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Relapse in Chronic Schizophrenics following Abrupt Withdrawal of Tranquillizing Medication*

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Physicians are often faced with the problem of determining whether long-stay schizophrenics require continuous treatment with tranquillizers. Prolonged ingestion of ataractics has both physical and economic disadvantages. Recent reports on oculo-cutaneous changes (3, 13, 20, 27, 28), persistent dyskinesia (6, 18) and sudden deaths (16, 25) have focused attention on the potential dangers of prolonged use of tranquillizing medication. On the other hand, discontinuation of medication may lead to recurrence of acute psychotic behaviour. The literature on drug withdrawal provides no solution to the dilemma. The results from drug discontinuation studies are complex and contradictory. Some investigators report extremely high relapse rates while others report little deterioration even when drugs are withdrawn for long periods of time. A brief review of the literature will give some indication of the contradictory nature of results.

Most drug withdrawal studies were patterned after a study of Good, Sterling, and Holzman (12). Active medication was abruptly withdrawn and a placebo was substituted, usually for a period of three to six months. A few studies deviated from this model. Caffey *et al.* (5) and Garfield *et al.* (10) gradually reduced dosage before withdrawing active medication. Caffey reported a high incidence of deteriorated behaviour and Garfield a low incidence over a four-month period. Olson and Peterson (22) and Judah, Josephs, and Murphee (19) did not substitute placebo after withdrawing medication. Both reported substantially higher relapse rates than most of the investigators using placebo. However, Whitaker and Hoy (29) used both placebo and complete withdrawal of all pills in the same study and found no difference between the two treatments.

The least favourable report on drug discontinuation was that of Olson and Peterson (22) who withdrew phenothiazines from 127 chronic schizophrenics. By the end of six months, 74 per cent. of the patients had deteriorated to a point requiring resumption of medication. Judah *et al.* (19) removed medication from 519 chronic schizophrenics for 90 days; during this period 72 per cent. of the patients had to be returned to medication because of regressed behaviour. Zeller (31) interrupted chlorpromazine and reserpine treatment for one month in 40 psychotic patients, and found that 68 per cent. relapsed. Whitaker and Hoy (29) withdrew perphenazine from 39 long stay schizophrenics. Approximately 40 per cent. required the drug within 10 weeks. Caffey *et al.* (5) found that 45 per cent. of 171 male chronic schizophrenics on placebo had to be returned to active medication during a 16 week study period. Blackburn and Allen (2) reported a similar relapse rate, 43 per cent., over a four-month period. Brooks (4) reported significant regression within a month following withdrawal of medication.

In contrast, five investigators report relatively little regression resulting from phenothiazine withdrawal. Freeman and Alson (9) removed

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medication from 48 chronic male psychotics for a period of six months and found that only 27 per cent. required resumption of medication. At the end of three months, only 13 per cent. of the patients had relapsed. Garfield *et al.* (10) administered placebo to 18 female chronic schizophrenics. Only 22 per cent. had to be returned to active medication during a five-month study period. Good *et al.* (12), using a sample of 112 chronic schizophrenics, concluded that chlorpromazine could be withdrawn for a period of three months without any noticeable regression in behaviour; though withdrawal for longer periods produced a significant increase in pathology. Rothstein (26) also reported that medication could be withdrawn for three months without significant increase in pathology. Finally, Hughes and Little (17) withdrew chlorpromazine from 21 female psychotics and found that only 19 per cent. had to be returned to medication during an 18-month period.

Efforts to identify patients who can tolerate long periods off medication have not been very successful. Denber and Bird (7) found that probability of relapse was related to severity of illness but not to length of hospitalization or clinical diagnosis. Winkleman (30) suggested that patients on medication long enough to achieve ego reorganization were less likely to relapse when drugs were discontinued. Freeman and Alson (9) found that sicker patients, particularly those who were confused or apathetic, were poorer risks for discontinuation. Diamond and Marks (8) also reported that withdrawn patients seemed to require tranquillizers more than patients in whom thinking disorders predominated. On the other hand, Caffey *et al.* (5) found no evidence to show that probability of relapse was related to clinical diagnosis, duration of illness, length of hospitalization, or length and amount of previous medication. Judah *et al.* (19) reported that clinical diagnosis, length of illness, and duration, dosage or type of drug were not factors affecting relapse. Finally, Good *et al.* (12) and Brooks (4) found no relationship between relapse and dose or type of previous tranquillizing medication.

