

Her TD greatly disabled her. The fluphenazine and benztropine were discontinued. Reserpine was started and gradually increased to 3.0 mg daily and maintained. Baclofen was added in doses up to 60 mg per day without benefit. Lithium carbonate was added with achievement of red-blood-cell level of 0.68 mmol/l and serum level of 1.01 mmol/l (ratio 0.7) without significant improvement. The lithium was discontinued. Lecithin was added and at 45 mg per day significantly decreased the severity of the dyskinesia; however, prominent movements remained. The baclofen was tapered to 30 mg/day, but dosages below this allowed an increase in movement severity to return.

Serum IgG against AChR, measured by immunoprecipitation assay,⁶ was 1.1 nmol/l, which is in the range of titres often found in patients with mild generalised myasthenia gravis.

The presence of this antibody could be some correlate of mental illness, it could be caused by the drug regimen, or it may not be related to either of these variables. Over the past 5 years we have done assays on more than seventy patients with myasthenia gravis and on more than a hundred controls, including healthy controls and patients with other neurological diseases. This is the only non-myasthenic patient we have found with antibody against AChR. If the antibody is drug induced, then many possibilities can be considered. Antibody against AChR may not cause TD but its existence may indicate that a spectrum of autoantibodies have been created. An autoimmune attack against other CNS antigens could be responsible for TD. The antibody against AChR might have further significance in that it could be responsible for the histochemical abnormalities of skeletal muscle which have been reported in some psychotic patients.⁷ An increased branching and sprouting of terminal motor axons has been observed in both myasthenics⁸ and psychotic patients.⁹ We would like to suggest further investigation of the hypothesis that drug-induced autoimmunity could cause or contribute to the development of TD associated with the use of neuroleptic drugs.

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APLASTIC ANÆMIA AFTER NAPROXEN?

SIR,—Serious blood dyscrasias have been reported after ingestion of various non-steroid-antirheumatics, such as pyrazole or phenylbutazone derivatives, gold, penicillamine, and indomethacin. Naproxen has been used for several years, predominantly in rheumatoid arthritis, without serious side-effects on the hæmopoietic system. We have seen a case of severe aplastic anæmia in a patient taking this drug.

A 47-year-old man was given naproxen for recurrent back pain in November, 1975, in January and May, 1976, and then from October, 1978, to February, 1979. The total dose was about 20 g. A multivitamin preparation, triamcinolone, and phenylbutazone (600 mg) were taken in May, 1976. Intake of drugs other than naproxen was repeatedly denied by the patient, his family, and his family physician for the time from October, 1978, to February, 1979.

In January, 1979, the patient became ill with a distinct bleeding tendency, pallor, and fatigue. 2 months later, pancytopenia was noticed (erythrocytes $2.5 \times 10^6/\mu\text{l}$, reticulocytes 7000/ μl , neutrophils 900/ μl , platelets 17 000/ μl). Bone-marrow biopsy showed severe aplasia with only a few erythroid and myeloid cells and no megakaryocytes. There was no evidence of paroxysmal nocturnal hæmoglobinuria or auto-

immune disease. Granulopoietic and erythropoietic progenitor cells were much diminished when bone-marrow mononuclear cells were cultured in agar. The patient required intensive supportive care with red cell and platelet substitution. He did not improve on androgens nor on a 2 week course of high-dose corticosteroids. In November, 1979, the patient died because of a gastrointestinal hæmorrhage.

Phenylbutazone has often been indicted as a cause of aplastic anæmia. However, this drug was given, in only a small dose, more than two years before the first symptoms of the blood dyscrasia. Hepatitis B surface antigen was not present. In absence of other potentially noxious factors, the possibility that naproxen caused the aplastic anæmia has to be considered, though the coincidence of naproxen therapy and the onset of "idiopathic" aplastic anæmia cannot be excluded.

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NEUROENDOCRINE DISTURBANCES AND THE DIAGNOSIS AND ÆTIOLGY OF ENDOGENOUS DEPRESSION

SIR,—Several investigators have discussed the possibility that a subgroup of patients with endogenous depression has disinhibited activity of the hypothalamic-pituitary-adrenal (HPA) axis. 40–50% of such patients fail to show normal suppression of plasma cortisol levels during a 24 h overnight dexamethasone suppression test (DST). In four studies,^{1–4} on a total of 195 depressed patients and 193 comparison patients, an abnormal DST result was found in 43% of the depressives while the specificity was 99% (i.e., only 1% of the comparison patients had an abnormal DST result). Thus the predictive value (or diagnostic confidence) attached to an abnormal DST result is very high (98%),⁵ and the DST is now being used increasingly as a laboratory test for endogenous depression.

The most suitable diagnostic application of the test will be in populations where endogenous depression is suspected and where the prevalence is high. The prevalence rate was 50% in the four studies cited above. We would stress that the test will not eliminate the need for careful clinical judgment in the evaluation of depressed patients. It can, however, be most useful with some difficult clinical problems⁶ and in evaluating the efficacy of treatment.⁷ We have found it especially helpful in patients whose endogenous depression was masked by "neurotic" features or by a character disorder, which has led some consultants to advise against somatic antidepressant treatments.

One question is whether psychotropic drugs can interfere with the DST. We have been unable to establish any systematic interfering effect of the common drugs such as lithium, tricyclic antidepressants, neuroleptics, or low-dosage benzodiazep-

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piners. A similar conclusion was reached by Brown et al.³ and by Schlessner et al.¹ These drugs do not cause false-positive DST results. Since the sensitivity of the test is only 40–50%, this is the most important consideration: a normal DST result does not rule out endogenous depression. In theory, high-dosage benzodiazepines might cause false-negative results,⁸ but such an effect has not yet been demonstrated in depressed patients.

