Brit. J. Psychiat. (1971), 118, 131–40

Correspondence

LITHIUM PROPHYLAXIS IN RECURRENT AFFECTIVE DISORDERS

DEAR SIR,

The methodological problems of evaluating the prophylactic claim for lithium in recurrent depressions were well illustrated by the papers in the June, 1970, issue of the *Journal*. The matter is still wide open to question.

The first paper on methodology (Grof, Schou, Angst, Baastrup and Weis, 1970) was clearly intended as a platform for the second, and consequently contained biases of its own. It perpetuated the view that double-blind studies on lithium are ethically dubious because the illnesses treated are lengthy, 'painful and dangerous.' Dr. Melia's study (Melia, 1970) demonstrated that patients are at most subjected to one more relapse among many before being diverted to known lithium or some other drug (preserving the trial code intact). The fact that others have terminated studies prematurely (Laurell and Ottosson, 1968) is at least as much due to preconceived notions and public hysteria as to data arising from the abandoned trial. Nor is the lack of a suitable control drug a worthy objection. Schou himself originally claimed that imipramine might have similar prophylactic effects (Schou, 1963), and Melia has now shown that placebo can be effective for long periods (Melia, 1970)

The contention that studies on chronic depression are not subject to placebo effects or observer bias was supported by criticizing the psychoanalytic literature. This tells us something about the problems of evaluating psychoanalysis but little about the influence of non-drug factors on depression. Honigfeld has surveyed the considerable influence that physician and patient attitudes may have in response to placebos or drugs in depression (Honigfeld, 1963). A recent collaborative study involving 555 depressed in-patients showed that placebo produces quite marked benefits on a number of symptoms and subtypes of depression. Furthermore, drug treatment differences accounted for only 10 per cent of the variance in outcome (Raskin, Schulterbrandt, Reatig, and McKeon, 1970). The view that chronic refractory illnesses treated by enthusiasts are not amenable to non-drug influences is barely credible if one considers that it is precisely such situations which compose the 'panacea paradigm' (Blackwell, 1969). In a recent review on the placebo effect, Shapiro (1970) has described a phenomenon called 'indirect iatroplacebogenesis' where placebo effects are 'produced or augmented when the physician is prestigous, dedicated to his theory and therapy, especially if it is his own innovation, or if he is a recent convert, or when the therapies are elaborate, detailed, expensive, time consuming, fashionable, esoteric, or dangerous.' Recent research has suggested that the placebo response in double-blind studies may vary from 24 to 76 per cent under the influence of such variables (Lowinger and Dobie, 1969).

The elegant data presented on the natural history of recurrent depressive illness may be misinterpreted. It does not establish the general law that all depressive illnesses become worse with time, since it depicts the mean illness behaviour of a heterogeneous sample.

There is clearly a point (this side of continuous ill-health) at which an illness cannot do anything except stay the same or improve (regress towards the mean illness behaviour). This is an important issue when considering the second paper (Angst, Weis, Grof, Baastrup and Schou, 1970). This showed (Tables III and V) that about half the patients treated with lithium improved—and half did not. In discussing the possible variables which influenced improvement, the authors underplay the observation (Table XII) that the illness frequency is most influenced when the patient has had five or more previous episodes of illness. Since the mean duration of total illness before lithium is 32·8 months (all patients) and an episode lasts six months on average, this suggests that the patients showing most benefit were almost continously ill (for at least 30 out of the 32·8 months?) Since any change would then represent an improvement, lithium intervention has been credited with what largely represents the phenomenon of regression toward mean illness behaviour.

Dr. Melia's paper (Melia, 1970) contains a methodological flaw which undermines most of its conclusions. All patients included in the study had been on lithium for 9 months before being continued on lithium or changed to placebo. Those placed on placebo may have experienced minor withdrawal effects or loss of familiar side effects which could account for their relapse. Dr. Melia's rather vague reassurance concerning side effects and the double-blind integrity must be set against

the preceding authors' comment that 'during long observation periods even slight side effects may render the blindness illusory' (Grof *et al.*, 1970). This source of physician bias in the double-blind study is well documented (Engelhardt, Margolis, Rudofer and Palay, 1969).

Its potential influence on the patient is even more profound and appears to be supported by the data (Table III). Putting aside those patients who remained well for the entire period of 730 days and the patient with toxicity, there is a marked difference in the relapse behaviour in the two treatment groups. Five of the six placebo patients fell ill within three months (92 days). At first sight, this appears to confirm the experimental hypothesis; but a comparison of the pre- and post-trial behaviour of the two groups suggests otherwise. The lithium group had a pre-treatment frequency of 3·14 episodes a year, amounting to an episode each 116 days (Table II). On lithium, they remained in remission for a mean of 111 days (234, 109, 66, and 35 days). The placebo group had a pre-treatment episode frequency of 2·50 episodes a year or an episode each 146 days. After initiation of placebo they had a mean relapse rate of 76 days (269, 92, 57, 48, 32, 27 and 8 days). These calculations suggest that the patients placed on lithium remained unchanged and unimproved, whilst those on placebo deteriorated.