In summary, the studies on drug withdrawal provide widely differing results. Even where the study designs appear quite similar, results are often strikingly different. Judah *et al.* (19) and Rothstein (26) suggest that part of this difference may be due to environmental effects. In particular, tolerance for deterioration may vary considerably from hospital to hospital and conceivably from ward to ward. A study by Rathod (24) comparing two wards on which discontinuation was carried out appears to support this view. Studies by Hamilton *et al.* (14, 15), Barrett *et al.* (1), Goldsmith and Drye (11) and Meszaros and Gallagher (21) also suggest that drug effect is related to treatment milieu.

The present study will investigate the effects of withdrawing ataractic medication from long stay schizophrenics at a number of hospitals. One purpose of this investigation was to determine whether hospital setting is an important variable affecting probability of relapse. A second purpose is to determine whether probability of relapse is related to patient and medication variables, such as length of hospitalization, age, severity of illness, and type and dose of previous medication.

Method

This investigation of drug discontinuation was part of a multi-hospital collaborative study on the relative effectiveness of various dose levels of phenothiazines in the treatment of chronic schizophrenic patients. The collaborative study was developed under the National Institute of Mental Health (NIMH) psychopharmacology programme. The general background of the project, the details of the research design, and the characteristics of the samples are presented elsewhere (23). A summary of the research design is provided here for orientation.

Seven public mental hospitals participated in this study: Boston State Hospital, Boston, Massachusetts; Broughton State Hospital, Morganton, North Carolina; Dorothea Dix State Hospital, Raleigh, North Carolina; Kentucky State Hospital, Danville, Kentucky; Manhattan State Hospital, New York, New York; St. Louis State Hospital, St. Louis, Missouri; and Springfield State Hospital, Sykesville, Maryland. These hospitals were selected to represent the entire urban–rural continuum. Three hospitals admitted patients exclusively from large urban centres, two hospitals served both urban and rural communities, and two hospitals served almost exclusively rural areas.

Approximately 120 chronic schizophrenics, half male and half female, were selected at each of the

...ls by the following criteria:
...mary diagnosis of schizophrenia.
...tween 19 and 55.
...inuous hospitalization of at least two

...idence of organic brain disease, lobotomy,
...l deficiency (IQ below 70), or medical
...tions contra-indicating the use of high

...an age of the patient sample was 41·6
...r cent. being over 40 years of age. Length
...ization ranged from 2 to 34 years, with
...14·5 years. 54 per cent. of the patients had
...italized over ten years.
...s were randomly assigned to one of four
...(1) high dose—2,000 mg. of chlorpromazine
...(2) low dose—300 mg. of chlorpromazine
...(3) placebo; and (4) physician's choice,
...of whatever medication or dose the
...chose to administer. Each treatment group
...of approximately 210 patients, 30 from
...pital.
...nts were observed on their normal hospital
...on for eight weeks. At the end of this eight-
...eline period, patients who had been assigned
...dose, and placebo were shifted to study
...ion. All medication was administered in
...rm under double-blind conditions. Patients
...ntained on their assigned treatment for
...ks.
...atient was considered relapsed if he regressed
...d to be returned to known medication before
...d of the 24-week period. The decision to termin-
...dy medication was usually made jointly by the
...al investigator and the treatment physician.
...returned to known medication patients were
...d at the discretion of the responsible physician.
...clinical status of the patient was assessed in
...ways. First, doctors made overall clinical judg-
...of severity of illness and degree of improvement.
...ad, specific psychopathology was rated by
...rs, nurses, and social workers. All patients were
...ated just before the study and at eight-week
...vals during the study period. Patients terminated
...e the end of 24 weeks were evaluated at the time
...left the study.

