic agents can alleviate symptoms of tardive dyskinesia is reported by Davis, Berger, and Hollister. They found that megadoses of choline, up to 16 grams per

day, in divided doses, achieved significant reduction in symptoms of one case of previously unresponsive buccolingual-masticatory dyskinesia.

DAVIS, K. L., BERGER, P. A., and HOLLISTER, L. E.: Choline for Tardive Dyskinesia. *N.E.J.M.* 293:152. July 17, 1975.

Case #1

This 61-year-old former accountant had suffered with recurrent anxiety and depression for 25 years before he consulted me in May, 1972. His dietary habits were poor, and he subsisted mostly on coffee, candy, and alcohol. He had been treated with nine electroconvulsive treatments in 1969 without benefit for his chronic anxiety and was therefore maintained on thioradazine, 400 mg per day for one and a half years, and then switched to haloperidol, averaging 6 mg per day for the next one and a half years. A month before consulting me he attempted to switch to diazepam because he felt increasingly nervous. At once he was bedridden with severe bodily contortions, grimacing, tongue-thrusting, and chewing movements. He therefore resumed haloperidol at 8 mg per day, and this partially suppressed the "nervousness," but the leg movements and grimacing persisted at one per second, and his tongue was raw from chewing. He thought his symptoms must be of psychological origin.

I advised that he immediately discontinue haloperidol. This released the dyskinesia in more severe degree. His symptoms were unresponsive to large doses of bztropine, trihexyphenidyl, and procyclidine. A trial on L-Dopa, 0.25 g, b.i.d., and then t.i.d., had to be stopped in four days as it made him confused and ataxic.

After four months he had not improved. His symptoms relented only in sleep and while reading. He could drive a car, just barely, and walking was precarious. Lithium carbonate, 300 mg, t.i.d., made him calmer for a week and

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then he became ataxic and with increased grimacing and eye-rolling. Although the serum level was only 0.75 mEq/l, it seemed wise to discontinue lithium. A trial period of niacin, 100 mg, and Pyridoxine, 100 mg, both t.i.d., left the dyskinesia unchanged, but he felt more alert and his mood brightened.

An earlier trial on manganese chelate, 5 mg, t.i.d., was unremarkable, and he discontinued it in a week. It was given with the thought of correcting possible deficiency, implied by low level of manganese detected in pubic hair (0.3 ppm). Now, four months later, he took manganese chelate, 10 mg, t.i.d., and there was definite improvement: leg movements were reduced by half, and tongue and jaw movements responded to a lesser degree. His wife exclaimed: "Manganese really helps."

Two months later, still suffering with residual symptoms, he accepted hospitalization in order to safely try Rauwol-fia. Manganese was stopped, and he was started on Serpasil, 0.5 mg per day, and after a week this was increased to t.i.d. His symptoms got worse, and two weeks later even more so when the Serpasil was stopped for he developed involuntary eyelid closure. When Serpasil was resumed at 1.25 mg, b.i.d., he reported some improvement in another two weeks, particularly a lessening of tongue movements. At the same time, however, manganese was increased from a previous level of 23 mg per day to 30 mg per day as chelate and 9 mg as inorganic manganese chloride in a multimineral supplement.

In another month he complained of lack of progress so I cautiously added haloperidol, 0.5 mg per day. This made him acutely worse, moaning, grunting, unable to relax enough to read, and with constant tremor. Haloperidol was discontinued in five days, but it took another week to recover. A month later Serpasil was once again increased to 0.5 mg, t.i.d., and after a few weeks he discontinued it on his own.

From July to October he attended a mental health clinic where he was again started on haloperidol, 6 mg per day. He remained on vitamin supplements and manganese 39 mg per day as before. At first his "nervousness" subsided, but after a month he suddenly became nervous again and started to have crying spells. He said that he did not feel sad or depressed, however. Imipramine, 25 mg, t.i.d., did not help, and he discontinued it in a few weeks. However he insisted on continuing haloperidol at a dose of 2 mg per day.

Then in December he "got fed up with pills" and impulsively stopped all medication, vitamins, and mineral supplements. Surprisingly, there was no exacerbation of dyskinesia symptoms (perhaps due to the manganese); however, in two weeks he began to have weeping spells, night and day. In desperation he consulted me. When he resumed manganese chelate, now 20 mg, t.i.d., the weeping stopped in three days, and the dyskinesia symptoms were reported to be 50 percent better.

I reduced the manganese intake to only 10 mg per day as a test and started him on a supplement containing 3 mg of copper, a manganese antagonist. At the next visit he reported that "nervous tension has been killing me since last time." The amplitude of his tremors was increased, and grimacing was more obvious.

At this juncture manganese chelate was increased to 20 mg, q.i.d., in hopes of further improvement. Within a month he reported that he now had no dyskinesia symptoms at all. He could stand still without marching and there was no grimacing. However he did have increased salivation, and therefore I advised him to discontinue manganese for a week. Sialorrhea ceased at once, according to his wife. He was then to continue manganese, 5 mg, t.i.d., and try methylphenidate, 5 mg, b.i.d.

