SIR,—The paper by Professor T. N. A. Jeffcoate and his colleagues (5 October, p. 19) is of great interest because of their confirmation of the association between puerperal thromboembolism and the use of oestrogens to inhibit lactation. There are differences between their findings and those of the original Cardiff Survey[1] which are not likely to be due to differences in dosage or the oestrogen used.

In the Princess Mary Maternity Hospital lactation is usually suppressed with stilboestrol to a total dosage of 110 mg. In the years 1961–6 inclusive there were 14,018 deliveries, and among the 44 cases of significant thromboembolism requiring anticoagulants, in no fewer than 19 (43.2%) of these cases the complication occurred during pregnancy. The relatively large number of venous thrombotic episodes in pregnancy, also noted in one of the Liverpool hospitals, appears to be a recent phenomenon. We are convinced that this high incidence represents a change in the pattern of the disease, rather than an improvement in diagnosis.

The incidence of puerperal thromboembolism is 1.6 per thousand births, which is very close to that found in Liverpool. We have formed a control group by selecting at random 1% of all case records during the period under study. There is every reason to believe that this group is representative of the population as a whole, and one can calculate that the incidence of thromboembolism in women who lactated was 0.5 per thousand, compared with an incidence of 3.0 per thousand in women whose lactation was suppressed. Although our numbers are small certain tentative conclusions are possible.

As in the other reported studies, suppression of lactation does not seem to affect the incidence of thromboembolism in women under the age of 25. Assisted delivery is associated with an increased risk of thromboembolism only in woman whose lactation was suppressed, and even among the latter group the increase was limited to patients delivered by caesarean section. Six of the 25 (24%) patients were delivered abdominally as compared with a section rate of 9% in the control group. We agree with Professor Jeffcoate and colleagues that the factors of increasing age and parity when coupled with oestrogen suppression together increase the risk of thromboembolism even when neither of them are effective separately.

A continuing paradox is the failure of the incidence of thrombosis in the puerperium to follow the change in breast feeding habits. Fifteen years ago 10% of patients in this hospital had lactation suppressed; since then the incidence has increased steadily until by 1965 75% were given oestrogens. These figures of the changing pattern of breast feeding agree more with the Scottish experience[2] than with that quoted for Liverpool. However, during this period, as in Liverpool, there has been no increase in the incidence of puerperal thromboembolism (in contrast to the marked changes in the rate of thromboembolism in pregnancy). This suggests that the association between puerperal thromboembolism and the use of synthetic oestrogens to suppress lactation is not as clear-cut as the Cardiff workers suggested. Because of the low incidence of the disease and the many causal factors involved it is unlikely that any retrospective study from a single centre can give any precise measure of the risk of oestrogen administration. It is encouraging that large controlled prospective studies are already in progress. These ought also to indicate whether oestrogens are effective or indeed necessary to suppress lactation, since the evidence on this point is far from clear.—We are, etc.,

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REFERENCES

1 Daniel, D. G., Campbell, H., and Turnbull, A. C., *Lancet*, 1967, 2, 287.
2 Arneil, G. C., *Scottish Health Service Study No. 6*, 1967. Edinburgh.

## Rare Cause of Precordial Pain

SIR,—A 57-year-old male was admitted urgently to the cardiac department of the Evangelismos Medical Center because of severe constricting retrosternal pain. This was of abrupt onset, although two to three weeks earlier he had experienced weakness, low-grade fever, mild dyspnoea, and cough.

On admission he was in a shocked state, blood pressure being 80/60 mm. Hg and pulse rate 140/min. There was dullness on percussion and greatly diminished breath sounds in the lower half of the left lung. W.B.C. were 22,000/cu.mm., with 88% polymorphs and E.S.R. 88 mm. in the first hour. Aspartate transaminase was 33 units, alanine transaminase 27 units, and serum amylase 120 Somogyi units %. Chest *x*-ray showed stippled densities throughout the left lower lobe due to alveolar infiltration and small amount of fluid in the left pleural cavity. E.C.G. showed sinus tachycardia, with negative or biphasic T waves in I, II, AVL and ST depression in $V_2$–$V_6$. The patient's condition continued to deteriorate rapidly, and he died 12 hours after his admission to the hospital.

