Psychological Medicine, 1975, **5**, 222–226

EDITORIAL

Time to evaluate long-acting neuroleptics?

'The use of routine maintenance therapy is widespread—estimates of its frequency being 70%–90% in State Hospitals' (Gunderson *et al.*, 1974). This comment on current practice in N. America can be matched by the chemotherapeutic treatment of schizophrenics in Great Britain and other European countries, where the majority of the patients have been receiving psychotropic drugs, mostly phenothiazines and butyrophenones, on a long-term basis for more than a decade. In the last five years the introduction of injected and oral long-acting drugs has given a marked impetus to this trend.

Unfortunately, the formation of a satisfactory judgement on long-acting preparations has been hampered by lack of information on a number of questions. Of these the most fundamental are concerned with the pharmacodynamic action of these compounds. While they are known to cause widespread interference with enzymes and transmitters of the autonomic and central nervous system, the connexion between these effects and the aetiology of schizophrenia remains tentative and the subject of much speculation (Hornykiewicz, 1966; Kety, 1967; Mattock, *et al.*, 1967; Vartanyan, 1969; Laduron, 1971; Stein and Wise, 1971; Matthyse, 1973, 1974; Fyrö *et al.*, 1974; Miller and Hiley, 1974; Pope, 1974; Rackensperger *et al.*, 1974; Taylor, 1974; Trabucchi *et al.*, 1974; Vogt, 1974). It is also unclear whether the drugs or their metabolites are the active agents and whether their effect is specific or merely symptomatic.

Since the relationship of drug concentrations in plasma and cerebrospinal fluid to their effects has not been established, the therapeutic dosage remains inevitably empirical. In practice, there appear to be enormous variations, which, of course, have a profound bearing on the important question of side-effects. Disquiet on this score has been increased by the use of long-term medication and is reflected in the current cataract of publications (De Alarcón and Carney, 1969; Simpson, 1970; Orlov *et al.*, 1971; Allan and White, 1972; Grove and Crammer, 1972; Kazamatsuri *et al.*, 1972; Mindham *et al.*, 1972; Prien and Klett, 1972; Andrews, 1973; Ayd, 1973, 1974; Martin, 1973; Carney, 1974; Chien *et al.*, 1974; McClelland *et al.*, 1974). In addition to the startling disparity in the reported incidence of side-effects (Simpson, 1970), it is surprising to find from controlled trials of maintenance treatment for schizophrenia, oral or injected, that anti-Parkinsonian medication is prescribed or increased as much for the patients on placebo as for those on active medication (Leff and Wing, 1971; Hirsch *et al.*, 1973). This strongly suggests that something is lacking in the clinical identification and assessment of extrapyramidal symptoms, a conclusion reinforced by the findings of a blind trial of the efficacy of standard anti-Parkinsonian medication which failed to show a significant difference from a placebo in its effect on Parkinsonian symptoms (Mindham *et al.*, 1972). The authors suggest that this 'calls into question the widespread practice of prescribing anticholinergic drugs in drug-induced Parkinsonism'. Comparing their own study with several others, they note that 'the evidence for the efficacy of anticholinergic drugs in Parkinson's disease itself is very limited' and conclude that 'All in all, the efficacy of anticholinergic drugs in drug-induced Parkinsonism is not well founded'.

On the other hand, severe reactions were noted in some subjects on neuroleptics from whom anti-Parkinsonian medication was withdrawn, which were relieved by a resumption of the drug (Orlov *et al.*, 1971; Grove and Crammer, 1972), though other workers have withdrawn anti-Parkinsonian drugs from patients on neuroleptics and have not reported such reactions (Ekdawi and Fowke, 1966; McClelland *et al.*, 1974). Simpson (1970) has indicated a probable source of part of the difficulty in demonstrating that the elements of the drug-induced extrapyramidal syndrome vary in incidence, dose dependence, time of appearance, persistence, and response to specific medication.

while Ekdawi and Fowke (1966) have indicated the difficulty of rating tremor and rigidity, partly because of their variation with the emotional state of the patient. Kennedy and his colleagues (1971), who have carefully and systematically recorded and identified these extrapyramidal disorders, were unable to demonstrate any relationship between anti-Parkinsonian medication and the severity of Parkinsonism. They comment:

'The major problem . . . is that the investigator's preconceptions of what constitutes the syndromes will bias his clinical judgements, with the result that the factors extracted from his data on analysis will err towards being fulfilments of his prophecies. Conscious attempts on the part of the clinical investigators to avoid such bias cannot eliminate it . . .' (Kennedy *et al.*, 1971).