He did not follow these instructions, however, but instead went back to the mental health clinic again. Perhaps the dyskinesia recurred when he did not resume the manganese, or possibly it was due to the methylphenidate trial. He did

not tell his wife about this, but the doctor once again prescribed haloperidol, 4 mg per day.

This time he did not improve, and he was then referred to a university neurology clinic. He then was continued on haloperidol, 2 mg per day, diazepam, 10 mg, b.i.d., and he was started on dimethylaminoethanol (Deanol), 100 mg, t.i.d., but without benefit. In fact, his symptoms got worse: grimacing was constant and leg movements were so disturbing that he could no longer sit still to read. Furthermore he developed two new symptoms: involuntary eye closure and dysphagia.

After three months he returned to my care (October, 1974). Haloperidol was discontinued at once, and he became restless but also more alert and able to read again. Crying spells ceased in a week. However he had constant grimacing and leg movements at a rate of about one per second, and his tongue movements were so awkward that he had slurred speech. He had awkward swallowing movements, but did not choke.

Increasing the dose of Deanol to 500 mg, t.i.d., was ineffective. Pentazocine (Talwin) 100 mg*, q.i.d., was also ineffective. Propoxyphene (Darvon), 65 mg, q.i.d., was helpful, and he definitely felt more comfortable and movements decreased about 25 percent in amplitude. Acetaminophen, 650 mg, q.i.d., was of no value. Cyproheptadine, 4 mg, t.i.d., made him ataxic, insomniac, and more restless and depressed. Amantadine promptly aggravated his dyskinesia symptoms and was discontinued in three days, but the bad effect persisted another week.

In January, 1975, manganese was resumed at a dose of 10 mg, t.i.d. No results were observed during the first week. Nor were there any results when niacin was resumed at a dose of 100 mg, t.i.d.

Case #2

This 46-year-old mathematician experienced paranoid schizophrenic episodes in 1953, 1959, 1964, and 1968.

He was treated by electroconvulsive therapy and with various phenothiazines after 1957, but was maintained mostly on chlorpromazine, averaging 200 mg per day until 1963 when involuntary eyelid closure became troublesome, especially in driving. His symptom improved, but did not entirely disappear in the next eight years when he was switched to thioridazine. He got much worse after he started on haloperidol, 4 mg per day, in 1971 along with procyclidine (Kemard-rin). He had three automobile accidents in the next year and, in addition, he noticed chewing movements and tongue biting for the first time.

He consulted me in September, 1972, and was withdrawn at once from haloperidol and procyclidine. I started him on manganese chelate, 5 mg, t.i.d., and an additional 8 mg per day of manganese in other supplements for a total intake of 23 mg per day. At first the eyelid closure became less frequent and the jaw and tongue movements disappeared. Previously when he had attempted to discontinue haloperidol he had an immediate "tailspin."

After a week, when he went back to his home state, he developed insomnia and the local psychiatrist kept him on thioridazine, 200 to 300 mg per day. His symptoms resumed and he was troubled by this turn of events so he maintained occasional telephone contact with me. I recommended niacin in gradually increasing doses to 1,000 mg, t.i.d., and he said it made his head feel clearer.

However, his local doctor advised him to stop taking vitamins, and thus the manganese was stopped also after only two months. Now he really began to get worse. The eyelid closure occurred more frequently than ever and also with involuntary grinding of his teeth. Dyskinesia interfered with his ability to work, and he was put on sick leave. This stress may have contributed to the insomnia, depression, and then relapse into schizophrenia in January, 1973. He was hospitalized for a few weeks and started again on haloperidol. The dyskinesia was worse after discharge, and a trial on

Serpasil, 2 mg, t.i.d., was of no benefit. It may have provoked a depressive episode because he was given isocar-boxazid (Marplan) at the same time and with disastrous results due to a near fatal hypertensive crisis. The dyskinesia was much aggravated after this, and tongue-thrusting, opisthotonos, restless legs, and eyelid closure with grimacing were all on display.

He consulted another doctor and improved upon discontinuing halo-peridol and starting on chlorpromazine, 50 mg, t.i.d., and benztropine. However after a few months he relapsed into mutism and severe anorexia and was hospitalized again. This time he was treated with fluphenazine. He now developed akathisia in addition to the previous symptoms. These have persisted for the past year and appear to be getting worse. He grinds his teeth and has jerking movements in his neck. His hands are in constant motion and only his leg movements have ceased with benztropine, fluphenazine, and amitriptyline.

His wife wrote to say that the manganese did seem to help while he took it and that he got sick after he stopped taking all medication and vitamins. She went on to complain: "No one here seems to know anything about dyskinesia and they think I'm nuts when I talk about it . . . the doctor didn't want to read your letter (describing dyskinesia treatment). Can you believe it?"

