two separate analyses^{2,3} we concluded that from 1956 to 1973 age-specific mortality from ischaemic heart disease increased in both sexes, but the increase was greater in women than in men, except in age groups above 55 years, and in young men this increase was less marked during the 1960s than it was in earlier years. The reasons for the different conclusions arise from the inclusion by Clayton *et al* of deaths due to hypertensive disease in their analyses of ischaemic heart disease trends. It is not, however, clear why they did this. With the introduction of effective treatment for hypertension there are reasonable grounds for believing that the reduction in mortality from hypertensive disease in recent years is real and not simply due to transfer of cases from hypertensive categories into ischaemic heart disease categories.⁴ If such transfer did occur one would expect it to have affected men and women to the same extent, but this did not happen.

If deaths attributable to hypertensive disease are excluded from analyses of ischaemic heart disease trends the conclusions of Clayton *et al* are consistent with ours and together they indicate the need to explain the recent increase in ischaemic heart disease among women.

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Poisoning with antidepressants

SIR,—We have read with interest recent correspondence (23 July, p 260; 20 August, p 523) concerning overdosage with the new tetracyclic antidepressant mianserin, particularly with regard to the apparent lack of cardiotoxic effects of this compound. Although changes in the electrocardiogram (ECG) can be seen even in healthy subjects taking tricyclic antidepressants,¹ the most serious effects occur after overdosage² or in patients with preexisting heart disease,³ though the latter has been disputed.⁴

We have recently completed a study (to be reported elsewhere) in which we demonstrated a lack of interaction between mianserin and phenprocoumon. Of the 60 hospital in-patients (aged 25-79 years) studied, 54 were suffering from cardiac disease: 38 had recent myocardial infarctions, five had cardiomyopathy, and 11 had cardiac failure. Most of the patients were severely ill and had gravely disturbed ECGs before the start of the study. The patients, all of whom had previously been stabilised on phenprocoumon, were randomly allocated to treatment with mianserin 60 mg daily, mianserin 30 mg daily, or placebo. Thirty-five patients (21 male, 14 female) received mianserin. Medication was given under double-blind conditions over three weeks in three doses each day, the total daily dose increasing to the full level by day six. Heart rate, blood pressure, and ECG were

monitored at variable intervals during the study. There were no sudden deaths during the study and no unexpected deteriorations indicative of adverse drug effects. Statistical comparison of the treatment groups is impeded because of the high level of baseline abnormalities, but comparison of the data from the three treatment groups did not reveal any apparent differences.

We consider that these data, together with recently published evidence from overdose cases⁵ and in-vitro animal studies,⁶ support the conclusion that mianserin lacks cardiotoxic effects even when given, in therapeutic doses, to subjects with pre-existing cardiac disease.

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"Zip injury" to the penis

SIR,—The complaint of zip fly injury to the penis is sometimes made by sexually promiscuous men attending hospital accident and emergency departments in order to avoid attending sexually transmitted disease clinics or to obtain prompt treatment. If the house officer is fully conversant with the appearance of a primary syphilitic sore or a spontaneously healing painless genital chancre the case is referred to a specialist. However, when he trusts the statement of such patients the correct diagnosis may be missed. If the patient is given an injection of penicillin or another treponemocidal drug the incubating syphilis will be masked and the disease will pass to the secondary stage.

Two such cases have recently been detected in the accident and emergency department at this hospital. The first patient was the French Algerian boy-friend of a local girl. He did not speak English and the girl was acting as interpreter. Under the circumstances he had little choice but to deny any other sexual contact. On persuasion he agreed to give blood, urine, and a urethral smear. His serum tests for syphilis proved positive, as did those of his girl-friend. The girl was treated and information was sent to her boy-friend in Paris.

The second case was that of a patient who had enlargement of the inguinal lymph nodes and a healed primary lesion on the penis. There was initial denial of sexual exposure. On examination a very scanty mucoid discharge was found. He was strongly seropositive and *Neisseria gonorrhoeae* was cultured from his urethral smear.

In such cases it is wise to follow the dictum that "any lesion on the external genitalia should be investigated on the lines of syphilitic chancre until proved otherwise."

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Levamisole-induced arthritis

SIR,—It is suggested by Dr A W Segal and his colleagues (27 August, p 555) that arthritis due to levamisole administration is a complication specifically related to Crohn's disease. The following case history suggests that this is not so.

A 67-year-old woman was noted to have severe mouth ulcers in 1966. In 1970 she developed a spontaneous deep venous thrombosis of the leg and has had recurrent bilateral superficial thrombophlebitis of the legs since then. In 1971 she had an episode of episcleritis and has required systemic steroids to prevent relapse. A clinical diagnosis of Behçet's syndrome was made in 1974 when oral ulceration again became a problem. No genital ulcers have been noted and apart from radiological evidence of right-sided sacroiliitis she has had no joint involvement.

Systemic steroids have not influenced her mouth ulcers and she has been unable to take chlorambucil, cyclophosphamide, and azathioprine because of bone marrow suppression. There was no improvement with local carbenoxolone, cromoglycate, and idoxuridine and systemic penicillamine, colchicine, and indomethacin. Her mouth ulcers were so bad that she tried local application of paw-paw fruit!

Levamisole has been shown to be effective in the treatment of recurrent aphthous stomatitis^{1,2} and this was given in a dose of 150 mg per day for three consecutive days every two weeks. After the first course she complained of diffuse arthralgia affecting mainly the knees and elbows, which settled spontaneously within 48 h of stopping the drug. Ten days later, following the second course, the patient was rendered immobile by severe and generalised arthralgia which again resolved spontaneously during the following week. Investigation showed no other cause for her symptoms.

Arthralgia may be a manifestation of Behçet's syndrome and it seems to have been drug-induced in this case. It has been suggested that levamisole may have a deleterious effect on the joints in rheumatoid arthritis.³ This reinforces the hope that elucidation of the mechanism of action of levamisole may help to determine the pathogenesis of arthritis.

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Interaction between azapropazone and warfarin

SIR,—Dr P R Powell-Jackson, reporting interaction between azapropazone and warfarin (7 May, p 1193), suggests that the mechanism may be similar to that of the warfarin-phenylbutazone interaction, since the drugs are chemically similar. The mechanism of the latter drug interaction may be twofold: (1) due to displacement of warfarin from plasma albumin binding sites or (2) due to an effect on the renal clearance of the R and S isomers of warfarin. Azapropazone is approximately 96% bound to plasma proteins¹ and hence may interfere with the binding of warfarin.

We have recently carried out some preliminary in-vitro studies on warfarin binding to albumin in both the presence and absence of azapropazone. An ultrafiltration technique was used for these binding studies; this is a modification of the method described by Blatt *et al*.² The binding medium used was 0.2% lyophilised human serum albumin in aqueous buffer (37°C, pH 7.4). This system