Of 64 patients with severe menopausal symptoms who were allocated to a four-month trial in which Premarin and placebo were each taken for two months, 44 had severe vasomotor symptoms; a further 56 patients with less severe symptoms were allocated to a longer, 12 month trial in which Premarin and placebo were each taken for six months. It is stressed that neither the patients nor the attending doctors knew which treatment was being given. Graphic rating scales,^{3,4} which are a widely accepted and sensitive method of measuring change, were used to assess the effects of therapy, and thus the argument that a flush count is not an objective way of evaluating therapy cannot apply to these trials.

During placebo therapy, with respect to control values, there was a small, non-significant reduction in hot flushes in patients on the four-month trial, and in patients on the 12-month trial this reduction was just statistically significant ($P < 0.05$). However, during oestrogen therapy, with respect to placebo values, there was a statistically significant reduction in hot flushes in patients on both the four-month ($P < 0.001$) and 12-month ($P < 0.001$) trials.

Furthermore, in the 64 patients on the four-month trial benefits of oestrogen therapy over placebo were observed for 11 additional symptoms. The improvement in such a large number of symptoms is to some extent a domino effect—that is, a reduction in vasomotor symptoms creates a favourable response in a large number of associated symptoms. This could be demonstrated by studying the 20 patients who had severe menopausal symptoms but no hot flushes; in this group significant improvements on oestrogen therapy were observed for only five (vaginal dryness, memory, anxiety, worry about self, and worry about age) of the 11 additional symptoms. However, the improvement in memory and anxiety in this subgroup suggests that the “mental tonic” effect of oestrogens described by Utian⁵ is an entity and is independent of vasomotor symptoms.

The dearth of good placebo studies on the evaluation of oestrogen therapy in the treatment of the menopausal syndrome initiated these trials. Our results indicate that a significant reduction in hot flushes and a significant improvement in wellbeing, both psychological and symptomatic, will be achieved by oestrogen therapy.

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² Campbell, S, and Whitehead, M, in *Clinics in Obstetrics and Gynaecology*, vol 4, No 1, ed R Greenblatt and J Studd. Philadelphia, Saunders. In press.

³ Guilford, S, *Psychometric Methods*. New York, 1936.

⁴ Lader, M H, and Wing, L, *Physiological Measures, Sedative Drugs and Morbid Anxiety*. Institute of Psychiatry Maudsley Monographs. London, Oxford University Press, 1966.

⁵ Utian, W H, in *Frontiers in Hormone Research: Oestrogens in the Postmenopause*, ed P A van Keep and C Lauritzen, p 74. Basel, Karger, 1975.

Clonidine and facial flushing in rosacea

SIR,—A recent survey in this department¹ showed an association between migraine and rosacea, 44% of patients with rosacea having migraine, compared with only 13% of control subjects. As both conditions are associated with

abnormal vascular reactivity, drugs which are helpful in migraine could be of benefit in rosacea. In that same paper it was suggested that low doses of clonidine might reduce facial flushing. It was therefore decided to perform an oral and topical double-blind trial of clonidine in the treatment of rosacea with particular reference to flushing.

Seventeen patients entered the oral trial, which lasted for six months; all subjects had rosacea with some degree of facial erythema and flushing and were given either clonidine 0.05 mg twice daily or matched placebo tablets, the therapy being crossed over after three months. Twenty rosacea patients in whom flushing was the main feature entered the topical trial, in which 2% clonidine in a cream base was applied to one side of the cheek and the base alone to the other side four times daily for two weeks.

Both oral and topical active therapies were, on the whole, without effect, but five patients in the oral trial did notice an improvement in the frequency and severity of their attacks of facial flushing while on clonidine. In four patients with severe rosacea the oral trial had to be stopped because of a flare-up of the pustular element of their rosacea. In three of these patients this occurred during the three-month clonidine regimen. The lack of effect of the topical therapy could be due either to clonidine as a drug being totally ineffective in this condition or, alternatively, to the base in which the clonidine was incorporated being inappropriate.

From this evidence it would seem that there is no place for clonidine therapy in the routine treatment of rosacea, but it may occasionally be of benefit to patients whose predominant feature is flushing.

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¹ Tan, S G, and Cunliffe, W J, *British Medical Journal*, 1976, 1, 21.

D-Penicillamine and fatal obliterative bronchiolitis

SIR,—As stated by Dr D A Brewerton (18 December, p 1507), the death from obliterative bronchiolitis of four patients with rheumatoid arthritis was reported recently at a meeting of the Heberden Society. Two of these patients had been given D-penicillamine for their arthritis at Westminster Hospital, where some 60 rheumatoid patients had been maintained on the drug, and two had not.

In order to find out whether the same sort of thing was happening elsewhere I wrote to those in charge of 37 clinics asking (a) for the approximate numbers of patients who had received penicillamine for more than six

months, (b) for the mortality (from all causes) among them, and (c) for the numbers of such deaths that were from cardiopulmonary disease, excluding acute myocardial infarction.

The results of this inquiry are summarised in the accompanying table. The relatively high mortality from Wilson's disease and scleroderma is almost entirely the result of failures of the drug to control these diseases. Note also that most of the patients with Wilson's disease or cystinuria have been taking penicillamine for many years (up to 21), whereas most of the others have been on it for less than two years. Of the 15 non-acute pulmonary deaths, only two were definitely attributable to obliterative bronchiolitis and these were the two at Westminster Hospital. This diagnosis remains a possibility in two more, though an unlikely one in the case of the cystinuric patient.

There is therefore no reason to suppose that penicillamine causes death from obliterative bronchiolitis.

This letter has been drafted with the help of those who contributed the data upon which it is based, for which much thanks.

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Prostatic cancer

SIR,—We agree with Dr A Rostom (16 October, p 942) and Mr E P N O'Donoghue and Mr G D Chisholm (27 November, p 1324) on the need to improve the treatment of carcinoma of the prostate. We also agree that lymphography is not necessarily a sufficiently accurate technique on which to base a therapeutic protocol.¹ We are, however, concerned that clinical trials are apparently being considered for so-called “localised” prostatic carcinoma involving as a basis for therapeutic protocols currently available techniques to fulfil TNM requirements for classification. As with virtually every other solid tumour, the whole problem of prostatic carcinoma is that therapeutically essential staging—that is, the distinction between those patients who have truly localised or regional disease as distinct from those who have disseminated micro-metastases not detectable by current screening methods—is not possible at present. The concept that this therapeutically vital distinction cannot be made is not recent, having been pointed out by Franks in 1956,² and the same problem also applies to other tumours such as lung, breast, and head and neck cancers.

In our opinion any logical trial aimed at improving the survival time in prostatic cancer should compare local or regional techniques such as surgery or radiotherapy with local therapy plus systemic therapy with antitumour drugs. It is a depressing fact that only 10% of the currently available antitumour drugs

Mortality of patients under treatment with D-penicillamine

	Approximate No of patients treated	Deaths (all causes)	Deaths from non-acute cardiopulmonary disease	Deaths from obliterative bronchiolitis
Rheumatoid arthritis ..	2861	64	8	2 (+ 1 uncertain)
Scleroderma ..	76	8	6	0
Wilson's disease ..	300	37	0	0
Cystinuria ..	69	3	1	1 (uncertain)
Other ..	50	0	0	0
Total	3356	112	15	4