Case #3

This 70-year-old housewife and former legal secretary has had resting tremor of the upper extremities for the past 10 years. There was a prodrome of action tremor for seven years before that when attempting to sign checks. There is also a history of rheumatic fever with chorea at age six, and in high school she already had tremor of her hands when nervous. This prevented her from taking the lead in a musical production. Anxiety attacks began following a hysterectomy at age 45. She had ECT in 1948, 1953, 1959, and 1963 for depressions of agitated type. She was

hospitalized continuously from 1963 to 1969 because of persistent agitation and maintained on thioradazine, 100 mg, mornings, and 50 mg at midday. Tremor has been disabling since 1963. Her arms and hands are in constant motion except in sleep. Before 1963 she noticed tremor only when discontinuing medication upon discharge from her hospitalizations and for a month or so thereafter.

Under my care in May, 1973, she discontinued the benztropine without adverse effect. However when thioridazine was reduced she suffered prompt increase of "nervousness," restless legs, akathisia, and uncontrollable tongue movements. With the addition of manganese chelate, 5 mg, t.i.d., and 8 mg in vitamin-mineral supplements, total 23 mg per day, her tremor was improved and thioradazine reduced to only one dose of 100 mg per day. Unfortunately I did not connect the use of manganese with therapy of dyskinesia at that time, or I would have increased the dose. Instead I recommended a trial on Serpasil 0.4 mg per day in late June. This aggravated her depression and ulcer and she became quite agitated and suicidal. Furthermore the tremor was made worse and involved not only her arms, but also her shoulders and back.

Before the six weeks on Serpasil, she showed marked initial improvement on vitamin supplements and spring water to lower her fluoride intake.

Spectrographic analysis of her hair had revealed a marked elevation of fluoride, over 10 ppm. Analysis of the local water revealed the presence of naturally occurring fluorides at a concentration of 1.9 ppm. Since she drank over eight glasses of water per day, she was probably ingesting over 4 mg per day of fluoride all of her life. This may explain the severe arthritis that has affected her hands, feet, and spine for the past 18 years. In addition, her teeth, devoid of cavities, began to disintegrate due to fracture of the brittle fluoride apatites and all had to be removed in August. Inability to chew food and consequent poor diet added to her depression.

In September she was operated for nontoxic thyroid malignancy. After total thyroidectomy and maintenance on 60 mg desiccated thyroid per day her tremors significantly improved, up to 75 percent better, she said. She tried manganese gluconate, equivalent to 50 mg of manganese, b.i.d., for a week, but without apparent benefit. Before she could try chelated manganese she became depressed, was hospitalized, and died suddenly of a stroke.

Case #4

This 25-year-old former college student, shipyard worker, and waiter had an acute anxiety attack in 1968. This was precipitated by poor diet and overdose of caffeine tablets while hitchhiking across the continent. Since then he has had frequent attacks of anxiety for no apparent reason. These have so confused and unnerved him that he developed agoraphobia. Psychoanalytic treatment failed to help him, and he became housebound and dependent on his parents.

When he consulted me in March, 1973, the family history of diabetes seemed important and the glucose-tolerance test confirmed this: it ranged from a high of 273 mg percent to a low of 46 mg percent. He almost fainted during the reactive hypoglycemia and this, by demonstrating to him a major source of his symptoms, cleared away some confusion. He improved greatly with dietary management, hypnotherapy, and eventually behavior therapy.

A moderate degree of tremor of the head on the neck was observed at the first examination: he was unable to hold his head steady for funduscopy. This had come on since he had been treated with thioradizine, 25 mg, t.i.d., for five years and with occasional doses of up to 200 mg. As a child he had neck tension after scarlet fever. This tremor was not improved by earlier treatment with diazepam. After discontinuing thioradizine he soon reported that he felt less mood depression and more freedom of movement; however the

tremor persisted and spread to involve his tongue and lips for several days.

Seven months later I prescribed manganese chelate, 10 mg, t.i.d. The tremor cleared up completely in five days. When he switched to another chelate providing only 8.4 mg of manganese per day the tremor returned. When the dose was raised once again to 30 mg per day the symptom vanished.

Case #5

This 20-year-old college student developed acute paranoid schizophrenia in June, 1973, and was hospitalized at a university psychiatric service in July. He was treated with fluphenazine, 10 mg, t.i.d., and benztropine, 1 mg, b.i.d. After two days he received intramuscular fluphenazine enanthate, 100 mg, and in two more days the oral dose was raised to 15 mg, t.i.d. Four days later a second dose of 100 mg was given by the intramuscular route. Four days later the benztropine was increased to 2 mg, b.i.d. The discharge summary indicates that on the day before benztropine was increased the patient began complaining of extrapyramidal symptoms and "the mother became obsessed with the patient's physical symptoms."

Two months later he was seen at my office. He still displayed a moderately severe impairment of extrapyramidal function. There was marked tremor, rigidity, and mask-like facies and akinetic gait and posture with limited arm swings. This was clearly an improvement from the "continuous twitchings" that he suffered for two weeks after he left the hospital. Diazepam, diphenhydramine, and niacinamide (1,000 mg, t.i.d.) had offered insignificant relief.