Of particular relevance to the administration of long-term neuroleptics is the vexed question of a progressive, irreversible 'tardive dyskinesia'. Estimates of the incidence of this distressing condition vary from 1% to 41% (Kazamatsuri *et al.*, 1972) and it has been found to continue on cessation of medication in 65% of one series of cases (Uhrbrand and Faurbye, 1960). The uncertain state of opinion concerning therapy may be judged by the variety of remedies recommended and their inadequate assessment (Kazamatsuri *et al.*, 1972). The facts that dyskinesia sometimes first appears on cessation of treatment and that a higher dosage of neuroleptics has been found to diminish it (Richmond, 1968; Polvan, 1970) support the suggestion of Degkwitz and his colleagues (1966) that the rigidity thus produced masks abnormal movements whose true incidence, together with the brain damage they betokened, remain concealed by the continuation of drug therapy.

On the basis of published evidence, the duration of treatment remains equally uncertain. The longer the drugs are administered, the greater appears to be the possibility of serious harmful effects (*British Medical Journal*, 1964, Hunter *et al.*, 1964). Termination of treatment carries a varying risk, averaging 40%, of relapse (Prien and Klett, 1972). A reduced or intermittent dosage diminishes —but by no means eliminates—the chance of relapse (Greenberg and Roth, 1966) and requires more supervision for these patients than is customarily feasible.

In view of these several doubts, it may therefore justifiably be asked why long-term neuroleptics have become so widely used. One powerful argument put forward is the certainty of ingestion after parenteral administration, which overcomes the indifference or antagonism to treatment so prevalent among schizophrenics, and thus reduces defaulting (Blackwell, 1973). Some benefit may also arise from administering long-term medication because of the contact and supervision by psychiatric agents afforded through special clinics for injection or prescription of the drug. It is noticeable, for instance, that patients on a placebo were hospitalized notably less frequently than those having no medication and, in fact, after a year of trial, the admission rate for patients on placebo was no greater than for those on drugs (Engelhardt and Freedman, 1969). It seems likely that this advantage is partly due to the skilled oversight incidental to distribution of the medicament.

For these reasons, it is claimed, the number of patients who can be 'maintained' out of hospital has been markedly increased (Mason *et al.*, 1963; Crumpton, 1967, 1968; Blake, 1969; Freeman, 1969, 1973; Lowther, 1969; Itil and Keskiner, 1970; Gottfries, 1971; Davis *et al.*, 1972; Chien, 1973; Crawford and Forrest, 1974). However, while controlled clinical trials of maintenance therapy in schizophrenia show that, initially at any rate, it reduces the considerable hospital readmission rate (Engelhardt *et al.*, 1960; Pasamanick *et al.*, 1967; Leff and Wing, 1971; Hirsch *et al.*, 1973), this effect diminishes with time (Engelhardt *et al.*, 1963; Engelhardt and Freedman, 1969; Davis *et al.*, 1972), possibly because benefit from this mode of treatment is limited to patients whose prospects are best regardless of treatment (Shepherd and Watt, 1975).

What seems to be more certain is the establishment of modified systems of long-term supervision in which there is a considerable saving of doctors' time, with much of the responsibility passed to community nurses. This pattern has become an adjuvant to the current policy of early discharge and extramural care. Indeed, it has been argued that the principal justification for the use of long-acting neuroleptics is that they make easier the extramural care of schizophrenics (Crumpton, 1968; Platt, 1968; Carney and Sheffield, 1973; Chien, 1973; Cole *et al.*, 1973; Freeman, 1973; Stevens, 1973).

