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NEUROTOXIC REACTIONS RESULTING FROM CHLORPROMAZINE ADMINISTRATION

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and
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• Neurotoxic reactions were observed in 36 of 90 patients who received chlorpromazine over a period of about two months. The earliest findings were cogwheeling of the limbs and loss of associated movements. The latter together with rigidity of limbs and of face were most frequent. Tremor, skin changes, disturbances of gait, drooling, and general poverty of movement were also observed.

The syndrome resembled paralysis agitans. Patients of the hebephrenic type were especially susceptible, but intensity of symptoms was not strongly correlated with dosage or psychiatric improvement, and there was no relation to hepatic dysfunction.

Improvement generally occurred within a month of the time when administration of chlorpromazine was discontinued, but six patients still showed neurological signs 60 days or more thereafter.

Many recent reports on the use of chlorpromazine as a therapeutic agent in mental illness have stressed the occurrence of Parkinsonism as a toxic or side-effect of its administration. There have been variable findings about the incidence of this phenomenon, and some of the reports describe in neurological terms the general features of Parkinsonism while others simply use this term without amplification. It is the purpose of this paper to describe the development of neurological abnormalities resembling those seen in paralysis agitans (Parkinson's disease) in a group of chronic cases in semidisturbed schizophrenics at Agnews State Hospital who received chlorpromazine (Thorazine) for about two months. The term Parkinsonism refers to a specific group of neurological signs and symptoms resulting from lesions affecting the basal ganglions and substantia nigra. Some of the abnormalities in motor function observed in this study, though similar to Parkinsonism, are different from the classical signs of Parkinsonism. Therefore it is felt that a more appropriate term to apply to these phenomena is "neurotoxic reaction."

Some of the early reports by American investigators [1] do not mention neurotoxic complications of chlorpromazine administration. Even a paper given as recently as December, 1954,[2] makes no reference to the phenomena in a large series of patients. Anton-Stephens [3] described two patients considered to have had "overdosage" who entered a state of "dissociation," with bewilderment, incontinence, and, in one patient, perseveration of speech. In the other patient retardation almost to the point of mutism developed. With reduction of dosage these symptoms cleared by the 7th and 10 days respectively. Lehmann [4] stated in reference to this problem, "Patients receiving large doses of Chlorpromazine exhibit definite motor retardation, with an unsteady gait, while the facial expression becomes rather wooden and the general appearance resembles that of Parkinsonism but there is no muscular rigidity. With smaller doses these phenomena are less pronounced. There is usually marked drowsiness, which may increase to the point of somnolence. Deep and superficial reflexes may be unaltered or slightly depressed. . . . The effects of the drug persist for about 48 hours after termination of treatment." However, he does not give the incidence of the above abnormalities in a group of 71 patients.

Thiebaux [5] described three cases in which there was the appearance of "contracture," with cogwheeling, tremor, and disturbance of gait, speech, and salivation. These signs were found in varying degree in the majority of patients treated with chlorpromazine. The signs disappeared without sequelae as soon as the therapy was stopped in serious cases and terminated spontaneously during the course of treatment in mild cases. In 100 patients studied by Azima [6] the incidence of neurotoxic reaction was 4%. The patients developed "a syndrome resembling Parkinsonism" about the 21st day of administration, showing "generalized cogwheel rigidity, tremor,

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Chlorpromazine was supplied as Thorazine for this study by Smith, Kline & French Laboratories, Philadelphia.

masklike facies, and marked motor retardation." This syndrome gradually disappeared over a period of two months. Kinross-Wright [7] commented, "The development of Parkinsonism is an unexpected and intriguing phenomenon in a few patients. It recedes uneventfully when chlorpromazine is stopped. It may have profound neurophysiological implications but for practical clinical purposes is analagous to the moon face and hirsutism of Cushing's disease seen in some patients on adrenocortical hormones." His paper does not present any quantitative data regarding the incidence of Parkinsonism from the use of this drug.

