subsequent 5 h was collected under supervision. A meal containing sodium (10 mmol) and potassium (40 mmol) was taken 2 h after frusemide, and free intake of water was allowed. Plasma uric acid was measured by an automated phosphotungstate colorimetric method (Nishi, 1967) and concentrations of sodium and potassium were measured by flame photometry using lithium as the internal standard.

There was a significant positive correlation between the level of plasma uric acid 1 week before treatment and the urinary excretion of potassium following frusemide ($r = +0.89$, $P < 0.02$, Figure 1) and a negative correlation between plasma uric acid and the urinary Na/K ratio following frusemide ($r = -0.94$, $P < 0.01$, Figure 1). Correlations between plasma uric acid and the urinary volume and sodium excretion were not significant (Table 1).

It is worthy of note that the intersubject differences in potassium excretion following frusemide were large (range 15-68 mmol/5 h) and that approximately 80% of this variation could be accounted for in terms of the plasma uric acid level prior to treatment.

The observation that the level of plasma uric acid before treatment can be related to the apparent responses to both spironolactone (Ramsay *et al.*, 1975) and to frusemide suggests that the phenomenon is unlikely to be related specifically to diuretics, but rather may reflect a relationship between electrolyte excretion and uric acid homeostasis in normal subjects. Further study is required to elucidate the mechanism of these observations and to determine whether they have any therapeutic implications.

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PUPIL RESPONSIVENESS TO TYRAMINE IN DEPRESSED PATIENTS TREATED WITH AMITRIPTYLINE

Tyramine is an effective pupil dilator. When instilled locally, tyramine (120 μg) causes a 30% increase in the pupil diameter within 1 hour; a larger dose (500 μg) causes a dilatation of up to 90% (Palm, Fengler, Güllner, Planz, Quiring, May, Helmstaedt, Lammer, Moon & Holler, 1971). As tyramine is an indirectly acting sympathomimetic amine (Burn & Rand, 1958), the pupil dilation is presumably due to the action of noradrenaline released by tyramine from sympathetic nerve terminals. It has been reported that tricyclic antidepressants block the uptake of tyramine into sympathetically innervated tissues (Brodie, Costa, Groppetti & Matsumoto, 1968), and thus prevent the pharmacological actions of tyramine. The abolition of the pressor response to tyramine has been used in humans as an indicator of the effect of tricyclic antidepressants on peripheral uptake mechanisms (Freyschuss, Sjöqvist & Tuck, 1970). There have been no reports, however, how tricyclic antidepressants modify the responsiveness of the pupils to tyramine. We wish to report here some preliminary work which shows how pupil responsiveness to tyramine changes during the course of treatment with amitriptyline.

Three female patients (aged 23, 49 and 56 years, respectively) were included in this study. All three of them were diagnosed, on the basis of the psychiatric examination prior to their admission, as suffering from depressive illness. After their admission to hospital, they received no medication for the first two days. On each of these days the base-line (pretreatment) pupil response was assessed (see below), and the symptoms of depressive illness were rated using the Hamilton Rating Scale (Hamilton, 1960). On the third day, antidepressant drug treatment started (amitriptyline (Lentizol), 100 mg *nocte*). Pupil

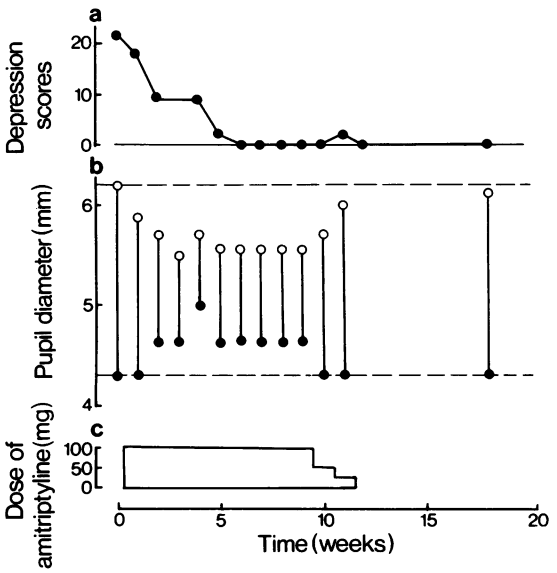

Figure 1 Pupillary responses to tyramine and depression scores of a depressed patient treated with amitriptyline (Lentizol). a: depression scores obtained from Hamilton Rating Scale. b: pupil diameter (mm) before (•) and 60 min after the instillation of tyramine (190 μg) (○); broken lines indicate values obtained before the start of treatment. c: dose of amitryptyline (Lentizol).

responsiveness was tested, and depression scores were obtained at weekly intervals.

A photographic method was used (Palm *et al.*, 1971) in order to assess pupil responsiveness to tyramine. First the pupils were photographed. Then tyramine (190 μg in one drop of artificial tear) was instilled into the conjunctival sac of the right eye. Finally the pupils were re-photographed after 60 minutes. The response to tyramine was measured as an increase in pupil diameter following the instillation of tyramine.

In all three patients we could observe a reduction in the size of the response to tyramine while the patient was treated with amitriptyline (size of maximum decrease in response: 50%; 65% and 100% respectively). After the cessation of treatment the original base-line response recovered. The data obtained in one of the patients are shown in Figure 1. It is apparent that the pupil responsiveness decreased gradually to a steady level, and stayed at this low level while the treatment continued. As the dosage of the drug was gradually decreased, the original control response gradually recovered. It can also be seen from Figure 1 that there was an increase in the resting diameter of the pupil during treatment with amitriptyline. This is in agreement with earlier observations (Silverstone & Turner, 1974).

The scores obtained for depression decreased gradually to zero during the first 4-6 weeks of treatment, and stayed at this low level during the rest of the treatment and after its termination. It is apparent from Figure 1 that pupil responsiveness is indicative of the presence of the drug, and not of the therapeutic effect. Similar curves were obtained with the other two patients.

These preliminary results show that the responsiveness of the pupils to tyramine may be a good objective indicator of the presence of tricyclic antidepressant drugs. In all three patients reported here amitriptyline (Lentizol, 100 mg *nocte*) apparently maintained a plasma concentration of amitriptyline which was sufficient to block the uptake of tyramine. Further studies are in progress with healthy volunteers in order to correlate changes in pupil responsiveness with plasma levels of amitriptyline.

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