Results

The placebo group had a significantly higher
...pse rate than the groups receiving active
...dication. Forty per cent. of the placebo
...ients relapsed, compared to only 13 per cent.
...the low-dose patients and 6 per cent. of the
...h-dose patients. Chi square analyses showed that the differences between placebo and each of the groups were significant at the ·01 level. The remainder of this paper will deal primarily with placebo results. Detailed results for the other treatment groups are presented elsewhere (23).

Fig. 1 shows the cumulative percentage of placebo patients who relapsed at various periods during the study. It may be seen that very few relapses occurred during the first six weeks on placebo. Most relapses, 72 per cent., occurred between week 6 and week 16. Relapse was generally characterized by the return of hallucinations, delusions, and confusion, or by disrupting symptoms such as extreme hostility, excitement, and threatening or destructive behaviour.

Probability of relapse was significantly related to the dose of tranquillizing medication the patient was receiving before he was put on placebo—the higher the dose the greater the probability of relapse. Fig. 2 shows the cumulative percentage of relapses for patients on three dose levels of pre-study tranquillizing medication, "low" (under 300 mg./day), "moderate" (300 to 500 mg./day), and "high" (over 500 mg./day).* Only 18 per cent. of the 65 patients on low doses of pre-study medication relapsed when medication was withdrawn. In contrast, 47 per cent. of the 60 patients on moderate doses and 58 per cent. of the 53 on high doses relapsed when drugs were withdrawn. Chi square analyses showed that the difference in relapse rate between low dose and each of the other dose levels was highly significant ($p < ·01$). There was no significant difference between moderate and high dose ($p > ·05$). Fig. 2 also gives the relapse rate for patients who received no tranquillizing medication prior to the study. Only one of the 18 patients, 6 per cent., failed to complete the full 24 weeks on placebo.

Younger patients (i.e. patients under 40) had a higher relapse rate than older patients. However, this was due to the fact that younger patients were receiving higher doses of tranquillizing medication before the study. Table I shows the relationship between dose of

* All doses of pre-study tranquillizing medication were converted to equivalent doses of chlorpromazine.

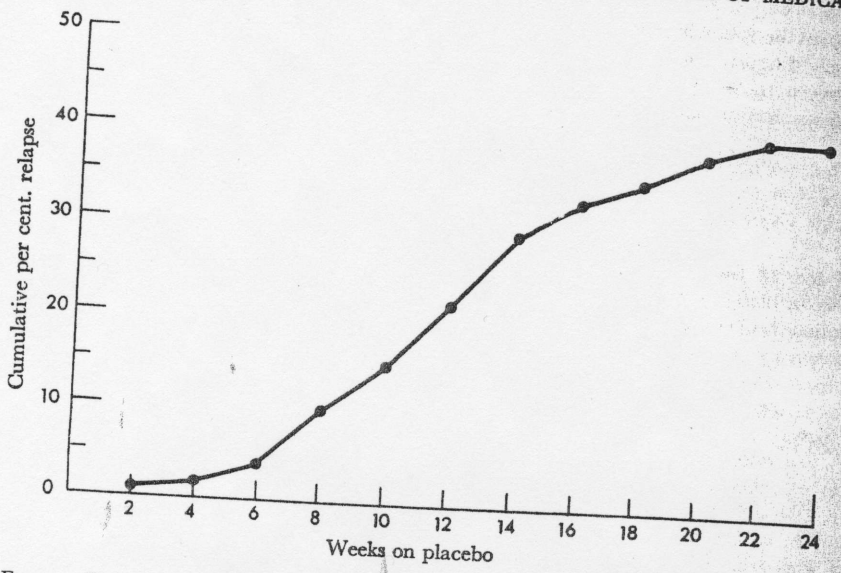

FIG. 1.—Relapses on placebo (includes only patients receiving tranquillizing medication before the study).