A study by Goldman [8] of 500 patients receiving chlorpromazine reports that 54 showed a "paralysis agitans–like syndrome" and states, "The minimal manifestations are development of blank facies and some rigidity of the extremities, with a stooped posture. In others these symptoms are exaggerated and the characteristic pill-rolling tremor develops, with changes in gait and speech and salivation of varying degree." A later report by the same author [9] gives an incidence of 15%, the highest previously reported incidence to date, to our knowledge. Interestingly, Lehmann [10] stated that four patients with paralysis agitans had diminution of rigidity and reduction of frequency of tremor when given chlorpromazine, and four patients with choreoathetotic movements responded with a reduction of involuntary movements. Goldman [9] reported improvement in patients with hereditary chronic progressive chorea with mental deterioration (Huntington's chorea) who received this drug.

Methods

This report arises from a controlled double-blind investigation of the therapeutic efficacy of chlorpromazine in the treatment of chronic cases in semidisturbed schizophrenics. The psychiatric aspects have been discussed elsewhere.[11] Early in the study evidence of neurotoxic reactions was noted in a few patients simply by observation of gross changes in their motor behavior, especially gait and related motor functions. Neurological examinations were not done on any of the patients in the period immediately preceding the administration of the medicament; however, the development of signs and symptoms of neurotoxic reaction, with progression during continued administration of the drug, and, in general, abatement with reduction or termination of dosage, usually made the relationship of these abnormalities to chlorpromazine administration quite definite. Some of the milder, and especially the equivocal cases, of neurotoxic reaction could have been more adequately evaluated if premedication examinations had been done.

Ninety patients (including three not reported in a previous paper [11] due to incomplete psychological studies) in this study received chlorpromazine in varying dosages over a period of 64 to 66 days. Dosage was gradually increased in all patients in a similar manner and usually was constant during the last half of the period of administration. All patients showing any evidence of possible neurotoxic changes, as noted by ward nurses, technicians, or physicians, were given detailed neurological examinations by one or more of the staff physicians, and if neurological abnormalities were detected they were descriptively recorded. Subsequent examinations were performed at intervals on each patient showing neurotoxic reactions. The histories of these patients were reviewed for evidence of any previous central nervous system disturbances. Cerebrospinal fluid examination was performed on 26 patients who showed neurotoxic reactions.

The neurological signs appearing in each patient who showed neurotoxic reactions were tabulated, and each sign was rated according to severity from one to four plus, corresponding to equivocal, mild, moderate, and severe. Severity was rated relative to the neurological signs seen in this group of patients and not in terms of the severity of such or similar signs seen in patients with classical Parkinsonism. An over-all rating of degree of neurotoxic reaction, using the same four grades of severity, was given to each patient by taking into consideration the number and severity of neurological abnormalities exhibited. Other data were obtained from each patient's records and studied with regard to the appearance, abatement, persistence, or worsening of the neurotoxic condition.

TABLE 1.—*Initial Signs of Neurotoxic Reactions*

Signs	Patients	
	No.	%
Cogwheeling of limbs	24	66
Loss of associated movements	23	64
Rigidity of limbs	17	47
Facial rigidity	14	39
Tremor	12	33
Skin changes	6	17
Gait disturbances	3	8
Drooling	3	8
Poverty of movement	2	5
Impaired convergence	0	0

Results

Thirty-six patients (40%) developed evidence of neurotoxic condition. The initial signs noted in these patients include one or more neurological abnormalities first noted by any of the hospital personnel and confirmed by neurological examination. The frequencies of these initial signs are given in table 1. Cogwheeling of the limbs, usually the arms, was one of the several initial signs in 23 patients, and it was the only initial sign in one patient. It is felt that evaluation of the presence of slight cogwheeling is quite difficult, especially in severely psychotic patients whose ability to cooperate for this examination is often impaired. Loss of associated movements while walking was the initial sign in 23 patients. This was manifested by reduction or loss of arm swing or head and neck movements while walking and turning. Many of the patients showing loss of arm swing held their arms semiflexed but out some distance in front of their bodies, with their forearms and hands projecting horizontally in front of them in a peculiar fashion. This positioning, suggestive of catatonic posturing but disappearing after the treatment was withdrawn, was often maintained whether the patient was sitting, standing, or walking. However, voluntary movements were fairly readily accomplished (usually with slowness and poverty of movement), with a return to this unusual posture when the voluntary act was completed. Loss of associated movements occurred as an initial sign only in association with one or more other signs.