But who does the caring? This question has been firmly raised by the National Schizophrenia Fellowship (1973), on behalf of relatives of schizophrenics, who comment that, 'more and more mental health patients have been forced out into the community at large'. The Fellowship (1974) also points out and illustrates the 'tremendous burden on the families of schizophrenics' (only partially relieved by neuroleptics (Stevens, 1973)) and recommends more explicit recognition that relatives constitute the real 'primary care' agents. It is becoming increasingly apparent that a trend which is widely regarded as constituting a self-evident benefit as well as an economy in resources must be appraised in the light of the facts revealed by studies of schizophrenics and their relatives under the impact of its operation. Thus, a British study carried out at the instance of the Department of Health and Social Security revealed that, among schizophrenics receiving intensive social work at home, at least one-third showed acute problems centring around marital conflicts, housing difficulties, and work problems. The author comments, 'burdens which husbands of chronic schizophrenic wives carry stand out starkly and so do physical and emotional deprivations suffered by many children in these households' (Goldberg, 1971).

This picture has been filled out in detail by a psychiatrically orientated sociological investigation which, while demonstrating the easing of the patients' behavioural difficulties by drugs, concluded that lack of drive and poor prospects of marriage force these patients into an unstimulating dependence on elderly relatives who carry the burden in terms of mental health, means, and leisure (Stevens, 1972, 1973). In another study of 160 patients treated with injected long-acting neuroleptics, 80% were characterized by an 'amotivational syndrome' consisting of lack of motivation and interest, drowsiness, restlessness, unadaptive and, in some, manipulative behaviour aimed at stopping injections or readmission to hospital by physical complaints, misdemeanours, and suicidal gestures (Andrews, 1973). That behaviour in hospital does not always correspond with that displayed at home was shown in a study in a large town, where the authors commented that the greatest difference in behaviour between day-centre and home was observed in respect of aggression (Byrne *et al.*, 1974). The painfully inadequate social support provided for such disabled people is dramatically illustrated by case reports compiled from relatives by the National Schizophrenia Fellowship (1973) and identified systematically in an extensive North American project (Davies *et al.*, 1972). Here a follow-up of two and a half years showed that a substantially higher proportion of schizophrenic patients having home care on maintenance drugs remained out of hospital compared with those treated in hospital or treated at home on a placebo. It is notable, however, that a third of those on placebo remained out of hospital for the period of follow-up. On five year follow-up there was no difference in the proportions of the three groups who had been hospitalized, and only a quarter of each was employed. The authors identified a number of social factors associated with hospital readmission centring around poor family support and disinclination to persist in cooperation with therapeutic agencies. They conclude that,

'Taking the programme to the family was necessary to stabilise the multiproblem families in which these schizophrenics were frequently a serious disorganising factor. . . . Without aggressive home care . . . the evidence is that routine community or hospital psychiatric care will not prevent or significantly retard deterioration . . . on domestic, vocational, social and marital variables' (Davies *et al.*, 1972).

In conclusion, long-acting neuroleptics look like becoming too uncritically accepted as the standard treatment for schizophrenia, thus taking a place comparable with that recently held by insulin coma therapy. If history is not to be repeated, it is clear that social as well as pharmacological and clinical measures must be brought to bear on the problem of their evaluation.

DAVID C. WATT

REFERENCES

Allan, R. N., and White, H. C. (1972). Side effects of parenteral long-acting phenothiazines. *British Medical Journal*, **1**, 221.

Andrews, W. N. (1973). Long-acting tranquillisers and the amotivational syndrome in the treatment of schizophrenia. In *Community Management of the Schizophrenic in Chemical Remission*, pp. 1–4. Edited by M. H. King. Excerpta Medica: Amsterdam.

Ayd, F. J., Jr (ed.) (1973a). *The Future of Pharmacotherapy. New Drug Delivery Systems.* International Drug Therapy Newsletter: Baltimore, Md.

Ayd, F. J., Jr (1973b). Side effects of depot fluphenazines. In *The Future of Pharmacotherapy. New Drug Delivery Systems*, pp. 69–76. International Drug Therapy Newsletter: Baltimore, Md.

Ayd, F. J., Jr (1974). Side effects of depot fluphenazines. *Comparative Psychiatry*, **15**, 277–284.

Blackwell, B. (1973). Drug deviation in psychiatric patients. In *The Future of Pharmacotherapy. New Drug Delivery Systems*, pp. 17–31. Edited by F. J. Ayd Jr. International Drug Therapy Newsletter: Baltimore, Md.

Blake, B. (1969). *The Use of Long-Acting Phenothiazines in a Rural Area.* Symposium on Long-acting Phenothiazines, Dublin, 15–26. E. & R. Squibb (U.K.).

