

CLINICAL PHARMACOLOGY and THERAPEUTICS

volume 13 number 6

November-December, 1972

Commentary

The drug defaulter

Barry Blackwell, M.D., M.R.C.Psych. Cincinnati, Ohio
Departments of Psychiatry and Pharmacology, University of Cincinnati

There have been over 50 studies on patients who fail to take their medications "as directed." The patients in these studies usually required chronic maintenance therapy for conditions including tuberculosis, schizophrenia, anemia, rheumatoid arthritis, and other diseases seen in general practice. Attention has also been paid to the special problems posed by geriatric patients and by children who depend for medication on their parents.

Although some doctors may cherish the illusion that they can intuitively detect drug defaulters, the evidence suggests otherwise. A study by Caron and Roth⁶ demonstrated that 27 physicians were unable to predict their patients' intake of antacids any more accurately than could be achieved by chance. Even skilled psychiatrists have been shown to err in up to 20 per cent of their predictions concerning which outpatients are taking drugs.²⁹ An earlier study³

had already shown that doctors fared no better than medical students in this type of guessing game. Health visitors appear to be equally inaccurate, since Dixon and associates¹⁰ found that one third of their predictions were wrong concerning which tuberculosis patients were taking para-aminosalicylic acid (PAS).

Methods used to detect drug defaulters

A variety of methods have been used to detect the drug defaulter, and these are discussed in the paragraphs that follow.

Interrogation. Bergsman and Werner³ found that 83 per cent of parents claimed their children were taking penicillin when 92 per cent of urines had no antibiotic activity. Somewhat smaller discrepancies have been reported in psychiatric patients.³⁴ Patients admit major discrepancies more often than trivial oversights, perhaps because they remember them more readily.⁴¹ They are also more willing to admit defaulting if questioned tactfully.¹³

Tablet estimates. There is no certainty

Presented to the American College of Neuropsychopharmacology, Las Vegas, January 19-21, 1972.

that what has left the bottle has been through the patient. Roth and associates⁴³ studied ulcer patients taking antacids labeled with bromide and found that the correspondence between bottle counts and blood bromide levels showed an error of up to 36 per cent between the two measures.

Markers. Stool markers have been used to check compliance in anemic²³ and psychiatric¹¹ patients. False negatives may occur in those who chew the marker or remain constipated for longer than its half-life. Urine markers, including riboflavin and phenol red, have been more often and more successfully used.^{9, 22, 44, 45}

Drug detection. This is the most certain method. Urine testing is the simplest, but serum levels are also useful.

Failure to dispense. Hammel and Williams¹⁶ found that out of 2,000 prescriptions 3 per cent were not filled within 10 days.

Extent, nature, and significance of drug defaulting

When these methods were used, 25 to 50 per cent of the population studied was shown to consist of defaulters. Drug defaulting may take a number of forms, of which failure to take the prescribed amounts is the most common. Episodic or excessive medication may also occur. Malahy²⁸ categorized the errors made by medical outpatients into 4 groups: errors of omission, errors of purpose (taking medicine for the wrong reason), errors of dosage, and errors in timing or sequence. Schwartz and associates⁴⁶ followed a similar classification when recording the errors made by chronically ill geriatric patients, but they added a group who took additional medications not prescribed by the doctor.

The significance of drug defaulting depends on the condition concerned. The fact that 9 of 10 children are no longer taking penicillin 9 days after the onset of a sore throat may be an index of overprescribing (if the condition is viral) or dangerous behavior (if the etiology is streptococcal). Patients who suffer from arthritis and default from anti-inflammatory drugs are at

worst titrating their own pain against the inconveniences of continuous medication. At the other extreme, a patient with tuberculosis risks his life if he fails to take PAS rather than experience gastrointestinal discomfort.

A more optimistic view was proposed by Uhlenhuth and associates,⁴⁸ who speculated that defaulting may reflect the patient's efforts at self-regulation to take account of the wide individual differences known to occur in drug metabolism.