Rigidity, usually of the arms, occurred as an initial sign in 17 instances but never as a single initial sign. It was usually "leadpipe" in nature. Again the difficulty in assessment of this sign in psychotic patients is worthy of mention. Cogwheeling and rigidity usually were found together, but there were a few instances of either occurring in the absence of the other and persisting in that manner throughout the duration of neurotoxic signs. In view of the unclear relationship of cogwheeling, tremor, and rigidity in classical Parkinsonism, it should be pointed out that tremor also occurred at times in the absence of the other two signs. Facial rigidity was present as a single initial sign in only one patient and occurred in association with other signs initially in 13 other cases. This rigidity varied from mildly impaired facial mobility with reduction of frontalis muscular action to severe rigid mask-like facies.

TABLE 2.—*Frequency of Neurotoxic Signs*

Signs	No. of Patients, by Severity Rating *				Total	
	++++	+++	++	+	No.	%
Loss of associated movements	12	11	7	2	32	89
Rigidity of limbs	0	8	22	2	32	89
Cogwheeling of limbs	1	4	19	5	29	80
Facial rigidity	5	13	7	0	25	69
Tremor	0	2	12	5	19	53
Poverty of movement	1	6	5	0	12	33
Skin changes	0	7	5	0	12	33
Gait disturbance	1	4	4	0	9	25
Drooling	1	3	2	0	6	17
Impaired convergence	0	2	1	0	3	8

* + = equivocal, ++ = mild, +++ = moderate, and ++++ = severe.

TABLE 3.—*Over-All Severity Rating of Neurotoxic Reactions*

Severity *	Patients	
	No.	%
++++	10	28
+++	8	22
++	14	39
+	4	11

* + = equivocal, ++ = mild, +++ = moderate, and ++++ = severe.

Tremor of the hands occurred as one of the presenting signs in 12 patients and eventually developed in 7 others. In 3 of these 19 patients an estimate of the rate, whether rapid or slow, was not specified. Ten patients showed a slow tremor of approximately the rate seen in Parkinsonism, i. e., 4 to 8 cps. None of these patients showed a classical "pill-rolling" tremor. Six patients exhibited a more rapid tremor that was less often present at rest, usually being evident on fine movements and positioning of the hands. Present initially in six patients, skin changes consisted of an oily or greasy facial skin, especially on the forehead, with at times a scaly to waxy change of the skin in this area. A few patients had a rather exudative waxy substance on their foreheads that would rub off, with pressure, on the examiner's finger.

Gait disturbances included variations of stooped, rigid posture with flexed head, shuffling steps with forward-leaning, "turning in one piece," and slowness of movement, besides the previously described loss of associated movements. Drooling was a phenomenon that occurred in only six of the patients, and it was severe in one case and moderate in three. The fluid was of a quite viscous, stringy or ropy consistency, and the patient with severe drooling had to carry a towel constantly to absorb the copious flow. Poverty of movement was the slow, deliberate, rather hesitant performance of voluntary motor acts. Impaired convergence was found in only three patients but is another sign that is difficult to elicit in a group of patients such as this. When found, it disappeared after chlorpromazine therapy was discontinued.