The aetiological significance (if any) of disinhibited HPA activity and abnormal DST responses is still uncertain. These are by no means universal findings among endogenous depressives. The genetic results of Schlessner et al.¹ could help to explain the heterogeneity of endogenous depressives with respect to HPA disinhibition. However, their classification system is not widely used, and no attempts to replicate their report have yet appeared.

We have made a limited review of our own patients, focusing on those with endogenous depression accompanied by affective delusions because their family histories had been carefully documented through contacts with relatives. Unlike Schlessner et al. we did not use systematic family interviews for all our cases, so we could be less confident about assigning most of our cases to their categories. Another reason for selecting delusional (psychotic) endogenous depressives is that the frequency of abnormal DST results is very high in this group.² We identified 14 patients with primary unipolar depressive illness, who met both the Washington University and research diagnostic criteria, confirmed by our own clinical diagnoses. 11 (79%) had an abnormal DST result. Using the genetic subtyping of Winokur et al.⁹ we classified 2 as familial pure depressive disease, 5 as sporadic depressive disease, and 6 as depression spectrum disease (DSD). 1 patient could not be classified by Winokur's criteria because she had a daughter with bipolar affective disorder. 5 of the 6 patients (83%) with DSD had a positive DST result. This contrasts with the 4% reported by Schlessner et al. Although we have studied only a highly selected group of patients, our results clearly indicate that disinhibited HPA activity can occur in patients diagnosed as DSD when a severe endogenous depression is present, and they cast doubt on the universality of the report by Schlessner et al. More extensive systematic studies will be needed to resolve this large difference between our results and theirs. We regard it as unlikely, however, that all the heterogeneity observed in the neuroendocrine studies will be accounted for by genetic factors.

Our own view is that the several neuroendocrine disturbances so far reported in endogenous depression, of which the abnormal DST response is established as the most specific, may represent indirect functional markers of the associated disturbance in the limbic system. That is, they may be indicators of "limbic system noise" with a temporal but epiphenomenal link to the primary pathology of the illness. This need not detract from the practical application of such tests (e.g., for diagnosis) or deter investigators from pursuing the possibility that the neuroendocrine disturbances result from the same neuro-transmitter imbalance(s) as does the mood disorder.¹⁰ Lacking good evidence, however, we cannot assume that this is true. The neuroendocrine research strategy has indeed given psychiatric investigators a "window" into the limbic system,¹¹ but we are still looking in from the outside, and the picture we have discerned so far is very tentative.

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CHANGES IN BETA-ADRENERGIC RECEPTOR SENSITIVITY ASSOCIATED WITH STRESS

SIR,—Diminished beta-adrenergic receptor sensitivity in peripheral tissues has been reported in individuals receiving beta agonists and in patients with catecholamine-secreting tumours.^{1,2} Synder has suggested that fluctuations in catecholamine output mediated by stressful environmental events may cause similar alterations in beta receptor sensitivity.³ However, to our knowledge such an effect has not been demonstrated.

We would like to report preliminary data from five male participants in the 1979 Iditarod Sled Dog Race who were studied before and after the competition. The race covers 1049 miles (1700 km) of the Alaskan interior from Anchorage to Nome and thus represented near continuous competition for more than two weeks.⁴ The level of cyclic AMP in the leucocytes both alone and in the presence of 10 μ mol/l isoproterenol was measured⁵ in venous blood drawn within 24 h of the start of the race and again within six hours of completion of the course. The amount of cyclic AMP produced in the presence of agonist divided by the basal level was designated the stimulation index and served as a measure of the reactivity of the leucocyte beta-receptors. Also, 24 h urine collections were started within two days of the start of the race and within 6 h of the finish. The samples were analysed for 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG)¹ a general indicator of central and peripheral catecholamine synthesis and metabolism.

CATECHOLAMINE TURNOVER AND REACTIVITY OF LEUCOCYTE BETA-RECEPTORS BEFORE AND AFTER SLED RACE

| Participant | Urinary MHPG (μ g/24 h) | | | Stimulation index | | |
|-------------|------------------------------|-------|--------|-------------------|-------|--------|
| | Before | After | Change | Before | After | Change |
| A | 2493 | 8504 | +6011 | 2.5 | 1.6 | -0.90 |
| B | 3580 | 2466 | -1114 | 1.9 | 1.8 | -0.10 |
| C | 2575 | 2621 | +46 | 1.4 | 1.8 | +0.40 |
| D | 3212 | 2193 | -1019 | 1.5 | 1.5 | 0.0 |
| E | 4302 | 5040 | +738 | 1.2 | 0.5 | -0.70 |

As the table shows, in two of the contestants (A and E) there was a substantial increase in the 24 h output of MHPG after the race. Furthermore, it was the white cells of these same men which showed the greatest decrease in sensitivity to isoproterenol. The remaining men, whose MHPG remained the same or decreased, showed little change or a increase in their stimulation index. One explanation is that the leucocyte beta receptors of A and E reduced their sensitivity to compensate for increasing concentrations of circulating catechols. This suggests that alterations in receptor sensitivity played a role in some of the participants' adjustment to physically and mentally taxing events. It also suggests that monitoring changes in receptor sensitivity may be a useful physiological index of stress.

We intend to study changes in receptor sensitivity in other normal populations exposed to stressful life events.

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