Some idea of the adverse consequences of noncompliance can be gauged from the finding that a controlled trial of isoniazid in psychiatric patients reduced the incidence of tuberculosis by 80 per cent in general patient populations but by only 18 per cent in schizophrenics.¹² The results that befall a schizophrenic who "cheeks" his phenothiazines have been intensely debated. After a review of the literature, Hughes and Little¹⁹ felt skeptical of the need for continuous medication among many schizophrenic inpatients. Patients in their study remained well after drug withdrawal but received intensive milieu therapy and support.

The results conflict with those of a collaborative VA study⁵ in which 45 per cent of patients on substituted placebo relapsed within 16 weeks. Similarly, schizophrenics in the community fare less well if medication is withdrawn. Though this proved difficult to confirm in a retrospective survey,³⁸ a controlled prospective evaluation⁴⁵ of schizophrenics discharged from hospital showed that after 6 to 18 months 82 per cent of drug-treated patients were still at home but only 37 per cent of those on placebo remained outside hospital.

Other consequences of drug defaulting include the economic wastage involved^{14, 17} and the hazard to health posed by cupboards stocked with unused or unidentifiable tablets. Nicholson³² carried out a systematic survey of an English town and found that 500 of 30,000 households had unused drugs available. Sedatives, tranquilizers, and hypnotics formed by far the largest

single category of drugs. Robin and Freeman-Browne⁴² examined unused medications in the homes of psychiatric patients and found that those with suicidal risk often had such supplies available.

Drug defaulting in therapeutic trials

Drug defaulting may play a part in distorting the controlled evaluation of drug therapy. The neglect accorded this factor was first remarked upon by Dixon and associates¹⁰ as long ago as 1957, when they noted that "many chemotherapy trials based on unsupervised oral medication have probably been built on very unsure foundations." The point has been emphasized as repeatedly as it has been ignored; it was commented on by Maddock²⁷ and again recently by Porter.³⁶ Both Joyce²² and Uhlenhuth and associates⁴³ have shown that this factor may modify the outcome or conclusion from a study.

Factors associated with drug default

Attempts made to identify features associated with drug defaulting have yielded conflicting results. As long ago as 1928, Hartshorne and May¹⁸ showed that individuals who are unreliable in one situation may not be in another. The drug defaulter, like the placebo reactor, is an ephemeral being, subject to change and circumstances. After extensive and repeated studies in general practice, Porter³⁶ concluded, "It has not proved possible to identify an uncooperative type. Every patient is a potential defaulter; compliance can never be assumed."

Despite this, features of the medication, the patient, the doctor, and milieu have been shown at times to play a contributory role in drug defaulting.

Medication. A number of studies have suggested that both the complexity of the regimen and the incidence of side effects may encourage defaulting.

Duration of treatment. Porter³⁶ found that duration of treatment was negatively correlated with taking iron in 62 pregnant women. This finding is particularly interest-

ing because the same factor did not influence compliance in 58 patients with serious medical conditions for which drugs such as digoxin were taken. This suggests that length of treatment may encourage deviation in relatively trivial illnesses but not in life-threatening conditions. The role that sheer forgetfulness or tedium may play in even serious conditions was shown by Luntz and Austin,²⁶ who found that deviation from PAS therapy rose progressively from 18 per cent at a year to 66 per cent at 4 years. This might also suggest that the longer a patient has remained well, the more he may be prepared to gamble on continued good health.

Complexity of treatment. Multiple medications or treatments discourage compliance. Francis and associates¹³ found that compliance by pediatric outpatients declined if 3 or more medications were prescribed or if 2 separate treatment methods were initiated simultaneously. Malahy²⁸ showed that the number of medications taken by the patient was the only variable (from among many) that significantly correlated with deviation. However, in a controlled study with 4 groups, she was unable to show that special instructions or labeling improved compliance. In geriatric outpatients, Schwartz and associates⁴⁰ showed that errors increased for up to 3 medications but not thereafter (possibly because of more meticulous instructions).