British Medical Journal (1964). Leading article: Side-effects of phenothiazine drugs, **2**, 1412.

Byrne, L., O'Connor, T., and Fahy, T. J. (1974). The home behaviour of schizophrenic patients living in the community and attending a day centre. *British Journal of Psychiatry*, **125**, 20–24.

Carney, M. W. P. (1974). Choreiform movements after depot injections of flupenthixol. *British Journal of Psychiatry*, **125**, 609.

Carney, M. W. P., and Sheffield, B. F. (1973). The long-term maintenance treatment of schizophrenic out-patients with depot flupenthixol. *Current Medical Research Opinion*, **1**, 423–426,

Chien, C.-P. (1973). A new modality for treating schizophrenics in the community. In *Community Management of the Schizophrenic in Chemical Remission*, pp. 5–9. Edited by M. H. King. Excerpta Medica: Amsterdam.

Chien, C.-P., DiMascio, A., and Cole, J. O. (1974). Antiparkinsonian agents and depot phenothiazine. *American Journal of Psychiatry*, **131**, 86–90.

Cole, J. O., Chien, C.-P., and Goldberg, H. (1973). Fluphenazine enanthate in community mental health in the United States. In *The Future of Pharmacotherapy. New Drug Delivery Systems*, pp. 33–35. Edited by F. J. Ayd Jr. International Drug Therapy Newsletter: Baltimore, Md.

Crawford, R., and Forrest, A. (1974). Controlled trial of depot fluphenazine in out-patient schizophrenics. *British Journal of Psychiatry*, **124**, 385–391.

Crumpton, N. (1967). Maintaining patients in the community. The rôle of drugs. *British Journal of Geriatric Practice*, **4**, 186–192.

Crumpton, N. (1968). The role of drugs in maintaining patients in the community. In *The Treatment of Mental Disorders in the Community*, pp. 15–24. Edited by G. R. Daniel and H. L. Freeman. Baillière: London.

Davis, A. E., Dinitz, S., and Pasamanick, B. (1972). The prevention of hospitalization in schizophrenia. *American Journal of Orthopsychiatry*, **42**, 375–388.

De Alarcon, R., and Carney, M. W. P. (1969). Severe depressive mood changes following slow-release intramuscular fluphenazine injection. *British Medical Journal*, **3**, 564–567.

Degkwitz, R., Wenzel, W., Binsack, K. F., Herkert, H., and Luxemburger, O. (1966). Zum Probleme der terminalen extrapyramidalen Hyperkinesen an Hand von 1600 langfristig mit Neuroleptica Behandelten. Arzneimittelforschung 16, 276–9, quoted in Kennedy *et al. British Journal of Psychiatry*, **118**, 509–518, 1971.

Ekdawi, M. Y., and Fowke, R. (1966). A controlled trial of anti-Parkinson drugs in drug-induced Parkinsonism. *British Journal of Psychiatry*, **112**, 633–636.

Engelhardt, D. M., and Freedman, N. (1969). Maintenance drug therapy: the schizophrenic patient in the community. In *Social Psychiatry*, vol. I, pp. 256–282. Edited by A. Kiev. Routledge: London.

Engelhardt, D. M., Freedman, N., Glick, B. S., Hankoff, L. D., and Mann, D. (1960). Prevention of psychiatric hospitalization with use of psychopharmacological agents. *Journal of the American Medical Association*, **173**, 147–149. E. & R. Squibb (U.K.).

Engelhardt, D. M., Rosen, B., Freedman, N., Mann, D., and Margolis, R. (1963). Phenothiazines in prevention of psychiatric hospitalization. II. Duration of treatment exposure. *Journal of the American Medical Association*, **186**, 981–983.

Freeman, H. L. (1969). *Long-Acting Phenothiazines in a Comprehensive Community Mental Health Service.* Symposium on Long-Acting Phenothiazines, Dublin, 33–38. E. & R. Squibb (U.K.).

Freeman, H. (1973). Long-acting neuroleptics and their place in the community mental health service. In *Community Management of the Schizophrenic in Chemical Remission*, pp. 10–13. Edited by M. H. King. Excerpta Medica: Amsterdam.