TABLE 4.—*Duration of Neurotoxic Reactions*

Days Beyond Cessation of Therapy	No. of Patients		
	Clear of Signs	With Persisting Signs	
		Questionable	Definite
0- 9	5	..	..
10-19	9	..	..
20-29	6	..	..
30-39	3	..	1
40-49	1	1	..
50-59	..	1	..
60-69	..	2	3
70-79	..	..	1
80-89	..	..	2
90-99	..	1	..

Table 2 lists the frequency of the above-discussed signs throughout the entire period of observation. It can be seen that the frequency of occurrence approximately parallels the frequency as an initial sign. A rating of the severity of each sign is included and shows, for example, that, of the 32 patients having impairment of associated movements, 12 had complete absence of arm swing (severe, or 4+). It is felt that this latter sign is rather a sensitive indicator of a neurotoxic reaction to chlorpromazine therapy. As shown in table 3 the over-all degree of neurotoxic reaction in 18 patients (50%) was rated as moderate or severe. Since manifestations of neurotoxic reactions were an unexpected development during the study, the onset of symptoms was not recorded with exactness in each instance. As closely as could be determined, the onset of neurotoxic reactions occurred in 3 patients between 20 and 29 days after starting treatment, in 11 between 30 and 39 days, in 11 between 40 and 49 days, in 5 between 50 and 59 days, in 5 between 60 and 69 days, and in one between 80 and 89 days. In one patient, it was not until 17 days after the treatment was stopped that signs of neurotoxic reaction were detected, and they were questionably present 93 days after completion of the administration of the drug.

TABLE 5.—*Dosage at Onset of Neurotoxic Reactions* *

	Mg./Day					
	150	225	300	375	450	600
Patients with neurotoxic reactions	1	1	2	1	19	8
Patients with no neurotoxic reactions †	2	5	6	4	26	5

* Four neurotoxic dosages missing, six non-neurotoxic dosages missing.
† Modal dosage during last four weeks of treatment.

The duration of neurotoxic reaction is shown in table 4. Twenty patients (56%) were free of signs within 29 days after the medication was stopped; however, six patients (17%) showed definite persisting neurological abnormalities 60 days or more after completion of drug administration. The daily dose of chlorpromazine at the time of onset of neurotoxic reactions is recorded in table

5. Also listed are the dosages of patients who did not develop neurotoxic reactions, the value recorded being the modal dosage in the last four weeks of treatment. Statistical analysis reveals only a weak association of neurotoxic reactions with dosage (Kendall's [11a] $\tau = 0.166$), despite the apparent trend in that direction. The incidence of neurotoxic reactions in the hebephrenic subgroup, as noted in table 6, indicates that this group has

TABLE 6.—*Diagnosis*

Classification	Patients: With Neurotoxic Reactions No.	%	Without Neurotoxic Reactions No.	%
Schizophrenic reaction				
Chronic undifferentiated type	6	26	17	74
Catatonic type	4	36	7	64
Hebephrenic type	14	61	9	39
Paranoid type	11	35	20	65
Without diagnostic type designated	..	..	1	..
Manic-depressive reaction				
Depressed type	1	..	..	..

a greater susceptibility to neurotoxic reactions. This was statistically significant ($p < 0.02$ [chi-square test]). Study of dosage versus diagnosis does not seem to indicate that hebephrenics received higher dosage, and we found no other ready explanation for this interesting association. Table 7, correlating age with neurotoxic reactions, suggests that the age group from 40 to 49 might be less susceptible to neurotoxic reactions than the others, but this is not statistically significant ($p < 0.20$ [chi-square test]).