I prescribed manganese chelate, 10 mg, t.i.d., and also zinc chelate, 10 mg, t.i.d. After one day the tremor and rigidity were much improved. After two days he was entirely free of dyskinesia!

Incidentally his schizophrenia was associated with twice weekly use of marijuana for two years while at college. At the same time he ate poorly at a cafeteria. His mother had been treating

him with food supplements, wheat germ, megavitamins, and mineral supplements for two months before consulting with me. This may account for the relatively high manganese level in his hair, 1.0 ppm, the second highest among this series of patients.

Case #6

This 39-year-old divorcee was hospitalized most of the time from age 18 to 35 with a diagnosis of undifferentiated schizophrenia. She was treated with most of the phenothiazines but mostly chlorpromazine, averaging about 200 mg, t.i.d. Fluphenazine was also used more recently. Aside from hepatitis at age 17, there was no other history of illness. She was struck by a car at age 26 and sustained a back injury, but not a head injury.

In September, 1972, she consulted me on an emergency basis because of dyskinesic movements of her jaw and tongue two weeks after resuming chlorpromazine, 100 mg, up to six times a day. The dyskinesia was so severe that she broke several front teeth due to lateral movements. She also had marked tremor of both upper extremities.

Chlorpromazine was discontinued, and she was started on benztropine 2 mg per day, and oxazepam, 30 mg, t.i.d. The tongue and jaw movements were gone in a couple of days; however the arm tremor persisted, more noticeable in the right upper extremity and worse in the mornings. In the next month she experienced increasing nervousness and so she self-medicated with alcohol. She had to be hospitalized after a serious fall due to intoxication, and three weeks later went through a paranoid reaction that was probably related to alcohol withdrawal. She recovered from auditory hallucinations in two weeks, but her thinking processes were retarded and she was depressed for another four months.

Meanwhile the tremor persisted and accompanied by intractable nervousness that I

belatedly recognized as akathisia. A therapeutic trial on reserpine, 2 mg, b.i.d., had to be terminated in six days as she became more agitated and began picking at herself. Sedation with combined oxazepam, 30 mg, hydroxyzine, 25 mg, and meprobamate, 400 mg, t.i.d., partially calmed her and thus reduced tremor to a degree. Methylphenidate made her worse.

Manganese 21.4 mg per day offered slight relaxation in a week. After two months with only partial results halo-peridol was started, 1 mg, b.i.d. This promptly suppressed the severe compulsive skin-picking, and the tremor subsided slightly more. A few days later, treatment with niacinamide up to 1,000 mg, t.i.d., was associated with absent tremor, dramatic elevation of her mood, and within a week clearing of her sensorium. After two weeks lithium, 300 mg, b.i.d., was added to prevent hypomania, and her tremor improved a degree more. She used haloperidol, 1 mg only three times a week for spells of anxiety after that.

Six months later, in the setting of an unstable love affair, she began taking haloperidol every day rather than infrequently as before. In addition she smoked marijuana and began drinking moderately after abstaining for the previous year. In another six months she had gained 40 pounds. She requested help with weight reduction and, in order to keep her under close supervision, I prescribed the HCG program as this required that she appear daily for an injection. After three weeks she had not lost a pound. She now confessed that she had been drinking regularly for four months, and she complained of nervousness. Thinking that her troubles were simply due to alcohol I prescribed diazepam, 10 mg.

A few days later I was called to see her at the emergency hospital because she had taken most of the bottle in one day, not as a suicide attempt but to control the severe "nervousness" that had overtaken her. At a glance I saw that she had dystonic movements of jaw and tongue and facial grimacing. I hadn't realized

that she had been taking haloperidol, one or two per day until she ran out two weeks earlier. She also confessed that she had not taken her vitamins or manganese in over six months.

This time the dyskinesia proved to be severe and more resistant to manganese and niacin and heavy sedation (she improved when lithium was stopped as she had built up serum level of 1.95 mEq per liter) and close supervision for the next four months. After a month the oral dyskinesia subsided, leaving tremor and akathisia still in full force. After another month these relented, but she went into an inert depression, reluctant to do more than get out of bed. After another month she became extremely agitated and had to be hospitalized briefly. This may have been aggravated by personality conflict with her nursing companion since she calmed down almost at once in the hospital. After a few days she felt well for the first time, and in the next two weeks went on into a mild "high." Then she sank back into serious depression. She is now showing marked improvement in mood after resolution of her former alienation from her family.

During this second period of dyskinesia she showed improvement with manganese chelate, in that the tremor of her upper extremities stopped. Akathisia was severe at times when her depression became agitated, and she required intravenous diazepam or diphenhydramine for relief.

By July 9th she was started on Deanol in 100 mg doses. This was beneficial in relieving jaw movements, but it required frequent doses as the effect wore off within an hour. She said it reduced jaw movements, but that the manganese effect was even stronger because it stopped tremor. Codeine proved helpful in quieting her, but required doses of 60 mg, up to six times a day. Pentazocine, 100 mg, q.i.d., was even more effective in sedating her and relieving anxiety and akathisia. Methylphenidate, 5 mg, up to three times a

day, clearly aggravated the dyskinesia and the anxiety, and was quickly stopped.