If more drugs encourage deviation, so should more doses of the same drug. This suspicion is confirmed by 4 studies, one in steroid therapy for arthritis³³ and 3 in general practice.^{15, 21, 36} Porter³⁶ found that pregnant women adhered more faithfully to once-daily iron than to a divided regimen, and Gatley¹⁵ showed in a prospective trial that the number of defaulters doubled when the number of tablets was increased from one to 4.

The formulation of a medication may also influence default rates. Wilson and Enoch³⁰ demonstrated that urines tested by the Forrest reagent changed from negative to positive in 8 schizophrenic patients who

were switched from chlorpromazine tablets to identical dosages of a liquid formulation.

Side effects of treatment. The patient with side effects might logically be expected to default. Wynn-Williams and Arris⁵¹ found that PAS had produced gastrointestinal upset in many more defaulters than in regular takers. Michaux³⁰ found a significant correlation between occurrence of side effects and dosage deviation in 180 male psychiatric outpatients, and Parkes and associates³² discovered that side effects were invoked by 7 of 55 schizophrenics who ceased medication after discharge from hospital. Renton and associates³⁸ also found that side effects (particularly sedation) were invoked by patients who ceased taking drugs. Since drugs generally produce more side effects than placebos, this factor may also account for important differences in the compliance of subjects in drug trials.^{22, 36}

The patient. A large number of the patient's personal, illness, and socioeconomic attributes may contribute toward a willingness or nonwillingness to take medication.

Sex and age. The finding of Bergsman and Werner³ that younger children (aged 2), took less medicine than older children (aged 5) is hardly surprising. A more unexpected and consistent observation in tuberculosis patients has been the reluctance of young women (under 30) to take PAS.^{10, 26, 51} The percentage of women defaulting in this age group is usually double that of men, an observation that caused Dixon and associates¹⁰ to preface their paper with Hillaire Belloc's despairing ditty:

Matilda told such dreadful lies,
It made one gasp and stretch one's eyes. . .

Social supervision. An equally consistent finding has been that the supervisory role of a partner or spouse aids in ensuring that medication is taken as ordered. Porter³⁶ found that living alone made the major contribution to noncompliance in general practice. Schwartz⁴⁶ also found that more serious medication errors were made by those living alone; individuals who were

widowed or divorced were more likely to deviate, as has also been indicated in tuberculosis patients.⁴ Fifty-two per cent of male psychiatric outpatients living alone failed to take drugs, compared to 35 per cent of those living with their wives.⁴⁹ Parkes and associates³⁵ found that 82 per cent of schizophrenic patients discharged into the community took their drugs as ordered when supervised by a relative or friend, compared to 46 per cent of those who were not supervised. An important corollary to this observation was the fact that there were 3 times as many patients in this unsupervised group. Renton and associates³⁸ also found that schizophrenics living with their families were less likely to default.

The fact that the quality of supervision may influence compliance has also been illustrated by the finding in pediatric practice⁷ that the mothers of compliant children were more often rated for positive features such as "organized," "responsible," and "clear thinking" by the physician on the Gough Adjective Check List. Mothers of noncompliant children were more often rated on negative features such as "unreliable."

Socioeconomic factors. Two reports linking the patient's color to compliance have yielded opposite results; among neurotic outpatients, Lipman and associates²⁵ found being white was correlated with compliance, while in the treatment of tuberculosis, the reverse was true.⁴ On the basis of clinical experience, Arnhold¹ suggested that ethnic and language barriers might contribute to low compliance in up to a quarter of patients. The results concerning social class and education are equally inconclusive. In pediatric outpatients, Francis and associates¹³ found no significant correlations between compliance and either social class or mother's educational standards. In tuberculosis patients,⁴ the trend was slightly in favor of educational standards being higher among defaulters, while the reverse was true for pregnant women taking iron.³⁶

The only study reporting a clear relation-

ship with socioeconomic factors was among neurotic outpatients treated with meprobamate,²⁵ where good compliance was associated with being middle-class, well educated, and white. These attributes led the authors to consider such patients as likely to "abide by the rules of the game."