Fyrö, B., Wode-Helgodt, B., Borg, S., and Göran, S. (1974). The effect of chlorpromazine on homovanillic acid levels in cerebrospinal fluid of schizophrenic patients. *Pharmacologia (Berl.)*, **35**, 287–294.

Goldberg, E. M. (1971). Research in social work. In *Portfolio for Health*, pp. 99–108. Edited by G. McLachlan. Oxford University Press: London.

Gottfries, C. G. (1971). Clinical trial of fluphenthixol decanoate as a depot neuroleptic. *Nordisk Psykiatrisk Tidsskrift*, **25**, 296–303.

Greenberg, L. M., and Roth, S. (1966). Differential effects of abrupt versus gradual withdrawal of chlorpromazine in hospitalized chronic schizophrenic patients. *American Journal of Psychiatry*, **123**, 221–226.

Grove, L., and Crammer, J. L. (1972). Benzhexol and side effects with long-acting fluphenazine therapy. *British Medical Journal*, **1**, 276–279.

Gunderson, J. G., Autry, III, J. H., and Mosher, L. R., with Buchsbaum, S. (1974). Special report: Schizophrenia 1974. In *Schizophrenia Bulletin*, vol. 9, p. 46. National Institute of Mental Health: U.S. Dept. of Health, Education, and Welfare, Md.

Hirsch, S. R., Gaind, R., Rohde, P. D., Stevens, B. C., and Wing, J. K. (1973). Outpatient maintenance of chronic schizophrenic patients with long-acting fluphenazine: double-blind placebo trial. *British Medical Journal*, **1**, 633–637.

Hornykiewicz, O. (1966). Dopamine (3-hydroxytyramine) and brain function. *Pharmacological Reviews*, **18**, 925–964.

Hunter, R., Earl, C. J., and Thornicroft, S. (1964). An apparently irreversible syndrome of abnormal movements following phenothiazine medication. *Proceedings of the Royal Society of Medicine*, **57**, 758–762.

Itil, T., and Keskiner, A. (1970). Fluphenazine hydrochloride, enanthate, and decanoate in the management of chronic psychosis. *Diseases of the Nervous System*, **31**, Suppl., 37–42.

Kazamatsuri, H., Chien, C.-P., and Cole, J. O. (1972). Therapeutic approaches to tardive-dyskinesia. *Archives of General Psychiatry*, **27**, 491–499.

Kennedy, D. F., Hershon, H. I., and McGuire, R. J. (1971). Extrapyramidal disorders after prolonged phenothiazine therapy. *British Journal of Psychiatry*, **118**, 509–518.

Kety, S. S. (1967a). Current biochemical approaches to schizophrenia. *New England Journal of Medicine*, **276**, 325–331.

Kety, S. S. (1967b). The hypothetical relationships between amines and mental illness. In *Amines and Schizophrenia*, pp. 271–277. Edited by H. E. Himwich, S. S. Kety, and J. R. Smythies. Pergamon: Oxford.

Laduron, P. (1971). Pimozide (Orap): metabolism and interactions with cerebral amines. *Journal of Clinical Trials*, **8**, Suppl. 2, 19–24.

Leff, J. P., and Wing, J. K. (1971). Trial of maintenance therapy in schizophrenia. *British Medical Journal*, **3**, 599–604.

Lowther, J. (1969). The effect of fluphenazine enanthate on chronic and relapsing schizophrenia. (Abstract.) *British Journal of Psychiatry*, **115**, 691–692.

McClelland, H. A., Blessed, G., Bhate, S., Ali, N., and Clarke, P. A. (1974). The abrupt withdrawal of anti-parkinsonian drugs in schizophrenic patients. *British Journal of Psychiatry*, **124**, 151–159.

Martin, I. C. A. (1973). Some side effects of long-acting psychotropic drugs: potential and actual. In *The Future of Pharmacotherapy. New Drug Delivery Systems*, pp. 89–95. Edited by F. J. Ayd. International Drug Therapy Newsletter: Baltimore, Md.

Mason, A. S., Forrest, I. S., Forrest, F. M., and Butler, H. (1963). Adherence to maintenance therapy and rehospitalization. *Diseases of the Nervous System*, **24**, 103–104.

Matthysse, S. (1973). Antipsychotic drug actions: a clue to the neuropathology of schizophrenia? *Federation Proceedings*, **32**, 200–205.