Necropsy showed the middle portion of the oesophagus infiltrated by a soft tumour mass which had ruptured into the mediastinum and to a lesser extent into the main bronchus of the left lung. Microscopic examination of the tumour showed squamous cell carcinoma. The heart was of normal size without any occlusion of the coronary arteries.

The object of describing this case is to draw attention to this rare cause of praecordial pain that may simulate acute myocardial infarction. Contemporary investigators have accepted between 86 and 200 cases of spontaneous perforations of the oesophagus reported in the literature.[1] On the other hand, spontaneous perforation of an oesophageal tumour without being previously subjected to radiotherapy seems to be extremely rare. Actually we were unable to find any case reported previously in the literature. Spontaneous perforation of the oesophagus, whether due to a tumour or not, may easily be confused with acute myocardial infarction. This is due to the location and character of the pain as well as the peripheral circulatory collapse that it may produce.[1] The lack of specific E.C.G. changes in the oesophageal rupture helps to establish the correct diagnosis, but it is well known that in many cases of myocardial infarction these changes are found only on serial electrocardiograms.—We are, etc.,

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REFERENCE

1 Tesler, M. A., and Eisenberg, M. M., *Int. Abstr. Surg.*, 1963, 117, 1.

## Unusual Cause of Yellow Skin

SIR,—Perhaps you would allow us to draw the attention of your readers to an interesting and hitherto unreported side-effect of Salazopyrin (sulphasalazine).

A 73-year-old lady undergoing treatment for long-standing recurrent ulcerative colitis developed a striking yellow pigmentation of the skin. Her serum was also bright yellow. The pigment was not bilirubin and her liver function tests were normal. In addition to local and systemic steroid therapy she was receiving sulphasalazine 4 g./day. She was known to have impaired renal function, a blood urea at a previous admission being 98 mg./100 ml., and the present exacerbation of her ulcerative colitis had precipitated a uraemic state, peak blood urea 328 mg./100 ml. Having noticed yellow staining of the tongue during administration of sulphasalazine, we guessed that abnormally high blood levels of the drug had been attained in our patient, due to inadequate renal excretion. Fearing the possibility of toxic side-effects, we carried out a peritoneal dialysis which rapidly returned the colour of her skin and serum to normal. Examination of the bright yellow serum, taken at the time of the pigmentation, by the method of Böttiger[1] identified the colour as being due to sulphasalazine in a concentration of 30 mg./100 ml. (a normal therapeutic blood level on a dose of 6 g./day is 3–4 mg./100 ml.). The patient recovered from her exacerbation of diarrhoea, and subsequent investigation revealed radiological evidence of chronic pyelonephritis. Her blood urea returned to 95 mg./100 ml. and a 24-hour creatinine clearance was 20 ml./min.

Despite the alarming yellow skin pigmentation and the high blood level of the drug inadvertently produced in this patient, we found no evidence of toxicity or other harmful effects. It is nevertheless worth making the point that sulphasalazine when given in normal dosage to patients with reduced renal function can cause yellow skin pigmentation which might be mistaken for jaundice.—We are, etc.,

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REFERENCE

1 Böttiger, L. E., *Scand. J. clin. Lab. Invest.*, 1958, 10, 108.

## Folate Deficiency in Pregnancy

SIR,—In your article on folic acid and combined iron and folic acid preparations in pregnancy (12 October, p. 102) the dosage of folic acid supplements for pregnant women at increased risk is discussed.