Twenty-six patients showing neurotoxic reactions and 11 patients on placebo therapy were given spinal fluid examinations. There was no significant difference in the cell count, total protein level, or gold curve of the spinal fluids of the two groups. However, 13 (50%) of the patients with neurotoxic reactions had elevated spinal fluid pressure (greater than 180 mm. H_2O, in horizontal position), while only 2 (18%) of the patients receiving placebos had this finding. The difference is statistically significant ($p < 0.02$). Prior somatic therapy, including insulin, pentylenetetrazol (Metrazol), electric convulsive therapy, and prefrontal lobotomy, had no statistically significant effect on susceptibility as far as can be determined in our sample. The relation of neurotoxic reactions and improvement of mental illness was investigated. Improvement was taken as estimated by psychiatrists and a psychologist. In the case of the psychologist, who was less aware of the neurotoxic conditions than the psychiatrists, no significant association was observed (Kendall's τ). The association exhibited by the psychiatrists' evaluation was weak but just statistically significant at the 5% level (Kendall's τ). The evidence that neurotoxic reaction is associated with degree of improvement is thus weak and equivocal.

Report of Cases

CASE 1.—A 42-year-old white man, admitted in 1938 and continuously hospitalized because of schizophrenic reaction, hebephrenic type, had received electroshock treatment without significant improvement and in recent years had become more aggressive and assaultive. On Dec. 11, 1954, administration of chlorpromazine therapy was begun. On the 50th day of treatment he was noted to have possible diminution of arm swing and mild cogwheel rigidity of the arms was found. Daily dosage of chlorpromazine at that time was 450 mg. Dosage was maintained at the same level, and there was no change in his neurological signs during the remaining 14 days of chlorpromazine administration. Four days later neurological examination showed no evidence of the previous signs. This case is described as an example of an equivocal neurotoxic reaction.

CASE 2.—A 46-year-old white man entered Agnews State Hospital in July, 1951, having been previously hospitalized twice for mental illness. A diagnosis of schizophrenic reaction, paranoid type, was made. On Dec. 11, 1954, he was started on chlorpromazine therapy and 51 days later was found to have mild impairment of associated movements, a mild slow tremor, and moderate cogwheeling of the arms. He was receiving 600 mg. of chlorpromazine daily at that time, and this dose was continued for the remaining 13 days of administration. Five days after therapy was stopped there was slight diminution of arm swing only, and two weeks later associated movements were normal. He was rated as showing mild neurotoxic reactions.

CASE 3.—A 41-year-old white man had been hospitalized since 1938 with schizophrenic reaction, hebephrenic type. On Dec. 17, 1954, chlorpromazine therapy was started. Forty-five days later he was found to have reduced associated movements, facial rigidity, and rigidity of the arms. Daily dosage of 600 mg. of chlorpromazine therapy was continued for 20 days, and the patient's signs progressed to almost complete absence of arm swing when walking, rather mask-like facies with greasy facial skin, moderate impairment of convergence, and moderate cogwheeling and rigidity of the arms—primarily the wrists and elbow flexors. He also developed nystagmus on lateral gaze to either side. He was rated as showing moderate neurotoxic reaction. Fifty-nine days after chlorpromazine therapy was discontinued he still exhibited diminished arm swing and equivocal rigidity of his arms and was considered as having questionable persisting signs of neurotoxic reaction.

CASE 4.—A 40-year-old white woman had been hospitalized since 1951 with a diagnosis of schizophrenic reaction, hebephrenic type. On Dec. 31, 1954, she was started on chlorpromazine therapy. Sixteen days later she developed reduction of arm swing, tremor, and cogwheeling of her limbs. Daily dosage was 300 mg. of chlorpromazine. Her signs progressed, with complete loss of arm swing, rigid facies, moderately severe slow tremor, and severe cogwheel rigidity of her arms. She was classed as showing severe neurotoxic reactions, and when dosage was diminished there was reduction in severity of her neurological signs. Thirty-seven days after chlorpromazine therapy was completed all of these signs had cleared.

