Eugynon 30 and Dermatitis

SIR,—We report an unusual case of eczematous lesion associated with the Eugynon 30 contraceptive pill, which contains 0.03 mg of dinorgestrel.

A 20-year-old woman was prescribed Eugynon 30 in November 1973 for menstrual irregularities. She had no adverse effect during December. Soon after starting the second pack in January 1974 she developed an eczematous rash on her right hand, mainly over the dorsal aspect of the fingers. She also had some redness and swelling of her face which subsided of its own accord. Subsequently a similar eczematous rash appeared on her left hand. She had never had any skin lesion in the past. No one in her family suffered from eczema or allergy.

As she worked as a packer, handling flour, the possibility of contact dermatitis was considered. All laboratory investigations, including a patch test, showed no abnormality and there was no improvement when she changed her job. Subsequently she volunteered the information that the eczematous lesions dried up during the week that she did not take her pills. Since then we have confirmed this association. The eczematous lesions appear four days after starting the monthly course of Eugynon 30, affect the extremities only, and remain "weepy" till the course is finished. The skin lesions virtually dry up during the week she does not take the pills. She had taken another contraceptive pill (Controvalar) for two months prior to starting Eugynon 30 and had never experienced similar cutaneous lesions.

We have not encountered this association before, nor can we find similar reports in the literature. We wonder if any one else has observed it.—We are, etc.,

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Aspirin and Atherosclerosis

SIR,—May I support the doubt expressed briefly in your leading article (9 March, p. 408) whether Dr. P. C. Elwood and his colleagues (p. 436) are correct in stating that "a dose of 300 mg [of aspirin] once a day . . . is well above that necessary to affect platelet aggregation to collagen and to ADP"? The authors base this statement on the publications of Born¹ and O'Brien *et al.*² who did not study the inhibition of thrombocyte aggregation by aspirin over a long period. More recently Stuart³ has described a prolonged effect of aspirin, but only two of his subjects were studied for longer than 28 days. However, Breddin *et al.*⁴ and Scharrer *et al.*⁵ showed that with a daily dose of 500 mg of aspirin the inhibition of platelet aggregation ceases after weeks or months in some subjects and that it is necessary to raise the dose to 1.0–1.5 g in order to obtain a continuous effect. Probably for this reason the majority of investigations are performed with a dose of aspirin exceeding 600 mg daily in the prevention not only of venous⁶ but also of arterial thrombosis.^{7,8} Should we "try harder" with aspirin in order to obtain statistically conclusive results?—We are, etc.,

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¹ Born, G. V. R., *Nature*, 1962, **194**, 927.

² O'Brien, J. R., Keywood, J. B., and Heady, J. A., *Haemorrhage*, 1966, **16**, 752.

³ Stuart, R. K., *Journal of Laboratory and Clinical Medicine*, 1970, **75**, 463.

⁴ Breddin, K., Scharrer, I., and Schepping, M., *Münchener medizinische Wochenschrift*, 1971, **113**, 1284.

⁵ Scharrer, I., Schepping, M., and Breddin, K., *Klinische Wochenschrift*, 1969, **47**, 1318.

⁶ Blättler, W., *Schweizerische medizinische Wochenschrift*, 1973, **103**, 747.

⁷ Peter, A., Regan, T. J., Jesrani, M. U., and Moschos, C. B., *Clinical Research*, 1970, **18**, 669.

⁸ Schmutzler, R., *Therapeutische Berichte* (Bayer, Leverkusen), 1971, **43**, 139.

Acute Brucellosis with Unexpected Source

SIR,—Dr. B. T. Rogers and others (29 June, p. 706) report a case of acute brucellosis as coming from an unexpected source, a central London hotel, but they do not comment on the public health aspects. A person using a London hotel is not likely to know that raw milk is being served. Public health investigation would not suspect a London hotel if a patient with brucellosis had also stayed elsewhere.

At the 1971 National Conference of Public Health Medical Officers the following resolution was passed as a reference to the Public Health Committee:

"That this Conference is concerned that raw milk is used in some hotels, boarding houses and restaurants without the customers being aware that it is not heat treated, and considers that legislation should be sought to make it obligatory for the management to post prominent notices stating that milk used on the premises is not heat treated."