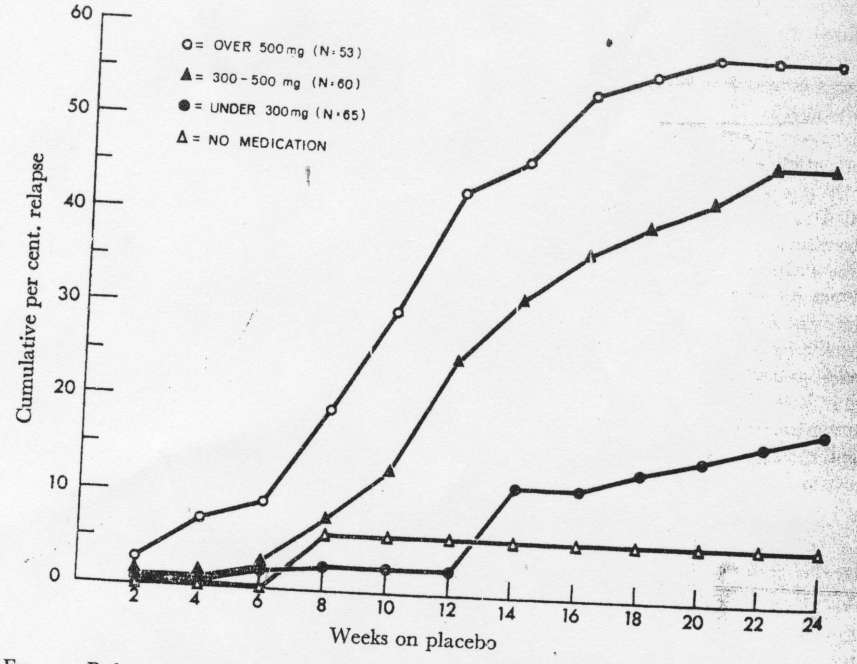

FIG. 2.—Relapses on placebo: by dose of pre-study tranquillizing medication (all doses were converted to equivalent doses of chlorpromazine).

TABLE I

Relapses on Placebo: By Age and Dose of Pre-study Tranquillizing Medication

Daily dose of pre-study medication*		Age in years Under 40	40–49	Over 50
Under 300 mg.	Total N	10	35	20
	N relapsed	2	5	5
	% relapsed	20	14	25
300 mg. and over	Total N	49	48	16
	N relapsed	28	22	8
	% relapsed	57	46	50
All doses	Total N	59	83	36
	N relapsed	30	27	13
	% relapsed	51	33	36

* All doses were converted to equivalent doses of chlorpromazine.

TABLE II

Relapses on Placebo: By Hospital and Dose of Pre-study Tranquillizing Medication

Daily dose of pre-study medication*		Hospitals A	B	C	D	E	F	G	Total
No medication	Total N	2	2	4	2	2	2	4	18
	N relapsed	0	0	1	0	0	0	0	1
	% relapsed	0	0	25	0	0	0	0	6
Under 300 mg.	Total N	4	8	7	11	8	12	15	65
	N relapsed	1	2	1	2	2	2	2	12
	% relapsed	25	25	14	18	25	17	13	18
300–500 mg.	Total N	11	10	7	7	10	8	7	60
	N relapsed	8	6	4	3	3	3	1	28
	% relapsed	73	60	57	43	30	38	14	47
Over 500 mg.	Total N	10	10	9	9	6	6	3	53
	N relapsed	8	6	6	6	3	2	0	31
	% relapsed	80	60	67	67	50	33	0	58
All doses	Total N	25	28	23	27	24	26	25	
	N relapsed	17	14	11	11	8	7	3	
	% relapsed	68	50	48	41	33	27	12	

* All doses were converted to equivalent doses of chlorpromazine.

study medication and age. There was no significant difference in relapse rate between the ous age groups within each dose level. This cates that dose, not age, was the critical or affecting relapse.

able II gives the number and percentage of psed patients at each hospital. It may be that relapse rate varied considerably ng hospitals, ranging from 12 per cent. to er cent. (the probability is less than ·01 this distribution of relapse rates could occurred by chance alone). The greatest rence between hospitals occurred with patients receiving moderate or high doses of pre-study medication. The relapse rate for patients on low doses of pre-study medication was relatively low at each hospital.