Mattock, G. L., Wilson, D. L., and Hoffer, A. (1967). Catecholamine metabolism in schizophrenia. *Nature*, **213**, 1189–1190.

Miller, R. J., and Hiley, C. R. (1974). Anti-muscarinic properties of neuroleptics and drug-induced Parkinsonism. *Nature*, **248**, 596–597.

Mindham, R. H. S., Gaind, R., Anstee, B. H., and Rimmer, L. (1972). Compariso of anmantidine, orphenadrine, and placebo in the control of phenothiazine-induced Parkinsonism. *Psychological Medicine*, **2**, 406–413.

National Schizophrenia Fellowship (1973). *Schizophrenia—the Family Burden*. National Schizophrenia Fellowship: London.

National Schizophrenia Fellowship (1974). *Living with Schizophrenia:—by the Relatives* (1974) National Schizophrenia Fellowship: London.

Orlöv, P., Kasparian, G., DiMascio, A., and Cole, J. O. (1971). Withdrawal of antiparkinson drugs. *Archives of General Psychiatry*, **25**, 410–412.

Pasamanick, B., Scarpitti, F. R., and Dinitz, S. (1967). *Schizophrenics in the Community*. Appleton-Century-Crofts: New York.

Platt, R. (1968). The long-acting phenothiazines: a nurse's view. *British Journal of Social Psychiatry*, **2**, 187–191.

Polvan, N. (1970). Fluphenazine hydrochloride and enanthate in the management of chronic psychosis. *Diseases of the Nervous System*, **31**, Suppl., 48–49.

Pope, A. (1974). Problems of interpretation in the chemical pathology of schizophrenia. *Journal of Psychiatric Research*, **11**, 265–272.

Prien, R. F., and Klett, C. J. (1972). An appraisal of the long-term use of tranquilizing medication with hospitalized chronic schizophrenics: a review of the drug discontinuation literature. *Schizophrenia Bulletin*, No. 5, 64–73.

Rackensperger, W., Gaupp, R., Mattke, D. J., Schwarz, D., and Stutte, K. H. (1974). Behandlung von akuten schizophrenen Psychosen mit Beta-Receptoren-Blockern. *Archive für Psychiatrie und Nervenkrankheiten*, **219**, 29–36.

Richmond, P. W. (1968). High-dosage fluphenazine. *British Medical Journal*, **2**, 178.

Shepherd, M., and Watt, D. C. (1975). *Impact of Long-Term Neuroleptics on the Community: Advantages and Disadvantages*. International Congress C.I.N.P., Paris. (In press.)

Simpson, G. M. (1970). Long-acting, antipsychotic agents and extrapyramidal side effects. *Diseases of the Nervous System*, **31**, Suppl., 12–14.

Stein, L., and Wise, C. D. (1971). Possible etiology of schizophrenia: progressive damage to the noradrenergic reward system by 6-hydroxydopamine. *Science*, **171**, 1032–1036.

Stevens, B. C. (1972). Dependence of schizophrenic patients on elderly relatives. *Psychological Medicine*, **2**, 17–32.

Stevens, B. C. (1973). Role of fluphenazine decanoate in lessening the burden of chronic schizophrenics on the community. *Psychological Medicine*, **3**, 141–158.

Taylor, K. M. (1974). Displacement of bound ^{14}C-fluphenazine by biogenic amines and antipsychotic drugs in homogenates of brain tissue. *Nature*, **252**, 238–241.

Trabucchi, M., Cheney, D., Racagni, G., and Costa, E. (1974). Involvement of brain cholinergic mechanisms in the action of chlorpromazine. *Nature*, **249**, 664–666.

Uhrbrand, L., and Faurbye, A. (1960). Reversible and irreversible dyskinesia after treatment with perphenazine, chlorpromazine, reserpine and electroconvulsive therapy. *Psychopharmacologia*, **1**, 408–418.

Vartanyan, M. E. (1969). *Anxiety and the Stress Reaction in Different Forms of Schizophrenia*, pp. 28–31. *British Journal of Psychiatry*, Special Publication No. 3.

Vogt, M. (1974). Behavioral effects of central catecholamines: concluding remarks. *Journal of Psychiatric Research*, **11**, 183–184.