Case #7

This 23-year-old former college student was hospitalized for 10 months in 1972 because of schizophrenia, undifferentiated type. He was treated with fluphenazine, 30 mg per day during that time, but he stopped taking it as soon as he was discharged because of the extrapyramidal effects. He had a previous hospitalization in 1968 for six months and was treated with chlorpromazine, 600 mg per day. Both episodes were preceded by his taking LSD.

In December, 1972, he consulted me for the first time. This was nine weeks after discharge from a state hospital, but he still had moderately severe extrapyramidal symptoms: mask-like facies, Parkinson's gait and posture, and resting tremor of thumb and forefinger. His thoughts were slowed, and his mood was very flat.

Initially he was treated with only 8.4 mg of manganese chelate per day in a vitamin-mineral supplement, and there was no improvement in two weeks. He showed prompt improvement, however, with additional manganese chelate, 5 mg t.i.d. The tremor promptly disappeared, posture and gait became normal, and facial expression returned. However mental dullness and flat affect did not improve until he started on niacin, 250 mg, t.i.d., three months later.

Nine months later he became attached to a girl. His depression gave way to a mild hypomanic mood. However she moved away and he then went overboard with alcohol, a repeat LSD trip, and poor diet without any supplements. He relapsed into schizophrenia, was hospitalized at a state hospital, and had a recurrence of dyskinesia on tranquilizers there.

Case #8

This 28-year-old Phi Beta Kappa, unemployed clerk consulted me in August, 1973, after 11 years of recurrent depression and agitation. He had been diagnosed as a schizophrenic, schizo-affective type, but has not had overt delusions or gross psychosis. He had six

electroconvulsive treatments at age 17, and since then has been on and off chlorpromazine and imipramine. Since mid-1973 he was maintained on chlorpromazine, 400 mg per day, and benz-tropine, 2 mg per day. During this time he became more depressed and increasingly agitated, particularly about his dwindling sexual function and frequent inability to achieve an erection or climax. Perverse fantasies were used to generate more sexual feeling, but they also increased his sense of alienation and ran counter to his self-image, hence aggravating his depression.

In October, 1973, another doctor started him on thiothixene, 15 mg per day, and in the next three months he became increasingly restless and unbearably "nervous." He interpreted this as guilt and depression and tried self-hypnosis and Transcendental Meditation without benefit. He improved remarkably after he was treated with manganese chelate, 15 mg, t.i.d., for three weeks in December. After having no erections for the preceding six months he now experienced up to seven orgasms per day. He rated himself as sexually the best in three years.

During the holiday season he discontinued the manganese and went on a careless diet with alcohol and marijuana to excess. In January he became restless, and he increased chlorpromazine to 400 mg per day and used methylphenidate to combat the oversedation. Within two weeks he was suffering with unbearable tremor and akathisia. Because he was taking 2 to 4 g of chloral hydrate during the daytime his doctor hospitalized him, stopped the chlorpromazine, and started him on haloperidol, 2 mg, t.i.d. After five days he was discharged only slightly improved and he became much worse when he increased the haloperidol to 5 mg, t.i.d. I diagnosed his akathisia, tremor, and leg movements as breakthrough tardive dyskinesia. He experienced an overnight cure on manganese

chelate, 15 mg, t.i.d.

However he continued taking chlorpromazine to sleep and, as the akathisia and tremor returned, he gradually built up to over 400 mg per day and became even more agitated as he felt himself backsliding. Rehospitalized under my care, I was forbidden to use vitamins and minerals in my treatment program at risk of expulsion from the medical staff! Nevertheless, the patient improved slightly in the hospital with imipramine and Tuinal and was discharged in two weeks on chlorpromazine, 100 mg, p.r.n.

At home he felt increasingly restless after a dose of chlorpromazine one morning. "It went away after I took manganese, 15 mg, three times that day, and by evening it was gone." After three weeks more he said he was no longer anxious or tense, but extremely depressed about the sexual preoccupation and relative lack of feeling. Niacin, up to 2,000 mg, t.i.d., was of no benefit. Self-hypnosis and Transcendental Meditation were of no benefit in dealing with depression at that time. Nevertheless, he was off chlorpromazine and on imipramine and then nortriptyline (Aventyl) without much benefit.

At this time cardiac catheterization studies showed the need for aortic valve replacement by open heart surgery. In June he underwent this procedure, tolerating it better than he expected. He resumed chlorpromazine, 200 mg per day since then, but says he is 80 percent recovered and feeling well at present (January, 1975).