Patients classified as "relapsed" were not the only patients to show clinical deterioration. Approximately 20 per cent. of the patients who completed the full 24 weeks on placebo also regressed,* though not severely enough to warrant resumption of medication. It is

* The criterion for regression was the Global Change Scale (23) which compared the patient's clinical condition at week 24 with his condition before treatment.

doubtful whether the behaviour of some of these patients would have been tolerated had the patient not been involved in a study. Table III shows the number and percentage of patients at each hospital who were able to complete 24 weeks on placebo without showing signs of clinical deterioration. Again, the difference between hospitals was quite pronounced. For example, 72 per cent. of the patients at Hospital G were able to remain off medication without showing signs of clinical deterioration, compared to only 12 per cent. of the patients at Hospital A.

Discussion

The results show that the large majority of patients on low doses of tranquillizers are able to remain off drugs for six months without significant deleterious effects. This suggests that drug discontinuation is a feasible treatment policy for patients currently receiving low doses of ataractic medication at public mental hospitals. Patients receiving moderate to high doses of medication, on the other hand, show relatively high relapse rates when drugs are discontinued. Probability of relapse appears too high to commend long term drug withdrawal as a treatment policy for this group of patients.

Some investigators advocate treatment programmes for chronic patients which involve periodic short-term withdrawal of phenothiazines (12, 22, 26). This study was not designed to evaluate the effectiveness of these "intermittent chemotherapy" programmes. However, our results do indicate that when such programmes are used with patients on moderate to high doses of tranquillizing medication, the drug-free period should not exceed six weeks. After this period, the probability of relapse and deterioration sharply increases.

The results also show that relapse rates vary considerably among hospitals. There are a number of possible explanations for this finding. First, it is possible that patients at high-relapse hospitals (e.g. hospital A) were initially more severely ill than patients at low-relapse hospitals (e.g. hospital G). This would explain why fewer patients at high-relapse hospitals were able to remain off medication. There is one drawback to this explanation. On the symptom rating scales, there was no significant difference in pre-study symptomatology between high- and low-relapse hospitals. However, this does not necessarily mean that differences did not exist. Tranquillizing medication may have effectively controlled the symptoms of patients

Table III

*Patients Completing 24 Weeks on Placebo with No Deterioration in Global Psychiatric State: By Hospital and Dose of Pre-study Tranquillizing Medication**

Daily dose of pre-study medication†		Hospitals A	B	C	D	E	F	G	Total
No medication	Total N	2	2	4	2	2	2	4	18
	N not worse	2	2	3	2	2	2	4	17
	% not worse	100	100	75	100	100	100	100	94
Under 300 mg.	Total N	4	8	7	11	8	12	15	65
	N not worse	3	5	4	8	5	9	12	46
	% not worse	75	63	57	73	63	75	80	71
300 mg. and over	Total N	21	20	16	16	16	14	10	113
	N not worse	0	6	4	7	7	8	6	38
	% not worse	0	30	25	44	44	57	60	34
All doses	Total N	25	28	23	27	24	26	25	
	N not worse	3	11	8	15	12	17	18	
	% not worse	12	39	35	56	50	65	72	

* Change in global psychiatric state was determined from the Global Change Scale comparing the patient's clinical condition at week 24 with his clinical condition prior to the study.

† All doses were converted to equivalent doses of chlorpromazine.

high-relapse hospitals so that they appeared no more ill than patients at low-relapse hospitals. Only when medication was withdrawn did the greater severity of illness of patients at high-relapse hospitals become apparent. This explanation also assumes that a large proportion of patients receiving tranquillizing medication at low-relapse hospitals were really in no need of ataractic drugs.