If a Regulation to that effect had been made by the Government persons in hotels, etc. where raw milk is served would know that they are drinking milk that has not been heat treated. In due course milk in this country may be brucellosis-free as well as free from tubercle bacilli, and then these two diseases will not be spread by milk. But other diseases are spread by raw milk—for example, the 1936 typhoid outbreak in Bournemouth and Poole was milk-borne. The posting of notices in hotels, etc. that milk used on the premises is not heat treated would alert persons to the possibility of infection.—I am, etc.,

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Adverse Reactions to Intra-amniotic Prostaglandin

SIR,—Having read the correspondence on the above subject from Mr. A. H. Ross and Mr. W. L. Whitehouse (30 March, p. 642) and Mr. R. Brown and Mr. A. M. Smith (18 May, p. 382) I would like to make a few comments.

The intraamniotic route for prostaglandin administration is safe and practical because the amniotic fluid acts as a depot for prostaglandins. The large doses of prostaglandins E₂ and F_{2α} thus administered gradually pass across the fetal membranes to the uterus, which they stimulate for several hours. The maternal levels of prostaglandins do not alter significantly because of rapid metabolism and inactivation of these compounds. A fraction of the intra-amniotic dose of either prostaglandin E₂ or prostaglandin F_{2α} given as a bolus intravenous injection is known to produce cardiovascular and gastrointestinal side effects.¹ Any increase in the rate of absorption of prostaglandins from the amniotic cavity into the systemic circulation would be expected to produce adverse reactions. In two of the three cases described by Mr. Ross and Mr. Whitehouse prostaglandin E₂ administration was preceded by intra-amniotic injection of urea. The study by Craft² with intra-amniotic urea and prostaglandin combination points to "alterations

in the dynamics of absorption of prostaglandins into the systemic circulation from the amniotic sac due to the simultaneous administration of urea." The explanation for the adverse reaction in the third case, in which no urea was administered but the liquor was blood-stained, seems logical.

In the case described by Mr. Brown the adverse reactions appeared after 2.5 mg of prostaglandin had been administered. It is unlikely that the adverse reaction could have been due to direct injection of prostaglandin into the patient's systemic circulation. One-tenth of this dose (0.25 mg) given as a bolus intravenous injection has been shown to produce an increase in systemic blood pressure and alteration in pulse rate in man.³ No changes in cardiovascular parameters occurred in Mr. Brown's case. It is likely that at least part of the dose was inadvertently injected into the peritoneal cavity; the nausea, vomiting, "goose pimples," and other symptoms described could have been secondary to strong contraction of the smooth muscle of the gastrointestinal tract.

The case of molar pregnancy described by Mr. Smith is particularly interesting. The usual intra-amniotic dose of prostaglandin E₂ for the termination of second-trimester pregnancy is 5 mg, though some investigators have used higher doses.¹ Given extra-amniotically the dose is around 200 µg administered at one- to two-hourly intervals. Even at this dosage extra-amniotic administration of prostaglandin E₂ is associated with some side effects, including transient hypotension.⁴ Because of the absence of fetal membranes in a molar pregnancy intrauterine administration of prostaglandin in this situation is similar to extra-amniotic administration. The dose of 20 mg employed by Dr. Smith was thus 100 times higher than the usual extra-amniotic dose. This must be the highest single dose of prostaglandin E₂ ever administered extra-amniotically to a pregnant woman. In spite of the adverse reaction the result of the above case is reassuring in the sense that such a massive dose did not prove fatal.—I am, etc.,

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¹ Prostaglandins, *Progress in Research*, ed. S. M. M. Karim. Oxford and Lancaster, M. T. P., 1972.

² Craft, I., *Lancet*, 1973, **1**, 1344.

³ Karim, S. M. M., Somers, K., and Hillier, K., *Cardiovascular Research*, 1971, **5**, 255.

⁴ Embrey, M. P., and Hillier, K., *British Medical Journal*, 1971, **1**, 588.

Cot Deaths

SIR,—Hyperpyrexia is a recognized hazard in (1) the management of premature infants; (2) febrile illness—for example, malaria; (3) exposure to hot and humid weather (heat stroke); (4) anaesthesia. Is this hazard underestimated when, overnight and unobserved, an apparently healthy postneonate develops febrile illness of abrupt onset from whatever cause (viraemia, toxæmia, immunization procedure) in the winter months when the mother believes that plenty of clothing and bedding protects from colds, chills, and flu? Fever combined with excessive insulation may be a dangerous combination in a condition such as roseola infantum.