Case #9

This 25-year-old college student has had three psychiatric hospitalizations since the age of 18 and suffers with persistent delusions about altered physical appearance, cancer, and vulnerability to mind reading. He has been treated with phenothiazines off and on for seven years and most recently with fluphenazine, 40 mg per day. When this dose was reduced to 20 mg per day he manifested a moderate degree of rigidity, parkinsonian facies and posture, akathisia and tremor at rest, particularly in the left foot.

After treatment with manganese gluconate, equivalent to 50 mg of manganese, t.i.d., he reported that the leg movements cleared up in two days but the tremor had increased in the left hand, making it difficult to write. He was switched to manganese chelate, 10 mg, t.i.d., and reported further improvement: the tremor of the foot was now absent and that of the left hand was barely perceptible. He remained on fluphenazine all the while, and I regard this as a breakthrough form of tardive dyskinesia, especially apparent as the dose of fluphenazine was reduced.

Two months later he abruptly discontinued taking fluphenazine on his own, but he continued on manganese chelate, 30 mg per day, and niacinamide, 900 mg per day, as he said that made his mind feel clear. He was restless for a week after terminating fluphenazine, but did not relapse into dyskinesia as I had feared. A later trial on niacin provoked a flush reaction at 100 mg, t.i.d., and above that dose he said he became mentally blank and "tranquilized."

Case #10

This 19-year-old college student was hospitalized at a state hospital from September, 1973, until mid-January, 1974, because of a paranoid schizophrenic disorder that occurred a year earlier after a prolonged period of inadequate nutrition and chronic, bloody diarrhea in Mexico. He was treated in the hospital with fluphenazine enanthate, 75 mg per week, mesoridazine, 50 mg, t.i.d., and thiothixene, 10 mg, q.i.d. Extrapyramidal symptoms were only partly controlled with trihexyphenidyl, 5 mg, t.i.d. He had moderate rigidity, mask-like facies, labored breathing, and foot tapping when first seen in January. There were no tongue or jaw movements; however he reported that on two occasions when he had eloped from the hospital he had to return because tremor and rigidity became incapacitating when he was off medications. Neurological evaluation at the hospital was

negative except that the electroencephalogram showed left temporal slowing on one occasion and bilateral frontal theta rhythm on another.

He consulted me a week after the last shot of fluphenazine, and I prescribed manganese, 10mg, q.i.d., and continued his other medications for nine days. There was little change in his condition so the thiothixene was stopped and mesoridazine and trihexyphenidyl reduced to b.i.d. only. Ten days later the tremor worsened and was associated with dry mouth, thirst, and diaphoresis. Manganese was increased to 20 mg, q.i.d., but the dyskinesia was even worse a week later with nausea, vomiting, salivation diaphoresis, and severe tremor of all his extremities at a rate over 300 per minute and amplitude of about two inches. The tremor was more marked on the right side. He could voluntarily stop the tremor for about 40 seconds, but it would recur at once with even greater intensity and spread to other areas. There were no movements of tongue, jaw, or face.

Because he could not walk without assistance or feed himself he was admitted to the hospital. He was given diphenhydramine, 50 mg, b.i.d., benz-tropine, 2 mg, b.i.d., and flurazepam, 60 mg, h.s. Manganese was discontinued because I feared that it might be aggravating his symptoms. Next day he was better, and after two days he was able to feed himself and so suppress the tremors for up to a minute. On the third day he was discharged, much improved, able to suppress the tremors for over a minute and on immediate repeat for another 13 seconds.

Within a few days the tremors relapsed. The reason is unclear. Since he began taking manganese again, 10 mg t.i.d., in achelate and 2.8 mg, t.i.d., in a multimineral, total 38.4 mg per day, I suspect that it might have aggravated the dyskinesia even though he was erratic about taking it.

Six weeks after the brief period of improvement and now nine weeks since termination of the fluphenazine, he was still disabled with severe dyskinesia, self-

rated as 60 percent as bad as when hospitalized for it. He now took a large initial dose of niacin, 500 mg, due to misunderstanding. This caused a strong flush reaction. It also vanquished the tremor almost completely within three hours. Disturbed by the flush he delayed resuming the niacin until the tremors gradually increased in the next four days. On resuming niacin at only 100 mg, t.i.d., the tremors disappeared almost 100 percent. In addition he reported that his mind was more alert and his initiative returned. He continued manganese chelate at 38.4 mg per day and increased niacin to 500 mg, t.i.d., and progressed to complete recovery within the next month.

Case #11

This 50-year-old divorced former tavern owner has had a manic depressive disorder for 10 years. Highs last about three days, and depressions last about six weeks. He was treated in 1964 with 22 electroconvulsive treatments and suffered significant memory loss as a result, he says. He has been hospitalized many times and maintained on fluphenazine, 10 mg per day, benztropine 2 mg per day, and lithium carbonate, 750 mg per day, for years. He appeared very depressed and fatigued at the initial visit in May, 1974, and had mild parkinsonism with limitation of an arm swing and a moderate tremor of the upper extremities at rest.

After treatment with manganese chelate, 10 mg, t.i.d., he reported decrease in tremor from the first day and his handwriting improved overnight. He felt better and looked better physically, even without improving his diet or taking other nutritional supplements.