A second possible explanation should not be overlooked. The criteria for relapse may have differed significantly between high-relapse and low-relapse hospitals. As was explained previously, a patient was considered "relapsed" if he deteriorated to the point where he was unable to remain on placebo for the full 24 weeks. It is possible that high-relapse hospitals showed less tolerance for deteriorated behaviour than low-relapse hospitals. High-relapse hospitals may have terminated the experiment at the first sign of deterioration, while low-relapse hospitals may have resumed medication only for severely disturbed behaviour. If this were true, it would account for the difference in relapse rate between hospitals. Evidence from the rating scales indicates that this was not the case. There was no significant difference in degree of deterioration between "terminated" patients at high-relapse hospitals and those at low-relapse hospitals. Also, patients at high-relapse hospitals were not put back on medication any earlier in the study than patients at low-relapse hospitals.

These findings on hospital differences have important implications for research on drug withdrawal. If the study had been conducted only at Hospital G (relapse rate 12 per cent.), we might have concluded, as some investigators have, that drug withdrawal is a feasible treatment policy for all long-stay patients. Conversely, if the study had been conducted only at Hospital A (relapse rate 68 per cent.), the conclusions would have been very different. If hospitals using the same study design show widely differing relapse rates, what agreement can be expected among single hospital studies using different selection criteria, evaluation instruments and methods of analysis? Hospital differences may well explain a good proportion of the contradictions noted in the drug withdrawal literature. More important, these findings indicate that considerable caution should be observed in generalizing from studies involving a single hospital or ward.

Summary

In a seven-hospital collaborative study, 210 chronic schizophrenics were assigned to a placebo for a 24-week period. During that time, 40 per cent. of the patients relapsed and had to be returned to active medication. Probability of relapse was related to two variables: (1) the hospital conducting the study and (2) the dose of tranquillizing medication the patient was receiving before being put on placebo. Patients receiving low doses of tranquillizing medication before the study were less likely to relapse than patients receiving moderate to high doses. The practical and theoretical implications of these findings are discussed.

References

1. Barrett, W. W., Ellsworth, R. B., Clark, L. D., and Enniss, J. (1957). "Study of the differential behavioral effects of reserpine, chlorpromazine and a combination of these drugs in chronic schizophrenics." *Dis. nerv. Syst.*, **18**, 209–215.
2. Blackburn, H., and Allen, J. (1961). "Behavioral effects of interrupting and resuming tranquilizing medication among schizophrenics." *J. nerv. ment. Dis.*, **133**, 303–307.
3. Bock, R., and Swain, J. (1962). "Ophthalmological findings in patients on long-term chlorpromazine therapy." *Amer. J. Ophthal.*, **56**, 808–810.
4. Brooks, G. W. (1959). "Withdrawal from neuroleptic drugs." *Amer. J. Psychiat.*, **115**, 931–932.
5. Caffey, E. M., Diamond, L. S., Frank, T. V., Grasberger, J. C., Herman, L., Klett, C. J., and Rothstein, C. (1964). "Discontinuation or reduction of chemotherapy in chronic schizophrenics." *J. chron. Dis.*, **17**, 347–358.
6. Crane, G., and Paulson, G. (1967). "Involuntary movements in a sample of chronic mental patients and their relation to the treatment with neuroleptics." *Int. J. Neuropsychiat.*, **3**, 286–291.
7. Denber, H. D., and Bird, E. G. (1955). "Chlorpromazine in the treatment of mental illness. II. side effects and relapse rates." *Amer. J. Psychiat.*, **112**, 465–468.
8. Diamond, L. S., and Marks, J. D. (1960). "Discontinuance of tranquilizers among chronic schizophrenic patients receiving maintenance dosage." *J. nerv. ment. Dis.*, **131**, 247–251.
9. Freeman, L. S., and Alson, E. (1962). "Prolonged withdrawal of chlorpromazine in chronic patients." *Dis. nerv. Syst.*, **23**, 522–525.

10. GARFIELD, S., GERSHON, S., SLETTEN, I., NEUBAUER, H., and FERREL, E. (1966). "Withdrawal of ataractic medication in schizophrenic patients." *Ibid.*, **27**, 321–325.

11. GOLDSMITH, J., and DRYE, R. (1963). "Milieu as a variable in clinical drug research." *Ibid.*, **24**, 742–745.

12. GOOD, W. W., STERLING, M., and HOLZMAN, W. H. (1958). "Termination of chlorpromazine with schizophrenic patients." *Amer. J. Psychiat.*, **115**, 443–448.