Dr. Melia's study, therefore, appears to support the following conclusions:

1. Both lithium and placebo may produce prolonged remission in a few instances.

2. Lithium occasionally causes serious toxicity.

3. Other patients do not improve on lithium, but may be made worse if switched to placebo. This is possibly because they detect the subterfuge because of the appearance of withdrawal effects or disappearance of side effects.

The last conclusion invokes psychological as well as physiological mechanisms and is difficult to test, but it may be supported by observing that the patients who were selected for this study were those whose attendance and compliance was most faithful, and who might be most attuned to detect change, and consequently most affected by it. At least one physiological mechanism that might account for the patients' subliminal perception of change would be alterations in REM sleep patterns that occur with lithium (Kupfer, Wyatt, Greenspan, and Snyder, 1970). Suppression of REM sleep and withdrawal rebound may partly account for dependency on many psychotropic drugs (Oswald and Priest, 1965; Kales, Preston, Tan and Allen, 1970) and can certainly produce disturbing and detectable symptoms in the patient.

Apparently we must continue to await the outcome of other double-blind studies now in progress before concluding that lithium has a prophylactic effect which justifies exposing patients to its undesirable toxicity for prolonged periods. Meanwhile, the conviction of lithium disciples in the face of flimsy evidence is reminiscent of the response which sociologists found among religious fanatics confronted with the failure of their prediction that the world would end (Festinger, Rieken, and Schachter, 1956). Their faith was strengthened.

BARRY BLACKWELL.

Department of Psychiatry,
University of Cincinnati College of Medicine,
Cincinnati General Hospital,
Cincinnati, Ohio 45229, U.S.A.

REFERENCES

ANGST, J., WEIS, P., GROF, P., BAASTRUP, P. C., and SCHOU, M. (1970). 'Lithium prophylaxis in recurrent disorders.' *Brit. J. Psychiat.*, **116**, 604–19.

BLACKWELL, B. (1969). 'Lithium: prophylactic or panacea?' *Medical Counterpoint.* 1 (**no. 8**), 52–9.

ENGLEHARDT, D. M., MARGOLIS, A., RUDOFER, L., PALAY, H. M. (1969). 'Physician bias and the double-blind.' *Arch. gen. Psychiat.*, **20**, 315–20.

FESTINGER, L., RIEKEN, H. W., and SCHACHTER, S. (1956). In, *When Prophecy Fails.* University of Minnesota Press, Minneapolis.

GROF, P., SCHOU, M., ANGST, J., BAASTRUP, P. C., and WEIS, P. (1970). 'Methodological problems of prophylactic trials in recurrent affective disorders.' *Brit. J. Psychiat.*, **116**, 599–619.

HONIGFELD, G. (1963). 'Physician and patient attitudes as factors influencing the placebo response in depression.' *Dis. nerv. Syst.*, **24**, 343–7.

KALES, A., PRESTON, T. A., TAN, T-L, ALLEN, C. (1970). 'Hypnotics and altered sleep-dream patterns.' *Arch. gen. Psychiat.*, **23**, 211–8.

KUPFER, D. J., WYATT, R. J., GREENSPAN, K., and SNYDER, F. (1970). 'Lithium carbonate and sleep in affective illness.' *Arch. gen. Psychiat.*, **23**, 35–40.

LAURELL, B., and OTTOSSON, J. O. (1968). 'Prophylactic lithium.' *Lancet*, *ii*, 1245–46.

LOWINGER, P., and DOBIE, S. (1969). 'What makes placebos work? A study of placebo response rates.' *Arch. gen. Psychiat.*, **20**, 84.

MELIA, P. I. (1970). 'Prophylactic lithium: A double-blind trial in recurrent affective disorder.' *Brit. J. Psychiat.*, **116**, 621–4.

OSWALD, I., PRIEST, R. G. (1965). 'Five weeks to escape the sleeping pill habit.' *Brit. med. J.*, *ii*, 1093–99.

RASKIN, A., SCHULTERBRANDT, J. G., REATIG, N., MCKEON, J. J. (1970). 'Differential response to chlorpromazine, imipramine, and placebo.' *Arch. gen. Psychiat.*, **23**, 164–73.

SCHOU, M. (1963). 'Normothymotics, mood normalizers.' *Brit. J. Psychiat.*, **109**, 803–6.

SHAPIRO, A. K. (1970). 'Placebo effects in psychotherapy and psychoanalysis.' *J. clin. Pharmac.*, **10**, 73–8.