TABLE 7.—*Correlation of Age and Neurotoxic Reactions*

Age, Yr.	Patients: With Neurotoxic Reactions No.	%	Without Neurotoxic Reactions No.	%
20-29	3	43	4	57
30-39	12	57	9	43
40-49	10	30	23	70
50-59	11	40	17	60
60-69	0	0	1	100

Comment

The incidence of neurotoxic reactions as determined in this study is much greater than has previously been reported, though smaller dosages of chlorpromazine were used in this project than have been given in many similar investigations. Also, we find no significant association of dosage and neurotoxic reactions within the dosage range used. It is possible that closer attention to the detection of any of these abnormalities was given by us; yet a systematic neurological evaluation of every patient who

received the drug was not performed. Furthermore, it is felt that the use of the double-blind method in this study gives reliability to our findings. Only three patients receiving placebos showed signs interpreted as evidence of chlorpromazine neurotoxic reactions, two patients having been rated as equivocal. The third patient died during the course of the study, with symptoms of central nervous system pathology including signs of extrapyramidal system dysfunction.

The neurotoxic reactions occurring with this drug can best be described as a "Parkinson-like syndrome," but with differences from the classic Parkinsonism as previously described. Extrapyramidal motor system dysfunction is certainly apparent and seems correlated with increased cerebrospinal fluid pressure. However, no pathological studies are available for study with regard to possible morphological changes within the central nervous system. The possible relationship of the manifestations of neurotoxic reaction to a subclinical impairment of liver function, as suggested by others,[12] has been considered by us. Many of the patients who were found to demonstrate signs of extrapyramidal system dysfunction were studied for evidence of liver disorder by means of liver function tests and needle biopsy, the findings of which will be fully reported in a subsequent communication. There appears to be no positive correlation between neurotoxic reactions and liver dysfunction. On the other hand, the clearly increased association of neurotoxic reactions with the hebephrenic subtype in our sample seems to deserve further investigation and explanation. Since hebephrenics are perhaps the "most schizophrenic of schizophrenics" one might speculate whether the still somewhat hypothetical organic predisposition to this disease might also predispose to neurotoxic reactions. It would be interesting to know if nonschizophrenic patients have the same susceptibility to neurotoxic reactions. Some stress might be given to the fact that we found only a weak and equivocal association of neurotoxic reactions with psychiatric improvement. Considerable emphasis has been placed on such an association by discussants during two recent conferences on chlorpromazine.

Summary

Of 90 patients who received chlorpromazine (Thorazine) for about two months, 36 (40%) showed evidence of neurotoxic reactions. The neurological abnormalities that were noted can best be described as a "Parkinson-like syndrome." Six patients showed persisting neurological signs 60 days or more after administration of the drug was completed.

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CLINICAL NOTES

ORGANIZATION OF A FLUID AND ELECTROLYTE BALANCE SERVICE

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The importance of an adequate study of fluid and electrolyte balance in patients is slowly but surely being recognized by the medical profession. Such studies not only may save the lives of critically ill patients but will prevent patients from becoming seriously ill as a result of a gradual accumulation of small daily deficits or excesses in fluids and electrolytes. The more general use of such studies is still being seriously retarded because of several factors, particularly in smaller hospitals. Now, with the availability of the flame photometer with which sodium and potassium levels are readily determined, the average hospital laboratory can perform the necessary tests rapidly, accurately, and economically. However, the greatest deterrent to the use of such studies is probably that the subject seems too overwhelming for the average busy practitioner and that the set-up of a fluid and electrolyte service sounds like too formidable an undertaking. This is particularly true in small hospitals, where the volume of work does not warrant the fine type of service described by Statland.[1] Nickerson [2] has written a pamphlet that is helpful in organizing such a service. A fluid and electrolyte balance service has been put into operation at St. Luke's Hospital. It was set up to make its use as convenient and simple as possible for the attending physician as well as for the nursing and laboratory services.

Organization of the Fluid and Electrolyte Service

To keep a fluid and electrolyte service operating smoothly and efficiently, it is necessary first of all to have available instructions for all the interested services. Secondly, after all the data have been recorded on the fluid and electrolyte balance sheet, the most important step is the final analysis of the data, the evaluation of the patient, and the ordering of more fluids, electrolytes, and other necessary medicaments by the attending physician or intern. It is fully realized that there is a great need for readily available information about this complicated

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