Illness. In psychiatric patients the capacity to cooperate may be eroded by the illness. Renton and associates³⁸ found that default rates were highest in schizophrenics who were most ill at time of discharge but found it difficult to disentangle the question of whether default was the cause or result of further deterioration. Those who were less ill attended outpatient clinics and adhered to medication more faithfully.

Poor compliance occurs not only in psychotic states where insight may be lost, but has been shown to occur also in neurotic illnesses. In their study of anxious outpatients, Lipman and associates²⁵ found that deviation was highest among the most anxious patients who had been given a poorer prognosis and had been treated elsewhere before. They speculate that the treatment was rejected by this group of patients as being insufficiently potent.

Patients may sense in other ways when treatment is inadequate or inappropriate. It is interesting that in Willcox and associates⁴⁹ study on psychiatric outpatients, the highest default rate was among depressed patients treated with chlorpromazine. Seventy per cent of this group deviated, compared to 32 per cent of schizophrenics given chlorpromazine and 44 per cent of depressed patients given imipramine.

Schwartz and associates⁴⁶ have reviewed the literature concerning severity of illness and compliance in pediatrics and quote the conflicting evidence. However, the findings of Charney and associates⁷ support their own finding that mothers who perceive their child's illness as severe are more likely to be compliant, though this relates as much to attending appointments as to following instructions about medication.

Patient attitudes. Explorations of the patient's attitudes in relation to compliance

have ranged from descriptive to speculative. Among the latter has been the psychoanalytic reminder⁴⁷ that pills and capsules resemble nothing so much as the breast and the penis (elixirs presumably fall into the category of mother's milk).

One problem of studying patient attitudes in relation to drug deviation is the obvious fact that those who do not wish to comply are equally likely to stay away; the drug deviator who remains to be questioned is the curiously ambivalent individual who does not do what he is told but continues to attend. A collaborative VA study of outpatients yielded some information in this respect.³⁰ Patients were prescribed medication by one doctor but attended for psychotherapy with another. Resistance to medication expressed verbally to the therapist was later found to correlate significantly with deviation. In addition, a group of 37 extreme deviators were studied separately³⁷ and compared to the remaining patients. They were found to show a greater degree of overt hostility and aggression (but also expressed angry feelings toward psychotherapy). It is interesting to note that the 10 least compliant patients in Roth and associates⁴³ study on antacid ingestion had normal scores on the MMPI lie scale, suggesting that failure to comply may indeed be an overt demonstration of hostility rather than a covert sign of deceit.

A particularly interesting study was carried out by Bakker and Dightman² in women taking the contraceptive pill. A battery of personality tests showed that those who failed to take the pill regularly were more immature, irresponsible, and impulsive. These risk-taking personality characteristics were combined with the fact that their personality profiles deviated more from their husbands than did those of women who took the pill regularly.

Perhaps the commonest symptoms associated with drug deviation in the psychiatrist's practice are the paranoid delusions that cause the schizophrenic to equate drugs with poison. This was demonstrated by Wilson and Enoch,⁵⁰ who found that

out of 8 schizophrenics with persistently negative urines, 7 had paranoid delusions (compared with 2 of a control group).

A much more detailed study was carried out by Richards¹⁰ using Osgood's semantic differential rating scale to determine the attitudes of 30 schizophrenic inpatients who were either known acceptors or refusers of medication. The group of extreme refusers rated medicine less favorably and held unfavorable attitudes to home in general and in particular to both parents. In addition, they held unfavorable attitudes toward authority. The authors' stereotype of the chronic schizophrenic medication refuser was of "a closed ward patient who resents coercion, yet doesn't value freedom highly and doesn't dislike the hospital but dislikes his parents. He has been in the hospital for 5 or 6 years, yet hasn't been convinced that taking medicine will make him better."

