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Correspondence

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BENIGN MYALGIC ENCEPHALOMYELITIS

DEAR SIR,

An epidemic of benign myalgic encephalomyelitis occurred in the north of England a few months before the Royal Free Hospital was involved. The basic clinical picture of lymphadenopathy, pyrexia, liver and splenic tenderness, with objective neurological changes in 20 per cent of the cases, was similar in both parts of the country. The most likely explanation appeared to be a country-wide infectious illness until Drs. McEvedy and Beard suggested that the Royal Free epidemic was due to hysteria (*British Medical Journal*, 1970, *i*, 7) and reaffirmed their idea in their recent report in your *Journal* (**122**, February, p. 141). On reading Dr. A. L. Wallis's account (M.D. Thesis, University of Edinburgh, 1967) of the effect of the epidemic on his practice at Dalston, Cumberland, for evidence of mass hysteria, one finds that he describes an illness resembling glandular fever, with morphological changes in lymphocytes in 30 per cent cases but with negative Paul Bunnell tests. The epidemic started amongst primary schoolchildren, with maximal incidence in boys age 5 to 11, but by March and April 1955, had spread to adults, who in general were more severely affected. Some patients showed evidence of either upper or lower motor neurone lesions, with patches of tenderness in the muscles of the legs and hyperaesthesiae in the overlying skin. Mental depression was common, with sleep inversion in some cases. The hysterical features emphasized in the Royal Free cases by Drs. McEvedy and Beard appeared to be infrequent, though temper tantrums in young children were common. Comparison of the two epidemics suggests that the infectious illness in the north did spread south to affect the Royal Free Hospital, but in the circumscribed population of young female adults hysterical reactions were more frequent, especially amongst nurses with a past history of mental illness.

Dr. S. B. G. Innes has suggested (*Lancet*, 1970, *i*, 969) that the involvement of the central nervous system in this condition is allergic in nature. This could explain why an agent could be transferred to rhesus monkeys from patients involved in the Adelaide epidemic (Pellew, R. A. A., and Miles, J. A. B. (1955), *Medical Journal of Australia*, **42**, ii, 480) but could not be retransmitted. The recurrences may be the result of a self-perpetuating immunological mechanism precipitated by the infection in susceptible individuals, as may be the case in rheumatoid arthritis. Certainly, in Drs. McEvedy and Beard's follow-up of cases there is evidence of hypersensitivity reactions such as asthma, eczema and possibly thrombocytopenic purpura in probands and their families.

Acceptance of the hysteria hypothesis presents two dangers. First, the search for an underlying aetiological agent may be abandoned. Some of the cases of the benign myalgic encephalitis syndrome in Japan were found to be due to sensitivity to the drug clioquinol. Secondly, the patient may be labelled a hysteric and denied the assistance he would get if it was considered he had an organic disability. The few patients with this syndrome referred to this centre in recent years have responded to a programme of graded physical activity in a similar manner to those with other organic diseases of the central nervous system.

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MYASTHENIA GRAVIS AND SCHIZOPHRENIA—A RARE COMBINATION

DEAR SIR,

We were very interested in the paper in the March 1973 (pp. 343–4) issue by Drs. Gittleson and Richardson on a case of schizophrenia and myasthenia gravis, because we have ourselves recently had such a case.

A married woman of 51, was first seen in her home in the evening of 18 October 1972. She was shaking with terror and unable to face another night in her house because of the things she felt the neighbours were doing to her with electrical machines through the walls and so on. She was forthwith admitted to

hospital. There was a history of increasing uneasiness, with onset of delusions and hallucinations of a paranoid nature, especially during the previous seven days.

A diagnosis of myasthenia gravis had been made in June 1971, and the patient had been established on a regime including 'Mestinon', prostigmin and atropine. For a few weeks before she was seen the myasthenia appeared to become uncontrolled and the dosage of anti-myasthenic drugs had been increased.

When admitted she was hallucinated, deluded, depressed and very anxious. The degree of fear she showed seemed so unusual that we wondered for a considerable time whether her condition could be a toxic state caused by the anti-myasthenic drugs, but there was no element of confusion. Within three days the psychotic symptoms and signs disappeared; her myasthenia, which had at times seemed quite severe, came under control, and she was discharged home on 13 November 1972, after trial weekend leave. She had apparently recovered from the psychotic episode, and the myasthenia was under control with almost exactly the same dosage of anti-myasthenic drugs as before the acute psychosis. She had had no anti-psychotic treatment other than her admission to the hospital and general nursing care.

Within three days of discharge she relapsed and had to be re-admitted. She had once again become hallucinated, deluded and terrified. The myasthenia was again out of control. This time she was treated with phenothiazines and later with antidepressives. The anti-myasthenic drugs were continued. The symptoms of both disorders again abated very rapidly, and after a more prolonged period of observation and trial leave, she was discharged on 18 January 1973, and has done well since.

We are now left wondering whether it was the schizophrenic illness that caused the myasthenia to go out of control, because the latter fluctuated pari passu with the former. (Unit No. 13365/72.)

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AN EXPLANATORY STATISTICAL MODEL FOR PLASMA LEVELS OF IMIPRAMINE AND DESMETHYLIMIPRAMINE DURING LONG-TERM THERAPY

Dear Sir,

In 1967, in this *Journal*, Moody, Tait, and Todrick (1) presented plasma levels of imipramine and desmethylimipramine (DMI) in 24 patients receiving long-term imipramine therapy. Because of 'considerable variations in the plasma imipramine and DMI levels', they concluded that these levels 'were not primarily related to the dosages (of imipramine) given'. We have considered Moody's conclusion of a lack of dose response and have addressed ourselves to the problem of identifying what factors relate to the plasma levels.

In addition to plasma levels, Moody presented sex, age, weight, dose, time after commencement of therapy, and other drugs the patients were taking. To enable us to compare dosages for persons of different body weights, we expressed dosages as Q = dose/weight, with units mg./lb. A regression model of the following form is fitted by the method of least squares:

$$Y = Q(aS+bA+cT)$$

where a, b, and c are constants to be determined

S is the patient's sex: +1 for males, −1 for females

A is the patient's age (years)

T is the patient's time after commencement of therapy (months)

Y is the patient's plasma level of imipramine, DMI, or total (mcg./l.).

The concurrent mediation was not considered because of its variety, and a lack of knowledge of how it can be incorporated into the mathematical model.

The regression analysis yielded estimates for coefficients and their probabilities are as below:

The multiple correlation coefficient R, which is the fraction of the total variation explained by the model, was computed. For imipramine, DMI, and total, the observed Rs (unadjusted for the mean) were 0·83, 0·92, 0·93 respectively, and all are significant at the 1 per cent level.

Category	Imipramine	DMI	Total
(a) Sex	−2·94 (P = 0·860)	−67·34 (P = 0·019)	−70·28 (P = 0·045)
(b) Age	1·57 (P < 0·001)	3·55 (P < 0·001)	5·12 (P < 0·001)
(c) Time	2·35 (P = 0·249)	9·91 (P = 0·005)	12·26 (P = 0·006)