A trial concluded recently (in press) was limited to pregnant women in a population with exceptionally poor nutritional status. In addition, all the women were multiparous and the pregnancy immediately preceding the index pregnancy had been complicated by defective folate metabolism. It was found that 500 μg. folic acid daily was adequate to prevent folate deficiency in pregnancy and was as effective for this purpose as a dosage of 5 mg. daily. The population studied were known to be poorly motivated and were poor attenders at the antenatal clinics, but, as

judged by this trial, the 500 μg. dosage provided a reasonable safety margin to allow for irregular taking of therapy.

A similar trial on pregnant patients with established folate deficiency, administering either 500 μg. or 5 mg. folic acid *three* times daily, also showed no significant difference in response between the two dosage groups. Nevertheless, the need for continued clinical and laboratory supervision needs emphasis, since, even when 15 mg. folic acid is given daily, a small proportion of patients fail to show a satisfactory response.

Could we also draw attention to a minor error in your article? It is stated that oral preparations of folic acid alone in the microgramme range are generally not available. A tablet of folic acid B.P. 100 μg. is now available and is manufactured by McCarthy. —We are, etc.,

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## Herpesvirus hominis Infections

SIR,—We noted the letter of Drs. Eleanor J. Bell and Constance A. C. Ross (26 October, p. 254) and find we are in complete agreement with it. We were considering the diagnosis of *Herpesvirus hominis* from the clinicians' point of view on the day of the patient's admission (12 October, p. 89). It was not intended as a comparison of the isolation of the virus on different cell lines; it is well appreciated that the W.I. 38 cells and human amnion are extremely sensitive to *Herpesvirus hominis* infections and may give a typical cytopathic effect in a few days. In our laboratory, the cell lines employed for routine isolation of suspected herpesvirus infections are HEp. 2 and HeLa, though W.I. 38 are used when they are available; the routine use of primary human amnionic cells in some laboratories is not encouraged because their advantages are outweighed by their disadvantages.

A further observation that we should make is that it took, on average, 14.5 days for the virus to be isolated from corneal scrapings as compared with 4.3 days from skin scrapings. This shows that the cell system as regards skins is of a high sensitivity for virus isolation, and that the length of time taken for isolating *Herpesvirus hominis* from eye lesions was solely as a result of the extremely small inoculum, which is fully explained in our paper. Moreover, on the few occasions (not reported) where eye scrapings were used solely for isolation of virus and not for fluorescence as well, the length of time for isolating the virus became as short as that from skin material.

The last point on which we would like to comment is on the question of specificity. Our present reagents do not appear to react with the few cases of florid chicken-pox and herpes zoster that we have examined and have described, material being selected from vesicular lesions. It is possible that with other preparations, cross-reactions may be obtained and in this respect we have so far been fortunate. It is of the utmost importance that fluorescent techniques, for the diagnosis of either *Herpesvirus hominis* or, for that matter, any other virus, should be specific, accurate, and reliable and acceptable as respectable virus procedures.—We are, etc.,

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SIR,—We write to make two observations on the article by Dr. P. S. Gardner and others (12 October, p. 89).

Firstly, although we have used the immunofluorescent technique to study herpes infections in animals and human brain (as have others before us[1 2]) we do not think it has any advantage for the routine diagnosis of superficial infections. Drs. Eleanor J. Bell and Constance A. C. Ross (26 October, p. 254) commented on the rapidity of virus isolation in human amnion cells, and our results are similar: for 113 isolations, in 1968, of *Herpesvirus hominis* from skin and mouth lesions, the mean time to appearance of characteristic cytopathic effect was 1.7 days (range 1–5). For 63 isolations, in 1965–6, from corneal scrapings the mean time to appearance of cytopathic effect was 1.4 days (range 1–3). When virus can be grown so rapidly fluorescent staining is either just additional labour or a poor alternative to virus isolation.