An obvious shortcoming of many studies on drug deviation is that they have used objective indices without questioning the patient. Two studies shed some light on this issue. Mohler and associates³¹ found that the 3 most common reasons given for not taking penicillin were that the patient felt well (37 per cent), carelessness (27 per cent), and insufficient money (17 per cent). Another 19 per cent either simply refused or misunderstood the purpose of treatment. Finally, Francis and co-workers¹³ investigated doctor-patient relationships in a children's outpatient department. It was found that compliance was reduced when the mother perceived the doctor as unfriendly and if she felt that he did not understand the complaint. In general, those who were highly satisfied with the initial contact showed high compliance (53 per cent) compared to those who were highly dissatisfied, of whom far fewer showed high compliance (17 per cent).

The doctor. Implicit in the work of Francis and associates¹³ is the fact that the doctor's behavior and attitudes will influence patient compliance. This has been invoked as the reason pediatric compliance

is better in private practice than in clinics.²⁴ The matter was more precisely elucidated by Charney and associates,⁷ who showed that compliance was much better when the child was seen by a familiar doctor rather than by a partner and was also related to the number of years that the doctor had cared for the family. This matter was also investigated by Reynolds and associates³⁹ in psychiatric outpatients prescribed barbiturates in a drug study. An unexpected finding in the study was the different outcome in patients assigned to the two therapists. Therapist A ("promoting") had patients who deviated less, complained less often of side effects, and reported benefit more often; the patients of Therapist B ("protecting") deviated and complained more. Thus, the "promoting" therapist inquired after improvement and reassured for side effects, while the "protecting" physician probed for side effects and gave less hope for improvement. In schizophrenia, Irwin and associates²⁰ found that 39 per cent of outpatients defaulted if they were treated by a physician who did not believe in drugs, compared to 25 per cent of those cared for by a physician who viewed medications as essential. However, the number of patients studied was small and the difference not significant.

The setting. Hare and Willcox¹⁷ have shown that the incidence of drug defaulting increases progressively from 19 per cent among inpatients, 37 per cent among day patients, to 48 per cent among outpatients at the same hospitals, using heterogeneous patient samples and identical methods of detection. In support, Irwin and associates²⁰ found that deviation occurred in 7 per cent of schizophrenics in a closed ward compared to 32 per cent of open-ward patients; when the closed-ward patients went on Christmas vacation, the default rate rose to 63 per cent by the time they returned to the ward after 2 to 4 weeks at home.

Conclusion

Since there is no archetypal drug defaulter, there is also no simple or single

solution to the question of how this problem should be handled. Whether or not a patient takes medication correctly results from a complex interaction between the patient, his illness, the doctor, and the medication he prescribes. Identification of the "at risk" patient, simplification of the treatment regimen, and tactful detection of the drug defaulter are all factors worth consideration. If this problem were more widely recognized and these measures implemented, they might result in direct benefit to the individual patient and indirect benefit from improved evaluation of new drugs.

I am grateful to Charlotte Bagenstose for a literature search and to Drs. Fred and Irene Forrest for stimulating my interest in this subject.