Case #12

This 22-year-old college senior has had three hospitalizations because of schizophrenia in the past year and a half. The first of these occurred after a broken engagement. He

turned to marijuana and neglected his diet. The medical history was pertinent in that he had experienced episodes of mental confusion when playing varsity basketball. The electroencephalogram revealed bilateral frontal slowing to delta frequencies during hyperventilation.

At our initial visit in March, 1974, he had tremor in his arm and legs but not in his neck, jaw, or tongue. In addition there were mask-like fades, parkinson's gait and posture, and moderately severe rigidity. He had been treated with fluphenazine enanthate injections for three months, 25 mg per week. In addition he had been taking trifluoperazine, 10 mg, b.i.d., and benztropine 2 mg, b.i.d., for a month.

After 10 days off trifluoperazine and two weeks off fluphenazine and taking chlorpromazine, 50 mg h.s., the tremor was gone and rigidity was reduced. This was before he took manganese supplements. He did complain of blurred vision and dry mouth. After he was given manganese chelate, 8.4 mg, and zinc chelate, 15 mg per day, he reported that these latter symptoms were gone in three days and he could see well enough to read once again. In fact he felt so much better that he stopped taking chlorpromazine.

After another two weeks he experienced increased "nervousness," lasting for about two weeks even after niacinamide, 300 mg, t.i.d., and diphenhydramine, 50 mg h.s., were added. It was my impression that his nervousness represented withdrawal akathisia and that this resolved better than expected considering the extent of the initial symptoms. Was it a coincidence that his anticholinergic symptoms of blurred vision and dry mouth cleared up after he started on manganese?

Case #13

This 30-year-old, divorced mother of two has had multiple hospitalizations for schizophrenia since the age of 17. She has been treated with heavy doses of chlorpromazine much of the time until the past three years, during which time

she has had six hospitalizations and has been maintained on fluphenazine, 125 mg I.M., per week, and haloperidol, 110 mg, at bedtime.

When she first consulted me in June, 1974, she suffered with mask-like facies, Parkinson's gait and posture and oculogyric crises almost hourly in spite of treatment with benztropine, 6 mg, per day. She said that she had had severe spasms and tremors of her arms until she had started herself on B-complex vitamins, calcium, magnesium, niacinamide, and inorganic mineral salts two weeks earlier. "The only thing that keeps me together are the vitamins ... I'm much more relaxed now. Why do they have such a terrible drug on the market?"

She said that the eye-rolling improved markedly after she began taking vitamins, but that there were no further benefits from the inorganic Schuessler's salts, 6 tablets, q.i.d., added two weeks later. With the addition of manganese chelate, 5 mg, t.i.d., the oculogyric crises ceased almost completely in a day.

Interestingly, she reported that continued improvement occurred after she discontinued mega dose ascorbic acid after she discovered that a 1,000 mg dose would activate the eye movements!

Case #14

This 37-year-old divorced artist was hospitalized for almost a year at age 28 because of schizophrenia and depression. Treatment included trifluoperazine up to 100 mg, per day, and desipramine, chlorpromazine, and fluphenazine at various times. Finally she required 12 electroconvulsive treatments to dispel persistent suicidal ideation. She was maintained on trifluoperazine, 5 mg per day, ever since because when she had tried to discontinue it several times she experienced severe anxiety and interminable restlessness.

She consulted me in January, 1974, because of increased anxiety. Extrapyramidal disorder

was not obvious at that time. Six months later she returned because her anxiety was worsening. I considered her symptoms as possibly due to akathisia and recommended that she start taking manganese gluconate, 50 mg, t.i.d. She delayed doing so and then took it briefly and then stopped. Then the dyskinesia symptoms became more pronounced and she recognized her reaction as similar to when she had previously stopped trifluoperazine. Examination revealed moderate tremor of the extremities, cogwheel rigidity, greater on the right side, and moderately severe tremor of the tongue. She was restless, but there were no involuntary alternating movements of the lower extremities. Anticholinergic manifestations of dry mouth and blurred vision were also noted.

Trifluoperazine was discontinued and so was manganese, just to be sure that exposure to the large dose of gluconate was not to blame. Clearly it was not, because in the next 10 days the akathisia became more severe along with nausea, anorexia, and severe anxiety. This persisted for two weeks during which time she took no pills because of vomiting. Tremor returned, as well as marked rigidity and bradykinesia. Mentation became very retarded and mental imagery, once a vivid trait, was absent.

When manganese was resumed, 50 mg, 2x/day, the cogwheel tremor all but disappeared within two days. Rigidity and bradykinesia gradually dissipated in 10 days more. A trial on methylphenidate aggravated her agitation. Diazepam 20 mg, up to q.i.d., offered some relief of the sense of conflict that she described in her perception of simultaneous tremor and rigidity. Niacin, 500 mg, b.i.d., seemed to enhance her alertness a bit, but she exhibited a mental torpor for almost three months. Then she abruptly went into a state of excitement, with insomnia, and within a week relapsed into a severely confused schizophrenic psychosis. She is now maintained on trifluoperazine, 10 mg, b.i.d., and chelated manganese, 5 mg, b.i.d., and an additional 2 mg per day of manganese chloride in a multimineral. She has not

developed akathisia on this program so far after a month. Perhaps the manganese is protective, or the higher dose of trifluoperazine is suppressing what may be even worse trouble ahead.