13. GREINER, A. C., and NICOLSON, G. A. (1964). "Pigment deposition in viscera associated with prolonged chlorpromazine therapy." *Canad. med. Ass. J.*, **91**, 627–635.

14. HAMILTON, M., HORDERN, A., WALDROP, F. N., and LOFFT, J. (1963). "A controlled trial on the value of prochlorperazine, trifluoperazine and intensive group treatment." *Brit. J. Psychiat.*, **109**, 510–522.

15. —— SMITH, A. L., LAPIDUS, H. E., and CADOGEN, E. P. (1960). "A controlled trial of thiopropazate dihydrochloride, chlorpromazine and occupational therapy in chronic schizophrenics." *J. ment. Sci.*, **106**, 40–55.

16. HOLLISTER, L. E., and KOSEK, J. C. (1965). "Sudden death during treatment with phenothiazine derivatives." *J. Amer. med. Ass.*, **192**, 1035–1038.

17. HUGHES, J. S., and LITTLE, J. C. (1967). "An appraisal of the continuing practice of prescribing tranquillizing drugs for long-stay psychiatric patients." *Brit. J. Psychiat.*, **113**, 867–873.

18. HUNTER, R., EARL, C. J., and THORNICROFT, S. (1964). "An apparently irreversible syndrome of abnormal movements following phenothiazine medication." *Proc. Roy. Soc. Med.*, **57**, 758–762.

19. JUDAH, L. N., JOSEPHS, Z. M., and MURPHEE, O. D. (1961). "Results of simultaneous withdrawal of ataraxics in 500 chronic psychotic patients." *Amer. J. Psychiat.*, **118**, 156–158.

20. MARGOLIS, L., and GOBLE, J. (1965). "Lenticular opacities with prolonged phenothiazine therapy." *J. Amer. med. Ass.*, **193**, 95–97.

21. MESZAROS, A. F., and GALLAGHER, D. L. (1958). "Measuring indirect effects of treatment on chronic wards." *Dis. nerv. Syst.*, **19**, 167–172.

22. OLSON, G. W., and PETERSON, D. B. (1960). "Sudden removal of tranquilizing drugs from chronic psychiatric patients." *J. nerv. ment. Dis.*, **131**, 252–255.

23. PRIEN, R. F., and COLE, J. O. (1968). "High dose chlorpromazine therapy in chronic schizophrenia." *Arch. gen. Psychiat.*, **18**, 4, 482–495.

24. RATHOD, N. H. (1958). "Tranquillizers and patients' environment." *Lancet*, *i*, 611–613.

25. RICHARDSON, H. L., GRAUPNER, K. I., and RICHARDSON, M. E. (1966). "Intramyocardial lesions in patients dying suddenly and unexpectedly." *J. Amer. med. Ass.*, **195**, 254–260.

26. ROTHSTEIN, C. (1960). "An evaluation of the effects of discontinuation of chlorpromazine." *New Eng. J. Med.*, **262**, 67–69.

27. SIDDALL, J. (1965). "The ocular toxic findings with prolonged and high dosage chlorpromazine intake." *Amer. med. Ass., Arch. Ophthal.*, **74**, 460–464.

28. WETTERHOLM, D., SNOW, H., and WINTER, F. (1965). "A clinical study of pigmentary change in cornea and lens in chronic chlorpromazine therapy." *Ibid.*, **74**, 55–56.

29. WHITAKER, C. B., and HOY, R. M. (1963). "Withdrawal of perphenazine in chronic schizophrenia." *Brit. J. Psychiat.*, **109**, 422–427.

30. WINKLEMAN, N. M. (1957). "An appraisal of chlorpromazine." *Amer. J. Psychiat.*, **113**, 961.

31. ZELLER, W. W. (1956). "Use of chlorpromazine and reserpine in the treatment of emotional disorders." *J. Amer. med. Ass.*, **160**, 179–185.

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