References

1. Arnhold, R. G.: Do your patients take their drugs? *Clin. Pediatr.* 6:139, 1967.
2. Bakker, C. B., and Dightman, C. R.: Psychological factors in fertility control, *Fertil. Steril.* 15:559-567, 1964.
3. Bergsman, A. B., and Werner, R. J.: Failure of children to receive penicillin by mouth, *N. Engl. J. Med.* 268:1334-1338, 1963.
4. Berry, D., Ross, A., and Deuschle, K.: Tuberculosis patients treated at home, *Am. Rev. Resp. Dis.* 88:769-772, 1963.
5. Caffey, E. M., Diamond, L. S., Frank, T. V., Grasberger, J. C., Herman, L., Klett, J. C., and Rothstein, C.: Discontinuation or reduction of chemotherapy in chronic schizophrenics, *J. Chronic Dis.* 17:347-358, 1964.
6. Caron, H. S., and Roth, H. P.: Patients' cooperation with a medical regimen: Difficulties in identifying the non-cooperator, *J. A. M. A.* 203:922-926, 1968.
7. Charney, E., Bynam, R., Eldredge, D., Frank, D., MacWhinney, J. B., McNabb, B., Scheiner, A., Sumpter, E. A., and Iker, H.: How well do patients take oral penicillin? A collaborative study in private practice, *Paediatr.* 40:188-195, 1967.
8. Davis, M. S.: Variations in patients' compliance with doctors' orders: Analysis of congruence between survey responses and results of empirical investigations, *J. Med. Educ.* 41:1037-1048, 1966.
9. Deuschle, K. W., Jordahl, C., and Hobby, G. L.: Clinical usefulness of riboflavin-tagged isoniazid for self-medication in tuberculosis patients, *Am. Rev. Resp. Dis.* 82:1-10, 1960.
10. Dixon, W. M., Stradling, P., and Woolton, I. D. P.: Out-patient P.A.S. therapy, *Lancet* 2: 871-872, 1957.
11. Esser, A. H., Kline, N. S., and Vestergaard, P.: Custom-packed once-a-day medication with barium sulphate tracer for use in drug research, *Physician's Drug Manual* 1:86-88, 1969.
12. Ferebec, S. H.: The schizophrenic and oral medication, *Lancet* 2:147, 1964.
13. Francis, V., Korsch, B. M., and Morris, M. J.: Caps in doctor-patient communication, *N. Engl. J. Med.* 280:535-540, 1969.
14. Gardiner, Q.: The need for drug monitoring in psychiatric practice, *Br. J. Psychiatry* 114:877-881, 1968.
15. Gatley, M. S.: To be taken as directed, *J. R. Coll. Gen. Pract.* 16:39-44, 1968.
16. Hammel, R. W., and Williams, P. O.: Do patients receive prescribed medication? *J. Am. Pharm. Assoc.* NS4:331-334, 1964.
17. Hare, E. H., and Willcox, D. C.: Do psychiatric in-patients take their pills? *Br. J. Psychiatry* 113:1435-1439, 1967.
18. Hartshorne, H., and May, M. A.: Studies in deceit, New York, 1928, The MacMillan Company.
19. Hughes, F. S., and Little, J. C.: An appraisal of the continuing practice of prescribing tranquilizing drugs for long-stay psychiatric patients, *Br. J. Psychiatry* 113:867-873, 1967.
20. Irwin, D. S., Weitzel, W. D., and Morgan, D. W.: Phenothiazine intake and staff attitudes, *Amer. J. Psychiatry* 127:1631-1635, 1971.
21. Jenkins, W.: Are patients true to t.i.d. and q.i.d. doses? *G.P.* 9:66-69, 1954.
22. Joyce, C. R. B.: Patient cooperation and the sensitivity of clinical trials, *J. Chronic Dis.* 15: 1025-1036, 1962.
23. Kilpatrick, G. S.: The pre-symptomatic diagnosis of anaemia, *Proc. R. Soc. Med.* 59:1220-1222, 1966.
24. Leistyna, J. A., and McCauley, J. C.: Therapy of streptococcal infections. Do Paediatric patients receive prescribed oral medication? *Am. J. Dis. Child.* 111:22-26, 1966.
25. Lipman, R. S., Rickels, K., Uhlenhuth, E. H., Park, L. C., and Fisher, S.: Neurotics who fail to take their drugs, *Br. J. Psychiatry* 111:1043-1049, 1965.
26. Luntz, R. W. N., and Austin, R.: New stick test for P.A.S. in urine, *Br. Med. J.* 1:1679-1682, 1960.
27. Maddock, R. K.: Patient cooperation in taking medicines, *J. A. M. A.* 199:169-172, 1967.
28. Malahy, B.: The effect of instruction and labelling on the number of medication errors made by patients at home, *Am. J. Hosp. Pharm.* 23:283-292, 1966.
29. McClellan, T. A., and Cowan, G.: Use of anti-psychotic and antidepressant drugs by chronic-