Case #15

This 37-year-old former secretary consulted me in September, 1972, after eight years on trifluoperazine at doses ranging from 8 to 20 mg per day. Her schizophrenia became overt in 1961 after an abortive love affair, but did not become severe until 1964 when she was treated with streptomycin and isoniazid for tuberculosis. She recovered partially after electroconvulsive therapy and was started on trifluoperazine. She has been unable to get off this medication because every attempt brought on an episode of severe akathisia, jaw movements, and tremor of her hands followed by relapse of severe trigeminal neuralgia which has plagued her a few times a year since an episode of colitis in the midst of her initial illness in 1961.

She relapsed into psychosis in 1970, but in 1971 noted great improvement with megavitamin therapy. In particular she found that twice weekly injections of vitamin B12 made her feel calmer. Because of tremor and akathisia that subsequently broke through, even while on trifluoperazine, she was started on benztropine in 1971.

Although she did well on megavitamins, she actually felt better when doses were lowered by herself and readjusted at RDA levels of vitamins and minerals except for vitamin E, 400 units, and vitamin C, up to 12 g per day in case of neuralgia or recurrence of bronchitis or asthma that she has had since childhood. Unfortunately, after a few months of progress she placed herself on a starvation diet and lost 20 pounds in a month. This seemed to lower her resistance, and she had a flare-up of asthmatic bronchitis that persisted for over three months. Her neuralgia recurred, then pneumonia and then more neuralgia kept

her ill for much of the next six months until she moved to a sunnier climate.

Interestingly enough, the manganese level in her hair was a substantial 1.3 ppm in October, 1972, and then dropped to 0.2 ppm in May, 1973, after four months of continuous illness and weight loss of 23 pounds. In September, 1973, it was up to 1.6 ppm after a 60-pound weight gain since March. In November she felt better while losing 13 pounds on a ketogenic diet under my supervision. Neuralgia was then better controlled also, with chlorphenesin (Maolate).

Trifluoperazine was reduced at the initial visit to 4 mg per day along with benztropine, 2 mg per day. However she began "climbing the walls" and required more benztropine, 4 and even 8 mg per day. Two months later she tried to reduce the trifluoperazine to 2 mg per day, but the neuralgia recurred and on the average she maintained herself on 4 mg per day along with benztropine and diazepam, 20 mg per day.

Benztropine was discontinued altogether in March, 1973, and diazepam was reduced to 10 mg per day while trifluoperazine was switched to perphenazine (Trilafon). She became quite "nervous" and shaky, however, and had to be switched back to trifluoperazine, 4 mg per day. After 10 days the dose was reduced to 2 mg per day without the previously encountered withdrawal symptoms. At this time she was taking multimineral supplements providing 6.5 mg of manganese chelate per day and her diet was better as she was gaining weight following illness.

In October, 1973, trifluoperazine was again adjusted downward to 4 mg per day after three months at higher doses because of neuralgia. This time there were no withdrawal symptoms at all, evidently due to increased intake of manganese chelate, 5 mg, t.i.d., and 6 mg more in multimineral supplement for a total of 21 mg per day.

Author's Note: For most of the above cases I used Mn Plus and for some I used Mn chelate. Those wishing information on where these products may be obtained may write to the Canadian Schizophrenia Foundation, 2135 Albert Street, Regina, Saskatchewan, Canada S4P 2V1.

SUMMARY

1. Fifteen cases of withdrawal and tardive dyskinesia were treated with manganese chelate, and 10 of these with niacin or niacinamide also.
2. Review of frequency of occurrence and mechanisms of cause and treatment in drug-induced dyskinesia are discussed.
3. There were four cases (27 percent) of dramatic and almost immediate cure, after manganese treatment. In nine other cases (60 percent) definite improvement occurred in two to five days. Only one case was unresponsive to manganese treatment.
4. In one case unresponsive to manganese, niacin therapy was dramatically successful, associated with almost complete cure in a matter of hours.
5. In eight of nine other cases in which niacin was used it was associated with significant elevation of mood and clearing of sensorium. In seven of seven cases that also were treated with niacinamide similar clearing of sensorium was noted and, in two cases, significant improvement in extrapyramidal symptoms.
6. It is concluded that manganese appears to be of value in many cases of tardive and withdrawal dyskinesia.
7. It also appears that manganese may be of value in preventing the occurrence of tardive and withdrawal dyskinesia.
8. It is likely that niacin and niacinamide are of some value in many cases of drug-induced extrapyramidal syndrome.
9. More extensive and better controlled studies are needed to evaluate all of these observations and impressions.

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