Secondly, we agree with Dr. Gardner and his colleagues that when rapid diagnosis is really essential immunofluorescence is a useful technique, and we have applied it to 11 biopsy specimens of human brain when herpes encephalitis was suspected and therapy with iododeoxyuridine was being considered. Part of the sample was used for histology, part for virus isolation, and part was blocked in gelatin, sectioned in a cryostat, and stained with fluorescent antibody. We consider sections preferable to smears, because they are uniform and facilitate replication (usually 3-fold) of test and control staining. The specimen from one patient showed equivocal fluorescence, but virus was isolated from it. Specimens from three other patients showed specific fluorescence of infected neurones (5–20 per section) and a strong presumptive diagnosis was made in three hours. Virus was isolated from these specimens one or two days later. Specimens from the other seven patients showed no evidence of herpes virus by immunofluorescence or culture and the patients subsequently proved not to have herpes encephalitis.

Observations on the post-mortem brains of three patients showed that herpes antigen was most easily detected in the cortex, and it is therefore important to include this tissue in the biopsy sample examined.—We are, etc.,

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REFERENCES
1 Sabin, A. B., and Messore, G., in *Encephalitides*, edited by L. van Bogaert, J. Radermecker, J. Hozay, and A. Lowenthal, 1961. Amsterdam.
2 Johnson, R. T., *J. exp. Med.*, 1964, **119**, 343.

## Accidental Poisoning in Childhood

SIR,—Dr. R. H. Jackson and others (26 October, p. 245) underestimate the problem in stating that the incidence of accidental poisoning in children is slowly rising. The Ministry of Health and General Register Office reports on hospital inpatient inquiries[1] show that the number of children admitted to hospitals in England and Wales from the effects of poisons has risen from 4,100 in 1958 to 14,360 in 1965, an increase of three and a half times in seven years. In 1965 there were, on an average, 1,000 hospital beds in daily use for cases of accidental poisoning in children.

Dr. Jackson's figures confirm that the majority of poisons taken are now tablets and not domestic substances, and of the tablets about half are aspirins. It seems probable that between three and four thousand children are admitted to hospital each year with aspirin poisoning. A personal study of 200 such cases over the last four years has shown that the drug has nearly always been taken in the form of junior flavoured aspirin, and that the child practically always finishes the bottle or packet, which usually contains initially 50 tablets (4 g.). A simple preventive measure would be to stop the sale of junior aspirin in packages of more than a dozen (1 g.). This amount of aspirin is unlikely to give rise to toxic effects.

Of the several preventive measures suggested by Dr. Jackson one of the simplest and most practicable would be to insist on the labelling of containers with the name of the drug. This has been advocated by all sections of the medical profession, by the Pharmaceutical Society, and strongly recommended by the Committee on the Safety of Drugs. The time has surely arrived for the Minister to enforce this by regulation.—I am, etc.,

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REFERENCE
1 *Report on Hospital In-Patient Enquiry for the year* 1965, Part I, Tables, H.M.S.O., London, 1968.

## Cardiomyopathy of Pregnancy

SIR,—In their report of a primipara with fatal brain damage associated with cardiomyopathy of pregnancy (2 November, p. 285) Dr. I. M. Ledingham and his colleagues stated that exhaustive investigations in this patient had been unsuccessful in identifying a specific aetiological factor. However, it seems relevant to mention that we had obtained serological evidence of active infection with herpes simplex virus during this patient's illness.

Her neurological symptoms started on 16 January 1967. Serial specimens or sera collected during her illness and tested in parallel showed a rising complement-fixing titre for herpes simplex—namely, 1 in 16 (16 January), 1 in 64 (28 January), 1 in 1,024 (18 February), and 1 in 512 (15 March). The complement-fixing titre for varicella-zoster showed only a twofold rise from 1 in 8 to 1 in 16 during the whole period. We were also able to obtain a specimen of serum which had been collected for routine antenatal tests on 26 December 1966, before her illness began. This showed the same titre for herpes simplex as that collected on 16 January at the beginning of her illness. This