- ally ill patients, *Am. J. Psychiatry* **26**:1771-1773, 1970.
30. Michaux, M. W.: Side effects, resistance, and dosage deviations in psychiatric out-patients treated with tranquilizers, *J. Nerv. Ment. Dis.* **133**:203-212, 1961.
31. Mohler, D. N., Wallin, D. G., Dreyfus, E. G., and Bakst, H. J.: II. Studies in the home treatment of streptococcal disease, *N. Engl. J. Med.* **254**:45-49, 1955.
32. Nicholson, W. A.: Collection of unwanted drugs from private homes, *Br. Med. J.* **3**:730-731, 1967.
33. Nugent, C. A., Ward, J., McDiarmid, W. D., McCall, J. C., Baakol, J., and Tyler, R. H.: Glucorticoid toxicity, *J. Chronic Dis.* **18**:323-332, 1965.
34. Park, L. C., and Lipman, R. S.: A comparison of patient dosage deviation reports with pill counts, *Psychopharmacologia* **6**:299-302, 1964.
35. Parkes, C. M., Brown, G. W., and Monck, E. M.: The general practitioner and the schizophrenic patient, *Br. Med. J.* **1**:972-976, 1962.
36. Porter, A. M. W.: Drug defaulting in a general practice, *Br. Med. J.* **1**:218-222, 1969.
37. Raskin, A.: A comparison of acceptors and resisters of drug treatment as an adjunct to psychotherapy, *J. Consult. Clin. Psychol.* **25**:366, 1961.
38. Renton, C. A., Afflech, J. W., Carstairs, G. M., and Forrest, A. D.: A follow-up of schizophrenic patients in Edinburgh, *Acta. Psychiatr. Scand.* **39**:548-600, 1963.
39. Reynolds, E., Joyce, C. R. B., Swift, J. L., Tooley, P. H., and Weatherall, M.: Psychological and clinical investigation of the treatment of anxious out-patients with 3 barbiturates and placebo, *Br. J. Psychiatry* **111**:84-95, 1965.
40. Richards, A. D.: Attitude and drug acceptance, *Br. J. Psychiatry* **110**:46-52, 1964.
41. Rickels, K., and Briscoe, E.: Assessment of dosage deviation in out-patient drug research, *J. Clin. Pharmacol.* **10**:153-160, 1970.
42. Robin, A. A., and Freeman-Browne, D. L.: Drugs left at home by psychiatric inpatients, *Br. Med. J.* **3**:424-425, 1968.
43. Roth, H. P., Caron, H. S., and Hsi, B. P.: Measuring intake of a prescribed medication. A bottle count and a tracer technique compared, *Clin. Pharmacol. Ther.* **11**:228-230, 1970.
44. Ryan, W. L., Carver, M. J., and Halier, J.: Phenolsulfonphthalein as an index of drug ingestion, *Am. J. Pharm.* **134**:168-171, 1962.
45. Scarpatti, F. R., Lefton, M., Dinitz, S., and Pasamanick, B.: Problems in a home care study for schizophrenics, *Arch. Gen. Psychiatry* **10**:143-154, 1964.
46. Schwartz, D., Wang, M., Leitz, L., and Goss, M. E. W.: Medication errors made by elderly, chronically ill patients, *Amer. J. Public Health* **52**:2018-2029, 1962.
47. Scott, C. W.: In Sarwer-Foner, G. H., editor: *The dynamics of psychiatric therapy*, Springfield, Ill., 1960, Charles C Thomas, Publisher, p. 319.
48. Uhlenhuth, E. H., Park, L. C., Lipman, R. S., Rickels, K., Fisher, S., and Moek, J.: Dosage deviation and drug effects in drug trials, *J. Nerv. Ment. Dis.* **141**:95-99, 1965.
49. Willcox, P. R. C., Gillan, R., Hare, E. H.: Do psychiatric patients take their drugs? *Brit. Med. J.* **2**:790, 1965.
50. Wilson, J. D., and Enoch, M. D.: Estimation of drug rejection by schizophrenic in-patients with analysis of clinical factors, *Br. J. Psychiatry* **113**:209-211, 1967.
51. Wynn-Williams, N., and Arris, M.: On omitting P.A.S., *Tubercule* **39**:338-342, 1958.